

**STUDIES ON CATALYTIC
MACROCYCLIZATION TOWARDS THE
SYNTHESIS OF MACROCYCLIC KETONES,
MACROLACTONES AND MACROLACTAMS**

विद्या वाचस्पति की उपाधि की अपेक्षाओं की आंशिक पूर्ति में प्रस्तुत शोध प्रबंध

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*This Thesis is Dedicated to My
Beloved Parents, My Brother,
My Wife, all My Teachers and
Friends for Their Unwavering
Love and Support in making all
My Success Possible*

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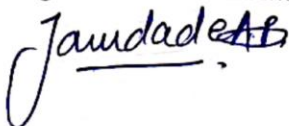
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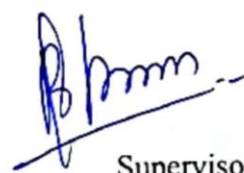
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This is to certify that the work incorporated in this thesis entitled "*STUDIES ON CATALYTIC MACROCYCLIZATION TOWARDS THE SYNTHESIS OF MACROCYCLIC KETONES, MACROLACTONES AND MACROLACTAMS*" submitted by **Akash Bandu Jamdade**, was carried out by the candidate under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

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ABBREVIATIONS

° C	Degrees Celsius	equiv.	Equivalents
M	Molar	HRMS	High-resolution mass spectroscopy
mM	Micromolar	ESI TOF	Electrospray ionization time-of-flight
Aq	Aqueous	ESI	Electron spray ionization
Bn	Benzyl	m/z	mass to charge ratio
Me	Methyl	[M] ⁺	Molecular ion
Et	Ethyl	GC	Gas chromatography
bs	Broad singlet	NMR	Nuclear magnetic resonance
Ph	Phenyl	h	Hour (s)
rt	Room temperature	Hz	Hertz
t _R	Residence time (in continuous flow)	FTIR	Fourier-transform infrared spectroscopy
Ar	Argon atmosphere	<i>J</i>	Coupling constant in NMR
N ₂	Nitrogen atmosphere	DEPT	Distortionless enhancement by polarization transfer
E1	Elimination reaction- first order	IR	Infra-red
S _N 1	Nucleophilic substitution reaction	g	Gram(s)
calcd.	Calculated	mg	Milligram(s)
cat.	Catalyst	mL	Mililitre(s)
conc.	Concentration/ concentrated	dr	Diastereomeric ratio
CDCl ₃	Deuterated chloroform	TLC	Thin layer chromatography
ICP	Inductive plasma coupled spectroscopy	TMS	Tetramethyl silane
DCM	Dichloromethane	HF	Hydrofluoric acid
DCE	Dichloroethane	HNO ₃	Nitric acid
MeOH	Methanol	H ₂ SO ₄	Sulphuric acid
EtOH	Ethanol	HCl	Hydrochloric acid
DMF	<i>N, N</i> -Dimethyl formamide	DCC	<i>N, N'</i> -Dicyclohexylcarbodiimide
DMSO	Dimethyl sulfoxide	DMAPO	4-Dimethylaminopyridine
Acetone-d ⁶	Deuterated acetone	DEAD	Diethyl azodicarboxylate
DMSO-d ⁶	Deuterated dimethyl sulfoxide	MNBA	2-Methyl-6-nitrobenzoic anhydride
MeCN	Acetonitrile	DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
AcOH	Acetic acid	NaBARF	Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
THF	Tetrahydrofuran	dppe	1,2-Bis(diphenylphosphino)ethane
PhH	Benzene	TBAF	Tetra- <i>n</i> -butylammonium fluoride
EtOAc	Ethyl acetate	PEG	Polyethylene glycol
Et ₃ N	Triethyl amine	LiCl	Lithium chloride
NaOH	Sodium hydroxide	DIPEA	<i>N, N</i> -Diisopropylethylamine
KOH	Potassium hydroxide	KHMDS	Potassium bis((trimethylsilyl)amide)
<i>t</i> -BuOK	Potassium tertiary butoxide	LHMDS	Lithium bis((trimethylsilyl)amide)
K ₂ CO ₃	Potassium carbonate	DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
Cs ₂ CO ₃	Cesium carbonate	KOAc	Potassium acetate
Int	Intermediate	K ₃ PO ₄	Tripotassium phosphate
Ru	Ruthenium	MWI	Microwave irradiation
Cu	Copper	Ir	Iridium
Fe	Iron	Rh	Rhodium
Ni	Nickel	Pd	Palladium
Sn	Tin	Toluene-d ⁸	Deuterated toluene

PREFACE

In chemistry, macrocycles are an important class of cyclic molecules, and they have shown their omnipresence in numerous natural products, synthetic musks, and drugs. The biological activity of many macrocyclic drugs mainly arises due to the presence of a macrocyclic core. Macrocycles are known to gain a bioactive conformation because of their preorganization ability. Hence, they are crucial for drug target engagements and especially for the protein-protein interaction. Moreover, they are an indispensable constituent of supramolecular chemistry. Usually, macrocycles (e.g. crown ethers) have the ability to form complexes with various metals via non-covalent interactions. Furthermore, they can engage in host-guest interactions with small drug molecules, thereby enhancing drug efficacy. Notably, macrocycles find applications in diverse fields such as nanotechnology, catalysis, sensors, etc. Owing to the importance of macrocycles, the development of new synthetic strategies for their construction is highly fascinating for research endeavors.

This thesis covers the research findings toward the “Studies on Catalytic Macrocyclization Towards the Synthesis of Macrocyclic Ketones, Macrolactones and Macrolactams,” which comprises five chapters.

Chapter 1: Introduction to Macrocycles

The thesis begins with an overview of macrocycles, including the history and applications of macrocycles in drug discovery and supramolecular chemistry. After this, the challenges associated with their synthesis, followed by the potential solutions, are discussed. Various strategies for macrocyclization are then examined. The thesis also introduces catalysis, especially hydrogen borrowing catalysis, and its application for the construction of C-C, C-O, and C-N bonds. Finally, the aim and rationale of the thesis is elucidated.

Chapter 2: Ru-MACHO-Catalyzed Direct Intermolecular Macrocyclization of Alcohols and Ketones

In this chapter, we present a new strategy for the synthesis of macrocycles via intermolecular reaction of various diols and aminoacetophenones in the presence of Ru-MACHO as a catalyst and KOH as a base. Initially, this study includes a literature overview of both classical and catalytic approaches for macrocyclization. Subsequently, it describes the aim of the work followed by the detailed optimization studies for the macrocyclization. Later, the substrate scope with a variety of macrocycles, unsuccessful results, and a plausible mechanism for the macrocyclization are delineated.

Chapter 3: Dehydrogenative Intramolecular Macrolactonization of Dihydroxy Compounds using Ru-MACHO Catalyst: Studies towards the Synthesis of Corniculatolide A

This chapter describes an innovative method, based on the acceptorless dehydrogenation of alcohols for the synthesis of biologically important macrolactones. This chapter is subdivided into two sections. In Section A, we have described the acceptorless dehydrogenation of primary diols in the presence of Ru-MACHO as a catalyst and cesium carbonate as a base for macrolactonization. Subsequently, a thorough literature survey for macrolactonization, especially reports based on the activation of seco acids, are discussed. Later, the objective underlying this work is elucidated. Furthermore, a detailed optimization study followed by the substrate scope for macrolactonization is described. Next, with the help of various intermediate trapping experiments, the mechanism for the methods is depicted. In Section B, the application of acceptorless dehydrogenative macrolactonization for the synthesis of the natural product corniculatolide A is discussed. Intriguingly, the synthesis of starting material for the construction of methylcorniculatolides is achieved in 2 steps, whereas methylcorniculatolides are achieved in 3 steps using the acceptorless dehydrogenation of diol.

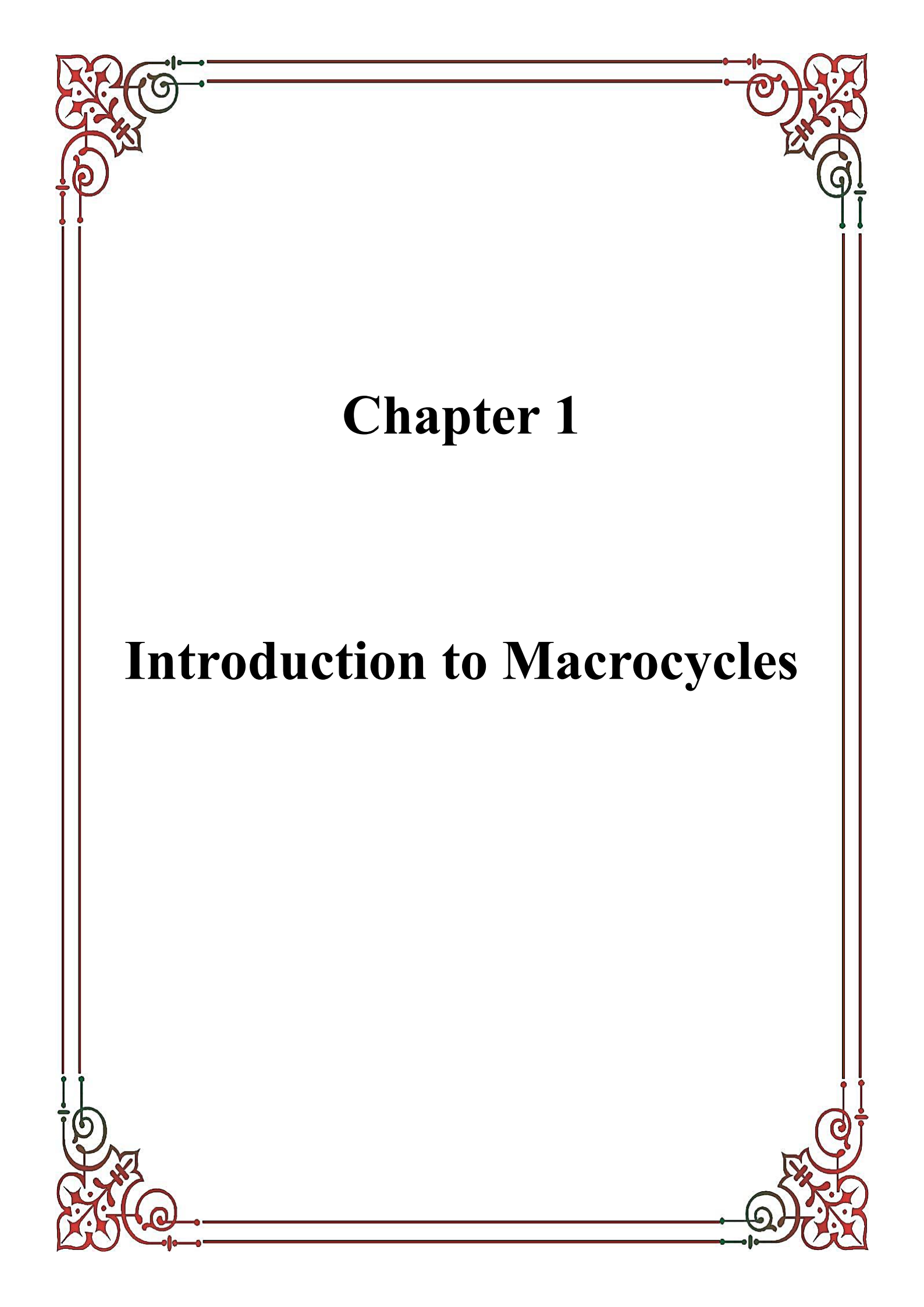
Chapter 4: Synthesis of Macrolactams from Macrolactones using Ru-/Ir-Catalytic System under Neutral Conditions

This chapter presents a new approach towards the synthesis of a macrocycle from another macrocycle. This is mainly focused on the synthesis of macrolactams from macrolactones using a ring-opening and ring-closing strategy. Initially, a brief literature overview, including both catalytic and non-catalytic methods for amidation and macrolactamization, is provided. Next, detailed optimization studies for both ring-opening and ring-closing strategies are discussed. Subsequently, the utilization of optimization results for the substrate scope, along with unsuccessful results is highlighted. Finally, the reaction mechanisms for both ring-opening and ring-closing strategies are elucidated with the help of trapped intermediates.

Chapter 5: Ru-Zeolite Catalyzed Dehydrative *N*-Alkylation of Amides for the Construction of Macrolactams under Continuous Flow Module

A new method for the synthesis of macrolactams using a Ruthenium supported on zeolite as a heterogeneous catalyst under the continuous flow module is described in this chapter. This chapter represents an excellent example of the intramolecular *N*-alkylation of amide with alcohols for macrolactamization using a heterogeneous catalyst. Most importantly, this dehydration method forms only water as the benign byproduct from the reaction. At the outset, a detailed literature background for the construction of C-N bonds is provided. Then, a brief introduction to continuous flow chemistry followed by the literature reports for macrocyclization under continuous flow are

described. Later, the aim and rationale of this work are highlighted. Subsequently, a detailed optimization study under batch and flow is described. The substrate scope with various amides using the optimized results under a continuous flow module is discussed. Furthermore, the high reusability and recyclability of the heterogeneous catalyst are demonstrated by using a one-time packed bed reactor for 16 reaction cycles. The synthetic utility of this method on gram scale is shown. Eventually, the plausible mechanism for the dehydrative *N*- alkylation is depicted.



Chapter 1

Introduction to Macrocycles

1. Introduction to Macrocycles

1.1 Abstract

Macrocycles are imperative cyclic structures that cover a remarkable segment within the field of chemistry. Their chemical diversity has significantly expanded during the past few decades, driven by the advancement in bioinformatics and synthetic methodology. Thus, they have had an enormous impact on human lives over the years. The present chapter delves into the concept, the foundations and the historical evolution of macrocycles. The extensive utility of macrocycles in drug discovery and supramolecular chemistry has also been highlighted. Additionally, enduring challenges associated with macrocyclization followed by possible solutions, have been discussed. A detailed examination of the literature, including classical and mainly catalytic approaches for macrocyclization, is provided. Concerns regarding waste generation during macrocyclization and potential solutions for waste minimization are addressed. Finally, the objectives and motivations underlying this work are elucidated.

1.2 Introduction

Ever since the emergence of humanity on the earth, humans have been highly dependent on nature for various needs, which mainly include the use of plant sources for medicinal and other applications. Nature has been the greatest artist of formulating various medicinally important organic molecules, including cyclic compounds such as flavonoids, alkaloids, polyphenols, polysaccharides, saponins, etc. The biological activity of these medicinally important molecules arises because of the omnipresence of the cyclic structure. Due to their invaluable ability to treat various diseases, these cyclic molecules have long captivated chemists and biologists.

In the study of cyclic organic molecules, the principle of angle strain plays a fundamental role. In 1885, Von Baeyer pointed out that the construction of cyclic molecules involves strain. This strain arises due to the deviation from the ideal bond angle of $109^{\circ}28'$ (tetrahedral) of a sp^3 carbon. Thus, the angle strain is also known as the '*Baeyer strain*'.^{1a} For example, in cyclopropane (three-membered ring), the actual bond angle is distorted by $24^{\circ}44'$ from an ideal bond angle and hence, it has the highest angle strain and enthalpy of combustion among all the cyclic molecules (Figures 1a and 1b). The angle strain and enthalpy of combustion are also dominating in the 4-membered rings because of distorted bond angles (less distorted as compared to the 3-membered rings). In the case of 5-membered planar cyclic molecules, angle strain is the lowest among all cyclic molecules, whereas the enthalpy of

combustion is minimal in a 6-membered ring (Figures 1a and 1b). Further, in 7 to 17-membered cyclic compounds, the angle strain steadily increases (Figure 1a), while the enthalpy of combustion peaks at a 9-membered ring and then gradually decreases with larger cyclic structures (Figure 1b).^{1a,1b}

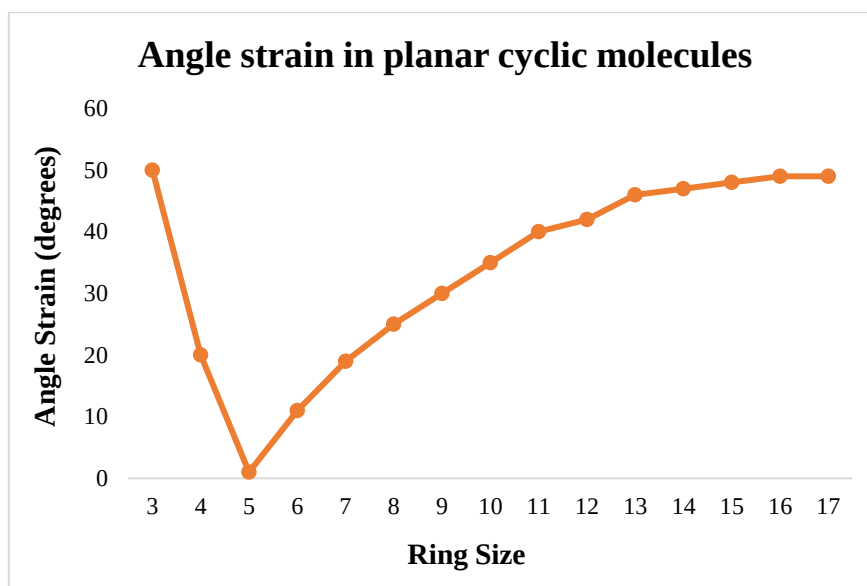


Figure 1a: Angle strain in planar cyclic molecules

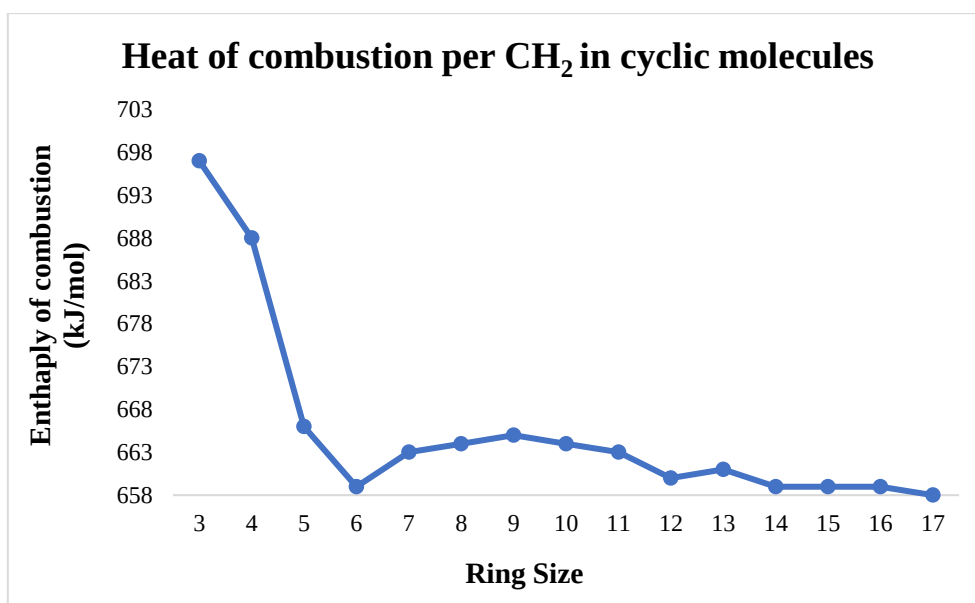


Figure 1b: Enthalpy of combustion per CH₂ in cyclic molecules

In the domain of cyclic organic molecules, macrocycles (the large cyclic molecules) are indispensable entities in the field of organic synthesis, supramolecular chemistry and drug discovery. Macrocycles are cyclic molecular structures comprising at least 12 or more atoms in the ring. In nature, macrocycles with ring sizes of 14, 16, and 18 atoms are the most commonly observed. However, it's noteworthy that naturally occurring macrocycles can

possess even larger rings, extending beyond 50 atoms. Nature showcases an extensive repository of complex macrocyclic compounds from porphyrin derivatives like heme or vitamin B12 to cyclic oligopeptides such as cyclosporin A.² This nature's repository can be classified into many sub-types depending on the functional group present in the macrocyclic core. Examples include macroketones (featuring ketone functional group), macroamines (featuring amine functional group), macrolactones (featuring ester functional group), macrolactams (featuring amide functional group), macroethers (featuring ether as the functional group), etc. (Figure 2a).

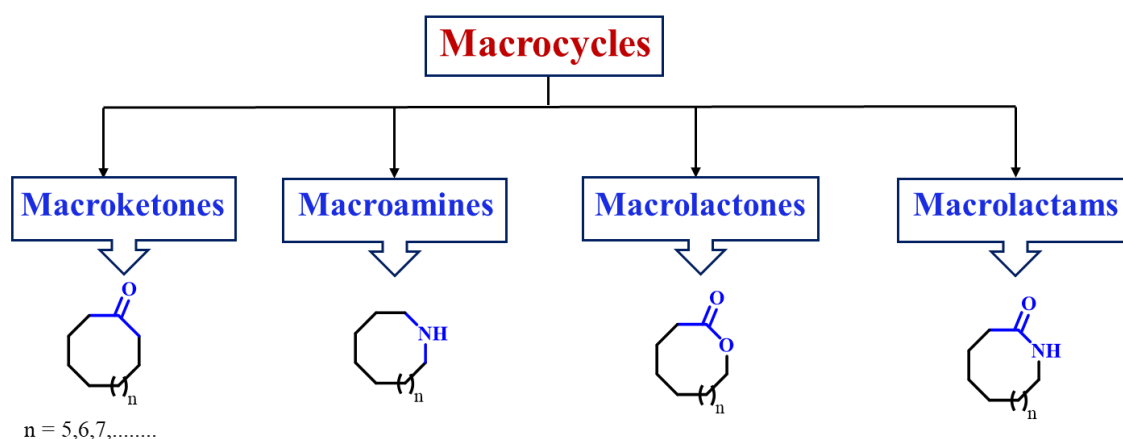


Figure 2a: Classification of macrocycles based on the functional group

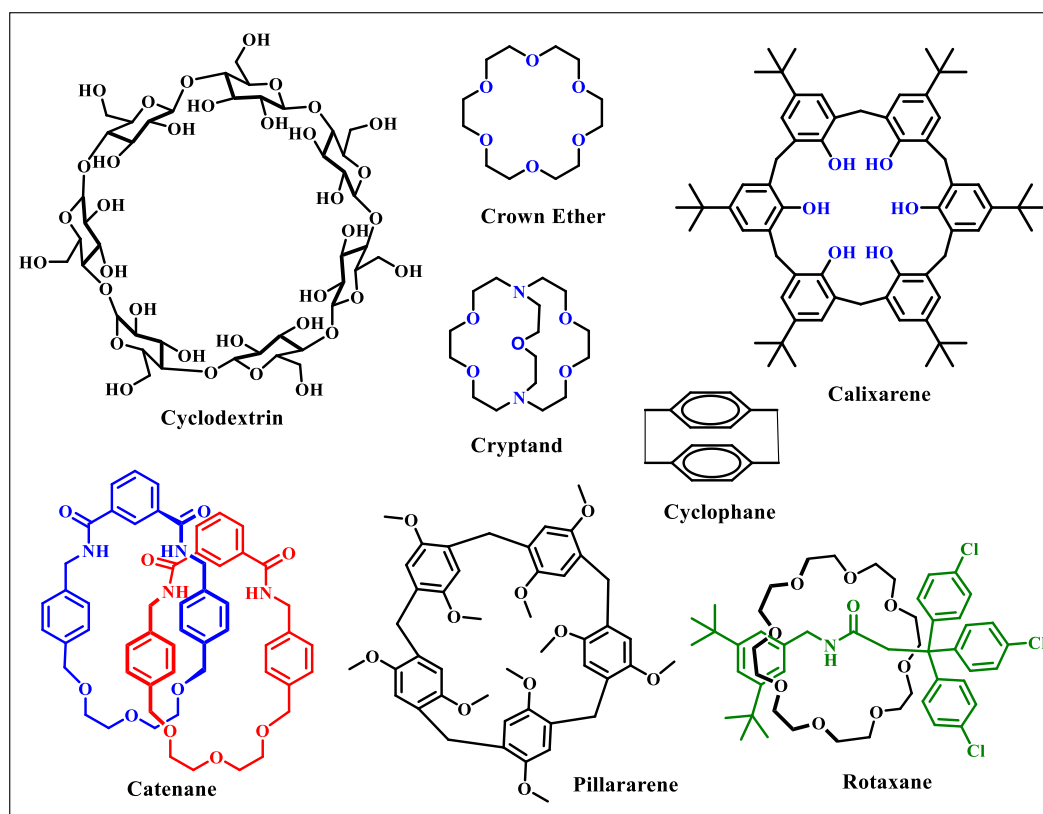


Figure 2b: Macrocycles contributing to supramolecular chemistry

Over the years, a diverse array of macrocycles including cyclodextrins, crown ethers, cryptands, calixarenes, pillararenes, cyclophanes, rotaxanes, catenane, cucurbiturils, etc. (Figure 2b), have been synthesized or isolated from natural sources. These macrocycles have various functional groups (mentioned in Figure 2a) in the macrocyclic core, resulting in versatile applications across various domains such as host-guest chemistry,³ molecular machines,⁴ chemical sensing,⁵ molecular recognition,⁶ and bioimaging.⁷ As a consequence, they comprehensively contribute to the evolution and advancement of supramolecular chemistry (Figure 2c).

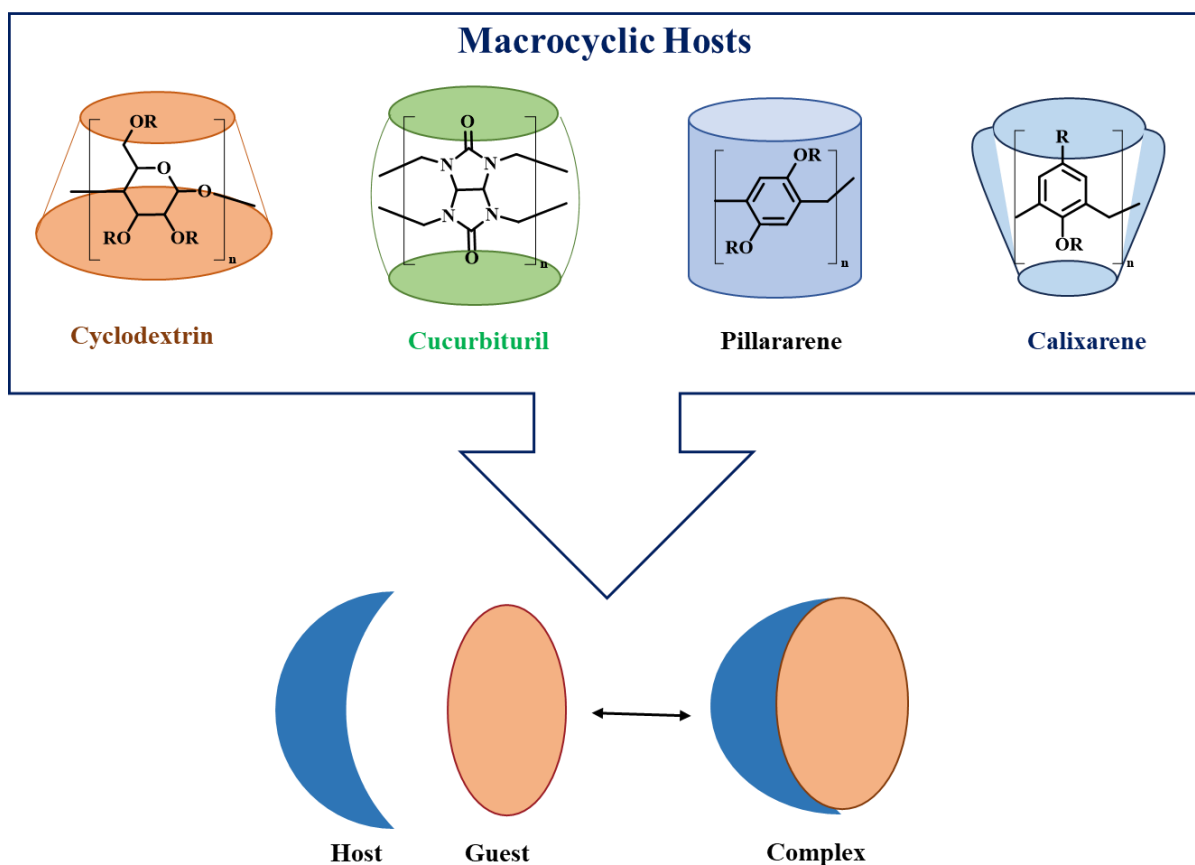


Figure 2c: Schematic representation of host-guest interaction in supramolecular chemistry

1.2.1 History of Macrocycles

However, the history of macrocycles starts with the discovery of the earliest known macrocycle- cyclodextrin (macrocyclic oligosaccharides). In 1891, Antoine Villiers became the first scientist who isolated the oligosaccharides produced by starch.⁸ With this remarkable achievement, the era of macrocyclization began. Shortly thereafter, in 1903, Franz Schardinger introduced the description of cyclodextrin's properties and established the groundwork for cyclodextrin chemistry (Figure 3).⁹ Next, in 1912, Paul Ruggli attempted the earliest known

macrocyclization with high dilution conditions for the synthesis of cyclosuccinyldiamidotolan.¹⁰ Ruzicka elucidated civetone and muscone in 1926,^{11a} whereas a year later, in 1927, McCrae synthesized a macrolactone, known as exaltolide, which transformed the world of perfume industries (Figure 3).^{11b} Macrocylic compounds that laid the foundation for supramolecular chemistry are crown ethers¹² and cryptands,¹³ pioneered by C. J. Pedersen and Jean-Marie Lehn in 1949 and 1967, respectively. Further, in 1978, David Gutsche synthesized calixarenes.¹⁴ After 2 years, in 1980, Stoddart synthesized mechanically interlocked molecules, rotaxane and catenane, also known as molecular machines, in which a macrocycle remarks as a core moiety.¹⁵ Due to the groundbreaking contributions of Jean-Marie Lehn, Donald J. Cram, and Charles J. Pedersen to supramolecular chemistry, they were collectively awarded the ‘*Nobel Prize*’ (in 1987) in Chemistry for their advancements in the development of crown ethers, cryptands, and other macrocyclic compounds (Figure 3).

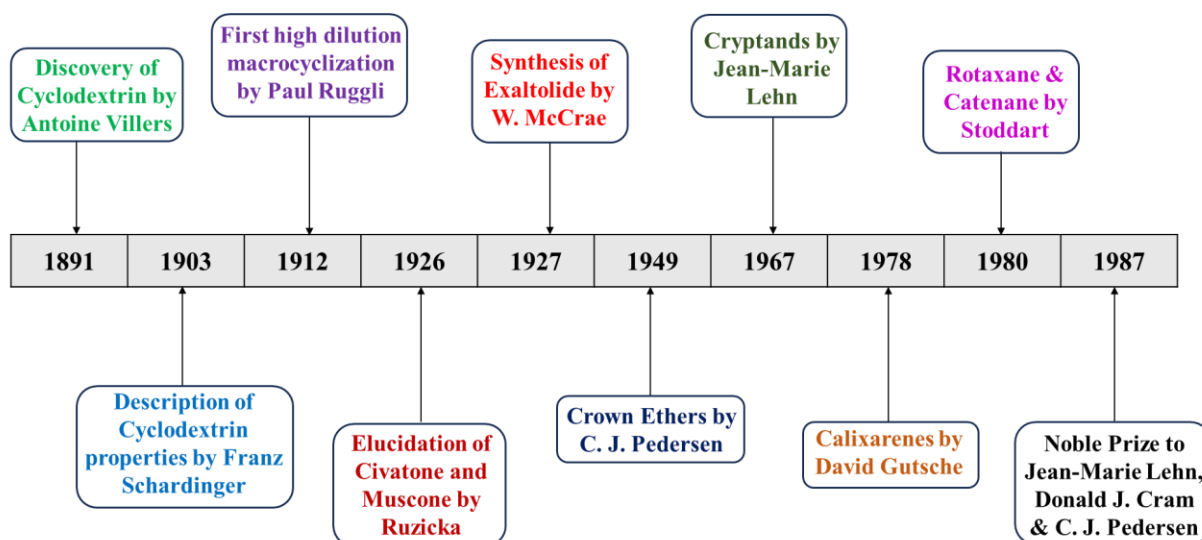


Figure 3: Historical timeline of macrocycles

1.3 Macrocylics in Drug Discovery

During the preceding period of the late 20th century, macrocycles gained much attention in drug discovery due to their capacity to bind with proteins, particularly addressing the challenging protein-protein interactions, thereby overcoming difficulties associated with drug target engagement (Figure 4).^{2,16a} Macrocycles typically have high binding affinity and can occupy larger chemical space that small molecules cannot cover (Figure 4). They occupy a space between two structural extremes (biological drugs and small drug molecules) because of their drug-like properties similar to small drug molecules and the ability to interact with extended binding sites (Figure 4). More importantly, they also demonstrate notable stability under physiological conditions. Macrocylics are conformationally preorganized molecules

because of the restricted bond rotations within the molecule but are not fully rigid and hence provide a low entropy cost of binding. After binding with the target, the macrocycle gains its bioactive conformation. The macrocyclic drugs, exemplified by cyclosporine and vancomycin, represent the therapeutic efficacy of this molecular class, notably in combating diseases with limited treatment options.^{16b} Currently, more than 100 drugs have been approved or under clinical trials featuring macrocycle as a bioactive core.¹⁷

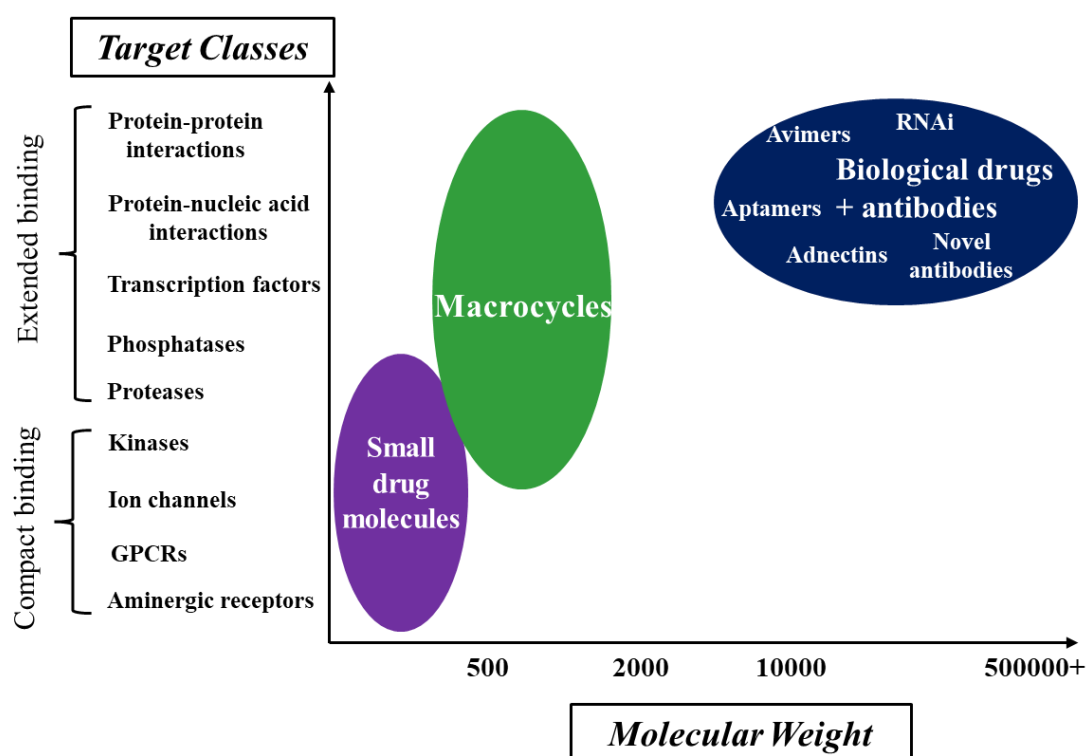


Figure 4: Chemical space of macrocycles

Furthermore, macrocycles are well recognized in supramolecular chemistry, which is dedicated to elucidate and harness various non-covalent interactions like hydrogen bonding, π - π interactions, and hydrophobic interactions that play a pivotal role in molecular self-assembly, host-guest chemistry, and molecular recognition.¹⁸ More interestingly, the high amenability of small drug guests upon interaction with macrocyclic hosts (shown in Figure 2c) enhances the solubility, shields them from degradation, and alters the bioavailability.¹⁹ This understanding is foundational for developing drugs engineered to bind selectively to precise biological targets, including receptors or enzymes implicated in disease pathways.

The increasing recognition of macrocycles as a unique therapeutic category leads to intensified research endeavors aimed at developing new synthetic strategies and refining their pharmacokinetic properties, increasing oral availability, and diminishing off-target effects.

1.4 Challenges in Macrocyclization

Despite the proven utility of macrocyclic structures for drug discovery and supramolecular chemistry, their synthesis is a long-standing challenge for chemists. The challenges are intensified in the case of 11-13 membered macrocycles, where angle strain within these macrocyclic structures results in a slower macrocyclization reaction and subsequently results in poor yields of macrocyclic products. Macrocycles with 14 and more than 14 members are easy to synthesize compared to 11-13-membered macrocycles because of their ability to adopt a conformation with low-angle strain (Figure 1a). Therefore, the enthalpy of combustion in these macrocycles is found to be low (Figure 1b). Although macrocycles adopt a conformation with lesser angle strain, their synthesis is difficult as compared to 5 and 6-membered cyclic structures.¹

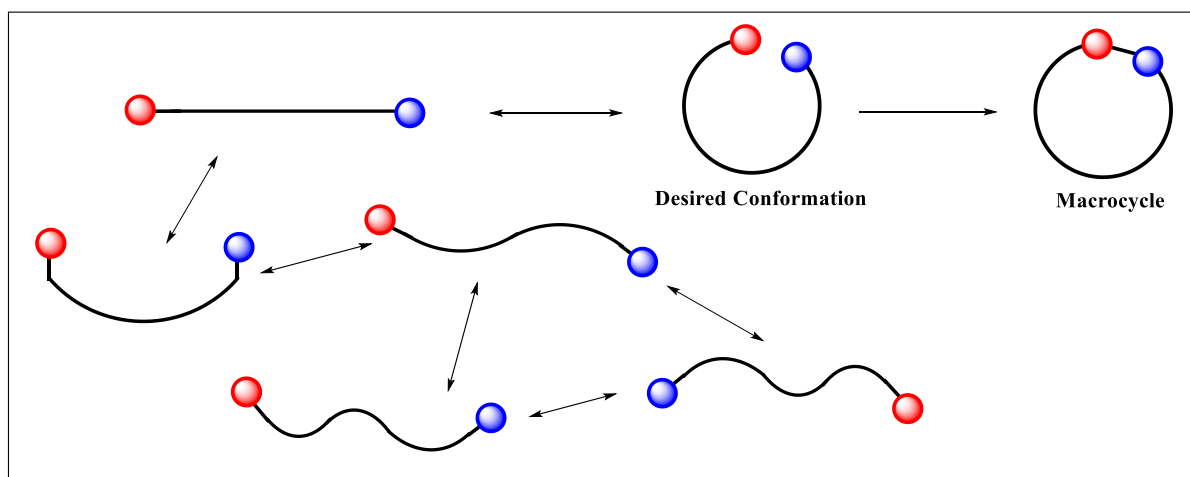


Figure 5a: Different conformations of long-linear molecule and macrocyclization

Besides angle strain, entropy is another crucial determinant in the synthesis of macrocycles. In the intramolecular macrocyclization of a long linear chain molecule, the two reaction centres are usually far away from each other, posing a challenge in achieving the desired conformation in which both reaction centres are in close proximity to form a macrocycle (Figure 5a). The molecule may adopt multiple conformations (shown in Figure 5a) because of single-bond rotations, resulting in a higher entropy for the macrocyclization reactions.²⁰ Due to the different conformations, less strained dimers or oligomers could be formed as competitive undesired side products (Figure 5b).²¹ The main reason behind oligomerization is the higher rate of intermolecular reaction compared to the rate of intramolecular reaction.

To reduce or eliminate side products and to achieve macrocyclization efficiently, high dilution conditions can be employed. The high dilution could be achieved by diluting starting

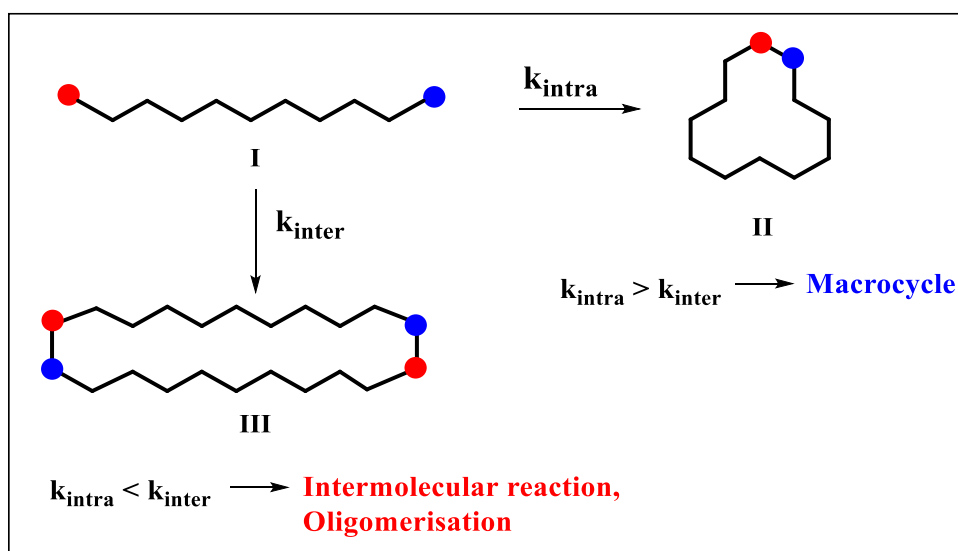


Figure 5b: Intramolecular *versus* intermolecular reaction for macrocyclization

materials from 0.001 M to 0.01 M in order to increase the rate of intramolecular reaction (Figure 5c). The increased rate of intramolecular reactions results in higher yields of macrocyclic products. Hence, most of the macrocyclization reactions are more frequently performed using high dilution conditions. For intermolecular (two different reactants) macrocyclization, slow addition with a high dilution of reactants can effectively mitigate undesired side products (homomers).

Effective molarity explains the effect of dilution on the rate of macrocyclization reaction. The effectiveness of high dilution strategies arises from the distinct molecularity of the intramolecular macrocyclization reaction compared to the intermolecular dimerization reaction. The ratio of the rate constants, k_{intra} for macrocyclization and k_{inter} for dimerization, defines the effective molarity (EM). For a strain-free macrocyclization process, this ratio is anticipated to be one.²² As the dilution of the reactant increases, the rate of macrocyclization increases while the rate of dimerization decreases. In contrast, as the concentration of reactant increases, the rate of macrocyclization decreases.^{21a}

1.5 Literature Overview for Macrocyclization

In spite of several challenges associated, a significant amount of work has been dedicated to macrocyclization, encompassing the synthesis of numerous natural products, drugs, and various macrocyclic molecules. These macrocyclic molecules are employed as ion sensors,²³ perfumery musks,²⁴ catalysis,^{25a} catalytic ligands,^{25b} and in environmental remediation efforts.²⁶ This chapter comprehensively covers the literature on macrocycle synthesis (Figure 6).

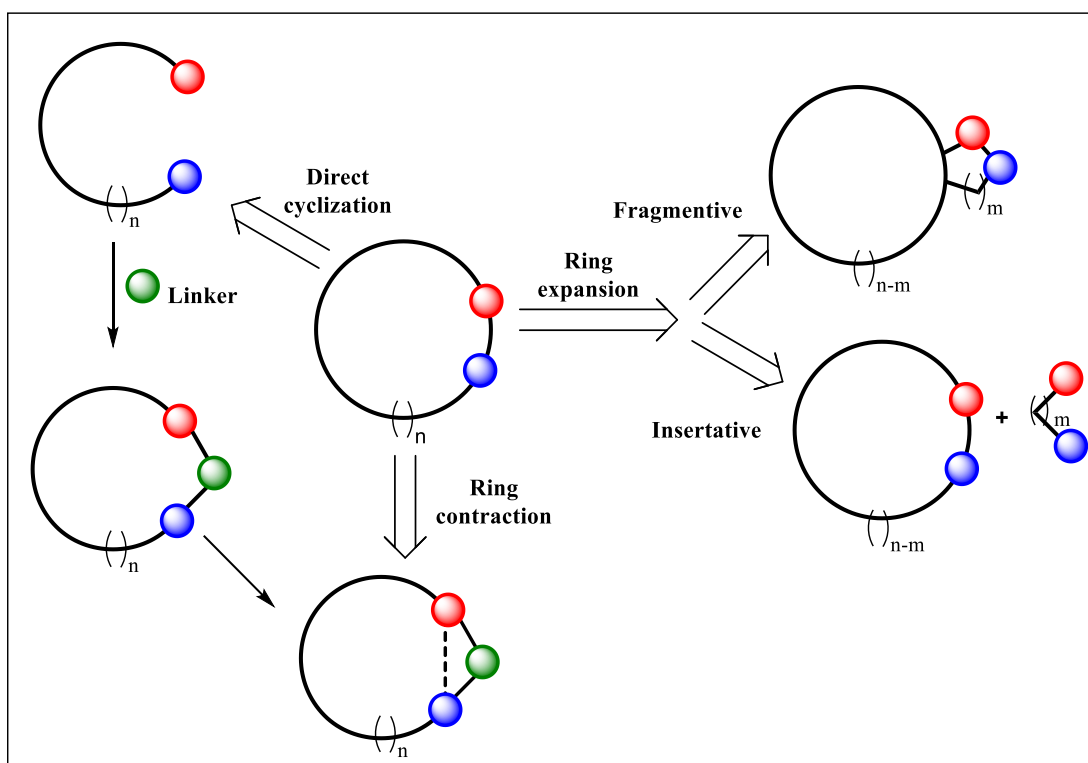
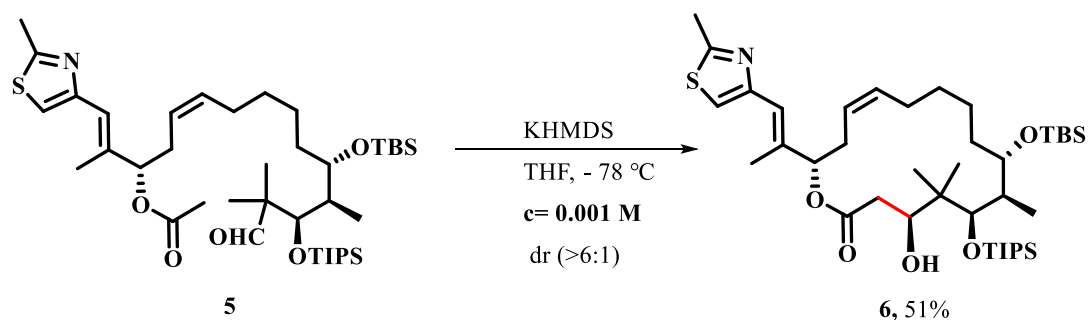


Figure 6: Various macrocyclization strategies

For clarity and ease of understanding, these strategies can be categorized into the following types (Figure 6): i) direct macrocyclization (intramolecular reaction), ii) ring expansion macrocyclization, iii) ring contraction macrocyclization and iv) macrocyclization using linker (intermolecular reactions) (Figure 6). Direct macrocyclization could be achieved by an end-to-end cyclization of two reaction centres using a high dilution condition. Subsequently, a linker can be added and an intermolecular reaction would provide a macrocyclic product. Next, the ring contraction of a big macrocycle can provide another macrocycle. Moreover, macrocyclization can be achieved through the ring expansion of two cyclic molecules either via fragmentation or insertion.

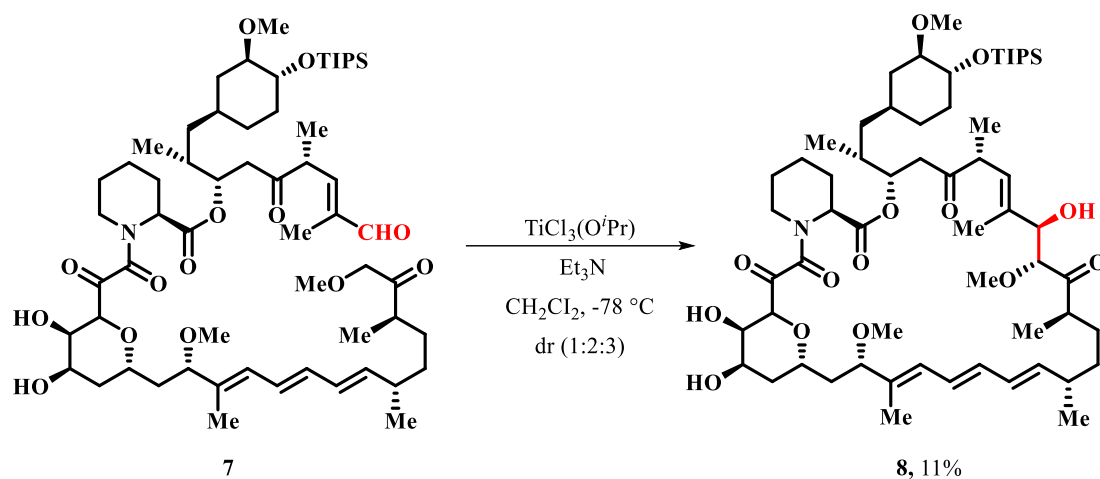
1.5.1 Direct Macrocyclization Approaches:



Scheme 2a: Intramolecular aldol condensation for the synthesis of epothilones

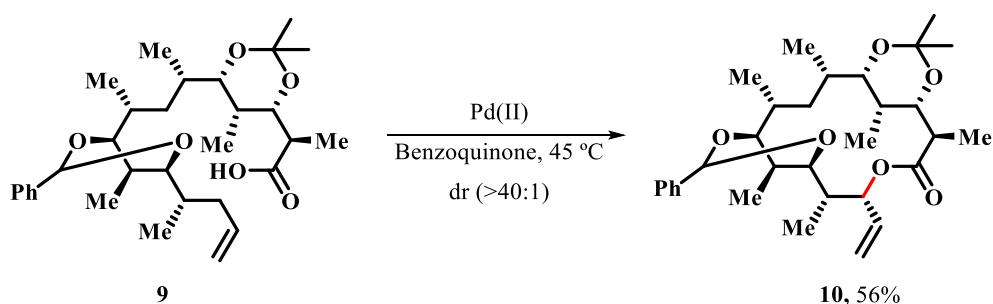
Danishefsky and his group conducted a direct macrocyclization using KHMDS (potassium bis(trimethylsilyl)amide) as a base for the intramolecular aldol condensation reaction of **5** to yield epothilones **6** (Scheme 2a).²⁷

In the year of 1993, the same research group performed a titanium-mediated intramolecular aldol condensation reaction of **7** to achieve the natural product ‘rapamycin’ **8** with 11% yield and the diastereomeric ratio of 1:2:3 (Scheme 2b).²⁸



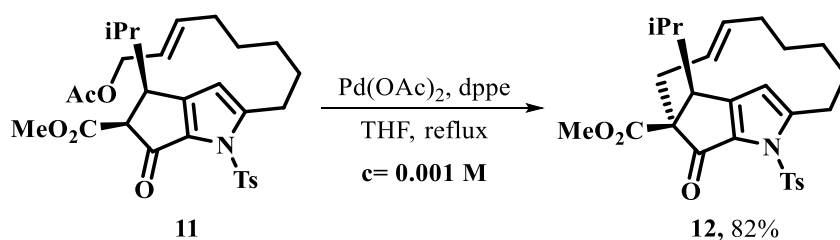
Scheme 2b: Intramolecular aldol condensation for the synthesis of rapamycin

The direct macrocyclization can also be achieved by using palladium chemistry. In 2009, White and coworkers developed a strategy for macrolactonization via allylic C-H activation and subsequent coupling with carboxylic acids using a Pd(II) complex and benzoquinone as an external oxidant. This process is utilized for the synthesis of the natural product 6-deoxyerythronolide B (**10**) (Scheme 3a).²⁹



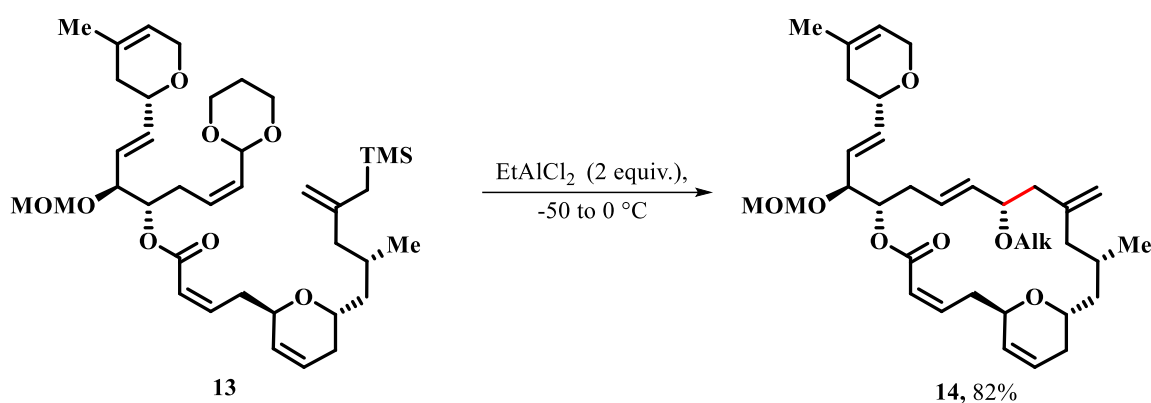
Scheme 3a: Allylic C-H activation using Pd-catalyst for macrolactonization

Further, Frontier and his research group performed an intramolecular Tsuji-Trost type reaction of **11** by using a Pd-catalyst for the synthesis of precursor (**12**) of (±)-Roseophilin (Scheme 3b).³⁰



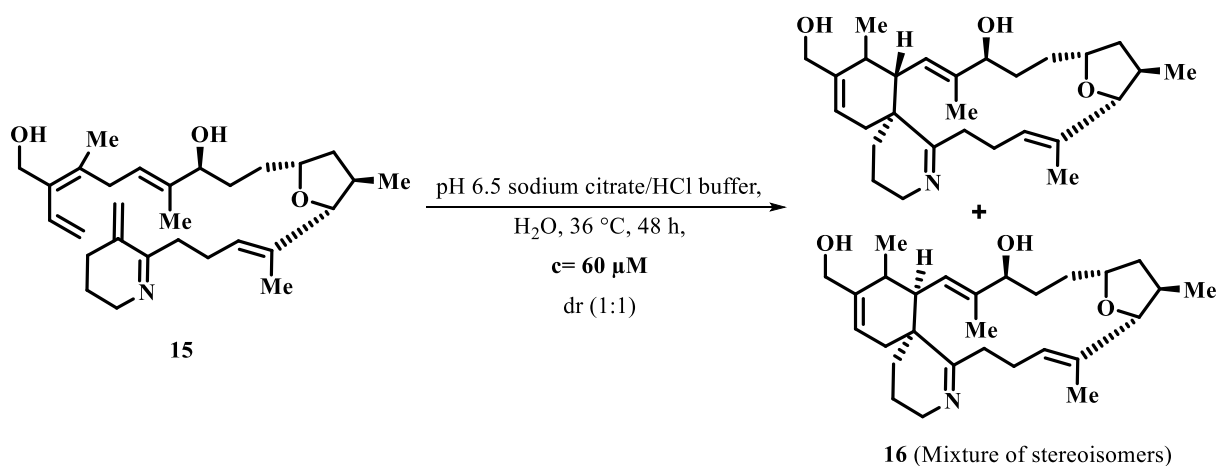
Scheme 3b: Tsuji-Trost type reaction for macrocyclization

Additionally, the reaction of a nucleophile to the oxocarbenium also facilitates direct macrocyclization. For instance, Mulzer and coworkers performed an allyl transfer reaction for the synthesis of the natural product laulimalide (**14**) with 82% yield (Scheme 4).³¹



Scheme 4: Allyl transfer reaction for the synthesis of laulimalide

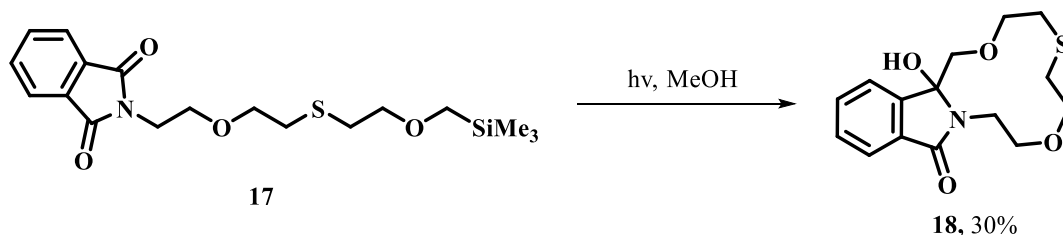
More interestingly, cycloaddition reaction such as Diels-Alder ([4+2]-cycloaddition) were found to be efficient for direct macrocyclization. In 2005, Kishi's research group utilized the Diels-Alder reaction for the synthesis of the biomimetic macrocycle-gymnodimine (**16**) (Scheme 5).³²



Scheme 5: Diels-Alder reaction for the synthesis of gymnodimine

Moreover, the intramolecular photochemical addition of α -silyl ether to phthalamide

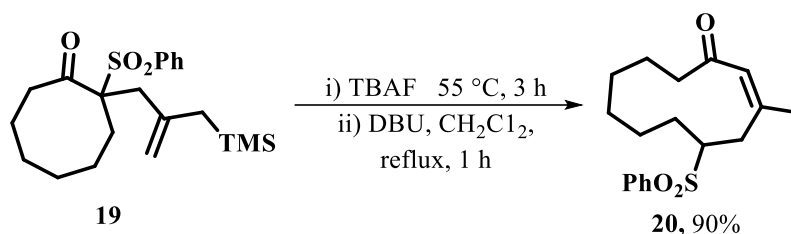
gives the macrocyclic product (**18**) with a 30% yield, but the mechanism for this approach is not completely studied (Scheme 6).³³



Scheme 6: Photochemical cyclization of silyl ether to phthalamide

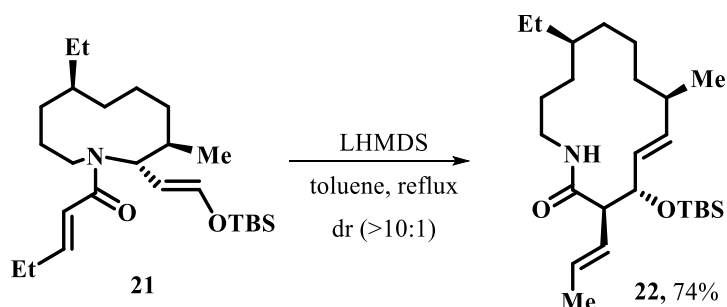
1.5.2 Ring-Expansion Macrocyclization Approaches:

Ring expansion is an alternate way of achieving macrocycles. The representative examples include a three-carbon condensation expansion for the synthesis of muscone precursor (**20**) (Scheme 7).³⁴

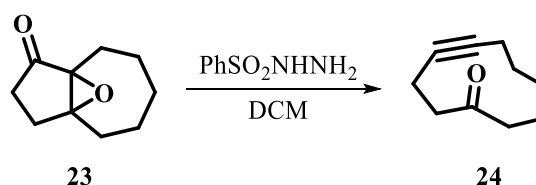


Scheme 7: Ring expansion for the synthesis of muscone

Macrolactams are achieved by the ring expansion of **21** using LHMDs (lithium bis(trimethylsilyl)amide) for the synthesis of precursor (**22**) of Fluvirucinine A₂ with 74% yield (Scheme 8).³⁵



Scheme 8: Ring expansion for the synthesis of the precursor of Fluvirucinine A₂

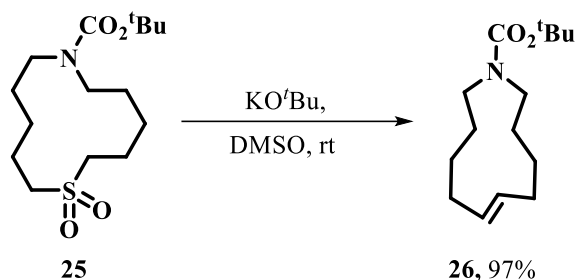


Scheme 9: Eschenmoser fragmentation for macrocyclization

A well-known reaction, the Eschenmoser-fragmentation reaction also delivers a macrocyclic product via fragmentation of epoxyketones in the presence of arylsulphonylhydrazides (Scheme 9).³⁶

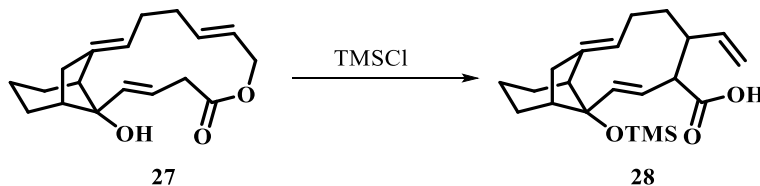
1.5.3 Ring-Contraction Macrocyclization Approaches:

Employing a Ramberg-Bäcklund reaction of **25** to synthesize the requisite azacycloundecene ring (**26**) is a crucial step for the total synthesis of marine alkaloid manzamine C (Scheme 10).³⁷



Scheme 10: Ramberg-Bäcklund reaction for ring-contraction macrocyclization

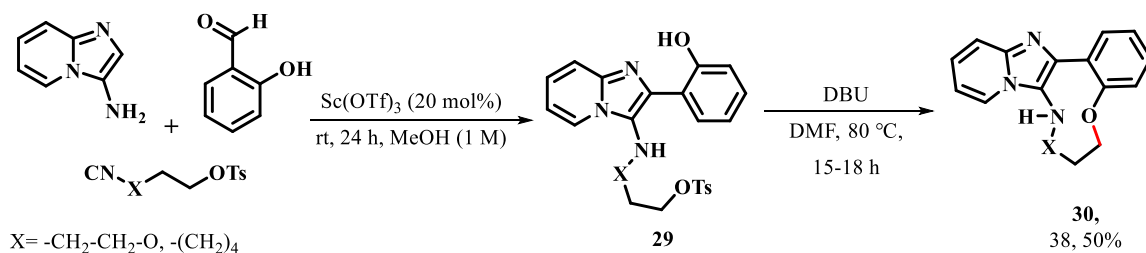
Fascinatingly, Plummer's research group used an Ireland-Cope reaction (sigmatropic reaction) for the ring contraction of **27** to achieve the product **28**, which was crucial for the synthesis of isocyclocitrinol (Scheme 11).³⁸



Scheme 11: Ireland-Cope reaction for ring-contraction macrocyclization

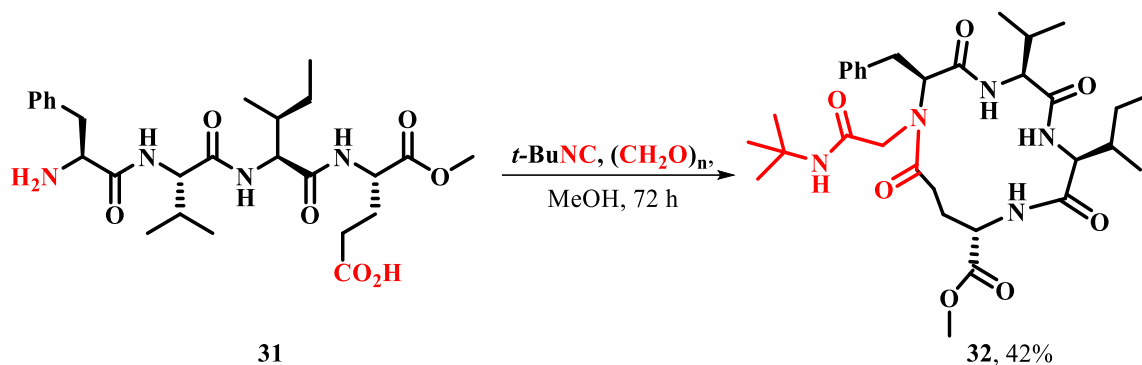
1.5.4 Macrocyclization using Multicomponent Reaction:

The reaction involving three or more reactants known as multicomponent reactions (MCRs), can deliver macrocycles. The reaction of imidazopyridinamine with aldehydes and isocyanoalkylmethylbenzenesulfonate in the presence of scandium triflate as a catalyst provides macrocycles (**30**) in two steps (Scheme 12).³⁹

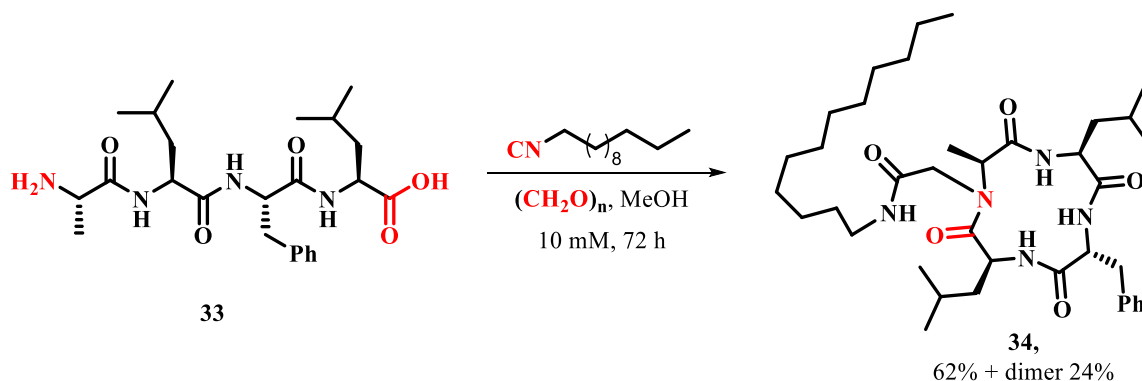


Scheme 12: Intermolecular followed by intramolecular reaction for macrocyclization

Peptide macrocyclization using multicomponent reaction is another way of achieving macrocyclic peptides. An excellent example is the Ugi reaction of tetrapeptide **31** to synthesize macrocyclic peptide **32** with a 42% yield (Scheme 13a). It is also used to synthesize macrocyclic lipopeptide **34** with a 62% yield (Scheme 13b).⁴⁰



Scheme 13a: Ugi reaction for macrocyclization



Scheme 13b: Synthesis of macrocyclic lipopeptide

1.6 Catalysis

The synthetic community has dedicated substantial efforts toward the synthesis of macrocyclic compounds and the exploration of the scope of various macrocyclization reactions. Prior to the formulation of green chemistry principles, many of the aforementioned strategies for macrocyclization had already been established. These earlier-developed synthetic methodologies do not rely on catalysis. Hence, these methods are now regarded as classical approaches or non-catalytic approaches.⁴¹ In classical approaches, a stoichiometric amount of reagent (usually acts as a coupling reagent) is used for the reaction, which is consumed entirely during the reaction. As a result, it produces side products as waste from the reaction in stoichiometric amounts. Moreover, classical approaches proceed with a high activation energy, resulting in a decreased rate of reaction (Figure 7).

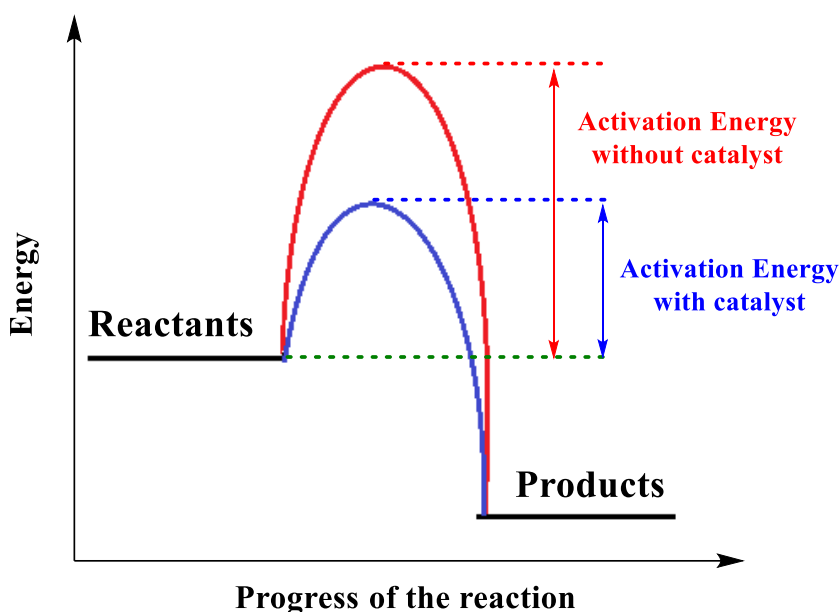


Figure 7: Energy profile diagram for catalytic and non-catalytic reaction

On the other hand, the involvement of a catalyst in the reaction accelerates the rate of reaction, with the catalyst being regenerated in the catalytic cycle. The low activation energy is the main reason behind faster reactions (Figure 7). In addition, catalytic reactions are known to generate minimal or no waste.

In 1835, Berzelius (a Swedish chemist) coined the term '*Catalysis*'. Approximately 60 years later, in 1894, the precise definition of catalysis was introduced by Ostwald.⁴² Catalysis is a pivotal technology essential for achieving chemical processes in an environmentally benign manner with increased efficiency and sustainability.⁴³ It occupies a prominent role in both academic research and industry, with wide-ranging applications in the production of chemicals, life science molecules, and everyday life products.⁴⁴ Moreover, catalysis is indispensable for synthesizing fine and bulk chemicals, pharmaceuticals, and agrochemicals. Notably, it plays a vital role in petrochemicals, energy technologies, material science, and environmental remediation processes.⁴⁵

In today's industrialized world, catalysis is fundamental and forms the backbone of numerous applications without which many processes would be impractical. The figure-6 demonstrates the use of catalysts in various industrial and other fields, which represent the invaluable role of catalysis.

Traditionally, catalysts are classified into two types: a) Homogeneous catalysts and b) Heterogeneous catalysts. The majority of reactions employing homogeneous catalysts take place in the liquid phase, where the catalyst dissolves in the solvent. A wide array of

homogeneous catalysts is known, including Brønsted and Lewis acids utilized in organic synthesis, metal complexes, organometallic complexes, and organic molecules extending up to biocatalysts (artificial enzymes). However, nowadays, reactions involving organometallic or coordination complexes are considered homogeneous catalysis.⁴⁶

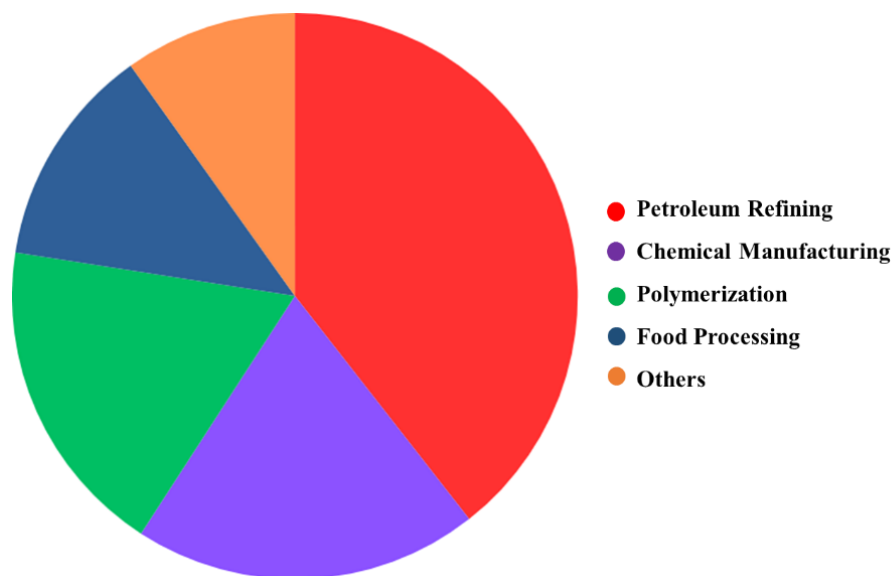


Figure 8. Catalysis in industrial applications and global market review

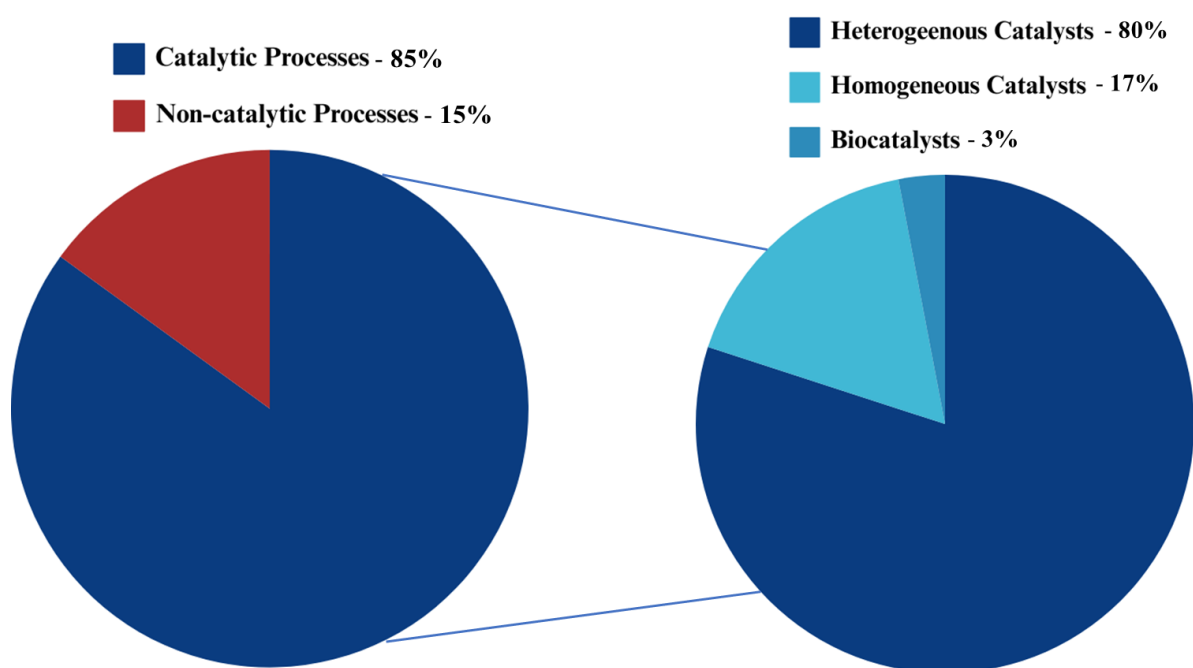


Figure 9. Percentage of utilizing different types of catalysts in industrial processes.

In contrast, heterogeneous catalysts typically exist in solid form and do not dissolve in the solvent. Heterogeneous catalysts are highly recognized in industrial processes due to easy

recovery and reusability (Figure 9). Both the homogeneous and heterogeneous catalysts were found important in their respective domain of utility due to their unique properties.

The major advantages/disadvantages of homogeneous *versus* heterogeneous catalysts are summarized in Table 1 below.

Table 1: Advantages/Disadvantages of Homogeneous v/s Heterogeneous Catalysts

Property	Homogeneous Catalyst	Heterogeneous Catalyst
Catalyst Recovery	Difficult	Easy
Thermal Stability	Poor	Good
Selectivity	Excellent- single site of binding	Poor- multiple sites of binding

Heterogeneous catalysts have a major advantage over homogeneous catalysts on account of the catalyst recovery and reusability. On the other hand, homogeneous catalysts have more advantages over heterogeneous catalysts on account of selectivity. Homogeneous catalysts have a single site of binding, leading to excellent selectivity. Therefore, the mechanism elucidation of the reaction catalyzed by a homogeneous catalysis is easy. Conversely, heterogeneous catalysis happens on a solid surface that has multiple sites of binding, providing poor selectivity during reactions. Owing to the different properties of homogeneous and heterogeneous catalysts, these are considered to be connected to two different areas of chemistry: homogeneous catalysis is connected to molecular organometallic chemistry, and heterogeneous catalysis is closer to surface science and solid-state chemistry.⁴⁷

In spite of this consideration, both homogeneous and heterogeneous catalysis offer a sustainable route for chemical transformations by enabling reactions under milder conditions. Additionally, both (homogeneous and heterogeneous) catalysts inclusively enhance efficiency and selectivity while decreasing energy consumption and waste generation. Furthermore, catalytic processes frequently employ renewable feedstocks and safer reaction conditions, thereby reducing environmental impact.⁴⁸

Ultimately, catalysis serves as a cornerstone of green chemistry, driving advancements toward more sustainable and environmentally benign chemical processes. Considering the efficiency, reducing waste and minimizing environmental impact in chemical synthesis and manufacturing process, the concept of "*Catalysis*" occupies a central position within the principles of green chemistry.

1.7 Borrowing Hydrogen Catalysis

Owing to the importance of catalysis, the ‘borrowing hydrogen (BH) catalysis’ emerged as a new tool for synthesizing complex organic molecules in the 20th century. It is also known as hydrogen auto-transfer process. It represents a potent strategy that integrates transfer hydrogenation, which bypasses the direct use of molecular hydrogen with sequential intermediate reactions to synthesize complex molecules. The basis of this concept is that hydrogen sourced from a donor molecule (usually alcohol) temporarily resides within a catalytic metal fragment $[MH_2]$ and is released during the

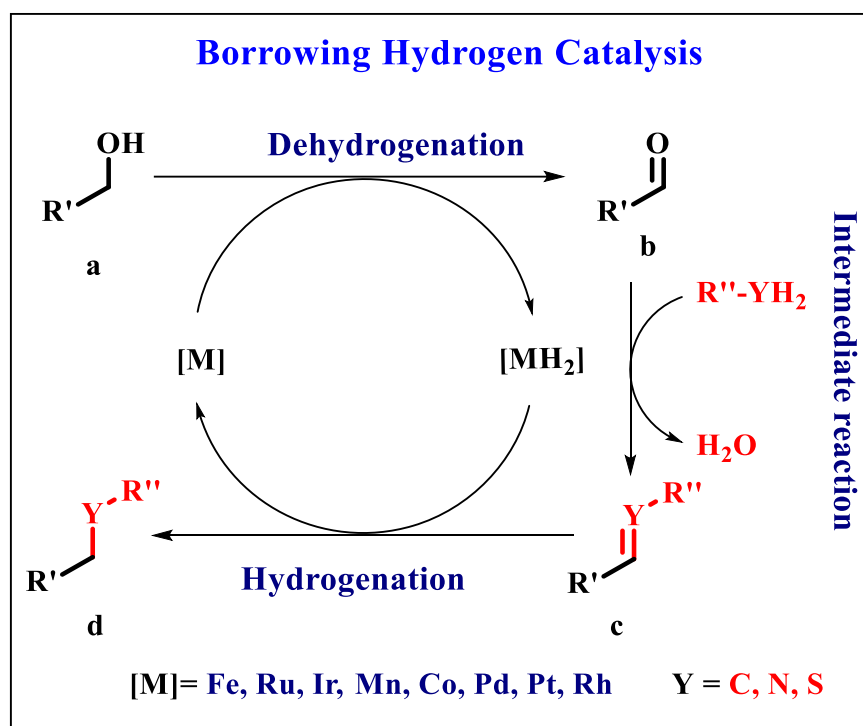


Figure 10: Borrowing hydrogen catalysis

final hydrogenation step (Figure 10). This strategy involves three sequential steps: (i) dehydrogenation of alcohol **a** to form aldehyde **b**, (ii) condensation reaction of an aldehyde **b** with a nucleophile to produce intermediate **c**, and (iii) hydrogenation of unsaturated adduct **c**, to provide the desired product **d** (Figure 10). As a consequence, BH catalysis circumvents the necessity for laborious separation or isolation procedures by performing three sequential reactions in one pot.

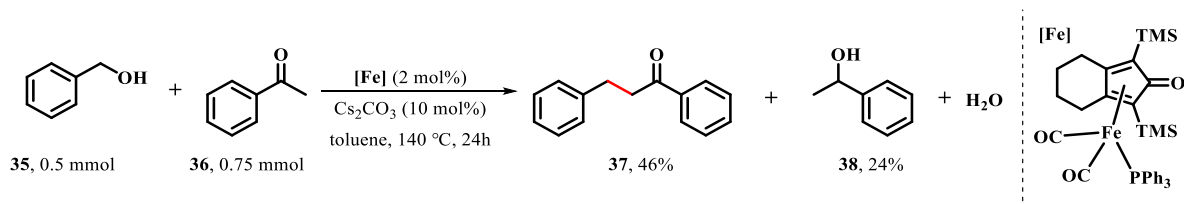
Additionally, BH catalysis follows most of the 12 green chemistry principles, making it a commendable and widely acknowledged process from both environmental and synthetic perspectives while also offering economic advantages.⁴⁹ Thus, this catalytic process is widely explored to construct C-C, C-O, and C-N bonds to synthesize various organic molecules via C-alkylation, esterification, and N-alkylation, with alcohols respectively. A few illustrative

examples showcasing the construction of diverse organic molecules through BH catalysis are provided below.

1.7.1 Literature Overview for Homogeneous Borrowing Hydrogen Catalysis

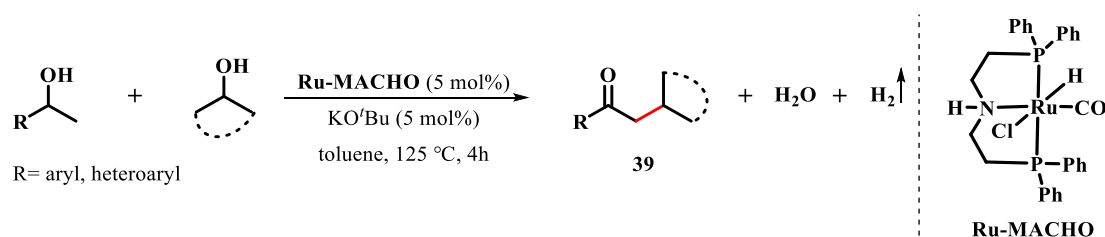
1.7.1.1 Construction of C-C bonds:

Darcel's research group demonstrated the α -alkylation of ketones with primary alcohols using an iron catalyst to achieve product **37** with 46% yield and the alcohol **38** (reduction of ketone **36**) with 24% yield (Scheme 14a).⁵⁰



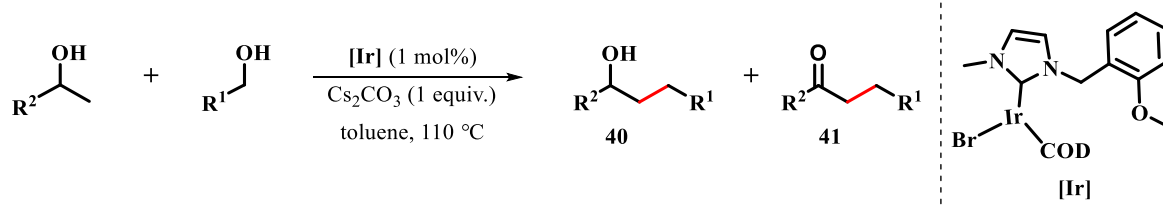
Scheme 14a: α -Alkylation of ketones with alcohols using iron catalyst

Next, Gunanathan and his research group developed an elegant approach for the cross-coupling of two secondary alcohols using Ru-MACHO as a catalyst to yield the various ketone derivatives (**39**) by overcoming the homocoupling challenge (Scheme 14b).⁵¹



Scheme 14b: Ru-MACHO catalyzed cross-coupling of secondary alcohols

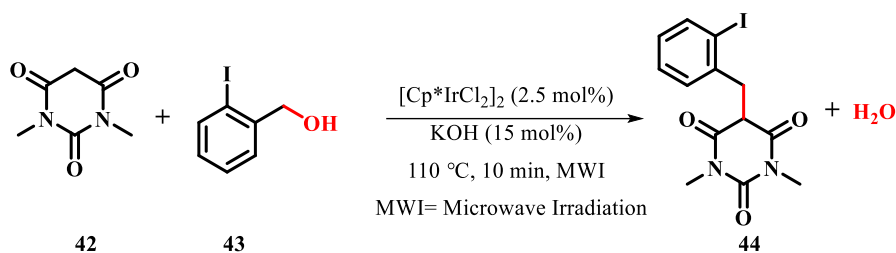
An Iridium catalyst is also used for the β -alkylation of secondary alcohols using primary alcohols to furnish product **40** and the unreduced ketone **41** (Scheme 14c).⁵²



Scheme 14c: Ir-catalyzed β -alkylation of secondary alcohols using primary alcohols

More interestingly, BH catalysis is used for the monoalkylation of active methylene compounds using alcohols. For example, the monoalkylation of 1,3-dimethylpyrimidine-2,4,6-trione (**42**) with alcohol (**43**) using $[\text{Cp}^*\text{IrCl}_2]_2$ as a catalyst under microwave irradiation,

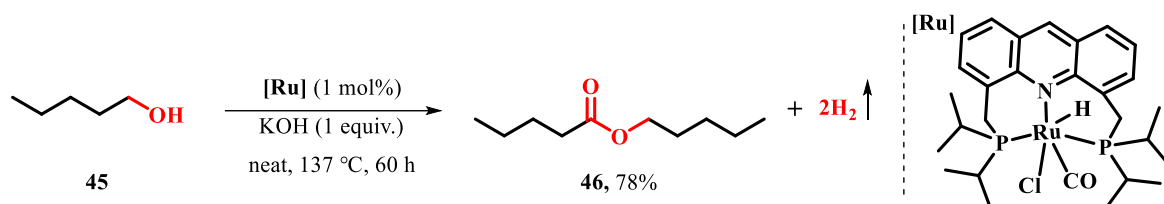
provided 5-(2-iodobenzyl)-1,3-dimethylpyrimidine-2,4,6-trione (**44**) (Scheme 14d).⁵³



Scheme 14d: Monoalkylation of active methylene compounds using Ir-catalyst

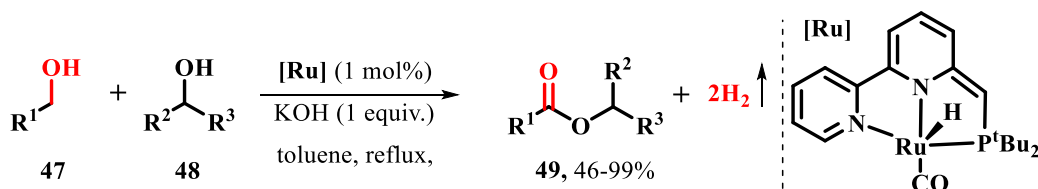
1.7.2 Construction of C-O bonds:

The construction of the C-O bond is crucial in the organic synthesis to form esters. A process till the intermediate reaction in the BH catalytic cycle, known as acceptorless dehydrogenation (AD), enables an efficient and elegant way for the construction of esters. Homocoupling of pentanol (**45**) in the presence of Ru-PNP complex and KOH yields pentyl pentanoate (**46**) with a 78% yield (Scheme 15a).⁵⁴ Most importantly it produces hydrogen as the only by-product from the reaction.



Scheme 15a: Homocoupling of alcohol to ester

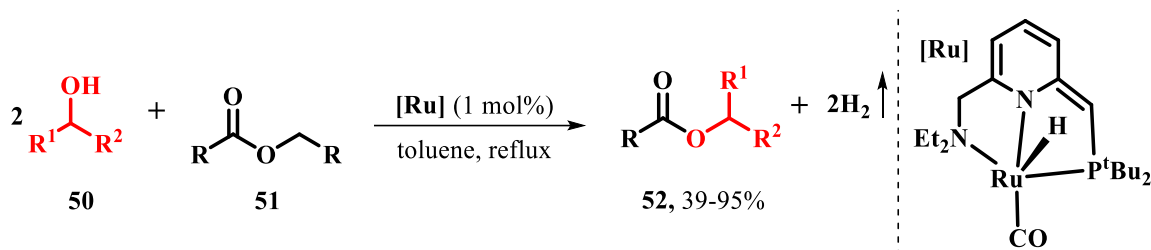
Further, Milstein's research group demonstrated the cross-coupling of primary alcohol (**47**) with secondary alcohol (**48**) in the presence of 1 mol% of Ru-PNN complex to get the ester product **49** (Scheme 15b) where the secondary alcohol was used in excess amount (2.5 mmol).⁵⁵



Scheme 15b: Cross-coupling of primary alcohol and secondary alcohol to ester

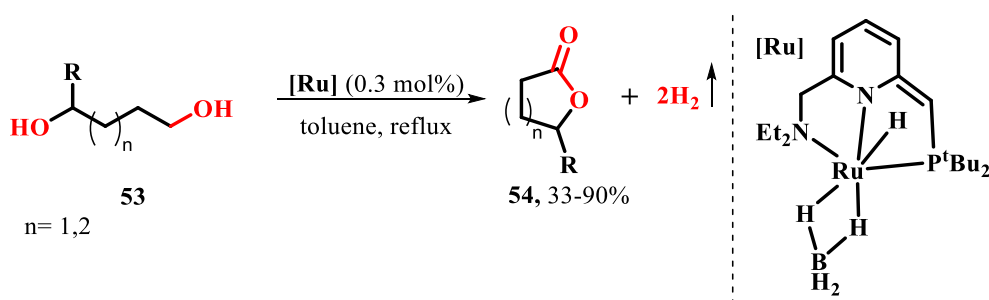
Transesterification which is the process of converting one ester into another, is an alternative route for the synthesis of esters. However, it is not atom-economical due to the co-production of an equal amount of alcohol along with the desired ester. To address the atom economy, the same group introduced a unique approach to transesterification. In this method, instead of producing alcohols as by-products, hydrogen gas is generated when esters react with

secondary alcohols under the catalysis of Ru-complex (Scheme 15c). The cross-selectivity arises due to the slower dehydrogenation of the secondary alcohol into the corresponding ketone, in contrast to the dehydrogenative coupling of the primary alcohol with the ester (Scheme 15c).⁵⁶



Scheme 15c: Transesterification using secondary alcohols

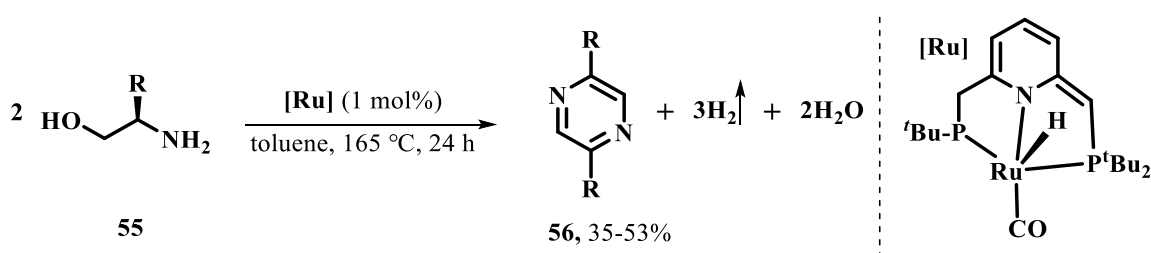
Next, the intramolecular reaction of diols to form lactones (5- and 6-membered) using a Ru-PNN complex is also demonstrated by the same research group (Scheme 15d).⁵⁷



Scheme 15d: Intramolecular reaction of diols to lactones

1.7.3 Construction of C-N bonds:

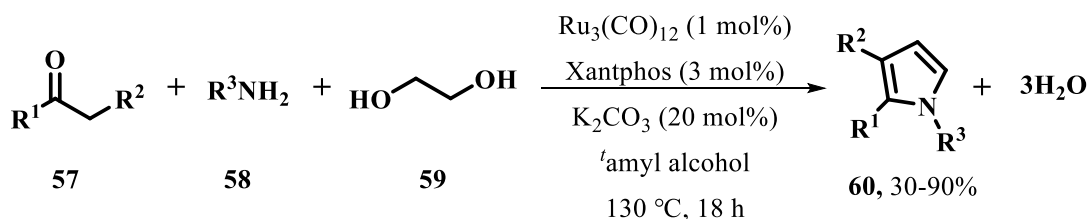
The establishment of new C-N bonds facilitates the emergence of new organic molecules, encompassing *N*-heterocycles, amides, and *N*-substituted amines. BH catalysis is an excellent alternative to construct new C-N bonds by overriding issues such as low atom economy, use of halogenated electrophiles, and production of unwanted waste. Using amino alcohols (55) in presence of Ru-complex, facilitates the synthesis of pyrazines (56) (Scheme 16a) with the removal of hydrogen and water as by-products.⁵⁸



Scheme 16a: Synthesis of pyrazines using amino alcohols

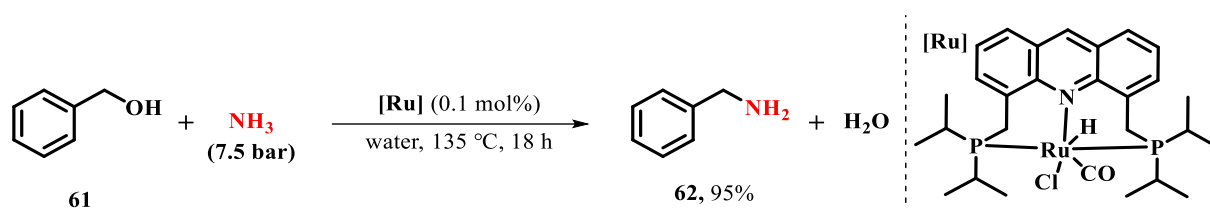
Moreover, a 3-component reaction of ketone 57, amine 58 and ethylene glycol 59 in

the presence of $\text{Ru}_3(\text{CO})_{12}$, xantphos and potassium carbonate provides a variety of pyrroles (**60**) (Scheme 16b).⁵⁹



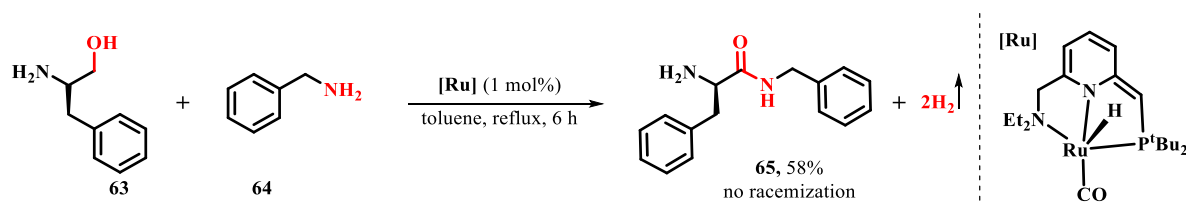
Scheme 16b: Synthesis of pyrroles

Furthermore, primary amines (**62**) can be synthesized by reacting primary alcohol (**61**) and ammonia gas (7.5 bar) by using a Ru-PNP complex (Scheme 16c).⁶⁰



Scheme 16c: Synthesis of primary amines using ammonia

The presence of the amide core is pervasive in numerous drugs and natural compounds, rendering it a pivotal structural motif in organic chemistry. Usually, amides are synthesized from acids and amines using coupling reagents. However, the coupling reagents generate a stoichiometric amount of waste after the reaction. Thus, such kind of processes are associated with a high E-factor. Another way of amidation is reacting ester with primary amines in the presence of acid catalysts. Again, this process is found inefficient for the synthesis of primary amides and eliminates alcohol as the byproduct from the reaction which is not advisable in the atom economy perspective. BH catalysis enables a new route for the synthesis of amides by reacting amines and alcohols in the presence of a metal catalyst, which produces only hydrogen as the by-product (Scheme 16d).⁶¹



Scheme 16d: Amidation using primary amine and primary alcohol

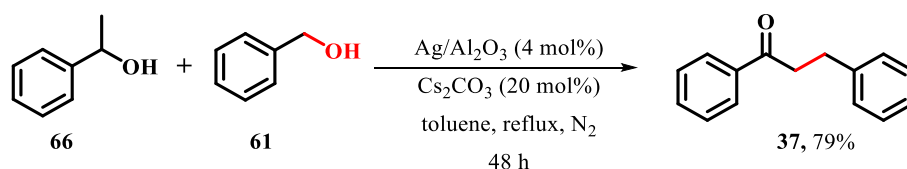
1.7.2 Literature Overview for Heterogeneous Borrowing Hydrogen Catalysis

Nevertheless, homogeneous and heterogeneous catalysis are different fields, many efforts have been made to bridge between homogeneous and heterogeneous catalysis. One

possible solution is to make heterogeneous metal complexes on solid supports such as alumina, zeolites, nanoparticles, etc. However, a good amount of work has been dedicated toward C-C and C-N bond construction using metal supported heterogeneous BH catalysis. Those methods include metals such as Ru, Pd, Pt, Ir, Ni, Fe, Cu, Au, Ag, etc., supported on various solid supports, which creates the organometallic centre in close proximity to the solid surface. A few illustrative examples are provided below.

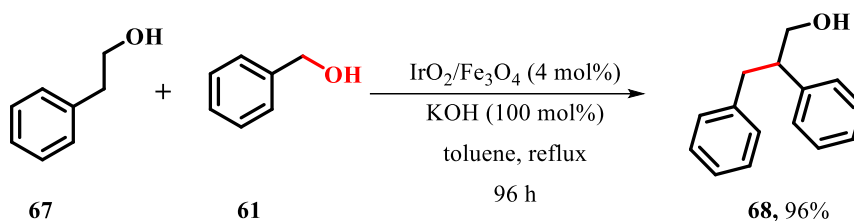
1.7.2.1 Construction of C-C bond:

A heterogeneous catalyst of silver supported on aluminium oxide efficiently facilitates the cross-coupling of primary alcohol (**61**) and secondary alcohol (**66**) to furnish product **37** with a 79% yield (Scheme 17a).⁶²



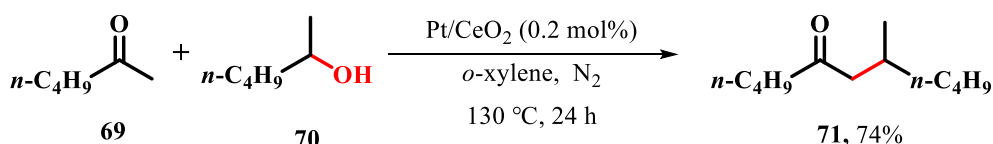
Scheme 17a: Ag/Al₂O₃ catalyzed cross-coupling of primary and secondary alcohol

Another example illustrates the iridium oxide supported on the iron nano-particles catalyzed cross-coupling of two primary alcohols to provide product **68** with 96% yield (Scheme 17b).⁶³



Scheme 17b: IrO₂/Fe₃O₄ catalyzed cross-coupling of primary alcohols

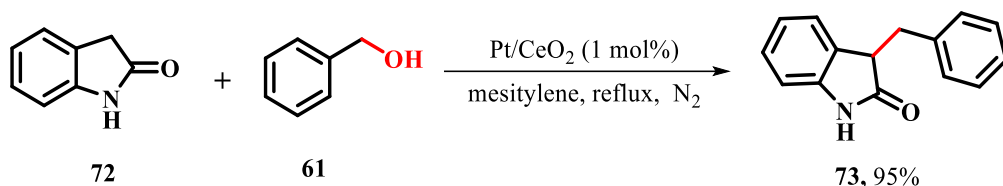
Further, α -alkylation of ketone **69** with secondary alcohol **70** is demonstrated by a Pt/CeO₂ catalyst which gives product **71** with 74% yield (Scheme 17c). In this reaction, the aldol condensation is carried out by the CeO₂.⁶⁴



Scheme 17c: Pt/CeO₂ catalyzed α -alkylation of ketone with alcohol

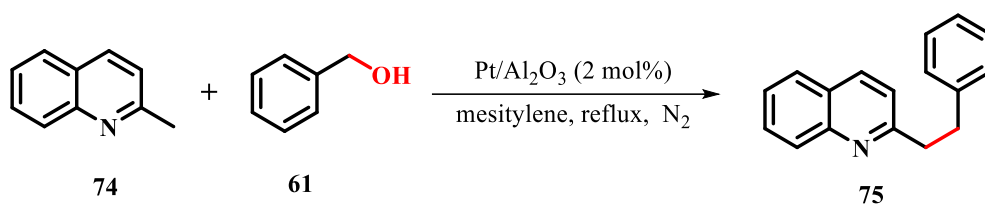
Alkylation of heterocyclic compounds using alcohol as an alkylating agent is a fascinating process that reduces halogenated waste by eliminating the use of halogenated

electrophiles for alkylation. The alkylation of oxindole **72** with benzyl alcohol **61** provided a 95% yield of product **73** (Scheme 17d).⁶⁵



Scheme 17d: α-alkylation of oxindole with alcohol

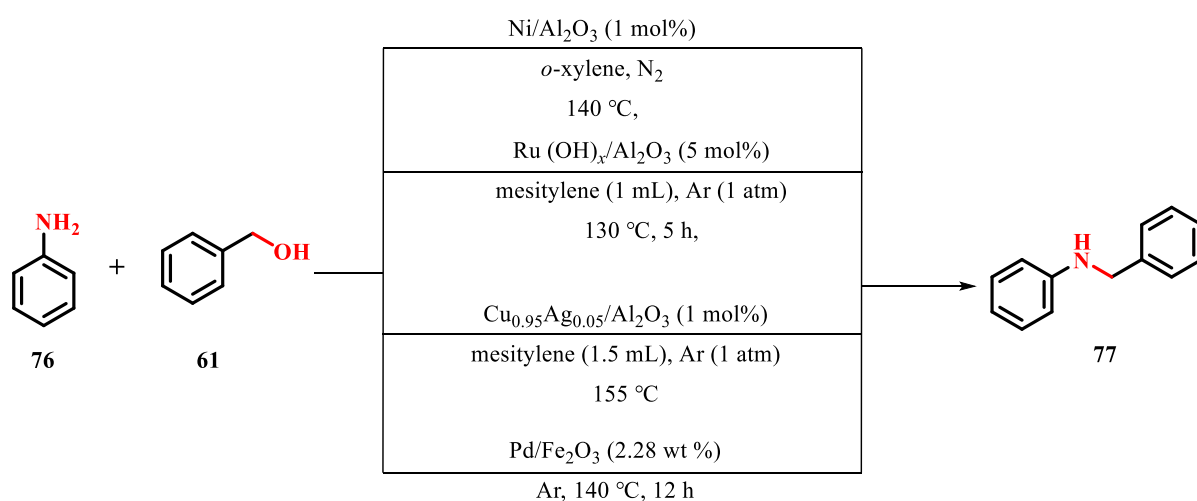
Furthermore, alkylation at the methyl group of methyl quinoline is also studied using platinum supported on an aluminium oxide heterogeneous catalyst. This method has been well demonstrated with a series of alcohols and methyl quinolines for the alkylation (Scheme 17e).⁶⁶



Scheme 17e: Pt/Al₂O₃ catalyzed alkylation at the methyl group of methyl quinoline

1.7.2.1 Construction of C-N bond:

Numerous approaches have been developed for the *N*-alkylation of amine with alcohols, which utilizes various supported heterogeneous catalysts such as Ni/Al₂O₃,⁶⁷ (Ru(OH)_x/Al₂O₃),⁶⁸ Cu_{0.95}Ag_{0.05}/Al₂O₃,⁶⁹ and Pd/Fe₂O₃ (Scheme 17f).⁷⁰



Scheme 17f: C-N bond construction using different heterogeneous catalysts

In essence, borrowing hydrogen (BH) catalysis is a widely acknowledged process that shows intense applications in synthetic organic chemistry. More interestingly, by using alcohol as an alkylating agent, it avoids halogenated waste and produces water and hydrogen as benign

byproducts. Therefore, BH catalysis exhibits notable advantages in green chemistry parameters like atom economy, waste minimization, catalytic efficiency, and the use of benign reagents.

1.8 Aim and Rationale of Thesis Work:

Despite widespread applications of borrowing hydrogen catalysis in organic synthesis, it is limited to the synthesis of acyclic and small cyclic molecules. Macrocycles, being an imperative class of cyclic compounds, no efforts had been made toward their synthesis using borrowing hydrogen catalysis. The primary objective of the thesis work is to investigate the feasibility of macrocyclization by employing the Borrowing Hydrogen Catalysis. As a consequence, the coupling agents and halogenated reagents would be avoided, which would result in reduced waste generation. Notably, BH catalysis utilizes alcohol as a starting material and generates water or hydrogen as benign by-products from the reaction. This represents a substantial advancement towards greener macrocyclization by minimizing environmental impact. Ultimately, BH catalysis emphasizes the commitment to sustainable and environmentally benign chemical processes, aligning with the principles of green chemistry. Indeed, a significant breakthrough in sustainable chemistry is achievable if the issues following macrocyclization are effectively addressed through the implementation of the BH catalysis by promoting safer chemistry, sustainability, high atom economy, and minimal environmental impact.

➤ Ru-MACHO-Catalyzed Direct Intermolecular Macrocyclization of Alcohols and Ketones

This study aims to devise a new synthetic strategy for intermolecular macrocyclization using diols and amino acetophenones. Conventional methods for macrocyclization typically rely on halogenated electrophiles, phosphine-related reagents/ligands, and dehydrating/coupling agents, resulting in the generation of stoichiometric waste after the completion of the reaction. Thus, our aim is to devise a technique that circumvents the use of toxic/halogenated reagents, phosphine reagents, and coupling agents, yielding only environmentally benign by-products while maintaining a high atom economy. To accomplish this objective, the intermolecular macrocyclization of long-chain diols with aminoacetophenones is achievable by employing a catalyst (which facilitates BHC) and a base. As a result, the aim of developing a protocol with low environmental impact would be fulfilled by forming only water as the sole benign by-product of the macrocyclization reaction.

➤ **Dehydrogenative Intramolecular Macrolactonization of Dihydroxy Compounds Using Ru-MACHO Catalyst and its Application Towards Synthesis of Corniculatolide-A**

Macrolactones are a class of macrocycles with an ester group in the cyclic core, defining their importance in natural products, drugs, and synthetic musks. Due to their importance, classical macrolactonization strategies have been developed. Generally, these classical macrolactonization strategies are based on the cyclization of seco-acids (long-chain molecules having acid and alcohol at the two ends) either activation of carboxylic acids or activation of alcohols using coupling reagents such as *N*-methyl-2-chloro-pyridinium iodide (Mukaiyama salt), anhydrides (e.g., MNBA) and acid chlorides (e.g., 2,4,6-trichloro-benzoylchloride). These coupling reagents were used in stoichiometric amounts and produced a side product after the completion of the reaction, which is waste. Moreover, catalytic approaches use external oxidants or additives in the macrolactonization reaction. Hence, the objective of this work is to develop a new catalytic method to achieve macrolactones without using any external oxidant or additive in the reaction. This could be achieved by utilizing an acceptorless dehydrogenative strategy, where long-chain diols are used as starting materials and produce only hydrogen as the by-product. In the acceptorless dehydrogenation reactions, a catalyst and a base can efficiently transform diols into macrolactones by excluding the use of an external oxidant. Finally, we aim to implement this method for the synthesis of the natural product corniculatolide-A to achieve step economy.

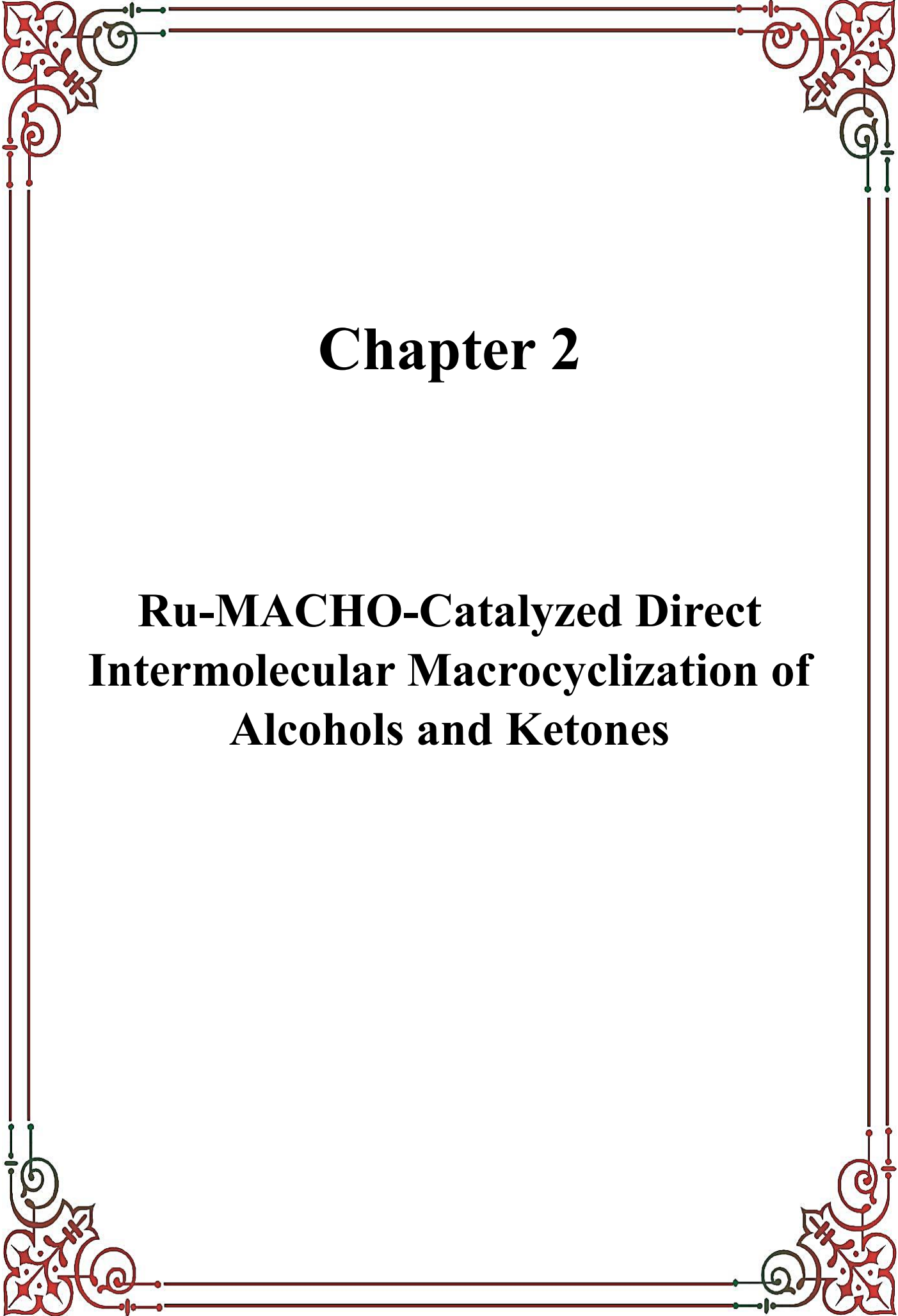
➤ **Ring-Opening and Ring-Closing Approach for the Macrolactams from Macrolactones under Neutral Condition**

Macrolactamization represents an underexplored domain within macrocyclization despite its ubiquitous presence in drugs and natural products such as vacenistatin, cyclomenal-A, and rifaximin. Further, the significance of macrolactamization extends to peptide chemistry, where it serves as a crucial method for synthesizing diverse cyclopeptides. Unfortunately, the available strategies for direct macrolactamization are limited. The indirect approaches involve alkene-alkene metathesis, alkene-alkene cross-coupling, and Ullmann coupling reactions, requiring specially designed starting materials. Therefore, these methods require protection and deprotection chemistry, leading to reduced atom economy. To address these limitations, we sought to develop a new ring-opening and ring-closing strategy for macrolactam

synthesis. Leveraging a pre-established macrolactonization approach to synthesize macrolactones, the ring opening of macrolactones could be induced using a catalyst and various amine sources to yield amides. Subsequently, these amides can react intramolecularly (*N*-alkylative ring closure), which is facilitated by a catalyst, affording the desired macrolactams.

➤ **Ru-Zeolite Catalyzed Dehydrative *N*-Alkylation of Amides for the Construction of Macrolactams under Continuous Flow Module**

Despite the efficacy of BH catalysis, it exhibits limitations in scalability due to the requirement of an additional setup, such as a sealed reaction vessel. The main objective of this work is to overcome the scalability issue of BHC and to make the macrocyclization more sustainable by showing the synthetic utility of the process from milligrams to grams. Heterogeneous catalysis is found efficient over homogeneous catalysis by virtue of its abilities, such as ease of separation from the reaction mixture, recyclability and reusability. In this strategy, our intent is to adopt a heterogeneous catalysis that facilitates the dehydration of alcohol and further intramolecular reaction with amide to achieve the macrolactam product with the removal of only water as the benign by-product.



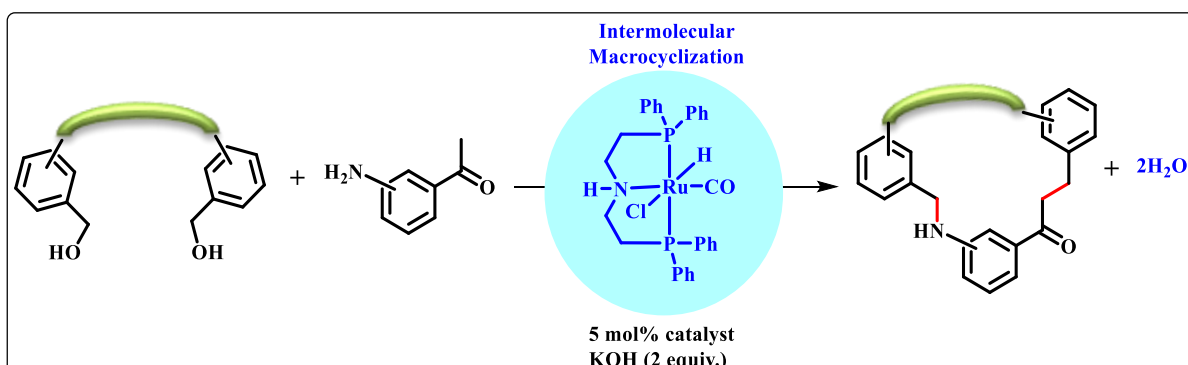
Chapter 2

Ru-MACHO-Catalyzed Direct Intermolecular Macrocyclization of Alcohols and Ketones

2. Ru-MACHO-Catalyzed Direct Intermolecular Macrocyclization of Alcohols and Ketones

2.1 Abstract:

In this study, a new method for the synthesis of macrocycles via an intermolecular cyclization process has been introduced. This method involves the dehydrogenative coupling of alcohols and ketones facilitated by a Ru-MACHO catalyst. Notably, this approach exhibits atom efficiency and sustainability over other approaches, making it applicable to a wide range of substrate molecules. Importantly, the reaction generates only water as a byproduct, highlighting its environmentally benign nature. Furthermore, the effect of maintaining high dilution of the reactants is pivotal for achieving efficient macrocyclization with high-yields. Finally, with the intermediate trapping experiment, the mechanism of the reaction is established.



2.2 Introduction:

In the realm of organic chemistry, macrocycles represent a distinct category of chemical compounds characterized by their expansive cyclic structures. Macrocycles, especially bearing amine and ketone functional groups serve as integral components in natural products and display extensive applications in pharmaceuticals (figure 11).⁷¹ Moreover, they are found useful in the field of materials science,⁷² and supramolecular chemistry.⁷³ Nonetheless, synthesizing macrocycles through the closure of end groups of elongated linear chains presents a formidable challenge due to the complex entropy processes involved, which can give rise to competing undesired intermolecular reactions and oligomerization (discussed in Figures 5a and 5b, Chapter I).²¹ Achieving selectivity during macrocyclization poses further difficulties, as potential side reactions can diminish the yield of the desired product. Thus, maintaining a high

dilution of starting materials plays an important role in macrocyclization. In spite of these challenges, a plethora of approaches have been devised for macrocycle construction.

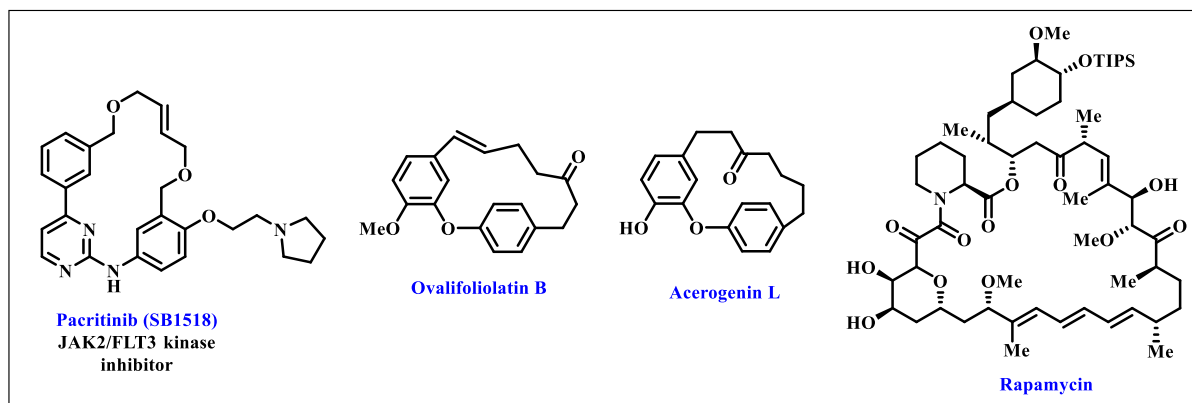
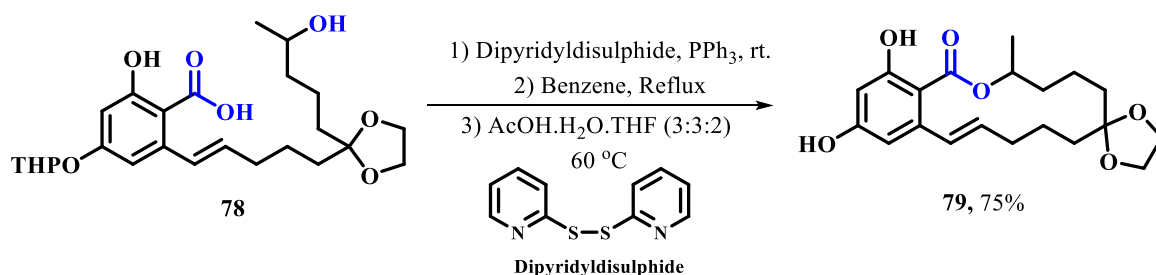


Figure 11: Drugs and natural products bearing amine and ketone functional group

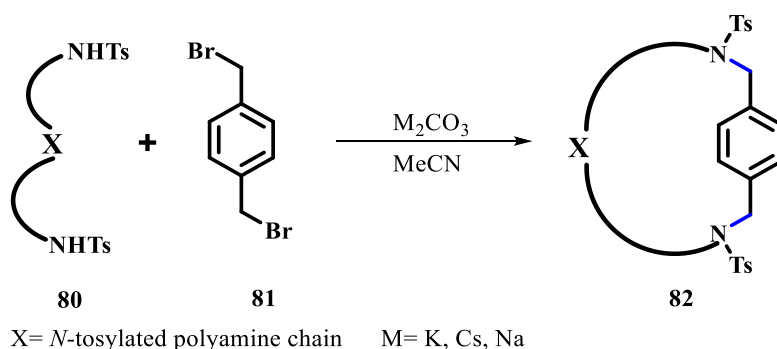
2.2.1 Classical Approaches:

In 1974, K. C. Nicolaou and his research group attempted the synthesis of zearalenone precursor **79** using dipyridyl disulfide as a coupling reagent and triphenylphosphine for the intramolecular coupling of carboxylic acid and alcohol (Scheme 18).⁷⁴



Scheme 18: Dipyridyldisulphide for macrocyclization

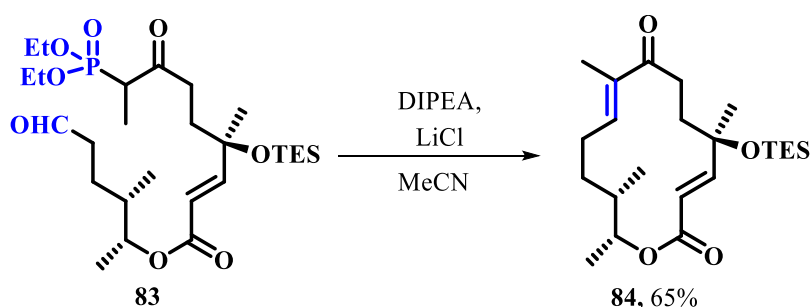
Next, in 1993 Luis's research group achieved macrocyclization via intermolecular $\text{S}_{\text{N}}2$ reaction of *N*-tosylated amines and alkyl bromides using metal carbonates as base to synthesize polyaza[*n*]paracyclophanes **82** (Scheme 19).⁷⁵



Scheme 19: $\text{S}_{\text{N}}2$ reaction for macrocyclization

Further, Orelli and his team performed the modified Wittig reaction, which is also

known as the Horner-Wadsworth-Emmons (HWE) reaction, for the macrocyclization. In this reaction, a modified Wittig reagent reacts with aldehyde intramolecularly in order to afford a macrocyclic product **84** with 65% yield (Scheme 20).⁷⁶



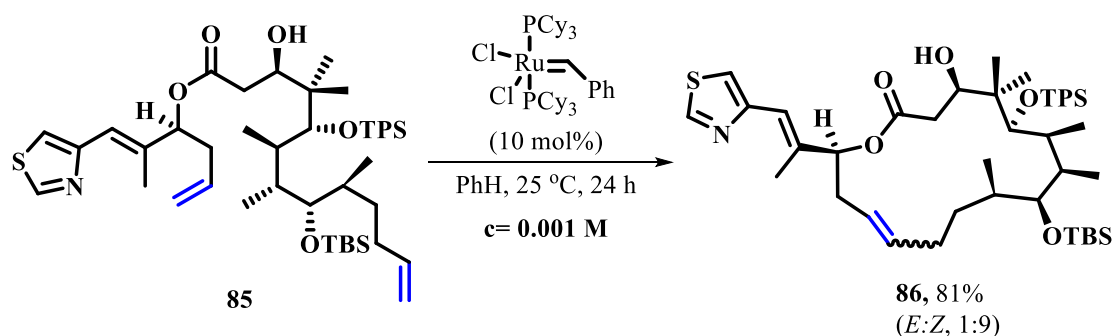
Scheme 20: HWE reaction for macrocyclization

Although classical methods are useful for inter- or intramolecular macrocyclization and the synthesis of natural products, they are associated with several limitations, such as the use of toxic halogenated and phosphine reagents and the use of the stoichiometric amount of coupling reagents, which creates waste in large amount. Consequently, these procedures present significant sustainability concerns.

In contrast, the catalytic approaches have overcome all these concerns and limitations.

2.2.2 Catalytic Approaches:

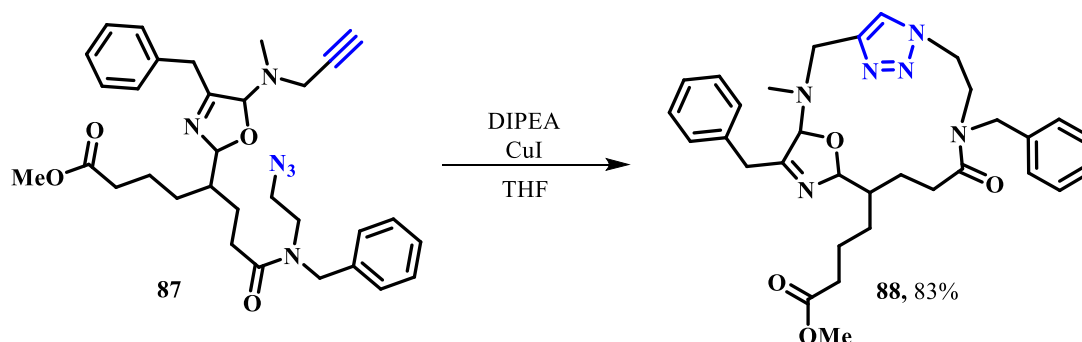
These contemporary strategies leverage transition-metal-catalyzed reactions with diverse end-group functionalities. These approaches have gained significant attention owing to their selectivity, efficiency, high atom economy, minimal byproduct generation, and sustainability. Consequently, multiple methods have been explored for inter- and intramolecular macrocyclization utilizing transition metals as catalysts. Prominent synthesis strategies are ring-closing metathesis (RCM),⁷⁷ cycloaddition reactions employing alkyne-azide chemistry,⁷⁸ guest-mediated macrocycle synthesis,⁷⁹ foldamer-templated reactions,⁸⁰ cross-coupling reactions,⁸¹ and C-H activation.⁸²



Scheme 21: Grubb's metathesis for macrocyclization

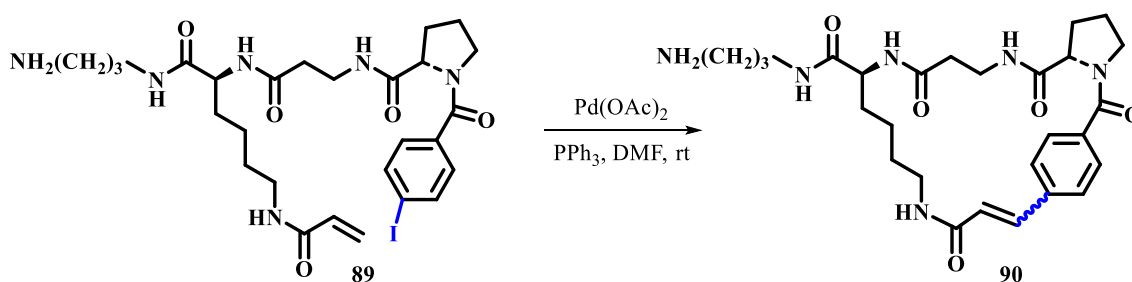
In 1997, D. Meng and his team attempted the synthesis of epothilones using Grubb's catalysis for the metathesis of alkenes to achieve a macrocyclic precursor of epothilone **86** with 81% yield (Scheme 21).

In 2012, G. C. Tron's research group innovatively synthesized macrocyclic peptide mimetics through an intramolecular click reaction involving azide and terminal alkyne. This approach yielded macrocyclic compound **88**, featuring a 5-membered triazole ring (Scheme 22).

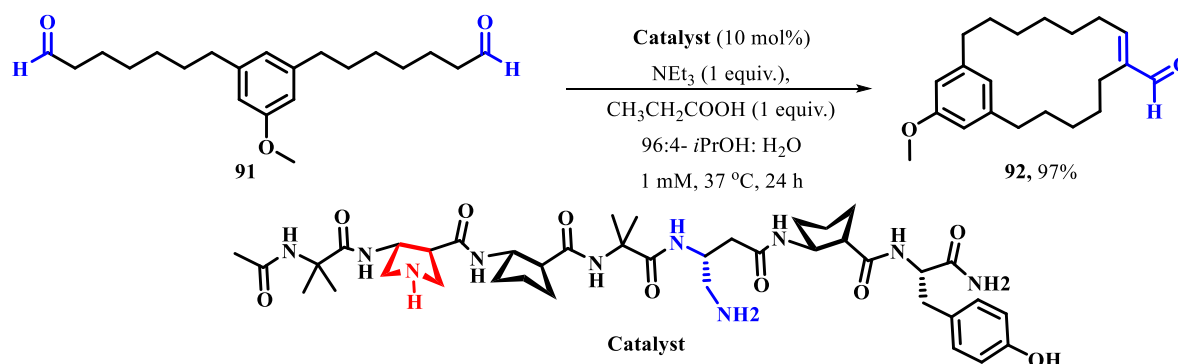


Scheme 22: Intramolecular click reaction for macrocyclization

More interestingly, palladium-catalyzed cross-coupling reactions are extensively utilized for macrocyclization. For instance, D. Mench and coworkers attempted the synthesis of the macrocyclic core of rhizopodin **90** by a Heck macrocyclization strategy using Pd(OAc)₂ as the catalyst (Scheme 23).



Scheme 23: Heck reaction for macrocyclization



Scheme 24: Foldamer-templated macrocyclization

Furthermore, Gellman's research group developed a new method for macrocyclization using a peptide as a catalyst, also known as a foldamer. This foldamer template-mediated macrocyclization involves long-chain dialdehydes as a starting material which further reacts with amine groups (indicated in red and blue colour in Scheme 23) to provide macrocycle **92** with 97% yield (Scheme 24).

Despite having the aforementioned catalytic approaches for macrocyclization, the pursuit of a new synthetic methodology for efficient macrocyclization with enhanced selectivity and sustainability remains a paramount objective.

2.3 Rationale of Current Work:

In the 21st century, metal-catalyzed transformations operating through the borrowing hydrogen (BH) catalysis have emerged as an important strategy for C-C and C-N bond-forming reactions, owing to their numerous advantages. As a consequence, fundamental reactions for borrowing hydrogen (BH) catalysis with various catalytic systems have been explored. However, the application of this methodology for macrocycle synthesis remains unexplored. Hence, we aimed to develop a new approach, that should mark the first instance of describing macrocyclization by employing alcohols and ketones through intermolecular borrowing alkylation.

2.4 Results and Discussions:

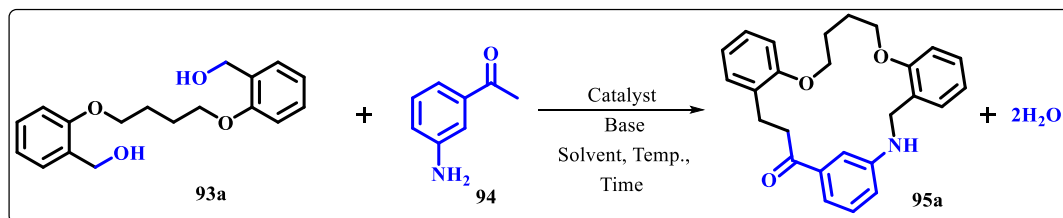
We initiated our research by exploring the concept of BHC, beginning with the synthesis of macrocycle **95a** using 3-aminoacetophenone and a diol featuring a butyl spacer. These starting materials subjected to various reaction conditions, including diverse temperatures, catalysts, bases, and solvents. Upon comprehensive screening, we observed promising outcomes when employing Ru-MACHO [carbonylchlorohydrido{bis-[2-(diphenylphosphinomethyl)ethyl]-amino}ethyl]amino}-ruthenium(II)]⁸³ (for structure, see Figure 8) as the catalyst, toluene as the solvent, and NaOH as the base. Building upon this preliminary success, we proceeded with optimization studies aimed to maximize the yield of macrocycle.

2.4.1 Optimization Studies:

Our investigation commenced with the dehydrogenative coupling of compound **93a** and 1-(3-aminophenyl)ethan-1-one (**94**) as a model reaction. A controlled experiment underscored the indispensability of both catalyst and base for this transformation (Table 2, entries 1 and 2). Notably, employing 5 mol % of Ru-MACHO catalyst and NaOH (1 equiv.) provided a 17% isolated yield of product **95a** (Table 2, entry 3). The use of 2 equiv. of NaOH

led to a reduction in product yield (Table 2, entry 4). Next, decreasing the temperature to 140 °C, a decrease in the yield was found (Table 2, entry 5).

Table 2: Optimization Table for Intermolecular Macrocyclization



Entry	Catalyst (5 mol %)	Base (equiv.)	Conc. (93a:94) in toluene (M)	Time (h)	Yield of 95a (%)
1	-	KOH (2)	0.1: 0.1	16	traces
2	Ru-MACHO	-	0.1: 0.1	16	-
3	Ru-MACHO	NaOH (1)	0.1: 0.1	16	17
4	Ru-MACHO	NaOH (2)	0.1:0.1	16	13
5 ^b	Ru-MACHO	NaOH (1)	0.1:0.1	16	14
6 ^c	Ru-MACHO	NaOH (1)	0.1:0.1	16	30
7 ^c	Ru-MACHO	NaOH (1)	0.08: 0.04	24	36
8 ^c	Ru-MACHO	NaOH (2)	0.08: 0.04	24	38
9 ^c	Ru-MACHO	<i>t</i> -BuOK (2)	0.08: 0.04	24	40
10 ^c	Ru-MACHO	KOH (2)	0.08: 0.04	24	42
11 ^c	Ru-MACHO	KOH (2)	0.05: 0.02	24	49
12 ^c	Ru-MACHO	KOH (2)	0.05: 0.02	48	54
13 ^{c,d}	Ru-MACHO	KOH (2)	0.05: 0.02	48	44
14 ^c	RuCl ₃ . <i>x</i> H ₂ O	KOH (2)	0.05: 0.02	48	trace
15 ^c	Ru-PNN	KOH (2)	0.05: 0.02	48	28
16 ^c	Ru(H ₂)CO(PPh ₃) ₃	KOH (2)	0.05: 0.02	48	30
17 ^c	Ru-NHC	KOH (2)	0.05: 0.02	48	34
18 ^c	Ru-MACHO	KOH (2)	0.01: 0.01	48	67
19 ^c	-	KOH (2)	0.01: 0.01	48	trace

^aReaction Conditions: Compounds **93a** and **94** (M solution in toluene, see table), Ru-MACHO (5 mol %), and base (see table) were stirred in a preheated oil bath at 160 °C for different time periods (see table). ^bReaction mixture heated at 140 °C. ^cReaction mixture heated at 180 °C. ^d1,4-Dioxane was used as a solvent.

An increase in temperature to 180 °C, enhancement in the yield of the product **95a** was observed (Table 2, entry 6). Moreover, dilution significantly influences macrocyclization to furnish an increased yield (36%) of **95a** (Table 2, entry 7). No improvement in yield was observed when 2 equiv. Of NaOH is used (Table 2, entry 8). Bases, such as *t*-BuOK and KOH, yielded 40% and 42% of the product, respectively (Table 2, entries 9 and 10). Further, using KOH as the optimal base, we increased the dilution of **93a** to afford **95a** with 49% (Table 2, entry 11). Furthermore, a prolonged reaction time (48h) resulted in a slight increment in product formation (Table 2, entry 12). Another solvent, like 1,4-dioxane, proved inefficient for the synthesis of **95a** (Table 2, entry 13). Various Ruthenium catalysts (Figure 12a) such as RuCl₃·*x*H₂O, Ru-PNN, RuH₂(CO)(PPh₃)₃, and Ru-NHC were explored, yielding poor-to-moderate yields (Table 2, entries 14–17). Lowering the starting material concentration to 0.01 M, enhanced yield was observed (Table 2, entry 18). No reaction occurred in the absence of a catalyst at 180 °C (Table 2, entry 19).

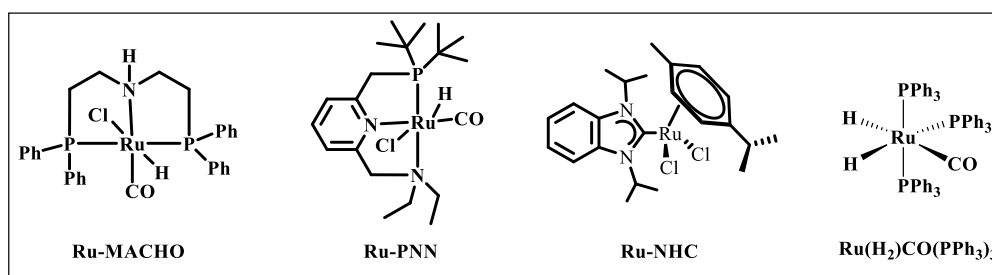


Figure 12a: Catalysts used for optimization

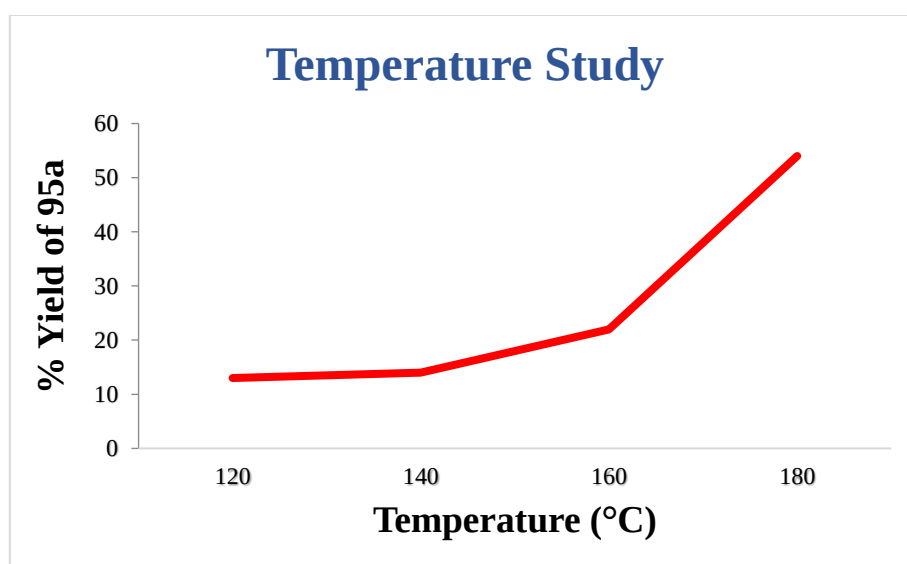


Figure 12b: Temperature Study

Furthermore, to investigate the influence of temperature and concentration on macrocyclization we conducted several reactions by varying temperature and concentration.

Our findings demonstrated a direct correlation between reaction temperature and macrocycle yield, as depicted in Figure 12b. Specifically, elevating the reaction temperature resulted in higher yields of the macrocycle. Conversely, as illustrated in Figure 12c, increasing the concentrations of both starting materials led to a decrease in macrocycle yield. These results clearly prove that the macrocyclization highly depends on the temperature and the dilution.

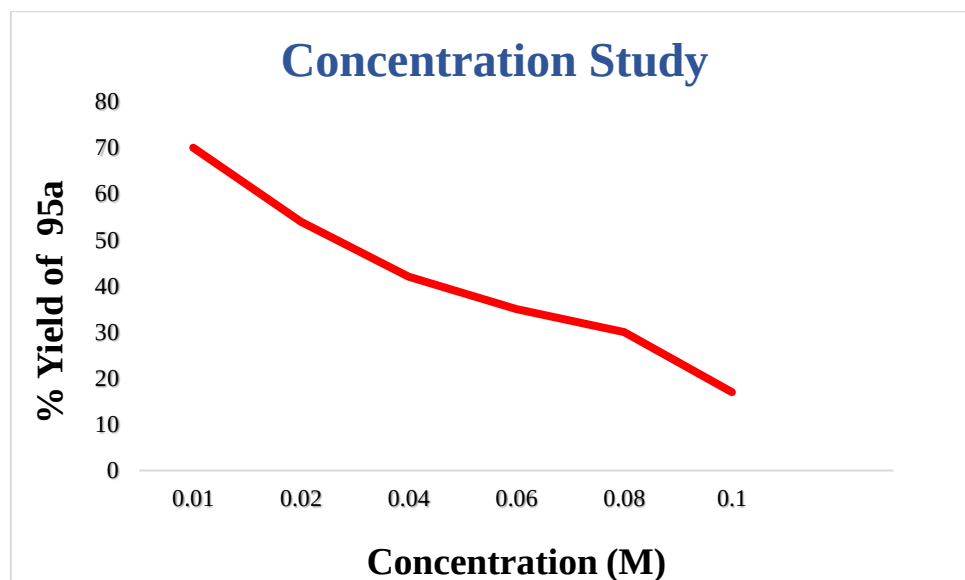
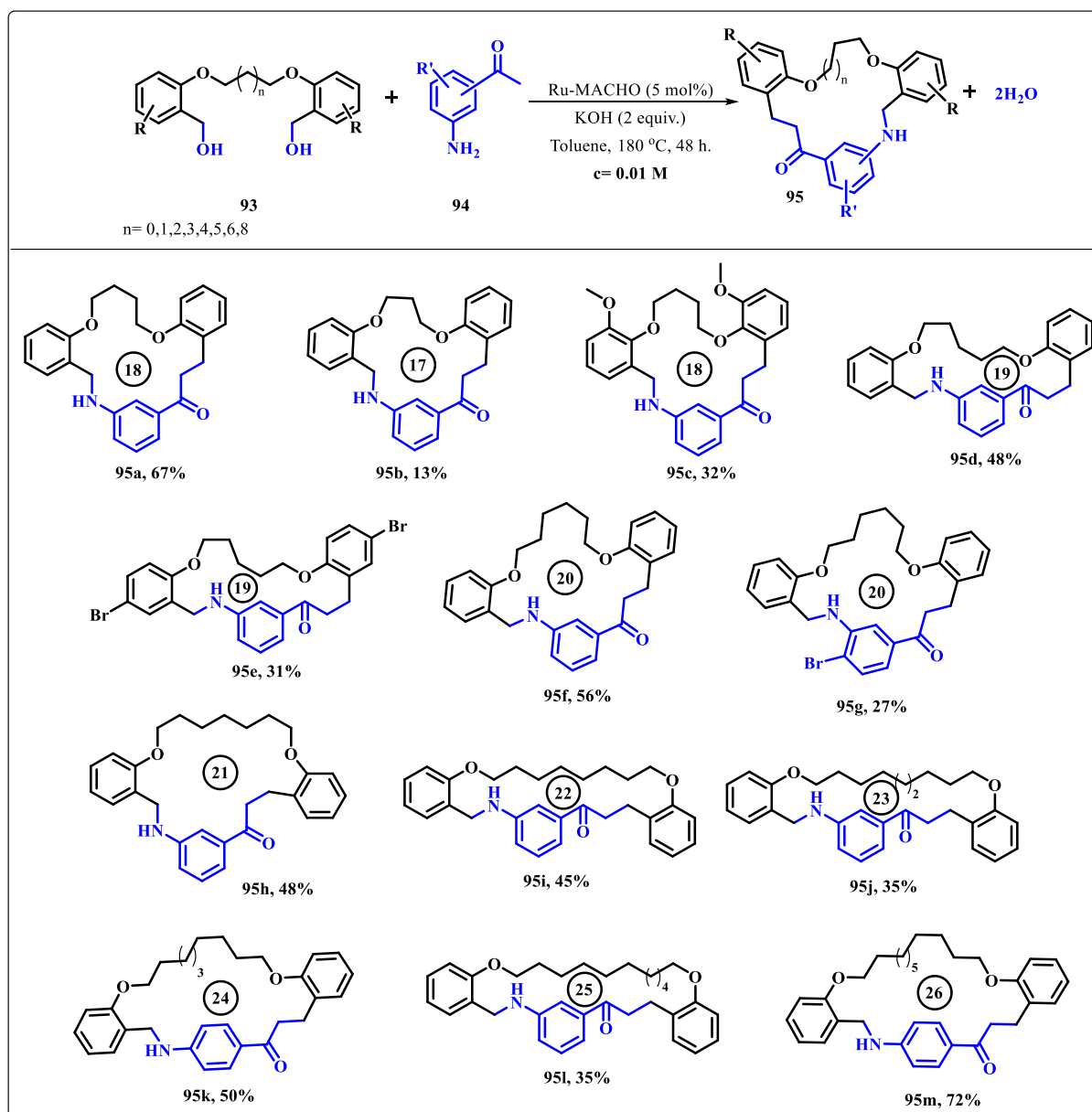


Figure 12c: Concentration Study

2.4.2 Substrate Scope for Intermolecular Macrocyclization:

Inspired by optimized results, we investigated substrate scope with various diphenyldimethanol derivatives. A butyl spacer diol afforded compound **95a** with 67% yield, while propyl spacer diol yielded **95b** with 13% yield (Scheme 25). Diols with ethyl and methyl spacers failed to promote macrocyclization. Employing methoxy substituents on aromatic ring, furnished macrocycle **95c** with 32% yield (Scheme 25). Further, a pentyl spacer diol and a dibromo-substituted diol afforded products **95d** and **95e** with 48 and 31% yields, respectively (Scheme 25). Next, a hexyl spacer diol reacted with 3-aminoacetophenone and 3-amino-4-bromo-acetophenone provided 56 and 27% yields of compounds **95f** and **95g**, respectively (Scheme 25). Other long-chain spacers such as heptyl, octyl, nonyl, and undecyl yielded compounds **95h**, **95i**, **95j**, and **95l** with 35-48% yields (Scheme 25). The structure of compound **95h** was also confirmed by the single crystal X-ray diffraction (CCDC= 2093560, Figure 13) with the largest cavity diameter of 9.77 Å. Furthermore, employing 4-aminoacetophenone with diols afforded 24- and 26-membered macrocycles **95k** and **95m** with 50 and 72% yields respectively (Scheme 25).



Scheme 25: Substrate scope for intermolecular macrocyclization

Reaction conditions: Diphenyldimethanol derivatives **93** (0.166 mmol, 2 equiv., 0.01 M in toluene), aminoacetophenone **94** (0.083 mmol, 1 equiv., 0.01 M in toluene), Ru-MACHO (5 mol %, 0.0042 mmol), and KOH (0.166 mmol, 2 equiv.) were taken in a sealed tube and the mixture was heated to 180 °C for 48 h to achieve macrocycle products **95**.

In addition to the successful outcomes in the substrate scope, we encountered several instances of unsuccessful reactions. Treating *ortho*-diphenyldimethanols with propyl to heptyl spacers with 4-aminoacetophenone yielded no product formation. Similarly, when *meta*-diphenyldimethanols were subjected to 3-aminoacetophenone, no product formation was observed (Scheme 26). The underlying reason could be the unapproachable reaction centres.

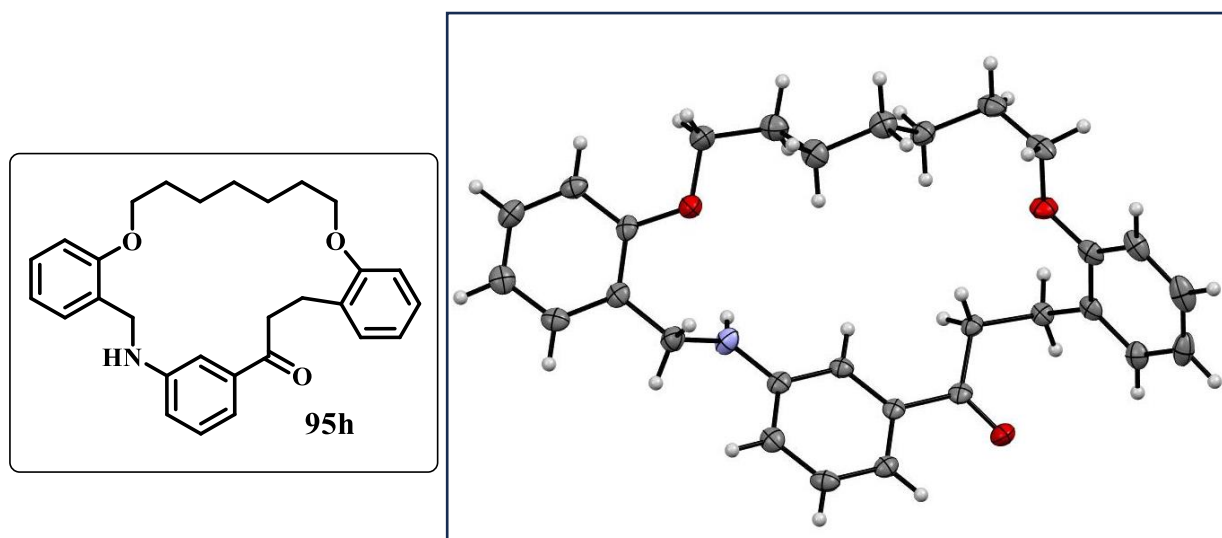
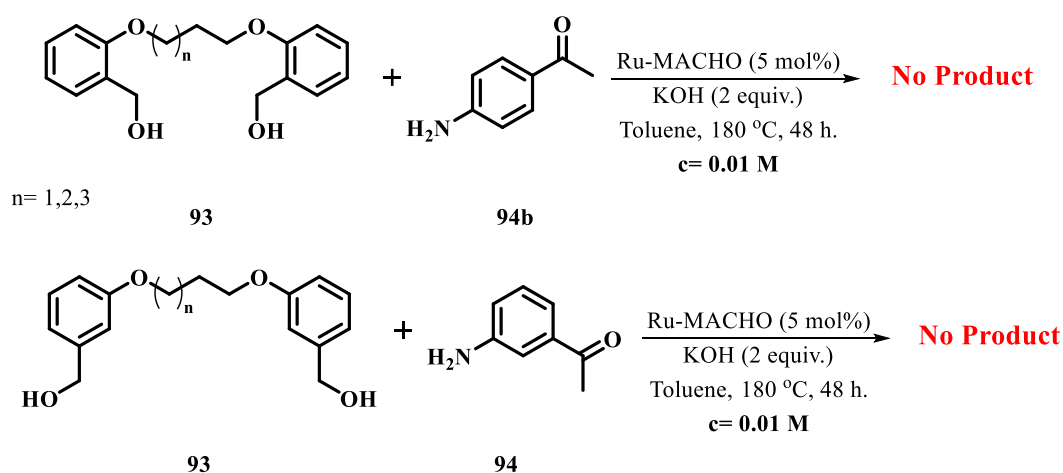


Figure 13: ORTEP drawing of **95h** showing thermal ellipsoids at the 50% probability level (temperature= 296 K)



Scheme 26: Unsuccessful substrate scope for intermolecular macrocyclization

2.5 Mechanistic Investigation:

To understand the mechanism of this intermolecular macrocyclization, we have performed an experiment to trap the intermediate **D** involved in the catalytic cycle. The diol **93d** and aminoacetophenone **94** were heated at 180°C. After 5 h, the reaction mixture was immediately cooled using the mixture of ice and sodium chloride. The resulting reaction mixture was directly injected into the HRMS (High-Resolution Mass Spectrometer) to trap the intermediate. Interestingly, the mass spectrum has shown the peak at $[M]^+ = 885.2257$, clearly indicating the reaction is proceeding through the intermediate **D** [Calculated mass $[M]^+ = 885.2286$] (Figure 14).

Based on a thorough literature review⁵¹ and analysis of trapped intermediates, we have

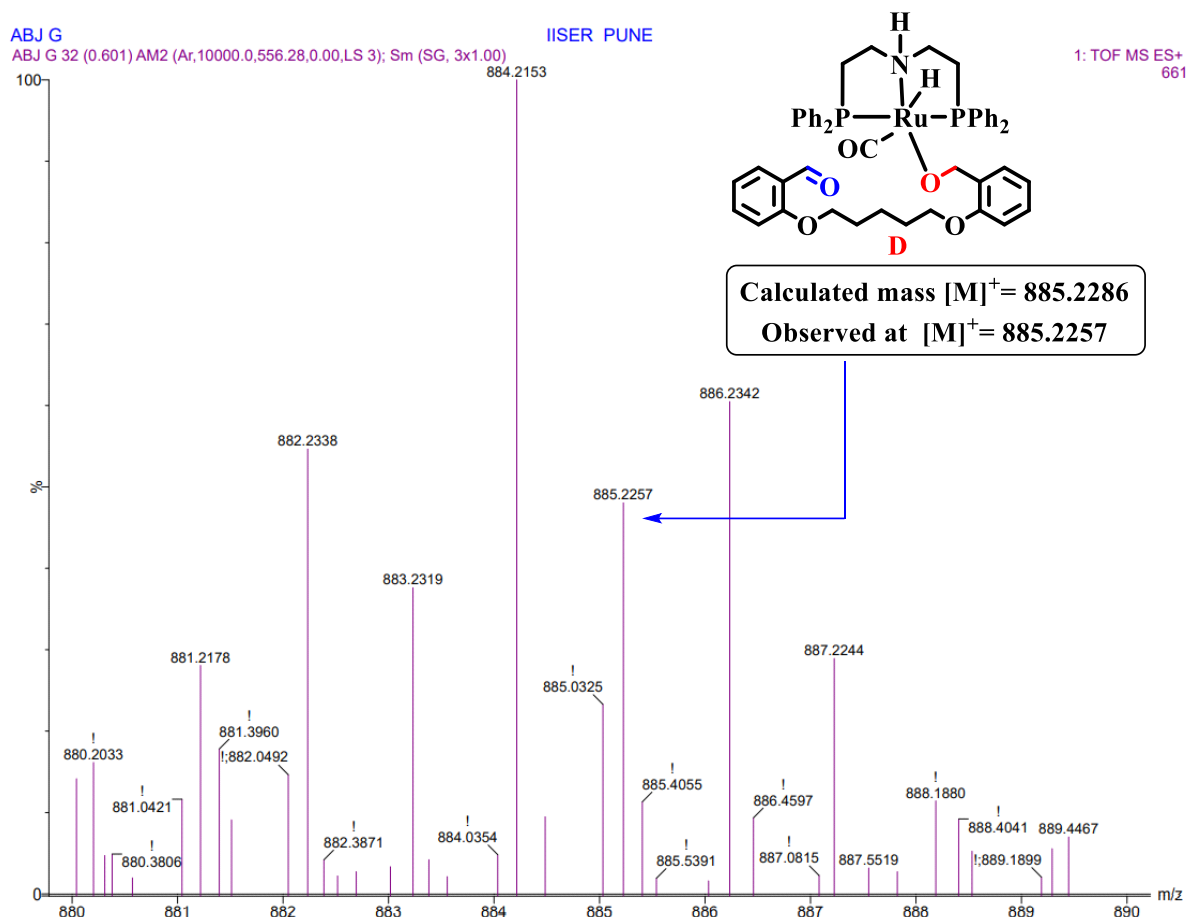
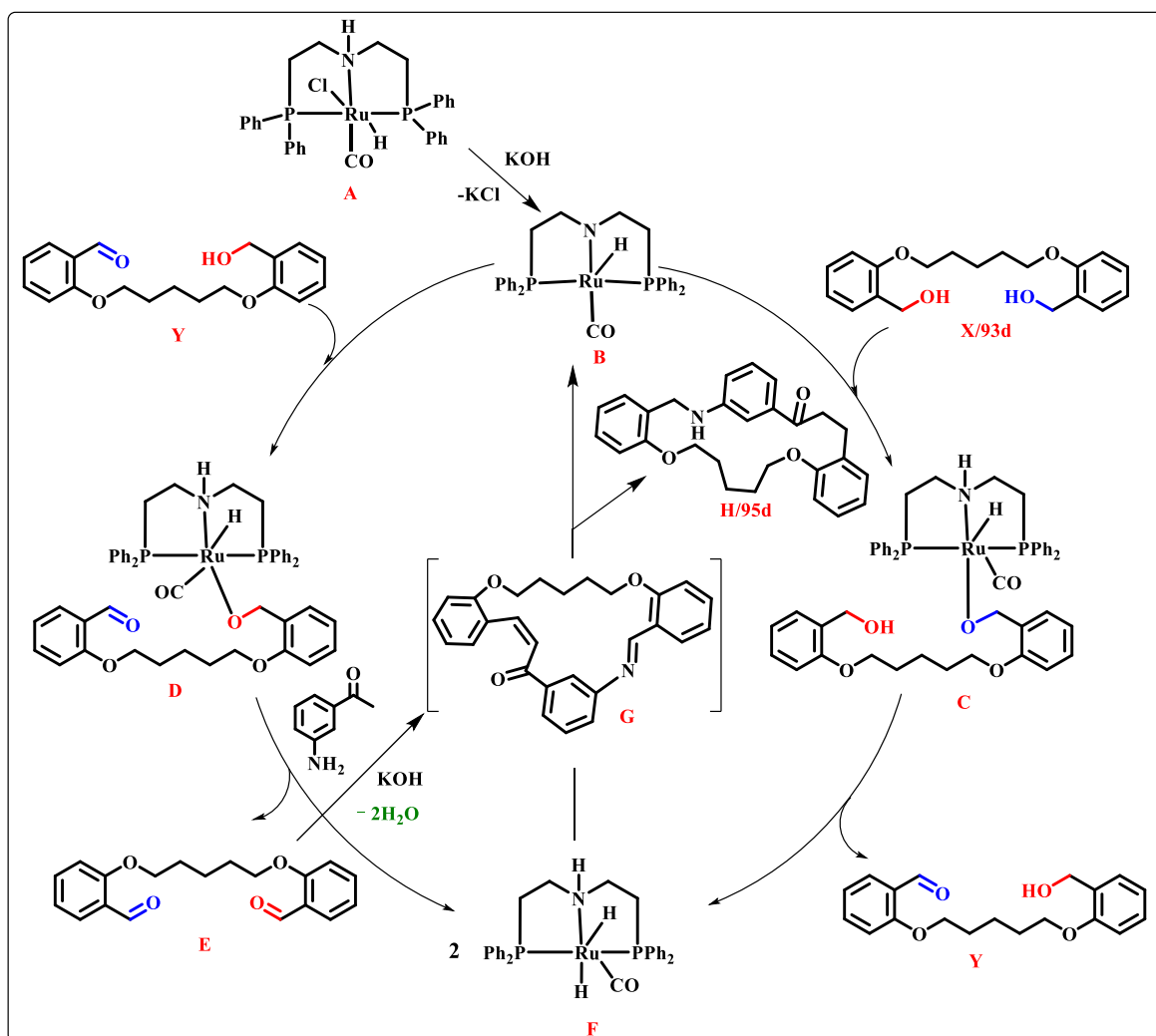


Figure 14: Intermediate **D** trapping by HRMS

drawn a plausible mechanism (Scheme 27) for intermolecular macrocyclization. Initially, the catalyst undergoes a reaction with KOH, yielding active species **B** with the removal of KCl. Subsequently, this active species reacts with the diol **X/93d** to generate intermediate **C** (Scheme 27). Further transformation involves β -hydride elimination, leading to the formation of partially oxidized intermediate **Y** and the Ru-hydride species **F**. Intermediate **Y** then engages with active species **B**, yielding intermediate **D**, which has been confirmed by HRMS analysis (Figure 14). **D** undergoes subsequent β -hydride elimination, resulting in the formation of dialdehyde species **E** and Ru-hydride **F** (Scheme 27). Next, the dialdehyde species **E** then reacts with aminoacetophenone in the presence of KOH, leading to the formation of intermediate **G** via a condensation reaction accompanied by water elimination. Intermediate **G** undergoes reduction in the presence of Ru-hydride species **F**, ultimately furnishing the desired macrocycle **H/95d**, while regenerating active species **B** to continue the catalytic cycle (Scheme 27).



Scheme 27: Plausible mechanism for intermolecular macrocyclization

2.6 Conclusion

In conclusion, we have devised a new method for synthesizing macrocycles via intermolecular macrocyclization, employing diphenyldimethanols and amino acetophenones in the presence of a Ru-MACHO catalyst. This method yields moderate quantities of diverse macrocycles ranging from 17 to 26-members in the ring. Notably, we have identified that temperature, high dilution, and optimal spacer lengths play crucial roles in facilitating efficient macrocyclization. Importantly, our proposed method demonstrates high sustainability, atom efficiency, and ease of synthesis, with water being the sole byproduct generated.

2.7 Experimental Section and Characterization Data:

2.7.1 General information and data collection:

The Ru-MACHO (CAS number- 1295649-40-9, SIGMA), 3-aminoacetophenone (CAS number- 99-03-6, SIGMA), 4-aminoacetophenone (CAS number- 99-92-3 SIGMA), 2-hydroxybenzylalcohol (CAS number- 90-01-7, SIGMA), 2-hydroxy-3-methoxybenzylalcohol

(CAS number- 4383-05-5, SIGMA), 5-bromo-2-hydroxybenzylalcohol (CAS number- 2316-64-5, SIGMA) and 2-aminoacetophenone (CAS number- 551-93-9, SIGMA) was purchased from Sigma-Aldrich. All the solvents used were dry grade. The column chromatographic separations performed over 100-200 mesh size Silica-gel. Visualization was accomplished with UV light, PMA, and CAM stain followed by heating. ^1H and ^{13}C NMR spectra were recorded on 400 and 100 MHz respectively, using a Bruker or JEOL spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiple. High-Resolution Mass Spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATIR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. Single-crystal diffraction analysis data were collected at 23 °C (296 k) with a Bruker Kappa Apex III CCD single-crystal diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo K α radiation and Cu K α radiation.

2.7.2 Experimental Procedure:

A) General experimental procedure for mono- and di-alkylation of 2/3-hydroxybenzylalcohol:⁸⁴

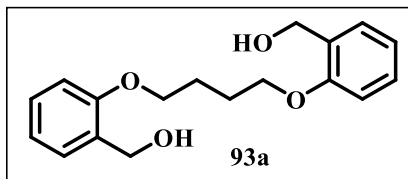
In a 100 mL round bottom flask were added 2/3-hydroxybenzylalcohol (2 equiv.), dibromoalkanes (1 equiv.) and potassium carbonate (K_2CO_3) (2 equiv.) in acetonitrile. The resulting reaction mixture was refluxed for 12-16 hrs. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the mixture of products (mono- and dialkylated) was extracted in water and dichloromethane. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography [EtOAc: *n*-hexane = 15:85 (for the mono-alkylated product) and 40:60 (for the di-alkylated product)].

B) General experimental procedure for macrocyclization of various diphenyldimethanol derivatives and 3/4-aminoacetophenone (Intermolecular pathway):^{51,85}

In a 50 mL Carousel tube were added Ru-MACHO (0.0042 mmol, 2.5 mg, 5 mol%), dimethanol compound (0.166 mmol, 2 equiv.), aminoacetophenone (0.083 mmol, 1 equiv.) and KOH (0.166 mmol, 9.5 mg, 2 equiv.) in toluene (24 mL). The tube was purged with N_2 and fitted with a cap. The reaction mixture was heated at 180 °C in a preheated oil bath or Carousel hot plate for 48 hrs. After completion of the reaction, the reaction mixture was diluted with dichloromethane and methanol. Further, a volatile component was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane = 15:85).

2.7.3 Spectroscopic data of products:

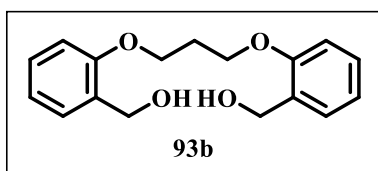
((butane-1,4-diylbis(oxy))bis(2,1-phenylene))dimethanol (93a): Prepared according to



general procedure **2.7.2.A**, using 2-hydroxybenzylalcohol (500 mg, 4.03 mmol, 2 equiv.) 1,4-dibromobutane (431.82 mg, 2.02 mmol, 1 equiv.) to afford desired product ((butane-1,4-diylbis(oxy))bis(2,1-phenylene))dimethanol **93a** (913

mg, 75 % yield) as a white crystalline solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.29 – 7.22 (dt, 4H), 6.93 (td, *J* = 7.5, 0.8 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 4.65 (s, 4H), 4.08 (t, 4H), 2.39 (s, 2H), 2.01 (m, *J* = 5.2 Hz, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 156.5, 128.9, 128.8, 128.7, 120.6, 110.9, 67.1, 61.8, 26.0. **FTIR** (neat): 3337, 2925, 1600, 1235 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₁₈H₂₂NaO₄ [M+Na]⁺: 325.1415, found: 325.1408.

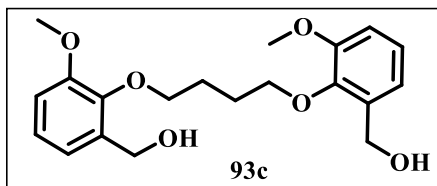
((propane-1,3-diylbis(oxy))bis(2,1-phenylene))dimethanol (93b): Prepared according to



general procedure **2.7.2.A**, using 2-hydroxybenzylalcohol (745 mg, 6.0 mmol, 2 equiv.) and 1,3-dibromopropane (605 mg, 3 mmol, 1 equiv.) to afford desired product ((propane-1,3-diylbis(oxy))bis(2,1-phenylene))dimethanol **93b** (1.26 gms,

73 % yield) as a white amorphous solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.25 (dt, *J* = 9.6, 8.2, 1.6 Hz, 4H), 6.93 (td, *J* = 7.5, 0.8 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 4.64 (s, 4H), 4.19 (t, *J* = 5.9 Hz, 4H), 2.70 (s, 2H), 2.30 (m, *J* = 5.9 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 156.5, 129.3, 129.0, 128.9, 121.0, 111.3, 65.0, 61.6, 29.3. **FTIR** (neat): 3338, 2930, 1600, 1236 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₁₇H₂₀NaO₄ [M+Na]⁺: 311.1259, found: 311.1249.

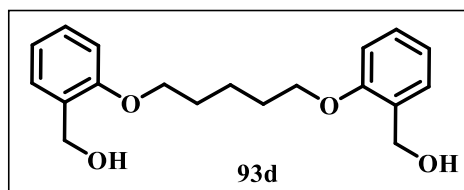
((butane-1,4-diylbis(oxy))bis(3-methoxy-2,1-phenylene))dimethanol (93c): Prepared



according to general procedure **2.7.2.A**, using 3-methoxy-2-hydroxybenzylalcohol (309 mg, 2 mmol 2 equiv.) and 1,4-dibromobutane (216 mg, 1 mmol, 1 equiv.) to afford desired product ((butane-1,4-diylbis(oxy))bis(3-

methoxy-2,1-phenylene))dimethanol **93c** (493 mg, 68 % yield) as a white crystalline solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.04 (t, *J* = 7.9 Hz, 2H), 6.93 (dd, *J* = 7.7, 1.5 Hz, 2H), 6.87 (dd, *J* = 8.1, 1.4 Hz, 2H), 4.70 (s, 4H), 4.12 (t, *J* = 5.6 Hz, 4H), 3.84 (s, 6H), 2.57 (s, 2H), 2.02 – 1.97 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 152.5, 146.0, 134.7, 124.0, 120.8, 112.2, 73.0, 61.5, 55.8, 27.0. **FTIR** (neat): 3391, 2934, 1585, 1268 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₂₀H₂₆NaO₆ [M+Na]⁺: 385.1626, found: 385.1627.

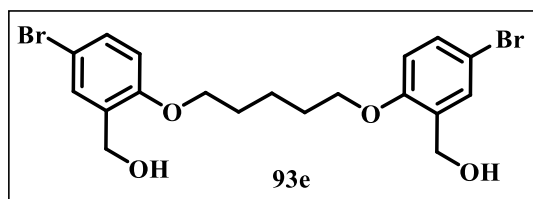
((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))dimethanol (93d): Prepared according to



general procedure **2.7.2.A**, using 2-hydroxybenzylalcohol (300 mg, 2.41 mmol, 2 equiv.) and 1,5-dibromopentane (275 mg, 1.2 mmol, 1 equiv.) to afford desired product ((pentane-1,5-

diylbis(oxy))bis(2,1-phenylene))dimethanol **93d** (495 mg, 1.5 mmol, 62 % yield) as a white crystalline solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.25 (dt, *J* = 20.0, 4.0 Hz, 4H), 6.92 (t, *J* = 7.4 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 4.67 (s, 4H), 4.02 (t, *J* = 6.1 Hz, 4H), 3.01 (s, 1H), 2.70 (s, 1H), 1.87 (dt, *J* = 12.3, 6.4 Hz, 4H), 1.68 (dq, *J* = 9.3, 5.3 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 156.7, 129.2, 128.8, 128.6, 120.6, 111.0, 67.6, 61.7, 29.0, 23.0. **FTIR** (neat): 3582, 2924, 1601, 1237 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₁₉H₂₄NaO₄ [M+Na]⁺: 339.1572, found: 339.1563.

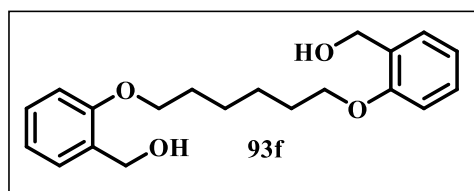
((pentane-1,5-diylbis(oxy))bis(5-bromo-2,1-phenylene))dimethanol (93e): Prepared



according to general procedure **2.7.2.A**, using 5-bromo-2-hydroxybenzylalcohol (300 mg, 1.48 mmol, 2 equiv.) and 1,5-dibromopentane (275 mg, 1.2 mmol, 1 equiv.) to afford the desired

product ((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))dimethanol **93e** (434 mg, 0.91 mmol, 62 % yield) as a white crystalline solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.42 (d, *J* = 2.4 Hz, 2H), 7.33 (dd, *J* = 8.7, 2.5 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 4.64 (s, 2H), 4.63 (s, 2H), 4.01 (t, *J* = 6.1 Hz, 4H), 1.92 – 1.83 (m, 4H), 1.70 – 1.62 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 155.7, 131.5, 131.4, 131.3, 113.0, 112.8, 68.0, 61.1, 29.0, 23.0. **FTIR** (neat): 3371, 2957, 1641, 806 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₁₉H₂₃Br₂O₄ [M+H]⁺: 494.9782, found: 494.9739.

((hexane-1,6-diylbis(oxy))bis(2,1-phenylene))dimethanol (93f): Prepared according to

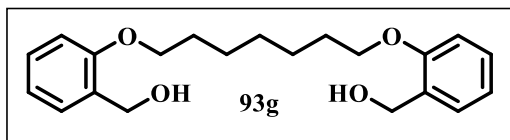


general procedure **2.7.2.A**, using 2-hydroxybenzylalcohol (300 mg, 2.40 mmol, 2 equiv.) and 1,6-dibromohexane (291.6 mg, 1.02 mmol, 1 equiv.) to afford desired product ((hexane-1,6-

diylbis(oxy))bis(2,1-phenylene))dimethanol **93f** (519 mg, 1.57 mmol, 65 % yield) as a white crystalline solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.30 – 7.21 (m, 4H), 6.92 (t, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 8.1 Hz, 2H), 4.66 (s, 4H), 4.02 (t, *J* = 6.3 Hz, 4H), 2.57 (s, 2H), 1.90 – 1.79 (m, 4H), 1.61 – 1.52 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 156.8, 129.2, 128.9, 128.6, 120.6,

111.1, 67.8, 62.1, 29.3, 26.0. **FTIR** (neat): 3359, 2926, 1601, 1237 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{20}\text{H}_{26}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 353.1728, found: 353.1722.

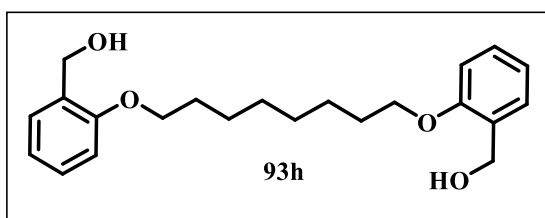
((heptane-1,7-diylbis(oxy))bis(2,1-phenylene))dimethanol (93g): Prepared according to



general procedure **2.7.2.A**, using 2-hydroxybenzylalcohol (300 mg, 2.4 mmol, 2 equiv.) and 1,7-dibromoheptane (309 mg, 1.2 mmol, 1

equiv.) to afford desired product ((heptane-1,7-diylbis(oxy))bis(2,1-phenylene))dimethanol **93g** (533 mg, 1.55 mmol, 64 % yield) as a white crystalline solid. **^1H NMR** (400 MHz, CDCl_3) δ 7.26 (dt, J = 13.5, 6.7, 2.6 Hz, 4H), 6.94 (td, J = 7.5, 0.9 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 4.70 (s, 4H), 4.03 (t, J = 6.4 Hz, 4H), 2.54 (s, 2H), 1.88 – 1.80 (m, 4H), 1.57 – 1.44 (m, 6H). **^{13}C NMR** (100 MHz, CDCl_3) δ 156.9, 129.3, 128.9, 128.7, 120.6, 111.1, 67.9, 62.2, 29.2, 29.1, 26.1. **FTIR** (neat): 3375, 2933, 1492, 1238 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{21}\text{H}_{28}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 367.1885, found: 367.1876.

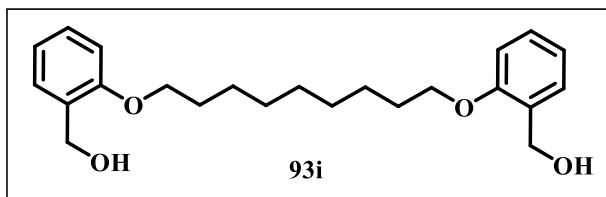
((octane-1,8-diylbis(oxy))bis(2,1-phenylene))dimethanol (93h): Prepared according to



general procedure **2.7.2.A**, using 2-hydroxybenzylalcohol (300 mg, 2.4 mmol, 2 equiv.) and 1,8-dibromooctane (325 mg, 1.2 mmol, 1 equiv.) to afford desired product

((octane-1,8-diylbis(oxy))bis(2,1-phenylene))dimethanol **93h** (580 mg, 1.62 mmol, 67 % yield) as a white crystalline solid. **^1H NMR** (400 MHz, CDCl_3) δ 7.25 (dt, J = 14.4, 7.2 Hz, 4H), 6.92 (t, J = 7.4 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 4.68 (s, 4H), 4.00 (t, J = 6.3 Hz, 4H), 2.64 (s, 2H), 1.86 – 1.76 (m, 4H), 1.48 (d, J = 6.7 Hz, 4H), 1.41 (d, J = 5.8 Hz, 4H). **^{13}C NMR** (100 MHz, CDCl_3) δ 156.8, 129.2, 128.8, 128.5, 120.5, 111.0, 67.9, 62.0, 29.3, 29.3, 26.1. **FTIR** (neat): 3360, 2929, 1601, 1237 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{22}\text{H}_{30}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 381.2041, found: 381.2032.

((nonane-1,9-diylbis(oxy))bis(2,1-phenylene))dimethanol (93i): Prepared according to

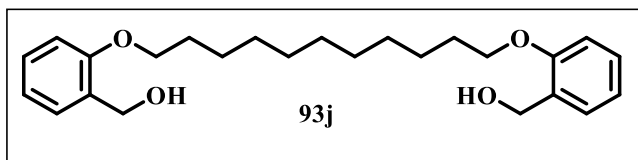


general procedure **2.7.2.A**, using 2-hydroxybenzylalcohol (300 mg, 2.4 mmol, 2 equiv.) 1,9-dibromononane (359 mg, 1.2 mmol, 1 equiv.) to afford the desired product

((nonane-1,9-diylbis(oxy))bis(2,1-phenylene))dimethanol **93i** (540 mg, 1.45 mmol, 60 % yield) as a white crystalline solid. **^1H NMR** (400 MHz, CDCl_3) δ 7.29 – 7.23 (m, 4H), 6.96 (t,

2H), 6.86 (d, 2H), 4.70 (s, 4H), 4.02 (t, $J = 6.5$ Hz, 4H), 2.18 (s, 2H), 1.86 – 1.78 (m, 4H), 1.47 (m, $J = 14.1, 6.3$ Hz, 4H), 1.38 (m, $J = 10.1, 3.8$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 157.11, 129.25, 129.03, 128.81, 120.64, 111.18, 68.05, 62.57, 29.58, 29.39, 26.29. FTIR (neat): 3361, 2928, 1601, 1238, 1114 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{23}\text{H}_{32}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 395.2098, found: 395.2194.

((undecane-1,11-diylbis(oxy))bis(2,1-phenylene))dimethanol (93j): Prepared according to

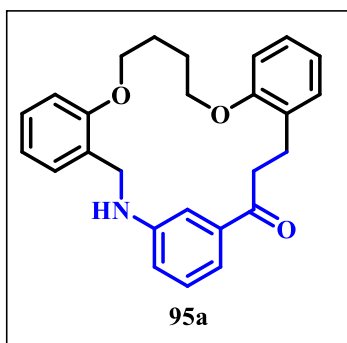


general procedure **2.7.2.A**, using 2-hydroxybenzylalcohol (200 mg, 1.61 mmol, 2 equiv.) 1,11-dibromoundecane (262 mg, 0.8 mmol, 1 equiv.) to afford

desired product ((undecane-1,11-diylbis(oxy))bis(2,1-phenylene))dimethanol **93j** (394 mg, 0.99 mmol, 61 % yield) as a white crystalline solid. ^1H NMR (400 MHz, CDCl_3) δ 7.25 (m, $J = 12.5, 3.7$ Hz, 4H), 6.93 (t, $J = 7.4$ Hz, 2H), 6.88 (d, $J = 8.5$ Hz, 2H), 4.69 (s, 4H), 4.02 (t, $J = 6.4$ Hz, 4H), 2.46 (s, 2H), 1.86 – 1.78 (m, 4H), 1.52 – 1.42 (m, 4H), 1.41 – 1.25 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3) δ 157.1, 129.2, 129.0, 128.8, 120.6, 111.2, 68.0, 62.6, 29.6, 29.6, 29.5, 29.4, 26.3. FTIR (neat): 3336, 2926, 1602, 1240 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{25}\text{H}_{36}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$: 423.2511, found: 423.2510.

Spectroscopic data of macrocycles:

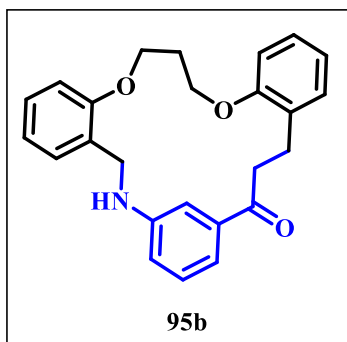
9,14-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclotetradecaphan-5-one (95a): Prepared



according to general procedure **2.7.2.B**, using dimethanol derivative **93a** (50 mg, 0.166 mmol, 2 equiv.) 3-aminoacetophenone (11.2 mg, 0.083 mmol, 1 equiv.) to afford desired macrocyclic product 9,14-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclotetradecaphan-5-one **95a** (22.2 mg, 0.055 mmol, 67 % yield) as a white semi-solid. ^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.22 (m, 3H), 7.16 (t, $J = 21.5, 15.5, 7.7$ Hz, 4H), 6.90 -

6.77 (m, 5H), 4.53 (s, $J = 5.1$ Hz, 1H), 4.35 (s, 2H), 4.07 (t, $J = 6.1$ Hz, 2H), 4.00 (t, $J = 6.7$ Hz, 2H), 3.12 – 3.06 (t, 2H), 2.98 – 2.91 (t, 2H), 2.06 – 1.90 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 156.9, 156.7, 148.4, 137.8, 130.8, 129.8, 129.6, 129.4, 128.8, 127.6, 126.9, 120.7, 117.0, 116.8, 114.8, 114.5, 111.5, 110.9, 67.4, 67.3, 44.9, 39.3, 28.0, 26.6, 25.8. FTIR (neat): 3403, 2923, 1674, 1595, 1236 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{26}\text{H}_{28}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 402.2069, found: 402.2068.

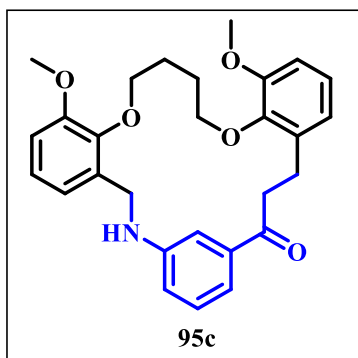
9,13-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclotridecaphan-5-one (95b): Prepared



according to general procedure **2.7.2.B**, using dimethanol derivative **93b** (50 mg, 0.166 mmol, 2 equiv.) and 3-aminoacetophenone (11.2 mg, 0.083 mmol, 1 equiv.) to afford desired macrocyclic product 9,13-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclotridecaphan-5-one **95b** (03 mg, 0.008 mmol, 13 % yield) as a white semi-solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.29 – 7.22 (m, 3H), 7.16 (t, *J* = 21.5, 15.5, 7.7 Hz, 4H), 6.90–

6.77 (m, 5H), 4.53 (s, *J* = 5.1 Hz, 1H), 4.35 (s, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 4.00 (t, *J* = 6.7 Hz, 2H), 3.12 – 3.06 (t, 2H), 2.98 – 2.91 (t, 2H), 2.06 – 1.90 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 201.4, 157.0, 156.2, 147.9, 131.4, 129.6, 129.4, 129.2, 128.6, 127.7, 121.2, 121.1, 119.2, 117.6, 114.6, 114.1, 112.1, 111.5, 64.3, 63.6, 43.6, 38.8, 29.8, 28.7. **FTIR** (neat): 3351, 2954, 1732, 1641 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₂₅H₂₆NO₃ [M+H]⁺: 388.1912, found: 388.1920.

1³,8³-dimethoxy-9,14-dioxa-3-aza-1,8(1,2),4(1,3) tribenzenacyclotetradecaphan-5-one (95c): Prepared according to general procedure **2.7.2.B**, using dimethanol derivative **93c** (59.6

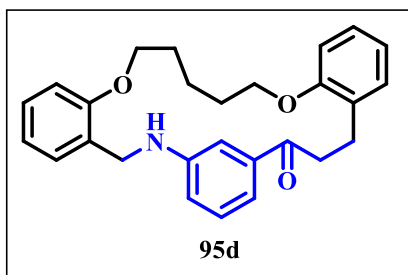


mg, 0.166 mmol, 2 equiv.), 3-aminoacetophenone (11.2 mg, 0.083 mmol, 1 equiv.) to afford desired macrocyclic product 1³,8³-dimethoxy-9,14-dioxa-3-aza-1,8(1,2),4(1,3)

tribenzenacyclotetradecaphan-5-one **95c** (12 mg, 0.026 mmol, 32 % yield) as a white semi-solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.40 – 7.32 (m, 2H), 7.29 – 7.23 (t, 1H), 7.03 (dd, *J* = 14.9, 6.9 Hz, 1H), 6.99 – 6.93 (m, 2H), 6.91 – 6.83 (m, 3H), 6.79 (dd, *J* =

8.1, 1.5 Hz, 1H), 4.42 (s, 2H), 4.18 (t, *J* = 5.8 Hz, 2H), 4.04 (t, *J* = 6.2 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.19 – 3.14 (t, 2H), 3.01 – 2.96 (t, 2H), 1.99 (m, *J* = 14.5, 10.6, 5.0 Hz, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 201.8, 152.7, 148.6, 146.7, 146.4, 137.9, 134.8, 132.1, 129.6, 124.0, 122.4, 121.5, 118.4, 117.4, 113.2, 112.2, 110.9, 73.2, 55.9, 44.5, 40.5, 29.8, 28.2, 27.8, 27.3. **FTIR** (neat): 3392, 2923, 1734, 1589, 1266 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₂₈H₃₂NO₅ [M+H]⁺: 462.2288, found: 462.2273.

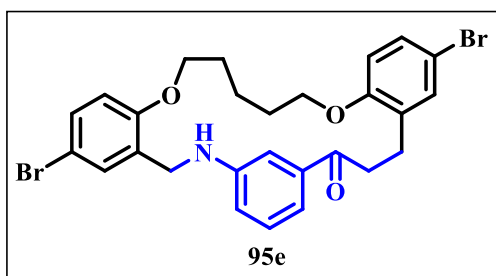
9,15-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclopentadecaphan-5-one (95d): Prepared



according to general procedure **2.7.2.B**, using dimethanol derivative **93d** (52.5 mg, 0.166 mmol, 2 equiv.), 3-aminoacetophenone (11.2 mg, 0.083 mmol, 1 equiv.) to afford desired macrocyclic product 9,15-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclopentadecaphan-5-one **95d** (15 mg, 0.036 mmol, 48% yield) as a white semi-solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.32 (td, *J* = 12.2, 4.5 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.23 (m, *J* = 7.4, 3.3 Hz, 2H), 7.17 (td, *J* = 7.9, 1.7 Hz, 1H), 6.95 – 6.83 (m, 5H), 4.40 (s, 2H), 4.10 (t, *J* = 5.2 Hz, 2H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.19 (t, *J* = 7.6 Hz, 2H), 3.02 (t, *J* = 7.6, 2H), 1.9-2.0 (m, 4H), 1.78-1.84 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 200.7, 157.1, 148.2, 137.9, 131.0, 129.6, 129.4, 129.0, 128.6, 127.5, 126.8, 120.6, 120.6, 117.8, 117.0, 114.5, 113.5, 111.3, 111.1, 68.4, 68.2, 43.8, 39.1, 29.8, 29.3, 27.5, 25.1. **FTIR** (neat): 3404, 2924, 1729, 1599, 1240 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₂₇H₃₀NO₃ [M+H]⁺: 416.2225, found: 416.2229.

1⁵,8⁵-dibromo-9,15-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclopentadecaphan-5-one

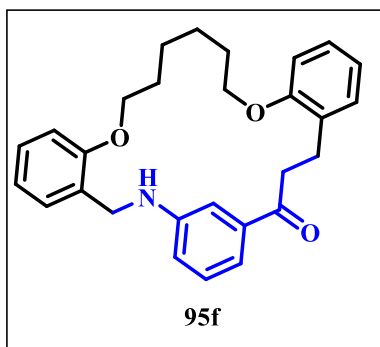
(95e): Prepared according to general procedure **2.7.2.B**, using dimethanol derivative **93e** (78.7



mg, 0.166 mmol, 2 equiv.), 3-aminoacetophenone (11.2 mg, 0.083 mmol, 1 equiv.) to afford desired macrocyclic product 1⁵,8⁵-dibromo-9,15-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclopentadecaphan-5-one **95e** (14.5 mg, 0.025 mmol, 31 % yield) as a white semi-solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.41

(dd, *J* = 6.3, 2.7 Hz, 2H), 7.33 (m, *J* = 5.5, 5.0, 2.3 Hz, 2H), 7.23 (dd, *J* = 8.3, 3.2 Hz, 2H), 6.87 (dd, *J* = 7.3, 1.8 Hz, 1H), 6.76 (dt, *J* = 6.1, 3.3 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 1H), 4.36 (s, 2H), 4.07 (t, *J* = 5.3 Hz, 2H), 3.97 (t, *J* = 5.8 Hz, 2H), 3.14 (t, *J* = 7.2 Hz, 2H), 2.97 (t, *J* = 7.2 Hz, 2H), 1.90 (m, *J* = 11.4, 5.9 Hz, 4H), 1.78 (m, *J* = 14.9, 7.6 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 199.9, 156.2, 156.0, 147.9, 138.0, 133.9, 132.4, 132.0, 131.3, 131.2, 130.2, 129.6, 129.4, 118.5, 117.4, 116.4, 113.0, 112.8, 112.5, 68.8, 68.5, 43.0, 38.6, 29.7, 29.2, 26.7, 25.0, 22.8. **FTIR** (neat): 3380, 2980, 1719, 1621, 809 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₂₇H₂₈Br₂NO₃ [M+H]⁺: 572.0436, found: 572.0438.

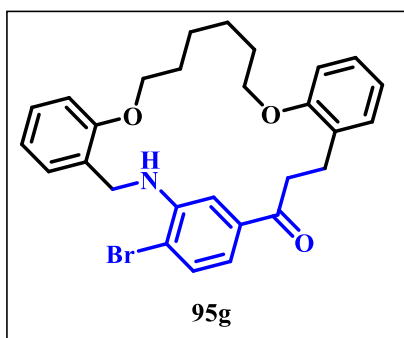
9,16-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclohexadecaphan-5-one (95f): Prepared



according to general procedure **2.7.2.B**, using dimethanol derivative **93f** (54.8 mg, 0.166 mmol, 2 equiv.), 3-aminoacetophenone (11.2 mg, 0.083 mmol, 1 equiv.) to afford desired macrocyclic product 9,16-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclohexadecaphan-5-one **95f** (19.9 mg, 0.046 mmol, 56% yield) as a white semi-solid. ^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.26 (m, 2H), 7.26 – 7.21 (m, 4H),

7.17 (td, $J = 7.9, 1.8$ Hz, 1H), 6.93 (td, $J = 7.4, 0.9$ Hz, 1H), 6.89 (s, 1H), 6.88 – 6.84 (m, 2H), 6.80 (d, $J = 8.0$ Hz, 1H), 4.33 (s, 2H), 3.99 (t, $J = 6.0$ Hz, 2H), 3.94 (t, $J = 6.1$ Hz, 2H), 3.24 (t, $J = 7.4$ Hz, 2H), 3.04 (t, $J = 7.4$ Hz, 2H), 1.70 (m, $J = 13.4, 6.8$ Hz, 4H), 1.47 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 200.5, 157.4, 156.9, 149.4, 148.9, 138.1, 130.6, 130.3, 129.3, 129.1, 127.5, 127.0, 120.5, 120.4, 116.9, 114.5, 113.5, 111.8, 110.9, 67.7, 67.0, 45.4, 39.0, 29.1, 26.4, 25.7. FTIR (neat): 3400, 3030, 1731, 1598, 1242 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{28}\text{H}_{32}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 430.2382, found: 430.2376.

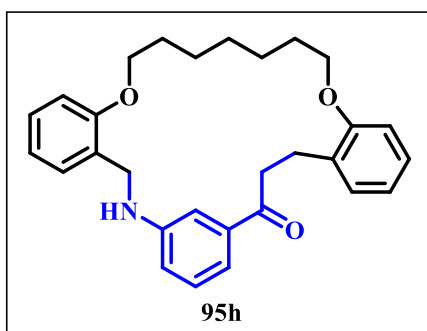
4⁶-bromo-9,16-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclohexadecaphan-5-one (95g):



Prepared according to general procedure **2.7.2.B**, using dimethanol derivative **93f** (59 mg, 0.178 mmol, 2 equiv.), 3-amino-4-bromoacetophenone (29 mg, 0.0133 mmol, 1 equiv.) to afford desired macrocyclic product 4⁶-bromo-9,16-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclohexadecaphan-5-one **95g** (15.7 mg, 0.027 mmol, 27% yield) as a yellowish semi-solid. ^1H NMR (400

MHz, CDCl_3) δ 7.29 (d, $J = 7.1$ Hz, 1H), 7.26 – 7.20 (m, 4H), 7.17 (td, $J = 7.9, 1.7$ Hz, 1H), 6.92 (t, $J = 7.4$ Hz, 1H), 6.90 – 6.83 (m, 3H), 6.80 (d, $J = 8.1$ Hz, 1H), 4.33 (s, 2H), 4.13 (s, 1H), 3.98 (t, $J = 6.0$ Hz, 2H), 3.93 (t, $J = 6.1$ Hz, 2H), 3.23 (t, $J = 7.4$ Hz, 2H), 3.03 (t, $J = 7.4$ Hz, 2H), 1.69 (m, $J = 13.6, 6.7$ Hz, 4H), 1.51 – 1.43 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 200.6, 157.5, 157.0, 148.9, 138.2, 130.7, 130.3, 130.1, 129.4, 129.1, 127.8, 127.1, 120.6, 120.4, 117.0, 113.6, 111.9, 110.9, 67.8, 67.1, 45.6, 39.1, 29.8, 29.2, 26.5, 25.8. FTIR (neat): 3391, 2934, 1722, 1604, 1190, 802 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{28}\text{H}_{31}\text{BrNO}_3$ $[\text{M}+\text{H}]^+$: 507.1409, found: 507.3947.

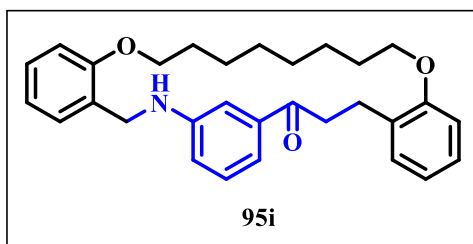
9,17-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacycloheptadecaphan-5-one (95h): Prepared



according to general procedure **2.7.2.B**, using dimethanol derivative **93g** (57 mg, 0.166 mmol, 2 equiv.), 3-aminoacetophenone (11.2 mg, 0.083 mmol, 1 equiv.) to afford desired macrocyclic product 9,17-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacycloheptadecaphan-5-one **95h** (17.7 mg, 0.04 mmol, 48% yield) as a white solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.30 (td, *J* = 11.0, 3.4 Hz, 2H),

7.27 – 7.22 (m, 3H), 7.19 – 7.13 (m, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.87 (t, *J* = 7.7 Hz, 3H), 6.81 (d, *J* = 8.1 Hz, 1H), 4.31 (s, 2H), 4.02 (t, *J* = 5.5 Hz, 2H), 3.98 (t, *J* = 5.7 Hz, 2H), 3.27 (t, *J* = 7.4 Hz, 2H), 3.04 (t, *J* = 7.3 Hz, 2H), 1.81 – 1.71 (m, 5H), 1.49 (m, *J* = 14.8, 6.8 Hz, 5H). **¹³C NMR** (100 MHz, CDCl₃) δ 200.5, 157.4, 157.1, 138.4, 131.0, 130.3, 129.9, 129.4, 129.1, 127.5, 126.7, 120.5, 120.3, 116.9, 116.8, 113.2, 111.4, 110.7, 67.9, 67.3, 45.0, 38.9, 29.6, 29.5, 27.3, 27.2, 26.1. **FTIR** (neat): 3407, 2925, 1724, 1600, 1243 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₂₉H₃₄NO₃[M+H]⁺: 444.2538, found: 444.2526. **Crystal data (CCDC= 2093560):** The crystals of compound **95h** were grown using dichloromethane and hexane as a solvent by slow evaporation. C₂₉H₃₃NO₃, *M* = 443.56, Triclinic, space group P -1 with *a* = 8.6468(6) Å, *b* = 11.5771(9) Å, *c* = 12.254(1) Å, α = 97.352(4)°, β = 106.866(4)°, γ = 92.780(4)°, *V* = 1159.52(16) Å³, *T* = 296(2) K, *R*₁ = 0.0644, *wR*₂ = 0.1645 for observed data, *z* = 2, *D*_{calcd} = 1.270 g cm⁻³, *F*(000) = 476.0, absorption coefficient = 0.641 mm⁻¹, λ = 1.54178 Å, 3121 reflections collected on a Bruker APEX-III CCD single-crystal diffractometer, and 3942 observed reflections (*I* ≥ 2σ(*I*)) with *S* = 1.065.

9,18-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclooctadecaphan-5-one (95i): Prepared

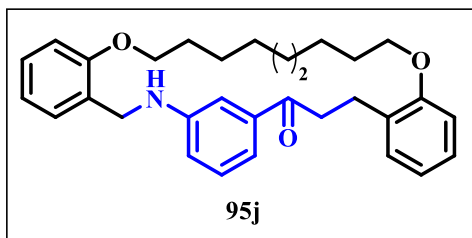


according to general procedure **2.7.2.B**, using dimethanol derivative **93h** (59.4 mg, 0.166 mmol, 2 equiv.) and 3-aminoacetophenone (11.2 mg, 0.083 mmol, 1 equiv.) to afford desired macrocyclic product 9,18-dioxa-3-aza-1,8(1,2),4(1,3)-

tribenzenacyclooctadecaphan-5-one **95i** (17.25 mg, 0.037 mmol, 45% yield) as a white semi-solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.32 – 7.26 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.15 (m, 2H), 6.91 (dd, *J* = 15.2, 5.1 Hz, 2H), 6.88 – 6.83 (m, 2H), 6.81 (d, *J* = 8.2 Hz, 1H), 4.29 (s, 2H), 4.00 – 3.96 (m, 2H), 3.94 (t, *J* = 5.4 Hz, 2H), 3.27 (t, *J* = 7.6 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 1.68 (m, *J* = 13.7, 11.5, 5.8 Hz, 5H), 1.48 – 1.32 (m, 7H). **¹³C NMR** (100 MHz, CDCl₃)

δ 200.3, 157.6, 157.2, 138.2, 130.6, 130.3, 130.0, 129.2, 127.5, 126.9, 120.5, 120.3, 117.7, 117.9, 114.5, 111.9, 111.6, 110.8, 68.1, 67.3, 45.2, 39.1, 29.6, 29.5, 29.5, 26.7, 25.9. **FTIR** (neat): 3406, 2924, 1680, 1599, 1240 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{30}\text{H}_{36}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 458.2695, found: 458.2701.

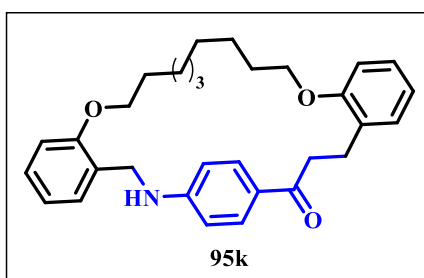
9,19-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclononadecaphan-5-one (95j): Prepared



according to general procedure **2.7.2.B**, using dimethanol derivative **93i** (61.7 mg, 0.166 mmol, 2 equiv.), 3-aminoacetophenone (11.2 mg, 0.083 mmol, 1 equiv.) to afford desired macrocyclic product 9,19-dioxa-3-aza-1,8(1,2),4(1,3)-

tribenzenacyclononadecaphan-5-one **95j** (13.3 mg, 0.29 mmol, 35 % yield) as a white semi-solid. **^1H NMR** (400 MHz, CDCl_3) δ 7.34 – 7.26 (m, 3H), 7.26 – 7.16 (m, 4H), 6.96 – 6.82 (m, 5H), 4.29 (s, 2H), 3.99 (t, $J = 5.7$ Hz, 2H), 3.95 (t, $J = 5.6$ Hz, 2H), 3.28 – 3.22 (m, 2H), 3.07 – 3.00 (m, 2H), 1.73 – 1.63 (m, 4H), 1.42 – 1.31 (m, 4H), 1.18 (dt, $J = 9.0, 7.1$ Hz, 4H), 1.04 – 0.95 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 200.0, 157.2, 156.8, 148.8, 137.7, 130.3, 130.1, 130.0, 129.2, 128.9, 127.2, 126.8, 120.3, 120.2, 117.1, 116.8, 114.3, 111.8, 111.6, 111.0, 67.6, 67.2, 44.7, 39.2, 29.4, 29.3, 29.2, 26.5, 26.2, 25.8, 25.6. **FTIR** (neat): 3393, 2924, 1735, 1600, 1242 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{31}\text{H}_{37}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 472.2851, found: 472.2851.

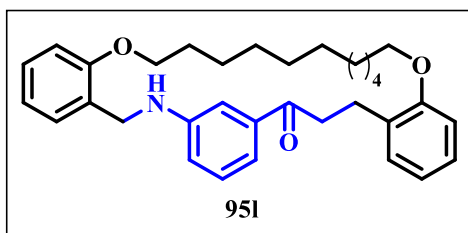
9,19-dioxa-3-aza-1,8(1,2),4(1,4)-tribenzenacyclononadecaphan-5-one (95k): Prepared



according to general procedure **2.7.2.B**, using dimethanol derivative **93i** (33.3 mg, 0.083 mmol, 2 equiv.), 4-aminoacetophenone (5.7 mg, 0.042 mmol, 1 equiv.) to afford desired macrocyclic product 9,19-dioxa-3-aza-1,8(1,2),4(1,4)-tribenzenacyclononadecaphan-5-one **95k** (10 mg, 0.021 mmol, 50% yield) as a white semi-solid.

^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 7.5$ Hz, 2H), 7.25 – 7.21 (m, 1H), 7.21 – 7.17 (m, 1H), 6.96 – 6.91 (td, 1H), 6.89 (d, $J = 7.4$ Hz, 2H), 6.83 (d, $J = 8.1$ Hz, 1H), 6.62 (d, $J = 8.8$ Hz, 2H), 4.34 (s, 2H), 3.99 (m, $J = 9.7, 5.6$ Hz, 4H), 3.20 – 3.14 (t, 2H), 3.04 – 2.98 (t, 2H), 1.80 (m, $J = 15.6, 5.9$ Hz, 3H), 1.69 (m, $J = 10.9, 5.7$ Hz, 2H), 1.48 – 1.29 (m, 9H). **^{13}C NMR** (100 MHz, CDCl_3) δ 200.3, 157.5, 157.2, 149.1, 137.8, 130.3, 130.0, 129.2, 129.1, 127.5, 126.9, 120.6, 120.4, 117.8, 117.5, 111.9, 111.8, 111.1, 68.2, 67.8, 44.8, 39.5, 29.4, 29.3, 29.2, 29.1, 29.0, 26.8, 26.7, 26.5. **FTIR** (neat): 3359, 2925, 1730, 1596, 1243 cm^{-1} . **HRMS** (ESI-TOF) m/z calcd for $\text{C}_{31}\text{H}_{38}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 472.2851, found: 472.2850.

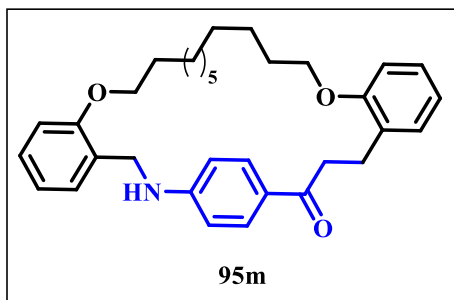
9,21-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclohenicosaphan-5-one (95l): Prepared



according to general procedure **2.7.2.B**, using dimethanol derivative **93j** (33.3 mg, 0.083 mmol, 2 equiv.), 3-aminoacetophenone (5.7 mg, 0.042 mmol, 1 equiv.) to afford desired macrocyclic product 9,21-dioxa-3-aza-1,8(1,2),4(1,3)-

tribenzenacyclohenicosaphan-5-one **95l** (7.3 mg, 0.015 mmol, 35% yield) as a white semi-solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.28 (dt, 1H), 7.17 (dt, *J* = 15.6, 7.5 Hz, 5H), 6.84 (m, *J* = 18.2, 15.7, 7.6 Hz, 6H), 4.25 (s, 2H), 3.96 (t, 2H), 3.92 (t, 2H), 3.23 (t, 2H), 3.19 (t, 2H), 1.68 (m, *J* = 10.9, 5.9 Hz, 5H), 1.44 – 1.30 (m, 6H), 1.22 – 1.14 (m, 7H). **¹³C NMR** (100 MHz, CDCl₃) δ 200.4, 157.5, 157.3, 149.1, 137.8, 130.4, 130.1, 129.2, 129.2, 127.6, 126.9, 120.6, 120.5, 117.9, 117.6, 111.9, 111.8, 111.1, 68.2, 67.9, 44.9, 39.5, 29.5, 29.4, 29.3, 29.2, 29.0, 26.9, 26.7, 26.5. **FTIR** (neat): 3395, 2923, 1727, 1600, 1242 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₃₃H₄₂NO₃ [M+H]⁺: 500.3164, found: 500.3174.

9,21-dioxa-3-aza-1,8(1,2),4(1,4)-tribenzenacyclohenicosaphan-5-one (95m): Prepared



according to general procedure **2.7.2.B**, using dimethanol derivative **93j** (33.3 mg, 0.083 mmol, 2 equiv.), 4-aminoacetophenone (05.7 mg, 0.042 mmol, 1 equiv.) to afford desired macrocyclic product 9,21-dioxa-3-aza-1,8(1,2),4(1,3)-tribenzenacyclohenicosaphan-5-one **95m** (15.2 mg,

0.032 mmol, 72% yield) as a white solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.6 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.25 – 7.16 (m, 2H), 6.97 – 6.81 (m, 4H), 6.61 (d, *J* = 8.8 Hz, 2H), 4.51 (s, 1H), 4.34 (s, 2H), 4.00 (dt, *J* = 8.6, 5.7 Hz, 4H), 3.23 – 3.15 (m, 2H), 3.08 – 2.98 (m, 2H), 1.86 – 1.69 (m, 4H), 1.47 (m, 4H), 1.36 – 1.23 (m, 6H), 1.17 (s, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 198.3, 157.4, 157.2, 152.4, 130.7, 130.6, 130.2, 129.5, 129.4, 127.5, 126.5, 126.1, 120.6, 120.4, 114.6, 111.6, 111.5, 110.7, 77.2, 67.8, 67.2, 44.1, 38.7, 29.7, 29.6, 29.4, 29.1, 29.0, 28.8, 27.2, 26.6, 26.6. **FTIR** (neat): 3360, 2929, 1719, 1602, 1243 cm⁻¹. **HRMS** (ESI-TOF) *m/z* calcd for C₃₃H₄₂NO₃[M+H]⁺: 499.3086, found: 499.3029.

2.8 Appendix I: Copies of ^1H and ^{13}C NMR spectra and crystal structure of representative compounds

Entry	Figure No.	Data	Page No.
93a	15 and 16	^1H and ^{13}C	68
93b	17 and 18	^1H and ^{13}C	69
93c	19 and 20	^1H and ^{13}C	70
93d	21 and 22	^1H and ^{13}C	71
95a	23 and 24	^1H and ^{13}C	72
95b	25 and 26	^1H and ^{13}C	73
95d	27 and 28	^1H and ^{13}C	74
95h	29 and 30	^1H and ^{13}C	75

2.8.1 Copies of NMR Spectrum:

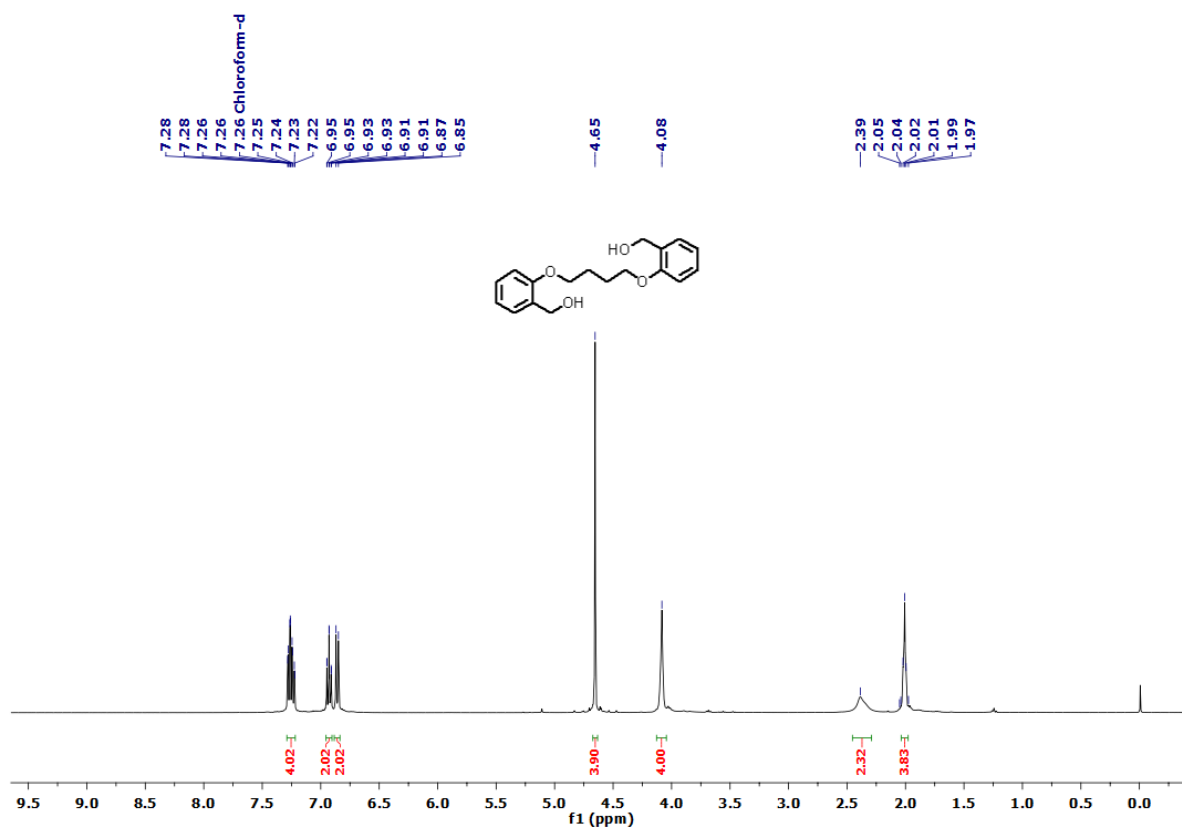


Figure 15. ¹H NMR spectra for compound **93a**, 400 MHz, CDCl₃

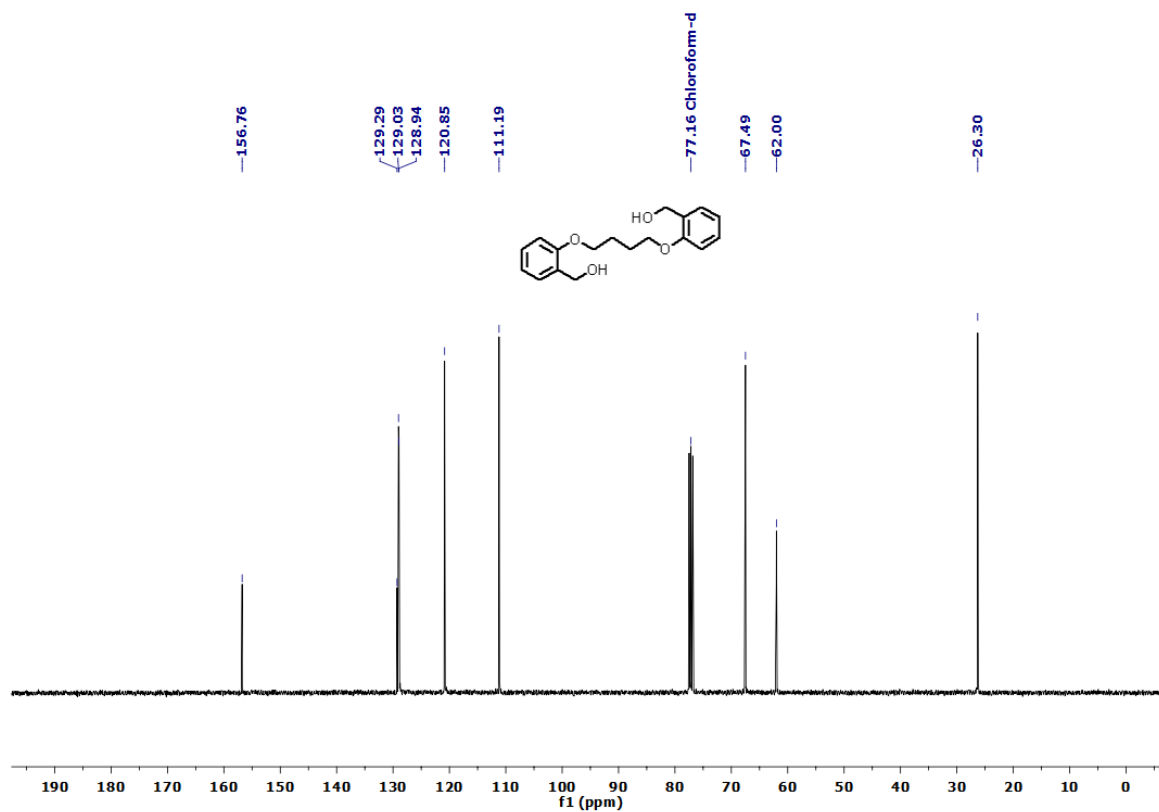


Figure 16. ¹³C NMR spectra for compound **93a**, 100 MHz, CDCl₃

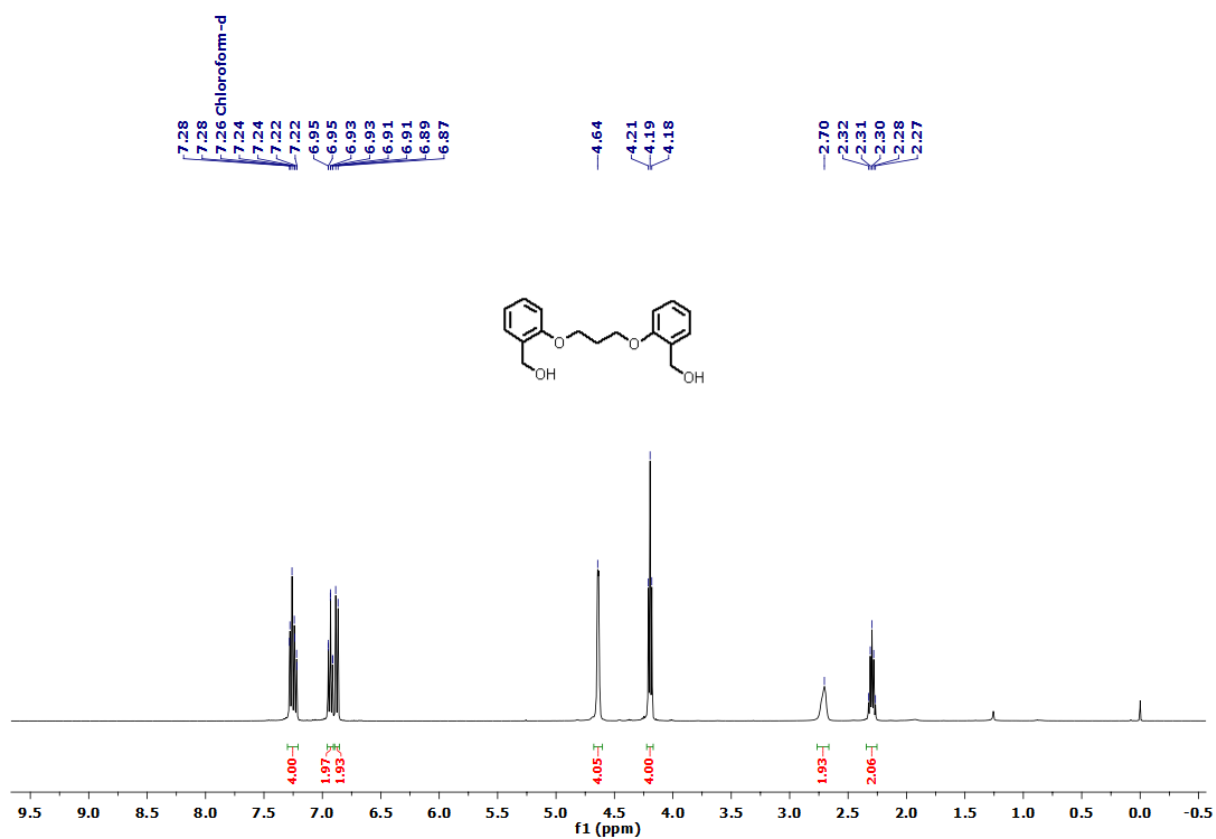


Figure 17. ¹H NMR spectra for compound **93b**, 400 MHz, CDCl₃

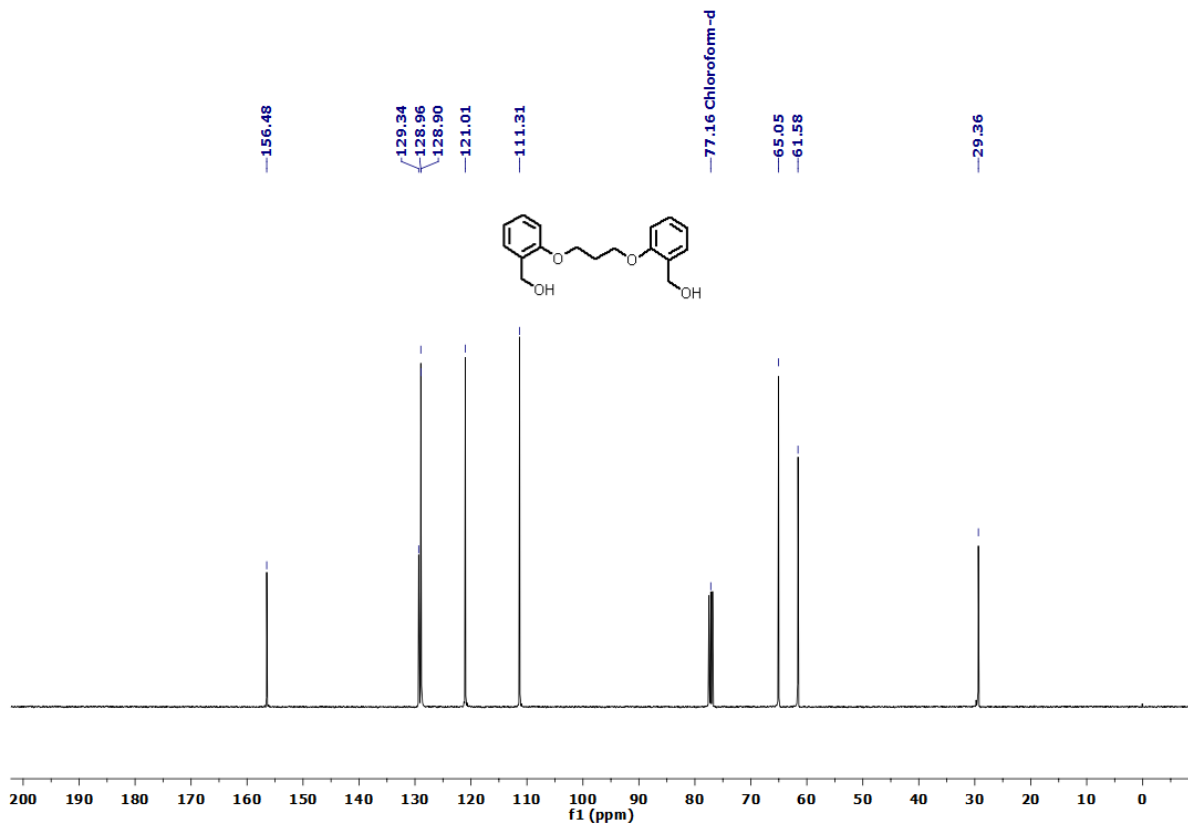


Figure 18. ¹³C NMR spectra for compound **93b**, 100 MHz, CDCl₃

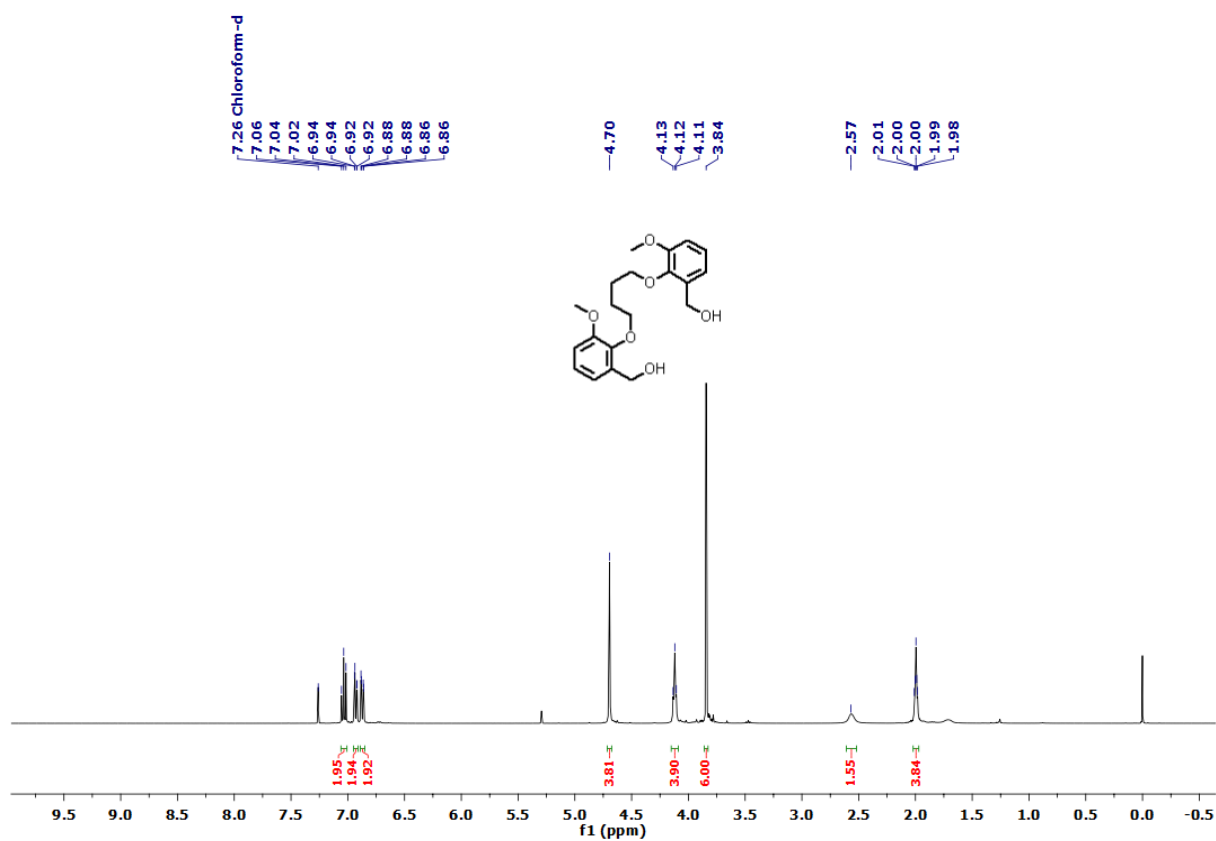


Figure 19. ¹H NMR spectra for compound **93c**, 400 MHz, CDCl₃

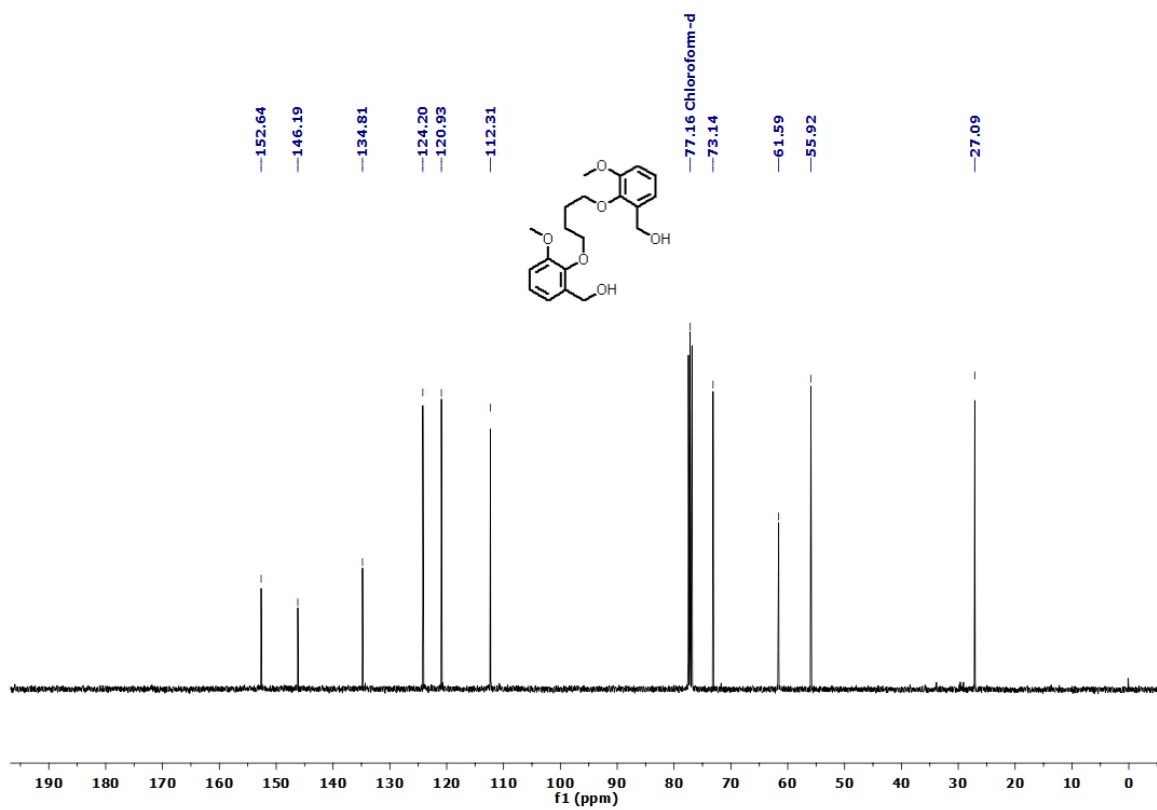


Figure 20. ¹³C NMR spectra for compound **93c**, 100 MHz, CDCl₃

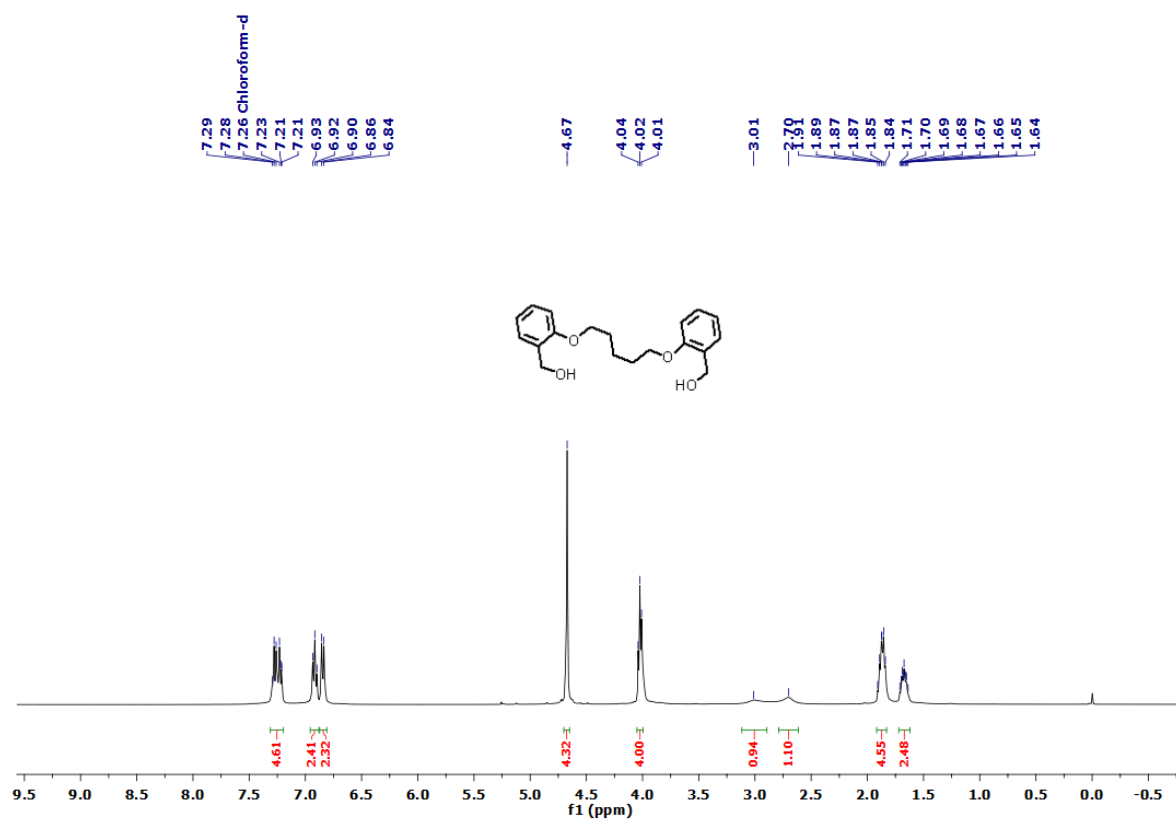


Figure 21. ¹H NMR spectra for compound **93d**, 400 MHz, CDCl₃

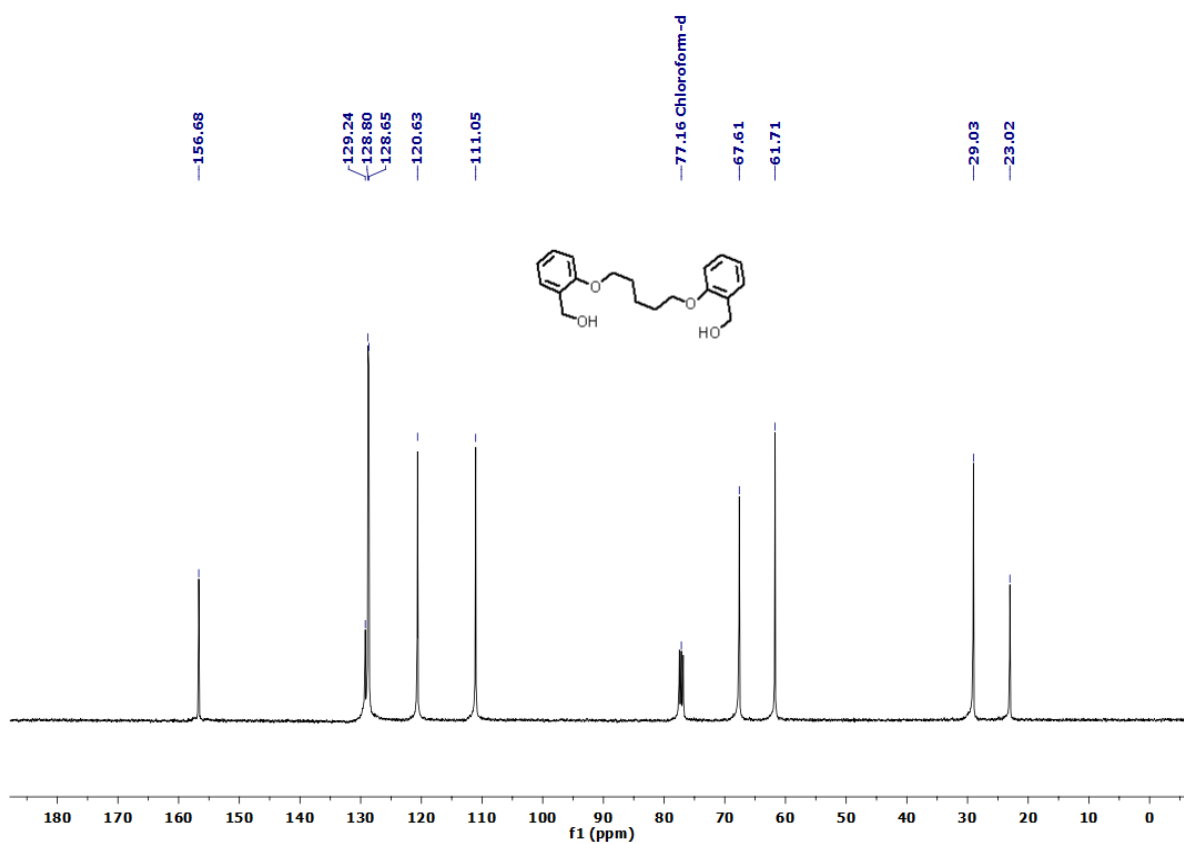


Figure 22. ¹³C NMR spectra for compound **93d**, 100 MHz, CDCl₃

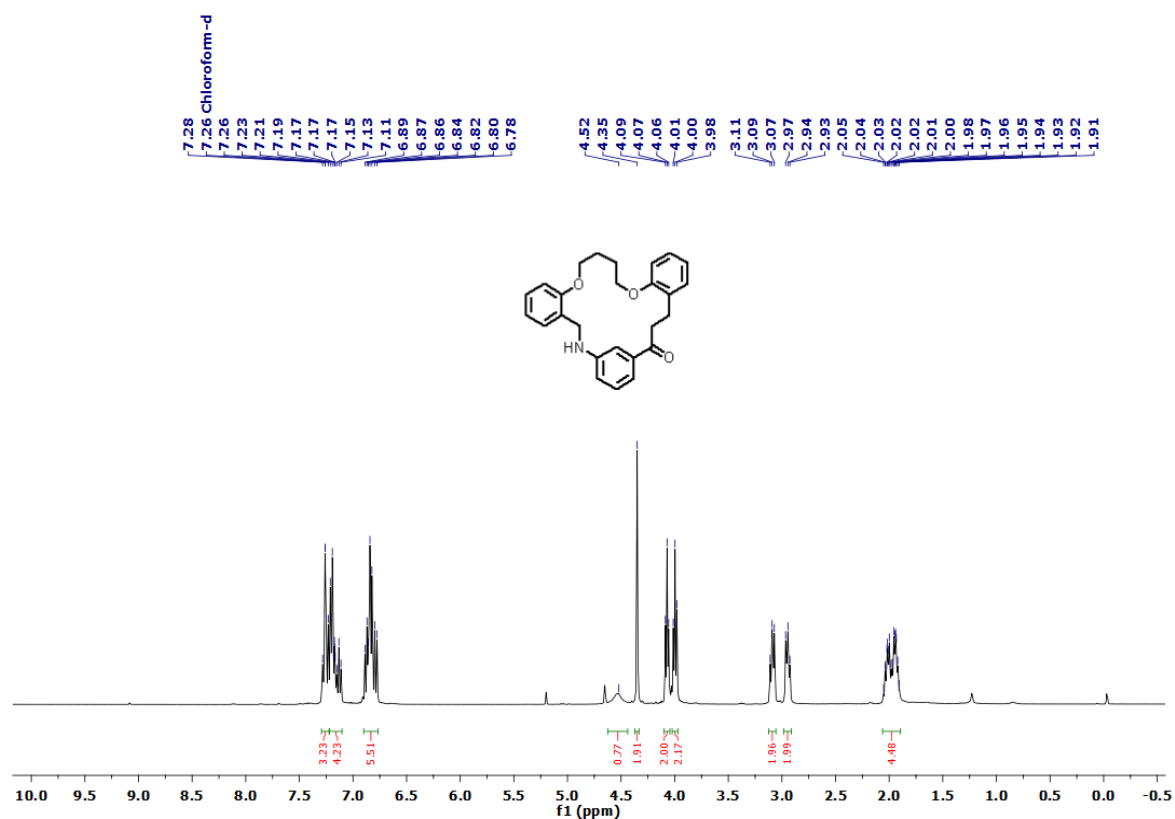


Figure 23. ¹H NMR spectra for compound **95a**, 400 MHz, CDCl₃

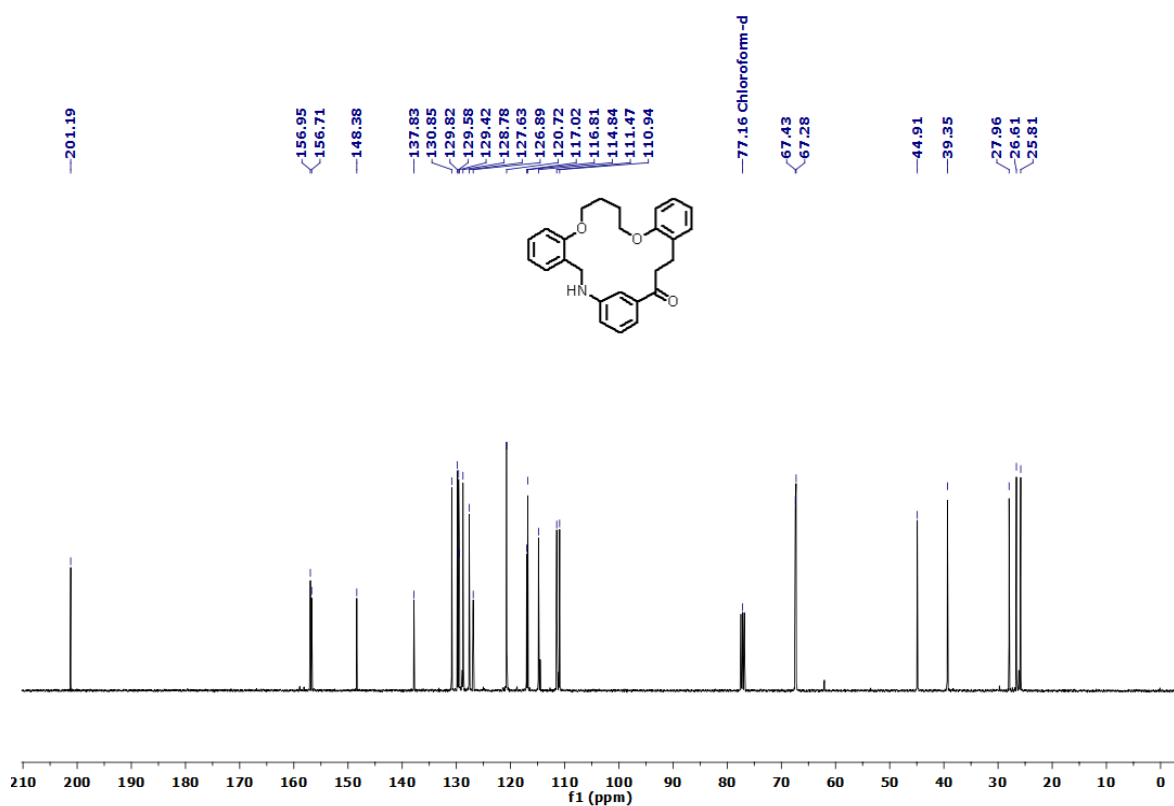


Figure 24. ¹³C NMR spectra for compound **95a**, 100 MHz, CDCl₃

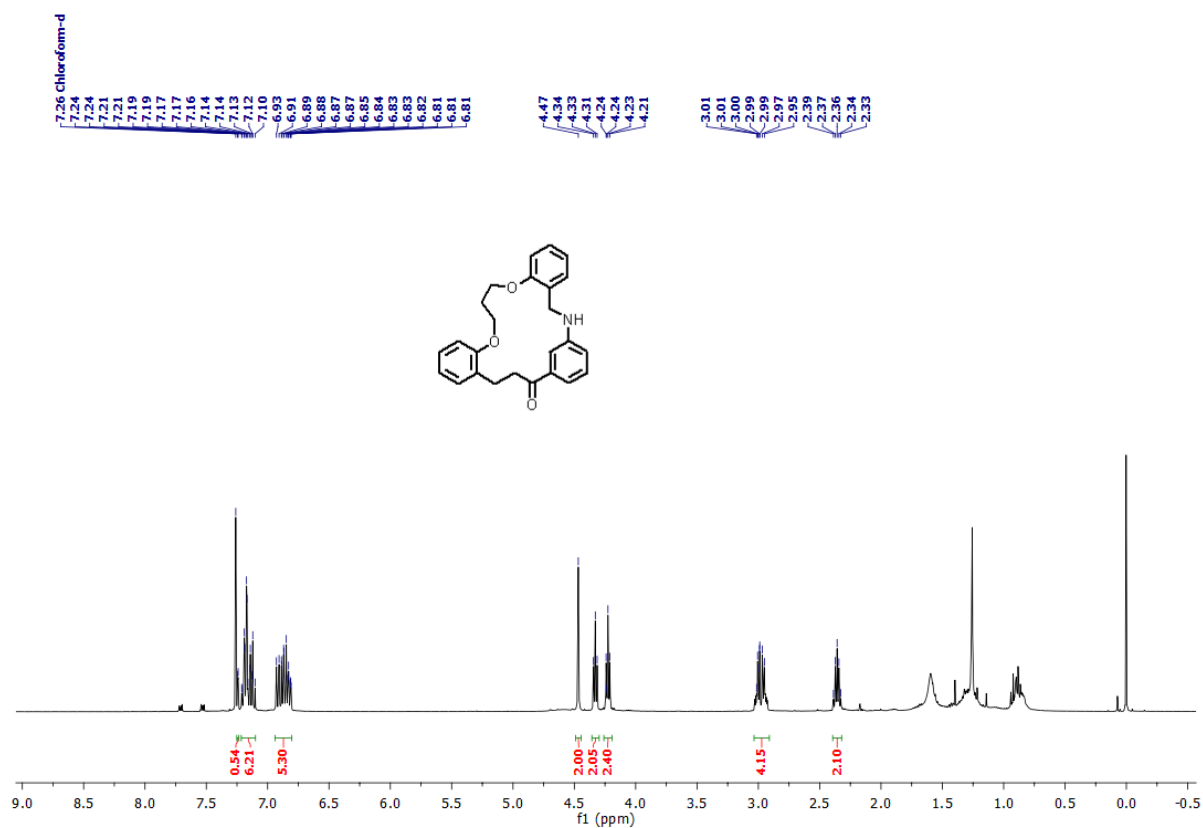


Figure 25. ¹H NMR spectra for compound **95b**, 400 MHz, CDCl₃

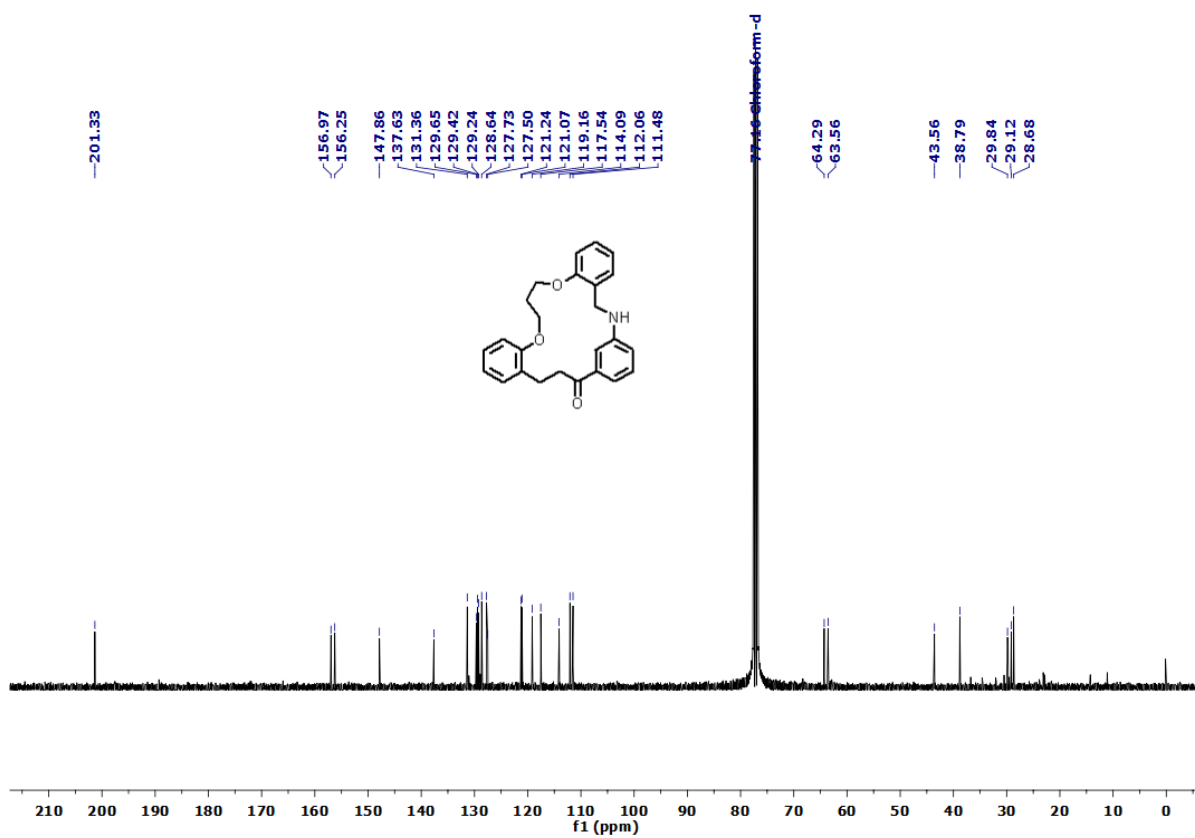


Figure 26. ¹³C NMR spectra for compound **95b**, 100 MHz, CDCl₃

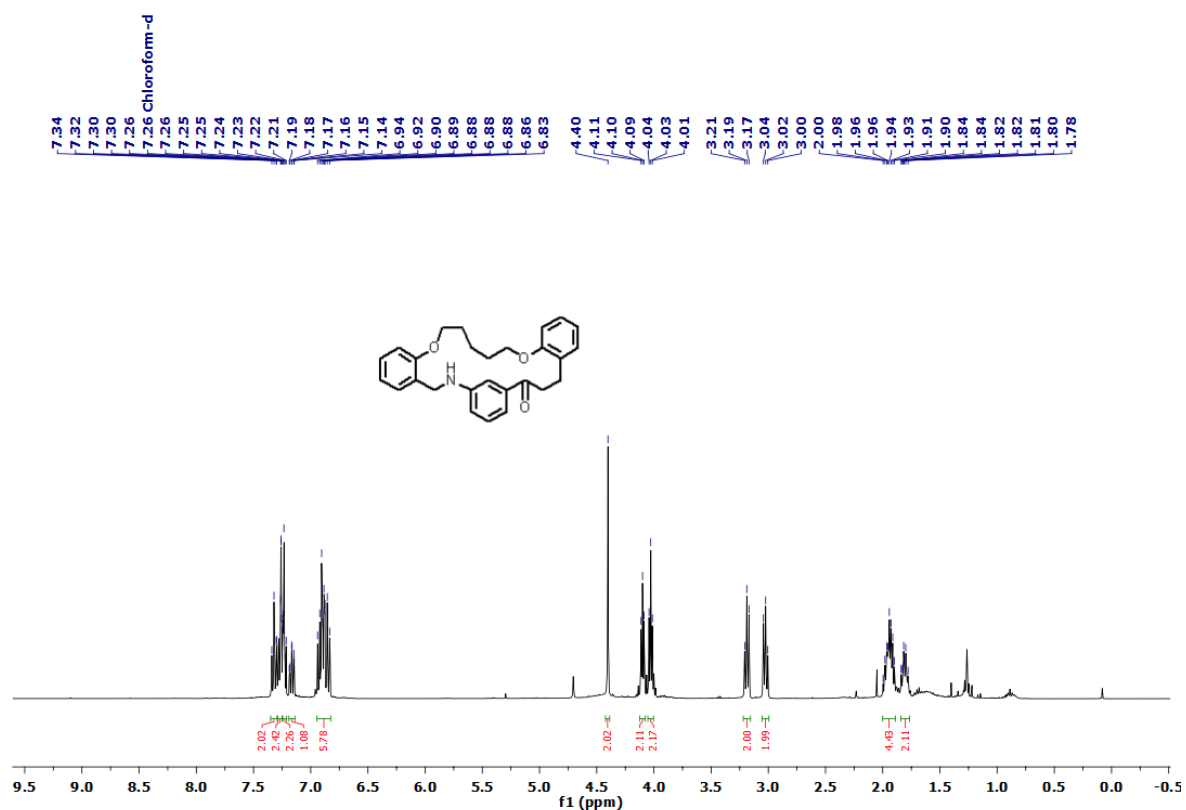


Figure 27. ¹H NMR spectra for compound **95d**, 400 MHz, CDCl₃

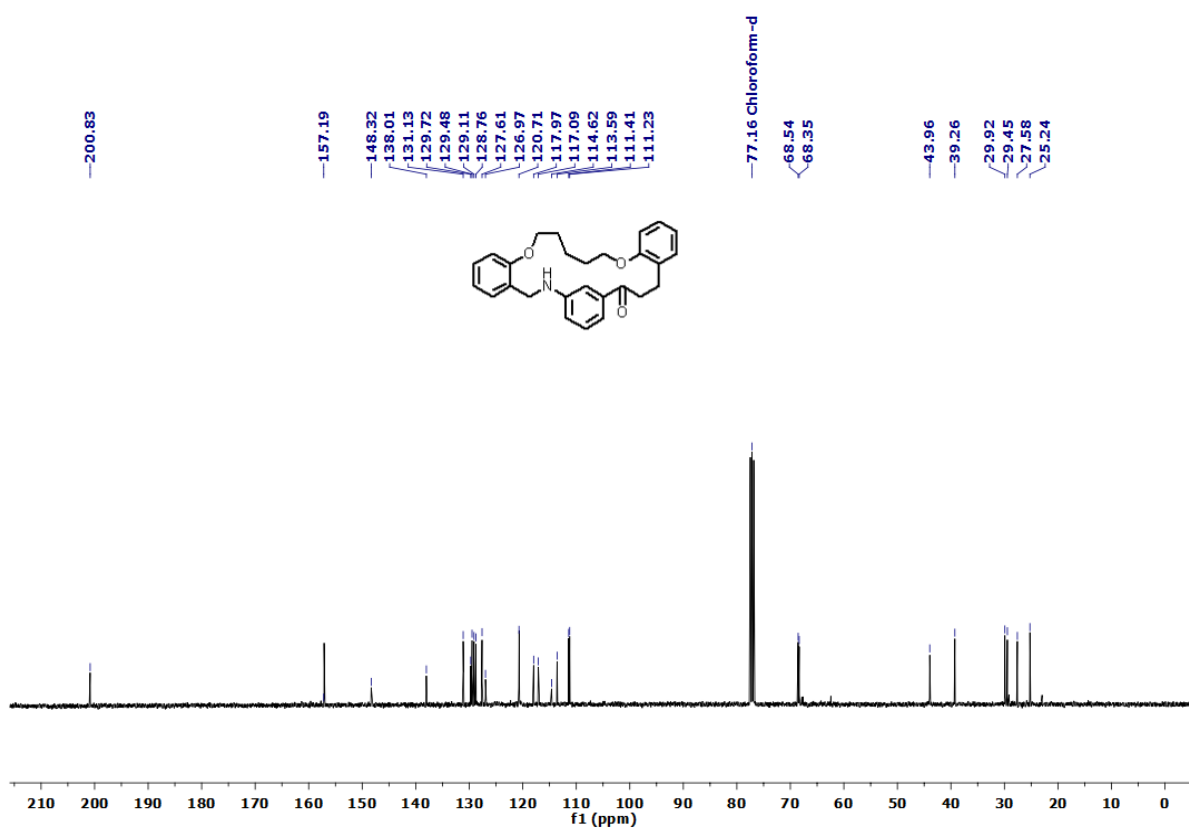


Figure 28. ¹³C NMR spectra for compound **95d**, 100 MHz, CDCl₃

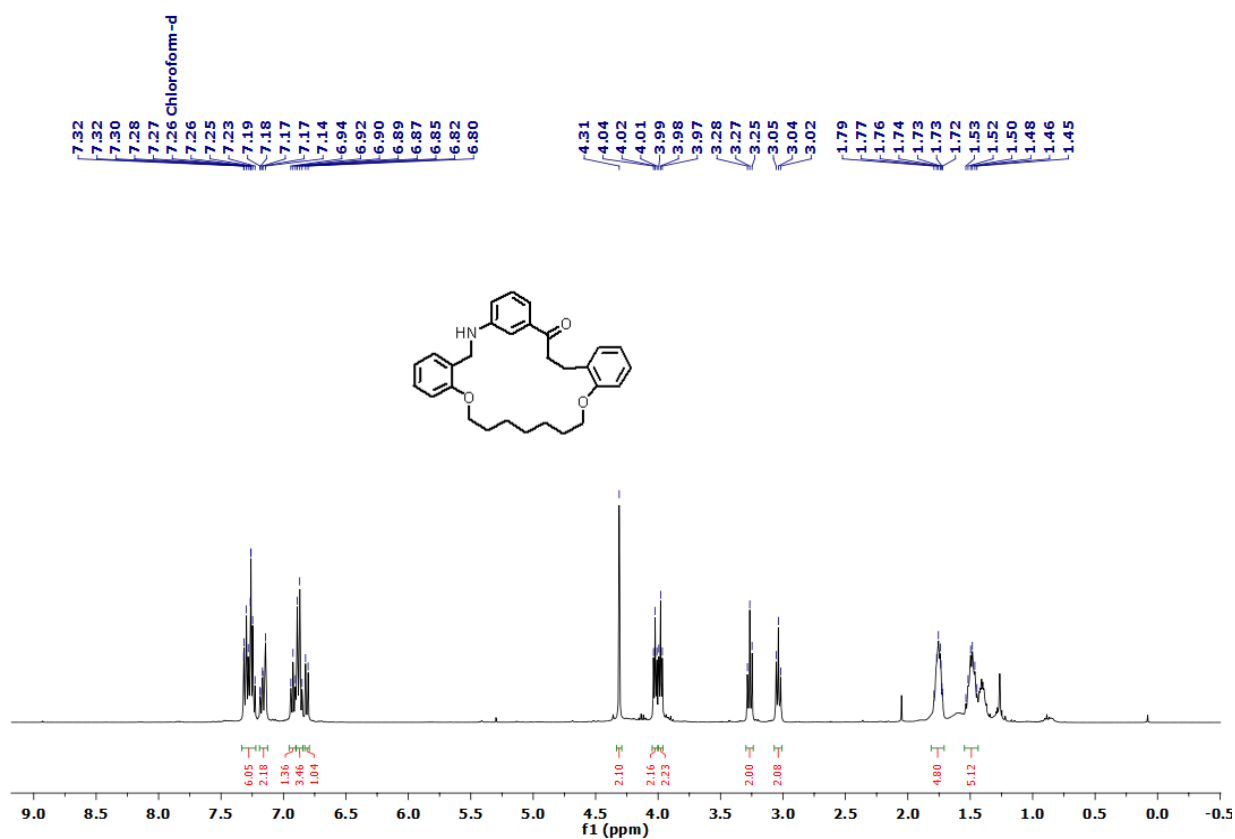


Figure 29. ¹H NMR spectra for compound **95h**, 400 MHz, CDCl₃

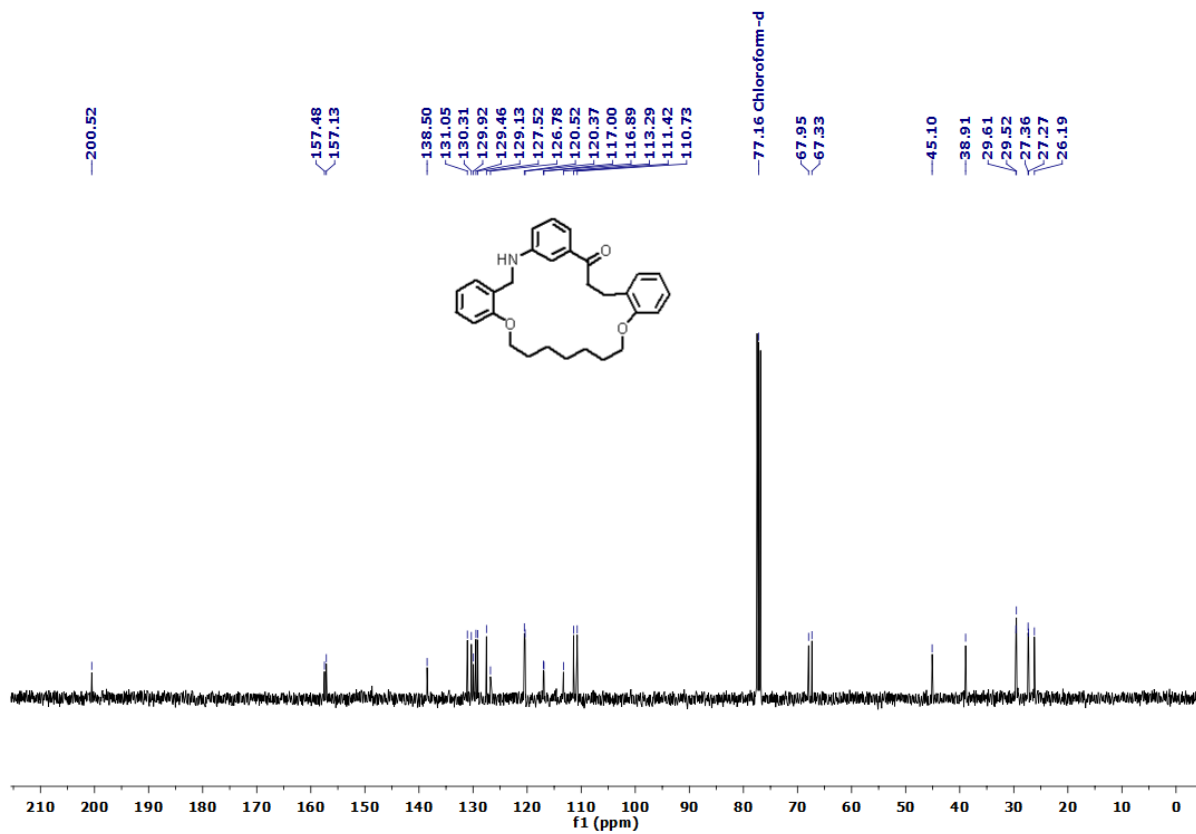
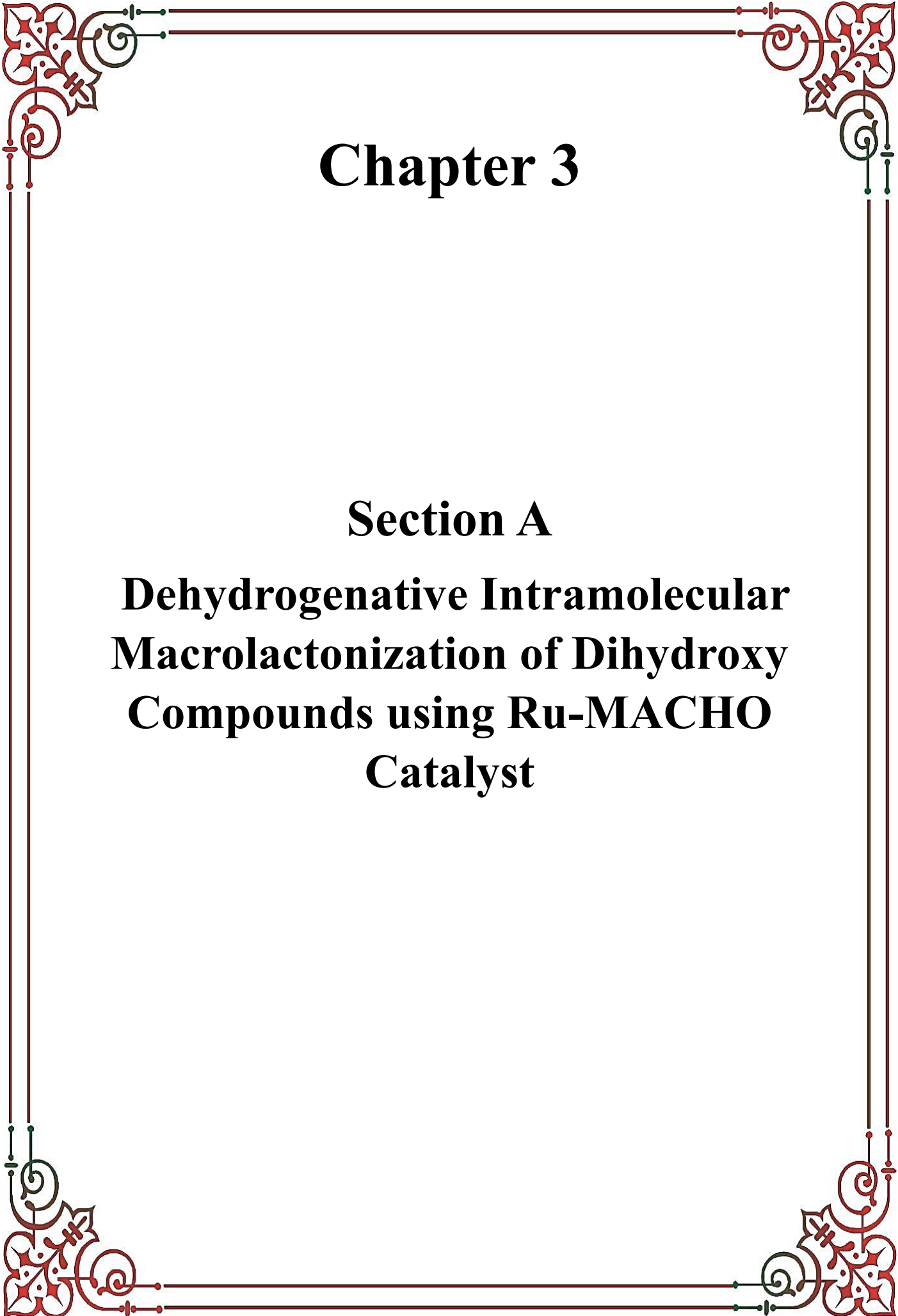


Figure 30. ¹³C NMR spectra for compound **95h**, 100 MHz, CDCl₃



Chapter 3

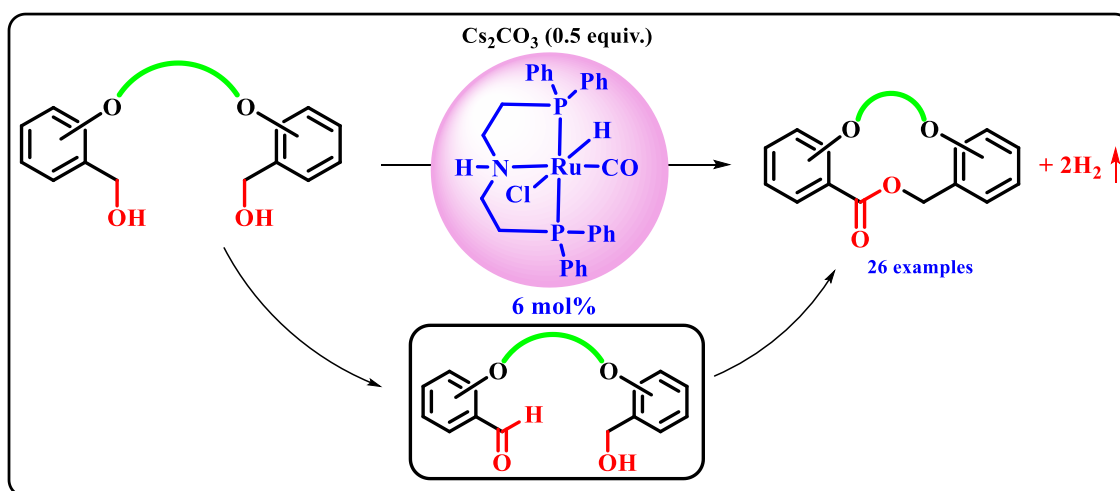
Section A

Dehydrogenative Intramolecular Macrolactonization of Dihydroxy Compounds using Ru-MACHO Catalyst

3A. Dehydrogenative Intramolecular Macrolactonization of Dihydroxy Compounds using Ru-MACHO Catalyst

3A.1 Abstract

In this chapter, an innovative method for synthesizing macrolactones using alcohols as starting materials has been discussed. It also demonstrates that macrolactonization can be achieved through intramolecular dehydrogenative coupling of primary alcohols, employing Ru-MACHO as a catalyst and Cs_2CO_3 as a base. Notably, it explores the substrate scope for macrolactonization across a range of sizes from 11 to 21-membered rings without using an external oxidant or additive. As a result, it eliminates the need for stoichiometric coupling reagents yielding hydrogen as the sole byproduct. Crucially, this study spotlights the macrocyclization without the utilization of halogenated or toxic chemicals, which are known for their higher E-factor.



3A.2 Introduction

Macrolactones (macroyclic compounds bearing an ester group as the core moiety) serve as fundamental structural elements in a myriad of biologically active natural compounds, pharmaceuticals, and fragrances (Figure 31). Particularly, medium- to large-sized macrocyclic lactones find extensive applications in perfumery,⁸⁶ cosmetics,⁸⁷ and pharmaceutical industries (Figure 31).⁸⁸ Consequently, numerous synthetic methodologies have been developed over recent decades, employing diverse strategies ranging from stoichiometric reagents to metal-catalysts. Selective macrolactonization poses a persistent challenge for organic chemists,

because of its entropically disfavoured nature (discussed in Figures 1 and 2, Chapter 1), often resulting in competitive intermolecular reactions leading to side product formation.²¹ The challenge of juxtaposing two reactive termini of a linear, elongated molecule to enable their proximity is inherently difficult. In macrolactonization, achieving a closer approach of two reaction centres necessitates a delicate balance between enthalpic and entropic factors.²²

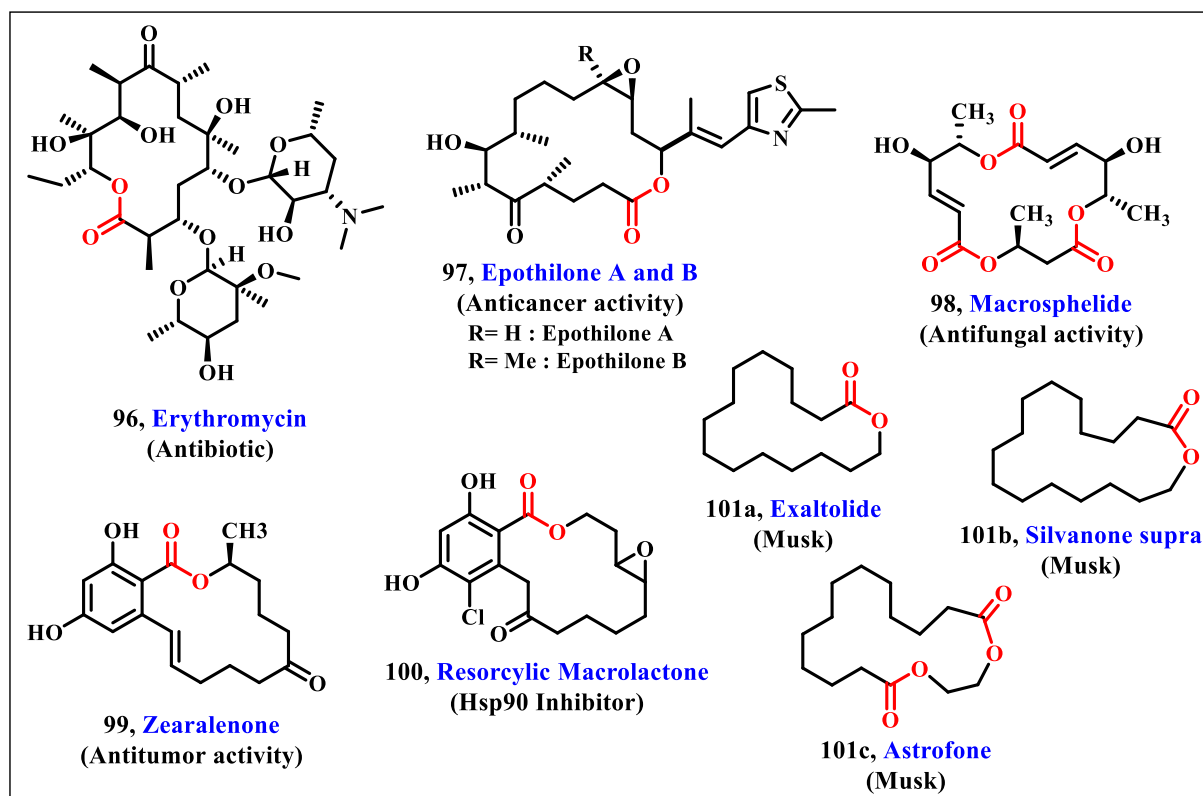
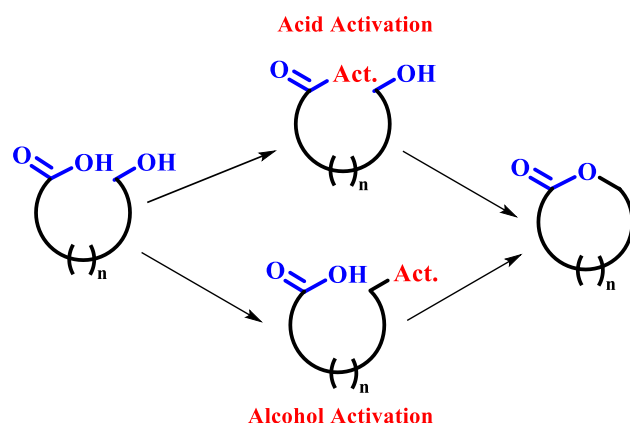


Figure 31: Macrolactone core in natural products, drugs and perfumery musks

3A.2.1 Approaches Based on Activation of Seco-Acids

Regardless of the various challenges associated with this process, tremendous efforts

Macrolactonization of Seco acids:



Acid Activation:

1. Yamaguchi (Mixed Anhydride)
2. Shiina (Mixed Anhydride)
3. Corey-Nicolaou (via thioester)
4. Stenglich-Boden-Keck (using DCC)
5. Mukaiyama (using pyridinium salt)
6. Pentafluorobenzoyl Chloride (Mixed Anhydride)
7. Yamide mediated macrolactonization

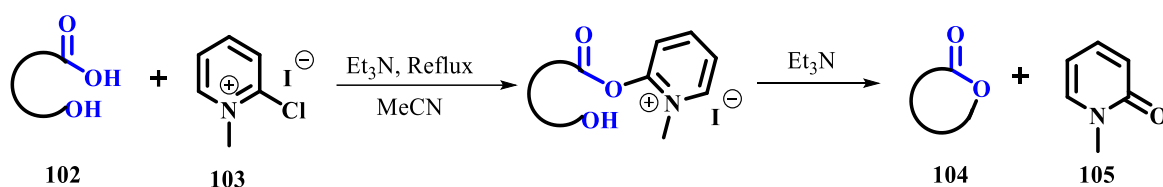
Alcohol Activation:

1. Mitsunobu Reaction (DEAD, PPh₃)

Figure 32: Macrolactonization of seco-acids

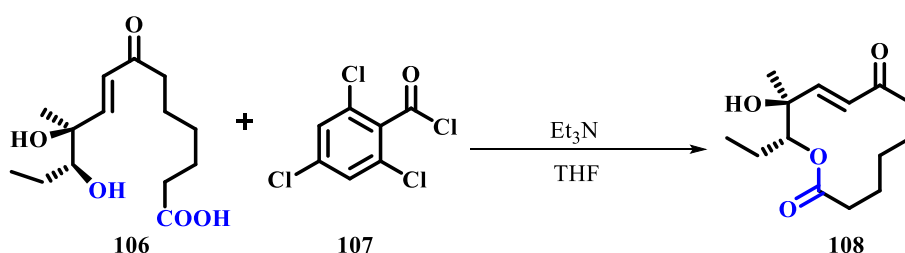
have been dedicated to macrolactonization. Conventional approaches typically involve the activation of either acids or alcohols for macrolactone synthesis. Notable methods include the Yamaguchi reaction,⁸⁹ Shiina macrolactonization,⁹⁰ Corey–Nicolaou strategy,⁹¹ Stenglich–Boden–Keck reaction,⁹² utilization of Mukaiyama salt,⁹³ pentafluorobenzoyl chloride,⁹⁴ and ynamide-mediated macrolactonization,⁹⁵ which predominantly focused on acid activation (Figure 32). A few illustrative instances of macrolactonization achieved through the activation of seco-acids are outlined below:

In 1976, Mukaiyama and his team developed a reagent, known as *N*-methyl-2-chloro pyridinium iodide **103** (Mukaiyama reagent) for the activation of carboxylic acid **102**. After activation of carboxylic acid, the intramolecular reaction with alcohol takes place in the presence of a triethyl amine (Et_3N) to furnish macrolactone product **104** (Scheme 28).



Scheme 28: Mukaiyama reagent for macrolactonization

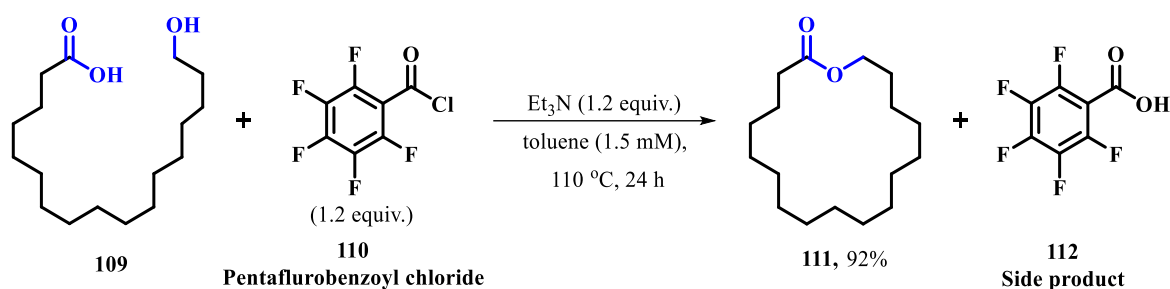
Later, in 1979, Yamaguchi's research group used 2,4,6-trichlorobenzoyl chloride **107** as a coupling reagent for the activation of carboxylic acid **106** to form a mixed anhydride and it further reacts with alcohol intramolecularly to furnish macrolactone **108** (Scheme 29). This process uses a stoichiometric amount of chlorinated coupling reagent and produces waste in stoichiometric amounts. Thus, it has a high E-factor. Despite associated limitations such as halogenated reagents and waste generation, the Yamaguchi reaction finds more frequent application in industries.



Scheme 29: Yamaguchi's method for macrolactonization

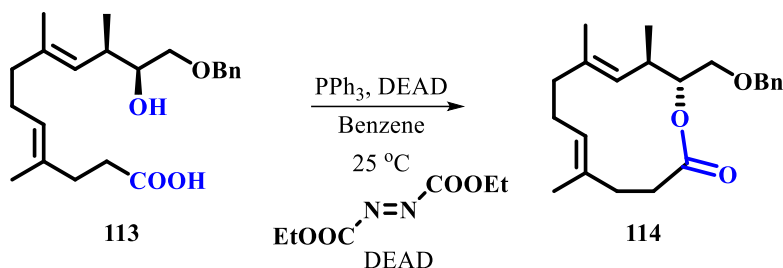
Furthermore, another reaction that includes the mixed anhydride concept is the reaction of seco-acids in the presence of pentafluorobenzoyl chloride **110**. In this reaction the pentafluorobenzoyl chloride forms mixed anhydride with carboxylic acid **109** and then reacts with alcohol intramolecularly to provide the macrolactone **111** with 92 % yield (Scheme 30).

Also, it produces pentafluorobenzoic acid **112** as a waste after the reaction.



Scheme 30: Pentafluorobenzoyl chloride for macrolactonization

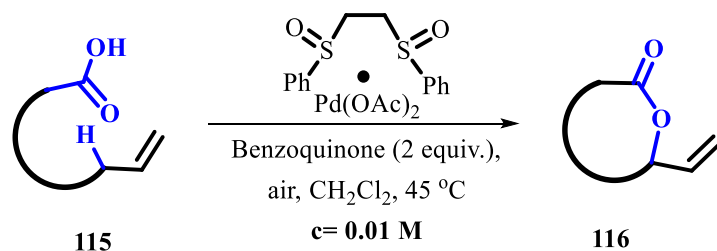
All aforementioned approaches mainly deal with the activation of carboxylic acids. Conversely, the Mitsunobu reaction proceeds via alcohol activation. In the Mitsunobu reaction, triphenylphosphine and the diethyl azodicarboxylate (DEAD) are used for the alcohol activation. After alcohol activation, the carboxylate attacks intramolecularly on carbon attached to the alcohol group to furnish macrolactone product **114** with inversion of the stereocentre (Scheme 31).⁹⁶



Scheme 31: Mitsunobu reaction for macrolactonization

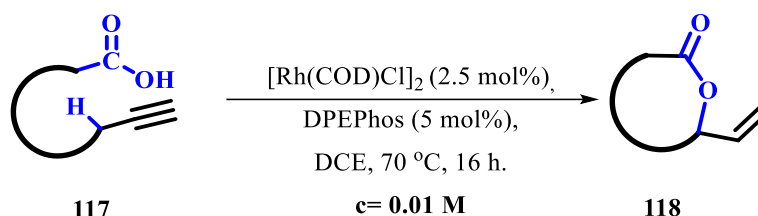
3A.2.2 Catalytic Approaches

However, the abovementioned methodologies are encumbered by several constraints, notably the employment of halogenated reagents leading to equimolar production of halogenated waste during the reaction. In response, White and coworkers devised a strategy for allylic C-H activation leveraging sulfoxide-promoted palladium acetate catalysis for macrolactonization of ω -alkenoic acids, with benzoquinone serving as an external oxidant (Scheme 32).⁹⁷



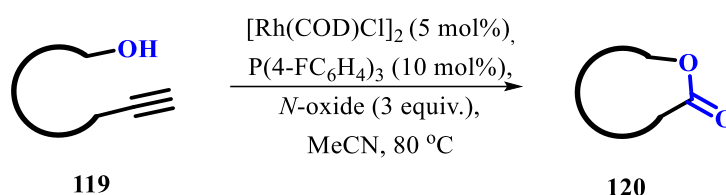
Scheme 32: Pd-catalyzed macrolactonization via hydrocarbon oxidation

Additionally, in 2011, Breit and coworkers introduced an elegant approach for macrolactonization through the redox-neutral coupling of terminal alkynes and carboxylic acids, employing $[\text{Rh}(\text{COD})\text{Cl}]_2$ as a catalyst and DPEphos as a ligand (Scheme 33). Notably, high dilution and prolonged reaction time directly influence this method's efficacy, impacting product yields.⁹⁸



Scheme 33: Macrolactonization using redox-neutral C-H propargylic oxidation

Recently, Li's research group demonstrated successful intramolecular macrolactonization of alkenyl alcohols **119** where alcohols react with terminal alkynes intramolecularly utilizing $[\text{Rh}(\text{COD})\text{Cl}]_2$ as a catalyst, supplemented by an external oxidant (Scheme 34). The mechanism for this process is still not understood.⁹⁹



Scheme 34: Macrolactonization of alkenyl alcohols

However, very few methodologies are available for alcohol activation which avoids external oxidants. The quest for a novel approach towards alcohol activation, offering an atom-economic, sustainable, and highly efficient pathway for macrolactone synthesis, remains a fascinating endeavor.

3A.3 Rationale of Current Work

In the past few decades, metal-catalyzed acceptorless dehydrogenation has emerged as a promising paradigm for C–O and C–N coupling reactions, promoting sustainability, minimal waste generation, avoiding the use of halogenated reagents, and a low E-factor. In 2005, Milstein and colleagues published a method for the coupling of primary alcohols to produce esters, employing $[\text{RuH}(\text{PNN})(\text{CO})]$ as a catalyst.¹⁰⁰ Following this breakthrough, several catalysts have been developed for the formation of esters and lactones (5- and 6-membered) from alcohols.¹⁰¹ However, macrolactonization via dehydrogenative coupling of alcohols using a metal catalyst remains uncharted territory. Hence, we aimed to synthesize macrolactones via

an acceptorless dehydrogenative strategy by avoiding external oxidants and toxic halogenated reagents and utilizing long-chain diols as the starting materials. Additionally, we endeavour to achieve the first instance of detailing a method for macrolactone synthesis that produces hydrogen as the sole by-product after the reaction.

3A.4 Results and Discussion

In this study, we present a new approach for synthesizing macrolactones through the activation of primary alcohols. Notably, this marks the first investigation into the macrolactonization of primary alcohols utilizing Ru-MACHO [carbonylchlorohydrido{bis-[2-(diphenylphosphinomethyl)ethyl]-amino}ethyl]amino}-ruthenium(II)] as a catalyst, in conjunction with Cs₂CO₃ as a base whereas toluene serves as the reaction solvent, with hydrogen being the sole byproduct generated.

3A.4.1 Optimization Studies

We initiated the optimization process for the intramolecular dehydrogenative coupling of diphenyldimethanol **93d**, which features a pentyl spacer. Our initial control experiments highlighted the indispensability of both the catalyst and the base for the conversion of **93d** into the macrolactone product **122a** (Table 3, entries 1 and 2). In the presence of 1 mol % Ru-MACHO catalyst, the formation of macrolactone **122a** was achieved with a yield of 12% (Table 3, entry 3). The product **122a** was also confirmed by X-ray analysis (Figure 33) with the largest cavity diameter of 5.79 Å. Alongside the desired product, the reaction produced partially oxidized dimethanol (monoaldehyde **F**) and monodecarbonylation¹⁰² products, which were obtained in yields of 20 and 11%, respectively. Adjusting the KOH loading to 10 mol % and 2

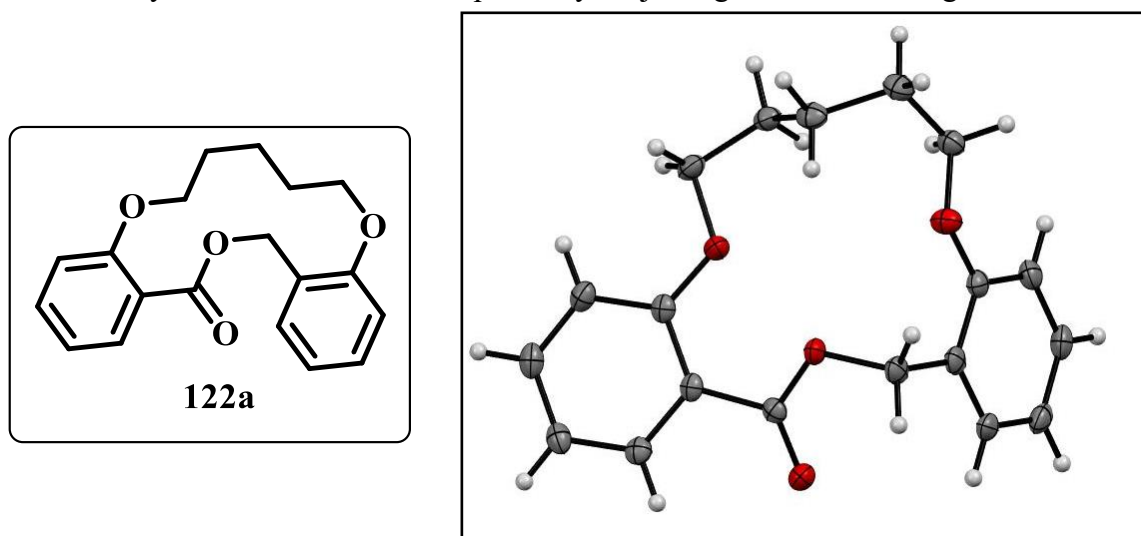
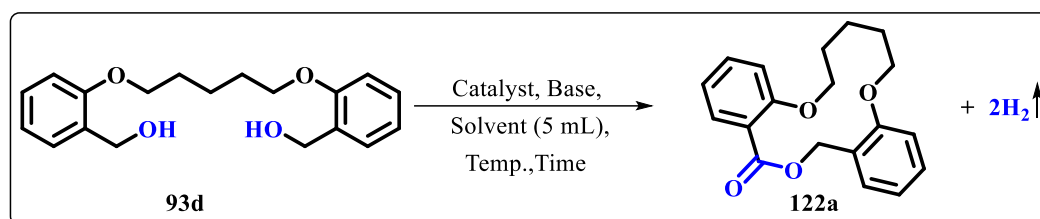


Figure 33. ORTEP drawing of **122a** showing thermal ellipsoids at the 50% probability level (temperature= 296 K)

Table 3: Optimization table for intramolecular macrolactonization



Sr. No.	Catalyst (mol%)	Base (equiv.)	Temp. (°C)	Yield of 122a (%)
1	Ru-MACHO (6)	-	180	-
2	-	KOH (2)	180	-
3	Ru-MACHO (1)	KOH (1)	180	12
4	Ru-MACHO (1)	KOH (0.1)	180	25
5	Ru-MACHO (6)	KOH (2)	180	21
6	Ru-MACHO (6)	KOH (1)	180	39
7	Ru-MACHO (6)	NaOH (1)	180	10
8	Ru-MACHO (6)	<i>t</i> -BuOK (1)	180	48
9	Ru-MACHO (6)	<i>t</i> -BuOK (1)	140/160	-/37
10	Ru-MACHO (6)	Cs ₂ CO ₃ (1)	180	69
11	Ru-MACHO (6)	Cs ₂ CO ₃ (0.5)	180	70
12	Ru-MACHO (6)	Cs ₂ CO ₃ (0.5)	180	57 ^b /63 ^c /71 ^d
13	Ru-MACHO (6)	Cs ₂ CO ₃ (0.5)	180	17 ^e
14	[Ru(Cl ₂)(<i>p</i> -cymene)] ₂ (6)	Cs ₂ CO ₃ (0.5)	180	21
15	Ru-PNN (6)	Cs ₂ CO ₃ (0.5)	180	49
16	Ru(H ₂)(CO)(PPh ₃) ₃ (6)	-	180	-
17	Ru(H ₂)(CO)(PPh ₃) ₃ (6)	Cs ₂ CO ₃ (0.5)	180	Trace
18	RuCl ₃ . <i>x</i> H ₂ O (10)	Cs ₂ CO ₃ (0.5)	180	11

^a**Reaction conditions:** Diphenyldimethanol derivative **93d** (0.166 mmol), catalyst (6 mol %), and base (see table) in toluene (5 mL) were stirred in a preheated parallel synthesizer at 180 °C. ^b140 °C. ^c160 °C for 48 h. ^d24 h. ^e40 h. ^f72 h. ^g1,4-Dioxane is used as a solvent to achieve macrolactone **122a**. The mentioned yields are isolated yields.

equiv. resulted in yields of 25 and 21% for compound **122a**, respectively (Table 3, entries 4 and 5). Noteworthy is the observation that using Ru-MACHO (6 mol %) alongside KOH (1 equiv.) led to a significant increase in yield, with 39% of product **122a** (Table 3, entry 6). In this reaction, alternative bases such as NaOH and *t*-BuOK yielded 10% and 48% of **122a**, respectively (Table 3, entries 7 and 8). Notably, the utilization of *t*-BuOK resulted in a substantial decrease in side product formation, reducing them to trace amounts. Additionally, a temperature investigation revealed that 140 °C and 160 °C were suboptimal for the conversion of **93d** into product **122a** (Table 1, entry 9). Moreover, employing Cs₂CO₃ (1 equiv.) yielded a 69% yield of **122a** (Table 3, entry 10), showcasing the efficiency of Cs₂CO₃ for this transformation. Intriguingly, using 0.5 equiv. of Cs₂CO₃ resulted in a 70% yield of **122a** (Table 3, entry 11). As a result, monoaldehyde and side product (monodecarbonylation) were effectively minimized through the utilization of Cs₂CO₃. Subsequent experimentation involved conducting reactions for 24, 40, and 72 hours using Cs₂CO₃ as the optimal base, resulting in yields of 57%, 63%, and 71% for product **122a**, respectively (Table 3, entry 12). Conversely, when 1,4-dioxane was employed as a solvent, only a 17% yield of **122a** was obtained (Table 3, entry 13). Various other Ru-catalysts, including [Ru(Cl₂)(*p*-cymene)]₂, Ru-PNN, RuCl₃·*x*H₂O, and Ru(H₂)(CO)(PPh₃)₃, proved inefficient for the transformation of **93d** into macrolactone **122a** (Table 3, entries 14 to 18).

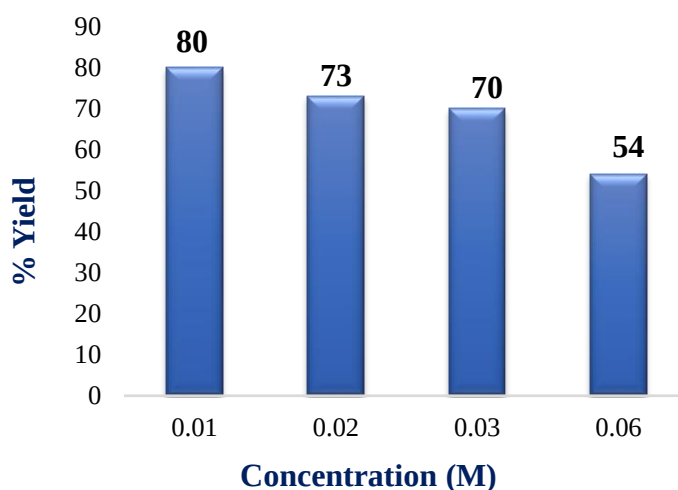
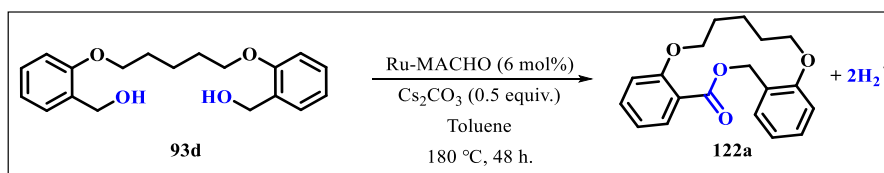


Figure 34: Concentration Study

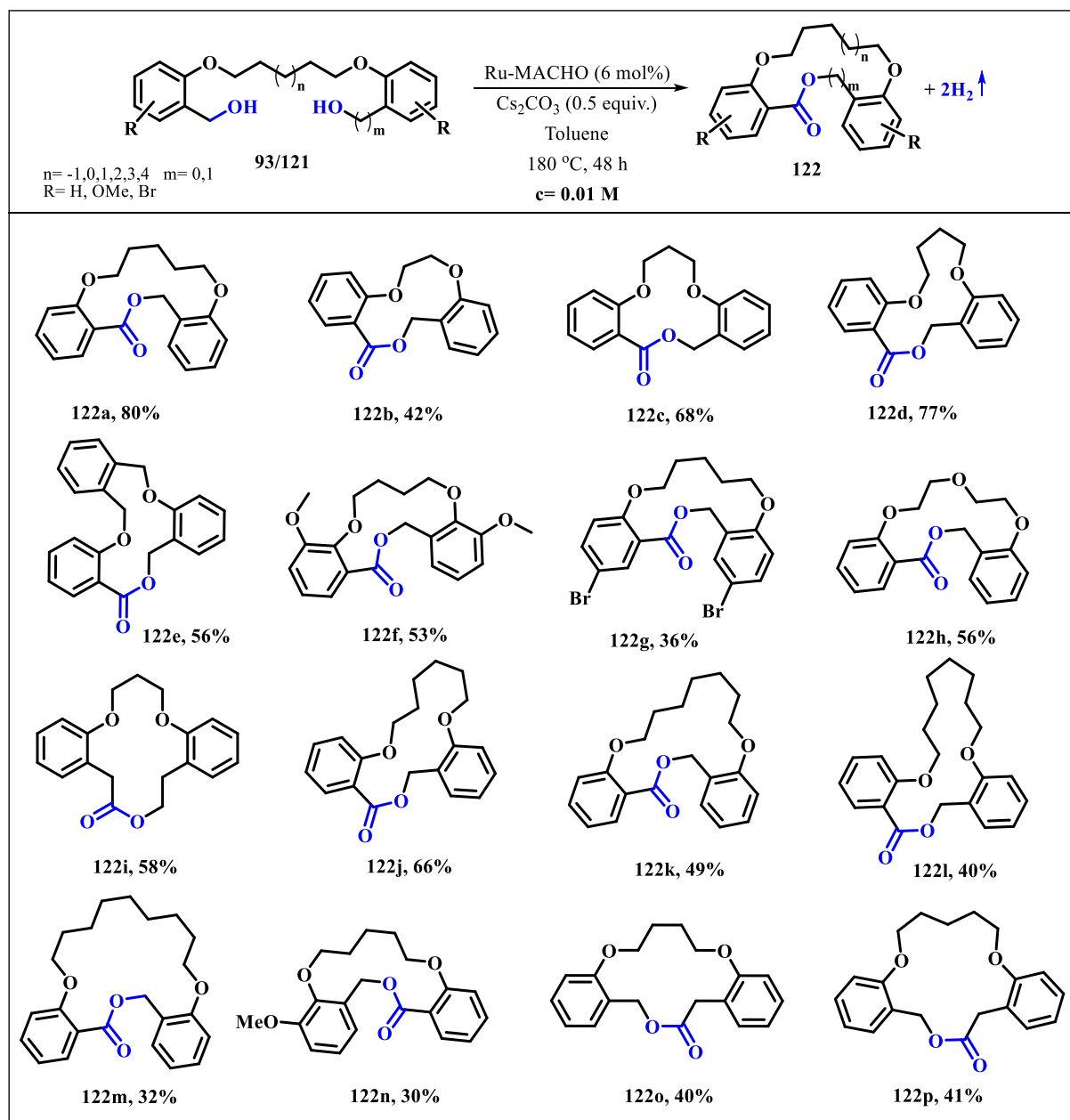
Next, to examine the impact of concentration, dilution experiments were conducted by reducing the concentration of **93d** in toluene to 0.01 M. The reaction was facilitated by 6 mol % of Ru-MACHO as a catalyst and Cs₂CO₃ (0.5 equiv.) as a base, resulting in a commendable yield (80%) of macrolactone **122a** (Figure 34). Dilution up to 0.02 M resulted in a 73% yield of **122a**. However, with concentrations of 0.03 M and 0.06 M of **93d**, a significant decrease in the yield of product **122a** (70% and 58%, respectively) was observed (Figure 34). This dilution study unequivocally demonstrates that the dilution of the starting material directly influences the yield of the macrolactone product.

3A.4.2 Substrate Scope

Following the initial investigation, we proceeded to examine the reactivity of the reaction with a variety of *ortho*-diphenyldimethanols (Scheme 35a) and *meta*-diphenyldimethanols (Scheme 36) containing diverse alkyl, aryl, and ether spacers at a concentration of 0.01 M.

Our initial focus was to synthesize 11- and 12-membered macrolactones, known to be challenging to synthesize compared to their counterparts. Surprisingly, we obtained a 42% yield for the 11-membered macrolactone **122b** (also confirmed by X-ray analysis (Figure 35) with the largest cavity diameter of 5.00 Å.) and a 68% yield for the 12-membered macrolactone **122c**. Notably, the 13-membered macrolactone **122d** was obtained in 77% yield (Scheme 35a). However, replacing the substitution of alkyl spacers with an aryl spacer, diphenyldimethanol **121d** resulted in no product formation due to decreased molecular flexibility attributed to the aryl spacer. Conversely, **121e** (the positional isomer of **121d**) provided a 56% yield of **122e**. Additionally, methoxy- and bromo-substituted macrolactones **122f** and **122g** were achieved with 53% and 36% yields, respectively (Scheme 35a). Substitution of the spacer with diethylene glycol afforded a 56% yield of **122h**. To expand the reaction scope to non-benzylic alcohols, diphenyldiethanol (**121g**) underwent macrolactonization to yield **122i** in 58% yield (Scheme 35a). Diphenyldimethanols with spacer lengths ranging from hexyl to nonyl, yielded 66%, 49%, 40%, and 32% yields of macrolactones **122j-122m**, respectively (Scheme 35a). The yield of macrolactones decreases as the spacer length increases. This trend may be attributed to the increasing likelihood of unfavourable conformations in long-chain diphenyldimethanols, leading to inefficient macrolactonization. Furthermore, unsymmetrical monomethoxy-diphenyldimethanol (**121a**) underwent crossed-macrolactonization to yield product **122n** in 30% yield (Scheme 35a), with the carbonyl moiety originating from the less sterically hindered alcohol.

Interestingly, benzyl alcohols were subjected to intramolecular reaction with linear non-benzylic alcohols, employing diols **121b** and **121c**, resulting in the two new crossed-macrolactone products, **122o** and **122p**, with yields of 40% and 41%, respectively (Scheme 35a). Notably, in these instances, oxidation occurred at the linear non-benzylic alcohol rather than the benzylic alcohol. This phenomenon may be attributed to the comparatively lower steric

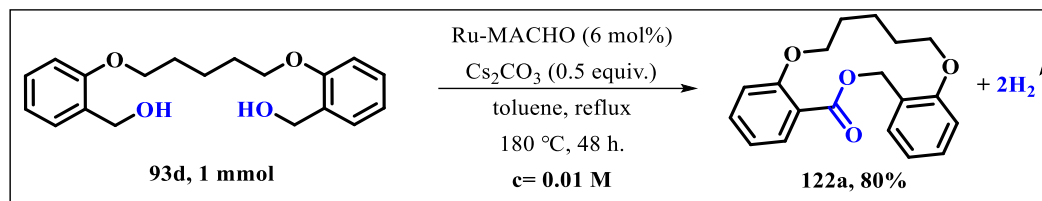


Scheme 35a: Substrate scope for macrolactonization of *ortho*-diphenyldimethanols

Reaction Condition: *o*-diphenyldimethanol derivatives **93/121** (0.069 mmol, 1 equiv.), Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv. (6 mol %)), and Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) in toluene (7 mL) were stirred in preheated parallel synthesizer at 180 °C for 48 h to achieve macrolactone **122**.

hindrance exhibited by the non-benzylic terminal alcohol compared to its benzylic counterpart. Examination of substrate scope revealed that the yields of macrolactones are predominantly influenced by the spacer length and the substituents attached to the phenyl rings.

To check the scalability, we performed a 1 mmol reaction with **93d** under optimized conditions and 80% yield of **122a** was observed (Scheme 35b).



Scheme 35b: Macrolactonization reaction with 1 mmol of **93d**

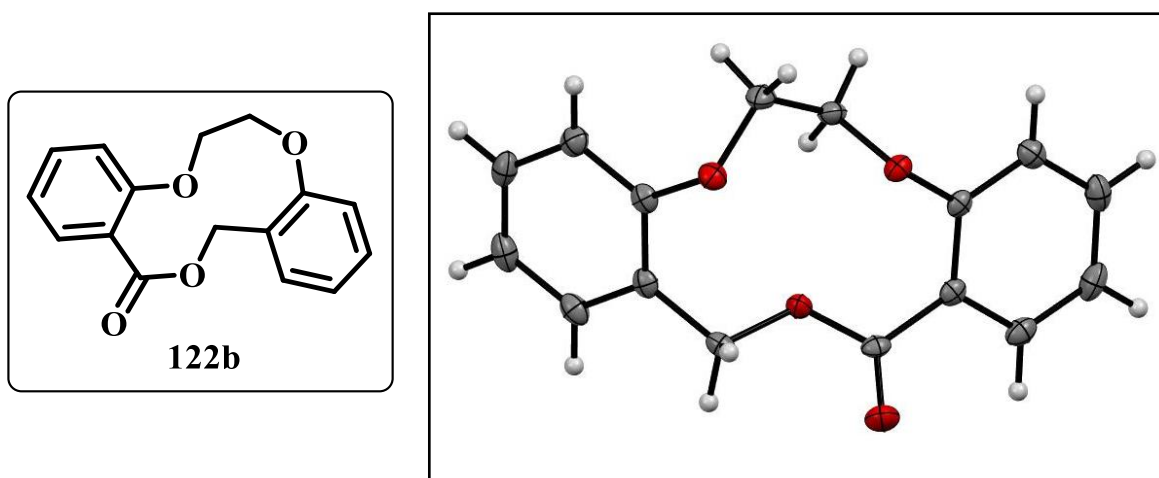


Figure 35. ORTEP drawing of **122b** showing thermal ellipsoids at the 50% probability level (temperature= 296 K)

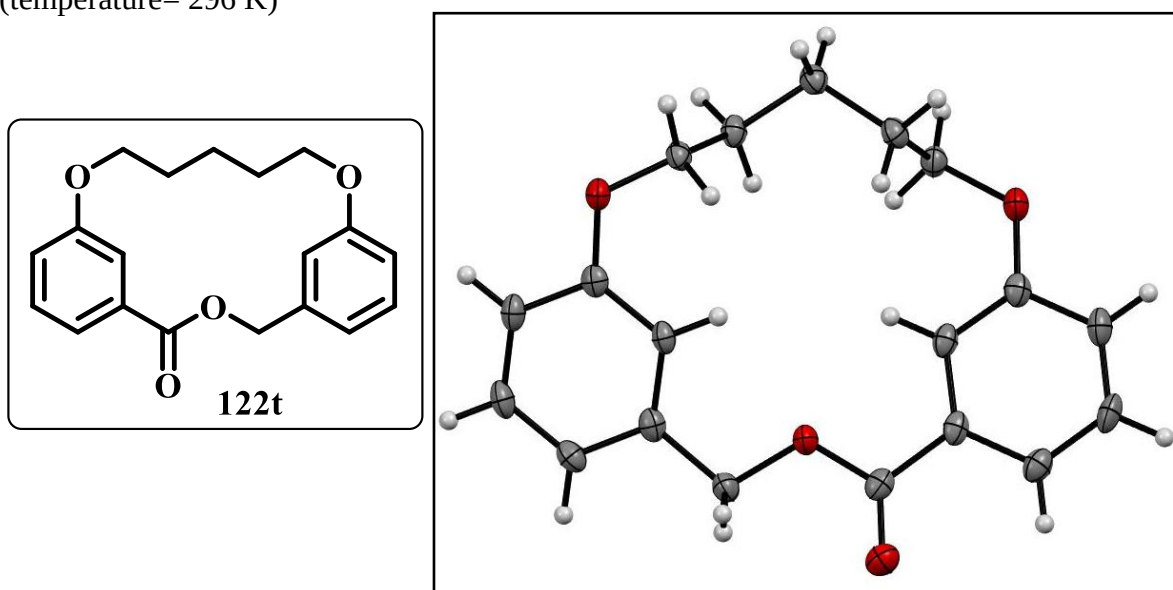
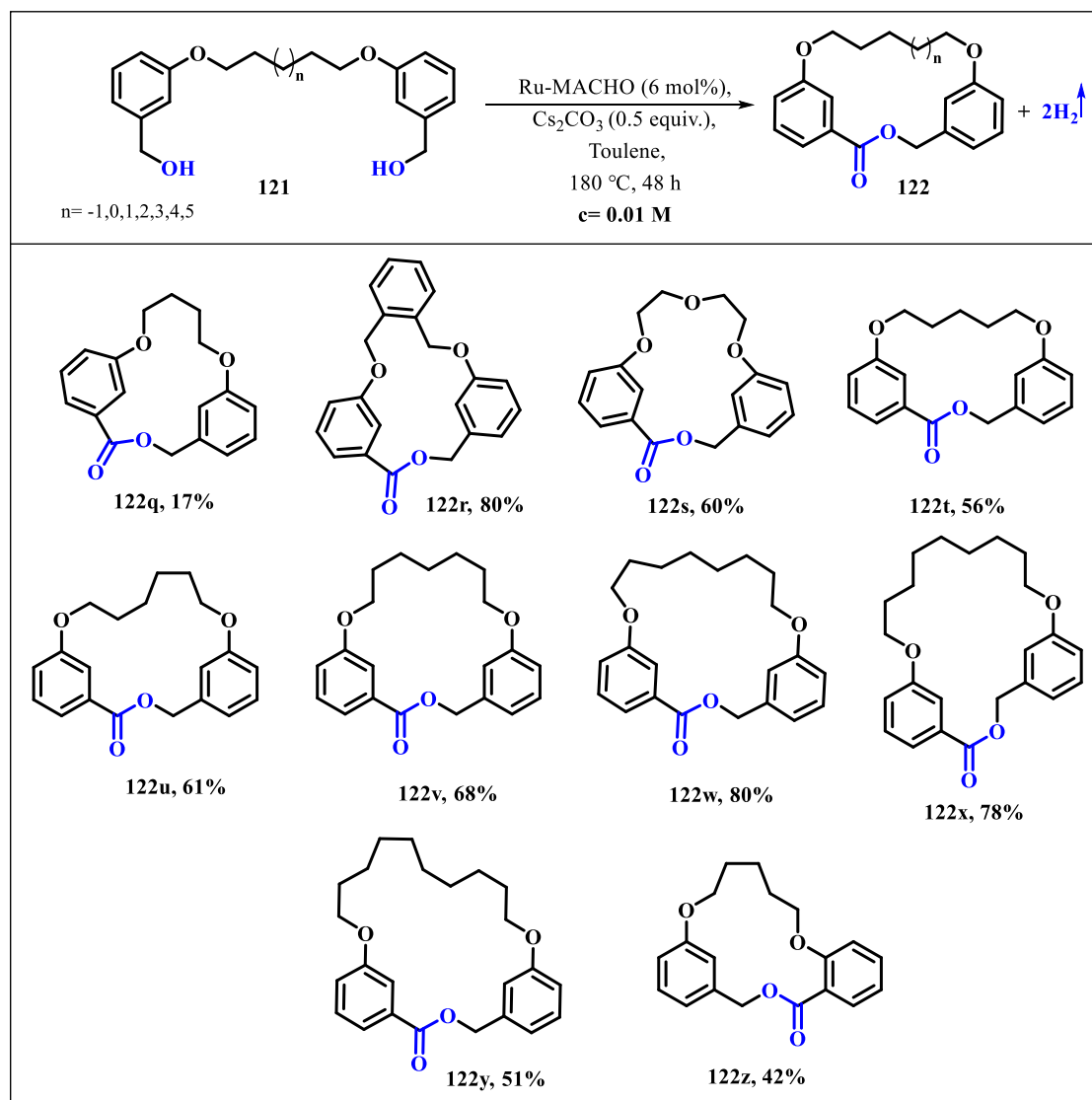


Figure 36. ORTEP drawing of **122t** showing thermal ellipsoids at the 50% probability level (temperature= 296 K)

Next, we extended our approach to *meta*-diphenyldimethanols (Scheme 36) for the synthesis of 15–21-membered macrolactones. A diphenyldimethanol with a butyl spacer was utilized in the presence of *t*-BuOK (1 equiv.), to achieve a 17% yield of **122q**, whereas no product formation was observed with Cs₂CO₃ (Scheme 36). Additionally, diphenyldimethanol with an aryl spacer (**121r**) and a diethylene glycol spacer yielded 80% and 60% of product **122r** and **122s**, respectively (Scheme 36). Intriguingly, as the spacer length increased from pentyl to nonyl, a notable enhancement in yields of products **122t–122x**, ranging from 56% to



Scheme 36: Substrate scope for macrolactonization of *meta*-diphenyldimethanols

Reaction conditions: *m*-diphenyldimethanol derivatives **121** (0.069 mmol, 1 equiv.), Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv. (6 mol %)), and Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) in toluene (7 mL) were stirred in preheated parallel synthesizer at 180 °C for 48 h to achieve macrolactone **122**.

80%, was observed (Scheme 36). The structure of macrolactone **122t** was also confirmed by X-ray analysis (Figure 36) with the largest cavity diameter of 6.65 Å. Furthermore, macrolactone **122y** was obtained with a 51% yield by treating the diol-bearing decyl spacer. Ultimately, a crossed macrolactone **122z** was synthesized with a 42% yield (Scheme 36) using the *ortho-meta*-diphenyldimethanol derivative (**121z**), where the carbonyl group originated from an electron-rich *ortho*-substituted benzyl alcohol with an electronic-rich nature. This substrate investigation highlights that increasing the spacer length from a butyl spacer to a decyl spacer leads to an increase in the yield of macrolactones.

3A.5 Mechanistic Investigation:

After the successful demonstration of a variety of substrates, we further moved towards the mechanism of macrolactonization. Several experiments were performed to probe the reaction mechanism, including the hydrogen gas detection and intermediate trapping experiment. More interestingly, we were successful in isolating the intermediate aldehyde, which is confirmed by spectroscopic techniques and mass analysis (Figures 39 and 40).

3A.5.1 Hydrogen Detection by Gas Chromatography:

Utilizing the standard condition, diol **93d** was allowed to react intramolecularly for 21 h instead of 48 h on a preheated parallel synthesizer. The reaction mixture was then allowed to cool at room temperature, and the upper-gaseous fraction of the reaction mixture was injected directly into the gas chromatography using a gas-tight syringe in order to detect the hydrogen evolved from the reaction. After sample injection, the chromatogram showed the peak of H₂ evolved from the reaction at 1.042 min. of residence time (Figure 37).

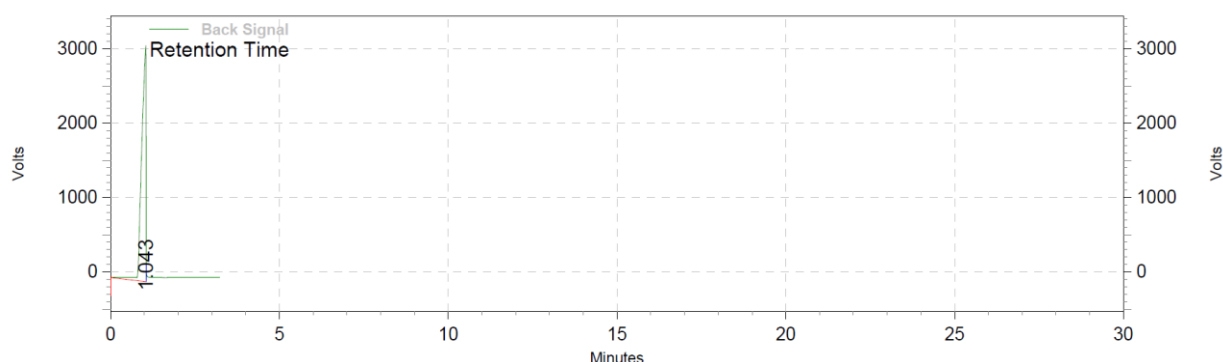


Figure 37: Hydrogen gas detection using GC

3A.5.2 Intermediate trapping by HRMS:

Utilizing the standard condition, diol **93d** was allowed to react intramolecularly using 5 mL of toluene. After 6 h, the reaction mixture was immediately allowed to cool at 0 °C in a beaker containing a mixture of ice and NaCl, followed by the direct injection of the reaction

mixture in the HRMS instrument in order to get the mass of the desired intermediate **D**.

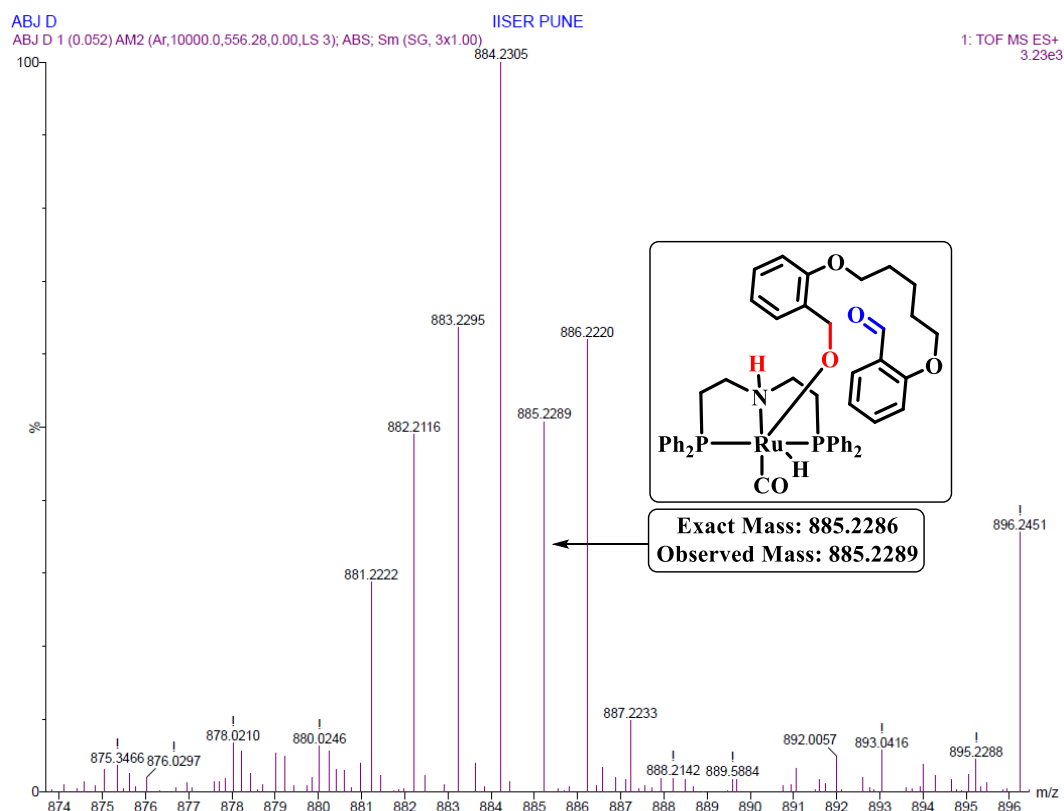


Figure 38: HRMS spectrum for the intermediate **D**

3A.5.3 NMR Spectrum of Intermediate **F**:

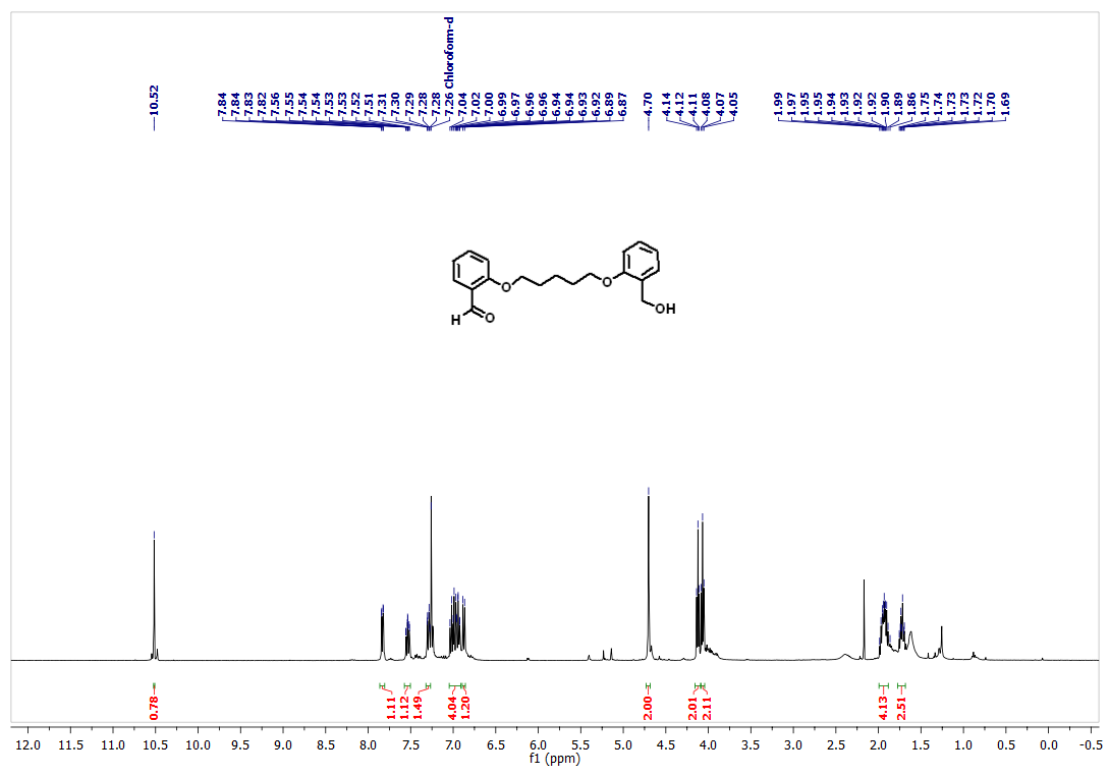


Figure 39. ^1H NMR spectra for Intermediate **F**, 400 MHz, CDCl_3

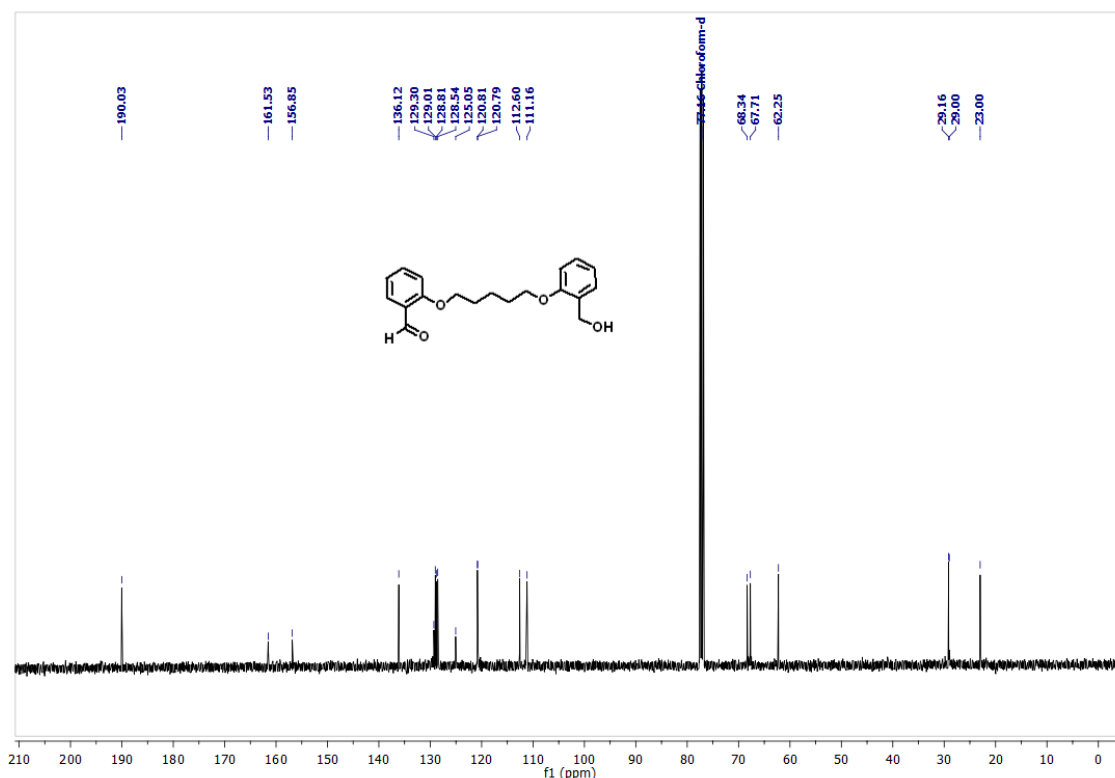
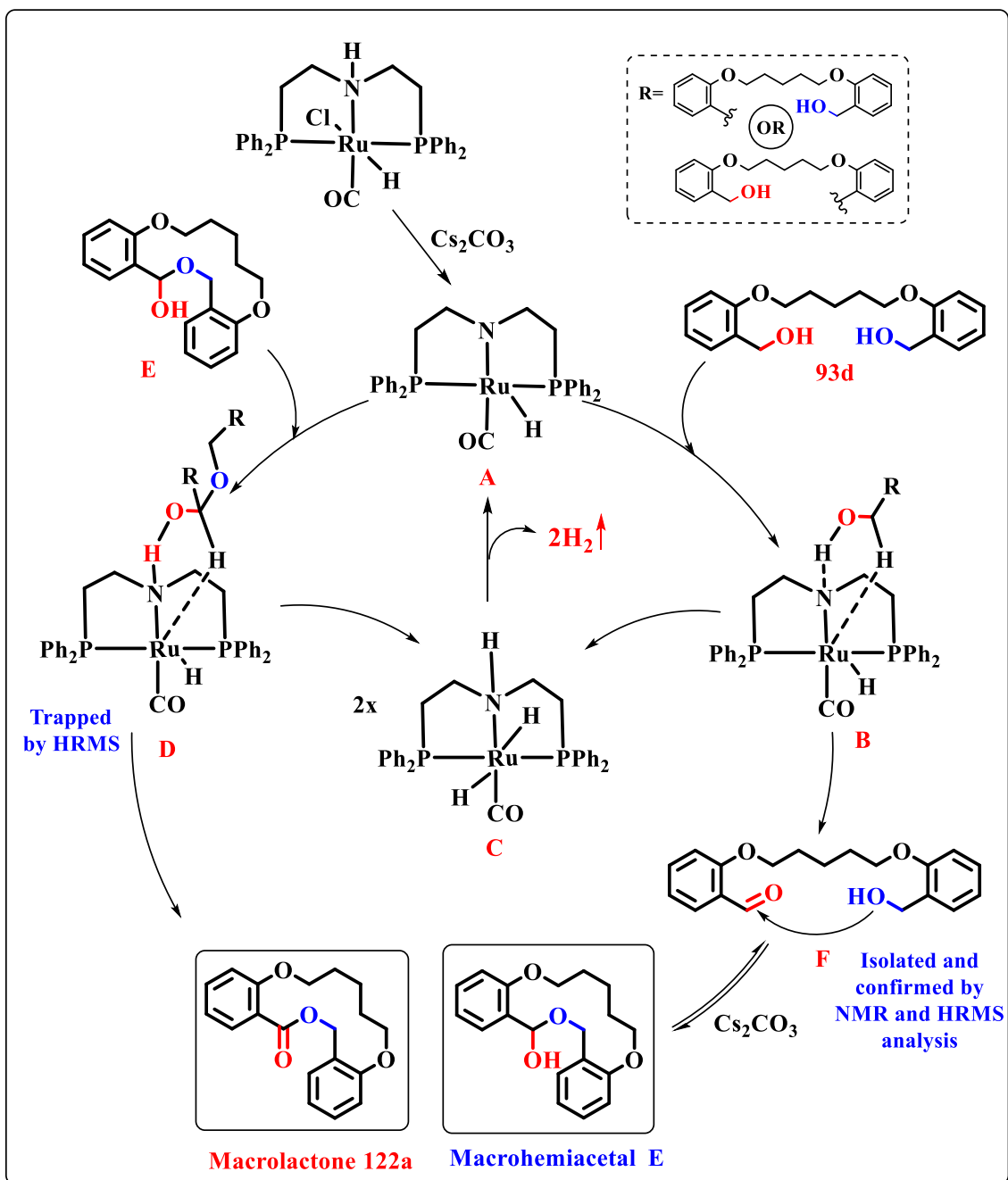


Figure 40. ¹³C NMR spectra for Intermediate **F**, 100 MHz, CDCl₃

Direct injection to the HRMS instrument indicated the peak at $[M]^+ = 885.2289$, whereas the exact mass of the intermediate **D** is $[M]^+ = 885.2286$ (Figure 38). This clearly proves that the reaction is proceeding through the intermediate **D** (Figure 38).

Based on existing literature reports¹⁰³ and the isolation and trapping of intermediates, we delineated the plausible reaction mechanism for the macrolactonization (Scheme 37). Initially, Ru-MACHO, in the presence of Cs₂CO₃, generates an active species **A**. Active species **A** undergoes a reaction with **93d** to form species **B**. Subsequently, **B** undergoes β -hydride elimination to yield Ru-Hydride intermediate **C** and monoaldehyde intermediate **F**, which was confirmed by NMR and HRMS analysis (Figure 39 and 40). Later, intermediate **F** reacts with Cs₂CO₃ intramolecularly to generate the macrocyclic hemiacetal intermediate **E**. Next, intermediate **E** reacts with active species **A** to form intermediate **D** (trapped by HRMS, Figure 38). Subsequently, intermediate **D** undergoes β -hydride elimination to yield macrolactone product **122a** and Ru-H intermediate **C**. Finally, intermediate **C** regenerates active species **A** in the catalytic cycle with the release of hydrogen gas (detected by gas chromatography, Figure 37). The reversible reaction from **122a** to **93d** is not feasible under these experimental conditions due to the very low hydrogen pressure generated in the reaction.



Scheme 37: Plausible mechanism for acceptorless dehydrogenative intramolecular macrolactonization

3A.6 Conclusion

In summary, we have unveiled the first protocol for the synthesis of valuable macrolactones via intramolecular dehydrogenative coupling of various long-chain diphenyldimethanols. This approach is facilitated by Ru-MACHO as a catalyst and Cs_2CO_3 as a base, affording 26 examples of 11–21-membered macrolactones with satisfactory to moderate yields. Furthermore, the successful implementation of the cross-coupling of benzylic alcohols

with non-benzylic linear alcohols has led to the synthesis of new crossed-macrolactones. The high yields of macrolactones are contingent upon spacer lengths and the utilization of high dilution of starting materials. Moreover, the mechanism for this protocol has been depicted with the support of intermediate trapping by HRMS and NMR analysis. The liberation of hydrogen gas was detected by the GC analysis. Overall, this method stands as a straightforward, atom-economic, and sustainable approach for macrolactone synthesis, obviating the need for external oxidants and producing hydrogen as the sole byproduct.

3A.7 Experimental section and characterization data

3A.7.1 General information and data collection:

The Ru-MACHO (CAS number- 1295649-40-9, SIGMA), 2-hydroxybenzylalcohol (CAS number- 90-01-7, SIGMA), 3-hydroxybenzylalcohol (CAS number- 620-24-6, SIGMA), 2-hydroxy-3-methoxybenzylalcohol (CAS number- 4383-05-5, SIGMA), 5-bromo-2-hydroxy benzyl alcohol (CAS number- 2316-64-5, SIGMA), 2-coumaranone (CAS number- 553-86-6, SIGMA) and dibromoalkanes was purchased from Sigma-Aldrich. Cesium carbonate (Cs_2CO_3) was purchased from FINAR (CASR- 534-17-8). All the solvents used were dry grade. The column chromatographic separations were performed over 100-200 mesh size Silica-gel. Visualization was accomplished with UV light and DNP stain. ^1H and ^{13}C NMR spectra were recorded on 400 and 100 MHz, respectively, using Bruker or JEOL spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiple. High-resolution mass Spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATIR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. Single-crystal diffraction analysis data were collected at 23 °C (296 K) with a Bruker Kappa Apex III CCD single-crystal diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo $\text{K}\alpha$ radiation and Cu $\text{K}\alpha$ radiation. More information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) with deposition numbers 2132244 (**122a**), 2171837 (**122b**), and 2132245 (**122t**). Melting points were recorded by using DBK Programmable Melting Point Apparatus (230 V).

3A.7.2 Experimental Section:

A) General experimental procedure for mono- and di-alkylation of 2/3-hydroxybenzylalcohol:⁸⁴

In a 100 mL round bottom flask, were added 2/3-hydroxybenzylalcohol (2 equiv.), dibromoalkanes (1 equiv.), and potassium carbonate (K_2CO_3) (2.2 equiv.) in acetonitrile. The

solution was refluxed for 12-16 hrs. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the mixture of products (mono- and di-alkylated) was extracted in water and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane = 15:85 (for the mono-alkylated product) and 40:60 (for the di-alkylated product)).

B) Experimental procedure for synthesis for 2-(2-hydroxyethyl)phenol (121''**):¹⁰⁴**

In a 100 mL round bottom flask was added 2-coumaranone (1 equiv., 3 mmol, 402.9 mg) in ethanol. The solution was allowed to cool at 0 °C and sodium borohydride (4 equiv., 12 mmol, 453.96 mg) was added gradually to the reaction mixture. Further, the reaction mixture was stirred at room temperature for one hour. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the product was extracted in the saturated aqueous solution of ammonium chloride and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (15% of EtOAc in *n*-hexane) to get pure compound 2-(2-hydroxyethyl)phenol (**121''**) in a 77% yield.

C) General experimental procedure for alkylation of 2-hydroxyalkylalcohol: Substrates were prepared according to literature.⁸⁴

In a 100 mL round bottom flask was added 2-(2-hydroxyethyl)phenol (**121''**)/ 3-methoxy-2-hydroxybenzylalcohol (1 equiv.), monobromoalkane (isolated with reaction performed using experimental procedure **3A.7.2A**) (1 equiv.), and potassium carbonate (K₂CO₃) (1.2 equiv.) in acetonitrile. The solution was refluxed for 12-16 hrs. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the product was extracted in water and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane).

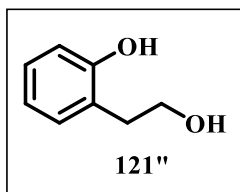
D) General experimental procedure for intramolecular macrolactonization of various *ortho*-/*meta*-diphenyldimethanol derivatives:⁸⁵

In a 20 mL re-sealable vial (equipped with a rubber septum and N₂ balloon) was added Ru-MACHO (0.0042 mmol, 2.5 mg, 0.06 equiv. (6 mol%)), *o*-/*m*-diphenyldimethanol compound (0.069 mmol, 1 equiv.), and Cs₂CO₃ (0.035 mmol, 11.4 mg, 0.5 equiv.) in the presence of toluene (7 mL) as a solvent. The tube was purged with N₂ and sealed with a cap using a crimper. The reaction mixture was heated at 180 °C in a preheated oil bath or parallel synthesizer for 48 hrs. After completion of the reaction, the reaction mixture was diluted with ethyl acetate.

Further, a volatile component was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane- 05-15%).

3A.7.3 Spectroscopic data of products:

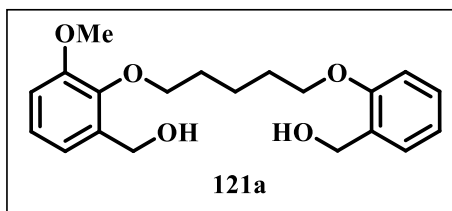
2-(2-hydroxyethyl)phenol (121''): Prepared according to general procedure **3A.7.2.B**, using



2-coumaranone (1 equiv. 3 mmol, 402.9 mg) and sodium borohydride (4 equiv., 12 mmol, 453.96 mg) to afford desired product 2-(2-hydroxyethyl)phenol **121''** (320 mg, 77% yield) as a colourless liquid (15% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 8.29 (s,

1H), 7.16 – 7.11 (dt, 1H), 7.06 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.90 – 6.83 (m, 2H), 3.94 – 3.88 (t, 2H), 3.47 (s, 1H), 2.90 – 2.84 (t, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 155.1, 131.1, 128.3, 126.6, 120.6, 116.7, 64.3, 34.5. **IR** (neat): 3372, 2953, 1600, 1202 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₈H₁₁O₂ 139.0759, Found: 139.0764.

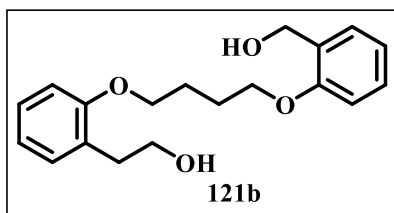
(2-((5-(2-(hydroxymethyl)-6-methoxyphenoxy)pentyl)oxy)phenyl)methanol (121a):



Prepared according to general procedure **3A.7.2.C**, using 2-hydroxy-3-methoxybenzylalcohol (154 mg, 1 mmol, 1 equiv.) and (2-((5-bromopentyl)oxy)phenyl)methanol (273 mg, 1 mmol, 1 equiv.) and K₂CO₃ (165 mg, 1.2 mmol, 1.2 equiv.) to

afford desired product (2-((5-(2-(hydroxymethyl)-6-methoxyphenoxy)pentyl)oxy)phenyl)methanol **121a** (377 mg, 80 % yield) as a colourless oily compound (50% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.29 – 7.21 (m, 2H), 7.02 (t, *J* = 7.9 Hz, 1H), 6.95 – 6.89 (m, 2H), 6.88 – 6.83 (m, 2H), 4.67 (d, *J* = 3.3 Hz, 4H), 4.03 (t, *J* = 6.3 Hz, 4H), 3.82 (s, 3H), 2.92 (s, 2H), 1.92 – 1.78 (m, 4H), 1.69 (m, *J* = 9.4, 5.6 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 156.7, 152.4, 145.9, 134.7, 129.1, 128.8, 128.7, 124.0, 120.6, 120.5, 112.0, 111.0, 73.0, 67.7, 61.8, 61.1, 55.7, 30.0, 29.0, 22.8. **IR** (neat): 3353, 2923, 1601, 1249 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₀H₂₆O₅Na 369.1677, found: 369.1671.

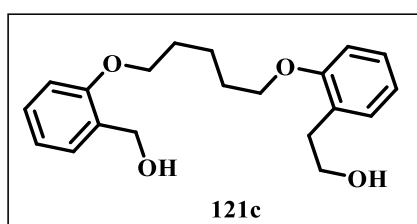
2-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-ol (121b): Prepared according



to general procedure **3A.7.2.C**, using (2-(4-bromobutoxy)phenyl)methanol (185.5 mg, 0.723 mmol, 1 equiv.), 2-(2-hydroxyethyl)phenol (**121''**) (100 mg, 0.723 mmol, 1 equiv.) and K₂CO₃ (1.2 equiv.) to afford desired

product 2-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-ol **121b** (160 mg, 70 % yield) as a colourless oily compound (40% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.30 – 7.24 (m, 2H), 7.23 – 7.15 (m, 2H), 6.96 (dd, *J* = 7.4, 0.8 Hz, 1H), 6.89 (ddd, *J* = 15.7, 9.3, 7.8 Hz, 3H), 4.70 (s, 2H), 4.12 (t, *J* = 5.5 Hz, 2H), 4.07 (t, *J* = 5.4 Hz, 2H), 3.80 (t, *J* = 6.7 Hz, 2H), 2.90 (t, *J* = 6.7 Hz, 2H), 2.08 – 2.01 (m, 4H), 1.70 (s, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 157.0, 156.9, 131.1, 129.2, 129.1, 129.1, 127.9, 127.2, 120.8, 111.2, 111.2, 67.5, 67.4, 63.0, 62.2, 34.4, 26.5, 26.4. **IR** (neat): 3328, 2927, 1594, 1178 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₉H₂₄O₄Na 339.1572, found: 339.1567.

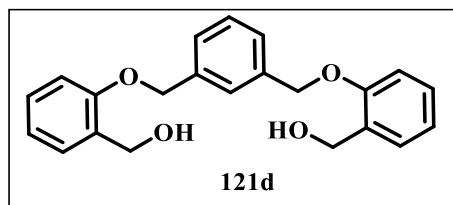
2-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (121c): Prepared



according to general procedure **3A.7.2.C**, using (2-((5-bromopentyl)oxy)phenyl)methanol (273 mg, 1 mmol, 1 equiv.), 2-(2-hydroxyethyl)phenol (**121''**) (138.16 mg, 1 mmol, 1 equiv.) and K₂CO₃ (1.2 equiv.) to afford desired product 2-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)

oxy)phenyl)ethan-1-ol **121c** (249.3 mg, 75.5 % yield) as a white solid (40% Ethyl Acetate: Hexane). **M.P.** = 55-57 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.31 – 7.22 (m, 2H), 7.22 – 7.13 (m, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.91 – 6.85 (m, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.70 (s, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 4.00 (t, *J* = 6.0 Hz, 2H), 3.80 (t, *J* = 6.9 Hz, 2H), 2.91 (t, *J* = 6.9 Hz, 2H), 1.94 – 1.83 (m, 4H), 1.77 – 1.66 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 157.0, 156.7, 130.8, 129.1, 128.8, 128.6, 127.7, 127.1, 120.6, 120.5, 111.1, 111.0, 77.1, 67.6, 67.6, 62.8, 61.9, 34.2, 29.2, 29.1, 23.3. **IR** (neat): 3340, 2926, 1601, 1237 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₀H₂₆O₄Na 353.1728, found: 353.1722.

((1,3-phenylenebis(methylene))bis(oxy))bis(2,1-phenylene)dimethanol (121d): Prepared

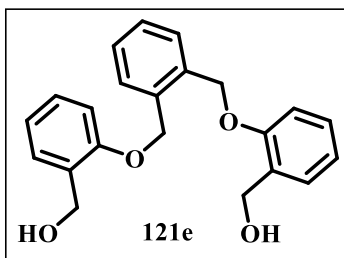


according to general procedure **3A.7.2.A**, using 1,3-bis(bromomethyl)benzene (398 mg, 1.5 mmol, 1 equiv.) and 2-hydroxybenzyl alcohol (368 mg, 3 mmol, 3 equiv.) and K₂CO₃ (2.2 equiv.) to afford the desired

product ((1,3-phenylenebis(methylene))bis(oxy))bis(2,1-phenylene)dimethanol **121d** (528 mg, 78 % yield) as a white amorphous solid (40% Ethyl Acetate: Hexane). **M.P.** = 79-81 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.56 (s, 1H), 7.47 – 7.33 (m, 5H), 7.28 (td, *J* = 7.6, 1.7 Hz, 2H), 6.98 (ddd, *J* = 13.9, 10.2, 4.5 Hz, 4H), 5.16 (s, 4H), 4.75 (s, 4H), 2.69 (s, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 156.4, 137.5, 129.5, 129.0, 129.0, 128.9, 126.8, 125.8, 121.2, 111.7, 69.8, 61.8.

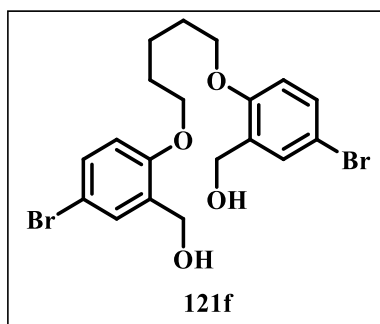
IR (neat): 3348, 2919, 1594, 1228 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{22}\text{O}_4\text{Na}$ 373.1415, found: 373.1405.

(((1,2-phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (121e): Prepared



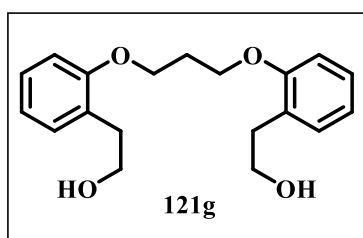
according to general procedure **3A.7.2.A**, using 1,2-bis(bromomethyl)benzene (264 mg, 1 mmol, 1 equiv.) and 2-hydroxybenzyl alcohol (248.2 mg, 2 mmol, 2 equiv.) and K_2CO_3 (2.2 equiv.) to afford desired product (((1,2-phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol **121e** (310 mg, 88 % yield) as a white solid compound (40% Ethyl Acetate: Hexane). **M.P.**= 81-83 $^{\circ}\text{C}$. **^1H NMR** (400 MHz, CDCl_3) δ 7.54 (s, 1H), 7.38 (dd, J = 16.6, 6.6 Hz, 3H), 7.33 (dd, J = 7.4, 1.5 Hz, 2H), 7.28 – 7.22 (td, 2H), 6.96 (td, J = 10.8, 4.0 Hz, 2H), 6.92 (d, J = 8.2 Hz, 2H), 5.13 (s, 4H), 4.73 (s, 4H), 2.73 (d, J = 19.6 Hz, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 156.3, 137.5, 129.6, 129.0, 128.9, 126.8, 125.7, 121.1, 111.7, 69.7, 61.7. **IR** (neat): 3350, 2930, 1600, 1204 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{22}\text{O}_4\text{Na}$ 373.1421, found: 373.1421.

((pentane-1,5-diylbis(oxy))bis(5-bromo-2,1-phenylene))dimethanol (121f): Prepared



according to general procedure **3A.7.2.A**, using 5-bromo-2-hydroxybenzylalcohol (406 mg, 2 mmol, 2 equiv.), 1,5-dibromopentane (230 mg, 1 mmol, 1 equiv.) and K_2CO_3 (2.2 equiv.) to afford desired product ((pentane-1,5-diylbis(oxy))bis(5-bromo-2,1-phenylene))dimethanol (304 mg, 64 % yield) as a white amorphous solid (38% Ethyl Acetate: Hexane). **M.P.**= 96-99 $^{\circ}\text{C}$. **^1H NMR** (400 MHz, CDCl_3) δ 7.42 (d, J = 2.4 Hz, 2H), 7.33 (dd, J = 8.7, 2.5 Hz, 2H), 6.72 (d, J = 8.6 Hz, 2H), 4.64 (d, J = 5.5 Hz, 4H), 4.01 (t, J = 6.1 Hz, 4H), 1.92 – 1.83 (m, 4H), 1.69 – 1.62 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 155.6, 131.4, 131.3, 131.3, 113.0, 112.8, 68.0, 61.1, 28.9, 23.1. **IR** (neat): 3326, 2934, 1486, 1238, 734 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{Br}_2\text{O}_4\text{Na}$ 494.9783, found: 494.9752.

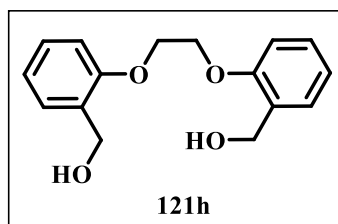
2,2'-((propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) (121g): Prepared



according to general procedure **3A.7.2.A**, using **121''** (276.3 mg, 2 mmol, 2 equiv.), 1,3-dibromopropane (202 mg, 1 mmol, 1 equiv.) and K_2CO_3 (2.2 equiv.) to afford desired product 2,2'-((propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) **121g** (228.3 mg, 60 % yield) as a

white amorphous solid (40% Ethyl Acetate: Hexane). **M.P.**= 79-81 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.21 (td, J = 7.9, 1.7 Hz, 2H), 7.16 (dd, J = 7.4, 1.6 Hz, 2H), 6.91 (m, J = 11.1, 6.0, 2.3 Hz, 4H), 4.19 (t, J = 6.0 Hz, 4H), 3.79 (t, J = 6.6 Hz, 4H), 2.90 (t, J = 6.6 Hz, 4H), 2.31 (m, J = 6.0 Hz, 2H), 2.08 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 131.0, 127.9, 127.1, 120.9, 111.4, 64.5, 62.7, 34.1, 29.4. **IR** (neat): 3345, 2931, 1596, 1189 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[M+Na]^+$ calcd for $C_{19}H_{24}O_4Na$ 339.1580, found: 339.1579.

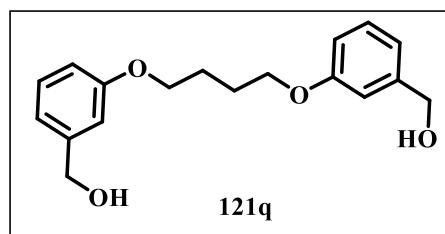
((ethane-1,2-diylbis(oxy))bis(2,1-phenylene))dimethanol (121h): Prepared according to



general procedure **3A.7.2.A**, using 1,2-dibromoethane (188 mg, 1 mmol, 1 equiv.) and 2-hydroxybenzyl alcohol (248.2 mg, 2 mmol, 2 equiv.) and K_2CO_3 (2.2 equiv.) to afford desired product ((ethane-1,2-diylbis(oxy))bis(2,1-phenylene))dimethanol **121h**

(310 mg, 88 % yield) as a white crystalline solid compound (40% Ethyl Acetate: Hexane). **M.P.**= 122-125 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, J = 7.9, 4.9, 1.9 Hz, 4H), 6.97 (dd, J = 11.0, 3.9 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 4.64 (s, 4H), 4.39 (s, 4H), 3.17 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 129.7, 129.7, 129.1, 121.6, 111.9, 66.9, 61.7. **IR** (neat): 3350, 2914, 1598, 1225 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[M+Na]^+$ calcd for $C_{16}H_{18}O_4Na$ 297.1108, found: 297.1107.

((butane-1,4-diylbis(oxy))bis(3,1-phenylene))dimethanol (121q): Prepared according to

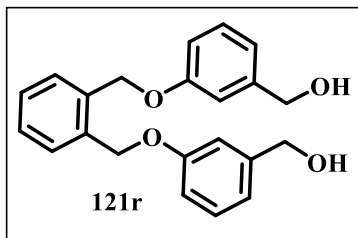


general procedure **3A.7.2.A**, using 3-hydroxybenzylalcohol (248 mg, 2 mmol, 2 equiv.), 1,4-dibromopropane (226 mg, 1 mmol, 1 equiv.) and K_2CO_3 (2.2 equiv.) to afford desired product ((butane-1,4-diylbis(oxy))bis(3,1-phenylene))dimethanol **121q** (182

mg, 60 % yield) as a white crystalline solid (40% Ethyl Acetate: Hexane). **M.P.**= 66-68 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, J = 8.0 Hz, 2H), 6.88 – 6.82 (m, 4H), 6.75 (dd, J = 8.1, 2.0 Hz, 2H), 4.58 (s, 4H), 3.98 (t, J = 5.7 Hz, 4H), 1.94 – 1.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 142.6, 129.7, 119.2, 113.9, 113.0, 67.5, 65.4, 26.1. **IR** (neat): 3341, 2921,

1635, 1260 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4\text{Na}$ 325.1415, found: 325.1402.

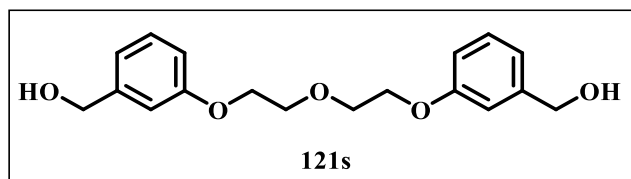
(((1,2-phenylenebis(methylene))bis(oxy))bis(3,1-phenylene))dimethanol (121r): Prepared



according to general procedure **3A.7.2.A**, using 3-hydroxybenzylalcohol (248 mg, 2 mmol, 2 equiv.), 1,2-bis(bromomethyl)benzene (264 mg, 1 mmol, 1 equiv.) and K_2CO_3 (2.2 equiv.) to afford the desired product (((1,2-phenylenebis(methylene))bis(oxy))bis(3,1-phenylene))

dimethanol **121r** (352 mg, 88% yield) as a white amorphous solid (40% Ethyl Acetate: Hexane). **M.P.** = 65–67 °C. **^1H NMR** (400 MHz, CDCl_3) δ 7.45 (s, 1H), 7.34 (s, 3H), 7.21 (t, J = 7.8 Hz, 2H), 6.94 (s, 2H), 6.86 (dd, J = 13.6, 8.4 Hz, 4H), 4.99 (s, 4H), 4.54 (s, 4H), 2.99 (s, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 158.8, 142.7, 137.4, 129.5, 128.8, 127.0, 126.4, 119.4, 114.0, 113.2, 69.7, 64.8. **IR** (neat): 3305, 2870, 1587, 1268, 1153 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{23}\text{O}_4$ 351.1600, found: 351.1600.

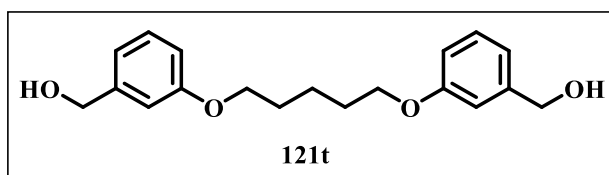
(((oxybis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))dimethanol (121s): Prepared



according to general procedure **3A.7.2.A**, using 3-hydroxybenzylalcohol (125 mg, 1 mmol, 1 equiv.), ditosyldiethyleneglycol (207.14 mg, 0.5

mmol, 0.5 equiv.) and K_2CO_3 (2.2 equiv.) to afford desired product (((oxybis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))dimethanol **121s** (125 mg, 78% yield) as a white amorphous solid (65% Ethyl Acetate: Hexane). **M.P.** = 78–79 °C. **^1H NMR** (400 MHz, CDCl_3) δ 7.20 – 7.14 (m, 2H), 6.84 (d, J = 2.4 Hz, 4H), 6.75 (dd, J = 8.4, 2.3 Hz, 2H), 4.53 (s, 4H), 4.08 – 4.04 (t, 4H), 3.84 (t, J = 4.9 Hz, 4H). **^{13}C NMR** (100 MHz, CDCl_3) δ 159.1, 142.7, 129.6, 119.4, 113.9, 113.3, 70.0, 67.6, 65.2. **IR** (neat): 3543, 2968, 1651, 1213 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{23}\text{O}_5$ 319.1548, found: 319.1548.

(((pentane-1,5-diylbis(oxy))bis(3,1-phenylene))dimethanol (121t): Prepared according to

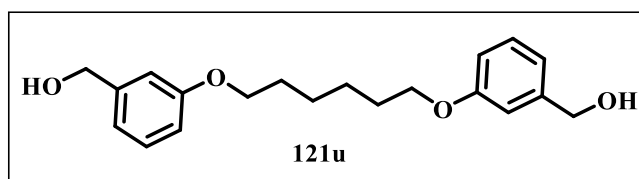


general procedure **3A.7.2.A**, using 3-hydroxybenzylalcohol (248 mg, 2 mmol, 2 equiv.), 1,5-dibromopropane (220 mg, 1 mmol, 1 equiv.) and K_2CO_3 (2.2 equiv.) to

afford desired product (((pentane-1,5-diylbis(oxy))bis(3,1-phenylene))dimethanol **121t** (209

mg, 66 % yield) as a white amorphous solid (45% Ethyl Acetate: Hexane). **M.P.**= 92-94 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.26 (t, *J* = 9.0, 7.1 Hz, 2H), 6.95 – 6.90 (m, 4H), 6.82 (d, *J* = 8.1 Hz, 2H), 4.65 (s, 4H), 4.00 (t, *J* = 6.4 Hz, 4H), 1.94 (s, 2H), 1.85 (m, *J* = 14.5, 6.7 Hz, 4H), 1.65 (m, *J* = 14.8, 4.6 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 159.4, 142.6, 129.7, 119.1, 113.98, 113.1, 67.8, 65.4, 65.2, 29.1, 22.8. **IR** (neat): 3364, 2924, 1594, 1262, 1151 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₉H₂₄O₄Na 339.1572, found: 339.1557.

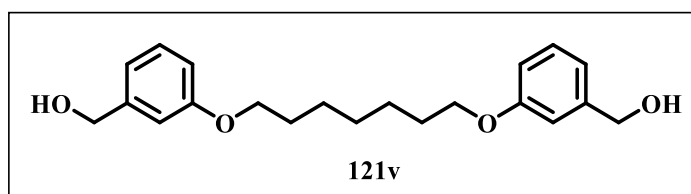
((hexane-1,6-diylbis(oxy))bis(3,1-phenylene))dimethanol (121u): Prepared according to



general procedure **3A.7.2.A**, using 3-hydroxybenzylalcohol (248 mg, 2 mmol, 2 equiv.), 1,6-dibromopropane (244 mg, 1 mmol, 1 equiv.) and K₂CO₃ (2.2 equiv.)

to afford desired product ((hexane-1,6-diylbis(oxy))bis(3,1-phenylene))dimethanol **121u** (231 mg, 70 % yield) as a white amorphous solid (45% Ethyl Acetate: Hexane). **M.P.**= 96-97 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.24 (dd, *J* = 9.2, 7.0 Hz, 2H), 6.92 – 6.88 (m, 4H), 6.83 – 6.79 (m, 2H), 4.64 (s, 4H), 3.94 (t, *J* = 6.5 Hz, 4H), 1.83 (s, 1H), 1.80 – 1.71 (m, 4H), 1.43 (m, *J* = 14.3, 6.6 Hz, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 159.5, 142.5, 129.6, 119.0, 113.9, 113.0, 68.0, 65.4, 29.5, 29.4, 29.3, 26.1. **IR** (neat): 3345, 2923, 1599, 1257, 1155 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₀H₂₆O₄Na 353.1728, found: 353.1713.

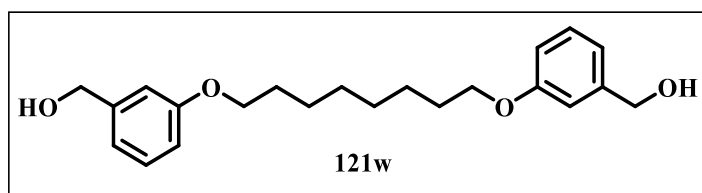
((heptane-1,7-diylbis(oxy))bis(3,1-phenylene))dimethanol (121v): Prepared according to



general procedure **3A.7.2.A**, using 3-hydroxybenzylalcohol (248 mg, 2 mmol, 2 equiv.), 1,7-dibromopropane (258 mg, 1 mmol, 1 equiv.) and

K₂CO₃ (2.2 equiv.) to afford desired product ((heptane-1,7-diylbis(oxy))bis(3,1-phenylene))dimethanol **121v** (250 mg, 72 % yield) as a white amorphous solid (40% Ethyl Acetate: Hexane). **M.P.**= 96-98 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.28 (dd, *J* = 9.0, 7.1 Hz, 2H), 6.96 – 6.92 (m, 4H), 6.84 (dd, *J* = 8.1, 1.8 Hz, 2H), 4.68 (s, 4H), 3.99 (t, *J* = 6.5 Hz, 4H), 1.82 (dt, *J* = 13.1, 6.5 Hz, 5H), 1.58 – 1.46 (m, 5H). **¹³C NMR** (100 MHz, CDCl₃) δ 159.5, 142.6, 129.7, 119.0, 113.9, 113.0, 68.0, 65.4, 29.3, 29.1, 26.1. **IR** (neat): 3352, 2923, 1598, 1259, 1154 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₁H₂₈O₄Na 367.1885, found: 367.1877.

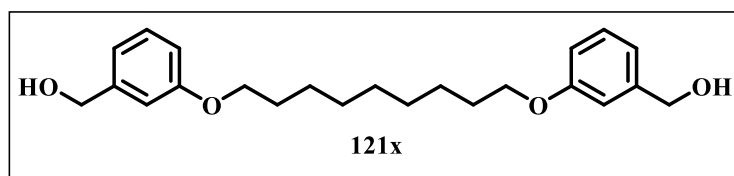
((octane-1,8-diylbis(oxy))bis(3,1-phenylene))dimethanol (121w): Prepared according to



general procedure **3A.7.2.A**, using 3-hydroxybenzylalcohol (248 mg, 2 mmol, 2 equiv.), 1,8-dibromopropane (272 mg, 1 mmol, 1

equiv.) and K_2CO_3 (2.2 equiv.) to afford desired product ((octane-1,8-diylbis(oxy))bis(3,1-phenylene))dimethanol **121w** (259 mg, 72 % yield) as a white amorphous solid (45% Ethyl Acetate: Hexane). **M.P.**= 98-100 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 8.0 Hz, 2H), 6.93 – 6.88 (m, 4H), 6.84 – 6.79 (m, 2H), 4.64 (s, 4H), 3.95 (t, J = 6.5 Hz, 4H), 1.83 – 1.72 (m, 6H), 1.51 – 1.38 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 142.5, 129.7, 119.1, 113.9, 113.0, 68.0, 65.4, 29.37, 29.3, 26.1. **IR** (neat): 3345, 2923, 1588, 1277, 1149 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[M+Na]^+$ calcd for $C_{22}H_{30}O_4Na$ 381.2041, found: 381.2051.

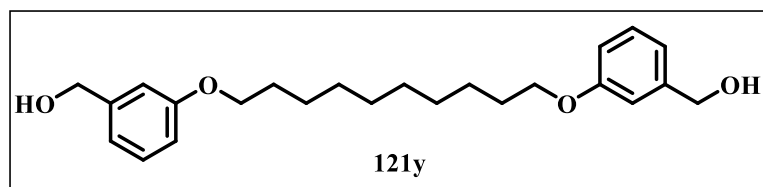
((nonane-1,9-diylbis(oxy))bis(3,1-phenylene))dimethanol (121x): Prepared according to



general procedure **3A.7.2.A**, using 3-hydroxybenzylalcohol (248 mg, 2 mmol, 2 equiv.), 1,9-dibromopropane (276 mg, 1

mmol, 1 equiv.) and K_2CO_3 (2.2 equiv.) to afford desired product ((nonane-1,9-diylbis(oxy))bis(3,1-phenylene))dimethanol **121x** (272 mg, 70 % yield) as a white amorphous solid (40% Ethyl Acetate: Hexane). **M.P.**= 99-101 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 9.0, 7.1 Hz, 2H), 6.92 (d, J = 7.1 Hz, 4H), 6.86 – 6.79 (m, 2H), 4.66 (s, 4H), 3.96 (t, J = 6.5 Hz, 4H), 1.83 – 1.70 (m, 6H), 1.51 – 1.42 (m, 4H), 1.36 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 142.6, 129.7, 119.0, 113.9, 113.0, 68.0, 65.4, 29.5, 29.3, 26.1. **IR** (neat): 3358, 2921, 1611, 1273, 1147 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[M+Na]^+$ calcd for $C_{23}H_{32}O_4Na$ 395.2198, found: 395.2198.

((decane-1,10-diylbis(oxy))bis(3,1-phenylene))dimethanol (121y): Prepared according to

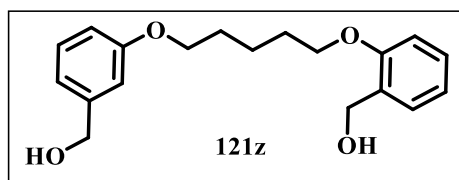


general procedure **3A.7.2.A**, using 3-hydroxybenzylalcohol (248 mg, 2 mmol, 2 equiv.), 1,10-dibromopropane (290

mg, 1 mmol, 1 equiv.) and K_2CO_3 (2.2 equiv.) to afford desired product ((decane-1,10-diylbis(oxy))bis(3,1-phenylene))dimethanol **121y** (260 mg, 67 % yield) as a white amorphous solid (40% Ethyl Acetate: Hexane). **M.P.**= 94-96 °C. 1H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J

= 9.1, 7.0 Hz, 2H), 6.91 (d, J = 7.6 Hz, 4H), 6.86 – 6.79 (m, 2H), 4.65 (s, 4H), 3.96 (t, J = 6.5 Hz, 4H), 1.84 – 1.73 (m, 6H), 1.45 (m, J = 14.1, 6.5 Hz, 4H), 1.33 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.5, 142.5, 129.6, 119.0, 113.9, 113.0, 68.0, 65.4, 29.5, 29.4, 29.3, 29.3, 26.1. IR (neat): 3348, 2922, 1589, 1278, 1150 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{34}\text{O}_4\text{Na}$ 409.2354, found: 409.2347.

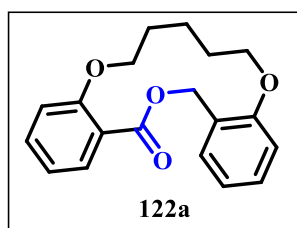
(2-((5-(3-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol (121z): Prepared



according to general procedure **3A.7.2.C**, using 3-hydroxybenzylalcohol (124 mg, 1 mmol, 1 equiv.), (2-((5-bromopentyl)oxy)phenyl)methanol (273 mg, 1 mmol, 1 equiv.) and K_2CO_3 (1.2 equiv.) to afford desired

product (2-((5-(3-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol **121z** (225 mg, 71 % yield) as a white amorphous solid (45% Ethyl Acetate: Hexane). **M.P.** = 54-56 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.28 – 7.21 (m, 3H), 6.95 – 6.87 (m, 3H), 6.85 (d, J = 8.1 Hz, 1H), 6.80 (dd, J = 8.2, 2.4 Hz, 1H), 4.66 (s, 2H), 4.61 (s, 2H), 4.01 (m, J = 12.8, 6.2 Hz, 4H), 2.60 (s, 1H), 2.42 (s, 1H), 1.86 (dq, J = 9.8, 6.5 Hz, 4H), 1.70 – 1.60 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.3, 156.8, 142.7, 129.6, 129.1, 128.9, 128.6, 120.66, 119.1, 113.7, 113.0, 111.0, 67.7, 67.6, 65.1, 62.1, 29.0, 28.9, 22.8. IR (neat): 3333, 2919, 1601, 1237 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{24}\text{O}_4\text{Na}$ 339.1572, found: 339.1566.

7,8,9,10-tetrahydro-6H,16H,18H-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one (122a)

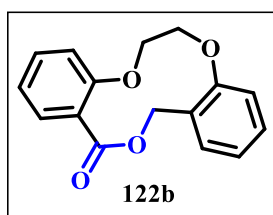


(CCDC = 2132244): Prepared according to general procedure **3A.7.2.D**, using ((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))dimethanol (**93d**) (21.8 mg, 0.069 mmol, 1 equiv.), Cs_2CO_3 (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 7,8,9,10-

tetrahydro-6H,16H,18H-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one **122a** (17.4 mg, 80% yield) as a yellowish crystalline solid (5% Ethyl Acetate: Hexane). **M.P.** = 86-89 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.82 – 7.75 (dt, 1H), 7.45 (d, J = 7.3 Hz, 1H), 7.41 – 7.35 (td, 1H), 7.35 – 7.28 (td, 1H), 6.97 – 6.87 (m, 3H), 6.84 (d, J = 8.3 Hz, 1H), 5.41 (s, 2H), 4.12 (t, J = 5.2 Hz, 2H), 3.98 (t, J = 5.0 Hz, 2H), 2.00 – 1.85 (m, 4H), 1.74 (dt, J = 14.9, 5.4 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.4, 158.4, 158.1, 133.1, 133.0, 131.8, 130.5, 123.8, 120.1, 120.0, 112.5, 111.3, 67.7, 64.8, 63.4, 27.1, 26.5, 20.4. IR (neat): 1695, 1598, 1245, 1121 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{O}_4\text{Na}$ 335.1259, found: 335.1258. **Crystal data:** The crystals of compound **122a** were grown using dichloromethane and hexane as a solvent by slow

evaporation. $C_{19}H_{20}O_4$, $M = 312.35$, Triclinic, space group P-1 with $a = 8.0125(11)$ Å, $b = 9.3432(12)$ Å, $c = 10.8050(14)$ Å, $\alpha = 81.224(4)^\circ$, $\beta = 79.517(4)^\circ$, $\gamma = 82.012(4)^\circ$, $V = 780.91(18)$ Å³, $T = 296$ K, $R_1 = 0.0385$, $wR_2 = 0.1089$ for observed data, $z = 2$, $D_{\text{calcd}} = 1.328$ g cm⁻³, $F(000) = 332.0$, absorption coefficient = 0.752 mm⁻¹, $\lambda = 1.54178$ Å, 2597 reflections collected on a Bruker APEX-III CCD single-crystal diffractometer, and 2301 observed reflections ($I \geq 2\sigma(I)$) with $S=1.054$.

6,7-dihydro-13*H*,15*H*-dibenzo[*e,j*][1,4,8]trioxacycloundecin-13-one (122b) (CCDC=



2171837): Prepared according to general procedure **3A.7.2.D**, using ((ethane-1,2-diylbis(oxy))bis(2,1-phenylene))dimethanol (**121h**)

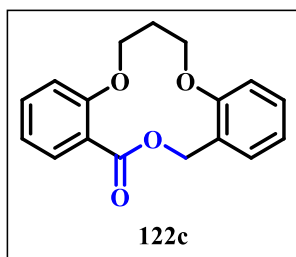
(19.2 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford

desired product 6,7-dihydro-13*H*,15*H*-

dibenzo[*e,j*][1,4,8]trioxacycloundecin-13-one **122b** (8 mg, 42% yield) as a yellowish crystalline solid (15% Ethyl Acetate: Hexane). **M.P.** = 143-146 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.60 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.38 – 7.33 (m, 1H), 7.31 – 7.27 (m, 2H), 7.12 – 6.99 (m, 3H), 6.95 (td, $J = 7.5, 1.0$ Hz, 1H), 5.31 (s, 2H), 4.47 – 4.43 (m, 2H), 4.09 – 4.05 (m, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 167.6, 158.9, 158.1, 132.8, 131.3, 130.6, 130.4, 127.9, 126.9, 124.3, 122.6, 122.5, 118.6, 74.3, 72.1, 65.0. **IR** (neat): 2923, 1715, 1600, 1224, 1121 cm⁻¹. **HRMS** (ESI-TOF) m/z : $[M+H]^+$ calcd for C₁₆H₁₅O₄ 271.0976, found: 271.0975. **Crystal data:**

The crystals of compound **122b** were grown using dichloromethane and hexane as a solvent by slow evaporation. C₁₆H₁₄O₄, $M = 270.27$, Monoclinic, space group P 2₁/n with $a = 9.952(3)$ Å, $b = 11.832(4)$ Å, $c = 11.215(3)$ Å, $\alpha = 90^\circ$, $\beta = 98.290(9)^\circ$, $\gamma = 90^\circ$, $V = 1306.8(7)$ Å³, $T = 296$ K, $R_1 = 0.0480$, $wR_2 = 0.1095$ for observed data, $z = 4$, $D_{\text{calcd}} = 1.374$ g cm⁻³, $F(000) = 568.0$, absorption coefficient = 0.099 mm⁻¹, $\lambda = 0.71073$ Å, 3259 reflections collected on a Bruker APEX-III CCD single-crystal diffractometer, and 2443 observed reflections ($I \geq 2\sigma(I)$) with $S=1.060$.

7,8-dihydro-6*H*,14*H*,16*H*-dibenzo[*b,g*][1,5,9]trioxacyclododecin-14-one (122c): Prepared

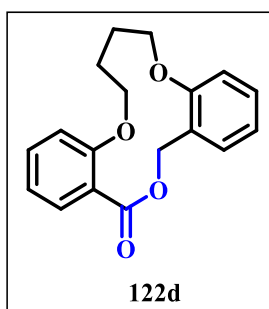


according to general procedure **3A.7.2.D**, using ((propane-1,3-diylbis(oxy))bis(2,1-phenylene))dimethanol (**93b**) (20.18 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.166 mmol, 1 equiv.) and Ru-MACHO (2.5 mg, 0.0045 mmol, 0.06 equiv.) to afford desired product 7,8-dihydro-6*H*,14*H*,16*H*-dibenzo[*b,g*][1,5,9]

trioxacyclododecin-14-one **122c** (13.5 mg, 68% yield) as a white crystalline solid (15% Ethyl

Acetate: Hexane). **M.P.**= 107-109 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.37 (td, *J* = 8.3, 7.5, 1.8 Hz, 1H), 7.35 – 7.28 (m, 2H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 6.90 (m, *J* = 15.7, 9.3, 5.2 Hz, 3H), 5.29 (s, 2H), 4.34 – 4.28 (t, 2H), 4.21 – 4.14 (t, 2H), 2.29 (m, *J* = 10.0, 5.0 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 168.9, 158.4, 157.7, 132.5, 131.5, 130.4, 130.0, 124.23, 123.3, 120.7, 120.3, 113.0, 112.1, 68.5, 67.8, 65.6, 28.8. **IR** (neat): 1709, 1600, 1254, 1128 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₇H₁₆O₄Na 285.1127, found: 285.1133.

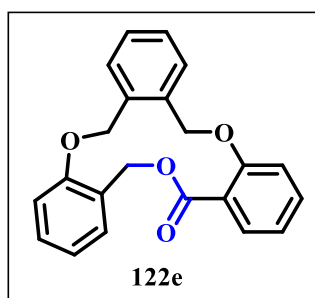
6,7,8,9-tetrahydro-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecin-15-one (122d):



Prepared according to general procedure **3A.7.2.D**, using ((butane-1,4-diylbis(oxy))bis(2,1-phenylene))dimethanol (**93a**) (21.6 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 6,7,8,9-tetrahydro-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecin-15-one **122d** (16.6 mg, 77% yield) as a yellowish oily compound (10%

Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.69 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.34 – 7.28 (td, 1H), 6.97 (m, *J* = 13.1, 8.4, 7.5, 1.0 Hz, 4H), 5.36 (s, 2H), 4.21 – 4.15 (t, 2H), 4.08 (t, *J* = 5.1 Hz, 2H), 2.03 (m, *J* = 14.9, 8.3, 3.7 Hz, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.9, 158.8, 158.4, 132.9, 132.3, 131.1, 130.5, 125.37, 123.7, 121.5, 120.9, 116.9, 114.0, 69.0, 64.4, 27.2, 26.7. **IR** (neat): 1706, 1599, 1250, 1121 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₈H₁₈O₄Na 321.1102, found: 321.1108.

6,11-dihydro-17*H*,19*H*-tribenzo[*b,g,k*][1,5,9]trioxacyclotridecin-17-one (122e): Prepared

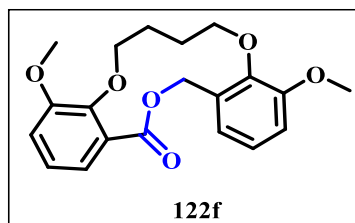


according to general procedure **3A.7.2.D**, using (((1,2-phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (**121e**) (24.5 mg, 0.166 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 6,11-dihydro-17*H*,19*H*-tribenzo[*b,g,k*][1,5,9]trioxacyclotridecin-17-one **122e** (13.5 mg,

56% yield) as a white crystalline compound (10% Ethyl Acetate: Hexane). **M.P.**= 182-184 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.18 (s, 1H), 7.79 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.20 – 7.11 (m, 2H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.01 – 6.86 (m, 4H), 6.81 (td, *J* = 7.4, 0.9 Hz, 1H), 5.53 (s, 2H), 5.32 (s, 2H), 5.02 (s, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 168.13, 157.54, 156.95, 138.06, 137.77, 133.53, 133.43, 132.35, 130.51, 127.83, 125.24, 125.12, 124.85, 124.17, 121.76, 121.33, 120.81, 113.32, 113.00, 69.33, 68.39, 62.33. **IR** (neat): 2925, 1720,

1604, 1205 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{19}\text{O}_4$ 347.1290, found: 347.1289.

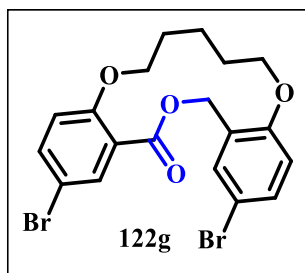
4,11-dimethoxy-6,7,8,9-tetrahydro-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecin-15-



one (122f): Prepared according to general procedure **3A.7.2.D**, using ((butane-1,4-diylbis(oxy))bis(3-methoxy-2,1-phenylene))dimethanol (**93c**) (25.36 mg, 0.166 mmol, 1 equiv.), Cs_2CO_3 (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product

4,11-dimethoxy-6,7,8,9-tetrahydro-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecin-15-one **122f** (13.1 mg, 53% yield) as a white crystalline solid (15% Ethyl Acetate: Hexane). **M.P.**= 146-148 $^{\circ}\text{C}$. ^1H **NMR** (400 MHz, CDCl_3) δ 7.53 – 7.49 (m, 1H), 7.32 – 7.25 (m, 3H), 7.23 (dd, J = 8.2, 1.7 Hz, 1H), 7.17 (dd, J = 7.7, 2.1 Hz, 1H), 5.66 (s, 2H), 4.51 (t, J = 6.7 Hz, 2H), 4.35 (t, J = 5.9 Hz, 2H), 4.09 (s, 3H), 4.07 (s, 3H), 2.35 – 2.26 (m, 2H), 2.25 – 2.16 (m, 2H). ^{13}C **NMR** (100 MHz, CDCl_3) δ 167.8, 153.5, 153.2, 148.7, 147.6, 129.4, 127.3, 124.5, 123.9, 123.8, 122.2, 115.4, 113.7, 74.3, 72.7, 63.6, 56.1, 55.9, 27.2, 25.2. **IR** (neat): 2919, 1704, 1584, 1261 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{22}\text{O}_6\text{Na}$ 359.1494, found: 359.1492.

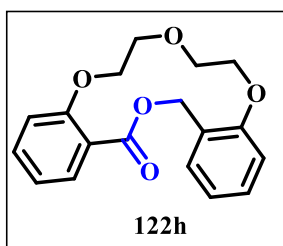
2,14-dibromo-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-



16-one (122g): Prepared according to general procedure **3A.7.2.D**, using ((pentane-1,5-diylbis(oxy))bis(5-bromo-2,1-phenylene))dimethanol (**93e/121f**) (33.19 mg, 0.069 mmol, 1 equiv.), Cs_2CO_3 (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product

2,14-dibromo-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one **122g** (11.8 mg, 36% yield) as a white amorphous solid (5% Ethyl Acetate: Hexane). **M.P.**= 164-166 $^{\circ}\text{C}$. ^1H **NMR** (400 MHz, CDCl_3) δ 7.88 (d, J = 2.6 Hz, 1H), 7.55 (d, J = 2.5 Hz, 1H), 7.47 (dd, J = 8.8, 2.6 Hz, 1H), 7.41 (dd, J = 8.7, 2.5 Hz, 1H), 6.75 (dd, J = 14.4, 8.8 Hz, 2H), 5.31 (s, 2H), 4.09 (t, J = 4.7 Hz, 2H), 3.98 – 3.92 (t, 2H), 1.89 (m, 4H), 1.73 (m, J = 10.1, 5.0 Hz, 2H). ^{13}C **NMR** (100 MHz, CDCl_3) δ 166.8, 157.6, 157.3, 135.9, 135.6, 134.5, 133.3, 125.7, 122.6, 114.5, 113.2, 112.1, 68.1, 65.3, 62.9, 27.0, 26.4, 20.3. **IR** (neat): 2918, 1633, 1263, 737 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{Br}_2\text{O}_4$ 468.9650, found: 468.9659.

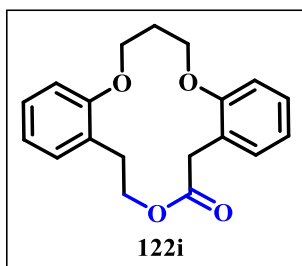
6,7,9,10-tetrahydro-16*H*,18*H*-dibenzo[*h,m*][1,4,7,11]tetraoxacyclotetradecin-16-one



(122h): Prepared according to general procedure **3A.7.2.D**, using (((oxybis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (22.28 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 6,7,9,10-tetrahydro-16*H*,18*H*-

dibenzo[*h,m*][1,4,7,11]tetraoxacyclotetradecin-16-one **122h** (12.3 mg, 56% yield) as a yellowish sticky compound (20% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.72 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.42 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.37 (td, *J* = 8.3, 7.5, 1.8 Hz, 1H), 7.33 – 7.27 (m, 1H), 6.98 – 6.89 (m, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 5.40 (s, 2H), 4.23 – 4.18 (m, 2H), 4.14 – 4.10 (m, 2H), 4.00 – 3.95 (m, 2H), 3.90 – 3.86 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 168.1, 158.1, 157.8, 132.9, 132.8, 131.3, 130.5, 124.0, 121.9, 120.47, 120.3, 112.8, 111.1, 69.6, 69.5, 68.1, 66.4, 63.6. **IR** (neat): 2924, 1687, 1598, 1243 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₈H₁₉O₅ 315.1236, found: 315.1235.

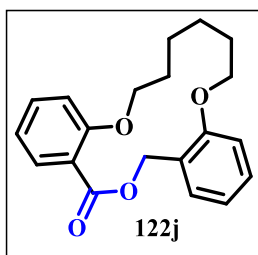
7,8,17,18-tetrahydro-6*H*-dibenzo[*f,m*][1,5,10]trioxacyclotetradecin-15(14*H*)-one (122i):



Prepared according to general procedure **3A.7.2.D**, using 2,2'-(propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) (**121g**) (21.8 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 7,8,17,18-tetrahydro-6*H*-

dibenzo[*f,m*][1,5,10]trioxacyclotetradecin-15(14*H*)-one **122i** (12.3 mg, 58% yield) as a white amorphous solid (10% Ethyl Acetate: Hexane). **M.P.** = 115-117 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.31 – 7.26 (td, 1H), 7.25 – 7.20 (m, 2H), 7.18 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.02 (dd, *J* = 7.4, 1.0 Hz, 1H), 6.97 (dd, *J* = 10.7, 4.3 Hz, 2H), 4.40 – 4.32 (t, 2H), 4.24 (m, *J* = 5.5, 2.6 Hz, 4H), 3.52 (s, 2H), 3.03 – 2.96 (t, 2H), 2.31 – 2.23 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 172.1, 157.7, 157.5, 131.4, 130.2, 128.8, 128.2, 127.8, 125.7, 122.5, 121.1, 117.0, 112.2, 68.2, 66.1, 65.1, 36.0, 29.9, 28.3. **IR** (neat): 2931, 1731, 1601, 1213 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₉H₂₀O₄Na 335.1265, found: 335.1264.

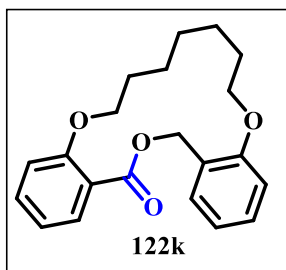
6,7,8,9,10,11-hexahydro-17*H*,19*H*-dibenzo[*b,g*][1,5,9]trioxacyclopentadecin-17-one



(122j): Prepared according to general procedure **3A.7.2.D**, using ((hexane-1,6-diylbis(oxy))bis(2,1-phenylene))dimethanol (**93f**) (23.5 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 6,7,8,9,10,11-hexahydro-17*H*,19*H*-dibenzo[*b,g*][1,5,9]

trioxacyclopentadecin-17-one **122j** (15.4 mg, 66% yield) as a yellowish sticky compound (5% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.70 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.45 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.37 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.5, 1.8 Hz, 1H), 6.94 – 6.85 (m, 4H), 5.42 (s, 2H), 4.14 – 4.10 (m, 2H), 4.09 – 4.04 (m, 2H), 1.89 – 1.81 (m, 2H), 1.81 – 1.73 (m, 4H), 1.70 – 1.61 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.9, 158.2, 157.5, 132.9, 132.8, 131.5, 130.4, 124.3, 121.9, 120.2, 120.0, 112.8, 111.5, 68.6, 68.5, 62.8, 28.8, 28.7, 27.4, 26.9. **IR** (neat): 1699, 1598, 1247, 1124 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₀H₂₂O₄Na 349.1415, found: 349.1412.

7,8,9,10,11,12-hexahydro-6*H*,18*H*,20*H*-dibenzo[*b,g*][1,5,9]trioxacyclohexadecin-18-one

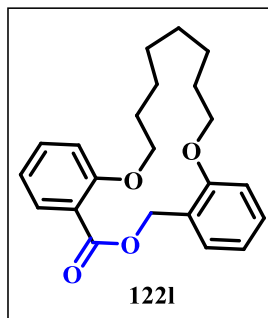


(122k): Prepared according to general procedure **3A.7.2.D**, using ((heptane-1,7-diylbis(oxy))bis(2,1-phenylene))dimethanol (**93g**) (24.11 mg, 0.069 mmol, 1 equiv.) Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 7,8,9,10,11,12-hexahydro-6*H*,18*H*,20*H*-dibenzo[*b,g*][1,5,9]trioxacyclohexadecin-18-one **122k** (11.7 mg,

49% yield) as a yellow oily compound (5% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.69 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.32 – 7.27 (m, 1H), 6.96 – 6.87 (m, 4H), 5.42 (s, 2H), 4.06 (t, *J* = 5.5 Hz, 2H), 4.02 (t, *J* = 5.4 Hz, 2H), 1.80 (m, 4H), 1.58 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.6, 158.3, 158.1, 132.8, 132.7, 131.4, 130.4, 129.5, 124.6, 120.5, 120.3, 114.0, 112.4, 69.1, 68.4, 62.4, 28.4, 28.2, 27.2, 26.4, 26.2. **IR** (neat): 1714, 1598, 1249, 1125 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₁H₂₄O₄Na 363.1572, found: 363.1571.

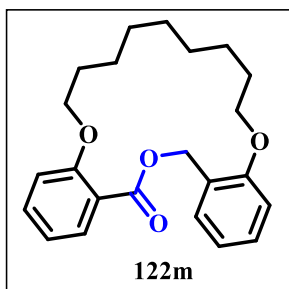
6,7,8,9,10,11,12,13-octahydro-19*H*,21*H*-dibenzo[*b,g*][1,5,9]trioxacycloheptadecin-19-one

(122l): Prepared according to general procedure **3A.7.2.D**, using ((octane-1,8-diylbis(oxy))bis(2,1-phenylene))dimethanol (**93h**) (25 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product



6,7,8,9,10,11,12,13-octahydro-19*H*,21*H*-dibenzo[*b,g*][1,5,9]trioxacycloheptadecin-19-one **122l** (9.9 mg, 40% yield) as a white amorphous solid (3% Ethyl Acetate: Hexane). **M.P.** = 74-76 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.65 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.43 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.30 (td, *J* = 8.1, 1.7 Hz, 1H), 6.97 – 6.84 (m, 4H), 5.39 (s, 2H), 4.13 – 4.07 (t, 2H), 4.01 – 3.95 (t, 2H), 1.76 (m, *J* = 12.5, 6.2 Hz, 2H), 1.64 – 1.51 (m, 6H), 1.44 – 1.34 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.0, 158.1, 157.9, 132.8, 132.1, 131.2, 130.2, 124.2, 121.5, 120.2, 119.8, 112.8, 111.5, 67.9, 67.7, 62.5, 29.4, 29.1, 28.6, 28.2, 27.3, 24.8, 24.6. **IR** (neat): 1720, 1597, 1243, 1123 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₂H₂₆O₄Na 377.1728, found: 377.1722.

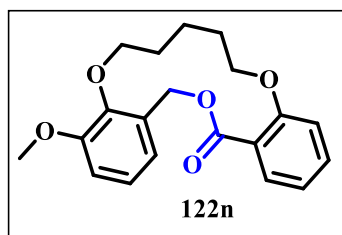
7,8,9,10,11,12,13,14-octahydro-6*H*,20*H*,22*H*-dibenzo[*b,g*][1,5,9]trioxacyclooctadecin-20-one



one (122m): Prepared according to general procedure **3A.7.2.D**, using ((nonane-1,9-diylbis(oxy))bis(2,1-phenylene))dimethanol (**93i**) (26 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 7,8,9,10,11,12,13,14-octahydro-6*H*,20*H*,22*H*-dibenzo[*b,g*][1,5,9]trioxacyclooctadecin-20-one **122m**

(8.4 mg, 32% yield) as a yellow amorphous solid compound (3% Ethyl Acetate: Hexane). **M.P.** = 106-108 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.68 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.44 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.39 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.31 – 7.26 (td, 1H), 6.95 (td, *J* = 7.5, 1.0 Hz, 1H), 6.93 – 6.85 (m, 3H), 5.42 (s, 2H), 4.08 – 4.04 (t, 2H), 4.04 – 3.99 (t, 2H), 1.85 – 1.73 (m, 4H), 1.53 (m, *J* = 11.0, 6.7 Hz, 4H), 1.43 (m, *J* = 9.3, 5.5 Hz, 4H), 1.39 – 1.34 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.7, 158.4, 157.5, 132.9, 131.2, 129.9, 124.7, 121.3, 120.4, 119.8, 112.8, 111.8, 69.1, 68.8, 61.7, 29.5, 29.3, 29.1, 28.8, 28.3, 27.0, 26.6. **IR** (neat): 1717, 1600, 1295, 1126 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₃H₂₈O₄Na 391.1885, found: 391.1893.

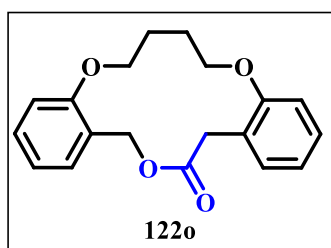
12-methoxy-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one (122n):



16-one (122n): Prepared according to general procedure **3A.7.2.D**, using 2-((5-(2-(hydroxymethyl)-6-methoxyphenoxy)pentyl)oxy)phenyl)methanol (**121a**) (24.3 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford

desired product 12-methoxy-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one **122n** (7.2 mg, 30% yield) as a yellowish semisolid (10% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.73 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.09 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.02 – 6.93 (m, 2H), 6.92 – 6.88 (m, 2H), 5.43 (s, 2H), 4.23 (t, *J* = 6.4 Hz, 2H), 4.05 (t, *J* = 5.0 Hz, 2H), 3.85 (s, 3H), 1.91 (m, *J* = 12.7, 6.3 Hz, 2H), 1.78 (t, *J* = 5.2 Hz, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 168.4, 157.7, 149.0, 148.2, 132.9, 131.5, 129.0, 124.7, 123.3, 121.7, 120.3, 113.6, 112.8, 73.3, 68.7, 62.3, 56.0, 29.3, 28.1, 22.7. **IR** (neat): 2930, 1701, 1601, 1249, 1128 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₀H₂₃O₅ 343.1545, found: 343.1540.

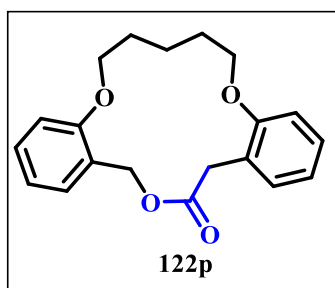
6,7,8,9-tetrahydro-15*H*-dibenzo[*b,h*][1,5,10]trioxacyclotetradecin-17(18*H*)-one (122o):



Prepared according to general procedure **3A.7.2.D**, using 2-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-ol (**121b**) (21.8 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 6,7,8,9-tetrahydro-15*H*-

dibenzo[*b,h*][1,5,10]trioxacyclotetradecin-17(18*H*)-one **122o** (8.8 mg, 40% yield) as a white amorphous solid (5% Ethyl Acetate: Hexane). **M.P.** = 117-119 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.35 (td, *J* = 7.9, 1.7 Hz, 1H), 7.29 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.28 – 7.23 (td, 1H), 7.18 (dd, *J* = 7.2, 0.9 Hz, 1H), 6.98 – 6.88 (m, 3H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.13 (s, 2H), 4.10 (t, *J* = 4.8 Hz, 2H), 4.00 (t, *J* = 4.7 Hz, 2H), 3.59 (s, 2H), 2.10 – 2.00 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 172.4, 158.8, 157.3, 131.6, 131.4, 130.6, 128.8, 124.6, 123.9, 120.7, 120.5, 113.2, 111.1, 68.3, 67.2, 64.4, 37.4, 26.3, 25.8. **IR** (neat): 1731, 1597, 1206, 1156 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₉H₂₀O₄Na 335.1259, found: 335.1259.

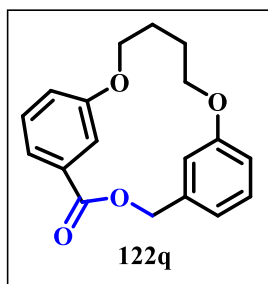
7,8,9,10-tetrahydro-6*H*,16*H*-dibenzo[*b,h*][1,5,10]trioxacyclopentadecin-18(19*H*)-one



(122p): Prepared according to general procedure **3A.7.2.D**, using 2-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (**121c**) (23.5 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 7,8,9,10-tetrahydro-6*H*,16*H*-dibenzo[*b,h*][1,5,10]trioxacyclopentadecin-18(19*H*)-

one **122p** (9.5 mg, 41% yield) as a white amorphous solid (5% Ethyl Acetate: Hexane). **M.P.**= 94-97 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 – 7.31 (m, 2H), 7.23 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.18 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.96 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.91 – 6.85 (m, 2H), 5.14 (s, 2H), 4.11 (t, *J* = 5.0 Hz, 2H), 4.01 (t, *J* = 4.6 Hz, 2H), 3.58 (s, 2H), 1.87 – 1.78 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 172.1, 157.8, 157.3, 132.3, 131.6, 130.6, 128.7, 124.2, 123.6, 120.4, 120.4, 111.6, 111.3, 67.6, 66.0, 63.2, 36.8, 28.8, 28.6, 22.6. **IR** (neat): 2924, 1735, 1603, 1246 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₀H₂₃O₄ 327.1596, found: 327.1585.

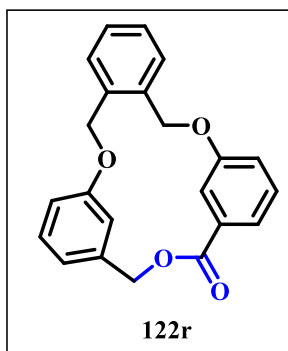
3,6,11-trioxa-1,5(1,3)-dibenzenacycloundecaphan-2-one (122q): Prepared according to



general procedure **3A.7.2.D**, using ((butane-1,4-diylbis(oxy))bis(3,1-phenylene))dimethanol **121q** (50 mg, 0.166 mmol, 1 equiv.), *t*-BuOK (18.6 mg, 0.166 mmol, 1 equiv.) and Ru-MACHO (6 mg, 0.00996 mmol, 0.06 equiv.) to afford desired product 3,6,11-trioxa-1,5(1,3)-dibenzenacycloundecaphan-2-one **122q** (8.4 mg, 17% yield) as a white amorphous solid (10% Ethyl Acetate: Hexane). **M.P.**= 142-144

°C. **¹H NMR** (400 MHz, CDCl₃) δ 7.74 – 7.69 (td, 1H), 7.62 (dd, *J* = 2.4, 1.5 Hz, 1H), 7.43 – 7.38 (td, 1H), 7.33 – 7.27 (t, 1H), 7.17 – 7.12 (m, 2H), 6.90 (dd, *J* = 8.2, 2.2 Hz, 2H), 5.36 (s, 2H), 4.24 – 4.16 (m, 4H), 1.92 – 1.86 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.6, 157.7, 157.6, 138.0, 131.4, 130.3, 130.1, 123.1, 122.3, 118.6, 117.6, 113.2, 110.4, 68.2, 67.5, 65.8, 23.7, 23.1. **IR** (neat): 1721, 1594, 1254, 1160 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: calcd for C₁₈H₁₉O₄ [M+H]⁺: 299.1283, found: 299.1283.

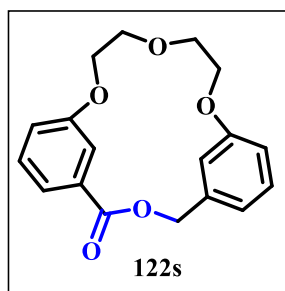
2,6,9-trioxa-1,7(1,3),4(1,2)-tribenzenacyclodecaphan-8-one (122r): Prepared according to



general procedure **3A.7.2.D**, using (((1,2-phenylenebis(methylene))bis(oxy))bis(3,1-phenylene))dimethanol (**121r**) (24.5 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 2,6,9-trioxa-1,7(1,3),4(1,2)-tribenzenacyclodecaphan-8-one **122r** (19.5 mg, 80% yield) as a white amorphous solid (5% Ethyl Acetate: Hexane). **M.P.**= 141-143

°C. **¹H NMR** (400 MHz, CDCl₃) δ 7.51 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.39 (s, 1H), 7.30 – 7.19 (m, 5H), 7.17 – 7.10 (m, 2H), 6.95 – 6.88 (m, 2H), 6.75 (d, *J* = 7.4 Hz, 1H), 5.19 (s, 2H), 5.15 (s, 2H), 5.13 (s, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.6, 159.0, 158.3, 138.5, 138.3, 137.3, 131.1, 130.1, 129.5, 129.5, 126.4, 126.2, 126.0, 123.1, 122.7, 120.2, 118.4, 114.3, 112.6, 71.1, 70.7, 66.0. **IR** (neat): 2923, 1718, 1596, 1204, 1162 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₂H₁₈O₄Na 373.1417, found: 373.1417.

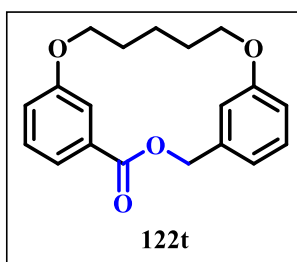
3,6,9,12-tetraoxa-1,5(1,3)-dibenzacyclododecaphan-2-one (122s): Prepared according to



general procedure **3A.7.2.D**, using (((oxybis(ethane-2,1-diyl))bis(oxy))bis(3,1-phenylene))dimethanol (**121s**) (22.3 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 3,6,9,12-tetraoxa-1,5(1,3)-dibenzacyclododecaphan-2-one **122s** (13.3 mg, 60% yield) as a

white amorphous solid (10% Ethyl Acetate: Hexane). **M.P.**= 114-116 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.11 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.50 (s, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.25 (t, *J* = 9.5, 6.2 Hz, 1H), 7.15 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 2H), 5.41 (s, 2H), 4.43 – 4.39 (t, 2H), 4.36 (t, *J* = 4.7 Hz, 2H), 3.84 – 3.80 (t, 2H), 3.80 – 3.77 (t, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.7, 160.1, 159.6, 138.4, 131.5, 129.7, 129.6, 123.0, 122.8, 118.7, 117.4, 115.3, 111.4, 71.9, 69.2, 69.2, 65.0. **IR** (neat): 2922, 1723, 1596, 1213 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₈H₁₉O₅ 315.1239, found: 315.1239.

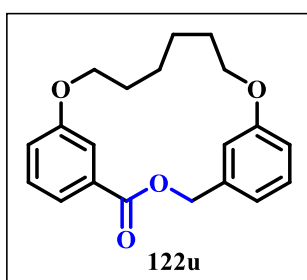
3,6,12-trioxa-1,5(1,3)-dibenzenacyclododecaphan-2-one (122t) (CCDC= 2132244):



Prepared according to general procedure **3A.7.2.D**, using ((pentane-1,5-diylbis(oxy))bis(3,1-phenylene))dimethanol (**121t**) (21.8 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 3,6,12-trioxa-1,5(1,3)-dibenzenacyclododecaphan-

2-one **122t** (12.3 mg, 56% yield) as a white amorphous solid (5% Ethyl Acetate: Hexane). **M.P.**= 86-88 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.72 (dd, *J* = 9.4, 1.8 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.14 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 6.92 – 6.85 (m, 2H), 5.37 (s, 2H), 4.26 – 4.17 (m, 4H), 1.93 – 1.83 (m, 4H), 1.59 – 1.52 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.6, 159.0, 158.7, 137.9, 131.4, 130.1, 129.9, 123.4, 122.6, 118.8, 117.8, 113.2, 110.5, 68.4, 68.1, 65.6, 27.7, 20.4. **IR** (neat): 1724, 1595, 1261, 1160 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₉H₂₁O₄ 313.1440, found: 313.1436. **Crystal data**: The crystals of compound **122t** were grown using dichloromethane and hexane as a solvent by slow evaporation. C₁₉H₂₀O₄, *M* = 312.35, Triclinic, space group P-1 with *a* = 7.6368(4) Å, *b* = 9.4364(5) Å, *c* = 11.2006(6) Å, α = 97.010(2)°, β = 95.383(2)°, γ = 100.898(2)°, *V* = 781.00(7) Å³, *T* = 296 K, *R*₁ = 0.0414, *wR*₂ = 0.1109 for observed data, *z* = 2, *D*_{calcd} = 1.328 g cm⁻³, *F*(000) = 332.0, absorption coefficient = 0.752 mm⁻¹, λ = 1.54178 Å, 2601 reflections collected on a Bruker APEX-III CCD single-crystal diffractometer, and 2360 observed reflections (*I* ≥ 2σ(*I*)) with *S*=1.044.

3,6,13-trioxa-1,5(1,3)-dibenzenacyclotridecaphan-2-one (122u): Prepared according to

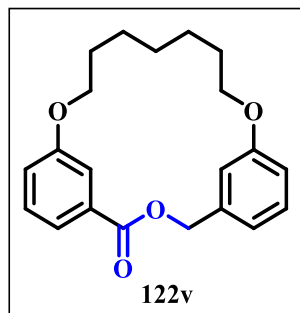


general procedure **3A.7.2.D**, using ((hexane-1,6-diylbis(oxy))bis(3,1-phenylene))dimethanol (**121u**) (23.5 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 3,6,13-trioxa-1,5(1,3)-dibenzenacyclotridecaphan-2-one **122u** (14 mg, 61% yield) as a white amorphous solid (5% Ethyl

Acetate: Hexane). **M.P.**= 113-115 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.71 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 9.2, 6.7 Hz, 1H), 7.22 (d, *J* = 1.7 Hz, 1H), 7.15 – 7.10 (m, 1H), 6.91 (dd, *J* = 7.9, 1.9 Hz, 2H), 5.36 (s, 2H), 4.17 (m, *J* = 15.0, 7.5 Hz, 4H), 1.82 (m, *J* = 6.9, 3.2 Hz, 4H), 1.58 – 1.47 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.9, 159.6, 158.7, 137.7, 131.5, 129.9, 129.8, 123.1, 122.8, 119.8, 117.6, 113.4,

112.4, 68.9, 68.7, 66.3, 28.7, 27.8, 24.9, 24.6. **IR** (neat): 1727, 1600, 1221, 1168 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{O}_4$ 349.1415, found: 349.1411.

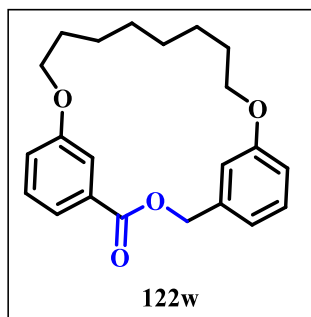
3,6,14-trioxa-1,5(1,3)-dibenzenacyclotetradecaphan-2-one (122v): Prepared according to



general procedure **3A.7.2.D**, using ((heptane-1,7-diylbis(oxy))bis(3,1-phenylene))dimethanol (**121v**) (24.1 mg, 0.069 mmol, 1 equiv.), Cs_2CO_3 (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 3,6,14-trioxa-1,5(1,3)-dibenzenacyclotetradecaphan-2-one **122v** (16.2 mg, 68% yield) as a white amorphous solid (5% Ethyl

Acetate: Hexane). **M.P.** = 71–73 $^{\circ}\text{C}$. **^1H NMR** (400 MHz, CDCl_3) δ 7.74 – 7.69 (m, 2H), 7.38 (t, J = 7.9 Hz, 1H), 7.30 – 7.24 (t, 2H), 7.12 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 6.87 (dd, J = 8.2, 2.6 Hz, 2H), 5.35 (s, 2H), 4.12 (m, J = 10.7, 4.0 Hz, 4H), 1.86 (m, J = 6.6 Hz, 4H), 1.56 – 1.45 (m, 6H). **^{13}C NMR** (100 MHz, CDCl_3) δ 165.8, 159.5, 158.9, 137.9, 131.4, 129.8, 129.6, 122.4, 121.2, 118.8, 114.9, 114.6, 112.1, 69.2, 68.8, 65.8, 28.3, 28.0, 27.9, 26.5, 26.1. **IR** (neat): 1723, 1594, 1265, 1161 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{25}\text{O}_4$ 341.1753, found: 341.1748.

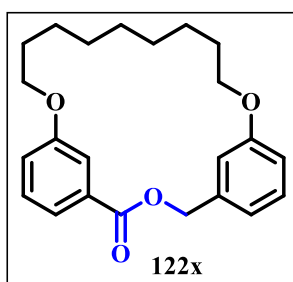
3,6,15-trioxa-1,5(1,3)-dibenzenacyclopentadecaphan-2-one (122w): Prepared according to



general procedure **3A.7.2.D**, using ((octane-1,8-diylbis(oxy))bis(3,1-phenylene))dimethanol (**121w**) (25.1 mg, 0.069 mmol, 1 equiv.), Cs_2CO_3 (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 3,6,15-trioxa-1,5(1,3)-dibenzenacyclopentadecaphan-2-one **122w** (20 mg, 80% yield) as a

yellow oily compound (5% Ethyl Acetate: Hexane). **^1H NMR** (400 MHz, CDCl_3) δ 7.72 – 7.68 (dt, 1H), 7.66 – 7.63 (m, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.27 (dd, J = 10.3, 5.4 Hz, 1H), 7.15 (s, 1H), 7.11 (ddd, J = 8.2, 2.6, 0.8 Hz, 1H), 6.91 – 6.85 (m, 2H), 5.35 (s, 2H), 4.08 (m, J = 6.4, 1.2 Hz, 4H), 1.85 – 1.75 (m, 4H), 1.49 (m, J = 12.8, 6.5 Hz, 4H), 1.44 – 1.37 (m, 4H). **^{13}C NMR** (100 MHz, CDCl_3) δ 166.0, 159.5, 159.0, 137.8, 131.4, 129.7, 129.6, 122.4, 120.7, 119.5, 115.5, 115.2, 113.1, 68.9, 68.4, 66.1, 28.5, 28.4, 28.2, 25.8, 25.7. **IR** (neat): 1724, 1594, 1278, 1163 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{27}\text{O}_4$ 355.1912, found: 355.1904.

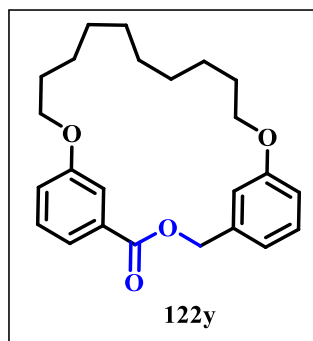
3,6,16-trioxa-1,5(1,3)-dibenzenacyclohexadecaphan-2-one (122x): Prepared according to



general procedure **3A.7.2.D**, using ((nonane-1,9-diylbis(oxy))bis(3,1-phenylene))dimethanol (**121x**) (26 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 3,6,16-trioxa-1,5(1,3)-dibenzenacyclohexadecaphan-2-one **122x** (20 mg, 78% yield) as a white crystalline solid (5% Ethyl

Acetate: Hexane). **M.P.** = 95-98 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.71 (d, *J* = 7.5 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.27 (td, *J* = 11.0, 4.8 Hz, 1H), 7.19 (s, 1H), 7.13 – 7.09 (dd, 1H), 6.86 (m, *J* = 10.9, 5.1 Hz, 2H), 5.35 (s, 2H), 4.07 – 4.01 (m, 4H), 1.87 – 1.77 (m, 4H), 1.50 (m, *J* = 6.6, 4.2 Hz, 4H), 1.42 (dd, *J* = 12.2, 7.8 Hz, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.1, 159.7, 159.1, 137.7, 131.4, 129.7, 129.6, 122.4, 120.1, 118.9, 114.8, 113.8, 112.8, 68.1, 67.7, 66.1, 28.7, 28.5, 28.3, 27.6, 27.5, 25.2. **FTIR** (neat): 1724, 1598, 1281, 1222 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₃H₂₉O₄ 383.2222, found: 383.2202.

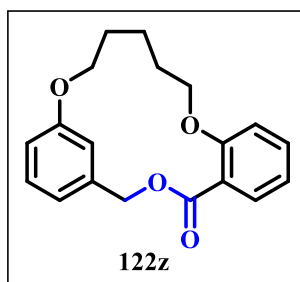
3,6,17-trioxa-1,5(1,3)-dibenzenacycloheptadecaphan-2-one (122y): Prepared according to



general procedure **3A.7.2.D**, ((decane-1,10-diylbis(oxy))bis(3,1-phenylene))dimethanol (**121y**) (27.1 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 3,6,17-trioxa-1,5(1,3)-dibenzenacycloheptadecaphan-2-one **122y** (13.7 mg, 51% yield) as a white solid (5% Ethyl Acetate: Hexane).

M.P. = 101-103 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.62 – 7.59 (t, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.27 (t, *J* = 10.2, 5.4 Hz, 1H), 7.13 – 7.06 (m, 2H), 6.93 – 6.84 (m, 2H), 5.34 (s, 2H), 4.05 – 3.99 (m, 4H), 1.83 – 1.74 (m, 5H), 1.53 – 1.44 (m, 5H), 1.35 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.2, 159.6, 159.0, 137.6, 131.4, 129.6, 129.6, 122.3, 119.8, 119.5, 115.5, 114.5, 113.4, 68.0, 67.6, 66.4, 29.8, 28.7, 28.5, 28.4, 28.0, 27.8, 25.8, 25.6. **IR** (neat): 1724, 1595, 1281, 1166 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₃H₂₉O₄ 369.2066, found: 369.2058.

3,6,12-trioxa-1(1,2),5(1,3)-dibenzenacyclododecaphan-2-one (122z): Prepared according to



general procedure **3A.7.2.D**, using (2-((5-(3-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol (**121z**) (21.8 mg, 0.069 mmol, 1 equiv.), Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv.) and Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv.) to afford desired product 3,6,12-trioxa-1(1,2),5(1,3)-dibenzenacyclododecaphan-2-one **122z** (9.2 mg, 42% yield) as a

white amorphous solid (5% Ethyl Acetate: Hexane). **M.P.**=144-146 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.70 (dd, *J* = 2.5, 1.4 Hz, 1H), 7.59 (dd, *J* = 6.4, 1.2 Hz, 1H), 7.42 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.29 (m, *J* = 7.5, 5.5, 2.8 Hz, 2H), 7.04 (ddd, *J* = 8.2, 2.7, 0.8 Hz, 1H), 6.98 – 6.91 (m, 2H), 5.41 (s, 2H), 4.25 – 4.20 (t, 2H), 4.08 (t, *J* = 6.6 Hz, 2H), 2.08 (m, *J* = 12.9, 6.5 Hz, 2H), 1.80 (m, *J* = 13.7, 6.9 Hz, 2H), 1.74 – 1.65 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.7, 158.8, 158.0, 132.3, 131.9, 131.3, 130.4, 129.8, 125.5, 122.3, 121.9, 121.1, 114.2, 113.5, 68.5, 67.4, 63.7, 27.6, 25.2, 21.5. **IR** (neat): 1722, 1595, 1235, 1111 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₉H₂₁O₄ 313.1440, found: 313.1452.

3A.8 Appendix II: Copies of ^1H and ^{13}C NMR spectra and crystal structure of representative compounds

Entry	Figure No.	Data	Page No.
121a	41 and 42	^1H and ^{13}C	117
121b	43 and 44	^1H and ^{13}C	118
121c	45 and 46	^1H and ^{13}C	119
122a	47 and 48	^1H and ^{13}C	120
122b	49 and 50	^1H and ^{13}C	121
122c	51 and 52	^1H and ^{13}C	122
122d	53 and 54	^1H and ^{13}C	123
122e	55 and 56	^1H and ^{13}C	124
122f	57 and 58	^1H and ^{13}C	125

3A.8.1 Copies of NMR spectra:

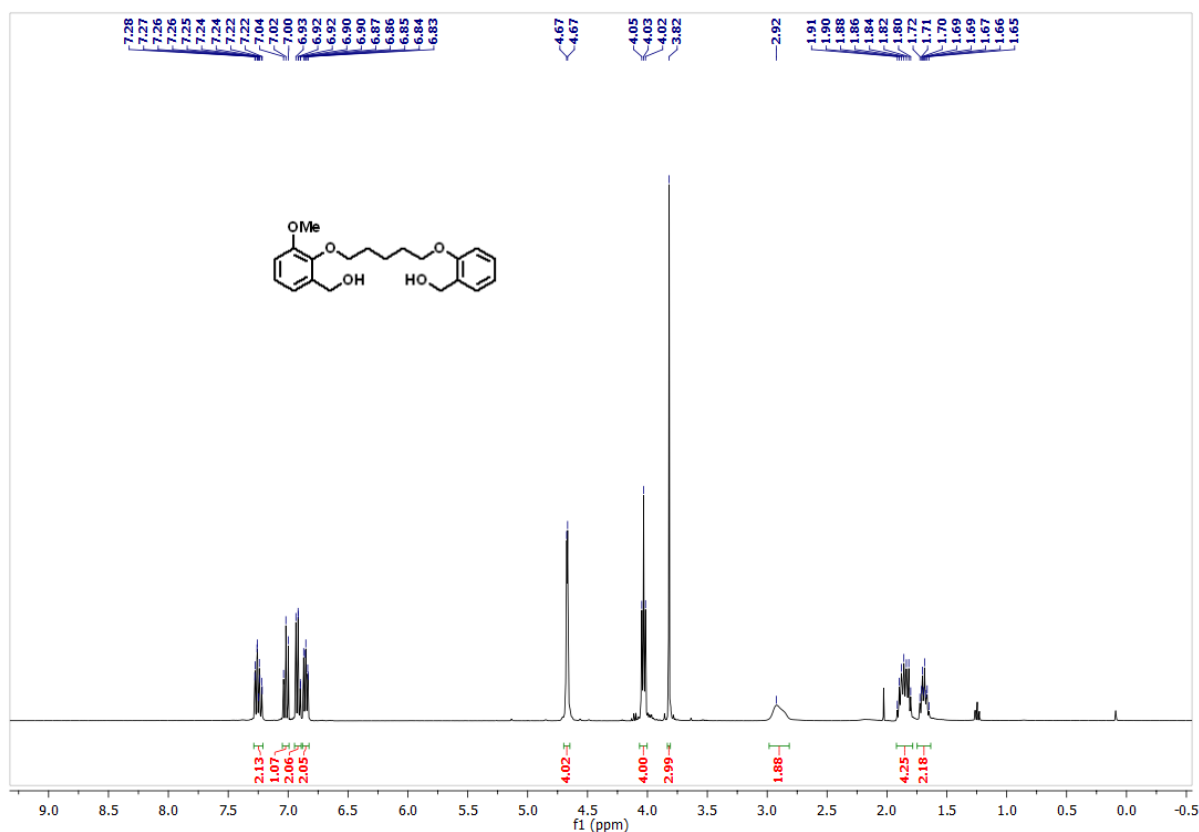


Figure 41. ^1H NMR spectra for compound **121a**, 400 MHz, CDCl_3

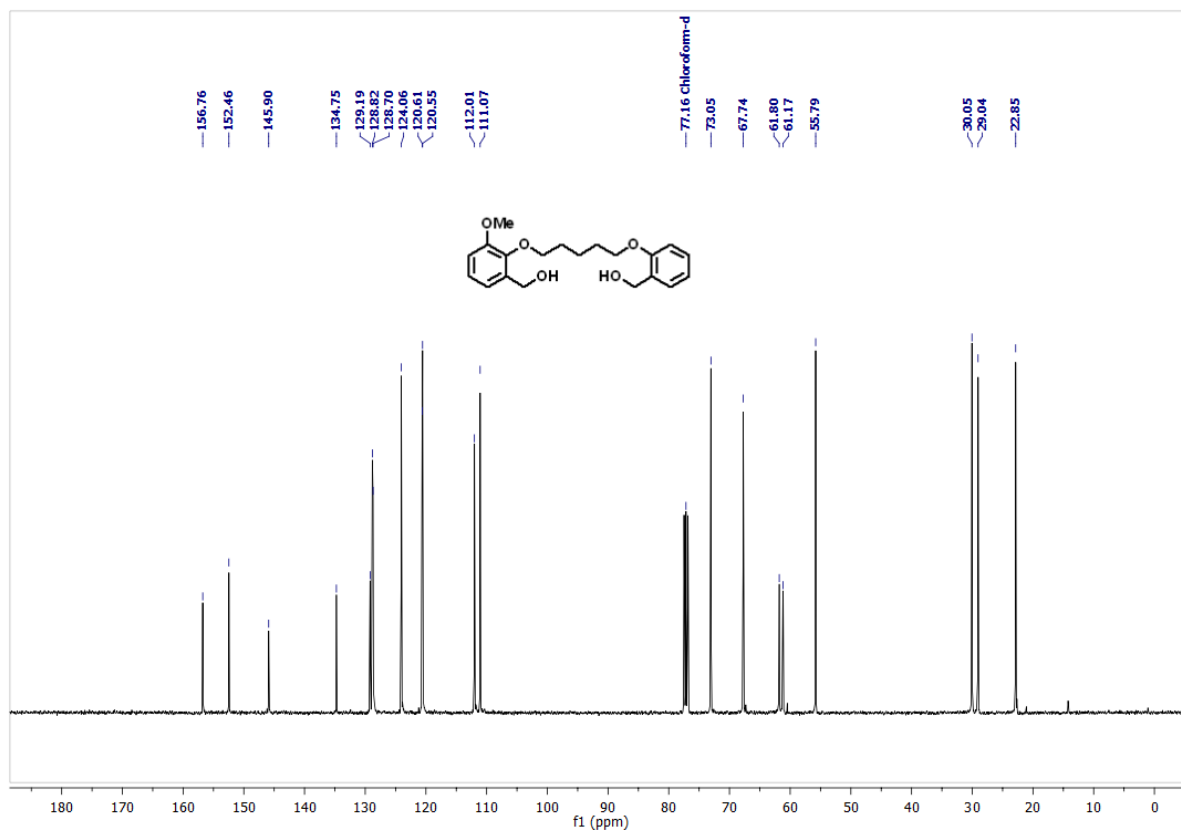


Figure 42. ^{13}C NMR spectra for compound **121a**, 100 MHz, CDCl_3

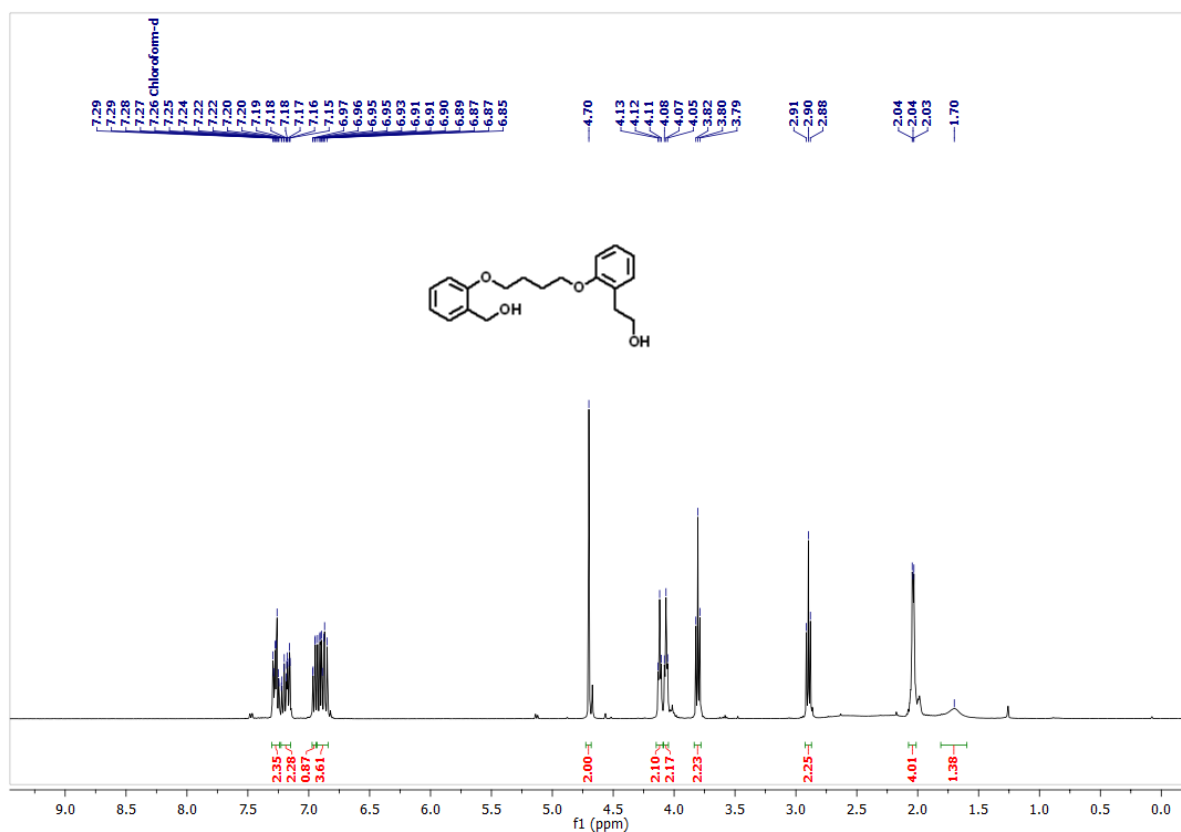


Figure 43. ¹H NMR spectra for compound **121b**, 400 MHz, CDCl₃

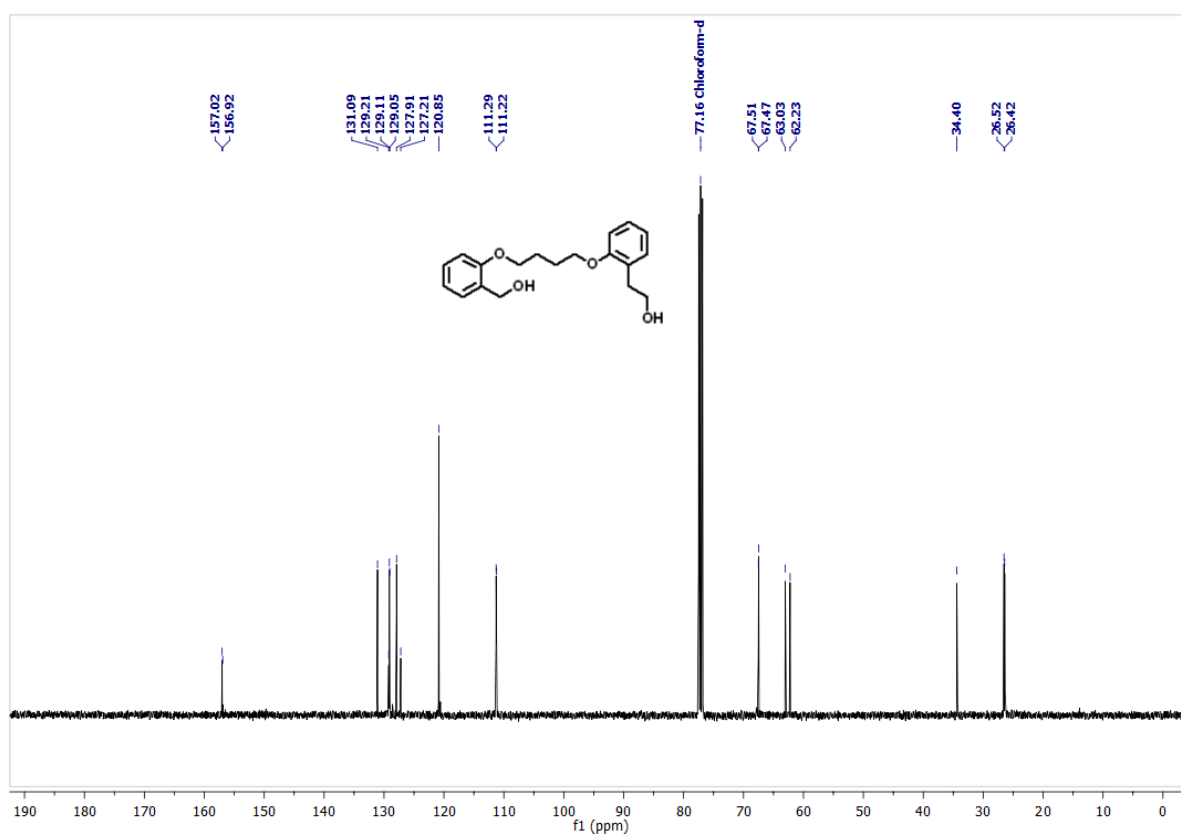


Figure 44. ¹³C NMR spectra for compound **121b**, 100 MHz, CDCl₃

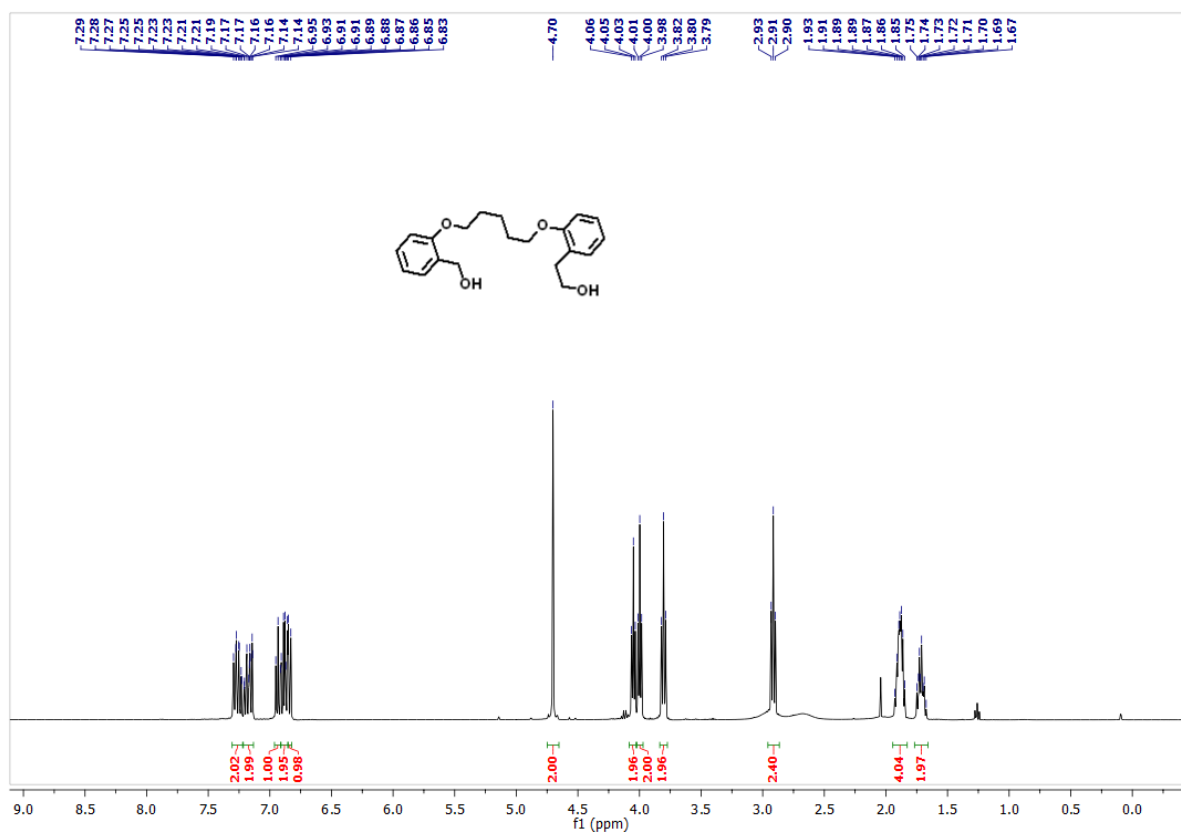


Figure 45. ¹H NMR spectra for compound **121c**, 400 MHz, CDCl₃

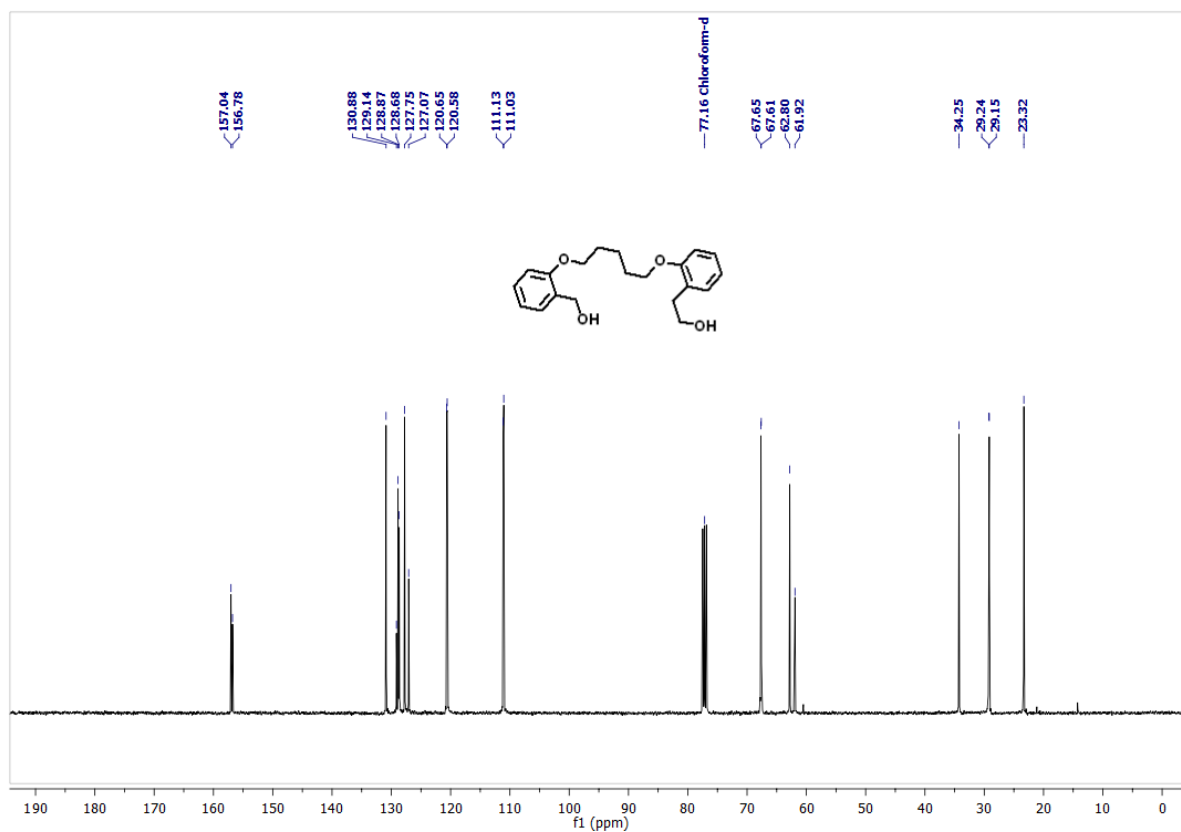


Figure 46. ¹³C NMR spectra for compound **121c**, 100 MHz, CDCl₃

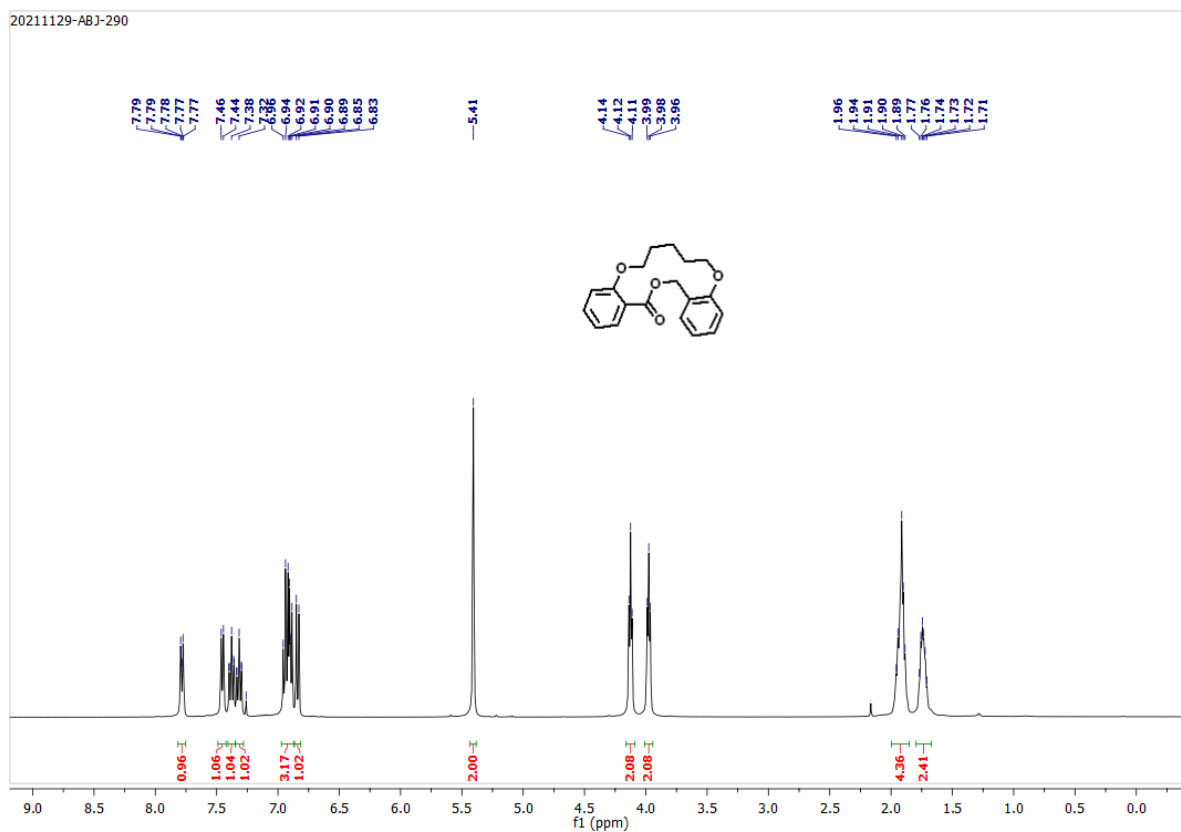


Figure 47. ^1H NMR spectra for compound **122a**, 400 MHz, CDCl_3

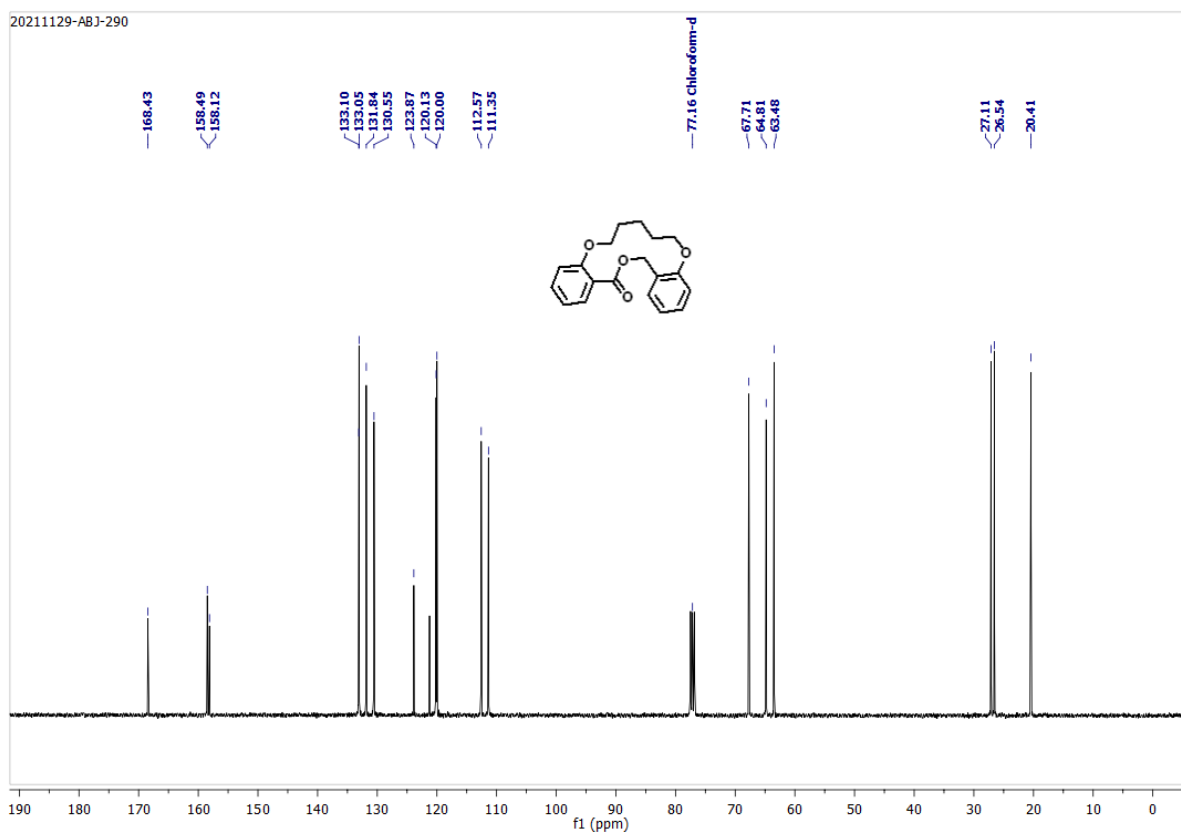


Figure 48. ^{13}C NMR spectra for compound **122a**, 100 MHz, CDCl_3

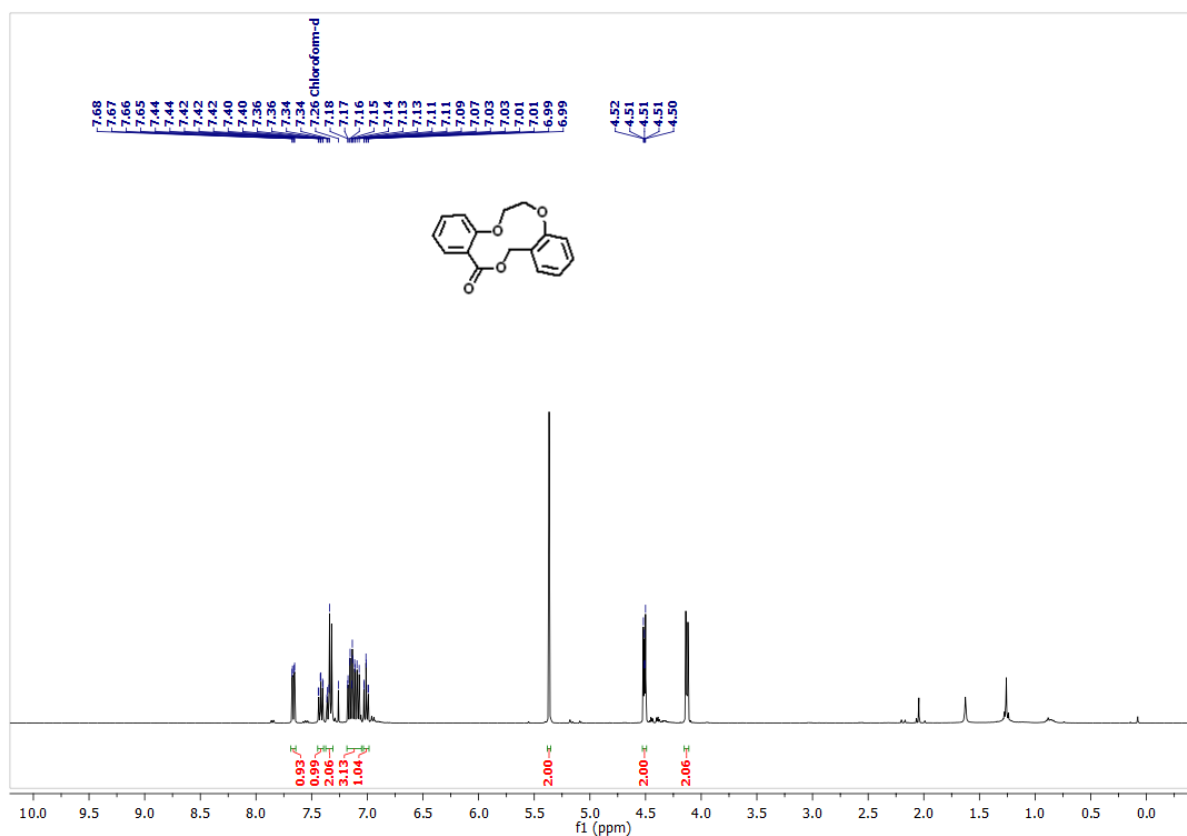


Figure 49. ¹H NMR spectra for compound **122b**, 400 MHz, CDCl₃

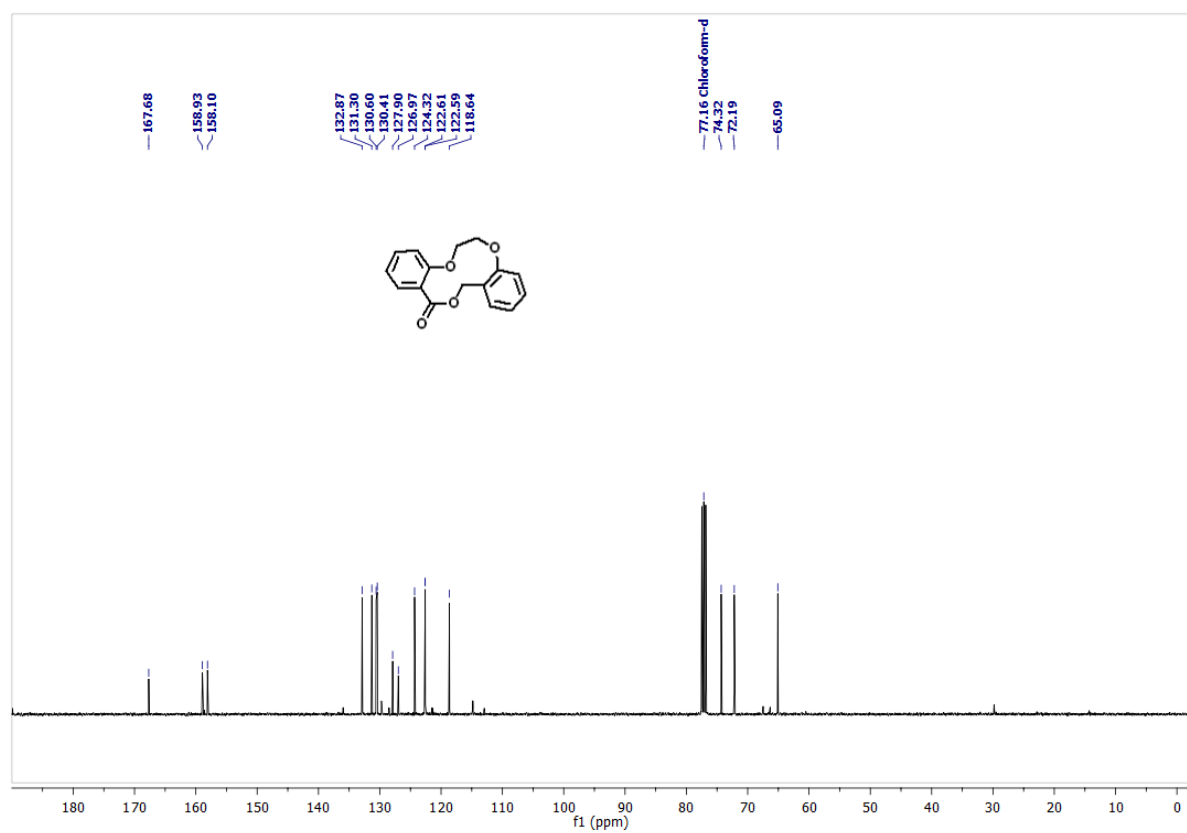


Figure 50. ¹³C NMR spectra for compound **122b**, 100 MHz, CDCl₃

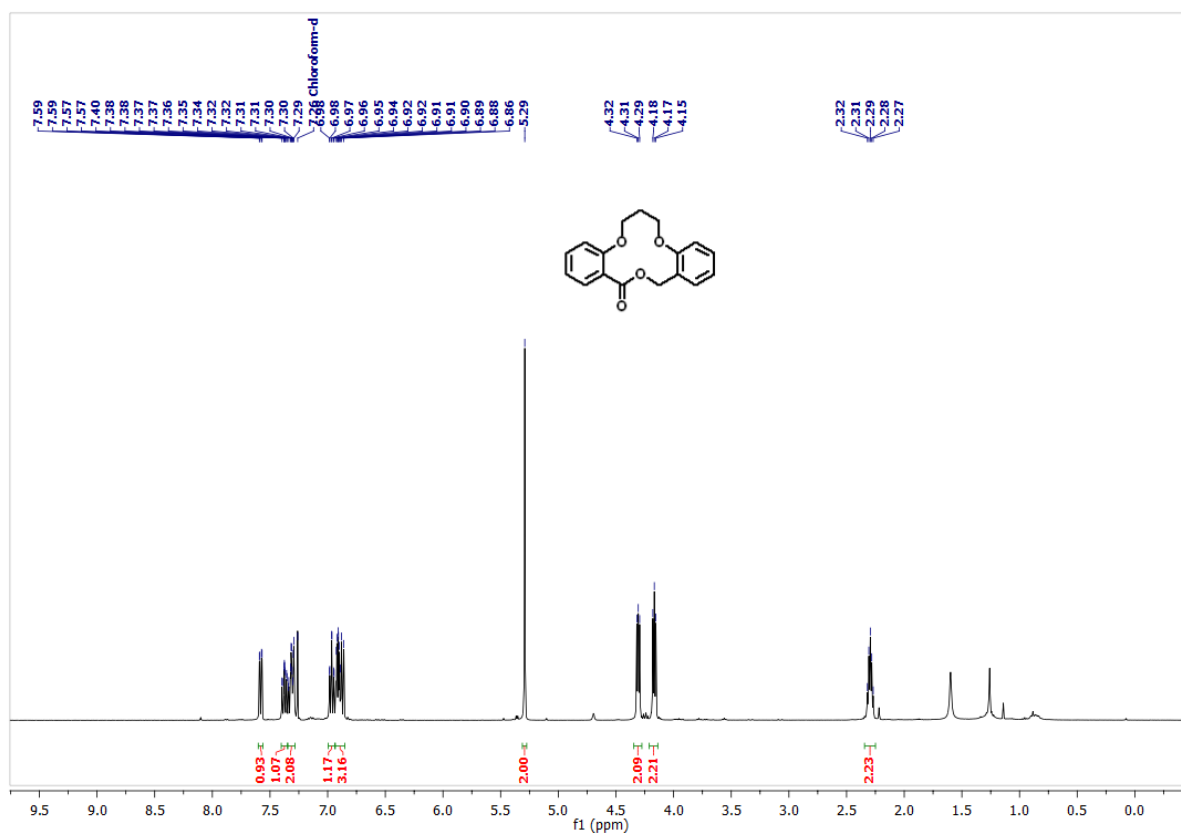


Figure 51. ¹H NMR spectra for compound **122c**, 400 MHz, CDCl₃

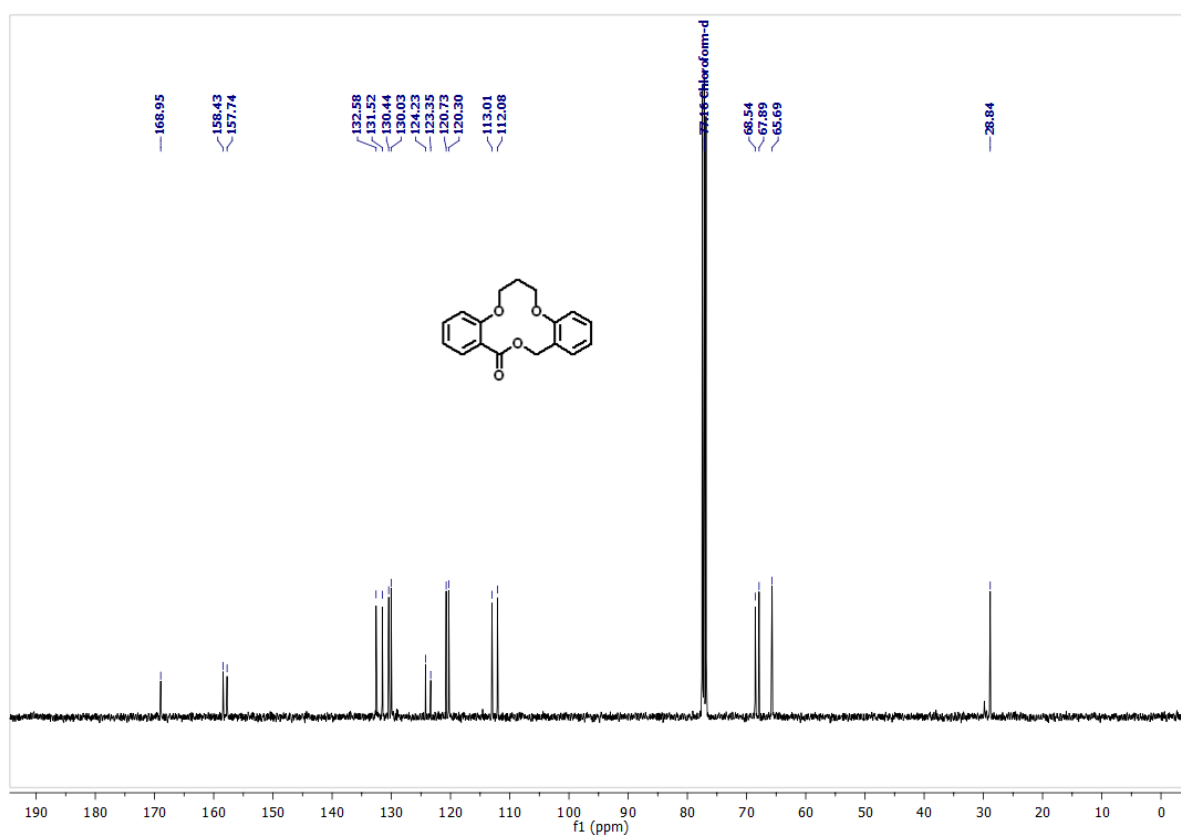
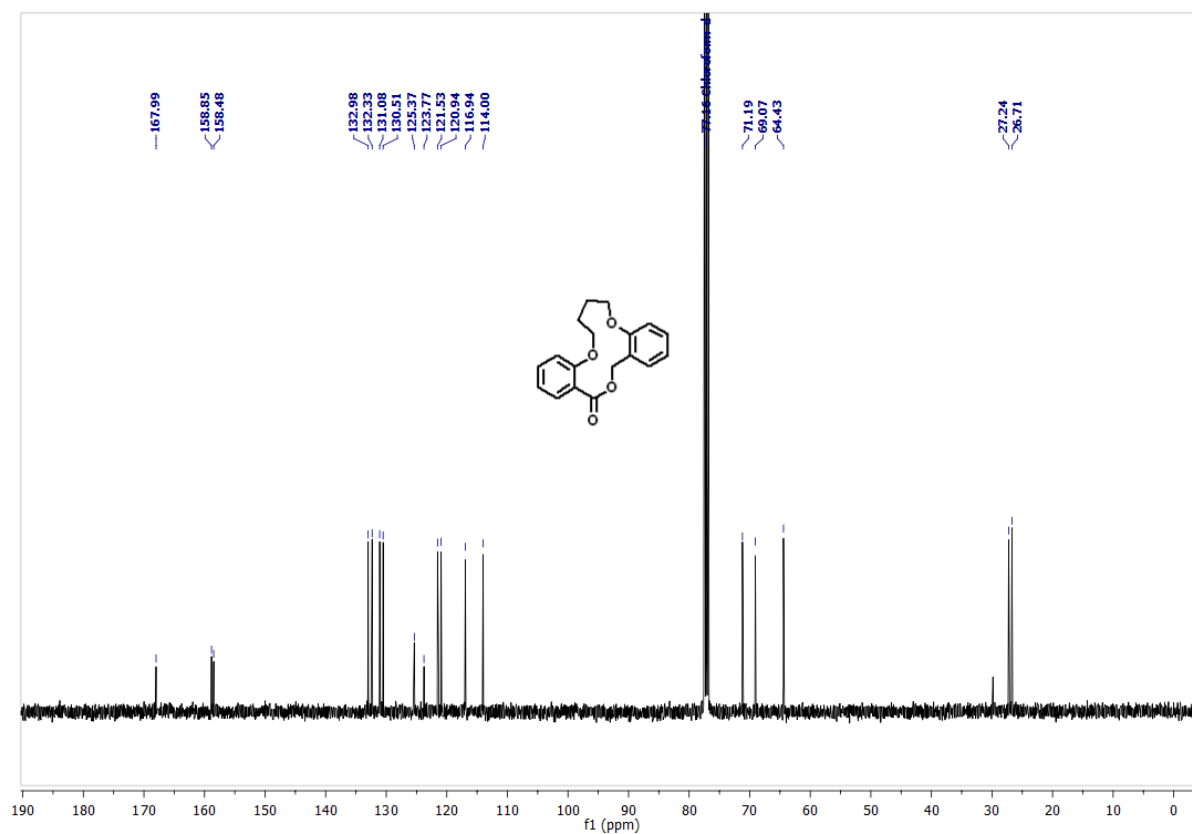
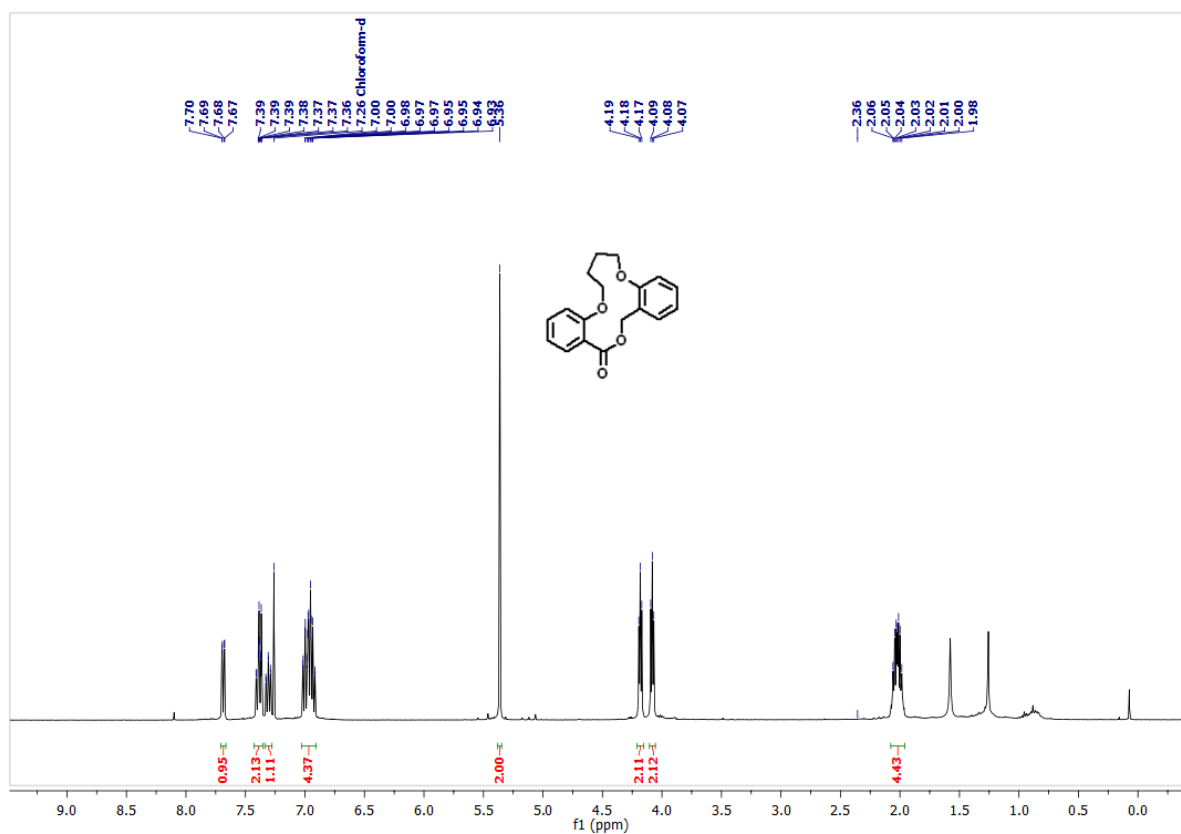


Figure 52. ¹³C NMR spectra for compound **122c**, 100 MHz, CDCl₃



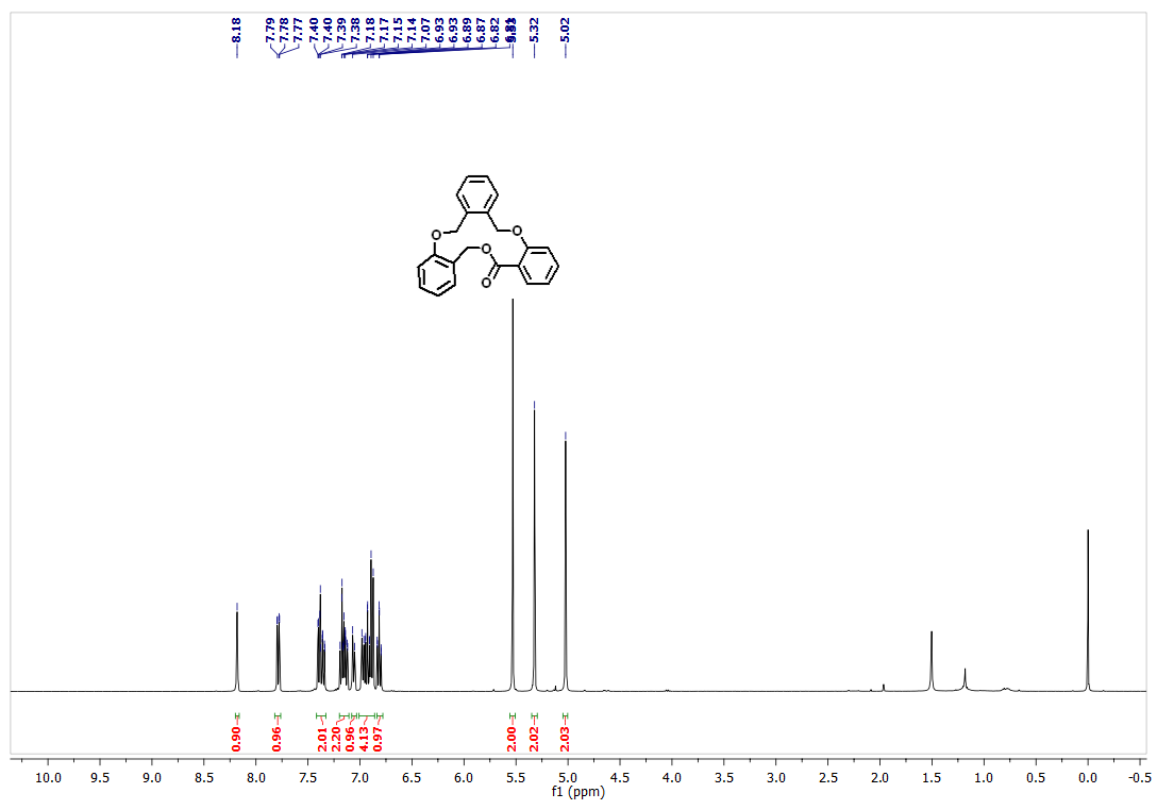


Figure 55. ¹H NMR spectra for compound **122e**, 400 MHz, CDCl₃

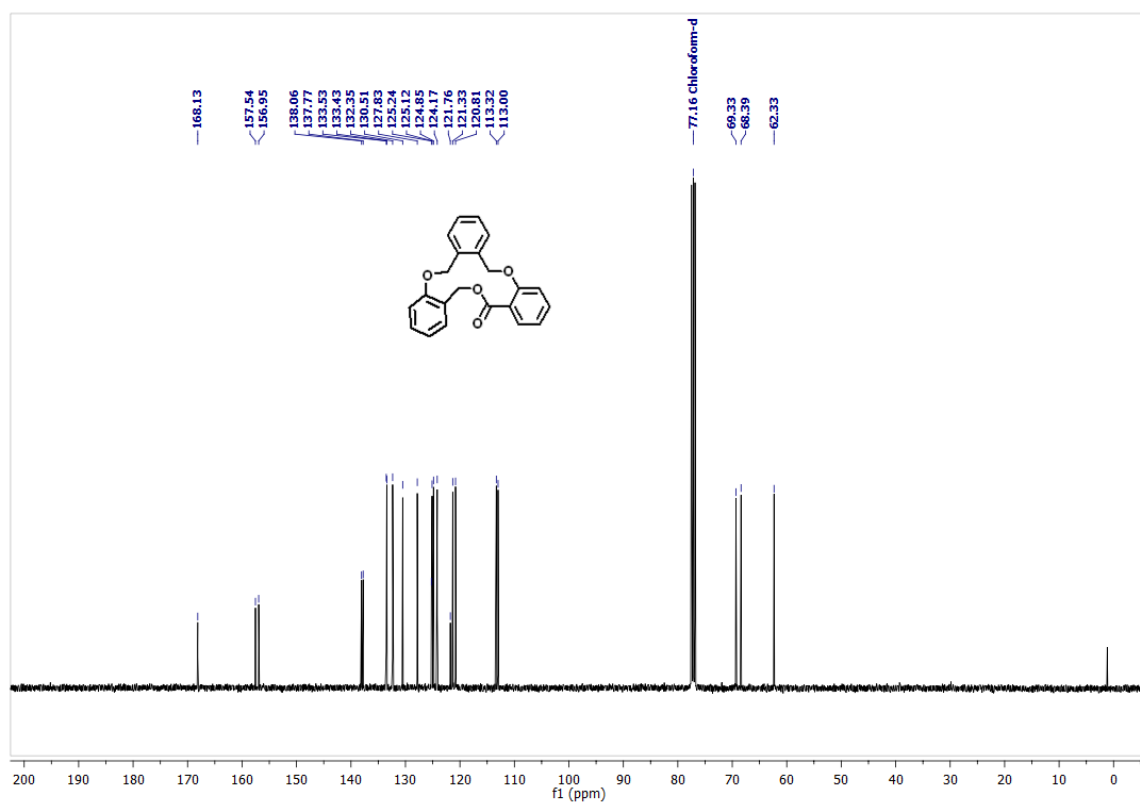


Figure 56. ¹³C NMR spectra for compound **122e**, 100 MHz, CDCl₃

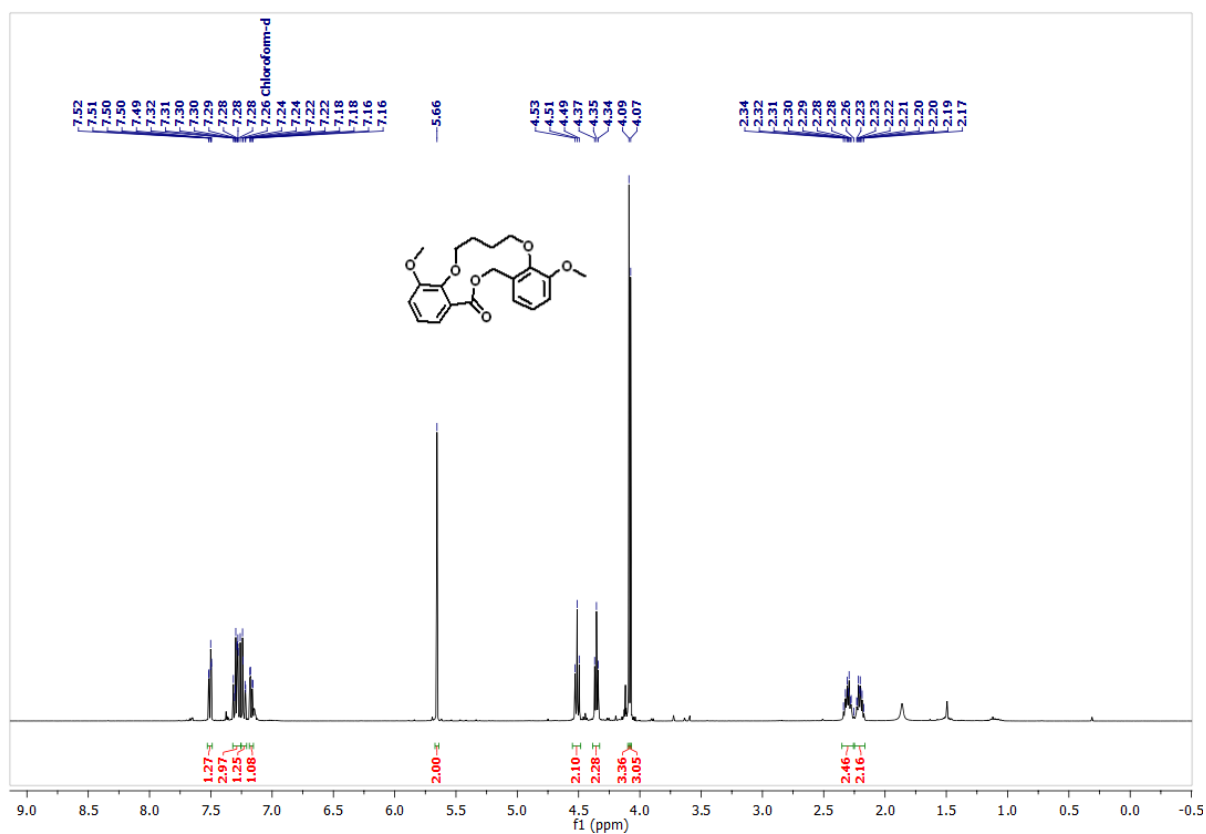


Figure 57. ¹H NMR spectra for compound **122f**, 400 MHz, CDCl₃

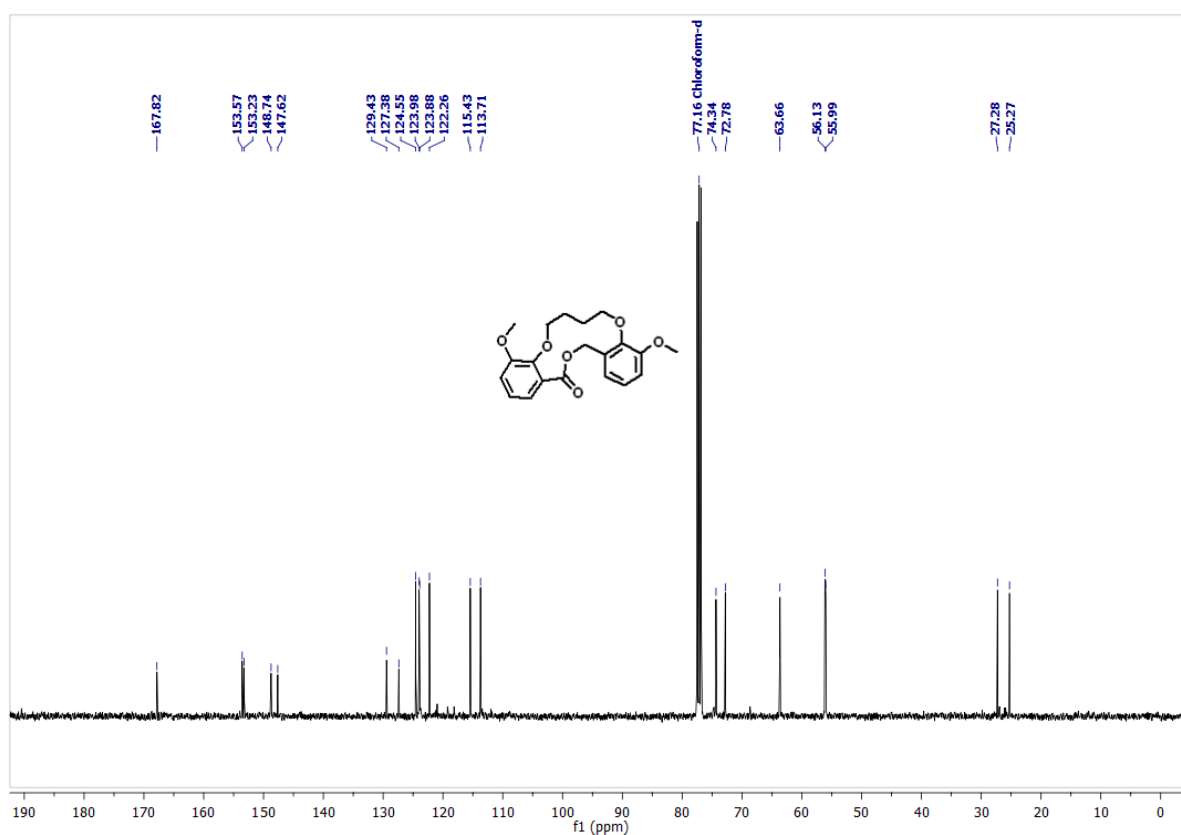
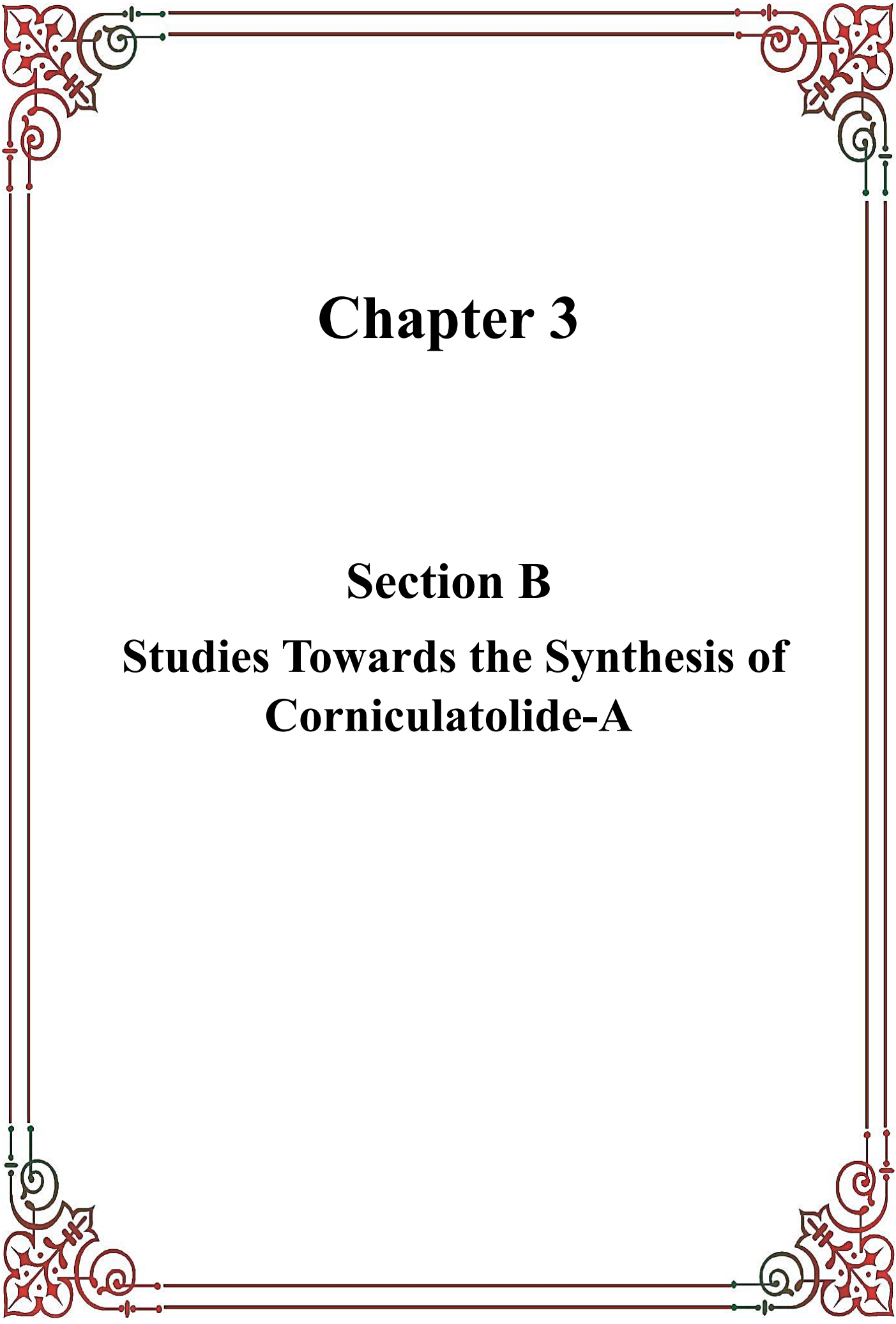


Figure 58. ¹³C NMR spectra for compound **122f**, 100 MHz, CDCl₃



Chapter 3

Section B

Studies Towards the Synthesis of Corniculatolide-A

3B. Studies Towards the Synthesis of Corniculatolide-A

3B.1 Abstract

This chapter focuses on the experimental efforts made towards the synthesis of a macrocyclic class of natural product, corniculatolide-A, also known as combrestatin D-4. The study utilizes the intramolecular acceptorless dehydrogenation strategy for the construction of macrolactone (discussed in Chapter 3A). More interestingly, the simple and straightforward synthesis of starting material in just 2 steps is also demonstrated. Moreover, the synthesis of methylcorniculatolides is achieved in only 3 steps, showcasing the step economical application of acceptorless dehydrogenation as compared to previous literature reports.

3B.2 Introduction

The combretastatin D series and its analogues, corniculatolides and isocorniculatolides are classified within the macrocyclic class of natural products called cyclic diaryl ether heptanoids (DAEH).^{104b} In recent years, the DAEH have acquired significant interest because of their structural and stereochemical characterization as well as their biological activities, such as antineoplastic, anti-inflammatory, and α -glucosidase inhibition.^{105,106} Thus, they show potent therapeutical applications. The biological activity is critically influenced by the presence or absence of certain functional groups, such as a *cis* double bond or the precise position of hydroxy and methoxy groups (Figure 56).

Corniculatolides and isocorniculatolides have been isolated by M. G. Ponapalli and his team from the small tree or shrub known as '*Aegeceras corniculatum*' (family Aegecerataceae) indigenous to mangrove swamps in Asia and Australia.¹⁰⁶ Traditionally this plant was used to treat asthma, diabetes, inflammation, and rheumatism.¹⁰⁷ Pharmacological studies of this plant have demonstrated cytotoxic, itchytoxic,^{108a} anti-inflammatory, antioxidant,¹⁰⁷ and tyrosine phosphatase 1B inhibitory activities.^{108b} Previous investigations have identified several bioactive compounds including saponins, triterpenes, sterols, and hydroquinones from this plant.^{107,108b,109} There are four new isomers have been isolated from this plant named 11-O-methylcorniculatolide A (**127**), 12-hydroxy-11-O-methylcorniculatolide A (**128**), isocorniculatolide A (**129**), 11-O-methylisocorniculatolide A (**130**), and the known corniculatolide A (**126**) (Figure 59).

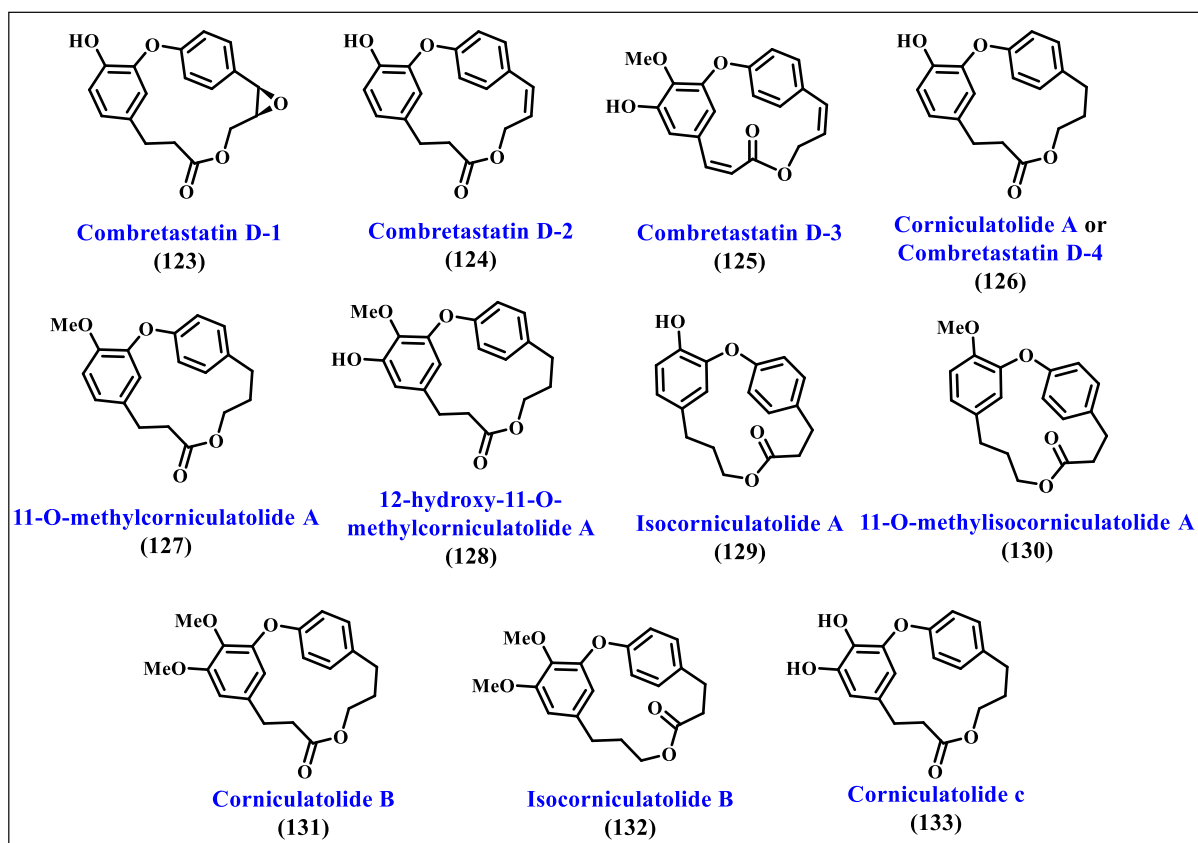
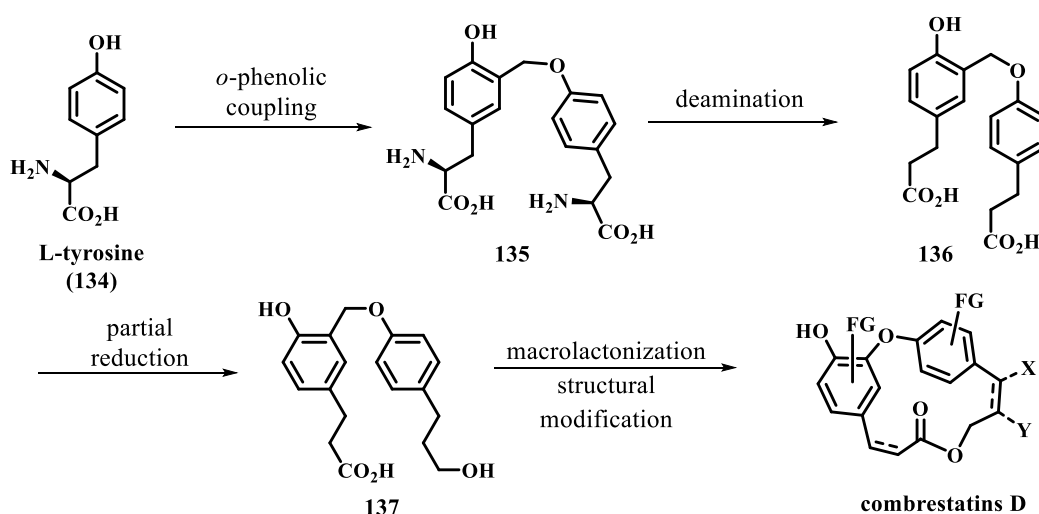


Figure 59: Structures of corniculatolides and isocorniculatolides (analogues of Combretastatin D)

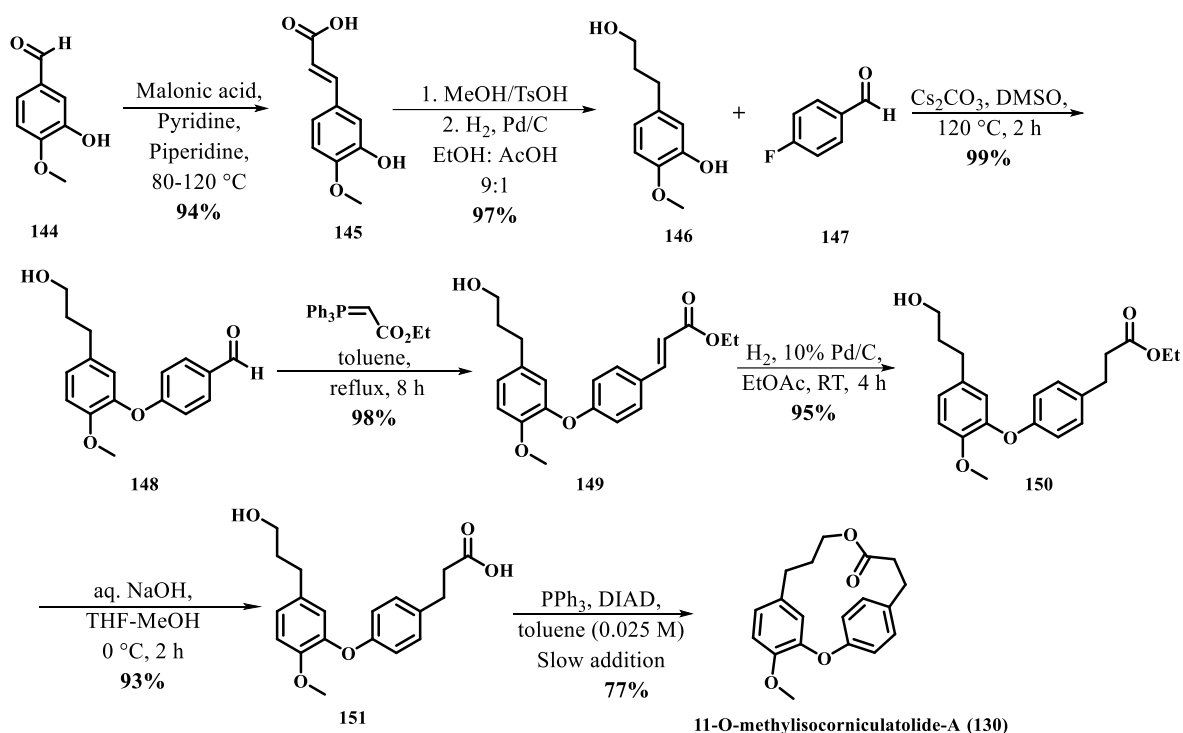
3B.2.1 Previous Synthetic Pathways:

By virtue of the importance of corniculatolides, there are two biosynthetic pathways have been developed. The first pathway was developed by Pettite and coworkers¹¹⁰ where tyrosin **134** is used as the starting material for the synthesis. Next, the phenol coupling followed by the deamination provides **136**.



Scheme 38: Biosynthetic pathway developed by Pettite and coworkers

available for the synthesis of combretastatin analogues, especially for combretastatin D-2.¹¹¹ Only one route is available in the literature for the synthesis of newly isolated corniculatolide analogues, which is developed by D. S. Reddy and coworkers.¹¹² They synthesized three natural macrolides named 11-O-methylcorniculatolide A (**127**), 11-O-methylisocorniculatolide A (**130**) and isocorniculatolide A (**129**) using two different multistep synthetic routes (Scheme 40).



Scheme 40: Synthetic route developed by Reddy and coworkers

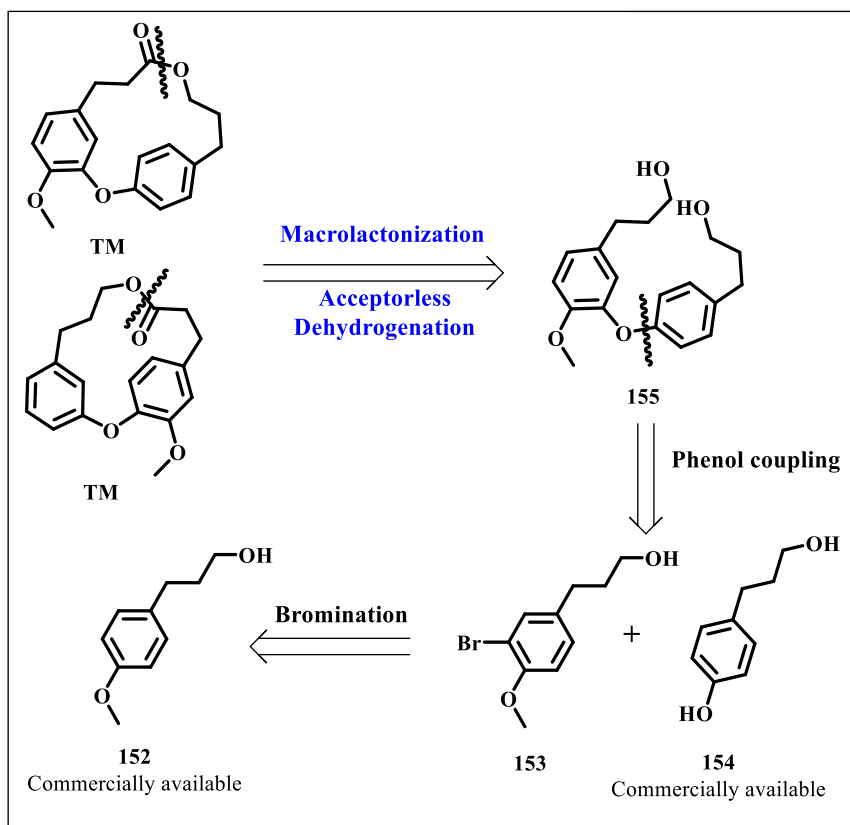
3B.3 Aim and Rationale of current work:

Literature extensively accounts for various approaches developed for the synthesis of all the analogues of combretastatin, including corniculatolides. These approaches typically involve multistep syntheses, which include various oxidation reactions using stoichiometric oxidants, Wittig reaction using phosphine reagent, and the use of Mitsunobu reaction for the macrolactonization step. As a result, these methods produce various kinds of waste after the completion of the reaction in stoichiometric amounts.

Thus, devising a new, step-economic, and cost-effective route for the synthesis of corniculatolides to minimize waste formation is a perpetual goal for organic chemists. Hence, we aimed to synthesize corniculatolide A, isocorniculatolide A, 11-O-methylcorniculatolide and 11-O-methylisocorniculatolide by utilizing the previously developed catalytic method, acceptorless dehydrogenative macrolactonization of dihydroxy

compounds which produces only hydrogen as the by-product after the reaction. The primary aim of this work is to reduce the steps involved in the synthesis thereby providing a step-economic pathway. Consequently, it provides a straightforward route for the synthesis of corniculatolides.

3B.3.1 Disconnection Approach:



Scheme 41: Disconnection approach for methylcorniculatolide

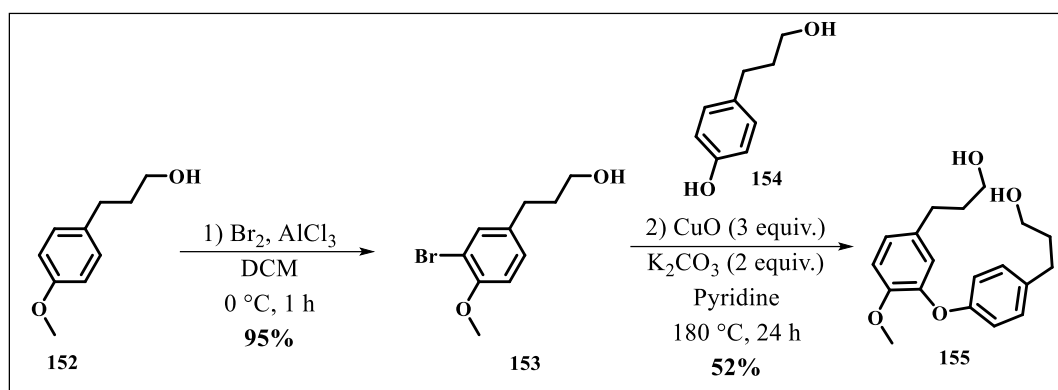
We started disconnection for the 11-O-methylcorniculatolide and 11-O-methylisocorniculatolide by disconnecting the C-O bond of the lactone. This C-O could be constructed using the acceptorless dehydrogenative macrolactonization of alcohols using the diol **155** (Scheme 38). Next, the diol **155** bearing a diaryl ether bond can be synthesized via a Ullmann or Chan-Lam coupling of compounds **153** and **154**. Compound **154** is commercially available whereas, **153** is achievable via bromination of commercially available compound **152** (Scheme 41).

With this disconnection approach, methylcorniculatolides could be achieved in only 3 steps, whereas corniculatolides could be achieved in 4 steps.

3B.4 Synthesis:

3B.4.1 Route 1: A) Synthesis of diol **155**:

We commenced the synthesis by reacting the commercially available 3-(4-methoxy-phenyl)-1-propanol (**152**) with bromine and aluminium trichloride in dry dichloromethane (DCM) as the solvent to afford 3-(3-bromo-4-methoxy-phenyl)-1-propanol (**153**) with 95% yield (Scheme 39).⁹⁶ Next, compound **153** underwent Ullmann coupling with commercially available 3-(4-hydroxy-phenyl)-1-propanol (**154**) in the presence of copper oxide (CuO) as a catalyst, K₂CO₃ as a base and pyridine as solvent (Scheme 39) to provide 52% yield of diol **155** (Scheme 42).⁹⁷



Scheme 42: Synthesis of diol **155**

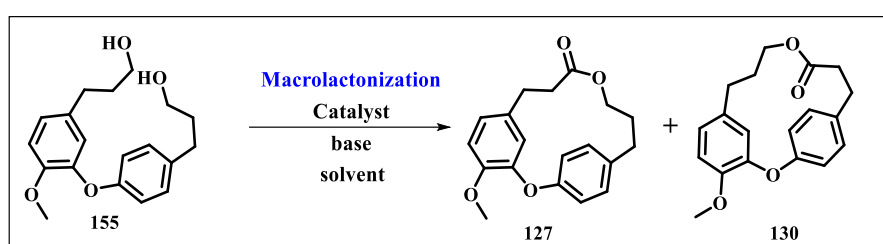
Reaction conditions: (1) 3-(4-methoxy-phenyl)-1-propanol (**152**) (10 mmol, 1 equiv.), bromine (10 mmol, equiv.), and AlCl₃ (10 mmol, equiv.) in dry dichloromethane (DCM) (15 mL) were stirred at 0 °C for 1 h to afford 3-(3-bromo-4-methoxy-phenyl)-1-propanol (**153**). (2) 3-(3-bromo-4-methoxy-phenyl)-1-propanol (**153**) (0.2 mmol, 1 equiv.), 3-(4-hydroxy-phenyl)-1-propanol (**154**) (0.2 mmol, 1 equiv.), K₂CO₃ (0.4 mmol, 2 equiv.) and CuO (0.6 mmol, 3 equiv.) in pyridine (4 mL) were heated at 180 °C for 24 h to achieve diol **155**.

3B.4.1 B) Synthesis of 11-O-methylcorniculatolide and 11-O-methylisocorniculatolide:

After the successful achievement of diol **155**, we further attempted the synthesis of 11-O-methylcorniculatolide and 11-O-methylisocorniculatolide via the acceptorless dehydrogenative macrolactonization (Table 3). We started screening different Ruthenium catalysts that facilitate acceptorless dehydrogenation. Initially, by maintaining the concentration of **155** at 0.01 M, we employed Ru-MACHO (For structure, see Chapter II, Figure 11) as a catalyst and Cs₂CO₃ as a base for the macrolactonization, afforded no product formation (Table 4, entry 1). Next, changing other bases, such as KOH and NaOH, afforded an inseparable mixture of products **127** and **130** with 20% yield in both cases (5 mg, as yellowish

sticky liquid) (Table 4, entries 2 and 3). The product was confirmed by the NMR, HRMS and IR analysis. Moreover, to check the effect of high dilution, the diol **155** was diluted 0.0025 M in toluene and refluxed in the presence of Ru-MACHO and KOH at 180 °C temperature. After 48 h only starting material diol **155** was observed in the reaction mixture (Table 4, entry 4). In the case of increased concentration of **155** to 0.05 M, provided 12% (3 mg) of the mixture of products **127** and **130** (Table 4, entry 5). Further, replacing the Ru-MACHO catalyst to $[\text{Cp}^*\text{IrCl}_2]_2$ and Ru-PNN (for structure, Chapter II, Figure 11), no product formation was observed (Table 4, entries 6 and 7).

Table 4: Attempts made for the acceptorless dehydrogenative macrolactonization



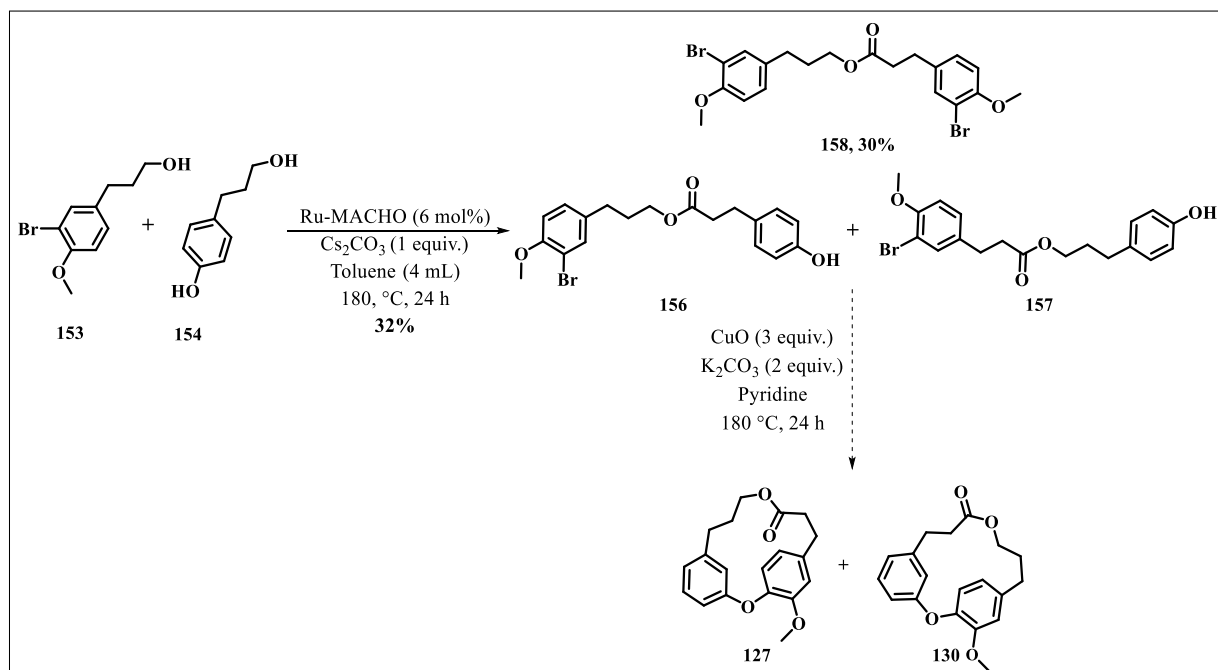
Sr. No.	Catalyst (mol%)	Base (equiv.)	Conc. (M)	Solvent (mL)	% Yield
1.	Ru-MACHO (6)	Cs_2CO_3 (1)	0.01	Toluene (8)	-
2.	Ru-MACHO (6)	KOH (1)	0.01	Toluene (8)	20
3.	Ru-MACHO (6)	NaOH (1)	0.01	Toluene (8)	20
4.	Ru-MACHO (6)	KOH (1)	0.0025	Toluene (32)	Diol recovered
5.	Ru-MACHO (6)	KOH (1)	0.05	Toluene (3)	12
6.	$[\text{IrCp}^*\text{Cl}_2]_2$ (6)	Cs_2CO_3 (1)	0.01	Toluene (8)	-
7.	Ru-PNN (6)	NaOH (1)	0.01	Toluene (8)	-

Reaction Conditions: Diol **155** (25.3 mg, 0.08 mmol, 1 equiv.), catalyst (0.0047 mmol, 0.06 equiv. (6 mol%)), and base (0.07 mmol, 1 equiv.) in toluene (for concentration, see table) were stirred in preheated parallel synthesizer at 180 °C for 48 h.

3B.4.2 Route 2:

After achieving the mixture of isomers of 11-O-methylcorniculatolide and 11-O-methylisocorniculatolide in synthetic route-1, we designed another route for their synthesis.

Instead of performing the acceptorless dehydrogenative macrolactonization at the last step, we performed it at the second step for the cross-esterification of compounds **153** and **154** to achieve an inseparable mixture of isomers **156** and **157** with 32% combined yield (Scheme 43). Besides, the reaction provided the homo-coupled esterification (**158**) of compound **153** with a 30% yield. Furthermore, the mixture of cross-esters was subjected to the intramolecular Ullmann coupling reaction to achieve **127** and **130**, but only starting materials were recovered back from the reaction mixture.



Scheme 43: Route 2 for the synthesis of corniculatolides

3B.5 Conclusion:

In summary, we have developed a new route for the three-step synthesis of macrolides known as 11-O-methylcorniculatolide and 11-O-methylisocorniculatolide. More interestingly, this route enables step-economy, cost-effectiveness and less waste production as compared to previous literature reports by synthesizing corniculatolides in 3 steps. Being used the acceptorless dehydrogenative macrolactonization, it produces only hydrogen as the by-product from the reaction. Moreover, the deprotection of phenolic-OH of methylcorniculatolide would provide corniculatolide A in 4 steps. Overall, this method provides a simple, atom-economic and straightforward route for the synthesis of 11-O-methylcorniculatolide and 11-O-methylisocorniculatolide.

3B.6 Experimental section and characterization data

3B.6.1 General information and data collection:

The 3-(4-methoxy-phenyl)-1-propanol (CAS number- 5406-18-8, BLD Pharm), 3-(4-hydroxy-phenyl)-1-propanol (CAS number- 10210-17-0, BLD Pharm) and copper (II) oxide (CAS number- 1317-38-0, BLD Pharm), were purchased from BLD Pharm. Aluminium trichloride (AlCl_3) (CAS number- 7446-70-0, Spectrochem) was purchased from Spectrochem. Potassium carbonate (K_2CO_3) was purchased from Sigma-Aldrich. Cesium carbonate (Cs_2CO_3) was purchased from FINAR (CASR- 534-17-8). All the solvents used were dry grade. The column chromatographic separations were performed over 100-200 mesh size Silica-gel. Visualization was accomplished with UV light and DNP stain. ^1H and ^{13}C NMR spectra were recorded on 400 and 100 MHz, respectively, using a Bruker spectrometer. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiple. High-resolution mass spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATIR) spectra were obtained with a Bruker Alpha-E infrared spectrometer.

3B.6.2 Experimental Section:

A) General experimental procedure for bromination:¹¹³

To a solution of 3-(4-methoxy-phenyl)-1-propanol **152** (1.66 gm, 10 mmol, 1 equiv.) in dry DCM (15 mL), were added Br_2 (0.5 mL, 10 mmol, 1 equiv.) and AlCl_3 (1.6 gm, 10 mmol, 1 equiv.) dropwise at 0 °C under an inert atmosphere. The reaction was allowed to stir at 0 °C for 1 h and was quenched with ice water. The aqueous layer was extracted with DCM. The combined organic fractions were washed with water, NaHCO_3 and brine, dried over sodium sulfate and concentrated under reduced pressure. Further, the crude reaction mixture was directly subjected to column chromatography using 20% ethyl acetate in pet ether as eluent to isolate brominated product **153** (2.34 gm, 95%) as colourless oil.

B) General experimental procedure for Ullmann coupling:¹¹⁴

To a resealable 20 mL tube, was added 3-(3-bromo-4-methoxy-phenyl)-1-propanol (**153**) (50 mg, 0.2 mmol, 1 equiv.), 3-(4-hydroxy-phenyl)-1-propanol (**154**) (30.4 mg, 0.2 mmol, 1 equiv.), K_2CO_3 (55 mg, 0.4 mmol, 2 equiv.) and CuO (47 mg, 0.6 mmol, 3 equiv.) in pyridine (4 mL). The resulting reaction mixture was heated at 180 °C. After 24 h, the reaction mixture was allowed to cool at room temperature, diluted using dilute HCl and extracted with ethyl acetate. The organic layer was washed with dilute HCl and evaporated under reduced pressure to achieve a crude product. The crude product was directly subjected to column

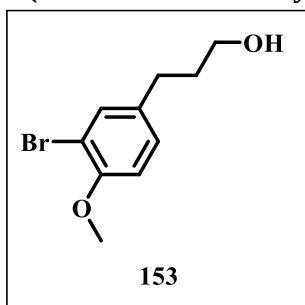
chromatography using 50% ethyl acetate in pet ether as eluent to isolate diol **155** (33 mg, 52%) as a yellowish sticky compound.

C) General experimental procedure for intramolecular macrolactonization of various *ortho*-/*meta*-diphenyldimethanol derivatives:¹¹⁵

In a 20 mL re-sealable vial (equipped with a rubber septum and N₂ balloon) was added catalyst (0.0047 mmol, 0.06 equiv. (6 mol%)), diol **155** (25.3mg, 0.08 mmol, 1 equiv.), and base (0.07 mmol, 1 equiv.) in the presence of toluene as a solvent. The tube was purged with N₂ and sealed with a cap using a crimper. The reaction mixture was heated at 180 °C in a preheated oil bath or parallel synthesizer for 48 h. After completion of the reaction, the reaction mixture was diluted with ethyl acetate. Further, a volatile component was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (15% EtOAc: n-hexane).

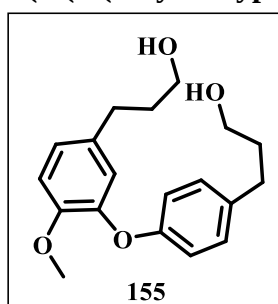
3B.6.3 Spectroscopic data of products:

3-(3-bromo-4-methoxyphenyl)propan-1-ol (153): Prepared according to general procedure



A, using 3-(4-methoxy-phenyl)-1-propanol **152** (1.66 gm, 10 mmol, 1 equiv.) in dry DCM (15 mL), Br₂ (0.5 mL, 10 mmol, 1 equiv.) and AlCl₃ (1.6 gm, 10 mmol, 1 equiv.) to afford the desired product 3-(3-bromo-4-methoxyphenyl)propan-1-ol **153** (2.34 gm, 95% yield) as colourless liquid compound. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 2.1 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.66 – 2.59 (m, 2H), 1.84 (m, 2H), 1.71 (s, 1H).

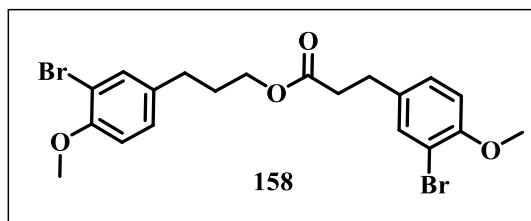
3-(4-(5-(3-hydroxypropyl)-2-methoxyphenoxy)phenyl)propan-1-ol (155): Prepared



according to general procedure B, using 3-(3-bromo-4-methoxyphenyl)-1-propanol (**153**) (50 mg, 0.2 mmol, 1 equiv.), 3-(4-hydroxyphenyl)-1-propanol (**154**) (30.4 mg, 0.2 mmol, 1 equiv.), K₂CO₃ (55 mg, 0.4 mmol, 2 equiv.) and Cu(II)O (47 mg, 0.6 mmol, 3 equiv.) in pyridine (4 mL) to afford the desired product 3-(4-(5-(3-hydroxypropyl)-2-methoxyphenoxy)phenyl)propan-1-ol **155** (33 mg,

52%) as a yellowish sticky compound. ¹H NMR (400 MHz, CDCl₃) δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.92 (s, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.79 (s, 1H), 3.82 (s, 3H), 3.66 (dt, *J* = 14.8, 6.4 Hz, 5H), 2.72 – 2.64 (m, 2H), 2.63 – 2.57 (m, 2H), 1.93 – 1.77 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 156.1, 149.6, 145.3, 135.9, 134.9, 129.5, 124.2, 120.8, 117.4, 112.9, 62.4, 62.3, 56.3, 34.4, 34.3, 31.4, 31.3, 29.8.

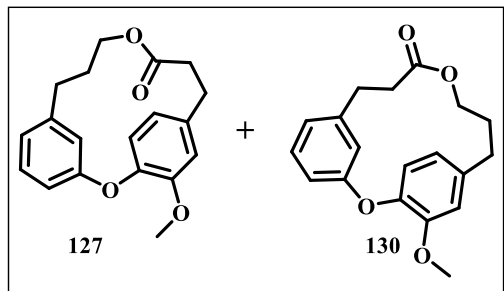
3-(3-bromo-4-methoxyphenyl)propyl 3-(3-bromo-4-methoxyphenyl)propanoate (**158**):



Prepared according to general procedure C, using 3-(3-bromo-4-methoxy-phenyl)-1-propanol (**153**) (50 mg, 0.2 mmol, 1 equiv.), in toluene (3 mL), Ru-MACHO (0.0047 mmol, 0.06 equiv. (6 mol%)) and base (0.07 mmol, 1 equiv.) to afford

the desired product 3-(3-bromo-4-methoxyphenyl)propyl 3-(3-bromo-4-methoxyphenyl)propanoate **158** (30% yield) as a colourless liquid compound. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39 (d, $J = 2.1$ Hz, 1H), 7.34 (d, $J = 2.1$ Hz, 1H), 7.11 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.03 (dd, $J = 8.4, 2.1$ Hz, 1H), 6.81 (dd, $J = 8.4, 1.5$ Hz, 2H), 4.06 (t, $J = 6.5$ Hz, 2H), 3.86 (d, $J = 6.0$ Hz, 6H), 2.87 (t, $J = 7.6$ Hz, 2H), 2.63 – 2.51 (m, 4H), 1.93 – 1.83 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 172.7, 154.5, 154.3, 134.9, 134.2, 133.2, 133.2, 128.4, 112.0, 111.6, 111.62, 63.7, 56.4, 56.3, 35.9, 31.0, 30.2, 29.8.

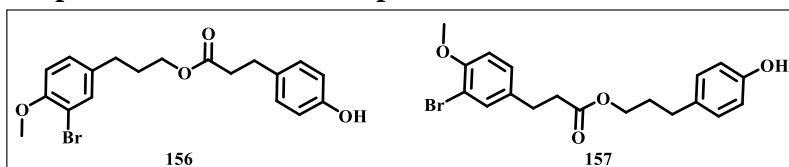
11-O-methylcorniculatolide (**127**) and 11-O-methylisocorniculatolide (**130**): Isolated as an inseparable mixture of compounds.



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.15 – 6.96 (m, 4H), 6.94 – 6.80 (m, 8H), 6.74 – 6.61 (m, 2H), 4.08 – 3.95 (m, 4H), 3.88 – 3.76 (m, 6H), 2.95 – 2.71 (m, 4H), 2.66 – 2.40 (m, 8H), 1.91 – 1.72 (m, 4H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 173.1, 172.9, 149.4, 146.2,

145.4, 129.6, 129.6, 129.5, 129.52, 124.39, 124.22, 123.78, 123.24, 121.2, 120.8, 120.7, 120.3, 118.7, 118.5, 118.3, 117.7, 117.6, 117.3, 117.0, 112.9, 112.8, 63.9, 63.8, 63.7, 63.5, 56.3, 56.3, 56.2, 56.2, 36.2, 36.1, 35.8, 35.7, 31.4, 30.3, 30.3, 30.3. **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ $\text{C}_{19}\text{H}_{21}\text{O}_4$, 313.1440 found: 313.1440 and $\text{C}_{38}\text{H}_{41}\text{O}_8$, 625.2801 found: 625.2797.

3-(3-bromo-4-methoxyphenyl)propyl 3-(4-hydroxyphenyl)propanoate (**156**) and 3-(4-hydroxyphenyl)propyl 3-(3-bromo-4-methoxyphenyl)propanoate (**157**): Isolated as an inseparable mixture of compounds.



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.80 (s, 1H), 7.37 (dd, $J = 20.4, 2.1$ Hz, 2H), 7.16 – 6.99

(m, 6H), 6.87 – 6.77 (m, 6H), 4.07 (td, $J = 6.5, 3.8$ Hz, 4H), 3.78 (d, $J = 5.0$ Hz, 6H), 2.88 (dt, $J = 9.7, 7.7$ Hz, 4H), 2.65 – 2.51 (m, 8H), 1.88 (tt, $J = 12.9, 6.5$ Hz, 4H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 173.1, 172.8, 158.2, 158.0, 154.5, 154.3, 135.0, 134.3, 133.3, 133.2, 132.6, 129.4,

129.3, 128.4, 114.0, 114.0, 112.1, 111.7, 64.0, 63.6, 56.4, 56.4, 55.4, 55.3, 36.2, 36.0, 31.3, 31.0, 30.5, 30.3, 30.2, 29.8.

3B.7 Appendix III: Copies of ^1H and ^{13}C NMR spectra and Mass spectrum of representative compounds

Entry	Figure No.	Data	Page No.
153	60	^1H	138
155	61 and 62	^1H and ^{13}C	138 and 139
Mix. of 127, 130	63 and 64	^1H and ^{13}C	139 and 140
Mix. of 156, 157	65 and 66	Mass Spectrum	140 and 141
158	67 and 68	^1H and ^{13}C	141 and 142

3B.7.1 Copies of NMR spectra:

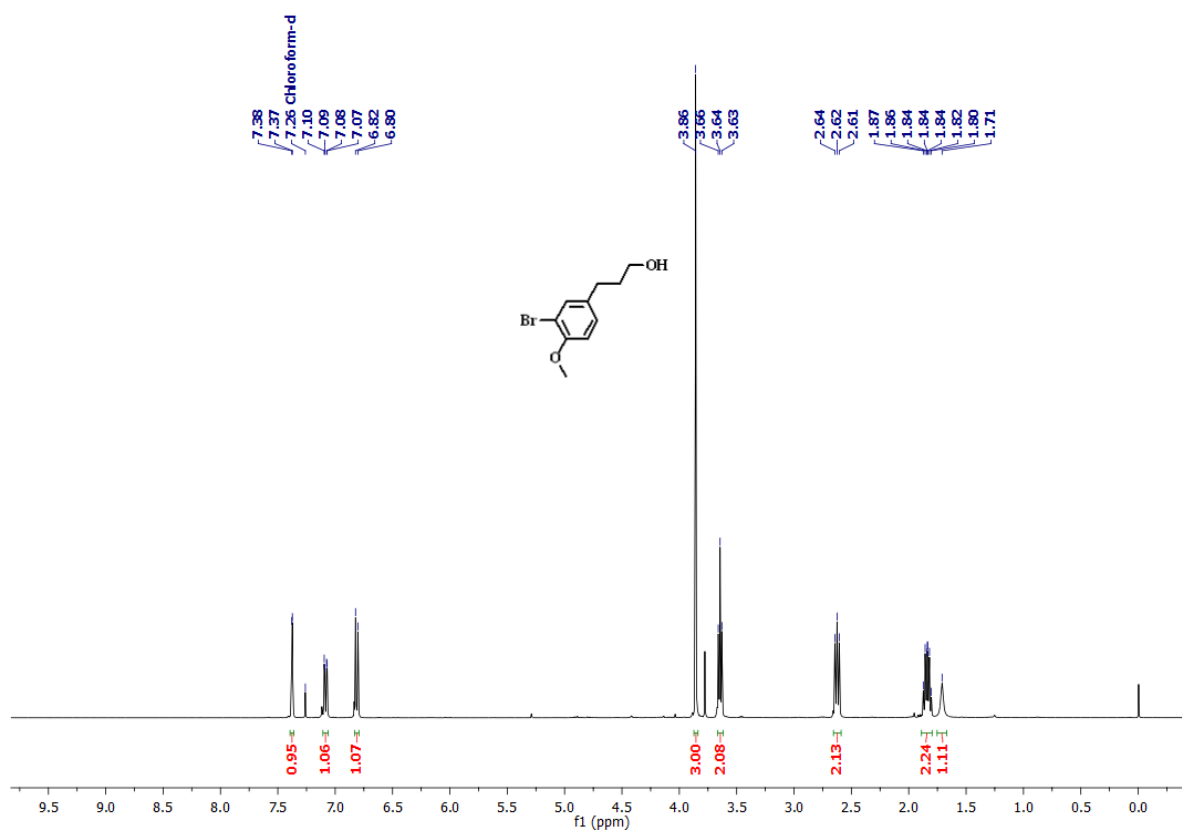


Figure 60. ¹H NMR spectra for compound 153, 400 MHz, CDCl₃

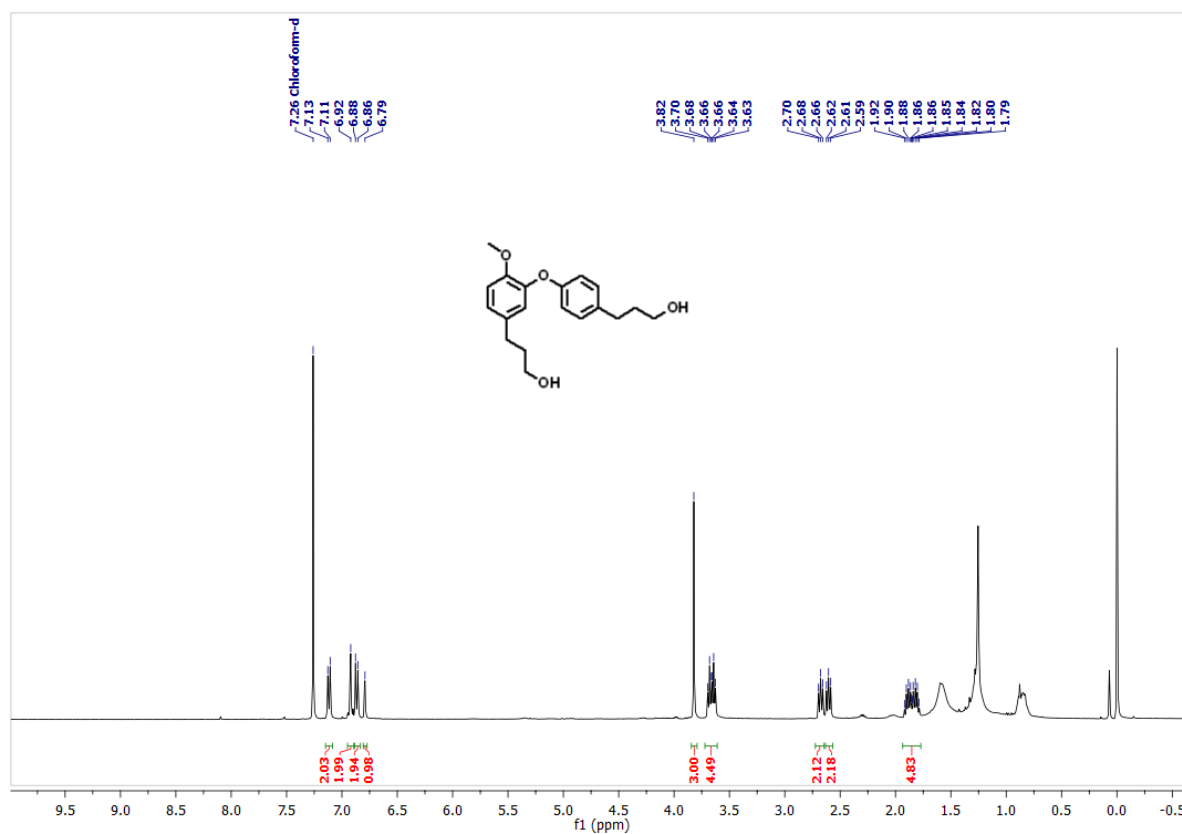


Figure 61. ¹H NMR spectra for compound 155, 400 MHz, CDCl₃

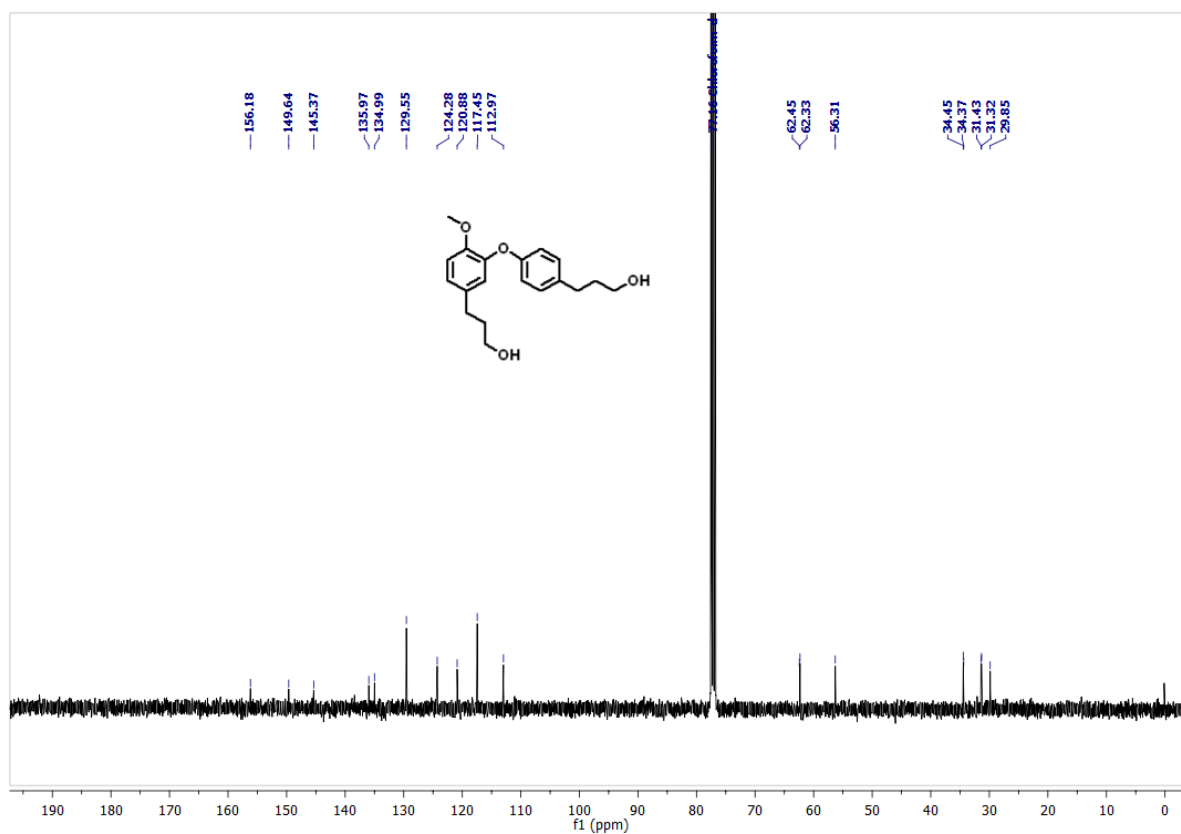


Figure 62. ¹³C NMR spectra for compound **155**, 100 MHz, CDCl₃

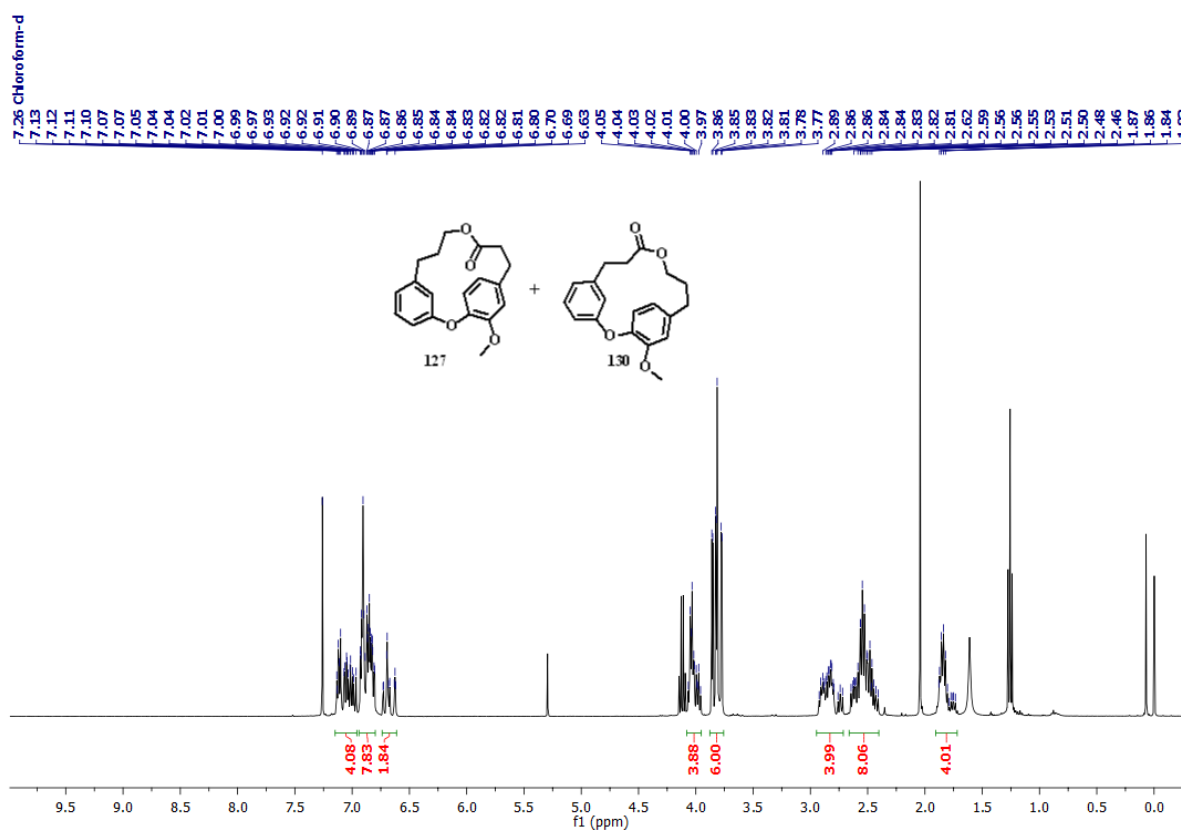


Figure 63. ¹H NMR spectra for the inseparable mixture of compounds **127** and **130**, 400 MHz, CDCl₃

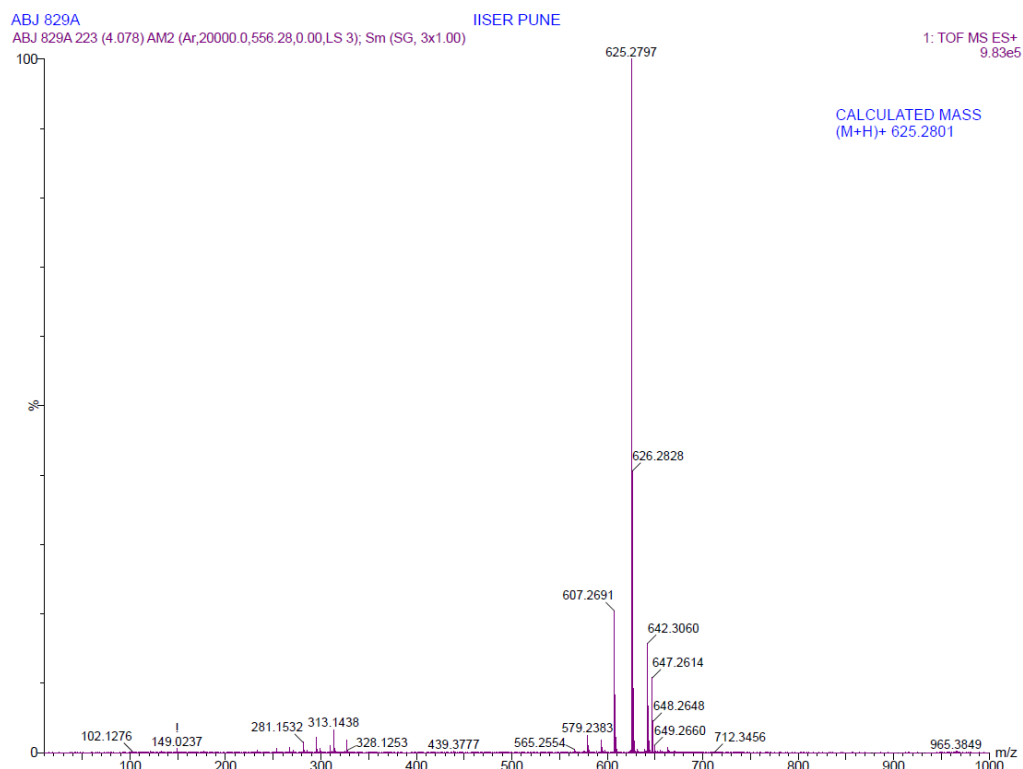


Figure 66. Mass spectrum for both isomers from the inseparable mixture of compounds **127** and **130**, HRMS (ESI-TOF) m/z: [M+H]⁺ calcd for C₃₈H₄₁O₈, 625.2801 found: 625.2797.

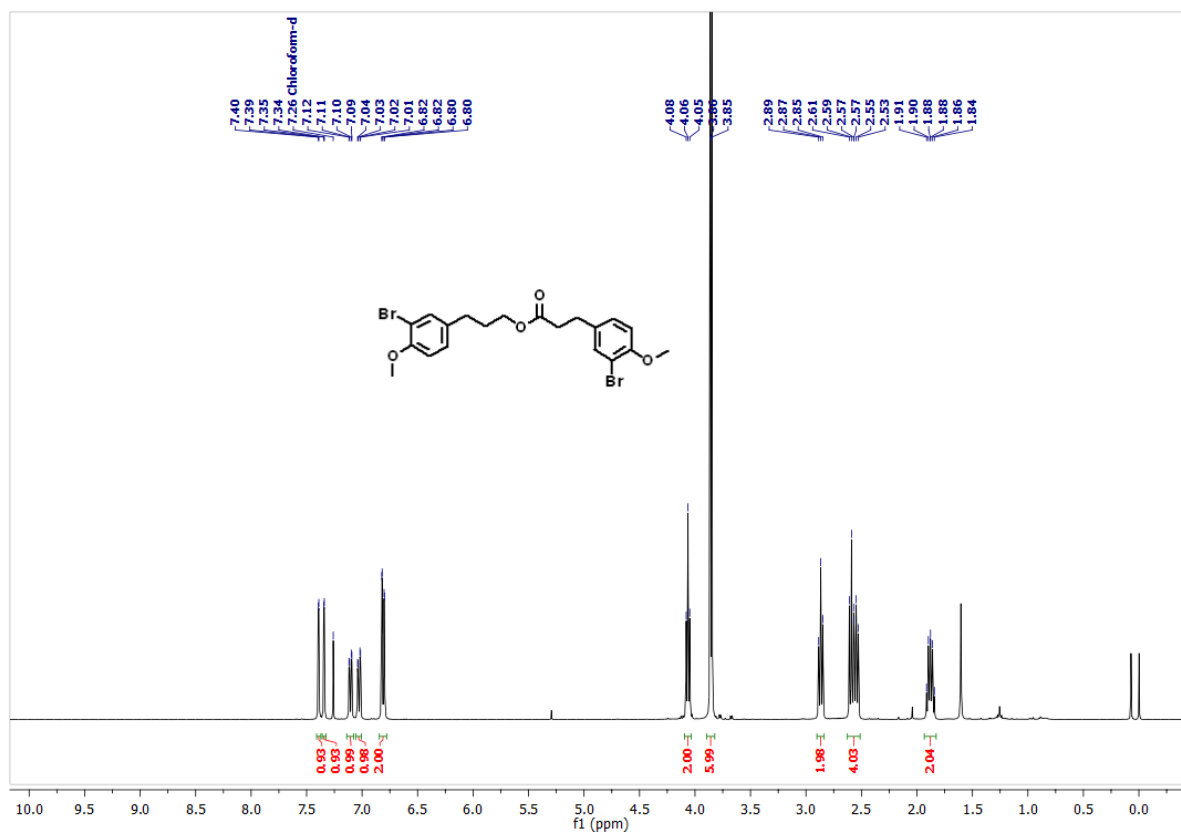
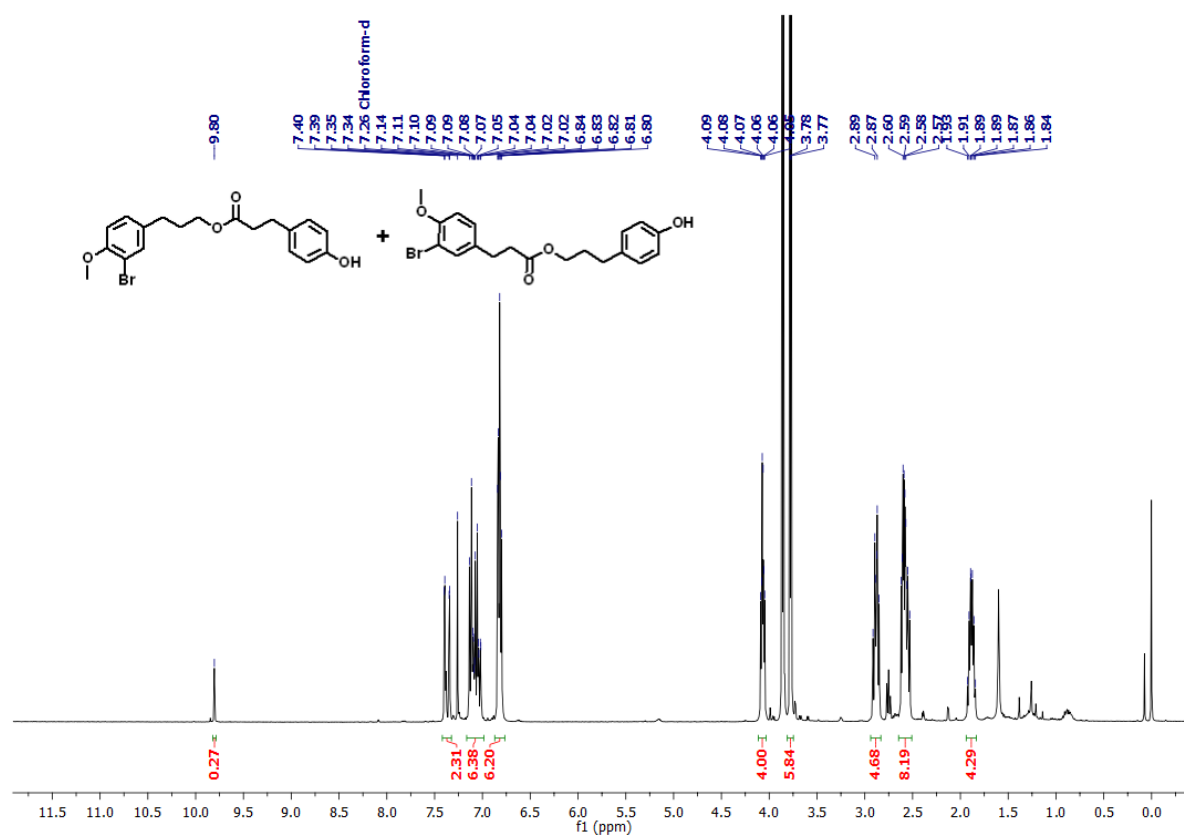
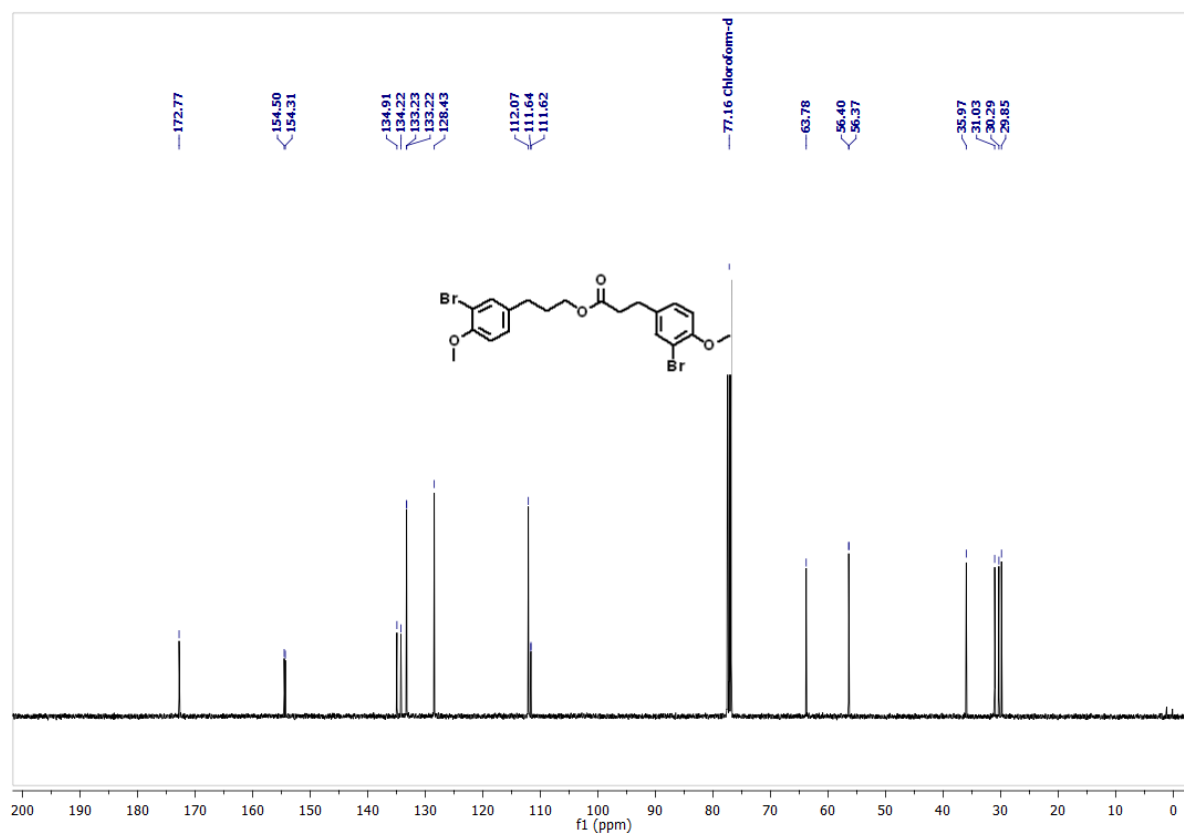


Figure 67. ¹H NMR spectra for compound **158**, 400 MHz, CDCl₃



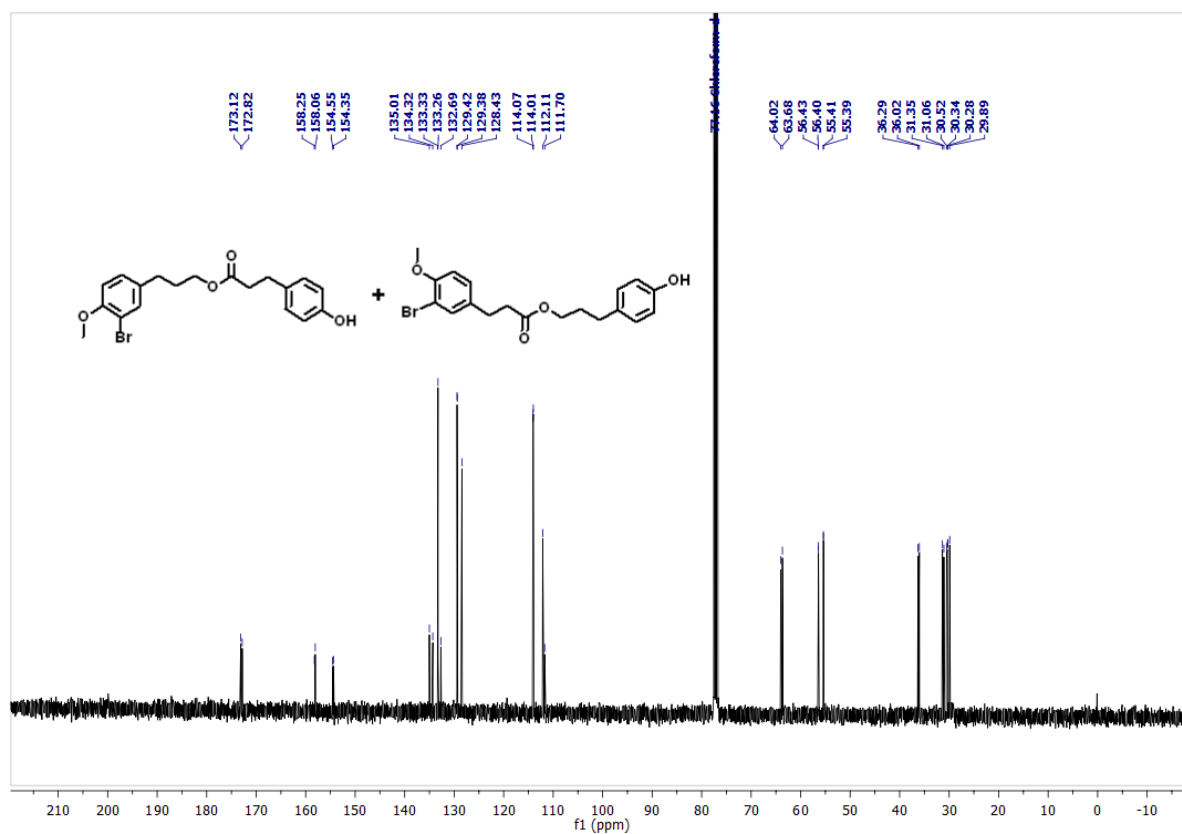
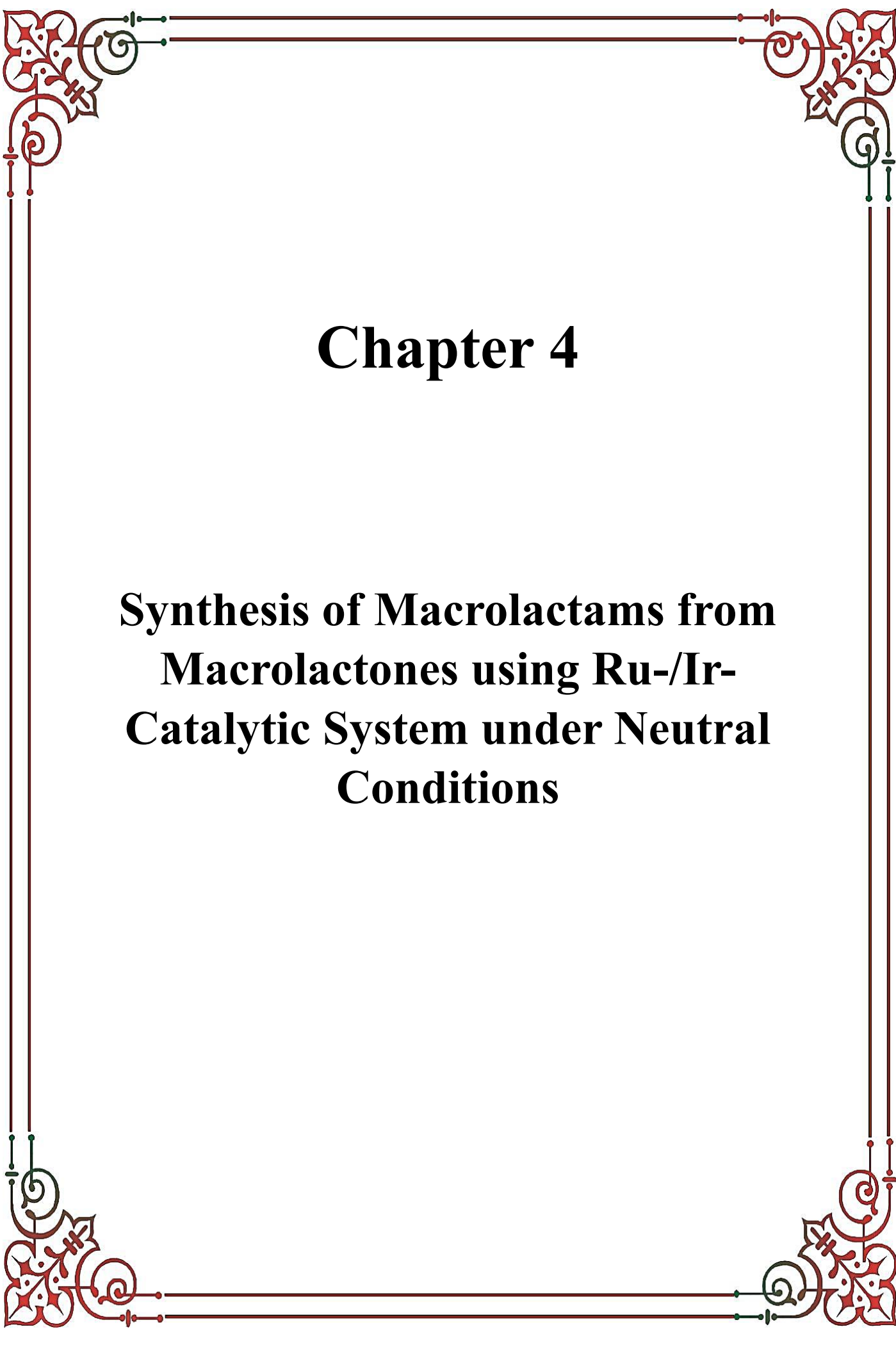


Figure 70. ¹³C NMR spectra for the inseparable mixture of compounds **156** and **157**, 100 MHz, CDCl₃



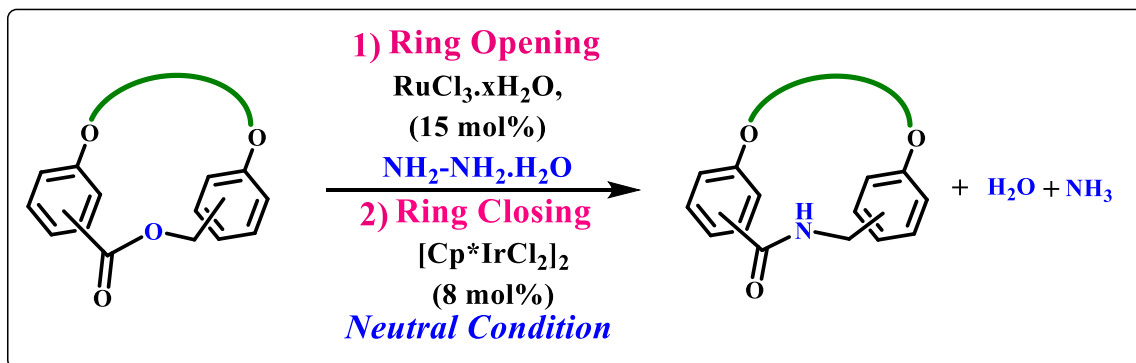
Chapter 4

Synthesis of Macrolactams from Macrolactones using Ru-/Ir- Catalytic System under Neutral Conditions

4. Synthesis of Macrolactams from Macrolactones using Ru-/Ir-Catalytic System under Neutral Conditions

4.1 Abstract:

This chapter describes the first study for the synthesis of a macrocycle from another macrocycle, especially focused on the synthesis of valuable macrolactams from macrolactones using Ru/Ir-catalysis. The ring-opening of the macrolactones and the amidation of acyclic esters were efficaciously facilitated by Ru-catalyst to generate 32 amides in the first step. Subsequently, intramolecular *N*-alkylative ring closure of these amides with alcohols was succeeded by Ir-catalyst in the second step to provide a series of 22 macrolactams with water as a byproduct. Moreover, this approach proceeded under neutral conditions and avoided the use of external additives.



4.2 Introduction:

Amides and macrolactams serve as fundamental structural cores in peptide chemistry, which contributes significantly to molecular diversity. More interestingly, a plethora of natural products and drugs having macrolactam as the core, show biological activities such as antibiotic, anticancer, antimicrobial, antifungal, etc.¹¹⁶ Thus, they exhibit their cruciality to drug discovery and the pharmaceutical industry. In the past few decades, macrolactams such as rifaximin,¹¹⁷ viridenomycin,¹¹⁸ vicienistatin,¹¹⁹ and cyclomenal A,¹²⁰ etc. (Figure 71) have gained much attention due to their wide spectrum of biological applications, making them promising candidates for further exploration in drug development and therapeutic innovation (Figure 71).

The synthesis of amides and macrolactams via the construction of C-N bonds has been a subject of intensive research, driven by their fundamental importance in organic chemistry,

drugs and pharmaceutical industries. As a consequence, numerous approaches have been developed by the scientific community for their synthesis.

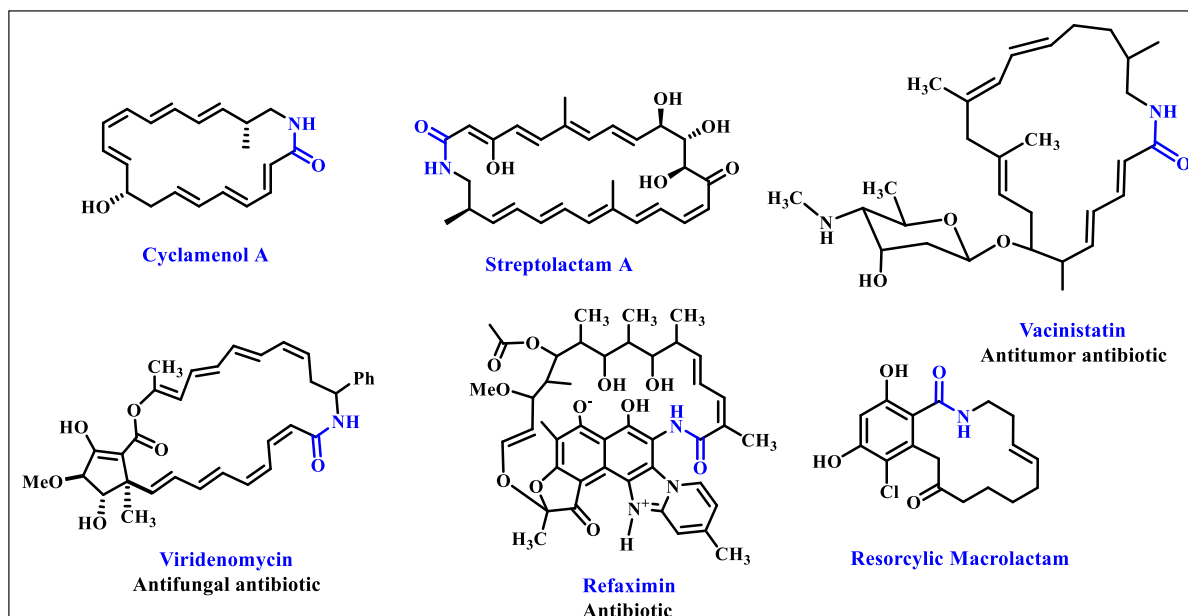
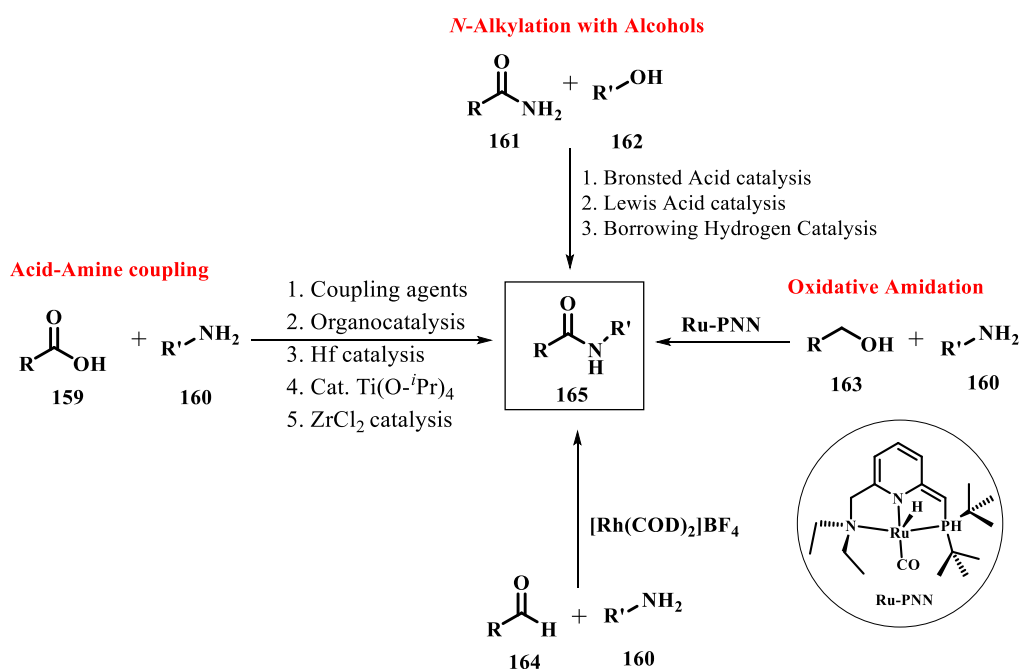


Figure 71: Macrolactam core in natural products and drugs

4.2.1 Literature Background for the Synthesis of Amides:



Scheme 44: Various approaches for the synthesis of amides

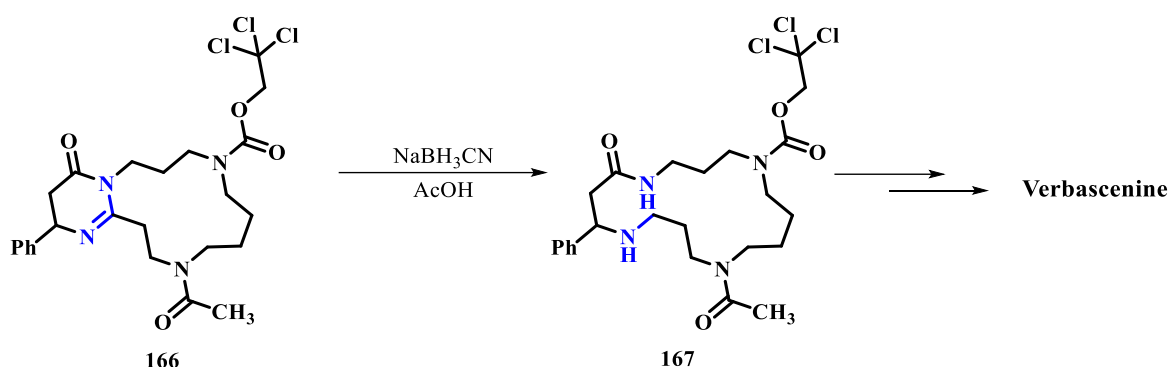
Amide bond formation is achieved through several methodologies, including the coupling of carboxylic acids with amines employing diverse coupling reagents,¹²¹ Lewis and Bronsted acid catalysis,¹²² metal catalysis,¹²³ oxidative amidation of alcohols and amines,¹²⁴

and organocatalysis.¹²⁵ These methods provide versatile routes to construct amides with varying efficiency and selectivity (Scheme 44).

4.2.2 Literature Background for Macrolactamization:

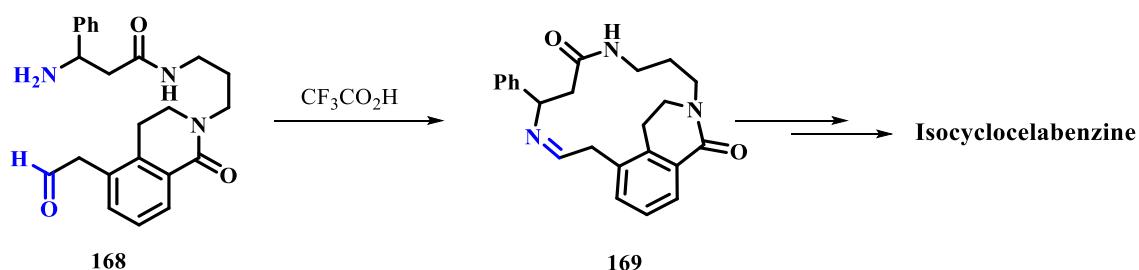
Subsequently, macrolactams, a subclass of macrocycles, are synthesized through various classical strategies such as ring expansion processes,¹²⁶ imine formations for ring closure,¹²⁷ coupling of amines with carboxylic acids¹²⁸ and esters,¹²⁹ and utilizing Mukaiyama salts for macrocyclization.¹³⁰

In 1983, Wasserman and his research group attempted the synthesis of a natural product, verbascenine. Synthesis of precursor **167** via ring expansion macrolactamization of **166** is an important step in the synthesis of this natural product (Scheme 45).



Scheme 45: Ring expansion approach for the synthesis of Verbascenine

Later, in 1986, Kikuchi and his team synthesized a natural product, isocyclocelabenzine. In this route, the intramolecular imination of **168** was performed using trifluoroacetic acid to afford precursor **169** (Scheme 46).

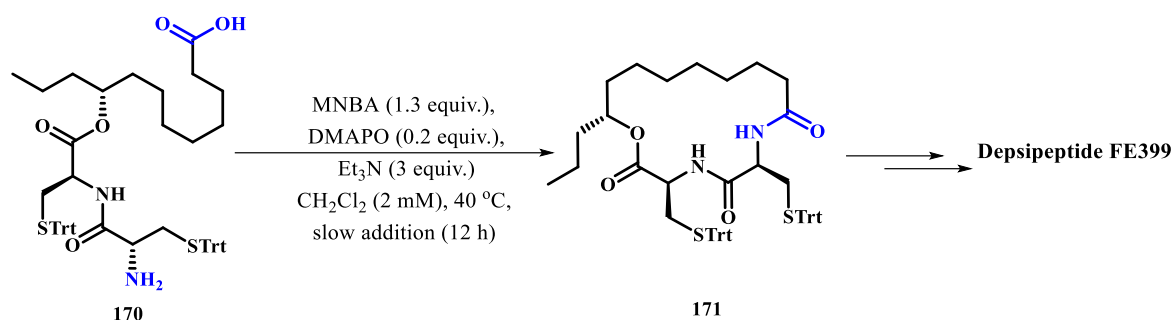


Scheme 46: Imination for the synthesis of Isocyclocelabenzine

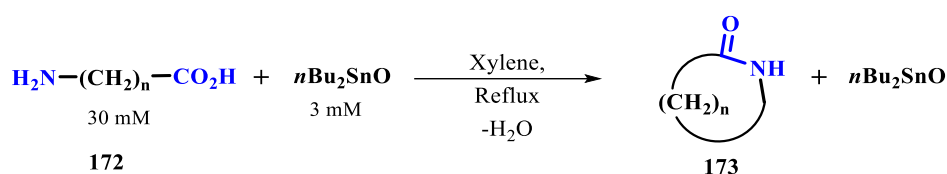
Recently, Shiina and coworkers demonstrated the macrolactamization of **170** using a coupling agent, 2-methyl-6-nitro benzoic anhydride (MNBA), via a mixed anhydride route to achieve compound **171** and subsequent steps afforded depsipeptide FE399 (Scheme 47).

Apart from the aforementioned traditional approaches, fewer catalytic methods have gained prominence due to their efficiency and atom economy. These catalytic methods include the Sn-

catalyzed double activation strategy (Scheme 48).¹³¹ A dibutyl tin oxide reacts with carboxylic acid and subsequent intramolecular coupling with amine, provided macrolactam product **173** (Scheme 48).

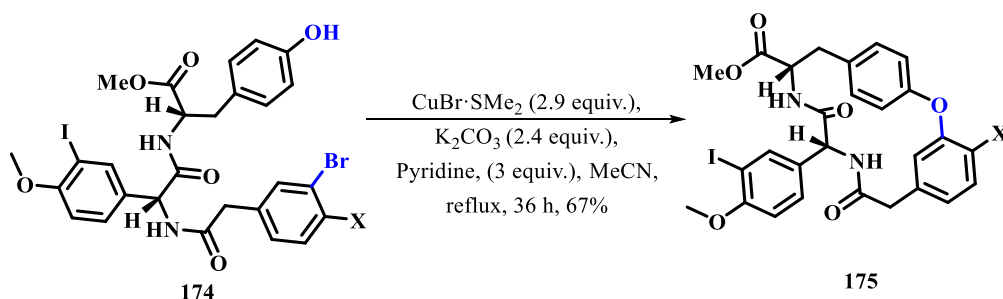


Scheme 47: Acid-amine coupling for the synthesis of Depsipeptide FE399

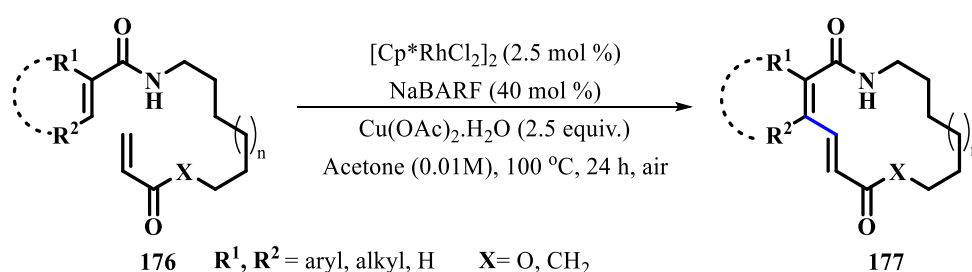


Scheme 48: Di-*n*-butyl tin oxide catalyzed macrolactamization

Further, copper-catalyzed intramolecular Chan-Lam coupling of phenol and aryl bromide afforded the macrolactam **175** (Scheme 49).¹³²



Scheme 49: Nicolaou's approach to macrolactamization



Scheme 50: Intramolecular oxidative cross-coupling of alkenes

Moreover, Loh and coworkers developed two new methods for the macrolactamization of **176** to achieve **177** that include a rhodium-catalyzed intramolecular oxidative cross-coupling

and ring-closing cross-coupling reactions of alkenes (Scheme 50). This method also uses Cu(II) as a co-catalyst, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) as an external additive and an external oxidant.¹³³

4.3 Aim and Rationale of Current Work:

After searching the literature thoroughly, we noticed that only a few catalytic approaches are available for macrolactamization, which include indirect macrocyclization in which the amide group is not directly involved in the reaction or remains unreacted (e.g., cross-coupling of alkenes and phenol coupling). Moreover, the synthesis of primary amides is another enduring challenge since high pressure of ammonia gas is needed. However, a notable gap persists due to the lack of reports on the direct synthesis of primary amides without using ammonia and macrolactamization via direct *N*-alkylation of amides with alcohols. Hence, we envisioned that a macrocycle could be converted to another macrocycle via a ring-opening and ring-closing strategy. This objective is achievable for the synthesis of macrolactams when macrolactones are converted to primary amides via the ring-opening and subsequent *N*-alkylative ring closure of amides with alcohols. This represents a significant challenge and an intriguing area for future development in organic synthesis.

Thus, the development of a new catalytic method capable of directly converting macrolactones into amides via ring-opening amidation and subsequently achieving *N*-alkylative ring closure poses a high scientific interest. Such advancements could potentially revolutionize the synthesis of complex macrocyclic structures and, thus, facilitate their application in medicinal chemistry and pharmaceutical sciences.

4.4 Results and Discussions:

Previously in Chapter 3A, we reported the macrocyclization of alcohols for the synthesis of macrolactones using Ru-MACHO as a catalyst via acceptorless dehydrogenation.¹¹⁵ Building upon this foundation, our objective was to convert these macrolactones into macrolactams, using a ring-opening and ring-closing strategy, thereby eliminating the need for halogenated toxic reagents, external oxidants, or additives.

Herein, we present a new strategy utilizing Ru and Ir catalysis, which efficiently converts macrolactones into macrolactams in two sequential steps with the removal of ammonia and water as byproducts. Specifically, the approach involves: i) $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ -catalyzed ring opening of macrolactones to form primary amides in the presence of hydrazine hydrate in the first step, and ii) $[\text{Cp}^*\text{IrCl}_2]_2$ (η^5 -pentamethylcyclopentadienyliridium chloride

dimer)¹³⁴ catalyzed intramolecular *N*-alkylation of amides with alcohols to achieve macrolactams under neutral conditions in the second step (Figure 72).

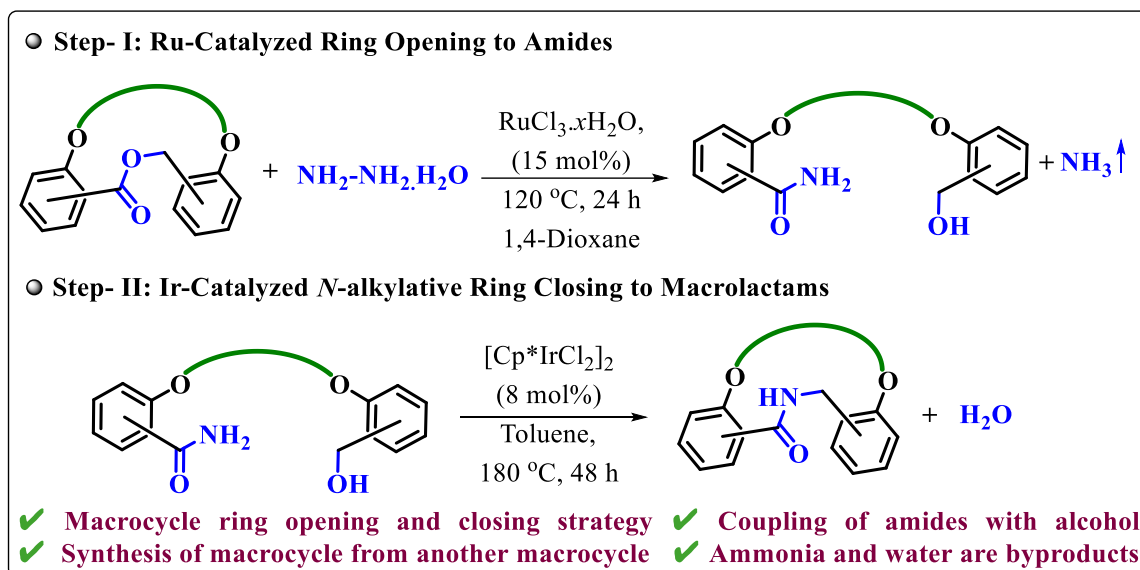


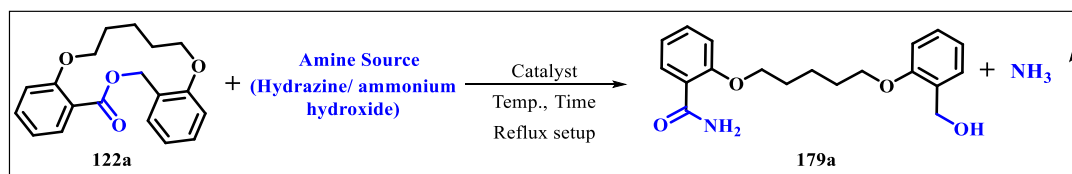
Figure 72: Ring-opening and ring-closing macrolactamization

4.4.1 Optimization Studies:

To investigate the concept of ring-opening and ring-closing macrocyclization, we first synthesized a variety of macrolactones through the acceptorless dehydrogenation of primary alcohols, as detailed in Chapter 3A. Subsequently, our focus shifted to exploring the ring-opening of macrolactone **122a** to yield amide **179a**, initiating an optimization study where various reaction parameters were systematically varied (Table 5). Macrolactone **122a** was reacted with 3 mL of hydrazine hydrate under reflux conditions at 120 °C, resulting in the formation of hydrazide product **179'** with 60% yield (Table 5, entry 1). Subsequently, varying the catalyst loading of $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (10, 15, and 20 mol%) and using 5 mL of hydrazine hydrate provided amide product **179a** with yields of 45, 48, and 40% respectively (Table 5, entries 2-4). Further optimization with 15 mol% catalyst loading and different volumes of hydrazine hydrate (Table 5, entries 5, 6, and 7) revealed that using 1.5 mL of hydrazine hydrate furnished the highest yield (63%) of the product **179a** (Table 5, entry 7). Additionally, adjusting the reaction temperature to 100 °C and 80 °C led to decreased yields of 50 and 39%, respectively, with the recovery of unreacted starting material (Table 5, entry 8). Maintaining the optimal temperature of 120 °C and using 1 mL of hydrazine hydrate, we evaluated the influence of solvents such as THF and 1,4-dioxane, providing yields of 45 and 68% for product **179a** respectively (Table 5, entries 9 and 10). Use of $\text{NH}_2\text{-NH}_2 \cdot 2\text{HCl}$ (1 equiv.) and KOH (2 equiv.) in toluene, afforded no product formation (Table 5, entry 11). Furthermore, the reaction of **122a**

with only ammonium hydroxide provided no product formation (Table 5, entry 12). Other catalysts, such as $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and MnCl_2 are found inefficient to provide a good yield of **179a** (Table 5 entries 13-15).

Table 5: Optimization table for ring-opening amidation of macrolactones



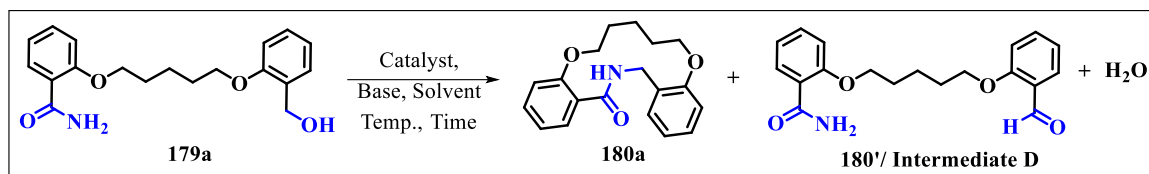
Sr. No.	Catalyst (mol %)	Amine Source (mL)	Temp. (°C)	Yield of 179a (%)
1.	-	3	120	-
2.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (10)	5	120	45
3.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15)	5	120	48
4.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (20)	5	120	40
5.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15)	4	120	40
6.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15)	3	120	48
7.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15)	1.5	120	63
8.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15)	1.5	100/80	50/39
9.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15)	1	120	45 ^b
10.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15)	1	120	68 ^c
11.	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15)	-	120	- ^d
12.	-	1	120	- ^e
13.	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (15)	1	120	Trace
14.	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (15)	1	120	Trace
15.	MnCl_2 (15)	1	120	Trace

^a**Reaction conditions:** Macrolactone **122a** (0.165 mmol, 1 equiv.), amine source (see table), $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (mol%) was refluxed at various temperatures (see table) for 24 h in ^bTHF (1 mL). ^c1,4-dioxane (1 mL). ^d $\text{NH}_2\text{-NH}_2 \cdot 2\text{HCl}$ (1 equiv.), toluene (3 mL) and KOH (2 equiv.) ^eAmmonium hydroxide is used instead of hydrazine hydrate to get the amide **179a**.

Subsequently, amides **179** underwent intramolecular *N*-alkylation to generate macrolactams **180**. Macrocyclization, a pivotal step in this process, presents several challenges, including (i) the potential formation of dimers or oligomers, (ii) Ir-catalyzed decarbonylation,¹³⁵ and (iii)

achieving high yields due to the unfavorable conformational requirements at two reaction centers (Discussed in chapter I, Figures 5a and 5b).

Table 6: Optimization table for *N*-alkylative macrolactamization.^a



Sr. No.	Catalyst (mol %)	Base (equiv.)	Temp. (°C)	Yield of 180a (%)
1.	[Cp*IrCl ₂] ₂	Cs ₂ CO ₃	160	13
2.	[Cp*IrCl ₂] ₂	KOH	160	25
3.	[Cp*IrCl ₂] ₂	<i>t</i> -BuOK	160	25
4.	[Cp*IrCl ₂] ₂	K ₃ PO ₄	160	-
5.	[Cp*IrCl ₂] ₂	KOAc	160	-
6.	[Cp*IrCl ₂] ₂	-	160	31
7.	[Cp*IrCl ₂] ₂	-	140/180	- / 70
8.	[Cp*IrCl ₂] ₂	-	180	Trace ^b
9.	[(COD)IrCl] ₂	- / Cs ₂ CO ₃	180	20 / -
10.	H ₂ ClIrPNP	-	180	-
11.	[Cp*RuCl ₂] ₂	-	180	-
12.	[Cp*IrCl ₂] ₂	-	180	54 ^c
13.	[Cp*IrCl ₂] ₂	-	180	70 ^d
14.	[Cp*IrCl ₂] ₂	-	180	73 ^e
15.	[Cp*IrCl ₂] ₂	-	180	75 ^f
16.	[Cp*IrCl ₂] ₂	-	180	67 ^g /70 ^h /75 ⁱ
17.	[Cp*IrCl ₂] ₂	-	180	62 ^j /58 ^k
18.	-	-	180	-

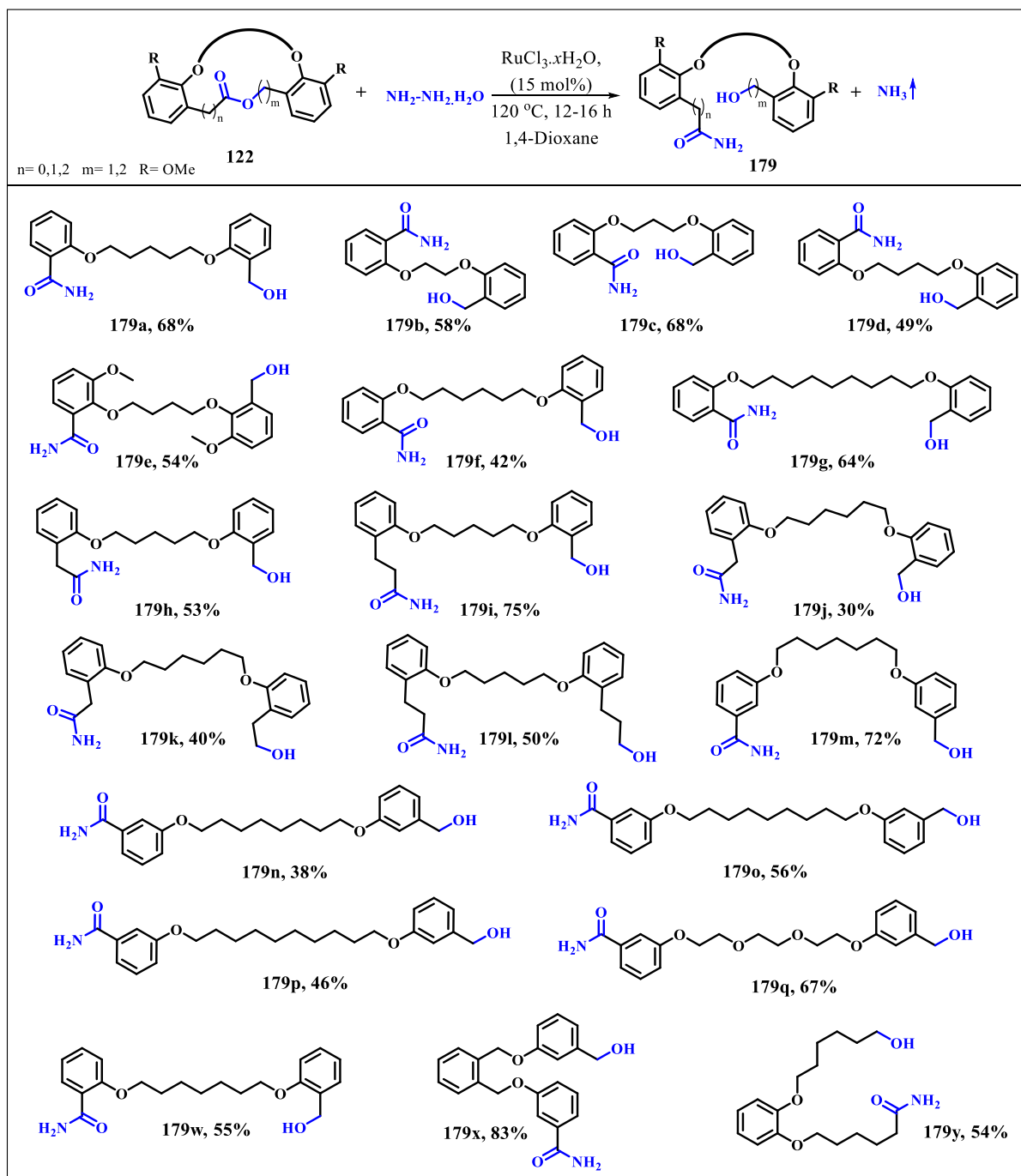
^a**Reaction conditions:** Hydroxyalkylbenzamide derivative **179a** (*c* = 0.01 M, 0.075 mmol), catalyst (5 mol %), and base (1 equiv., see table) in toluene (7.6 mL) were stirred in a preheated parallel synthesizer at 160 °C. ^b1, 4-dioxane as a solvent. ^c2.5 mol%, ^d6 mol%, ^e7 mol% and ^f8 mol% of catalyst loading for 48 h. ^g24 h, ^h38 h, ⁱ72 h. ^j*c* = 0.03 M and ^k*c* = 0.06 M. The mentioned yields are isolated yields.

To address these challenges, various reaction parameters were systematically optimized to enhance the yield of macrolactams. For instance, treatment of amide **179a** with $[\text{Cp}^*\text{IrCl}_2]_2$ catalyst (5 mol %) and Cs_2CO_3 (1 equiv.) in toluene (7.6 mL, $c = 0.01$ M) at 160 °C for 48 hours afforded 13% of the desired macrolactam **180a**, along with 50% of a partially oxidized intermediate **D/180'** (Table 6, entry 1). Maintaining the same concentration (0.01 M) of **179a**, different bases such as KOH and *t*-BuOK were screened, resulting in comparable yields of 25% for **180a** in both cases (Table 6, entries 2 and 3). In contrast, no product formation was observed with K_3PO_4 and KOAc (Table 6, entries 4 and 5).

Intriguingly, the reaction conducted without a base yielded 31% of **180a** alongside 40% of intermediate **D/180'**, suggesting that base-free conditions support product formation effectively (Table 6, entry 6). Interestingly, increasing the reaction temperature to 180 °C enhanced the yield of product **180a** to 70%, with a concomitant decrease in aldehyde **D** to 10%. Conversely, no product was obtained at 140 °C (Table 6, entry 7). When 1,4-dioxane was used as a solvent, only a trace amount of product was observed (Table 6, entry 8). The catalyst $[(\text{COD})\text{IrCl}]_2$ afforded 20% of **180a** under neutral conditions, while no product formation was noted in the presence of a base (Table 6, entry 9). Catalysts such as $\text{H}_2\text{ClIrPNP}$ and $[\text{Cp}^*\text{RuCl}_2]_2$ proved inefficient for this transformation (Table 6, entries 10 and 11). Catalyst screening identified $[\text{Cp}^*\text{IrCl}_2]_2$ as the optimal catalyst for this reaction. Furthermore, varying the catalyst loading from 2.5 to 8 mol% resulted in yields of 54, 70, 73, and 75% of **180a**, respectively (Table 6, entries 12 to 15). Using 8 mol% catalyst loading, we investigated reaction times of 24, 38 and 72 h, resulting in 67, 70, and 75% yields of **180a**, respectively (Table 6, entry 16). This study confirms that 48 h of reaction time is optimal for this transformation. Subsequently, amide **179a** was subjected to intramolecular reaction at different concentrations (0.03 M and 0.06 M), yielding 62 and 58% of **180a**, respectively (Table 6, entry 17), underscoring that 0.01 M of **179a** provides the highest yield (75%) of **180a** with minimal aldehyde formation. In a control experiment without a catalyst at 180 °C, only starting material **179a** was recovered (Table 6, entry 18). After screening all reaction parameters, we achieved the best-optimized condition (Table 6, entry 15), where the 8 mol% of catalyst loading provides macrolactam **180a** via intramolecular *N*-alkylative ring-closure reaction of amide **179a** under neutral conditions.

Having established optimized reaction conditions for ring-opening, we proceeded to transform several macrocyclic lactones into acyclic amides **179a-179q** (Scheme 51). Macrolactones featuring ethyl to pentyl spacers yielded products **179a-179d** with yields ranging from 68 to 49%. The formation of amide **179a** was also confirmed by single-crystal X-ray analysis (Figure 73).

4.4.2 Substrate Scope:



Scheme 51: Substrate scope for direct amidation from ring-opening of macrolactones

Reaction conditions: Macrolactones (**122**) (0.165 mmol, 1 equiv.), $\text{RuCl}_3\cdot x\text{H}_2\text{O}$ (15 mol%) and $\text{NH}_2\text{-NH}_2\cdot\text{H}_2\text{O}$ (1 mL) were refluxed at 120 °C for 24 h in 1,4-dioxane (1 mL) to achieve amides **179**. Mentioned yields are isolated yields.

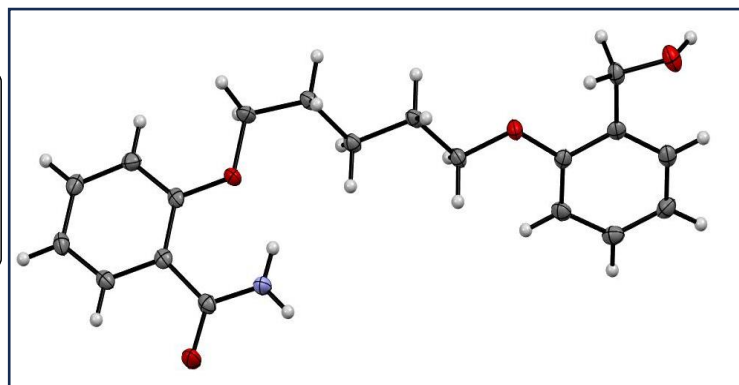
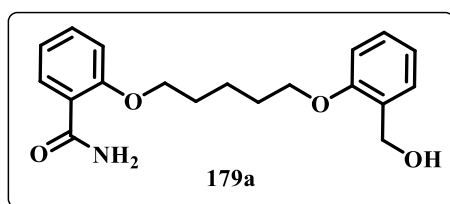
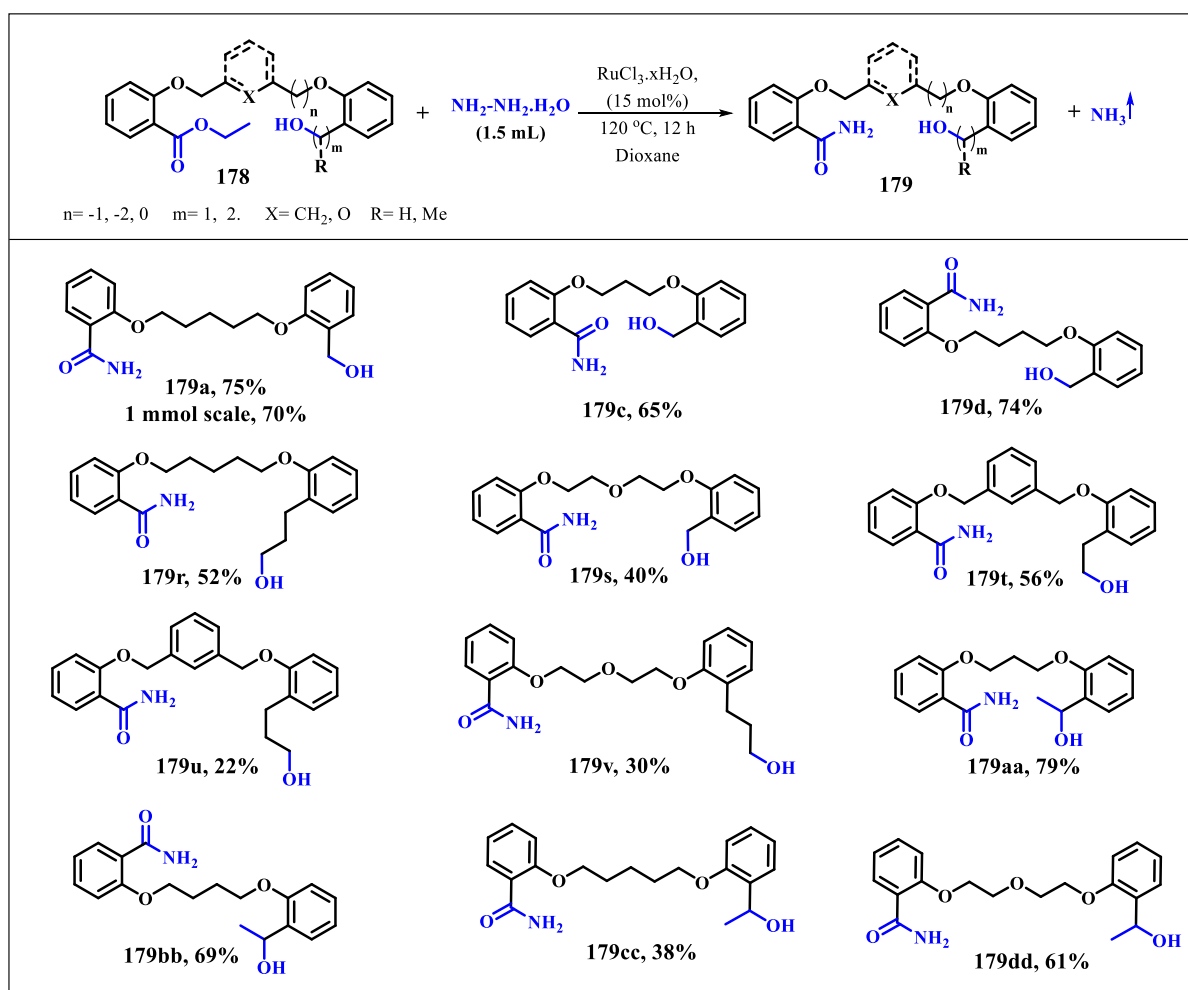


Figure 73. ORTEP drawing of **179a** (CCDC= 2266295) showing thermal ellipsoids at the 50% probability level (temperature= 296 K)



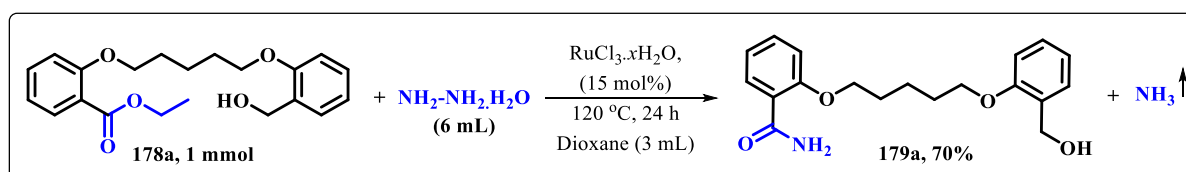
Scheme 52: Substrate scope for direct amidation from esters

Reaction conditions: Esters (**178**) (0.165 mmol, 1 equiv.), $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15 mol%) and $\text{NH}_2\text{-NH}_2 \cdot \text{H}_2\text{O}$ (1.5 mL) were refluxed at 120 °C for 24 h in 1,4-dioxane (1 mL) to achieve amides **179**. Mentioned yields are isolated yields.

Notably, the ring-opening of methoxy-substituted macrolactone yielded amide **179e** with a yield of 54%. Macrolactones with hexyl, nonyl, and heptyl spacers produced products **179f**, **179g**, and **179w** with yields of 42, 64, and 55%, respectively. Additionally, amides **179h**, **179i**, **179j**, **179k**, and **179l** were obtained with yields ranging from 75 to 40% (Scheme 51). Furthermore, *meta*-isomers of macrolactones bearing heptyl to decyl spacers and an ether functionality yielded amides **179m-179q** with yields of 72 to 38%. Lastly, amides **179x** and **179y** were synthesized with yields of 83 and 54%, respectively (Scheme 51).

Moreover, acyclic ethyl esters **178** underwent amidation to yield amides **179a**, **179c**, and **179d** with yields of 75, 65, and 74%, respectively (Scheme 52). Esters featuring non-benzylic alcohols, ethers, and aryl spacers produced amides **179r-179v** with yields of 52, 40, 56, 22, and 30%, respectively. Notably, esters containing secondary benzyl alcohols were well tolerated, providing amides **179aa-179dd** with yields ranging from 79% to 38% (Scheme 52).

To check the scalability of this approach, we performed a 1 mmol scale experiment starting with ester **178a**, and under optimized conditions, amide **179a** was obtained in 70% yield (Scheme 53).



Scheme 53: Ru-catalyzed amidation of ester **178a** on a 1 mmol scale

Under the optimized conditions of *N*-alkylative ring-closing (Table 6, entry 15), various *ortho*-hydroxymethylbenzamides (**179a-179g**) bearing various alkyl spacers underwent macrolactamization via *N*-alkylative ring closure reaction (Scheme 54). Initially, amide **179a** yielded 75% of macrolactam **180a**. The formation of macrolactam **180a** was also confirmed by single-crystal X-ray analysis (Figure 74) with the largest cavity diameter of 6.18 Å. Next, Amide **179b** afforded a 35% yield of the 11-membered macrolactam **180b** (Scheme 54). Amides bearing propyl and butyl spacers, **179c** and **179d**, afforded products **180c** and **180d** in 71 and 77% yields, respectively (Scheme 54). Additionally, methoxy-substituted compound **179e** yielded 52% of product **180e** and amide **179f** afforded a 39% yield of **180f** (Scheme 54). Conversely, amide **179w** bearing a heptyl spacer resulted in no product formation, yielding only the oxidized product. Amide **179g** with a nonyl spacer yielded a lower yield (21%) of product **180g**. Furthermore, *o*-hydroxymethylphenylacetamide **179h** and *o*-hydroxymethylphenylpropanamide **179i** yielded products **180h** and **180i** in 54 and 27% yields,

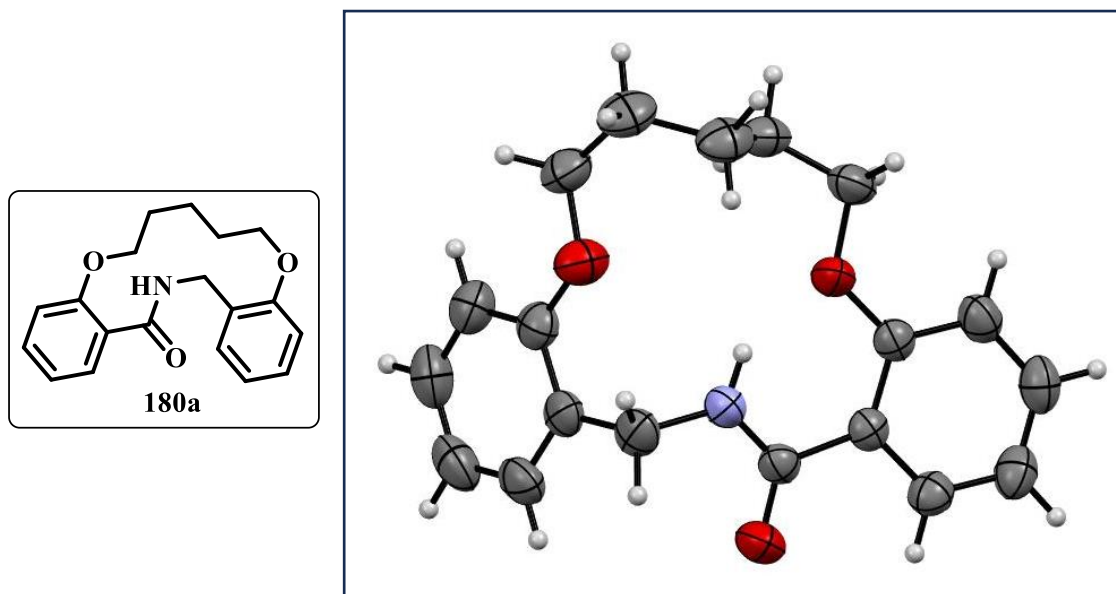
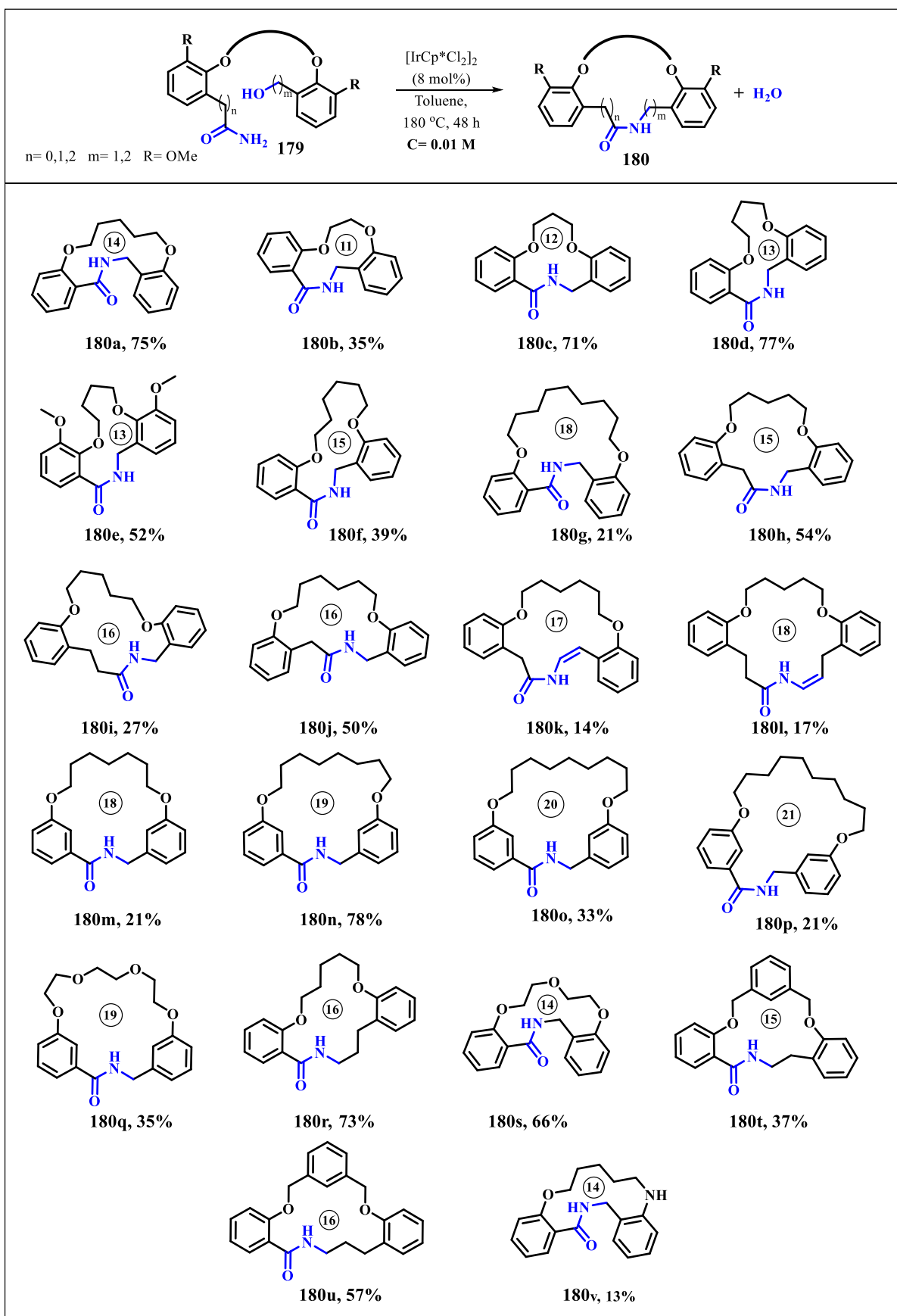


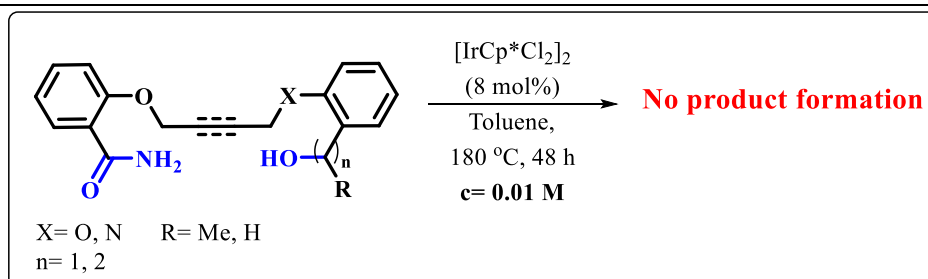
Figure 74. ORTEP drawing of **180a** (CCDC= 2245939) showing thermal ellipsoids at the 50% probability level (temperature= 296 K)

respectively (Scheme 54). Amide **179j** bearing a hexyl spacer provided 50% of **180j** (Scheme 54). The *N*-alkylation with *o*-hydroxyethylphenylacetamide **179k** and *o*-hydroxypropylphenylpropanamide **179l**, which yielded products **180k** and **180l** in 14 and 17% yields, respectively (Scheme 54). Interestingly, these two macrolactams exhibited an enamine-type carbon-carbon double bond after the isomerization of the intermediate imine bond (for mechanism, see Scheme 58). Subsequently, macrolactamization was performed with *meta*-hydroxymethylbenzamides **179m-179q**, bearing heptyl to decyl spacers and an ether spacer, yielding products **180m**, **180n**, **180o**, **180p**, and **180q** with 21 to 78% yields (Scheme 54). However, amides **179x** and **179y** did not yield the desired products due to inaccessible reaction centres. Additionally, intramolecular *N*-alkylative ring closure of amides **179r-179u** resulted in new macrolactams **180r-180u** (Scheme 50). Amide **179r** afforded 73% of **180r**, while amide **179s** with an ether spacer yielded 66% of **180s**. Moreover, amides **179t** and **179u** with aryl spacers reacted with non-benzylic alcohols to provide 37% and 57% of products **180t** and **180u**, respectively (Scheme 50). Conversely, amide **179v** yielded trace amounts of product. Amide **179hh**, with an amine spacer, afforded a 13% yield of **180v** (Scheme 54). Moreover, reactions of benzamides with secondary alcohols (**179aa-179dd**) resulted in only oxidized products rather than macrolactams, while amides **179ee**, **179ff**, **179gg**, and **179ii**, bearing alkene, alkyne, and amine spacers, failed to yield macrolactams (Scheme 54').

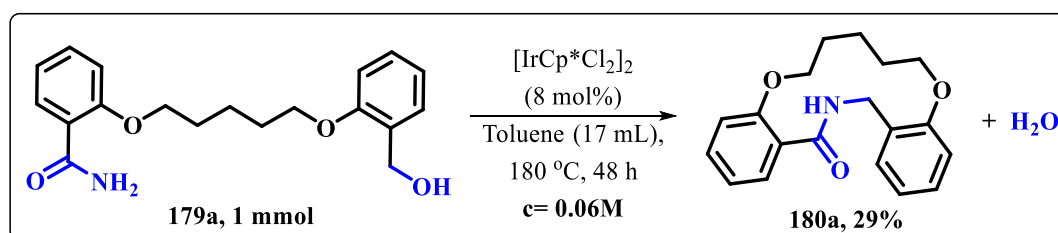


Scheme 54. Substrate Scope for *N*-Alkylative Ring Closure of Amides to Macrolactams.

Reaction condition: Amides (**179**) (0.075 mmol, 1 equiv.), [Cp*IrCl₂]₂ (4.8 mg, 0.006 mmol, 8 mol%) were heated at 180 °C in a preheated oil bath/ parallel synthesizer in toluene (7.6 mL) for 48 h in a sealed tube to achieve macrolactams **180**.



Scheme 54': Unsuccessful results for macrolactamization



Scheme 55. 1 mmol scale reaction of Ir-catalyzed N-alkylative ring-closing macrolactamization

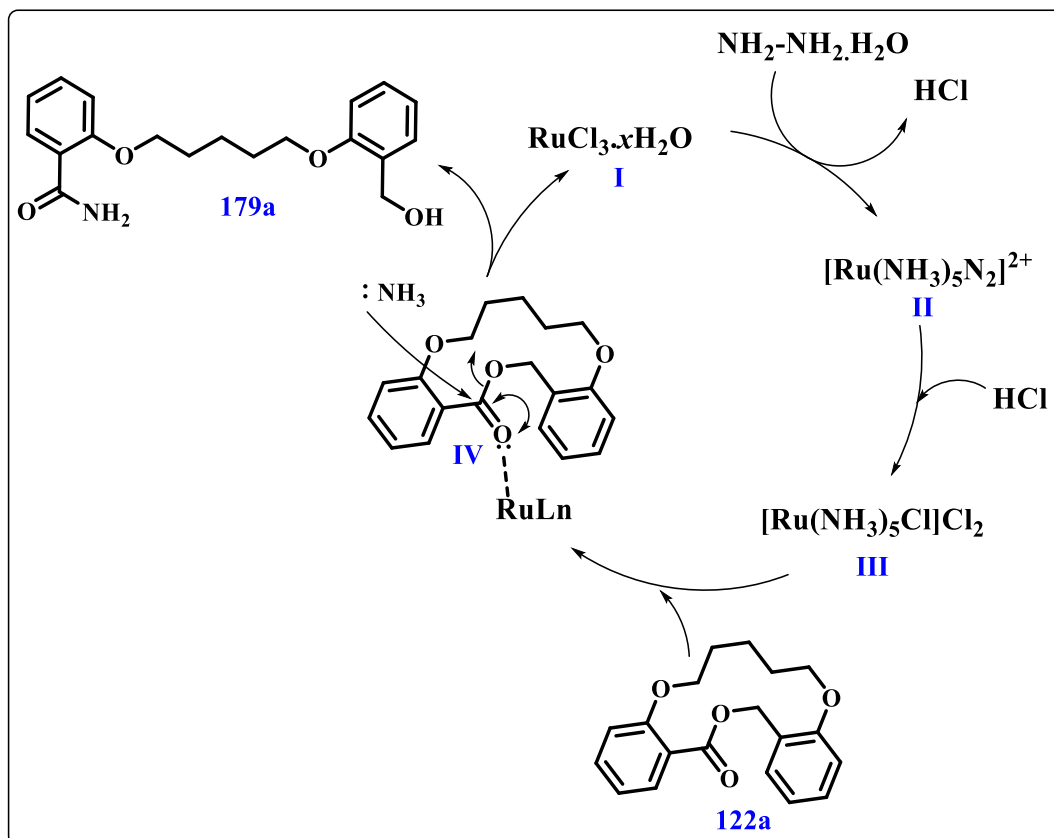
Reaction condition: Amide (**179a**) (1 mmol, 1 equiv.), [Cp*IrCl₂]₂ (0.006 mmol, 8 mol%) were heated at 180 °C in a preheated oil bath/ parallel synthesizer in toluene (17 mL) for 48 h in a sealed tube to achieve macrolactams **180a**.

Additionally, a 1 mmol of scale reaction was performed with **179a**. Due to the sealed reaction tube, the dilution up to 0.01 M was not possible because of the requirement of a bigger reaction apparatus and other adjustments for the reaction. Thus, the amide **179a** was diluted to 0.06 M in toluene and reacted under optimized reaction condition, to provide a 29% yield of macrolactam **180a** (Scheme 55). Generally, the yield of macrocyclization reactions is highly dependent on the high dilution of the starting material and 0.06 M is the non-optimized higher concentration for the reaction mentioned in Scheme 55.

4.5 Mechanistic Investigation:

A thorough literature survey helped to probe the mechanism of ring-opening of macrolactones to amides. Based on these literature backgrounds,¹³⁶ we depicted a plausible mechanism for the ring opening of macrolactone **122a** to amide **179a** (Scheme 52). Initially, refluxing RuCl₃·xH₂O (**I**) in the presence of hydrazine hydrate initially forms nitrogenpentaamineruthenium(II) intermediate **II**, accompanied by the release of HCl.

Subsequently, intermediate **III** is formed as HCl reacts further with **II**. Macrolactone **122a** then reacts with **III** to yield intermediate **IV**. In the subsequent step, ammonia attacks the carbonyl carbon, causing the cleavage of the macrolactone and the formation of amide product **179a**, thereby regenerating the $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ in the catalytic cycle (Scheme 56).



Scheme 56. Plausible mechanism for Ru-catalyzed ring-opening amidation

Next, we performed a few intermediate trapping experiments to depict the plausible mechanism for *N*-alkylative ring-closure macrolactamization.

4.5.1 Iridium-hydride detection by ^1H NMR spectroscopy:

To prove the reaction is proceeding through an Iridium-hydride intermediate, a hydride trapping experiment was performed. In a NMR tube equipped with a cap and N_2 balloon, $[\text{Cp}^*\text{IrCl}_2]_2$ (0.003 mmol, 2.4 mg, 0.04 equiv. (8 mol%)) and 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzamide (**179a**) (12.5 mg, 0.038 mmol, 1 equiv.) were added to toluene- d_8 (0.7 mL) as the solvent. The tube was purged with N_2 and sealed with a cap using Teflon tape. The reaction mixture was heated to 160 $^\circ\text{C}$ in a preheated oil bath. After 2 h and 20 min., the reaction mixture in the NMR tube was immediately subjected to ^1H -NMR analysis using a Bruker 600 MHz spectrometer. The observed peak at $\delta = -13.8$ indicates the presence of an iridium-hydride intermediate (Figures 75 and 76).

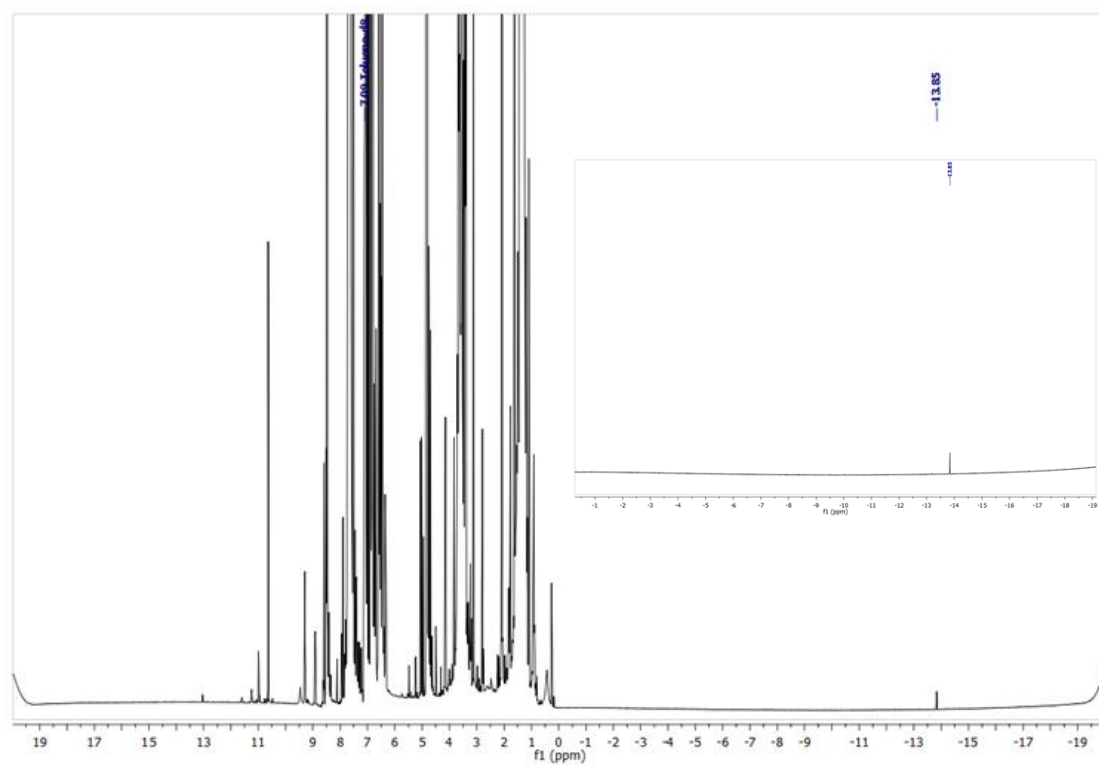


Figure 75. ^1H NMR for the Iridium-hydride

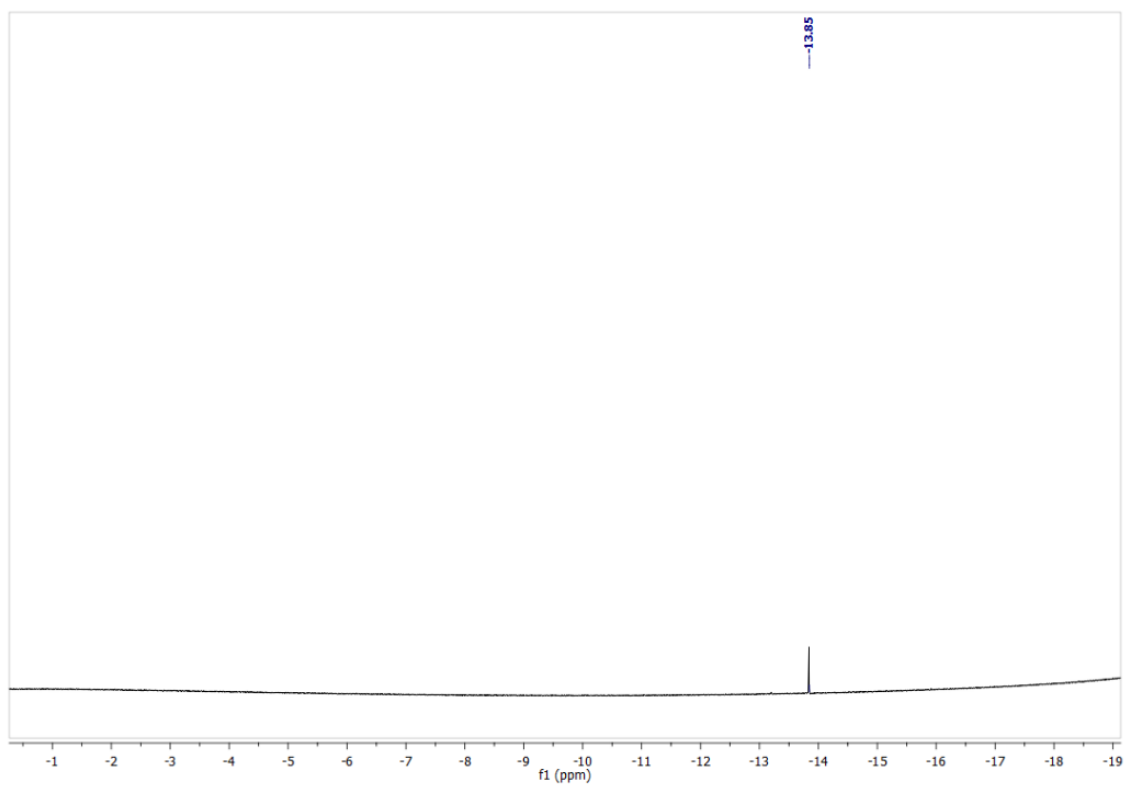


Figure 76. ^1H NMR for the Iridium-hydride

4.5.2 High-Resolution mass spectroscopy analysis for intermediate trapping:

Further, intermediate imine (**E**) and intermediate **G** were trapped by the HRMS analysis

via a direct injection of the reaction mixture into the HRMS instrument. Utilizing the optimized reaction condition (mentioned in Table 6, Entry 15), the reaction mixture was heated for 6 h. The reaction mixture was immediately allowed to cool at 0 °C in a beaker containing a mixture of ice and NaCl. The direct injection in the HRMS instrument provided the mass of the desired intermediates **E** and **G** (Figures 77 and 78).

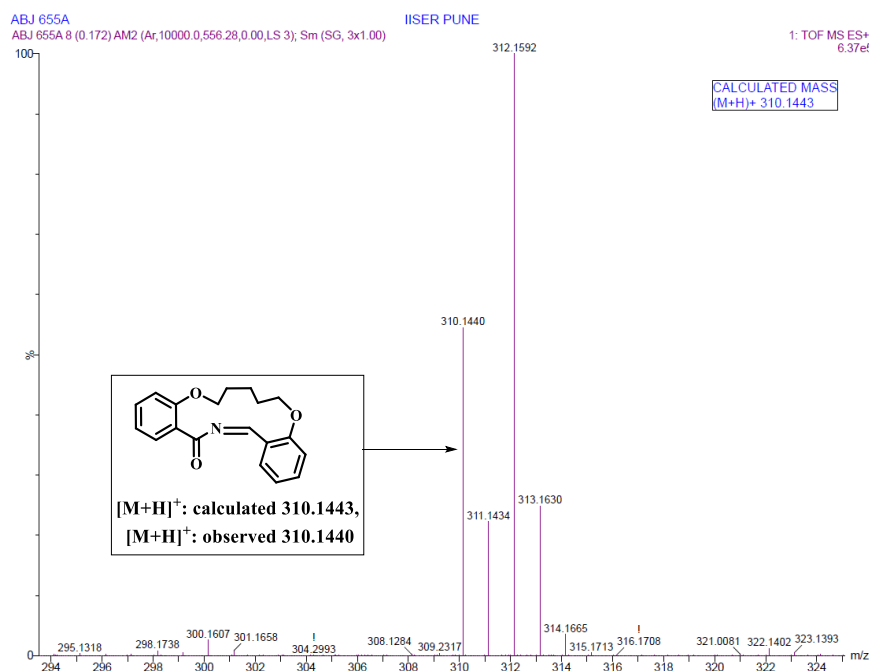


Figure 77. HRMS spectrum for the intermediate **E** (Imine)

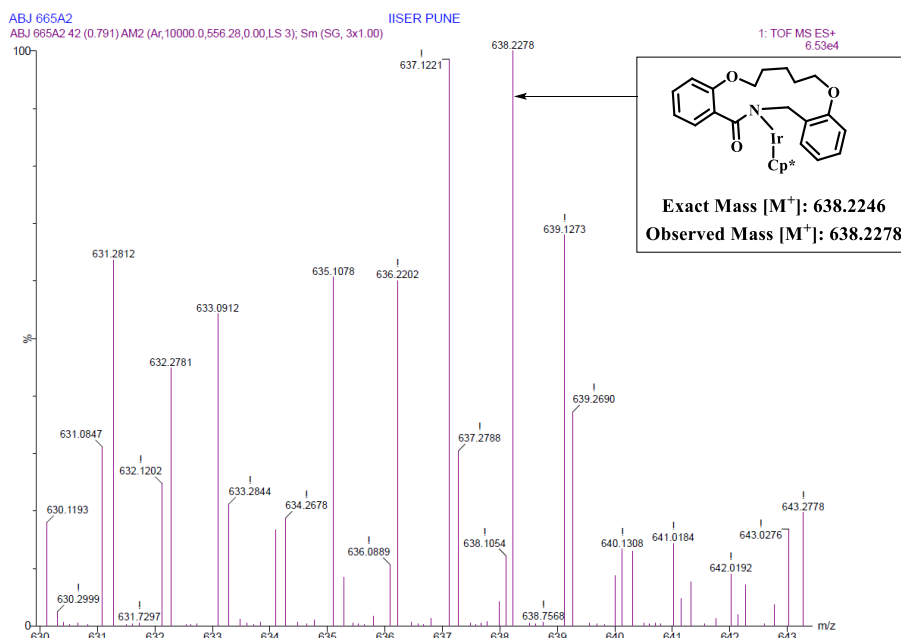


Figure 78. HRMS spectrum for the intermediate **G**

4.5.3 Copies of ^1H and ^{13}C NMR spectra for intermediate D:

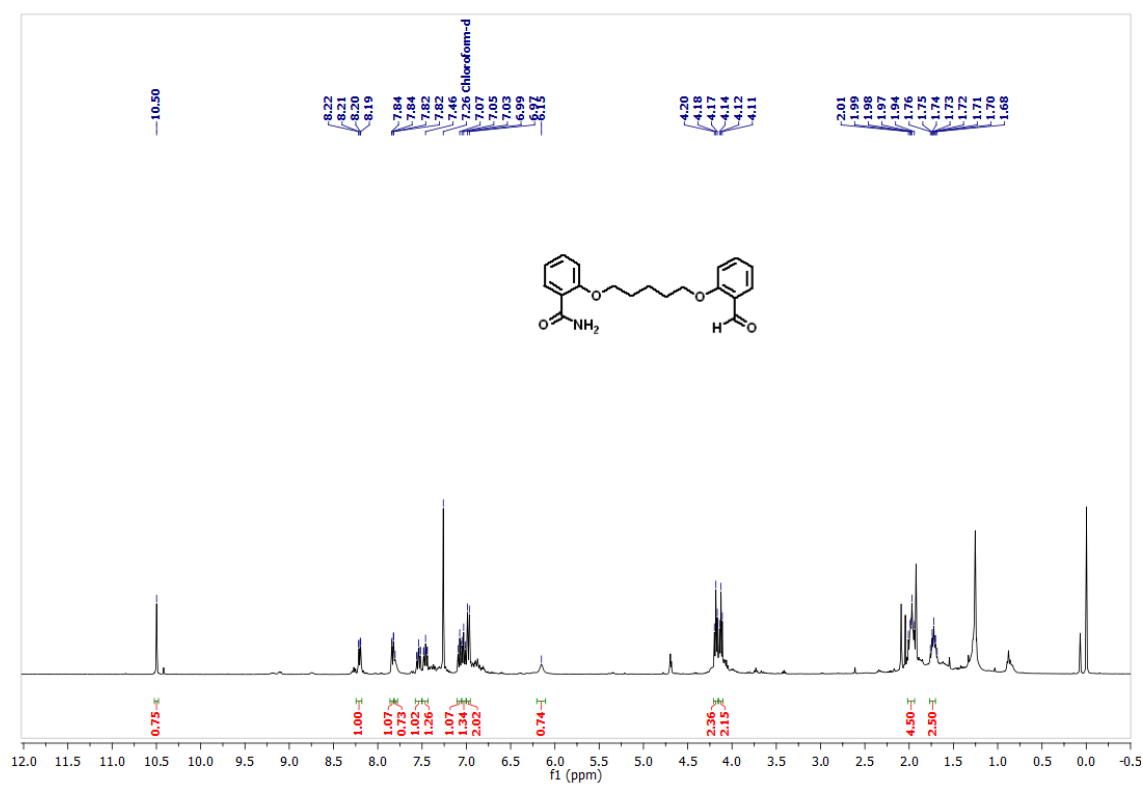


Figure 79. ^1H NMR spectra for Intermediate **D**, 400 MHz, CDCl_3

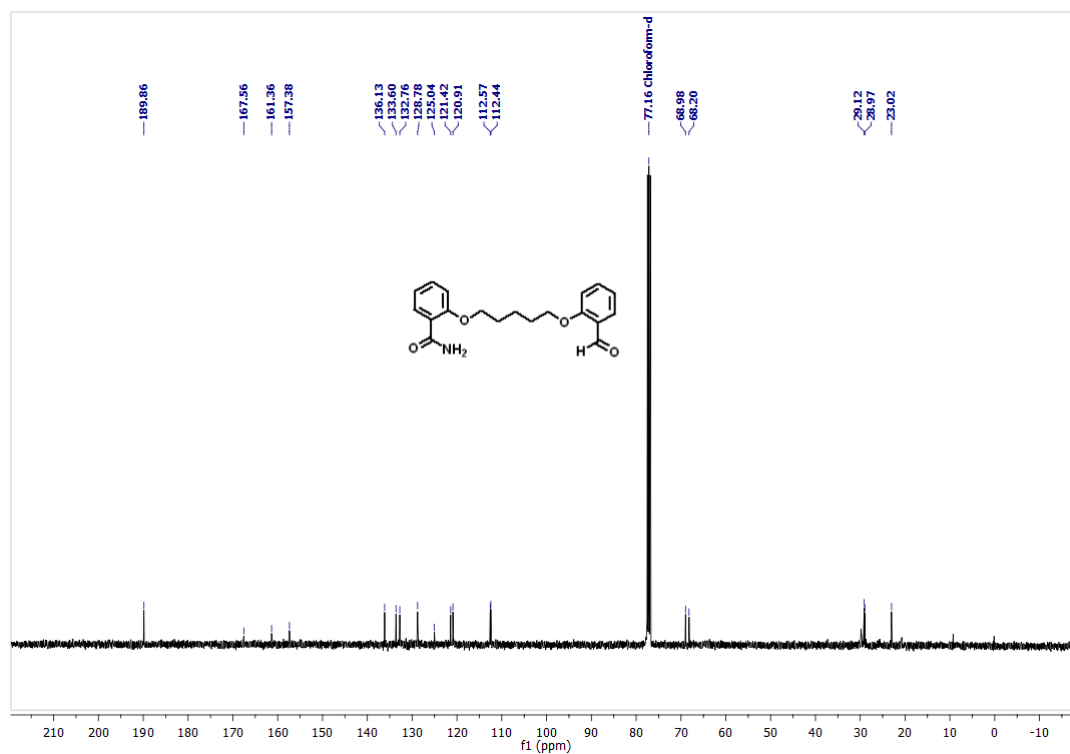
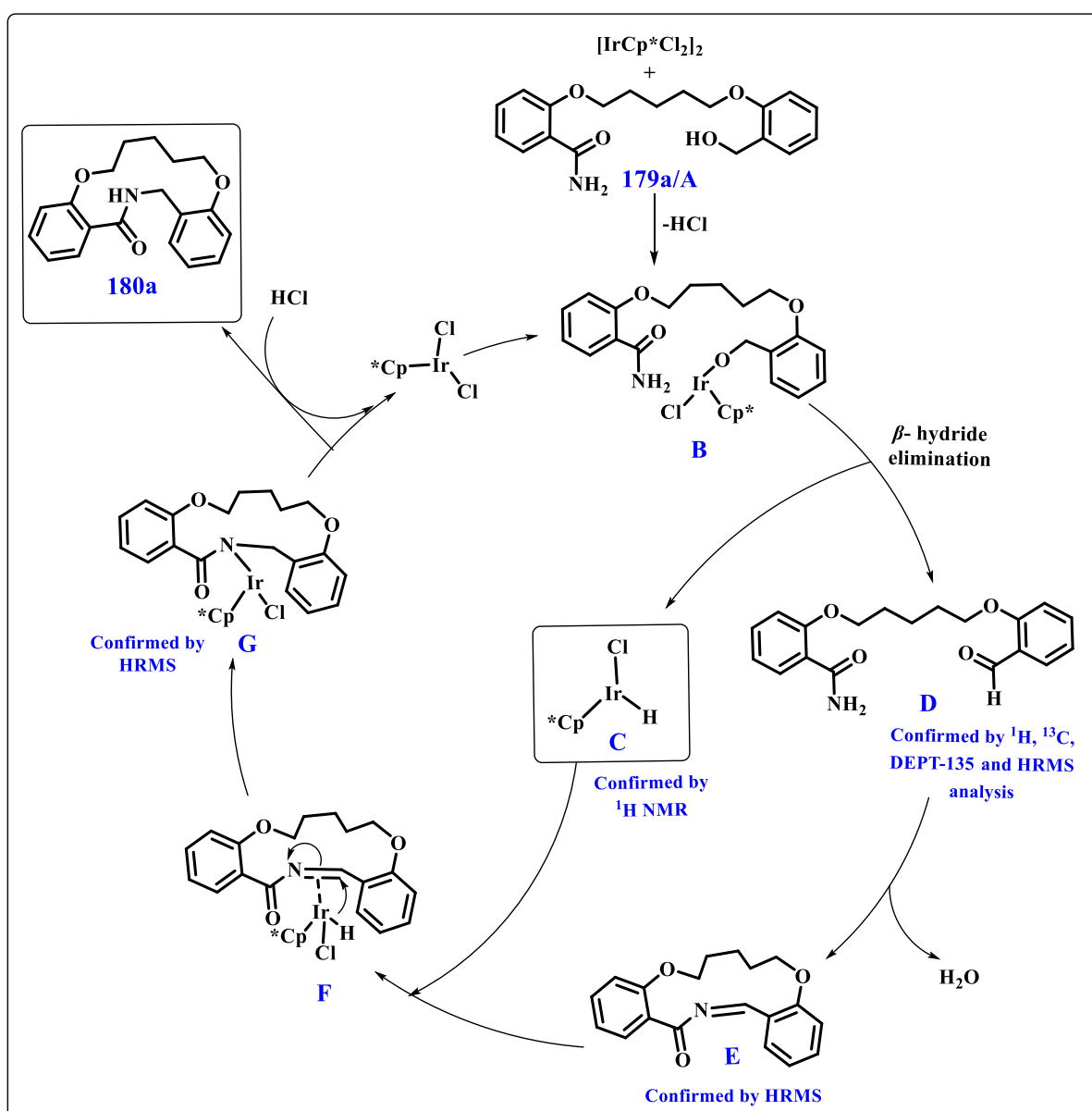


Figure 80. ^{13}C NMR spectra for Intermediate **D**, 100 MHz, CDCl_3

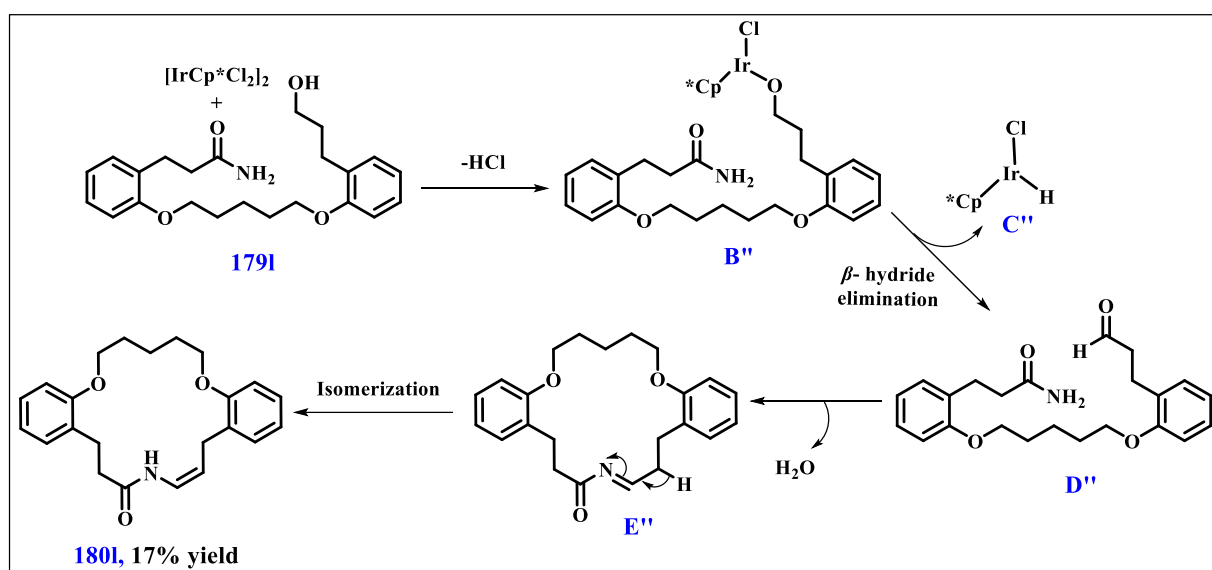
Based on trapped intermediates and literature precedents¹³⁷ we depicted the plausible mechanism for *N*-alkylative macrolactamization (Scheme 57). Initially, amide **179a/A** reacts with $[\text{Cp}^*\text{IrCl}_2]_2$ catalyst to form Iridium alkoxide species **B**, accompanied by proton loss. Subsequently, **B** undergoes β -hydride elimination to yield Ir-H (hydride) species **C** (confirmed by ^1H NMR at $\delta = -13.8$ ppm, Figures 75 and 76) and aldehyde intermediate **D**, which was isolated and characterized by ^1H , ^{13}C , DEPT-135, and HRMS analyses (Figures 79 and 80). In the next step, aldehyde **D** intramolecularly reacts with amide- NH_2 to form macrocyclic imine **E** (confirmed by HRMS analysis, Figure 77) with concomitant water elimination. Iridium hydride (**C**) then coordinatively binds to the imine, forming intermediate **F**. Further, **F** undergoes a hydride shift followed by *N*-coordination with iridium to generate intermediate **G**



Scheme 57. Plausible reaction mechanism for the macrolactamization

(confirmed by HRMS analysis, Figure 78) (Scheme 57). Finally, **G** abstracts protons from the reaction mixture, facilitating the formation of the desired macrolactam **180a** and regenerating iridium to the catalytic cycle (Scheme 57).

Furthermore, macrolactam products **180k** and **180l** exhibit an enamine-type double bond because of the availability of an adjacent α -carbon to the imine carbon in the imine intermediate **E''** (Scheme 58). Consequently, the reaction proceeds through the isomerization of an imine double bond to form a carbon-carbon double bond, resembling an enamine (**180l**). After the formation of an enamine, the Ir-H species formed during the first step of the reaction remain unreacted, causing the catalytic cycle to halt at the imine step. As a result, the products **180k** and **180l** provided lower yields as compared to other macrolactam products.



Scheme 58. Plausible mechanism for product **180l**

4.6 Conclusion:

In conclusion, we have developed a new method for synthesizing macrolactams from macrolactones and esters using Ru- and Ir-catalyzed systems. This study encompasses 32 examples of amides and 22 examples of macrolactams, demonstrating good to moderate yields. Significantly, this research represents the first instance of synthesizing a macrocycle from another macrocycle. The amidation reaction worked well when hydrazine hydrate was used as an amine source with 1,4-dioxane as the optimum solvent, generating ammonia as the only byproduct. The intramolecular *N*-alkylative ring closure reaction with primary alcohols operates effectively under increased dilution conditions. This straightforward protocol works well under neutral conditions, generating water as the sole byproduct while avoiding the use of external additives and oxidants. Mechanistic insights for the *N*-alkylative ring closure reaction

are supported by HRMS analysis, confirming the intermediates **C** (Ir-H), **E**, and **G**, alongside the direct isolation of intermediate **D**.

4.7 Experimental section and characterization data

4.7.1 General information and data collection:

The [Cp*IrCl₂]₂ (CAS number- 12354-84-6, SIGMA), Ru-MACHO (CAS number- 1295649-40-9, SIGMA), 2-hydroxybenzylalcohol (CAS number- 90-01-7, SIGMA), 3-hydroxybenzylalcohol (CAS number- 620-24-6, SIGMA), 2-hydroxy-3-methoxybenzylalcohol (CAS number- 4383-05-5, SIGMA), 2-coumaranone (CAS number- 553-86-6, SIGMA), 2*H*-chromen-2-one (Coumarin CAS number- 91-64-5, SIGMA), salicylic acid (CAS number-69-72-7, SIGMA) and dibromo alkanes were purchased from Sigma-Aldrich. Cesium carbonate (Cs₂CO₃, CASR- 534-17-8), and Hydrazine Hydrate (80% in water, CASR- 7803-57-8) were purchased from FINAR. All the solvents used were dry grade. The column chromatographic separations were performed over 60-120 mesh and 100-200 mesh size Silica-gel. Visualization was accomplished with UV light, DNP, Ninhydrin and PMA stains. ¹H and ¹³C NMR spectra were recorded on 400 and 100 MHz, respectively, using Bruker or JEOL spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiple. High-Resolution Mass Spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATIR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. Single-crystal diffraction analysis data were collected at 23 °C (296 K) with a Bruker Kappa Apex III CCD single-crystal diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Cu K α and Mo K α radiation. More information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) with deposition numbers 2266295 (**179a**), and 2245939 (**180a**). Melting points have been recorded using DBK programmable melting point apparatus (~230V).

4.7.2 Experimental Section:

A) Experimental procedure for synthesis for 2-(3-hydroxypropyl)phenol (**122'**):¹⁰⁴

In a 100 mL round bottom flask was added 2*H*-chromen-2-one (1 equiv., 13.6 mmol, 2 gm), in ethanol. The solution was allowed to cool at 0 °C temperature and sodium borohydride (4 equiv., 54.74 mmol, 2.08 gm) was added gradually to the reaction mixture. Further, the reaction mixture was stirred overnight at room temperature. After completion of the reaction, the product was extracted in an aqueous solution of ammonium chloride and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica

gel chromatography (20% of EtOAc in *n*-hexane) to get pure compound 2-(3-hydroxypropyl)phenol (**122''**) in 31% yield.

B) I) General experimental procedure for mono- and di-alkylation of 2/3-hydroxybenzylalcohol:⁸⁴

In a 100 mL round bottom flask, were added 2/3-hydroxybenzylalcohol or 2-(3-hydroxypropyl)phenol (**122''**) or 2-(2-hydroxyethyl)phenol (2 equiv.), dibromoalkanes (1 equiv.), and potassium carbonate (K_2CO_3) (2.2 equiv.) in acetonitrile. The solution was refluxed for 12-16 hrs. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the mixture of products (mono- and di-alkylated) was extracted in water and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane).

B) II) General experimental procedure for mono- and di-alkylation of 2/3-hydroxybenzylalcohol:⁸⁴

In a 100 mL round bottom flask, were added 2-(3-hydroxypropyl)phenol (2 equiv.) (**122''**) or 2-(2-hydroxyethyl)phenol (2 equiv.), mono-bromoalkylbenzylalcohol (2 equiv.), and potassium carbonate (K_2CO_3) (2.3 equiv.) in acetonitrile. The solution was refluxed for 12-16 hrs. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the product was extracted in water and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane)

C) I) General experimental procedure for mono- and di-alkylation of ethyl 2-hydroxybenzoate:⁸⁴

In a 100 mL round bottom flask, were added ethyl-2-hydroxybenzoate (1 equiv.), dibromoalkanes (1 equiv.), and potassium carbonate (K_2CO_3) (1.3 equiv.) in acetonitrile. The solution was refluxed for 16-24 hrs. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the mixture of products (mono- and di-alkylated) was extracted in water and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane).

C) II) General experimental procedure for alkylation of 2-hydroxybenzylalcohol or 2-(3-hydroxypropyl)phenol or 2-(2-hydroxyethyl)phenol with mono-bromo-ethyl-2-hydroxybenzoates:⁸⁴

In a 100 mL round bottom flask, were added 2-hydroxy benzyl alcohol/ 2-(2- hydroxyethyl)

phenol/ 2-(3-hydroxypropyl)phenol (1 equiv.), mono-bromo-ethyl 2-hydroxybenzoate (1 equiv.), and potassium carbonate (K_2CO_3) (1.2 equiv.) in acetonitrile. The solution was refluxed for 16-24 hrs. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the product was extracted in water and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane).

D) General experimental procedure for intramolecular macrolactonization of various *ortho*-/ *meta*-diphenyldimethanol derivatives:¹¹⁵

In a 20 mL re-sealable vial (equipped with a rubber septum and N_2 balloon) were added Ru-MACHO (0.004 mmol, 2.5 mg, 0.06 equiv. (6 mol%)), *o*-/ *m*-diphenyldimethanol or diols (0.069 mmol, 1 equiv.), and Cs_2CO_3 (0.035 mmol, 11.4 mg, 0.5 equiv.) in the presence of toluene (7 mL) as a solvent. The tube was purged with N_2 and sealed with a cap using a crimper. The reaction mixture was heated at 180 °C in preheated oil bath or parallel synthesizer for 48 hrs. After completion of the reaction, the reaction mixture was diluted with ethyl acetate. Further, a volatile component was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane- 05-15% EtOAc: *n*-hexane).

E) General experimental procedure for ring opening of various macrolactones using Ruthenium catalyst and hydrazine hydrate:

In a 25 mL long neck round bottom flask were added $RuCl_3 \cdot xH_2O$ (0.0247 mmol, 5.1 mg, 0.15 equiv. (15 mol%)), macrolactone/ ester (0.165 mmol, 1 equiv.), and hydrazine hydrate (1/1.5 mL) in the presence of 1,4-dioxane (1 mL) as a solvent. The reaction mixture was refluxed at 120 °C in a preheated oil bath for 24 hrs. After completion of the reaction, the reaction mixture was diluted and extracted with ethyl acetate and water. Further, a volatile component was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (40-90% EtOAc: *n*-hexane).

F) General experimental procedure for intramolecular ring closure of hydroxyalkylamides to macrolactam using Iridium catalyst via *N*-alkylation of amides under neutral conditions:

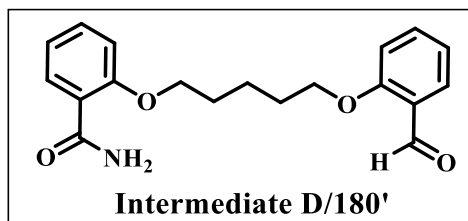
In a 20 mL re-sealable vial (equipped with a rubber septum and N_2 balloon) were added $[Cp^*IrCl_2]_2$ (0.006 mmol, 4.8 mg, 0.08 equiv. (8 mol%)), hydroxyalkylamide compounds (**179a-179y**) (0.075 mmol, 1 equiv.) in the presence of toluene (7.6 mL) as a solvent. The tube was purged with N_2 and sealed with a cap using a crimper. The reaction mixture was heated at 180 °C in a preheated parallel synthesizer for 48 hrs. After completion of the reaction, the reaction mixture was diluted with ethyl acetate. Further, a volatile component was evaporated

under a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane- 15-30%).

4.7.3. Analytical data of compounds: (for characterization data of reported *ortho/meta*-diphenyldimethanols and macrolactones, see- Chapter 3A)

A) Characterization data for Intermediate D/180', hydrazide (179'), diols, esters, and macrolactones:

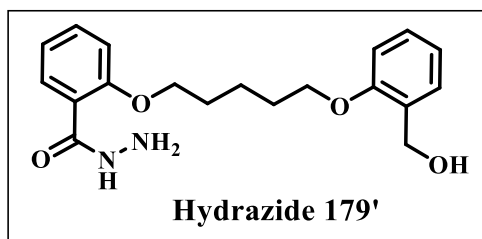
2-((5-(2-formylphenoxy)pentyl)oxy)benzamide (180'/D): (Yellowish white solid) ¹H NMR



(400 MHz, CDCl₃) δ 10.50 (s, 1H), 8.20 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.83 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.80 (s, 1H), 7.58 – 7.50 (m, 1H), 7.50 – 7.43 (m, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* =

8.4 Hz, 2H), 6.15 (s, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 2.02 – 1.94 (m, 4H), 1.77 – 1.70 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 189.8, 167.5, 161.3, 157.3, 136.1, 133.6, 132.7, 128.7, 125.0, 121.4, 120.91, 112.5, 112.4, 68.9, 68.2, 29.1, 28.9, 23.0. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₉H₂₂NO₄ 328.1549, found: 328.1544.

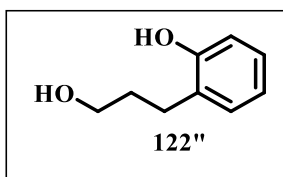
2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzohydrazide (179'): Prepared by



refluxing hydrazine hydrate (1 mL) to macrolactone **122a** (30 mg, 0.09 mmol, 1 equiv.) at 120 °C in 1,4-dioxane (1 mL) for 24 h to achieve 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzohydrazide **179'** (27 mg, 66% yield) as white solid (60% Ethyl

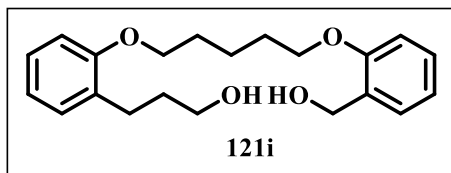
acetate: hexane). Melting Point: 106-108 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.97 (s, 1H), 8.17 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.48 – 7.39 (m, 1H), 7.31 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.85 (t, *J* = 8.2 Hz, 1H), 4.69 (s, 2H), 4.15 (t, *J* = 6.5 Hz, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 2.03 – 1.95 (m, 2H), 1.91 (m, 2H), 1.75 – 1.64 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 166.7, 156.9, 156.6, 133.1, 132.2, 129.3, 128.8, 128.7, 121.4, 120.7, 119.9, 112.3, 111.0, 69.0, 67.6, 61.5, 61.5, 29.0, 23.2. **IR** (neat): 3456, 2930, 1657, 1223, 1150 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₉H₂₅N₂O₄ 345.1814, Found: 345.1819.

2-(3-hydroxypropyl)phenol (122''): Prepared according to general procedure **4.7.2.A**, using



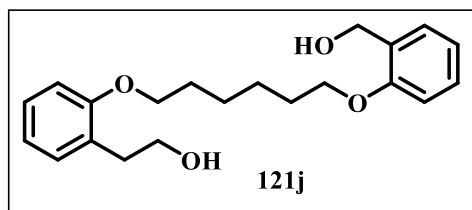
2*H*-chromen-2-one (Coumarine) (1 equiv. 13.6 mmol, 2 gms) and sodium borohydride (4 equiv., 54.7 mmol, 2 gm) to afford desired product 2-(3-hydroxypropyl)phenol **122''** (645 mg, 31% yield) as a colourless liquid (20% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.13 – 7.01 (m, 2H), 6.86 (dd, *J* = 13.7, 7.5 Hz, 2H), 3.63 (t, *J* = 5.9 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 1.92 – 1.79 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 154.3, 130.6, 127.5, 120.8, 115.8, 61.1, 32.3, 25.5. **IR** (neat): 3288, 2943, 1594, 1238 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₉H₁₃O₂ 153.0915, Found: 153.0921.

3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propan-1-ol (121i): Prepared



according to general procedure **4.7.2.B-II**, using 2-(3-hydroxypropyl)phenol (83 mg, 0.67 mmol, 1 equiv.) 2-((5-bromopentyl)oxy)phenylmethanol (200 mg, 0.67 mmol, 1 equiv.) and potassium carbonate (K₂CO₃) (138 mgs, 1 mmol, 1.5 equiv.) to afford desired 3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propan-1-ol **121i** (164 mg, 71% yield) as a colourless liquid (40% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.32 – 7.23 (m, 2H), 7.20 – 7.13 (m, 2H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.92 – 6.83 (m, 3H), 4.70 (s, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 4.02 (t, *J* = 6.2 Hz, 2H), 3.60 (t, *J* = 6.3 Hz, 2H), 2.73 (t, *J* = 7.4 Hz, 2H), 1.96 – 1.88 (m, 4H), 1.84 (m 2H), 1.77 – 1.67 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 156.8, 130.2, 130.1, 129.2, 128.9, 128.8, 127.2, 120.7, 120.7, 111.2, 111.1, 67.8, 62.1, 62.0, 33.0, 29.3, 29.2, 26.1, 23.3. **IR** (neat): 3360, 2935, 1596, 1287, 1117 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₁H₂₉O₄ 345.2066, Found: 345.2057.

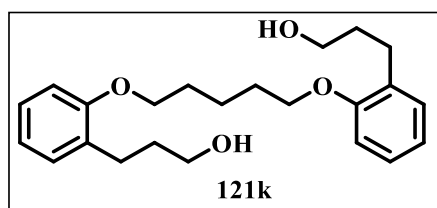
2-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)ethan-1-ol (121j): Prepared



according to general procedure **4.7.2.B-II**, using 2-(2-hydroxyethyl)phenol (138 mg, 1 mmol, 1 equiv.) 2-((5-bromopentyl)oxy)phenylmethanol (273 mg, 1 mmol, 1 equiv.) and potassium carbonate (K₂CO₃) (200 mgs, 1.5 mmol, 1.5 equiv.) to afford desired 2-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)ethan-1-ol **121j** (259 mg, 75% yield) as a colourless liquid (40% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.31 – 7.23 (m, 2H), 7.20 (td, *J* = 8.1, 1.7 Hz, 1H), 7.16 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.93 (ddd, *J* = 16.3, 7.5, 0.8 Hz, 2H), 6.87 (t, *J* = 7.6 Hz, 2H), 4.69 (s, 2H), 4.04 (t, *J* = 6.3 Hz, 2H), 3.99 (t, *J* = 6.3 Hz, 2H),

3.82 (t, $J = 6.5$ Hz, 2H), 2.90 (t, $J = 6.5$ Hz, 2H), 2.61 (s, 1H), 1.85 (m, 4H), 1.61 – 1.53 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 157.1, 156.8, 130.9, 129.2, 128.9, 128.6, 127.8, 127.2, 120.6, 120.6, 111.3, 111.1, 67.8, 67.7, 62.9, 62.1, 34.2, 29.3, 29.2, 26.0. IR (neat): 3354, 2937, 1488, 1236, 1114 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{NaO}_4$ 367.1885, Found: 367.1874.

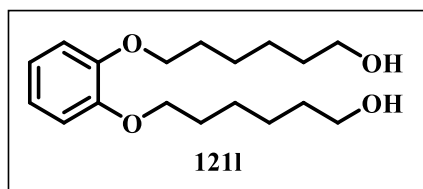
3,3'-((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))bis(propan-1-ol) (121k): Prepared



according to general procedure **4.7.2.B-II**, using 3-(2-((5-bromopentyl)oxy)phenyl)propan-1-ol (200 mg, 0.67 mmol, 1 equiv.) 2-hydroxybenzyl alcohol (83.2 mg, 0.67 mmol, 1 equiv.) and potassium carbonate (K_2CO_3) (138.2 mgs, 1 mmol, 1.5 equiv.) to afford desired 3,3'-((pentane-

1,5-diylbis(oxy))bis(2,1-phenylene))bis(propan-1-ol) **121k** (164 mg, 71% yield) as a colourless liquid (40% Ethyl Acetate: Hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.22 – 7.13 (m, 4H), 6.94 – 6.83 (m, 4H), 4.02 (t, $J = 6.2$ Hz, 4H), 3.61 (t, $J = 6.3$ Hz, 4H), 2.74 (t, $J = 7.3$ Hz, 4H), 1.96 – 1.82 (m, 8H), 1.76 – 1.66 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 156.8, 130.1, 127.1, 120.6, 111.2, 67.9, 61.9, 32.9, 29.2, 26.1, 23.1. IR (neat): 3351, 2934, 1594, 1236 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{33}\text{O}_4$ 373.2379, found: 373.2369.

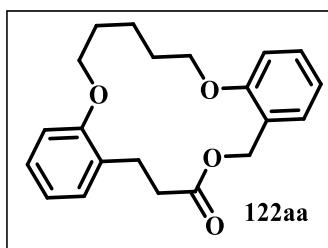
6,6'-(1,2-phenylenebis(oxy))bis(hexan-1-ol) (121l): Prepared according to general procedure



4.7.2.B-I, using 1,2-dihydroxybenzene (pyrocatechol) (200.22 mg, 2 mmol, 1 equiv.), 6-bromohexan-1-ol (720 mg, 4 mmol, 2 equiv.) and K_2CO_3 (650 mg, 5 mmol, 2.5 equiv.) to afford desired product 6,6'-(1,2-

phenylenebis(oxy))bis(hexan-1-ol) **121l** (405 mg, 65 % yield) as a white solid compound (60% Ethyl Acetate: Hexane). Melting Point: 50-52 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 6.87 (s, 4H), 3.98 (t, $J = 6.4$ Hz, 4H), 3.61 (t, $J = 6.7$ Hz, 4H), 2.90 (s, 2H), 1.86 – 1.75 (m, 4H), 1.58 (m, 4H), 1.54 – 1.46 (m, 4H), 1.42 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 149.1, 121.1, 114.0, 69.1, 62.5, 62.5, 32.6, 29.3, 26.0, 25.6. IR (neat): 3334, 2924, 1590, 1213, 1123 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{31}\text{O}_4$ 311.2222, found: 311.2209.

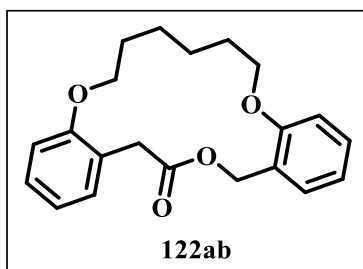
7,8,9,10,19,20-hexahydro-6*H*,16*H*,18*H*-dibenzo[*b,i*][1,5,11]trioxacyclohexadecin-18-one



(122aa): Prepared according to general procedure **4.7.2.D**, 3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propan-1-ol **121i** (23.8 mg, 0.069 mmol, 1 equiv.), Ru-MACHO (2.5 mg, 0.004 mmol, 0.06 equiv.) and Cs₂CO₃ (11.5 mg, 0.0345 mmol, 0.5 equiv.) were kept in 5 different sets (119 mg) and heated at 180

°C for 48 hr to afford desired product 7,8,9,10,19,20-hexahydro-6*H*,16*H*,18*H*-dibenzo[*b,i*][1,5,11]trioxacyclohexadecin-18-one **122aa** (74 mg, 62 % yield) as a white solid (10% Ethyl Acetate: Hexane). Melting Point: 166-169 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.29 (m, 2H), 7.23 – 7.13 (m, 2H), 6.96 – 6.84 (m, 3H), 6.81 (d, *J* = 8.1 Hz, 1H), 5.15 (s, 2H), 4.05 (t, 2H), 3.99 (t, 2H), 3.04 – 2.93 (t, 2H), 2.65 – 2.56 (t, 2H), 1.87 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 173.8, 158.4, 156.9, 131.8, 130.5, 129.9, 129.1, 127.7, 123.6, 120.2, 119.91, 110.7, 110.4, 67.3, 67.1, 64.0, 34.7, 29.8, 27.1, 24.5. IR (neat): 2934, 2838, 1707, 1596, 1237 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₁H₂₄NaO₄ 363.1572, found: 363.1566.

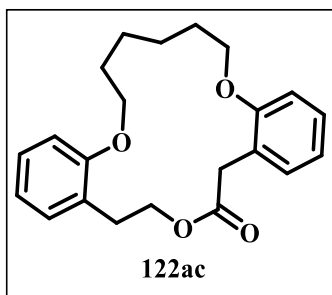
6,7,8,9,10,11-hexahydro-17*H*-dibenzo[*b,h*][1,5,10]trioxacyclohexadecin-19(20*H*)-one



(122ab): Prepared according to general procedure **4.7.2.D**, 2-(2-(((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)ethan-1-ol **121j** (23.8 mg, 0.069 mmol, 1 equiv.), Ru-MACHO (2.5 mg, 0.004 mmol, 0.06 equiv.) and Cs₂CO₃ (11.5 mg, 0.0345 mmol, 0.5 equiv.) were kept in 5 different sets (119 mg) and heated at 180 °C for 48 hr to afford desired product 6,7,8,9,10,11-

hexahydro-17*H*-dibenzo[*b,h*][1,5,10]trioxacyclohexadecin-19(20*H*)-one **122ab** (46 mg, 39 % yield) as a white solid (5% Ethyl Acetate: Hexane). Melting Point: 98-100 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.34 (ddd, *J* = 8.8, 7.6, 1.7 Hz, 2H), 7.24 (dt, *J* = 8.0, 2.1 Hz, 1H), 7.18 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.98 – 6.88 (m, 3H), 6.85 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 2H), 4.09 – 4.03 (t, 2H), 4.00 (t, *J* = 5.0 Hz, 2H), 3.63 (s, 2H), 1.89 – 1.82 (m, 2H), 1.82 – 1.75 (m, 2H), 1.76 – 1.65 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 158.4, 157.3, 132.3, 131.4, 130.6, 128.7, 123.7, 123.2, 120.3, 120.3, 111.5, 110.8, 69.7, 68.7, 63.5, 36.2, 30.1, 29.2, 28.1. IR (neat): 2929, 2864, 1732, 1598, 1246, 1117 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₁H₂₄NaO₄ 363.1572, found: 363.1568.

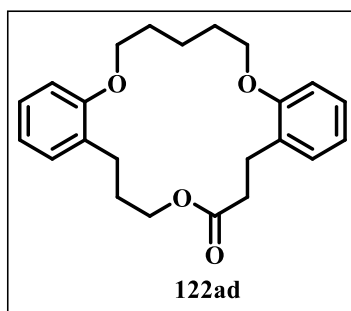
6,7,8,9,10,11,20,21-octahydrodibenzo[*b,i*][1,6,11]trioxacycloheptadecin-18(17*H*)-one



(122ac): Prepared according to general procedure **4.7.2.D**, 2,2'-((hexane-1,6-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) (25 mg, 0.069 mmol, 1 equiv.), Ru-MACHO (2.5 mg, 0.004 mmol, 0.06 equiv.) and Cs₂CO₃ (11.5 mg, 0.0345 mmol, 0.5 equiv.) were heated at 180 °C for 48 hr to afford desired product

6,7,8,9,10,11,20,21-octahydrodibenzo[*b,i*][1,6,11]trioxacycloheptadecin-18(17*H*)-one **122ac** (23.3 mg, 91 % yield) as a white solid (5% Ethyl Acetate: Hexane). Melting Point: 166-168 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.22 (td, 1H), 7.22 – 7.15 (m, 2H), 7.11 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.91 (td, *J* = 7.5, 0.8 Hz, 1H), 6.89 – 6.82 (m, 3H), 4.31 – 4.22 (t, 2H), 4.02 (m, 4H), 3.62 (s, 2H), 2.95 – 2.87 (m, 2H), 1.91 – 1.80 (m, 4H), 1.68 – 1.60 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 171.9, 157.7, 157.4, 131.2, 130.7, 128.6, 128.1, 125.7, 123.8, 120.6, 120.4, 111.7, 111.2, 68.5, 68.1, 63.9, 37.5, 30.7, 29.5, 29.4, 27.1, 26.7. IR (neat): 2926, 1722, 1595, 1242, 1163 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₂H₂₆NaO₄ 377.1728, found: 377.1727.

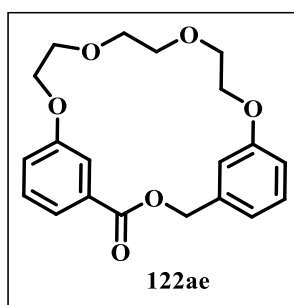
7,8,9,10,17,18,21,22-octahydro-6*H*,16*H*,20*H*-dibenzo[*b,k*][1,7,13]trioxacyclooctadecin-



20-one (122ad): Prepared according to general procedure **4.7.2.D**, 3,3'-((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))bis(propan-1-ol) **121k** (26 mg, 0.069 mmol, 1 equiv.), Ru-MACHO (2.5 mg, 0.004 mmol, 0.06 equiv.) and Cs₂CO₃ (11.5 mg, 0.0345 mmol, 0.5 equiv.) were kept in 2 different sets (52 mg) and heated at 180 °C for 48 hr to afford

desired product 7,8,9,10,19,20-hexahydro-6*H*,16*H*,18*H*-dibenzo[*b,i*][1,5,11]trioxacyclohexadecin-18-one **122ad** (48 mg, 92 % yield) as a white solid (5% Ethyl Acetate: Hexane). Melting Point: 100-102 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.24 – 7.15 (m, 4H), 6.95 – 6.87 (m, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 4.31 – 4.25 (t, 2H), 4.09 – 3.98 (t, 2H), 3.09 – 3.00 (t, 2H), 2.84 – 2.76 (t, 2H), 2.73 – 2.65 (t, 2H), 2.58-2.60 (t, 2H) 2.06 – 1.96 (m, 2H), 1.91 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 173.6, 157.1, 157.0, 130.1, 129.7, 129.2, 128.8, 127.6, 127.1, 120.3, 120.2, 110.7, 110.5, 67.5, 67.4, 64.3, 35.2, 30.1, 30.1, 28.7, 27.3, 27.2, 24.5. IR (neat): 2923, 1726, 1597, 1242, 1113 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₃H₂₈NaO₄ 391.1885, found: 391.1884.

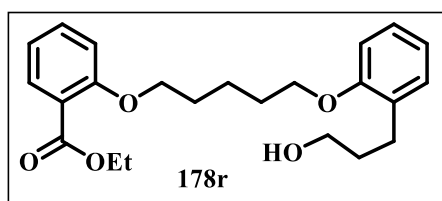
3,6,9,12,15-pentaoxa-1,5(1,3)-dibenzenacyclopentadecaphan-2-one (122ae): Prepared



according to general procedure **4.7.2.D**, 6,6'-(1,2-phenylenebis(oxy))bis(hexan-1-ol) (24.6 mg, 0.079 mmol, 1 equiv.), Ru-MACHO (2.5 mg, 0.004 mmol, 0.06 equiv.) and Cs₂CO₃ (11.5 mg, 0.0345 mmol, 0.5 equiv.) were kept in 5 different sets (125 mg) and heated at 180 °C for 48 hr to afford desired product 3,6,9,12,15-pentaoxa-1,5(1,3)-dibenzenacyclopentadecaphan-2-one **122ae** (65

mg, 51% yield) as a white solid (10% Ethyl Acetate: Hexane). Melting Point: 89-92 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.77 (dd, *J* = 2.4, 1.6 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 10.2, 5.3 Hz, 2H), 7.11 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.92 – 6.82 (m, 2H), 5.35 (s, 2H), 4.23 (dt, *J* = 10.7, 5.5 Hz, 4H), 3.83 (dd, *J* = 9.4, 5.2 Hz, 4H), 3.70 (s, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.8, 159.3, 158.8, 138.0, 131.5, 129.7, 129.6, 122.8, 121.4, 119.4, 115.5, 115.22, 113.0, 71.2, 71.2, 69.5, 69.4, 68.1, 67.9, 65.7. **IR** (neat): 2874, 1721, 1594, 1218, 1120 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₀H₂₃O₆ 359.1494, found: 359.1493.

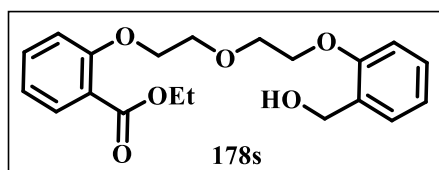
ethyl 2-((5-(2-(3-hydroxypropyl)phenoxy)pentyl)oxy)benzoate (178r): Prepared according



to general procedure **4.7.2.C-II**, using 2-(3-hydroxypropyl)phenol (152 mg, 1 mmol, 1 equiv.), ethyl 2-((5-bromopentyl)oxy)benzoate (315 mg, 1 mmol, 1 equiv.) and K₂CO₃ (250 mg, 1.3 mmol, 1.3 equiv.) to

afford desired product ethyl 2-((5-(2-(3-hydroxypropyl)phenoxy)pentyl)oxy)benzoate **178r** (300 mg, 94% yield) as a colourless liquid (30% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.78 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.19 – 7.11 (m, 2H), 6.97 (dd, *J* = 11.1, 4.4 Hz, 2H), 6.87 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 6.3 Hz, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.59 (t, *J* = 6.3 Hz, 2H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.49 (s, 1H), 1.97 – 1.83 (m, 6H), 1.77 – 1.67 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.6, 158.4, 156.8, 133.2, 131.4, 130.2, 130.0, 127.0, 120.7, 120.5, 120.0, 113.1, 111.2, 68.6, 67.8, 61.9, 60.8, 32.9, 29.0, 28.9, 26.1, 22.8, 14.3. **IR** (neat): 2932, 1710, 1455, 1242 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₃H₃₁O₅ 387.2171, found: 387.2177.

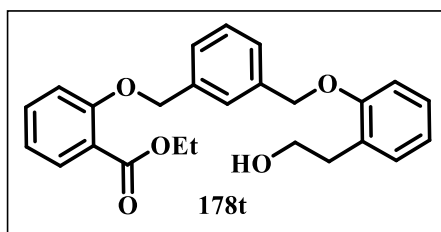
ethyl 2-(2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)ethoxy)benzoate (178s): Prepared



according to general procedure **4.7.2.C-II**, using 2-hydroxybenzylalcohol (124 mg, 1 mmol, 1 equiv.), ethyl 2-(2-(2-bromoethoxy)ethoxy)benzoate (275 mg, 0.55

mmol, 1 equiv.) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv.) to afford desired product ethyl 2-(2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)ethoxy)benzoate **178s** (145 mg, 40% yield) as a colourless liquid (40% Ethyl Acetate: Hexane). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.46 – 7.39 (m, 1H), 7.27 – 7.21 (m, 2H), 7.02 – 6.91 (m, 3H), 6.89 (d, $J = 8.4$ Hz, 1H), 4.65 (s, 2H), 4.32 (q, $J = 7.1$ Hz, 2H), 4.27 – 4.17 (m, 4H), 3.98 (ddd, $J = 11.7, 7.2, 3.8$ Hz, 4H), 1.36 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 166.3, 158.3, 157.1, 133.4, 131.6, 130.3, 129.2, 129.0, 121.3, 121.1, 120.7, 113.8, 112.4, 70.1, 69.7, 69.0, 68.1, 62.4, 60.9, 14.4. **IR** (neat): 3350, 2930, 2850, 1715, 1598, 1209 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NaO}_6$ 383.1470, found: 383.1464.

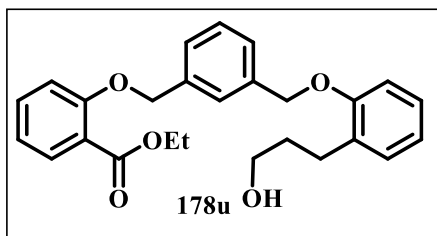
ethyl 2-((3-((2-(2-hydroxyethyl)phenoxy)methyl)benzyl)oxy)benzoate (178t): Prepared



according to general procedure **4.7.2.C-II**, using 2-(2-hydroxyethyl)phenol (42 mg, 0.3 mmol, 0.3equiv.), ethyl 2-((3-(bromomethyl)benzyl)oxy)benzoate (118 mg, 0.3 mmol, 0.3 equiv.) and K_2CO_3 (60 mg, 0.39 mmol, 1.3 equiv.) to afford desired product ethyl 2-((3-((2-(2-

hydroxyethyl)phenoxy)methyl)benzyl)oxy)benzoate **178t** (143 mg, 95% yield) as a colourless liquid (40% Ethyl Acetate: Hexane). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.82 (dd, $J = 8.0, 1.8$ Hz, 1H), 7.57 (s, 1H), 7.50 – 7.34 (m, 4H), 7.22 – 7.17 (m, 2H), 7.00 (dd, $J = 10.8, 4.5$ Hz, 2H), 6.96 – 6.90 (m, 2H), 5.19 (s, 2H), 5.10 (s, 2H), 4.35 (q, $J = 7.1$ Hz, 2H), 3.84 (t, $J = 6.6$ Hz, 2H), 2.96 (t, $J = 6.6$ Hz, 2H), 1.34 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 166.6, 158.0, 156.8, 137.5, 137.3, 133.4, 131.7, 131.1, 128.9, 127.8, 127.5, 126.7, 126.7, 125.8, 121.2, 121.0, 120.7, 113.9, 111.9, 70.6, 69.9, 62.85, 61.05, 34.2, 14.3. **IR** (neat): 2923, 1707, 1594, 1450, 1236 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{26}\text{NaO}_5$ 429.1677, found: 429.1678.

ethyl 2-((3-((2-(3-hydroxypropyl)phenoxy)methyl)benzyl)oxy)benzoate (178u): Prepared

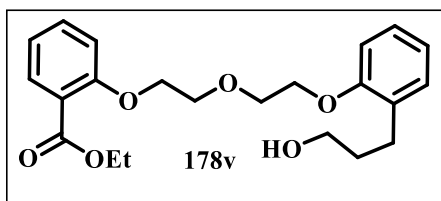


according to general procedure **4.7.2.C-II**, using 2-(3-hydroxypropyl)phenol (107 mg, 0.7 mmol, 1 equiv.), ethyl 2-((3-(bromomethyl)benzyl)oxy)benzoate (245 mg, 0.7 mmol, 1 equiv.) and K_2CO_3 (138 mg, 1 mmol, 1.3 equiv.) to afford desired product ethyl 2-((5-(2-(3-

hydroxypropyl)phenoxy)pentyl)oxy)benzoate **178u** (281 mg, 95% yield) as a colourless liquid (40% Ethyl Acetate: Hexane). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.83 (dd, $J = 7.7, 1.6$ Hz, 1H), 7.60 (s, 1H), 7.48 (d, $J = 6.9$ Hz, 1H), 7.43 (ddd, $J = 11.3, 6.5, 3.2$ Hz, 3H), 7.17 (dd, $J = 11.7,$

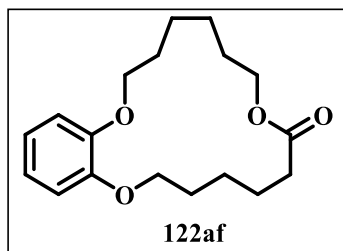
4.6 Hz, 2H), 7.00 (t, $J = 7.6$ Hz, 2H), 6.93 (t, $J = 7.2$ Hz, 2H), 5.20 (s, 2H), 5.10 (s, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 3.60 (t, $J = 6.3$ Hz, 2H), 2.78 (t, $J = 7.4$ Hz, 2H), 1.92 – 1.81 (m, 2H), 1.34 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 158.0, 156.6, 137.5, 137.3, 133.3, 131.7, 130.6, 130.3, 128.8, 127.22, 126.7, 126.6, 125.8, 121.2, 121.0, 120.7, 113.9, 111.8, 70.6, 70.0, 62.0, 61.0, 33.1, 26.3, 14.3. IR (neat): 2924, 1711, 1595, 1490, 1236, cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{28}\text{NaO}_5$ 443.1834, found: 443.1833.

ethyl 2-(2-(2-(2-(3-hydroxypropyl)phenoxy)ethoxy)ethoxy)ethoxy)benzoate (178v): Prepared



according to general procedure 4.7.2.C-II, using 2-(3-hydroxypropyl)phenol (152 mg, 1 mmol, 1 equiv.), ethyl 2-(2-(2-bromoethoxy)ethoxy)benzoate (155 mg, 0.55 mmol, 1 equiv.) and K_2CO_3 (200 mg, 1.4 mmol, 2.3 equiv.) to afford desired product ethyl 2-(2-(2-(2-(3-hydroxypropyl)phenoxy)ethoxy)ethoxy)ethoxy)benzoate **178v** (180 mg, 95% yield) as a colourless liquid (40% Ethyl Acetate: Hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.78 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.43 (ddd, $J = 8.5, 7.4, 1.8$ Hz, 1H), 7.16 (dd, $J = 12.4, 4.6$ Hz, 2H), 7.02 – 6.95 (m, 2H), 6.90 (td, $J = 7.5, 0.9$ Hz, 1H), 6.84 (d, $J = 7.9$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 4.27 – 4.21 (t, 2H), 4.17 – 4.11 (t, 2H), 3.99 (m, 4H), 3.51 (t, $J = 5.9$ Hz, 2H), 2.76 (t, $J = 7.0$ Hz, 2H), 1.86 – 1.76 (m, 2H), 1.36 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 158.3, 156.7, 133.4, 131.5, 130.6, 130.4, 127.1, 121.1, 121.0, 120.67, 113.8, 111.4, 70.2, 69.8, 69.0, 67.5, 61.1, 60.8, 33.6, 25.6, 14.3. IR (neat): 2928, 1712, 1600, 1211 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{NaO}_6$ 411.1783, found: 411.1776.

3,4,5,6,9,10,11,12,13,14-decahydrobenzo[*b*][1,4,11]trioxacycloheptadecin-7(2*H*)-one

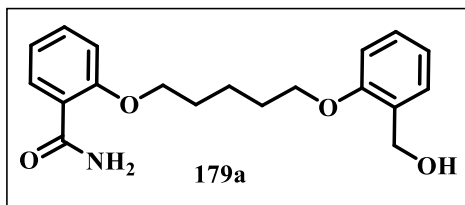


(122af): Prepared according to general procedure 4.7.2.D, 6,6'-(1,2-phenylenebis(oxy))bis(hexan-1-ol) (24.6 mg, 0.079 mmol, 1 equiv.), Ru-MACHO (2.5 mg, 0.004 mmol, 0.06 equiv.) and Cs_2CO_3 (11.5 mg, 0.0345 mmol, 0.5 equiv.) were heated at 180 $^\circ\text{C}$ for 48 hr to afford desired product 3,4,5,6,9,10,11,12,13,14-decahydrobenzo[*b*][1,4,11]trioxacycloheptadecin-7(2*H*)-one **122af** (21.8 mg, 89 % yield) as a white solid (7% Ethyl Acetate: Hexane). Melting Point: 71-73 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 6.88 (s, 4H), 4.18 – 4.12 (t, 2H), 4.04 – 4.00 (m, 2H), 4.00 – 3.97 (t, 2H), 2.42 – 2.34 (t, 2H), 1.82 (m, 4H), 1.78 – 1.71 (m, 2H), 1.71 – 1.67 (m, 2H), 1.62 – 1.53 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 149.3, 149.2, 121.1, 121.0, 114.1, 113.5, 69.2, 68.9, 64.3, 34.9, 29.6,

29.4, 28.5, 26.5, 26.4, 26.4, 25.4. **IR** (neat): 2927, 1726, 1592, 1249, 1162 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{26}\text{NaO}_4$ 329.1728, found: 329.1719.

B) Characterization Data for Amides:

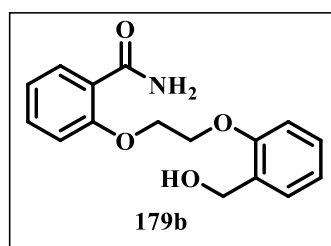
2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzamide (179a): Prepared according to



general procedure **4.7.2.E**, using 7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one **122a** (50 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.024 mmol,

0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzamide **179a** (34 mg, 68% yield) as a white crystalline solid (50% Ethyl Acetate: Hexane). Melting Point: 128-130 $^{\circ}\text{C}$. **^1H NMR** (400 MHz, CDCl_3) δ 8.19 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.76 (s, 1H), 7.44 (ddd, $J = 8.4, 7.4, 1.8$ Hz, 1H), 7.32 (dd, $J = 7.4, 1.4$ Hz, 1H), 7.27 – 7.21 (m, 1H), 7.10 – 7.02 (m, 1H), 6.99 – 6.91 (m, 2H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.40 (s, 1H), 4.70 (s, 2H), 4.16 (t, $J = 6.3$ Hz, 2H), 4.05 (t, $J = 6.0$ Hz, 2H), 2.79 (s, 1H), 1.93 (m, 4H), 1.81 – 1.63 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.4, 157.3, 156.7, 133.4, 132.6, 129.3, 128.9, 128.8, 121.3, 121.0, 120.8, 112.4, 111.1, 68.9, 67.5, 61.9, 29.1, 23.1. **IR** (neat): 3345, 2930, 1638, 1595, 1236, 1161 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{NNaO}_4$ 352.1524, found: 352.1515. **Crystal Data: CCDC= 2266295:** The crystals of compound **179a** were grown using dichloromethane and hexane as a solvent by slow evaporation. $\text{C}_{19}\text{H}_{23}\text{NO}_4$, $M = 329.38$, Monoclinic, space group $P 2_1/c$ with $a = 15.152(4)$ Å, $b = 7.8707(18)$ Å, $c = 13.909(3)$ Å, $\alpha = 90^{\circ}$, $\beta = 92.325(9)^{\circ}$, $\gamma = 90^{\circ}$, $V = 1657.4(7)$ Å³, $T = 273$ K, $R_1 = 0.0384$, $wR_2 = 0.1086$ for observed data, $z = 4$, $D_{\text{calcd}} = 1.320$ g cm^{-3} , $F(000) = 704.0$, absorption coefficient = 0.092 mm^{-1} , $\lambda = 0.71073$ Å, 2297 reflections collected on a Bruker APEX-III CCD single-crystal diffractometer, and 2815 observed reflections ($I \geq 2\sigma(I)$) with $S=1.035$.

2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)benzamide (179b): Prepared according to general

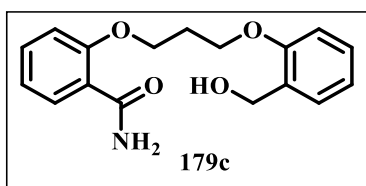


procedure **4.7.2.E**, using 6,7-dihydro-13*H*,15*H*-dibenzo[*e,j*][1,4,8]trioxacycloundecin-13-one **122b** (42 mg, 0.16 mmol, 1 equiv.), Hydrazine hydrate (1 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.024 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)benzamide **179b** (26 mg, 58% yield) as a white crystalline

solid (50% Ethyl Acetate: Hexane). Melting Point: 143-145 $^{\circ}\text{C}$. **^1H NMR** (400 MHz,

ACETONE- d^6) δ 7.98 (dd, J = 7.8, 1.7 Hz, 1H), 7.71 (s, 1H), 7.44 – 7.37 (m, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.18 – 7.09 (m, 2H), 6.97 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 6.66 (s, 1H), 4.54 (s, 2H), 4.51 – 4.47 (t, 2H), 4.41 – 4.36 (t, 2H). ^{13}C NMR (100 MHz, ACETONE- d^6) δ 166.6, 157.7, 156.1, 133.5, 132.5, 131.3, 128.3, 128.1, 122.6, 121.6, 121.3, 113.7, 111.7, 68.2, 66.9, 59.4. **IR** (neat): 3320, 2950, 1650, 1410, 1150 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{NNaO}_4$ 310.1055, found: 310.1056.

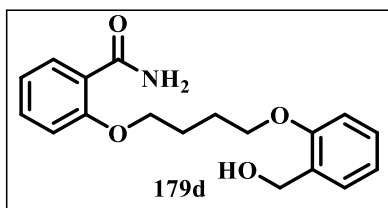
2-(3-(2-(hydroxymethyl)phenoxy)propoxy)benzamide (179c): Prepared according to



general procedure **4.7.2.E**, 7,8-dihydro-6*H*,14*H*,16*H*-dibenzo[*b,g*][1,5,9]trioxacyclododecin-14-one **122c** (47.5 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.024 mmol, 0.15 equiv.) in 1,4-dioxane

(1 mL) as a solvent to afford desired product 2-(3-(2-(hydroxymethyl)phenoxy)propoxy)benzamide **179c** (25 mg, 68% yield) as a white crystalline solid (50% Ethyl Acetate: Hexane). Melting Point: 99-102 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (dd, J = 7.8, 1.8 Hz, 1H), 7.69 (s, 1H), 7.46 (ddd, J = 8.4, 7.4, 1.9 Hz, 1H), 7.33 (dd, J = 7.4, 1.5 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.12 – 7.05 (m, 1H), 6.98 (ddd, J = 9.1, 8.2, 4.5 Hz, 2H), 6.88 (d, J = 8.0 Hz, 1H), 6.14 (s, 1H), 4.70 (s, 2H), 4.36 (t, J = 6.2 Hz, 2H), 4.22 (t, J = 5.9 Hz, 2H), 2.39 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 157.0, 156.3, 133.5, 132.7, 129.4, 129.1, 129.0, 121.6, 121.3, 112.5, 111.4, 66.2, 64.7, 61.6, 29.3. **IR** (neat): 3356, 2930, 1649, 1457, 1236, 1112 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{NNaO}_4$ 324.1212, found: 324.1210.

2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzamide (179d): Prepared according to general

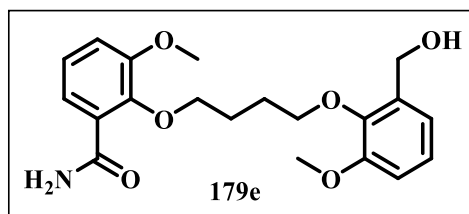


procedure **4.7.2.E**, 6,7,8,9-tetrahydro-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecin-15-one **122d** (64 mg, 0.21 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (6.6 mg, 0.0321 mmol, 0.15 equiv.) in 1,4-

dioxane (1 mL) as a solvent to afford desired product 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzamide **179d** (33 mg, 49% yield) as a white crystalline solid (50% Ethyl Acetate: Hexane). Melting Point: 127-130 $^{\circ}\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (dd, J = 7.8, 1.8 Hz, 1H), 7.75 (s, 1H), 7.45 (ddd, J = 8.4, 7.4, 1.9 Hz, 1H), 7.32 (dd, J = 7.4, 1.5 Hz, 1H), 7.26 (td, J = 7.8, 1.7 Hz, 1H), 7.11 – 7.03 (m, 1H), 6.96 (ddd, J = 8.4, 5.5, 1.8 Hz, 2H), 6.86 (d, J = 8.1 Hz, 1H), 6.29 (s, 1H), 4.70 (s, 2H), 4.21 (t, J = 6.0 Hz, 2H), 4.10 (t, J = 5.7 Hz, 2H), 2.56 (s, 1H), 2.14 – 1.98 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.5,

157.3, 156.5, 133.5, 132.6, 129.2, 129.0, 128.9, 121.4, 120.9, 112.42, 111.1, 68.8, 67.2, 61.7, 26.3, 26.3. **IR** (neat): 3333, 3944, 1651, 1451, 1235, 1112 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{NNaO}_4$ 338.1368, found: 338.1360.

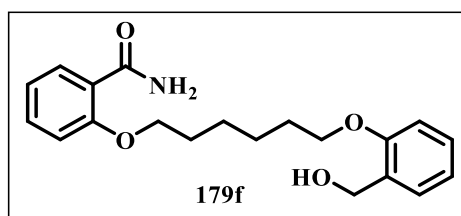
2-(4-(2-(hydroxymethyl)-6-methoxyphenoxy)butoxy)-3-methoxybenzamide (179e):



Prepared according to general procedure **4.7.2.E**, 4,11-dimethoxy-6,7,8,9-tetrahydro-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecin-15-one **122f** (53 mg, 0.15 mmol, 1 equiv.), Hydrazine hydrate (1 mL)

and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.024 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-(4-(2-(hydroxymethyl)-6-methoxyphenoxy)butoxy)-3-methoxybenzamide (30 mg, 54% yield) as a white crystalline solid **179e** (50% Ethyl Acetate: Hexane). Melting Point: 105-108 $^{\circ}\text{C}$. **^1H NMR** (400 MHz, CDCl_3) δ 7.90 (s, 1H), 7.64 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.12 (t, $J = 8.0$ Hz, 1H), 7.07 – 7.00 (m, 2H), 6.95 (dd, $J = 7.6, 1.4$ Hz, 1H), 6.85 (dd, $J = 8.1, 1.4$ Hz, 1H), 6.73 (s, 1H), 4.69 (s, 2H), 4.14 (t, $J = 6.5$ Hz, 2H), 4.06 (t, $J = 6.1$ Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 1.95 (m, 4H). **^{13}C NMR** (100 MHz, CDCl_3) δ 168.1, 152.7, 152.5, 147.1, 145.8, 134.8, 126.4, 124.3, 124.1, 122.9, 120.7, 115.9, 112.0, 74.2, 72.7, 61.1, 56.1, 55.8, 26.9, 26.8. **IR** (neat): 3360, 2931, 1655, 1574, 1468, 1264 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{NNaO}_6$ 398.1579, found: 398.1565.

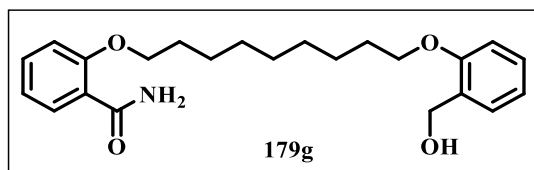
2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)benzamide (179f): Prepared according to



general procedure **4.7.2.E**, 6,7,8,9,10,11-hexahydro-17*H*,19*H*-dibenzo[*b,g*][1,5,9]trioxacyclopentadecin-17-one **122j** (53.8 mg, 0.15 mmol, 1 equiv.), Hydrazine hydrate (1 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.024 mmol,

0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-((10-(2-(hydroxymethyl)phenoxy)decyl)oxy)benzamide **179f** (19 mg, 42% yield) as a white crystalline solid (50% Ethyl Acetate: Hexane). Melting Point: 87-89 $^{\circ}\text{C}$. **^1H NMR** (400 MHz, CDCl_3) δ 8.19 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.83 (s, 1H), 7.49 – 7.41 (td, 1H), 7.32 – 7.27 (m, 1H), 7.24 (dd, $J = 12.2, 4.4$ Hz, 1H), 7.05 (t, $J = 7.2$ Hz, 1H), 6.94 (dd, $J = 15.2, 7.8$ Hz, 2H), 6.85 (d, $J = 8.2$ Hz, 1H), 6.55 (s, 1H), 4.69 (s, 2H), 4.12 (t, $J = 6.5$ Hz, 2H), 4.02 (t, $J = 6.3$ Hz, 2H), 1.95 – 1.87 (m, 2H), 1.87 – 1.80 (m, 2H), 1.62 – 1.51 (m, 4H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.7, 157.4, 156.7, 133.5, 132.5, 129.3, 128.8, 128.6, 121.1, 120.7, 120.69, 112.4, 111.1, 69.0, 67.7, 61.9, 29.2, 29.1, 26.0, 26.0. **IR** (neat): 3392, 2940, 1647, 1593, 1459, 1232 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{NNaO}_4$ 366.1681, found: 366.1679.

2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzamide (179g): Prepared according to



general procedure **4.7.2.E**, 7,8,9,10,11,12,13,14-octahydro-6*H*,20*H*,22*H*-

dibenzo[*b,g*][1,5,9]trioxacyclooctadecin-20-one

122m (40 mg, 0.11 mmol, 1 equiv.), Hydrazine

hydrate (1 mL) and RuCl₃·*x*H₂O (3.7 mg, 0.018 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as

a solvent to afford desired product 2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzamide

179g (25.7 mg, 64% yield) as a white crystalline solid (40% Ethyl Acetate: Hexane). Melting

Point: 95-98 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.21 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.84 (s, 1H),

7.45 (ddd, *J* = 8.4, 7.3, 1.9 Hz, 1H), 7.31 – 7.21 (m, 2H), 7.10 – 7.03 (m, 1H), 6.94 (ddd, *J* =

10.3, 8.2, 4.6 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 1H), 4.69 (s, 2H), 4.12 (t, *J* = 6.5 Hz,

2H), 4.01 (t, *J* = 6.4 Hz, 2H), 2.55 (s, 1H), 1.87 (m, 2H), 1.81 (m, 2H), 1.47 (m, 4H), 1.42 –

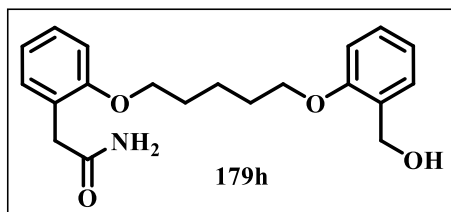
1.34 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.3, 157.5, 157.0, 133.4, 132.6, 129.3, 128.9,

128.7, 121.1, 120.8, 120.66, 112.4, 111.1, 69.2, 68.0, 62.4, 29.5, 29.3, 29.3, 29.2, 26.2, 26.2.

IR (neat): 3331, 2929, 1658, 1596, 1287, 1236 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd

for C₂₃H₃₁NNaO₄ 408.2151, found: 408.2137.

2-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)acetamide (179h): Prepared



according to general procedure **4.7.2.E**, 7,8,9,10-

tetrahydro-6*H*,16*H*-

dibenzo[*b,h*][1,5,10]trioxacyclopentadecin-18(19*H*)-

one **122p** (50 mg, 0.165 mmol, 1 equiv.), Hydrazine

hydrate (1 mL) and RuCl₃·*x*H₂O (5.1 mg, 0.025 mmol,

0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-(2-((5-(2-

(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)acetamide **179h** (28 mg, 53% yield) as a

brownish white crystalline solid (40% Ethyl Acetate: Hexane). Melting Point: 90-93 °C. **¹H**

NMR (400 MHz, CDCl₃) δ 7.31 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.23 – 7.19 (m,

1H), 6.93 (t, *J* = 7.4 Hz, 2H), 6.87 (t, *J* = 8.5 Hz, 2H), 5.85 (s, 1H), 5.76 (s, 1H), 4.70 (s, 2H),

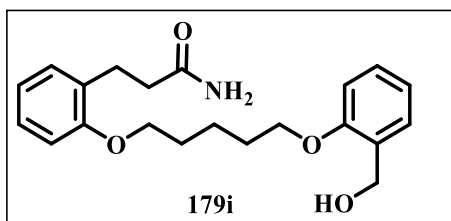
4.04 (dd, *J* = 13.4, 6.2 Hz, 4H), 3.56 (s, 2H), 1.93 – 1.83 (m, 4H), 1.75 – 1.66 (m, 2H). **¹³C**

NMR (100 MHz, CDCl₃) δ 174.7, 156.8, 131.4, 129.3, 129.0, 128.8, 123.6, 121.0, 120.7,

111.5, 111.1, 67.9, 67.8, 61.6, 38.4, 29.2, 29.2, 23.3. **IR** (neat): 3379, 2926, 1654, 1455, 1236

cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₀H₂₅NNaO₄ 380.1837, found: 380.1828.

3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propanamide (179i): Prepared



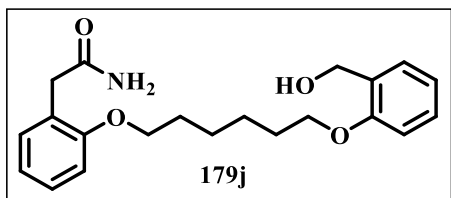
according to general procedure **4.7.2.E**, 7,8,9,10,19,20-hexahydro-6*H*,16*H*,18*H*-

dibenzo[*b,i*][1,5,11]trioxacyclohexadecin-18-one **122aa**

(50 mg, 0.144 mmol, 1 equiv.), Hydrazine hydrate (1 mL) and RuCl₃.xH₂O (5.1 mg, 0.0247 mmol, 0.15

equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propanamide **179i** (39 mg, 75% yield) as colourless liquid (50% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.30 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.24 (td, *J* = 7.9, 1.6 Hz, 1H), 7.17 (ddd, *J* = 7.4, 6.9, 2.9 Hz, 2H), 6.93 (td, *J* = 7.4, 0.8 Hz, 1H), 6.90 – 6.81 (m, 3H), 6.04 (s, 1H), 5.93 (s, 1H), 4.69 (s, 2H), 4.18 (s, 1H), 4.05 (t, *J* = 6.0 Hz, 2H), 4.00 (t, *J* = 6.1 Hz, 2H), 3.01 – 2.86 (t, 2H), 2.54 – 2.45 (t, 2H), 1.95 – 1.84 (m, 4H), 1.76 – 1.65 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 176.2, 156.7, 156.7, 130.0, 129.2, 129.0, 128.8, 128.5, 127.6, 120.6, 120.5, 111.1, 111.0, 67.8, 67.6, 61.6, 35.8, 29.2, 29.1, 26.3, 23.4. **IR** (neat): 3340, 2930, 1665, 1600, 1239 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₁H₂₇NNaO₄ 380.1837, found: 380.1828.

2-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)acetamide (179j): Prepared



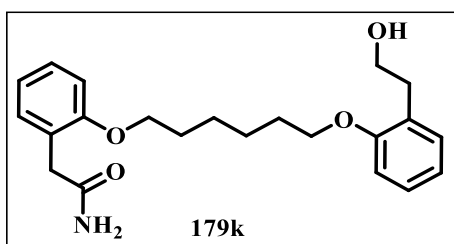
according to general procedure **4.7.2.E**, 6,7,8,9,10,11-hexahydro-17*H*-

dibenzo[*b,h*][1,5,10]trioxacyclohexadecin-19(20*H*)-one

(**122ab**) (32 mg, 0.10 mmol, 1 equiv.), Hydrazine

hydrate (1 mL) and RuCl₃.xH₂O (3.1 mg, 0.015 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)acetamide **179j** (11 mg, 30% yield) as a brownish sticky compound (40% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.30 – 7.26 (m, 2H), 7.25 – 7.20 (m, 2H), 6.93 (t, *J* = 7.4 Hz, 2H), 6.88 (t, *J* = 7.9 Hz, 2H), 5.74 (s, 1H), 5.66 (s, 1H), 4.68 (s, 2H), 4.03 (dd, *J* = 11.5, 6.1 Hz, 4H), 3.55 (s, 2H), 1.90 – 1.80 (m, 4H), 1.60 – 1.53 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 174.5, 156.9, 156.7, 131.4, 129.3, 129.0, 129.0, 128.8, 123.7, 121.0, 120.7, 111.7, 111.2, 68.0, 67.8, 62.2, 38.5, 29.3, 29.2, 26.0, 25.9. **IR** (neat): 3342, 2930, 1668, 1598, 1258 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₁H₂₇NNaO₄ 367.1885, found: 367.1874.

2-(2-((6-(2-(2-hydroxyethyl)phenoxy)hexyl)oxy)phenyl)acetamide (179k): Prepared



according to general procedure **4.7.2.E**,

6,7,8,9,10,11,20,21-

octahydrodibenzo[*b,i*][1,6,11]trioxacycloheptadecin-

18(17*H*)-one **122ac** (51 mg, 0.143 mmol, 1 equiv.),

Hydrazine hydrate (1 mL) and RuCl₃·xH₂O (5.1 mg,

0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-(2-

((6-(2-(2-hydroxyethyl)phenoxy)hexyl)oxy)phenyl)acetamide **179k** (12 mg, 40% yield) as a

white solid (50% Ethyl Acetate: Hexane). Melting Point: 68-71 °C. **¹H NMR** (400 MHz,

CDCl₃) δ 7.29 – 7.24 (m, 1H), 7.23 – 7.13 (m, 3H), 6.96 – 6.82 (m, 4H), 5.87 (s, 1H), 5.77 (s,

1H), 4.00 (dt, *J* = 12.7, 6.2 Hz, 4H), 3.80 (t, *J* = 6.6 Hz, 2H), 3.56 (s, 2H), 2.90 (t, *J* = 6.6 Hz,

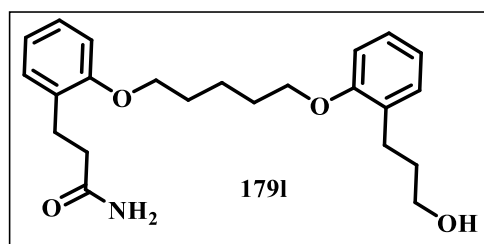
2H), 1.92 – 1.76 (m, 4H), 1.64 – 1.50 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 174.8, 157.1,

156.8, 131.4, 131.0, 129.0, 127.8, 127.2, 123.7, 121.0, 120.6, 111.6, 111.3, 68.0, 67.7, 62.9,

38.5, 34.3, 29.8, 29.3, 29.3, 26.0, 25.9. **IR** (neat): 3323, 2949, 2837, 1651, 1410, 1114 cm⁻¹.

HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₂H₂₉NNaO₄ 394.1994, found: 394.1984.

3-(2-((5-(2-(3-hydroxypropyl)phenoxy)pentyl)oxy)phenyl)propanamide (179l): Prepared



according to general procedure **4.7.2.E**,

7,8,9,10,17,18,21,22-octahydro-6*H*,16*H*,20*H*-

dibenzo[*b,k*][1,7,13]trioxacyclooctadecin-20-one

122ad (56 mg, 0.15 mmol, 1 equiv.), Hydrazine

hydrate (1 mL) and RuCl₃·xH₂O (5.1 mg, 0.0247

mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 3-(2-((5-(2-

(3-hydroxypropyl)phenoxy)pentyl)oxy)phenyl)propanamide **179l** (29 mg, 50% yield) as a

brownish sticky compound (50% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.22

– 7.11 (m, 4H), 6.87 (ddd, *J* = 12.5, 7.7, 2.7 Hz, 4H), 6.63 (s, 1H), 5.93 (s, 1H), 4.01 (td, *J* =

6.1, 3.0 Hz, 4H), 3.58 (t, *J* = 6.3 Hz, 2H), 2.95 (t, *J* = 7.7 Hz, 2H), 2.72 (t, *J* = 7.3 Hz, 2H), 2.58

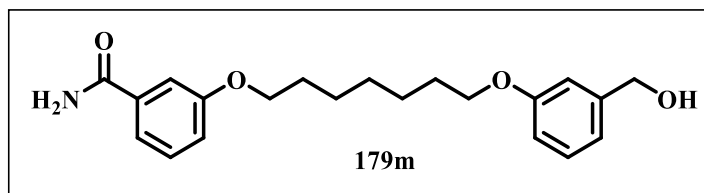
– 2.48 (t, 2H), 1.95 – 1.79 (m, 6H), 1.76 – 1.65 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 177.1,

156.8, 156.7, 130.2, 130.1, 128.9, 127.7, 127.2, 120.1, 120.6, 111.47, 111.3, 68.0, 67.8, 61.9,

36.0, 32.9, 29.2, 26.3, 26.1, 23.3. **IR** (neat): 3347, 2924, 1667, 1599, 1243 cm⁻¹. **HRMS** (ESI-

TOF) *m/z*: [M+H]⁺ calcd for C₂₃H₃₂NO₄ 386.2331, found: 386.2335.

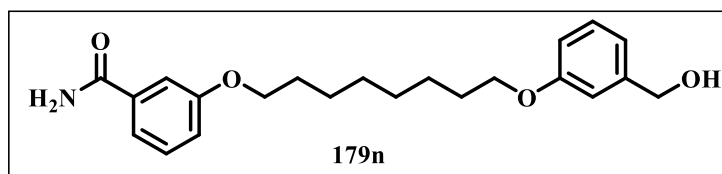
3-((7-(3-(hydroxymethyl)phenoxy)heptyl)oxy)benzamide (179m): Prepared according to



general procedure **4.7.2.E**, using 3,6,14-trioxa-1,5(1,3)-dibenzenacyclotetradecaphan-2-one **122v** (56 mg, 0.165 mmol, 1 equiv.),

Hydrazine hydrate (1 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 3-((7-(3-(hydroxymethyl)phenoxy)heptyl)oxy)benzamide **179m** (42 mg, 72% yield) as a white solid compound (50% Ethyl Acetate: Hexane). Melting Point: 86-88 °C. **¹H NMR** (400 MHz, ACETONE- d_6) δ 7.52 – 7.44 (m, 2H), 7.31 (t, J = 8.1 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 7.04 (ddd, J = 8.2, 2.5, 1.0 Hz, 1H), 6.91 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.74 (dd, J = 8.2, 2.3 Hz, 1H), 4.56 (s, 2H), 4.00 (t, J = 6.5 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 1.82 – 1.69 (m, 4H), 1.54 – 1.37 (m, 6H). **¹³C NMR** (100 MHz, ACETONE- d_6) δ 168.9, 160.1, 160.0, 144.9, 136.5, 136.5, 130.0, 129.8, 120.2, 119.1, 118.4, 114.0, 113.5, 113.2, 68.5, 68.1, 64.4, 26.6, 26.5. **IR** (neat): 3349, 3194, 2932, 1662, 1589, 1253 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{27}\text{NNaO}_4$ 380.1837, found: 380.1829.

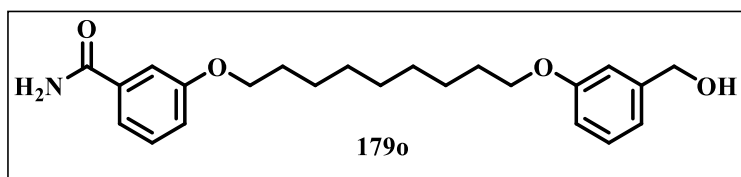
3-((8-(3-(hydroxymethyl)phenoxy)octyl)oxy)benzamide (179n): Prepared according to



general procedure **4.7.2.E**, using 3,6,15-trioxa-1,5(1,3)-dibenzenacyclopentadecaphan-2-one **122w** (58 mg, 0.165 mmol, 1

equiv.), Hydrazine hydrate (1 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 3-((8-(3-(hydroxymethyl)phenoxy)octyl)oxy)benzamide **179n** (23 mg, 38% yield) as a brownish white solid compound (50% Ethyl Acetate: Hexane). Melting Point: 110-112 °C. **¹H NMR** (400 MHz, ACETONE- d_6) δ 7.45 (d, J = 6.0 Hz, 2H), 7.30 (t, J = 8.1 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.03 (dd, J = 7.8, 1.8 Hz, 1H), 6.91 (s, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.78 – 6.70 (dd, 1H), 6.59 (s, 1H), 4.55 (s, 2H), 4.18 (s, 1H), 4.00 (t, J = 6.4 Hz, 2H), 3.94 (t, J = 6.4 Hz, 2H), 2.01 (m, 4H), 1.82 – 1.66 (m, 4H), 1.46 (m, 4H). **¹³C NMR** (100 MHz, ACETONE- d_6) δ 168.8, 160.2, 160.1, 145.0, 136.7, 130.1, 129.9, 120.3, 119.3, 118.5, 114.1, 113.6, 113.3, 68.6, 68.3, 64.5, 30.4, 29.2, 26.7, 26.7. **IR** (neat): 3350, 2924, 1658, 1591, 1261 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{29}\text{NNaO}_4$ 394.1994, found: 394.1989.

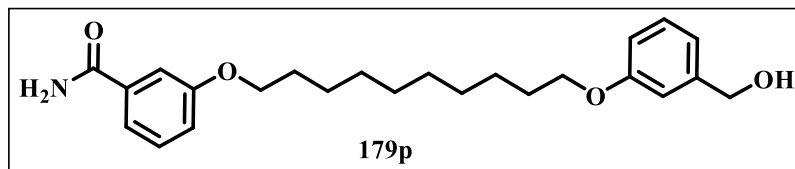
3-((9-(3-(hydroxymethyl)phenoxy)nonyl)oxy)benzamide (179o): Prepared according to



general procedure **4.7.2.E**, using 3,6,16-trioxa-1,5(1,3)-dibenzenacyclohexadecaphan-2-one **122x** (60 mg, 0.165 mmol, 1

equiv.), Hydrazine hydrate (1 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 3-((9-(3-(hydroxymethyl)phenoxy)nonyl)oxy)benzamide **179o** (35 mg, 56% yield) as a white solid compound (50% Ethyl Acetate: Hexane). Melting Point: 83-85 °C. **¹H NMR** (400 MHz, ACETONE- d_6) δ 7.61 – 7.57 (m, 2H), 7.43 (t, J = 8.1 Hz, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.04 (s, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.87 (dd, J = 8.2, 2.3 Hz, 1H), 4.69 (s, 2H), 4.12 (t, J = 6.5 Hz, 2H), 4.06 (t, J = 6.5 Hz, 2H), 1.92 – 1.80 (m, 4H), 1.57 (m, 4H), 1.47 (m, 6H). **¹³C NMR** (100 MHz, ACETONE- d_6) δ 168.9, 160.1, 160.0, 144.9, 136.6, 130.1, 129.8, 120.3, 119.2, 118.5, 114.0, 113.5, 113.2, 68.6, 68.2, 64.4, 30.3, 29.8, 29.4, 29.2, 26.7, 26.6. **IR** (neat): 3353, 3116, 2922, 1654, 1589, 1251 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{31}\text{NNaO}_4$ 408.2150, found: 408.2142.

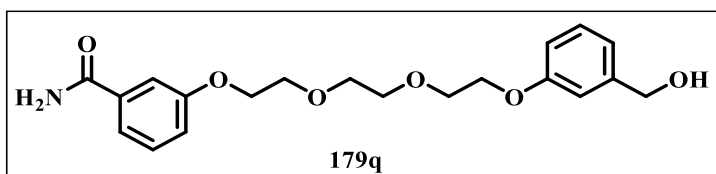
3-((10-(3-(hydroxymethyl)phenoxy)decyl)oxy)benzamide (179p): Prepared according to



general procedure **4.7.2.E**, using 3,6,17-trioxa-1,5(1,3)-

dibenzenacycloheptadecaphan-2-one **122y** (63 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 3-((10-(3-(hydroxymethyl)phenoxy)decyl)oxy)benzamide **179p** (30 mg, 46% yield) as a white solid compound (50% Ethyl Acetate: Hexane). Melting Point: 124-126 °C. **¹H NMR** (400 MHz, ACETONE- d_6) δ 7.49 – 7.43 (m, 2H), 7.31 (t, J = 8.1 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 7.04 (ddd, J = 8.2, 2.5, 1.0 Hz, 1H), 6.91 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.75 (dd, J = 8.2, 2.3 Hz, 1H), 6.60 (s, 1H), 4.55 (s, 2H), 4.00 (t, J = 6.5 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 1.79 – 1.69 (m, 4H), 1.44 (m, 4H), 1.35 (m, 8H). **¹³C NMR** (100 MHz, ACETONE- d_6) δ 168.8, 160.2, 160.1, 145.0, 136.7, 130.1, 129.9, 120.3, 119.3, 118.5, 114.1, 113.6, 113.3, 68.7, 68.3, 64.6, 64.4, 26.8, 26.7. **IR** (neat): 3352, 2921, 1656, 1592, 1265 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{33}\text{NNaO}_4$ 422.2307, found: 422.2300.

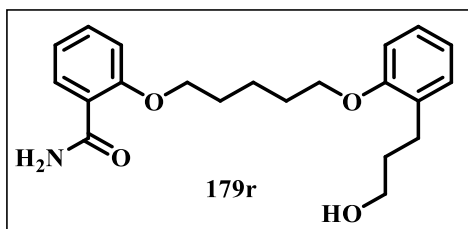
3-(2-(2-(2-(3-(hydroxymethyl)phenoxy)ethoxy)ethoxy)ethoxy)benzamide (179q):



Prepared according to general procedure **4.7.2.E**, using 3,6,9,12,15-pentaoxa-1,5(1,3)-dibenzenacyclopentadecaphan-2-

one **122ae** (56 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 3-((2-(2-(2-(3-(hydroxymethyl)phenoxy)ethoxy)ethoxy)ethoxy)benzamide **179q** (39 mg, 67% yield) as a white solid compound (90% Ethyl Acetate: Hexane). Melting Point: 60-62 °C. ^1H NMR (400 MHz, ACETONE- d_6) δ 7.38 (dd, J = 4.2, 2.4 Hz, 2H), 7.22 (t, J = 8.1 Hz, 1H), 7.08 (t, J = 7.9 Hz, 1H), 6.97 (dd, J = 7.8, 2.0 Hz, 1H), 6.83 (s, 1H), 6.78 (d, J = 7.5 Hz, 1H), 6.67 (dd, J = 8.1, 2.4 Hz, 1H), 4.46 (s, 2H), 4.07 – 4.02 (t, 2H), 4.01 – 3.96 (t, 2H), 3.70 (ddd, J = 9.7, 5.5, 4.1 Hz, 4H), 3.56 (s, 4H). ^{13}C NMR (100 MHz, ACETONE- d_6) δ 168.9, 159.8, 159.8, 144.9, 136.5, 130.1, 129.8, 120.5, 119.4, 118.5, 114.1, 113.6, 113.3, 73.2, 71.3, 70.2, 70.2, 68.3, 68.0. IR (neat): 3362, 2924, 1671, 1589, 1258 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_6$ 376.1760, found: 376.1738.

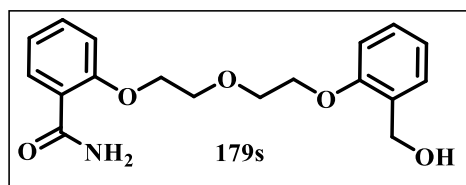
2-((5-(2-(3-hydroxypropyl)phenoxy)pentyl)oxy)benzamide (179r): Prepared according to



general procedure **4.7.2.E**, ethyl 2-((5-(2-(3-hydroxypropyl)phenoxy)pentyl)oxy)benzoate **178r** (64 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford

desired product 2-((5-(2-(3-hydroxypropyl)phenoxy)pentyl)oxy)benzamide **179r** (37 mg, 52% yield) as a brownish white solid compound (50% Ethyl Acetate: Hexane). Melting Point: 57-59 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (dd, J = 7.8, 1.8 Hz, 1H), 7.82 (s, 1H), 7.44 (ddd, J = 8.4, 7.4, 1.9 Hz, 1H), 7.15 (dd, J = 12.2, 4.6 Hz, 2H), 7.09 – 7.02 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.88 (td, J = 7.5, 0.8 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.57 (s, 1H), 4.15 (t, J = 6.2 Hz, 2H), 4.00 (t, J = 6.0 Hz, 2H), 3.62 (t, J = 6.3 Hz, 2H), 2.78 – 2.65 (t, 2H), 2.00 – 1.79 (m, 6H), 1.78 – 1.66 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 157.3, 156.7, 133.4, 132.6, 130.2, 130.1, 127.2, 121.3, 121.0, 120.8, 112.3, 111.2, 68.9, 67.6, 62.1, 32.8, 29.3, 29.1, 26.1, 23.3. IR (neat): 3454, 2938, 1657, 1590, 1234 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{NO}_4$ 358.2019, found: 358.2020.

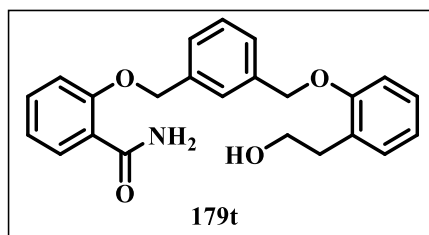
2-(2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)ethoxy)ethoxy)benzamide (179s): Prepared according



to general procedure **4.7.2.E**, ethyl 2-(2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)ethoxy)benzoate **178s** (60 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15

equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-(2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)ethoxy)ethoxy)benzamide **179s** (22 mg, 40% yield) as a brownish sticky compound (50% Ethyl Acetate: Hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.15 (d, J = 7.7 Hz, 1H), 7.95 (s, 1H), 7.49 – 7.40 (m, 1H), 7.28 (m, 2H), 7.08 (t, J = 7.6 Hz, 1H), 6.97 (t, J = 7.6 Hz, 2H), 6.88 (d, J = 8.1 Hz, 1H), 5.86 (s, 1H), 4.66 (s, 2H), 4.33 – 4.26 (t, 2H), 4.26 – 4.19 (t, 2H), 4.00 – 3.94 (t, 2H), 3.94 – 3.89 (t, 2H), 3.06 (s, 1H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.5, 157.0, 156.7, 133.2, 132.5, 129.9, 129.3, 129.0, 121.7, 121.7, 121.43, 113.0, 112.0, 69.8, 69.3, 68.1, 67.8, 61.7. **IR** (neat): 3440, 2930, 1657, 1594, 1242 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{NNaO}_5$ 354.1317, found: 354.1315.

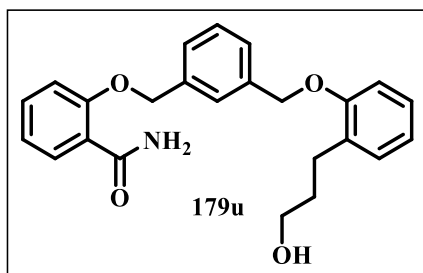
2-(((3-((2-(2-hydroxyethyl)phenoxy)methyl)benzyl)oxy)benzamide (179t): Prepared



according to general procedure **4.7.2.E**, ethyl 2-(((3-((2-(2-hydroxyethyl)phenoxy)methyl)benzyl)oxy)benzoate **178t** (96 mg, 0.236 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (7.4 mg, 0.0354 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-

(((3-((2-(2-hydroxyethyl)phenoxy)methyl)benzyl)oxy)benzamide **179t** (45 mg, 56% yield) as a white solid compound (50% Ethyl Acetate: Hexane). Melting Point: 119-122 $^{\circ}\text{C}$. **^1H NMR** (400 MHz, CDCl_3) δ 8.20 (dd, J = 7.8, 1.8 Hz, 1H), 7.62 (s, 1H), 7.56 (s, 1H), 7.50 – 7.35 (m, 4H), 7.19 (ddd, J = 9.5, 8.3, 1.5 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.03 (s, 1H), 5.20 (s, 2H), 5.11 (s, 2H), 3.85 (t, J = 6.7 Hz, 2H), 2.96 (t, J = 6.7 Hz, 2H), 2.40 (s, 1H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.3, 157.1, 156.6, 138.2, 136.2, 133.4, 132.7, 131.1, 129.2, 127.8, 127.5, 127.4, 126.5, 121.7, 121.4, 121.1, 112.8, 111.8, 71.2, 69.7, 62.6, 33.9. **IR** (neat): 3364, 2923, 1657, 1593, 1230 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{23}\text{NNaO}_4$ 400.1524, found: 400.1520.

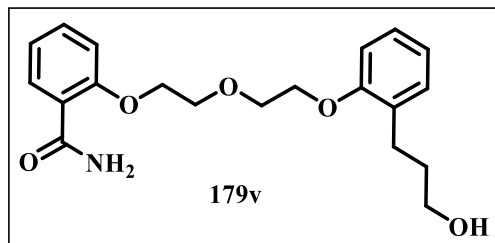
2-((3-((2-(3-hydroxypropyl)phenoxy)methyl)benzyl)oxy)benzamide (179u): Prepared



according to general procedure **4.7.2.E**, ethyl 2-((3-((2-(3-hydroxypropyl)phenoxy)methyl)benzyl)oxy)benzoate **178u** (70 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford

desired product 2-((3-((2-(3-hydroxypropyl)phenoxy)methyl)benzyl)oxy)benzamide **179u** (14 mg, 22% yield) as a brownish sticky compound (50% Ethyl Acetate: Hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.22 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.67 (s, 1H), 7.58 (s, 1H), 7.50 – 7.43 (m, 3H), 7.39 (dd, $J = 5.2, 3.3$ Hz, 1H), 7.21 – 7.14 (m, 2H), 7.13 – 7.08 (m, 1H), 7.06 (d, $J = 8.3$ Hz, 1H), 6.93 (ddd, $J = 14.3, 10.4, 4.5$ Hz, 2H), 5.88 (s, 1H), 5.21 (s, 2H), 5.12 (s, 2H), 3.60 (t, $J = 6.3$ Hz, 2H), 2.77 (t, $J = 7.4$ Hz, 2H), 1.92 – 1.81 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.2, 157.1, 156.4, 138.3, 136.2, 133.5, 132.8, 130.6, 130.3, 129.3, 127.6, 127.5, 127.3, 126.6, 121.7, 121.3, 112.8, 111.7, 71.3, 69.8, 62.0, 32.9, 26.2. **IR** (neat): 3338, 2926, 1717, 1595, 1264 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{25}\text{NNaO}_4$ 414.1681, found: 414.1693.

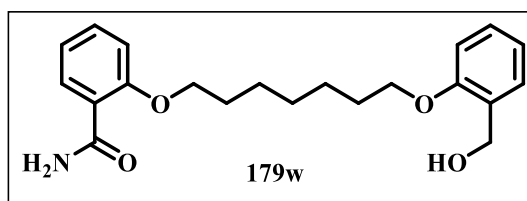
2-(2-(2-(2-(3-hydroxypropyl)phenoxy)ethoxy)ethoxy)benzamide (179v): Prepared



according to general procedure **4.7.2.E**, ethyl 2-(2-(2-(2-(3-hydroxypropyl)phenoxy)ethoxy)ethoxy)benzoate **178v** (64 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247

mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-(2-(2-(2-(3-hydroxymethyl)phenoxy)ethoxy)ethoxy)benzamide **179v** (18 mg, 30% yield) as a brownish sticky compound (50% Ethyl Acetate: Hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.16 (d, $J = 7.6$ Hz, 1H), 8.07 (s, 1H), 7.50 – 7.38 (m, 1H), 7.16 (t, $J = 7.0$ Hz, 2H), 7.08 (t, $J = 7.6$ Hz, 1H), 7.01 – 6.89 (m, 2H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.01 (s, 1H), 4.35 – 4.28 (t, 2H), 4.18 – 4.12 (t, 2H), 4.00 – 3.94 (t, 2H), 3.94 – 3.90 (t, 2H), 3.55 (t, $J = 5.9$ Hz, 2H), 2.75 (t, $J = 7.2$ Hz, 2H), 1.82 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.4, 157.1, 156.5, 133.3, 132.6, 130.5, 130.4, 127.2, 121.8, 121.4, 113.12, 111.5, 70.0, 69.5, 68.1, 67.6, 61.4, 33.2, 25.7. **IR** (neat): 3346, 2929, 1657, 1592, 1240 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{NNaO}_5$ 382.1630, found: 382.1624.

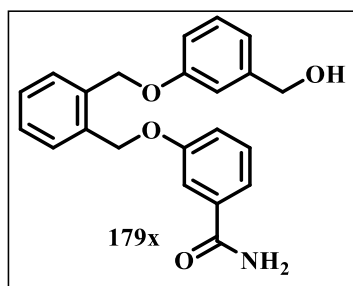
2-((7-(2-(hydroxymethyl)phenoxy)heptyl)oxy)benzamide (179w): Prepared according to



general procedure **4.7.2.E**, 7,8,9,10,11,12-hexahydro-6*H*,18*H*,20*H*-dibenzo[*b,g*][1,5,9]trioxacyclohexadecin-18-one **122k** (56 mg, 0.15 mmol, 1 equiv.), Hydrazine

hydrate (1 mL) and RuCl₃·*x*H₂O (5.1 mg, 0.024 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-((7-(2-(hydroxymethyl)phenoxy)heptyl)oxy)benzamide **179w** (19 mg, 55% yield) as a white crystalline solid (50% Ethyl Acetate: Hexane). Melting Point: 120-123 °C. **¹H NMR** (400 MHz, ACETOONE-*d*⁶) δ 8.19 (d, *J* = 7.5 Hz, 1H), 7.81 (s, 1H), 7.49 – 7.41 (m, 1H), 7.30 – 7.26 (m, 1H), 7.24 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.06 (dd, *J* = 11.1, 3.9 Hz, 1H), 6.99 – 6.90 (m, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.05 (s, 1H), 4.70 (s, 2H), 4.13 (t, *J* = 6.5 Hz, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 2.56 (s, 1H), 1.87 (m, 4H), 1.58 – 1.43 (m, 6H). **¹³C NMR** (100 MHz, ACETOONE-*d*⁶) δ 167.4, 157.4, 156.9, 133.4, 132.6, 129.3, 128.9, 128.8, 121.2, 120.7, 112.43, 111.1, 69.1, 67.8, 62.3, 29.2, 29.1, 29.0, 26.1. **IR** (neat): 3348, 2934, 1651, 1456, 1234 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₁H₂₇NNaO₄ 380.1837, found: 380.1829.

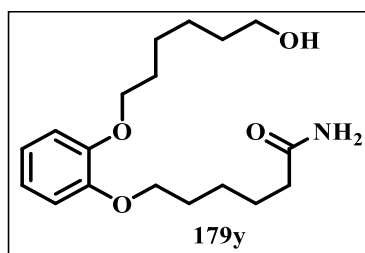
3-((2-((3-(hydroxymethyl)phenoxy)methyl)benzyl)oxy)benzamide (179x): Prepared



according to general procedure **4.7.2.E**, using 2,6,9-trioxa-1,7(1,3),4(1,2)-tribenzenacyclodecaphan-8-one **122r** (57 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1 mL) and RuCl₃·*x*H₂O (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 3-((2-((3-(hydroxymethyl)phenoxy)methyl)benzyl)oxy)benzamide **179x**

(49.5 mg, 83% yield) as a white solid compound (60% Ethyl Acetate: Hexane). Melting Point: 103-104 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.51 (s, 1H), 7.47 – 7.44 (m, 1H), 7.39 (s, 3H), 7.35 – 7.32 (m, 2H), 7.29 – 7.24 (m, 1H), 7.16 – 7.11 (m, 1H), 7.01 (s, 1H), 6.95 (d, *J* = 7.1 Hz, 1H), 6.89 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.39 (s, 1H), 6.18 (s, 1H), 5.12 (s, 2H), 5.09 (s, 2H), 4.66 (s, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 170.0, 159.0, 159.0, 142.7, 137.6, 137.1, 134.7, 129.8, 129.7, 129.1, 127.2, 127.1, 126.5, 119.7, 119.6, 119.3, 114.2, 113.8, 113.4, 70.1, 69.8, 65.2. **IR** (neat): 3338, 2922, 1663, 1597, 1249, 1160 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₂H₂₂NO₄ 364.1549, found: 364.1531.

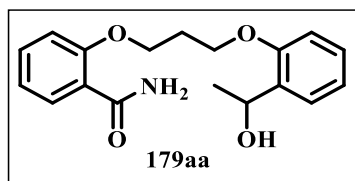
6-(2-((6-hydroxyhexyl)oxy)phenoxy)hexanamide (179y): Prepared according to general



procedure **4.7.2.E**, using 3,4,5,6,9,10,11,12,13,14-decahydrobenzo[*b*][1,4,11]trioxacycloheptadecin-7(2*H*)-one **122af** (50.6 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1 mL) and RuCl₃·xH₂O (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 6-

(2-((6-hydroxyhexyl)oxy)phenoxy)hexanamide **179y** (28.6 mg, 54% yield) as a brownish white solid compound (80% Ethyl Acetate: Hexane). Melting Point: 90-93 °C. **¹H NMR** (400 MHz, CDCl₃) δ 6.87 (s, 4H), 6.62 (s, 1H), 6.13 (s, 1H), 3.98 (t, *J* = 6.1 Hz, 4H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.25 (t, *J* = 7.5 Hz, 2H), 1.81 (m, 4H), 1.71 (m, 2H), 1.63 – 1.48 (m, 6H), 1.46 – 1.37 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 177.5, 149.1, 149.0, 121.3, 121.2, 114.1, 114.0, 69.1, 69.0, 62.6, 35.8, 32.6, 29.36, 29.0, 26.0, 25.9, 25.5, 25.3. **IR** (neat): 3345, 2932, 1666, 1504, 1253, 1120 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₈H₂₉NNaO₄ 346.1994, found: 346.1983.

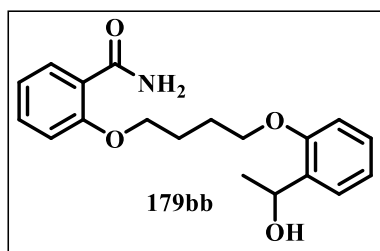
2-(3-(2-(1-hydroxyethyl)phenoxy)propoxy)benzamide (179aa): Prepared according to



general procedure **4.7.2.E**, ethyl 2-(3-(2-(1-hydroxyethyl)phenoxy)propoxy)benzoate (58 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and RuCl₃·xH₂O (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent

to afford desired product 2-(3-(2-(1-hydroxyethyl)phenoxy)propoxy)benzamide **179aa** (42 mg, 79% yield) as a white crystalline compound (40% Ethyl Acetate: Hexane). Melting Point: 52-55 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.69 (s, 1H), 7.49 – 7.43 (m, 1H), 7.41 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.22 (td, *J* = 7.9, 1.7 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.28 (s, 1H), 5.15 (q, *J* = 6.5 Hz, 1H), 4.36 (t, *J* = 6.2 Hz, 2H), 4.21 (t, *J* = 5.9 Hz, 2H), 2.39 (dt, *J* = 12.4, 6.3 Hz, 2H), 1.47 (d, *J* = 6.5 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.4, 157.0, 155.2, 134.0, 133.5, 132.6, 128.4, 126.2, 121.6, 121.4, 121.2, 112.5, 111.4, 66.2, 65.7, 64.7, 30.7, 29.6, 29.3, 23.4, 17.7. **IR** (neat): 3456, 2924, 1657, 1592, 1233 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₈H₂₁NNaO₄ 338.1368, found: 338.1369.

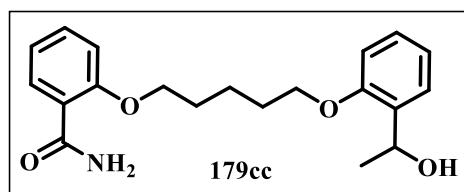
2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzamide (179bb): Prepared according to



general procedure **4.7.2.E**, ethyl 2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzoate (60 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzamide **179bb** (39 mg, 69% yield) as a brownish

white crystalline compound (40% Ethyl Acetate: Hexane). Melting Point: 108-110 °C. **^1H NMR** (400 MHz, CDCl_3) δ 8.18 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.77 (s, 1H), 7.49 – 7.42 (m, 1H), 7.40 (dd, $J = 7.5, 1.6$ Hz, 1H), 7.22 (td, $J = 7.9, 1.6$ Hz, 1H), 7.06 (t, $J = 7.5$ Hz, 1H), 7.00 – 6.93 (m, 2H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.71 (s, 1H), 5.15 (q, $J = 6.5$ Hz, 1H), 4.20 (t, $J = 5.9$ Hz, 2H), 4.08 (t, $J = 5.6$ Hz, 2H), 2.14 – 1.96 (m, 4H), 1.49 (d, $J = 6.5$ Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.7, 157.2, 155.4, 133.8, 133.4, 132.5, 128.2, 126.1, 121.3, 121.0, 120.8, 112.3, 111.1, 68.7, 67.0, 65.8, 26.3, 26.2, 23.4. **IR** (neat): 3447, 2922, 1657, 1593, 1268 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{NNaO}_4$ 352.1524, found: 352.1518.

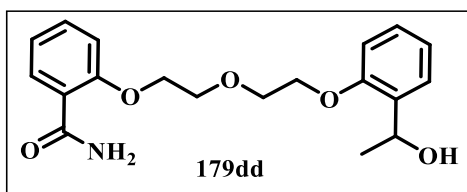
2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzamide (179cc): Prepared according to



general procedure **4.7.2.E**, ethyl 2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoate (61 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15 equiv.)

in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzamide **179cc** (22 mg, 38% yield) as a white crystalline compound (40% Ethyl Acetate: Hexane). Melting Point: 115-117 °C. **^1H NMR** (400 MHz, CDCl_3) δ 8.19 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.77 (s, 1H), 7.45 (ddd, $J = 8.3, 7.4, 1.8$ Hz, 1H), 7.38 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.22 (td, $J = 8.1, 1.7$ Hz, 1H), 7.11 – 7.03 (m, 1H), 6.96 (t, $J = 7.5$ Hz, 2H), 6.85 (d, $J = 8.2$ Hz, 1H), 6.34 (s, 1H), 5.12 (q, $J = 6.5$ Hz, 1H), 4.17 (t, $J = 6.3$ Hz, 2H), 4.05 (t, $J = 6.0$ Hz, 2H), 2.01 – 1.86 (m, 4H), 1.76 – 1.66 (m, 2H), 1.49 (d, $J = 6.5$ Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.5, 157.3, 155.7, 133.7, 133.4, 132.6, 128.3, 126.2, 121.3, 120.9, 112.3, 111.1, 68.9, 67.4, 66.2, 29.1, 29.0, 23.2, 23.1. **IR** (neat): 3457, 2932, 1658, 1593, 1235 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{NNaO}_4$ 366.1681, found: 366.1675.

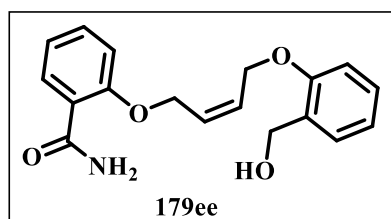
2-(2-(2-(2-(1-hydroxyethyl)phenoxy)ethoxy)ethoxy)benzamide (179dd): Prepared



according to general procedure 4.7.2.E, ethyl 2-(2-(2-(2-(1-hydroxyethyl)phenoxy)ethoxy)ethoxy)benzoate (62 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate (1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.0247 mmol, 0.15

equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-(3-(2-(1-hydroxyethyl)phenoxy)propoxy)benzamide **179dd** (35 mg, 61% yield) as a colourless liquid compound (60% Ethyl Acetate: Hexane). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.10 (d, $J = 7.8$ Hz, 1H), 7.94 (s, 1H), 7.38 (dd, $J = 10.6, 4.9$ Hz, 1H), 7.33 (dd, $J = 7.5, 1.3$ Hz, 1H), 7.16 (dd, $J = 10.8, 4.8$ Hz, 1H), 7.02 (t, $J = 7.5$ Hz, 1H), 6.96 – 6.88 (m, 2H), 6.81 (d, $J = 8.2$ Hz, 1H), 6.44 (s, 1H), 5.08 (q, $J = 6.5$ Hz, 1H), 4.28 – 4.17 (m, 2H), 4.13 (t, 2H), 3.98 – 3.76 (m, 4H), 1.45 (d, $J = 6.5$ Hz, 3H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.4, 156.9, 155.6, 134.1, 133.1, 132.3, 128.1, 126.3, 121.5, 121.4, 121.2, 112.9, 111.8, 69.6, 69.2, 68.0, 67.5, 65.7, 22.8. **IR** (neat): 3442, 2928, 1657, 1592, 1236 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{NNaO}_5$ 368.1473, found: 368.1471.

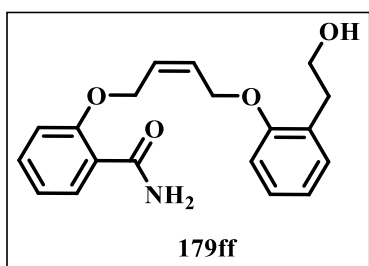
(Z)-2-((4-(2-(hydroxymethyl)phenoxy)but-2-en-1-yl)oxy)benzamide (179ee): Prepared



according to general procedure 4.7.2.C, (Z)-2-((4-bromobut-2-en-1-yl)oxy)benzamide (100 mg, 0.46 mmol, 1 equiv.) (synthesized from O-alkylation of 2-hydroxybenzamide and *cis*-1,4-dibromobutene), 2-hydroxy benzyl alcohol (57 mg, 0.46 mmol, 1equiv.) and K_2CO_3 (95 mg, 0.69 mmol, 1.5

equiv.) were refluxed in acetonitrile solvent to yield (Z)-2-((4-(2-(hydroxymethyl)phenoxy)but-2-en-1-yl)oxy)benzamide **179ee** (112 mg, 78% yield) as white solid compound (50% Ethyl Acetate: Hexane). Melting Point: 144-147 $^{\circ}\text{C}$. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.20 (dd, $J = 7.8, 1.9$ Hz, 1H), 7.69 (s, 1H), 7.45 (ddd, $J = 8.4, 7.4, 1.9$ Hz, 1H), 7.32 (dd, $J = 7.4, 1.5$ Hz, 1H), 7.29 – 7.22 (m, 2H), 7.14 – 7.05 (m, 1H), 6.98 (dd, $J = 11.9, 4.4$ Hz, 2H), 6.86 (d, $J = 8.2$ Hz, 1H), 6.12 (t, $J = 3.1$ Hz, 2H), 5.93 (s, 1H), 4.76 – 4.69 (t, 4H), 4.66 (s, 2H), 2.36 (s, 1H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 167.1, 156.8, 156.1, 133.4, 132.7, 130.2, 129.5, 129.1, 129.0, 127.1, 121.7, 121.3, 121.3, 112.9, 111.6, 69.0, 67.4, 62.0. **IR** (neat): 3451, 2868, 1651, 1591, 1453, 1283, 1160 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{NNaO}_4$ 336.1212 found: 336.1211.

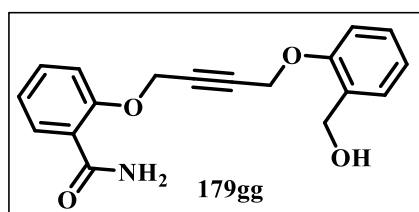
(Z)-2-((4-(2-(2-hydroxyethyl)phenoxy)but-2-en-1-yl)oxy)benzamide (179ff): Prepared



according to general procedure 4.7.2.C, (Z)-2-((4-bromobut-2-en-1-yl)oxy)benzamide (100 mg, 0.46 mmol, 1 equiv.) (synthesized from O-alkylation of 2-hydroxybenzamide and *cis*-1,4-dibromobutene), 2-(2-hydroxyethyl)phenol (63 mg, 0.46 mmol, 1equiv.) and K₂CO₃ (95 mg, 0.69 mmol, 1.5 equiv.) were refluxed in acetonitrile solvent to yield (Z)-2-((4-(2-(2-

hydroxyethyl)phenoxy)but-2-en-1-yl)oxy)benzamide **179ff** (74 mg, 52% yield) as white solid compound (60% Ethyl Acetate: Hexane). Melting Point: 89-91 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.73 (s, 1H), 7.48 – 7.40 (m, 1H), 7.22 – 7.15 (m, 2H), 7.07 (dd, *J* = 11.1, 4.0 Hz, 1H), 6.93 (ddd, *J* = 8.8, 8.1, 4.6 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.36 (s, 1H), 6.12 (q, *J* = 3.8 Hz, 2H), 4.70 (d, *J* = 3.2 Hz, 2H), 4.60 (d, *J* = 2.8 Hz, 2H), 3.84 (t, *J* = 6.7 Hz, 2H), 2.94 (t, *J* = 6.7 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.4, 156.9, 156.4, 133.4, 132.6, 131.2, 130.5, 127.8, 127.4, 126.6, 121.6, 121.2, 113.0, 111.7, 69.1, 67.3, 62.7, 34.2. IR (neat): 3326, 2923, 1650, 1590, 1452, 1228, 1109 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₉H₂₁NNaO₄ 350.1368 found: 350.1368

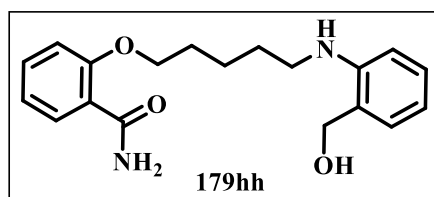
2-((4-(2-(hydroxymethyl)phenoxy)but-2-yn-1-yl)oxy)benzamide (179gg): Prepared



according to general procedure 4.7.2.C, 2-((4-bromobut-2-yn-1-yl)oxy)benzamide (100 mg, 0.46 mmol, 1 equiv.) (synthesized from O-alkylation of 2-hydroxybenzamide and 1,4-dibromobut-2-yne), 2-hydroxy benzyl alcohol (57 mg, 0.46 mmol, 1equiv.) and K₂CO₃ (95 mg, 0.69 mmol,

1.5 equiv.) were refluxed in acetonitrile solvent to yield (Z)-2-((4-(2-(2-hydroxyethyl)phenoxy)but-2-en-1-yl)oxy)benzamide **179gg** (77 mg, 51% yield) as white solid compound (50% Ethyl Acetate: Hexane). Melting Point: 135-137 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.52 (s, 1H), 7.43 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.33 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.23 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.15 – 7.09 (m, 1H), 7.00 (ddd, *J* = 8.4, 5.5, 1.7 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 1H), 5.78 (s, 1H), 4.86 (t, *J* = 1.7 Hz, 2H), 4.80 (t, *J* = 1.7 Hz, 2H), 4.69 (d, *J* = 5.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 155.8, 155.3, 133.3, 132.8, 130.0, 129.9, 129.2, 128.9, 122.4, 121.9, 113.2, 111.9, 83.6, 81.4, 61.7, 57.2, 56.0. IR (neat): 3454, 3356, 2925, 1652, 1593, 1221 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₈H₁₇NNaO₄ 334.1055, found: 334.1043.

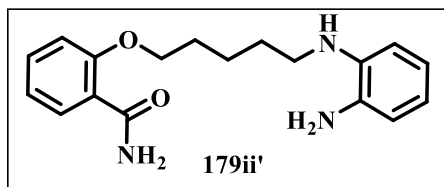
2-((5-((2-(hydroxymethyl)phenyl)amino)pentyl)oxy)benzamide¹³⁸ (179hh): To a 50 mL



RB flask was added 2-amino benzyl alcohol (123 mg, 1 mmol, 2 equiv.), Cs₂CO₃ (163 mg, 0.5 mmol, 1 equiv.) in dimethylformamide (DMF= 4 mL) and stirred the reaction mixture for 30 minutes at 25 °C. To the formed

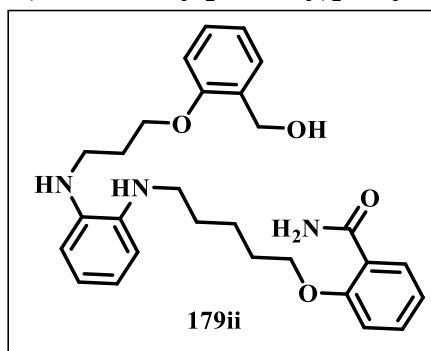
suspension in DMF was added 2-((5-bromopentyl)oxy)benzamide (142 mg, 0.5 mmol, 1 equiv.) (synthesized from *O*-alkylation of 2-hydroxybenzamide and 1,5-dibromopentane- General procedure C-I) and resulting reaction mixture was heated at 60 °C for 4 h to achieve 2-((5-((2-formylphenoxy)pentyl)oxy)benzamide **179hh** (70 mg, 21% yield) as white solid compound (50% Ethyl Acetate: Hexane). (followed Ref. No. 138). Melting Point: 76-78 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.15 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.73 (s, 1H), 7.44 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.20 (td, *J* = 7.9, 1.6 Hz, 1H), 7.09 – 7.02 (m, 2H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.64 (t, *J* = 7.3 Hz, 2H), 6.31 (s, 1H), 4.64 (s, 2H), 4.14 (t, *J* = 6.2 Hz, 2H), 3.19 (t, *J* = 6.5 Hz, 2H), 1.96 – 1.86 (m, 2H), 1.81 – 1.70 (m, 2H), 1.69 – 1.56 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.6, 157.2, 147.6, 133.3, 132.4, 129.4, 129.1, 124.4, 121.1, 120.9, 116.2, 112.3, 110.3, 68.9, 64.7, 43.0, 28.9, 28.9, 23.9. IR (neat): 3453, 2930, 1653, 1592, 1456, 1231 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₉H₂₄N₂NaO₃ 351.1684, found: 351.1685.

2-((5-((2-aminophenyl)amino)pentyl)oxy)benzamide (179ii')¹³⁸ To a 50 mL RB flask was



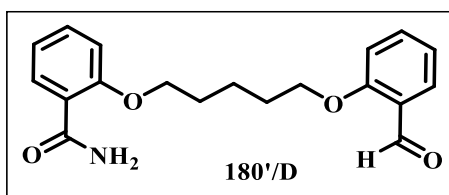
added *o*-phenylenediamine (108 mg, 1 mmol, 2 equiv.) and, Cs₂CO₃ (123 mg, 0.5 mmol, 1 equiv.) in dimethylformamide (DMF= 4 mL) and stirred the reaction mixture for 30 minutes at 25 °C. To the formed

suspension in DMF was added 2-((5-bromopentyl)oxy)benzamide) **179ii'** (142 mg, 0.5 mmol, 1 equiv.) and resulting reaction mixture was heated at 60 °C for 4 h to achieve 2-((5-((2-aminophenyl)amino)pentyl)oxy)benzamide (62 mg, 40% yield) as yellowish white compound (50% Ethyl Acetate: Hexane). Melting Point: 150-152 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.76 (s, 1H), 7.45 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.10 – 7.02 (m, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.83 (td, *J* = 7.5, 1.7 Hz, 1H), 6.73 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.67 (ddd, *J* = 8.9, 6.1, 1.2 Hz, 2H), 6.15 (s, 1H), 4.14 (t, *J* = 6.4 Hz, 2H), 3.33 (d, *J* = 6.7 Hz, 2H), 3.16 (t, *J* = 6.8 Hz, 2H), 1.98 – 1.87 (m, 2H), 1.76 (m, 2H), 1.69 – 1.59 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 157.3, 138.0, 134.1, 133.4, 132.6, 121.2, 121.0, 120.9, 118.6, 116.8, 112.4, 111.6, 69.0, 43.8, 29.2, 29.0, 23.8. IR (neat): 3452, 2930, 1656, 1586, 1456, 1232 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for 314.1868 C₁₈H₂₄N₃O₂ found: 314.1870.

5-(2-carbamoylphenoxy)pentyl**(3-(2-(hydroxymethyl)phenoxy)propyl) phthalate¹³⁸**

(179ii): To a 50 mL RB flask was added 2-((5-((2-aminophenyl)amino)pentyl)oxy)benzamide (313 mg, 1 mmol, 2 equiv.) (synthesized from *N*-alkylation of *o*-phenylenediamine and 2-((5-bromopentyl)oxy)benzamide), Cs₂CO₃ (123 mg, 0.5 mmol, 1 equiv.) in dimethylformamide (DMF= 4 mL) and stirred the reaction mixture for 30 minutes at 25 °C. To

the formed suspension in DMF was added (2-(3-bromopropoxy)phenyl)methanol (163 mg, 0.5 mmol, 1 equiv.) and resulting reaction mixture was heated at 60 °C for 4 h to achieve 5-(2-carbamoylphenoxy)pentyl (3-(2-(hydroxymethyl)phenoxy)propyl) phthalate **179ii** (107 mg, 22% yield) as yellowish solid compound (50% Ethyl Acetate: Hexane). Melting Point: 58-60 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.76 (s, 1H), 7.48 – 7.40 (m, 1H), 7.29 – 7.21 (m, 2H), 7.06 (t, *J* = 7.9 Hz, 1H), 6.93 (dd, *J* = 14.5, 7.7 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.84 – 6.77 (m, 2H), 6.76 – 6.67 (m, 2H), 6.09 (s, 1H), 4.67 (s, 2H), 4.18 (t, *J* = 5.7 Hz, 2H), 4.12 (t, *J* = 5.7 Hz, 2H), 3.35 (t, *J* = 6.3 Hz, 2H), 3.13 (t, *J* = 6.9 Hz, 2H), 2.21 (m, 2H), 1.96 – 1.85 (m, 2H), 1.74 (m, 2H), 1.61 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 157.3, 156.9, 137.6, 133.4, 132.7, 129.4, 129.2, 121.3, 120.9, 120.9, 119.7, 119.5, 112.4, 112.3, 111.9, 111.2, 68.9, 67.1, 61.9, 44.2, 42.7, 29.2, 29.1, 23.99. IR (neat): 3446, 2934, 1653, 1592, 1455, 1233 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₈H₃₆N₃O₄, 478.2706 found: 478.2704.

2-((5-(2-formylphenoxy)pentyl)oxy)benzamide (180'/D'):

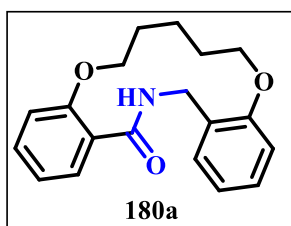
bromopentyl)oxy)benzamide (200 mg, 0.69 mmol, 1 equiv.) (synthesized from *O*-alkylation of 2-hydroxybenzamide and 1,5-dibromopentane- General procedure C-I), Salicylaldehyde (85 mg, 0.69 mmol, 1

equiv.) and K₂CO₃ (145 mg, 1.05 mmol, 1.5 equiv.) were refluxed in acetonitrile solvent to yield 2-((5-(2-formylphenoxy)pentyl)oxy)benzamide **180'/D'** (160 mg, 70% yield) as white solid compound (50% Ethyl Acetate: Hexane). Melting Point: 116-118 °C. ¹H NMR (400 MHz, CDCl₃) δ 10.49 (d, *J* = 0.6 Hz, 1H), 8.19 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.82 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.77 (s, 1H), 7.53 (ddd, *J* = 8.5, 7.4, 1.8 Hz, 1H), 7.45 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.13 (s, 1H), 4.17 (t, *J* = 6.5 Hz, 2H), 4.11 (t, *J* = 6.2 Hz, 2H), 2.02 – 1.90 (m, 4H), 1.77 – 1.66 (m, 2H). ¹³C NMR

(100 MHz, CDCl₃) δ 189.8, 167.3, 161.3, 157.3, 136.1, 133.4, 132.6, 128.7, 125.0, 121.3, 121.0, 120.8, 112.5, 112.4, 68.9, 68.1, 29.0, 28.9, 22.9. **IR** (neat): 3456, 2943, 2872, 1667, 1594, 1287, 1160 cm⁻¹. **HRMS** (ESI-TOF) m/z : [M+Na]⁺ calcd for C₁₉H₂₁NNaO₄ 350.1368, found: 350.1368

C) Characterization data for macrolactams:

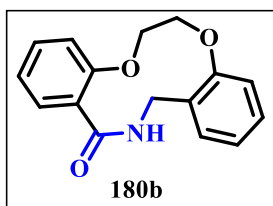
7,8,9,10,17,18-hexahydro-6*H*,16*H*-dibenzo[*b,g*][1,9]dioxo[5]azacyclotetradecin-16-one



(180a): Prepared according to general procedure 4.7.2.F, using 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzamide **179a** (25 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.8 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 7,8,9,10,17,18-hexahydro-

6*H*,16*H*-dibenzo[*b,g*][1,9]dioxo[5]azacyclotetradecin-16-one **180a** (17.6 mg, 75% yield) as a white crystalline compound (20% Ethyl Acetate: Hexane). Melting Point: 155-157 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.74 (s, 1H), 8.26 (dd, J = 7.8, 1.8 Hz, 1H), 7.41 (dd, J = 7.3, 1.6 Hz, 1H), 7.36 (td, J = 8.3, 1.8 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.05 – 6.99 (m, 1H), 6.94 – 6.86 (m, 2H), 6.84 (d, J = 8.2 Hz, 1H), 4.69 (d, J = 6.0 Hz, 2H), 4.16 (t, J = 5.6 Hz, 2H), 4.11 – 4.03 (t, 2H), 2.00 (m, 2H), 1.96 – 1.89 (m, 2H), 1.85 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.7, 157.4, 157.1, 132.6, 132.5, 131.3, 129.1, 126.7, 121.3, 120.9, 120.69, 111.4, 110.3, 68.0, 63.5, 40.0, 26.1, 25.6, 20.6. **IR** (neat): 3399, 2924, 1640, 1526, 1242 cm⁻¹. **HRMS** (ESI-TOF) m/z : [M+H]⁺ calcd for C₁₉H₂₂NO₃ 312.1599, found: 312.1596. **Crystal Data: CCDC= 2245939:** The crystals of compound **180a** were grown using dichloromethane and hexane as a solvent by slow evaporation. C₁₉H₂₁NO₃, M = 311.37, Triclinic, space group P -1 with a = 8.1119(9) Å, b = 9.3859(11) Å, c = 10.9075(11) Å, α = 81.331(3)°, β = 81.287(4)°, γ = 83.139(4)°, V = 807.53(15) Å³, T = 296 K, R_1 = 0.0657, wR_2 = 0.1962 for observed data, z = 2, D_{calcd} = 1.281 g cm⁻³, $F(000)$ = 332.0, absorption coefficient = 0.086 mm⁻¹, λ = 0.71073 Å, 2669 reflections collected on a Bruker APEX-III CCD single-crystal diffractometer, and 3920 observed reflections ($I \geq 2\sigma(I)$) with $S=1.159$.

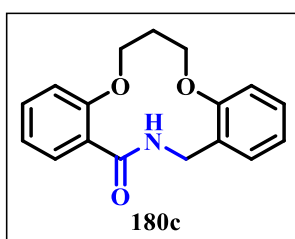
6,7,14,15-tetrahydro-13*H*-dibenzo[*e,j*][1,4]dioxo[8]azacycloundecin-13-one **(180b):**



Prepared according to general procedure 4.7.2.F, using 2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)benzamide **179b** (21.5 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.8 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,7,14,15-tetrahydro-13*H*-

dibenzo[*e,j*][1,4]dioxo[8]azacycloundecin-13-one **180b** (7.1 mg, 35% yield) as a white solid compound (20% Ethyl Acetate: Hexane). Melting Point: 136-138 °C. **¹H NMR** (400 MHz, CDCl₃) δ 9.22 (s, 1H), 8.03 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.44 – 7.38 (m, 1H), 7.38 – 7.34 (m, 1H), 7.26 – 7.20 (m, 2H), 7.12 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.04 – 6.97 (m, 2H), 4.59 (d, *J* = 6.5 Hz, 2H), 4.52 – 4.47 (t, 2H), 4.06 – 4.00 (t, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.3, 157.0, 156.4, 135.1, 132.7, 131.7, 131.0, 129.0, 127.2, 126.5, 125.48, 123.0, 122.5, 118.8, 117.5, 74.8, 69.9, 42.1. **IR** (neat): 3355, 2922, 1649, 1597, 1237, 1167 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₆H₁₆NO₃ 270.1130, found: 270.1130.

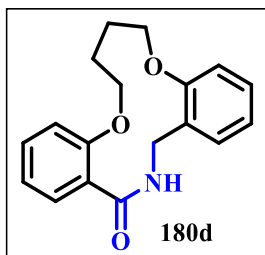
7,8,15,16-tetrahydro-6*H*,14*H*-dibenzo[*f,k*][1,5]dioxo[9]azacyclododecin-14-one (180c):



Prepared according to general procedure 4.7.2.F, using 2-(3-(2-(hydroxymethyl)phenoxy)propoxy)benzamide **179c** (22.3 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 7,8,15,16-tetrahydro-6*H*,14*H*-

dibenzo[*f,k*][1,5]dioxo[9]azacyclododecin-14-one **180c** (15 mg, 71% yield) as a white crystalline compound (20% Ethyl Acetate: Hexane). Melting Point: 164-166 °C. **¹H NMR** (400 MHz, CDCl₃) δ 10.21 (s, 1H), 8.18 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.25 (dd, *J* = 18.0, 7.2 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.95 – 6.83 (m, 3H), 4.66 (d, *J* = 5.8 Hz, 2H), 4.36 – 4.30 (t, 2H), 4.28 (t, *J* = 5.1 Hz, 2H), 2.43 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.4, 157.1, 156.9, 132.4, 131.9, 130.2, 128.6, 126.5, 122.5, 121.5, 121.1, 111.5, 111.5, 68.5, 68.0, 41.7, 28.8. **IR** (neat): 3356, 2923, 1649, 1597, 1297, 1167 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₇H₁₈NO₃ 284.1286, found: 284.1283.

6,7,8,9,16,17-hexahydro-15*H*-dibenzo[*b,g*][1,9]dioxo[5]azacyclotridecin-15-one (180d):

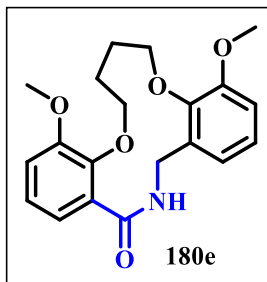


Prepared according to general procedure 4.7.2.F, using 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzamide **179d** (23 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,7,8,9,16,17-hexahydro-15*H*-

dibenzo[*b,g*][1,9]dioxo[5]azacyclotridecin-15-one **180d** (16.7 mg, 77% yield) as a white crystalline compound (20% Ethyl Acetate: Hexane). Melting Point: 127-129 °C. **¹H NMR** (400 MHz, CDCl₃) δ 9.59 (s, 1H), 8.26 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.39 (ddd, *J* = 8.3, 7.4, 1.9 Hz, 1H), 7.32 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.24 (dt, *J* = 8.2, 1.7 Hz, 1H), 7.09 – 7.03 (m, 1H), 6.96 – 6.87 (m, 3H), 4.69 (d, *J* = 5.8 Hz, 2H), 4.20 (t, *J* = 4.3 Hz, 2H), 4.14 (t, *J* = 4.5 Hz, 2H), 2.16

– 2.10 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.7, 157.6, 157.5, 132.6, 132.3, 130.6, 128.7, 126.6, 121.9, 121.4, 121.0, 112.8, 111.6, 69.8, 67.6, 41.8, 27.1, 26.7. IR (neat): 3387, 2925, 1642, 1531, 1239 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_3$ 298.1443, found: 298.1436.

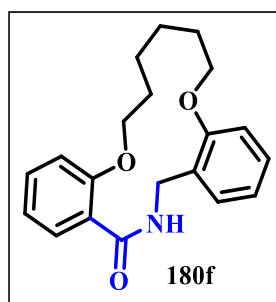
4,11-dimethoxy-6,7,8,9,16,17-hexahydro-15H-dibenzo[*b,g*][1,9]dioxo[5]azacyclotridecin-



15-one (180e): Prepared according to general procedure 4.7.2.F, using 2-(4-(2-(hydroxymethyl)-6-methoxyphenoxy)butoxy)-3-methoxybenzamide **179e** (25 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product

4,11-dimethoxy-6,7,8,9,16,17-hexahydro-15H-dibenzo[*b,g*][1,9]dioxo[5]azacyclotridecin-15-one **180e** (12.3 mg, 52% yield) as a brownish sticky compound (25% Ethyl Acetate: Hexane). Melting Point: 120–122 °C. ^1H NMR (400 MHz, CDCl_3) δ 9.02 (s, 1H), 7.73 (dd, J = 8.0, 1.6 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H), 7.04 – 6.95 (m, 3H), 6.87 (dd, J = 7.9, 1.8 Hz, 1H), 4.61 (d, J = 5.9 Hz, 2H), 4.39 (t, J = 5.8 Hz, 2H), 4.30 – 4.23 (t, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.16 – 2.09 (m, 2H), 2.08 – 2.02 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.0, 152.5, 152.5, 147.4, 147.1, 131.5, 126.4, 124.0, 123.7, 123.5, 123.0, 115.5, 112.8, 75.1, 71.5, 56.2, 55.9, 40.9, 27.9, 26.4. IR (neat): 3390, 2924, 1651, 1578, 1267, 1216 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_5$ 358.1654, found: 358.1647.

6,7,8,9,10,11,18,19-octahydro-17H-dibenzo[*b,g*][1,9]dioxo[5]azacyclopentadecin-17-one

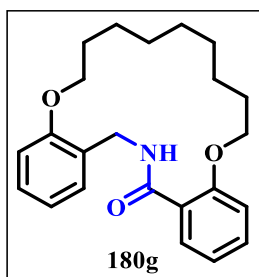


(180f): Prepared according to general procedure 4.7.2.F, using 2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)benzamide **179f** (25.3 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,7,8,9,10,11,18,19-octahydro-17H-dibenzo[*b,g*][1,9]dioxo[5]azacyclopentadecin-17-

one **180f** (9.3 mg, 39% yield) as a white solid compound (20% Ethyl Acetate: Hexane). Melting Point: 132–134 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.58 (s, 1H), 8.22 (dd, J = 7.8, 1.8 Hz, 1H), 7.52 (dd, J = 7.4, 1.7 Hz, 1H), 7.37 (ddd, J = 8.3, 7.4, 1.9 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.04 – 6.99 (m, 1H), 6.90 (ddd, J = 7.4, 3.8, 0.9 Hz, 2H), 6.86 (d, J = 8.3 Hz, 1H), 4.64 (d, J = 6.3 Hz, 2H), 4.20 – 4.14 (t, 2H), 4.14 – 4.10 (t, 2H), 1.96 (m, 2H), 1.89 (m, 2H), 1.81 – 1.73 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.0, 157.4, 157.0, 132.6, 132.6, 132.0, 128.9, 127.3, 121.7,

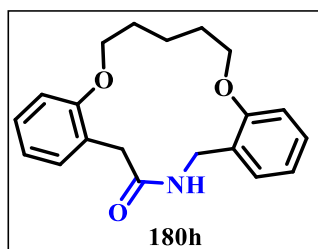
121.0, 120.7, 111.9, 111.1, 68.6, 68.4, 39.5, 28.8, 27.7, 27.4, 25.8. **IR** (neat): 3405, 2925, 1644, 1598, 1240, 1167 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_3$ 326.1756, found: 326.1746.

7,8,9,10,11,12,13,14,21,22-decahydro-6H,20H-



dibenzo[b,g][1,9]dioxo[5]azacyclooctadecin-20-one (180g): Prepared according to general procedure **4.7.2.F**, using 2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzamide **179g** (29 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 7,8,9,10,11,12,13,14,21,22-decahydro-6H,20H-dibenzo[b,g][1,9]dioxo[5]azacyclooctadecin-20-one **180g** (6 mg, 21% yield) as a white solid compound (20% Ethyl Acetate: Hexane). Melting Point: 125-127 °C. **¹H NMR** (400 MHz, CDCl_3) δ 8.19 (dd, J = 7.8, 1.8 Hz, 1H), 8.12 (s, 1H), 7.55 (dd, J = 7.5, 1.6 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.24 – 7.17 (m, 1H), 7.08 – 7.02 (m, 1H), 6.91 (t, J = 8.4 Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 4.75 (d, J = 6.2 Hz, 2H), 4.13 – 4.04 (m, 4H), 1.81 (m, 10H), 1.62 – 1.52 (m, 4H). **¹³C NMR** (100 MHz, CDCl_3) δ 166.1, 157.1, 156.5, 132.6, 132.4, 131.0, 128.5, 127.7, 122.3, 121.2, 120.7, 112.3, 111.4, 69.3, 68.4, 37.6, 29.8, 29.4, 28.4, 27.9, 27.6, 27.4, 26.2, 25.8. **IR** (neat): 3402, 2922, 1645, 1599, 1294, 1240 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_3$ 368.2225, found: 368.2215.

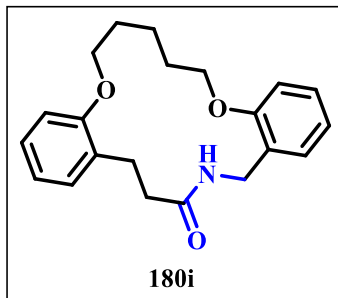
7,8,9,10,16,17-hexahydro-6H-dibenzo[b,h][1,10]dioxo[5]azacyclopentadecin-18(19H)-



one (180h): Prepared according to general procedure **4.7.2.F**, using 2-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)acetamide **179h** (22 mg, 0.07 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 7,8,9,10,16,17-hexahydro-6H-dibenzo[b,h][1,10]dioxo[5]azacyclopentadecin-18(19H)-one **180h** (11 mg, 54% yield) as a white solid compound (20% Ethyl Acetate: Hexane). Melting Point: 105-107 °C. **¹H NMR** (400 MHz, CDCl_3) δ 7.32 (dd, J = 7.4, 1.6 Hz, 1H), 7.29 (dd, J = 7.3, 1.6 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.20 (dd, J = 7.8, 1.6 Hz, 1H), 6.94 – 6.85 (m, 4H), 6.61 (s, 1H), 4.34 (d, J = 5.8 Hz, 2H), 4.14 – 4.08 (m, 4H), 3.50 (s, 2H), 1.89 (s, 6H). **¹³C NMR** (100 MHz, CDCl_3) δ 171.0, 157.3, 156.1, 131.6, 131.1, 129.1, 128.4, 126.6, 124.4, 121.0, 120.6, 111.2, 110.9, 66.3, 65.9,

40.6, 39.0, 27.9, 27.5, 22.4. **IR** (neat): 3356, 1641, 1488, 1235, 1135 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_3$ 326.1756, found: 326.1754.

7,8,9,10,16,17,19,20-octahydro-6*H*,18*H*-dibenzo[*b,i*][1,11]dioxo[5]azacyclohexadecin-18-

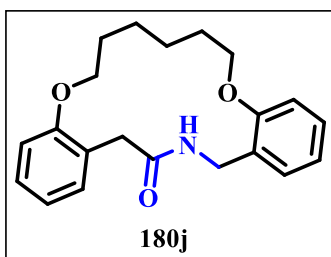


one (180i): Prepared according to general procedure **4.7.2.F**, using

3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propanamide **179i** (26 mg, 0.07 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product

7,8,9,10,16,17,19,20-octahydro-6*H*,18*H*-dibenzo[*b,i*][1,11]dioxo[5]azacyclohexadecin-18-one **180i** (6.5 mg, 27% yield) as a white solid compound (20% Ethyl Acetate: Hexane). Melting Point: 218-220 °C. **¹H NMR** (400 MHz, CDCl_3) δ 7.29 (d, J = 7.7 Hz, 2H), 7.18 (t, J = 7.6 Hz, 2H), 6.93 (d, J = 7.3 Hz, 1H), 6.90 – 6.84 (m, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 4.47 (d, J = 5.6 Hz, 2H), 4.11 (t, J = 5.0 Hz, 2H), 4.02 (t, J = 4.5 Hz, 2H), 2.98 – 2.90 (t, 2H), 2.39 – 2.31 (t, 2H), 2.00 – 1.93 (m, 2H), 1.92 – 1.84 (m, 4H). **¹³C NMR** (100 MHz, CDCl_3) δ 172.4, 157.5, 156.8, 130.6, 130.2, 129.3, 129.2, 127.7, 125.8, 120.7, 120.6, 110.5, 67.0, 66.6, 41.4, 38.8, 29.5, 29.3, 29.1, 24.7. **IR** (neat): 3300, 2921, 1636, 1533, 1247, 1197 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_3$ 340.1912, found: 340.1906.

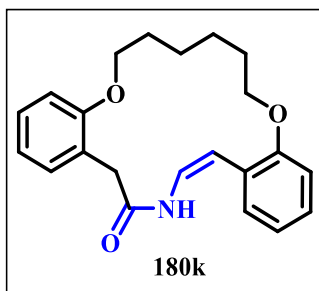
6,7,8,9,10,11,17,18-octahydrodibenzo[*b,h*][1,10]dioxo[5]azacyclohexadecin-19(20*H*)-one



(180j): Prepared according to general procedure **4.7.2.F**, using 2-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)acetamide **179j** (14 mg, 0.042 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (2.7 mg, 0.003 mmol, 0.08 equiv.) in toluene (5 mL) as a solvent to afford

desired product 6,7,8,9,10,11,17,18-octahydrodibenzo[*b,h*][1,10]dioxo[5]azacyclohexadecin-19(20*H*)-one **180j** (7 mg, 50% yield) as a white solid compound (20% Ethyl Acetate: Hexane). Melting Point: 136-138 °C. **¹H NMR** (400 MHz, CDCl_3) δ 7.38 (dd, J = 7.4, 1.7 Hz, 1H), 7.34 (dd, J = 7.4, 1.6 Hz, 1H), 7.25 – 7.18 (m, 2H), 6.94 – 6.82 (m, 4H), 6.59 (s, 1H), 4.31 (d, J = 6.1 Hz, 2H), 4.07 (dd, J = 10.2, 5.2 Hz, 4H), 3.48 (s, 2H), 1.95 – 1.84 (m, 4H), 1.83 – 1.69 (m, 4H). **¹³C NMR** (100 MHz, CDCl_3) δ 171.1, 157.4, 156.3, 131.7, 131.3, 129.1, 128.3, 126.5, 124.0, 121.0, 120.5, 111.0, 110.5, 68.7, 68.5, 39.9, 38.8, 29.7, 28.8, 28.6, 28.1. **IR** (neat): 3343, 2926, 1645, 1490, 1240 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_3$ 340.1912, found: 340.1911.

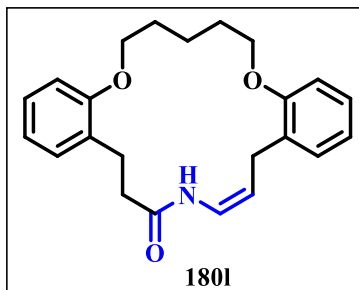
6,7,8,9,10,11,20,21-octahydro-17*H*-dibenzo[*b,i*][1,11]dioxo[6]azacycloheptadecin-



18(19*H*)-one (180k): Prepared according to general procedure 4.7.2.F, using 2-(2-((6-(2-(2-hydroxyethyl)phenoxy)hexyl)oxy)phenyl)acetamide **179k** (23 mg, 0.0619 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (3.9 mg, 0.0049 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,7,8,9,10,11,20,21-

octahydro-17*H*-dibenzo[*b,i*][1,11]dioxo[6]azacycloheptadecin-18(19*H*)-one **180k** (3 mg, 14% yield) as a white solid compound (20% Ethyl Acetate: Hexane). Melting Point: 111-113 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.35 (d, *J* = 10.9 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.08 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.94 (dt, *J* = 15.0, 9.2 Hz, 3H), 6.81 (d, *J* = 8.0 Hz, 1H), 5.63 (d, *J* = 9.9 Hz, 1H), 4.23 – 4.17 (t, 2H), 3.99 – 3.95 (t, 2H), 3.55 (s, 2H), 1.83 – 1.72 (m, 4H), 1.71 – 1.61 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 168.5, 156.9, 155.0, 131.9, 131.2, 128.7, 128.4, 123.1, 122.7, 122.2, 120.5, 115.7, 111.0, 106.6, 70.3, 68.3, 38.8, 29.4, 28.7, 26.6, 26.5. **IR** (neat): 3362, 2921, 1656, 1594, 1239 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₂H₂₆NO₃ 352.1913, found: 352.1921.

7,8,9,10,16,17,19,20,21,22-decahydro-6*H*,18*H*-



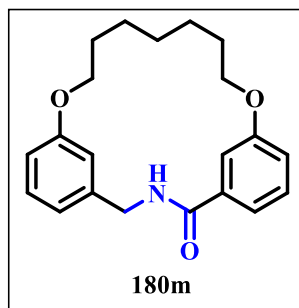
dibenzo[*h,q*][1,7]dioxo[13]azacyclooctadecin-18-one (180l):

Prepared according to general procedure 4.7.2.F, using 3-(2-((5-(2-(3-hydroxypropyl)phenoxy)pentyl)oxy)phenyl)propanamide **179l** (22 mg, 0.057 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (3.6 mg, 0.004 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to

afford desired product 7,8,9,10,16,17,19,20,21,22-decahydro-6*H*,18*H*-dibenzo[*h,q*][1,7]dioxo[13]azacyclooctadecin-18-one **180l** (3.9 mg, 17% yield) as a white solid compound (15% Ethyl Acetate: Hexane). Melting Point: 168-170 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.84 (d, *J* = 10.3 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.18 – 7.15 (m, 2H), 6.98 – 6.90 (m, 2H), 6.89 – 6.86 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.74 (dd, *J* = 10.3, 9.0 Hz, 1H), 5.04 (q, *J* = 8.5 Hz, 1H), 4.11 – 4.07 (t, 2H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.32 (d, *J* = 8.5 Hz, 2H), 3.03 – 2.96 (t, 2H), 2.61 – 2.54 (t, 2H), 2.10 – 1.94 (m, 4H), 1.88 – 1.78 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 170.2, 156.9, 155.9, 130.6, 130.2, 129.4, 128.8, 127.8, 127.6, 122.2, 122.1, 120.7, 114.0, 110.6, 109.6, 71.1, 67.4, 37.4, 29.6, 28.9, 28.1, 25.6, 24.6. **IR** (neat): 3369, 2922,

1659, 1497, 1241 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_3$ 366.2069, found: 366.2058.

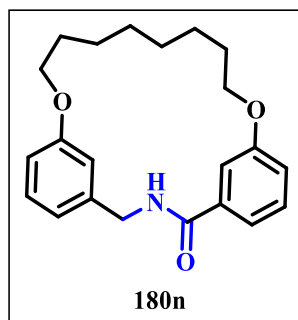
6,14-dioxa-3-aza-1,5(1,3)-dibenzenacyclotetradecaphan-2-one (180m): Prepared according



to general procedure **4.7.2.F**, using 3-((7-(3-(hydroxymethyl)phenoxy)heptyl)oxy)benzamide **179m** (26.8 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,14-dioxa-3-aza-1,5(1,3)-dibenzenacyclotetradecaphan-2-one **180m** (6 mg, 21% yield) as a

brownish solid compound (15% Ethyl Acetate: Hexane). Melting Point: 125-127 $^{\circ}\text{C}$. **^1H NMR** (400 MHz, CDCl_3) δ 7.37 (dt, $J = 15.3, 7.6$ Hz, 2H), 7.25 – 7.20 (m, 2H), 7.06 – 7.01 (m, 1H), 6.96 (s, 1H), 6.85 (d, $J = 7.6$ Hz, 1H), 6.81 (dd, $J = 8.2, 2.3$ Hz, 1H), 6.28 (s, 1H), 4.65 (d, $J = 5.9$ Hz, 2H), 4.12 (t, $J = 6.6$ Hz, 2H), 4.02 (t, $J = 6.6$ Hz, 2H), 1.80 – 1.69 (m, 4H), 1.45 (m, 4H), 1.37 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 168.7, 159.8, 158.9, 140.3, 137.0, 130.5, 129.9, 120.1, 119.9, 119.7, 115.2, 112.4, 111.1, 69.2, 68.5, 43.3, 29.8, 28.4, 27.8, 26.1. **IR** (neat): 3309, 2922, 1641, 1596, 1537, 1256 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_3$ 340.1912, found: 340.1938.

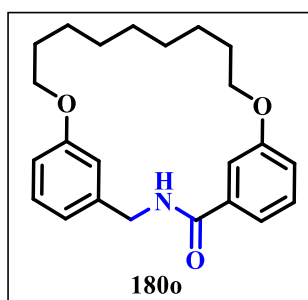
6,15-dioxa-3-aza-1,5(1,3)-dibenzenacyclopentadecaphan-2-one (180n): Prepared according



to general procedure **4.7.2.F**, using 3-((8-(3-(hydroxymethyl)phenoxy)octyl)oxy)benzamide **179n** (16.5 mg, 0.044 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (2.8 mg, 0.0035 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,15-dioxa-3-aza-1,5(1,3)-dibenzenacyclopentadecaphan-2-one **180n** (12.5 mg, 78% yield) as a white solid compound (15% Ethyl Acetate: Hexane).

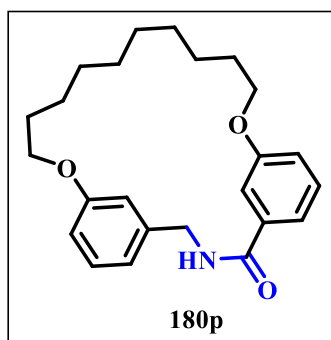
Melting Point: 148-149 $^{\circ}\text{C}$. **^1H NMR** (400 MHz, CDCl_3) δ 7.39 (dt, $J = 15.5, 7.6$ Hz, 2H), 7.23 (d, $J = 7.9$ Hz, 2H), 7.04 (ddd, $J = 8.1, 2.4, 1.2$ Hz, 1H), 6.94 (s, 1H), 6.86 (d, $J = 7.5$ Hz, 1H), 6.82 (dd, $J = 8.2, 2.3$ Hz, 1H), 6.27 (s, 1H), 4.67 (d, $J = 5.8$ Hz, 2H), 4.13 (t, $J = 6.9$ Hz, 2H), 4.04 (t, $J = 7.0$ Hz, 2H), 1.88 – 1.72 (m, 4H), 1.59 (m, 2H), 1.46 (m, 6H). **^{13}C NMR** (100 MHz, CDCl_3) δ 168.7, 159.8, 158.9, 140.3, 137.0, 130.5, 129.9, 120.1, 119.9, 119.6, 115.3, 112.4, 111.1, 69.2, 68.5, 43.3, 28.4, 27.8, 26.1, 26.0. **IR** (neat): 3289, 2921, 1640, 1594, 1297, 1247 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_3$ 354.2069, found: 354.2062.

6,16-dioxa-3-aza-1,5(1,3)-dibenzenacyclohexadecaphan-2-one (180o): Prepared according



to general procedure **4.7.2.F**, using 3-((9-(3-(hydroxymethyl)phenoxy)nonyl)oxy)benzamide **179o** (28.9 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,16-dioxa-3-aza-1,5(1,3)-dibenzenacyclohexadecaphan-2-one **180o** (9 mg, 33% yield) as a white solid compound (15% Ethyl Acetate: Hexane). Melting Point: 138-140 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.43 – 7.39 (m, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.02 (ddd, *J* = 8.1, 2.5, 1.2 Hz, 1H), 6.95 (s, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.81 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.35 (s, 1H), 4.64 (d, *J* = 5.8 Hz, 2H), 4.06 (t, *J* = 6.5 Hz, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 1.78 (m, 4H), 1.52 – 1.42 (m, 4H), 1.41 – 1.31 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 168.3, 159.9, 159.1, 140.1, 136.7, 130.2, 129.7, 119.9, 119.9, 118.4, 114.0, 112.6, 112.2, 68.4, 67.8, 43.5, 28.8, 28.7, 28.3, 28.2, 27.9, 25.6, 25.3. **IR** (neat): 3284, 2921, 1636, 1593, 1295, 1249 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₃H₃₀NO₃ 368.2225, found: 368.2215.

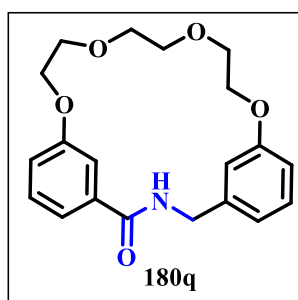
6,17-dioxa-3-aza-1,5(1,3)-dibenzenacycloheptadecaphan-2-one (180p): Prepared according



to general procedure **4.7.2.F**, using 3-((10-(3-(hydroxymethyl)phenoxy)decyl)oxy)benzamide **179p** (30 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,17-dioxa-3-aza-1,5(1,3)-dibenzenacycloheptadecaphan-2-one **180p** (6 mg, 21% yield) as a white solid compound (15% Ethyl Acetate: Hexane).

Melting Point: 120-122 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.40 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.02 (ddd, *J* = 7.9, 2.4, 1.2 Hz, 1H), 6.94 (s, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.31 (s, 1H), 4.63 (d, *J* = 5.8 Hz, 2H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.98 (t, *J* = 6.3 Hz, 2H), 1.82 – 1.71 (m, 4H), 1.46 (dd, *J* = 13.7, 6.9 Hz, 4H), 1.32 (s, 8H). **¹³C NMR** (100 MHz, CDCl₃) δ 167.9, 159.8, 159.1, 140.0, 136.4, 130.1, 129.7, 120.2, 119.5, 118.0, 114.3, 113.0, 112.6, 68.2, 67.6, 43.8, 28.8, 28.7, 28.6, 28.3, 28.0, 25.8, 25.7. **IR** (neat): 3329, 2923, 1642, 1592, 1256, 1171 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₄H₃₂NO₃ 382.2382, found: 382.2382.

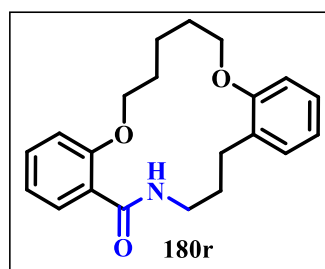
6,9,12,15-tetraoxa-3-aza-1,5(1,3)-dibenzenacyclopentadecaphan-2-one (180q): Prepared



according to general procedure **4.7.2.F**, using 3-(2-(2-(2-(3-(hydroxymethyl)phenoxy)ethoxy)ethoxy)ethoxy)benzamide **179q** (28 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,9,12,15-tetraoxa-3-aza-1,5(1,3)-dibenzenacyclopentadecaphan-2-one **180q**

(9 mg, 35% yield) as a white solid compound (20% Ethyl Acetate: Hexane). Melting Point: 119-121 °C. **¹H NMR** (400 MHz, CDCl₃) δ 7.43 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.05 (s, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.82 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.36 (s, 1H), 4.66 (d, *J* = 5.9 Hz, 2H), 4.34 – 4.27 (t, 2H), 4.24 – 4.17 (t, 2H), 3.79 (t, *J* = 4.6 Hz, 4H), 3.66 (s, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 168.5, 159.4, 159.3, 140.5, 136.8, 130.1, 129.8, 120.3, 120.0, 115.0, 113.4, 112.8, 71.3, 71.1, 70.2, 69.5, 68.7, 67.9, 43.5. **IR** (neat): 3345, 2924, 1645, 1263 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₀H₂₄NO₅ 358.1654, found: 358.1652.

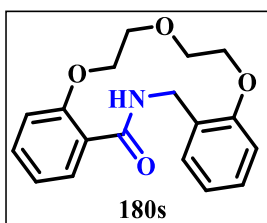
7,8,9,10,17,18,19,20-octahydro-6*H*,16*H*-dibenzo[*b,i*][1,11]dioxo[5]azacyclohexadecin-16-



one (180r): Prepared according to general procedure **4.7.2.F**, using 2-((5-(2-(3-hydroxypropyl)phenoxy)pentyl)oxy)benzamide **179r** (26 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford

desired product 7,8,9,10,17,18,19,20-octahydro-6*H*,16*H*-dibenzo[*b,i*][1,11]dioxo[5]azacyclohexadecin-16-one **180r** (18 mg, 73% yield) as a white solid compound (20% Ethyl Acetate: Hexane). Melting Point: 146-148 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.27 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.95 (s, 1H), 7.42 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.17 (dd, *J* = 11.6, 4.5 Hz, 2H), 7.11 – 7.04 (m, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.91 – 6.85 (m, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 4.22 (t, *J* = 5.3 Hz, 2H), 4.02 (t, *J* = 4.6 Hz, 2H), 3.64 (t, 2H), 2.77 – 2.68 (t, 2H), 2.04 – 1.94 (m, 4H), 1.92 – 1.84 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.7, 157.0, 156.8, 132.6, 130.5, 130.4, 130.4, 127.3, 121.6, 121.1, 120.6, 111.7, 110.7, 67.6, 66.5, 39.7, 29.8, 29.5, 28.4, 28.4, 23.5. **IR** (neat): 3344, 2927, 1641, 1531, 1252 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₁H₂₆NO₃ 340.1912, found: 340.1916.

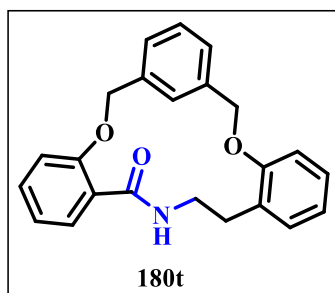
6,7,9,10,17,18-hexahydro-16*H*-dibenzo[*h,m*][1,4,7]trioxa[11]azacyclotetradecin-16-one



(180s): Prepared according to general procedure 4.7.2.F, using 2-(2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)ethoxy)benzamide **179s** (30 mg, 0.086 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 6,7,9,10,17,18-hexahydro-

16*H*-dibenzo[*h,m*][1,4,7]trioxa[11]azacyclotetradecin-16-one **180s** (19 mg, 66% yield) as a colourless sticky compound (25% Ethyl Acetate: Hexane). **¹H NMR** (400 MHz, CDCl₃) δ 8.77 (s, 1H), 8.23 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.44 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.36 (td, *J* = 8.3, 1.8 Hz, 1H), 7.23 (td, *J* = 7.9, 1.6 Hz, 1H), 7.06 – 6.98 (m, 1H), 6.90 (t, *J* = 7.1 Hz, 1H), 6.82 (dd, *J* = 14.9, 8.1 Hz, 2H), 4.70 (d, *J* = 6.3 Hz, 2H), 4.21 – 4.15 (t, 4H), 4.02 – 3.96 (t, 2H), 3.95 – 3.90 (t, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.8, 157.3, 156.8, 132.7, 132.5, 131.1, 128.9, 127.4, 121.7, 121.2, 120.9, 111.5, 110.6, 69.3, 68.6, 67.4, 66.0, 39.7. **IR** (neat): 3385, 2923, 1637, 1292, 1244 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₈H₂₀NO₄ 314.1392, found: 314.1384.

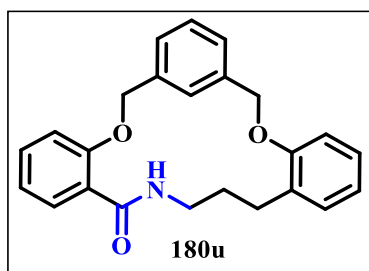
2,6-dioxa-9-aza-1,7(1,2),4(1,3)-tribenzenacycloundecaphan-8-one (180t):



Prepared according to general procedure 4.7.2.F, using 2-(((3-((2-(2-hydroxyethyl)phenoxy)methyl)benzyl)oxy)benzamide **179t** (28.3 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 2,6-dioxa-9-aza-1,7(1,2),4(1,3)-tribenzenacycloundecaphan-8-one **180t**

(10 mg, 37% yield) as a white solid compound (15% Ethyl Acetate: Hexane). Melting Point: 171-174 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.38 (s, 1H), 8.23 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.14 (s, 1H), 7.48 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 7.8, 5.6 Hz, 2H), 7.24 (dd, *J* = 4.6, 2.9 Hz, 2H), 7.16 – 7.11 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.98 (dd, *J* = 6.1, 2.6 Hz, 1H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1H), 5.25 (s, 2H), 5.23 (s, 2H), 3.70 (dd, *J* = 14.5, 6.1 Hz, 2H), 3.19 – 3.11 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 165.4, 156.5, 156.4, 138.8, 136.8, 132.7, 132.4, 130.3, 129.1, 128.6, 127.9, 125.8, 125.6, 123.9, 122.6, 121.8, 121.3, 112.3, 112.0, 70.4, 68.7, 40.0, 32.3. **IR** (neat): 3408, 3059, 2926, 1648, 1599, 1239 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₃H₂₂NO₃ 360.1599, found: 360.1598.

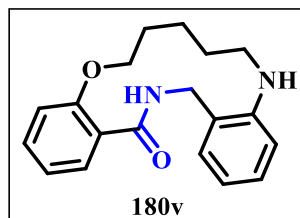
2,6-dioxa-9-aza-1,7(1,2),4(1,3)-tribenzenacyclododecaphan-8-one (180u): Prepared



according to general procedure 4.7.2.F, using 2-(((3-((2-(3-hydroxypropyl)phenoxy)methyl)benzyl)oxy)benzamide **179u** (29.4 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.7 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford desired product 2,6-dioxa-9-aza-1,7(1,2),4(1,3)-tribenzenacyclododecaphan-8-one

180u (16 mg, 57% yield) as a white solid compound (15% Ethyl Acetate: Hexane). Melting Point: 159-162 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.32 (dd, $J = 8.0, 1.9$ Hz, 1H), 8.06 (s, 1H), 7.95 (s, 1H), 7.48 (ddd, $J = 8.4, 7.4, 1.9$ Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 1H), 7.34 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.19 (dd, $J = 7.4, 1.5$ Hz, 1H), 7.15 – 7.10 (m, 2H), 6.99 – 6.90 (m, 2H), 5.24 (s, 2H), 5.10 (s, 2H), 3.59 (t, 2H), 2.84 – 2.76 (t, 2H), 1.97 – 1.87 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.6, 156.7, 156.6, 138.7, 136.4, 132.9, 132.7, 131.2, 130.8, 128.5, 127.4, 126.8, 126.8, 125.7, 121.9, 121.6, 121.3, 112.0, 111.6, 70.6, 68.9, 40.0, 30.3, 29.6. **IR** (neat): 3400, 2922, 2855, 1643, 1598, 1243 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_3$ 374.1756, found: 374.1754.

6,7,8,9,10,11,16,17-octahydro-18H-dibenzo[b,g][1]oxa[5,9]diazacyclotetradecin-18-one



(180v): Prepared according to general procedure 4.7.2.F, using 2-(((5-((2-(hydroxymethyl)phenyl)amino)pentyl)oxy)benzamide **(179hh)** (24.6 mg, 0.075 mmol, 1 equiv.), Pentamethylcyclopentadienyl Iridium dichloride dimer (4.8 mg, 0.006 mmol, 0.08 equiv.) in toluene (7.6 mL) as a solvent to afford

desired product 6,7,8,9,10,11,16,17-octahydro-18H-dibenzo[b,g][1]oxa[5,9]diazacyclotetradecin-18-one **180v** (03 mg, 13% yield) as a brownish solid compound (25% Ethyl Acetate: Hexane). Melting Point: 118-120 °C. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.15 (dd, $J = 7.8, 1.8$ Hz, 1H), 8.00 (s, 1H), 7.39 – 7.35 (m, 1H), 7.24 – 7.21 (m, 1H), 7.03 (ddd, $J = 11.1, 9.0, 4.2$ Hz, 2H), 6.86 (d, $J = 8.3$ Hz, 1H), 6.71 (t, $J = 7.4$ Hz, 2H), 4.62 (d, $J = 4.6$ Hz, 2H), 4.07 – 4.02 (t, 2H), 3.33 (t, $J = 6.0$ Hz, 2H), 1.91 – 1.84 (m, 2H), 1.78 – 1.71 (m, 4H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.2, 157.0, 135.1, 132.7, 132.1, 131.2, 129.5, 126.5, 121.1, 118.8, 118.8, 117.6, 111.9, 110.9, 68.4, 42.4, 39.9, 26.0, 24.5, 21.22. **IR** (neat): 3392, 2920, 2856, 1644, 1460, 1252 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_3$ 311.1760, found: 311.1755.

4.8 Appendix IV: Copies of ^1H and ^{13}C NMR spectra and crystal structure of representative compounds

Entry	Figure No.	Data	Page No.
179a	75 and 76	^1H and ^{13}C	207
179c	77 and 78	^1H and ^{13}C	208
179d	79 and 80	^1H and ^{13}C	209
179bb	81 and 82	^1H and ^{13}C	210
180a	83 and 84	^1H and ^{13}C	211
180c	85 and 86	^1H and ^{13}C	212
180d	87 and 88	^1H and ^{13}C	213
179l	89 and 90	^1H and ^{13}C	214

4.8.1 Copies of NMR spectra:

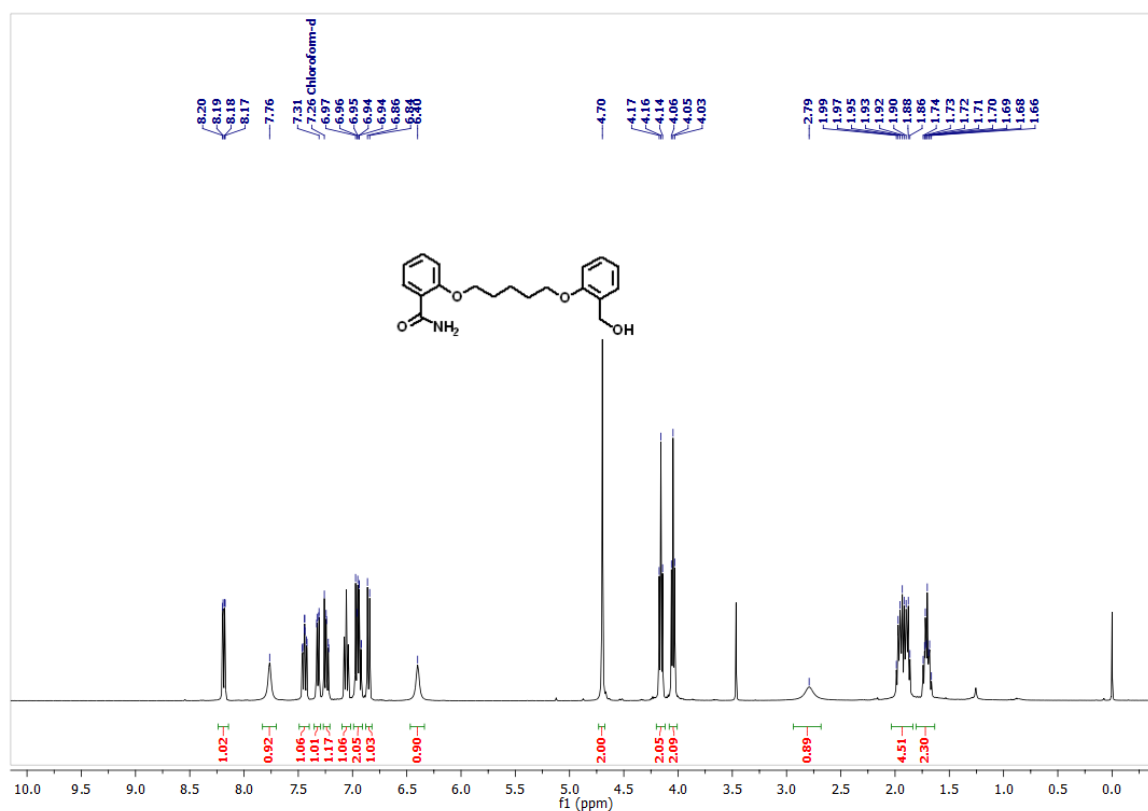


Figure 75. ¹H NMR spectra for compound 179a, 400 MHz, CDCl₃

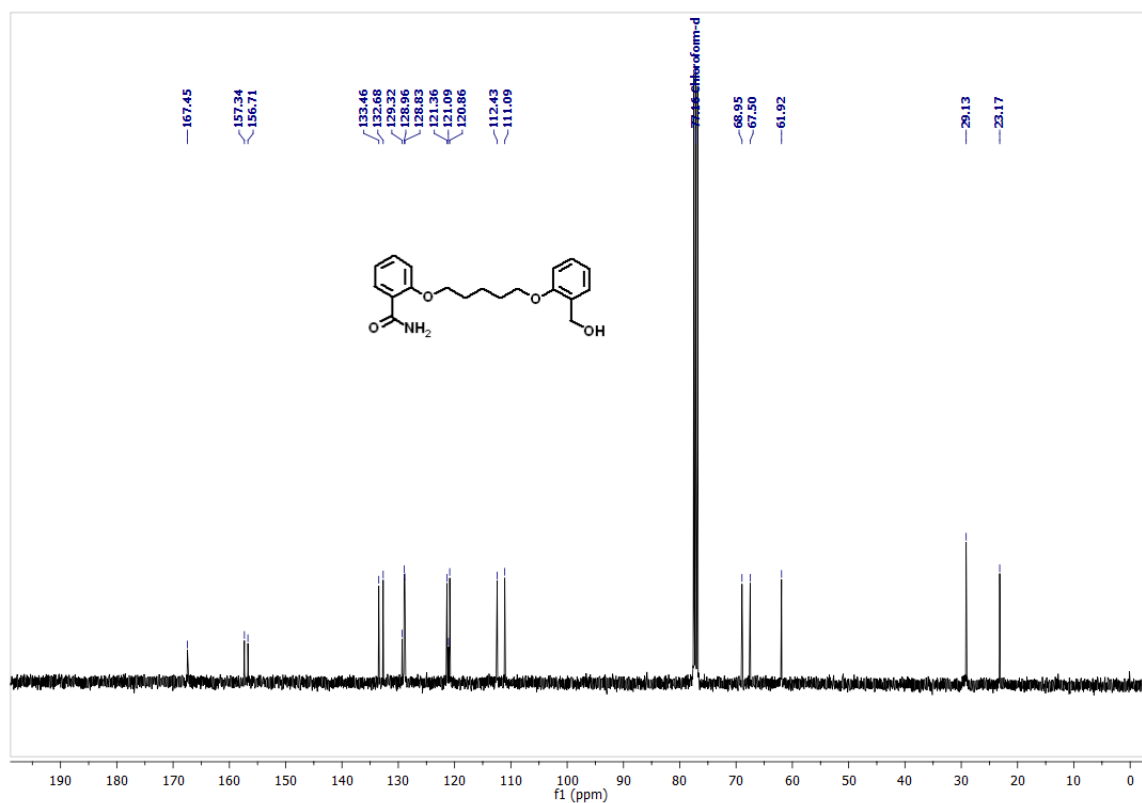


Figure 76. ¹³C NMR spectra for compound 179a, 100 MHz, CDCl₃

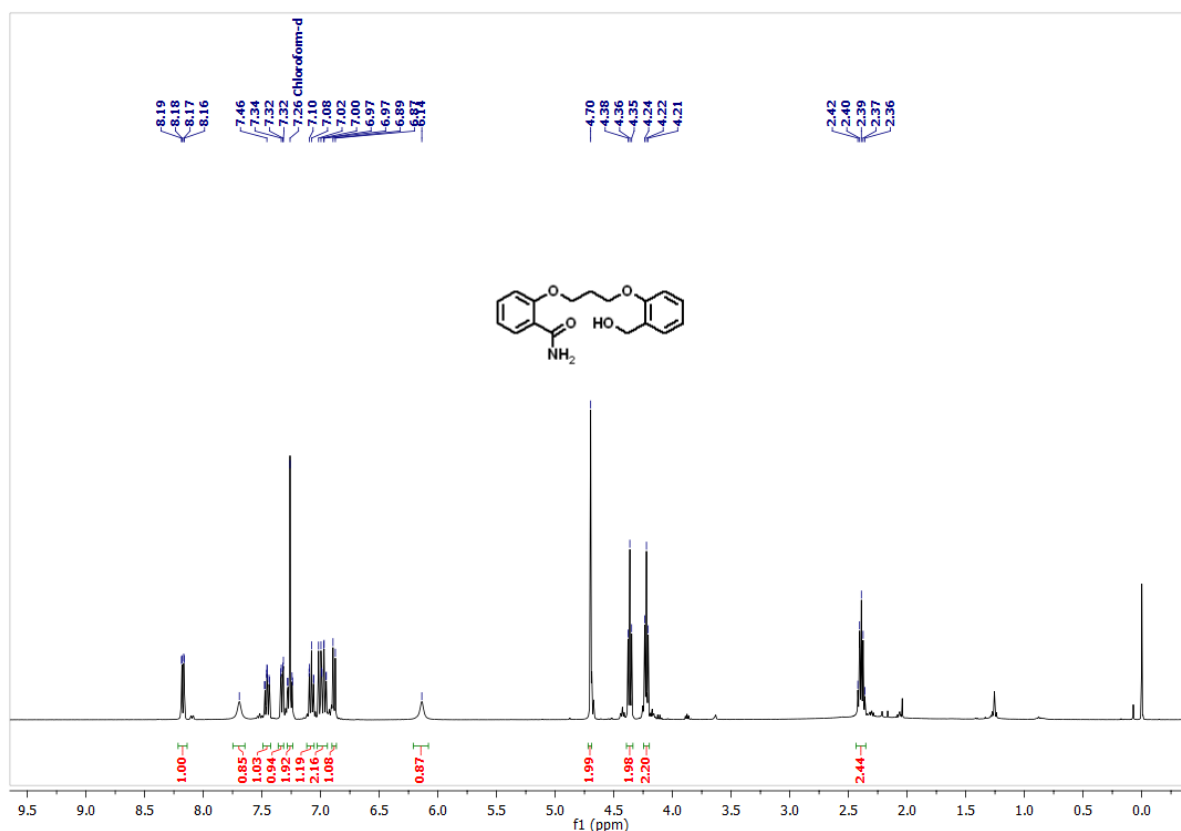


Figure 77. ¹H NMR spectra for compound **179c**, 400 MHz, CDCl₃

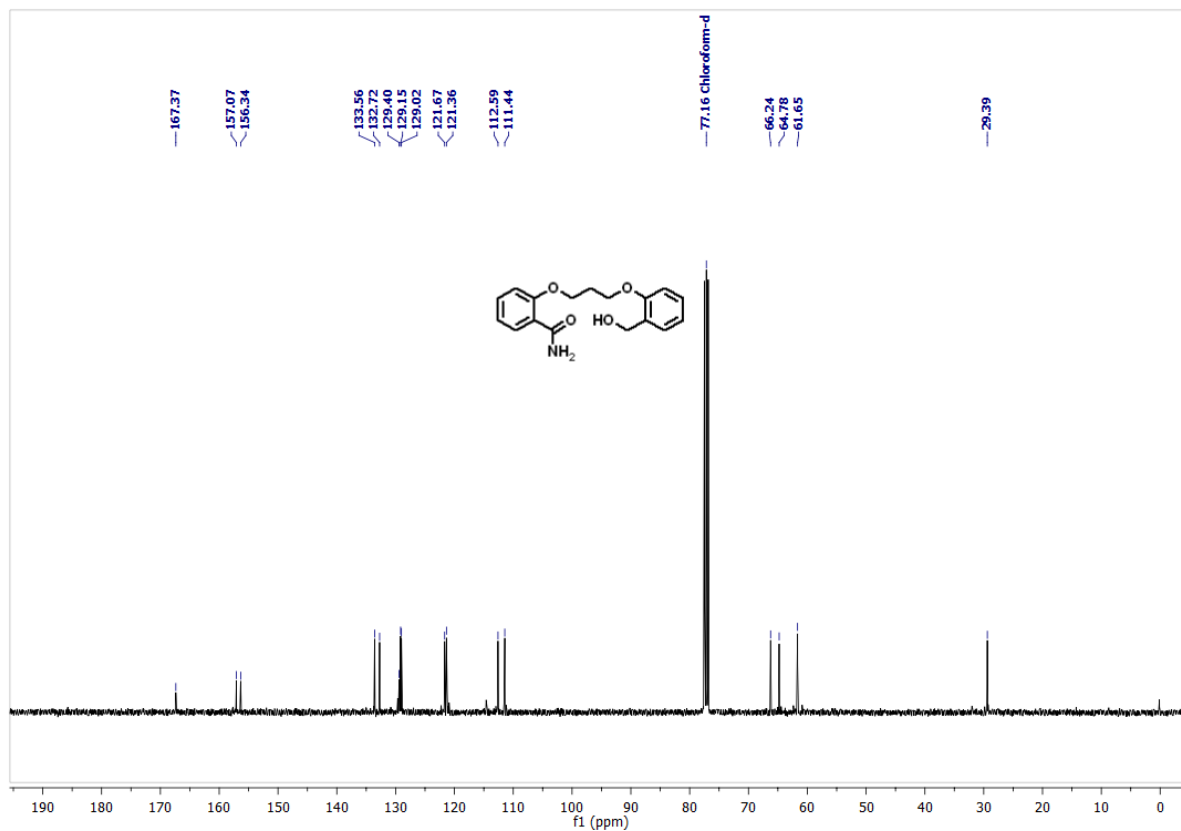


Figure 78. ¹³C NMR spectra for compound **179c**, 100 MHz, CDCl₃

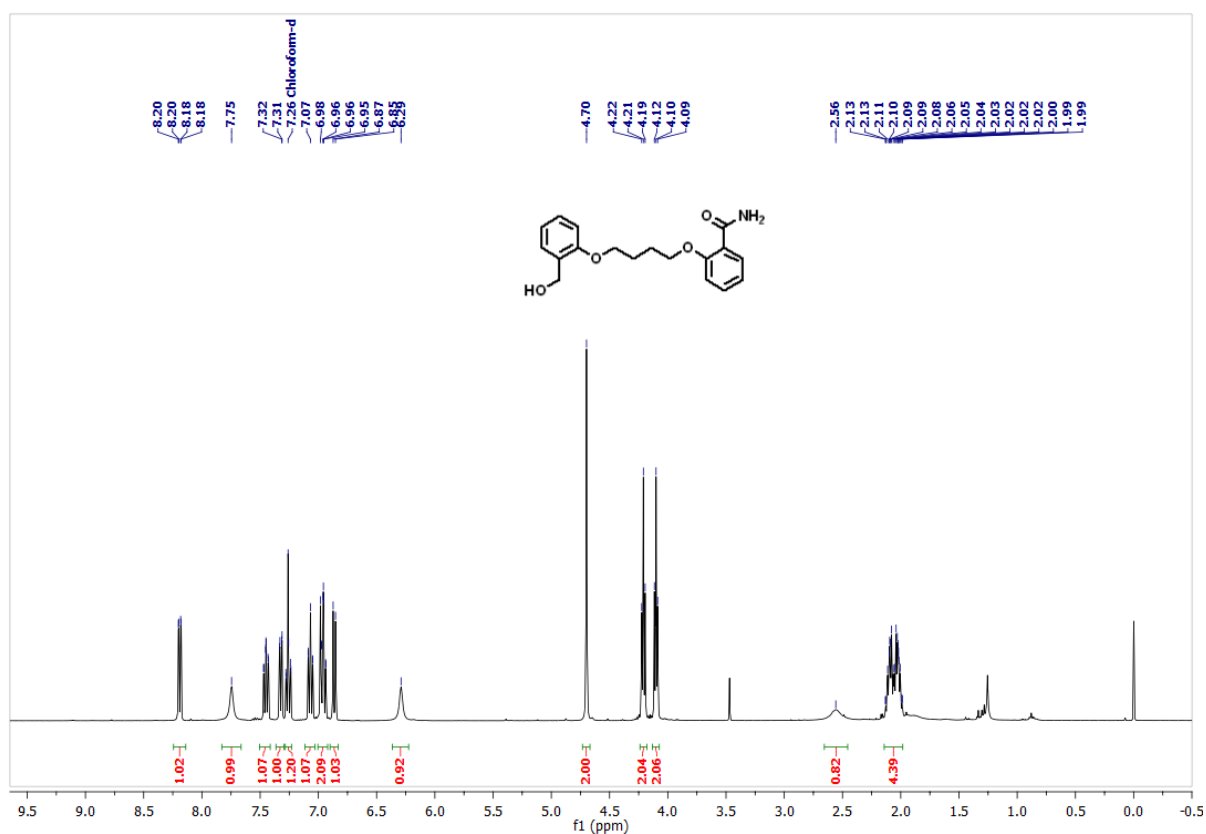


Figure 79. ¹H NMR spectra for compound **179d**, 400 MHz, CDCl₃

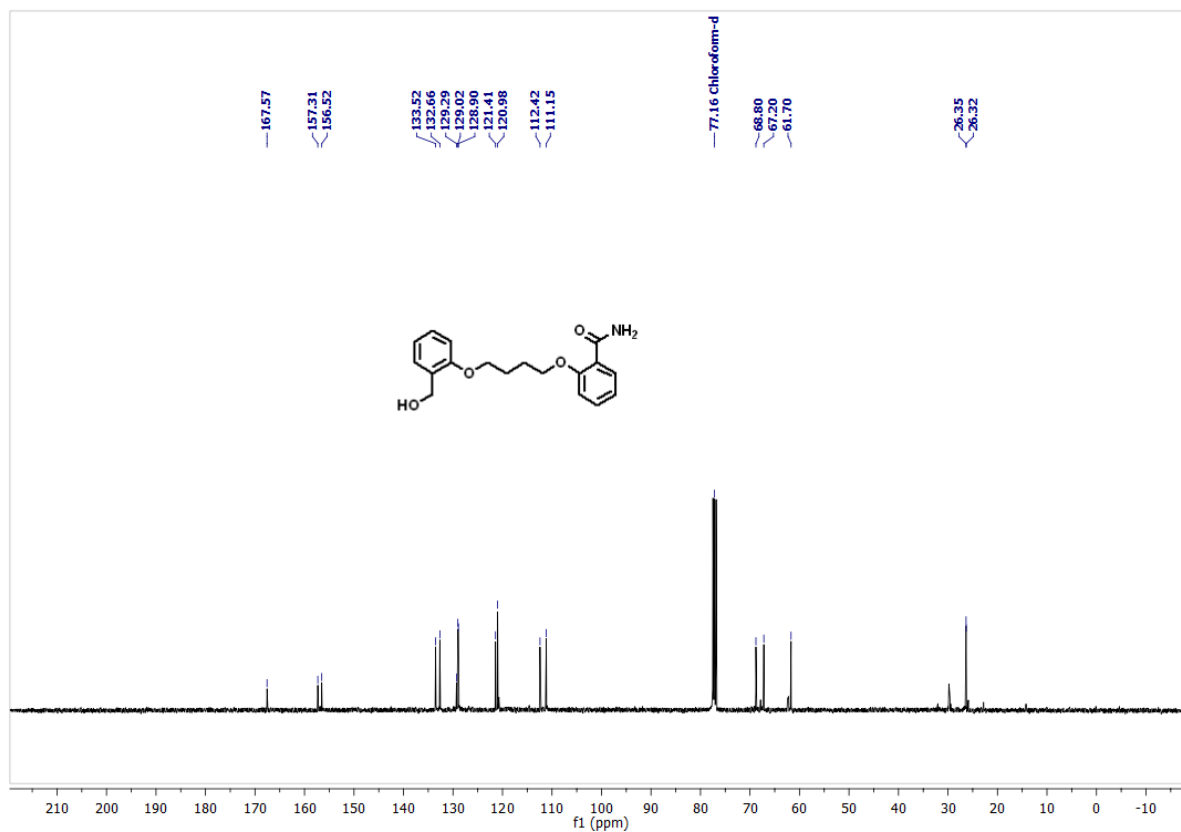


Figure 80. ¹³C NMR spectra for compound **179d**, 100 MHz, CDCl₃

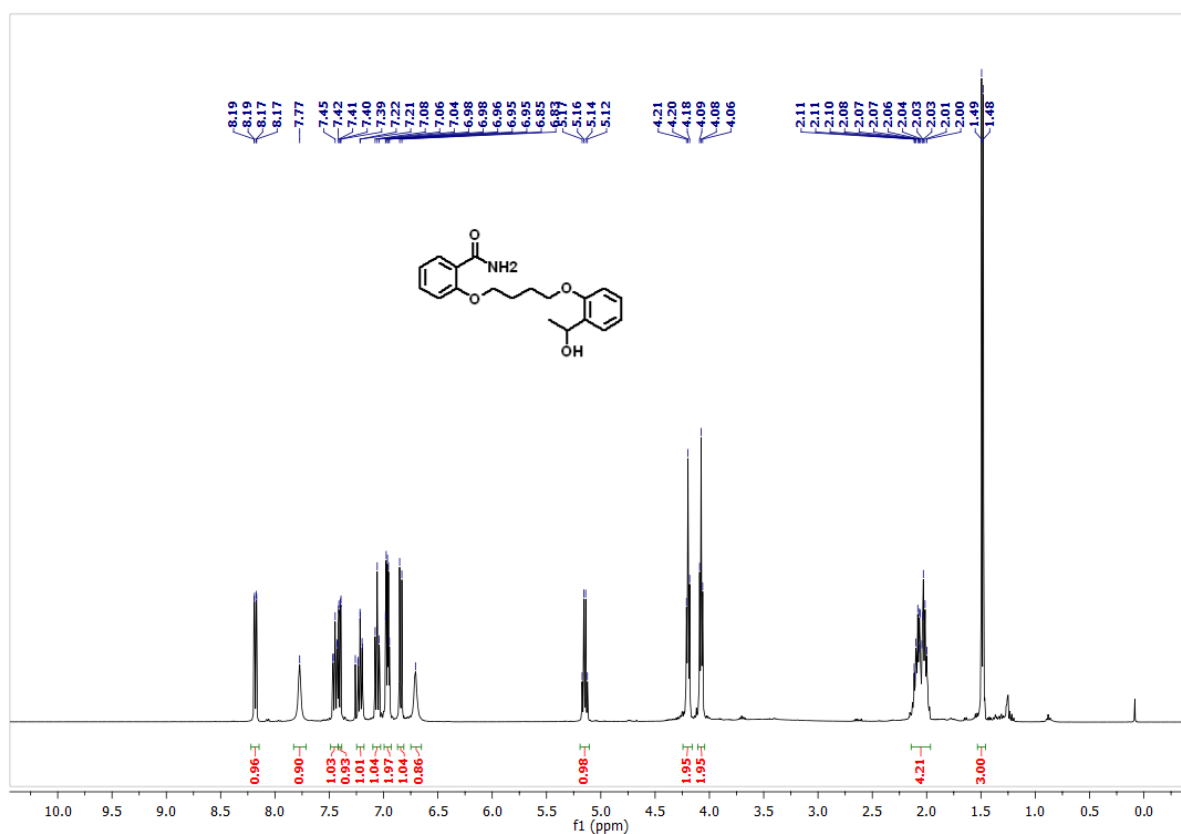


Figure 81. ¹H NMR spectra for compound **179bb**, 400 MHz, CDCl₃

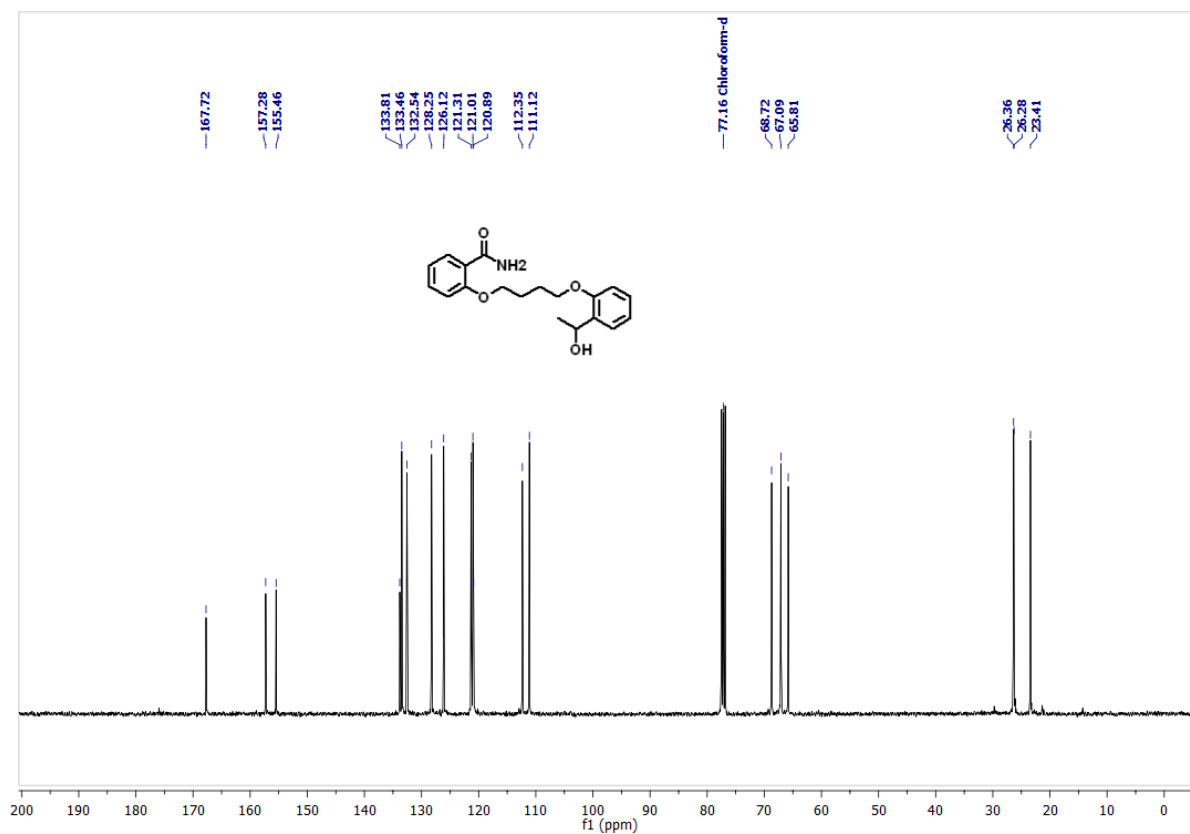
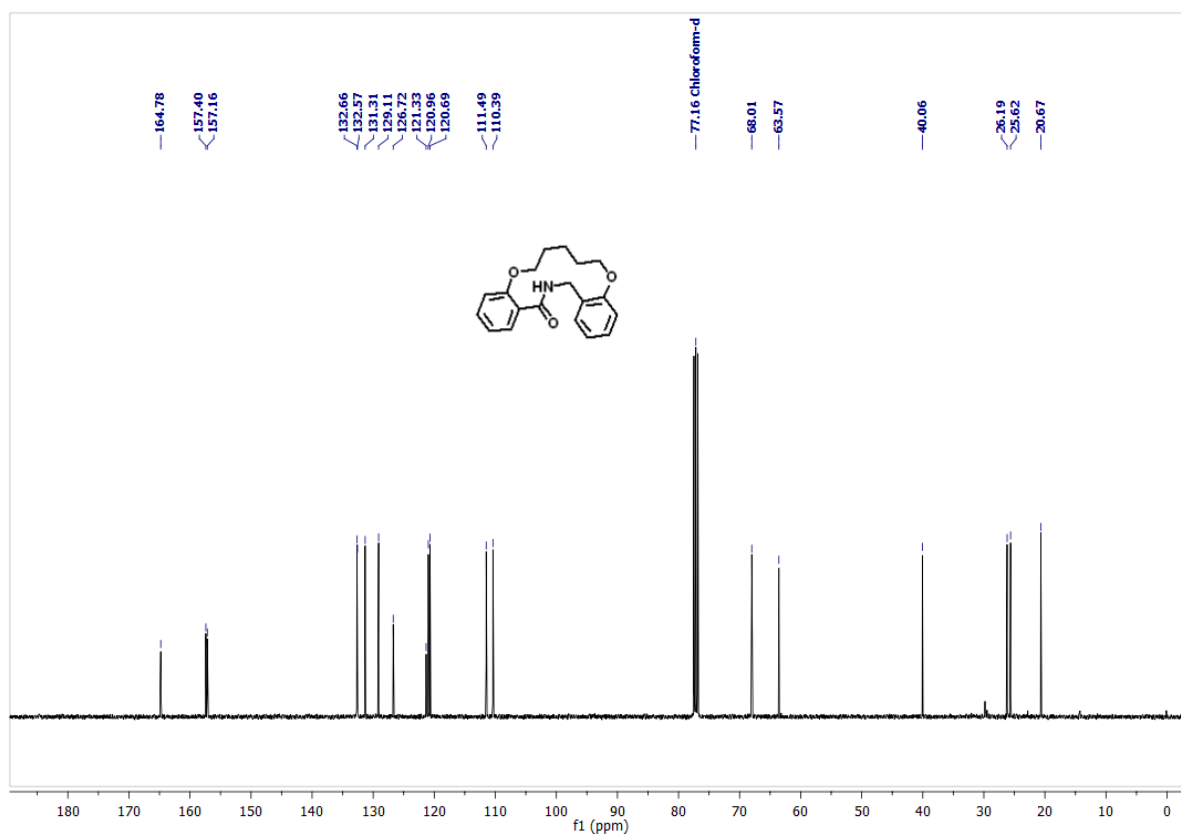
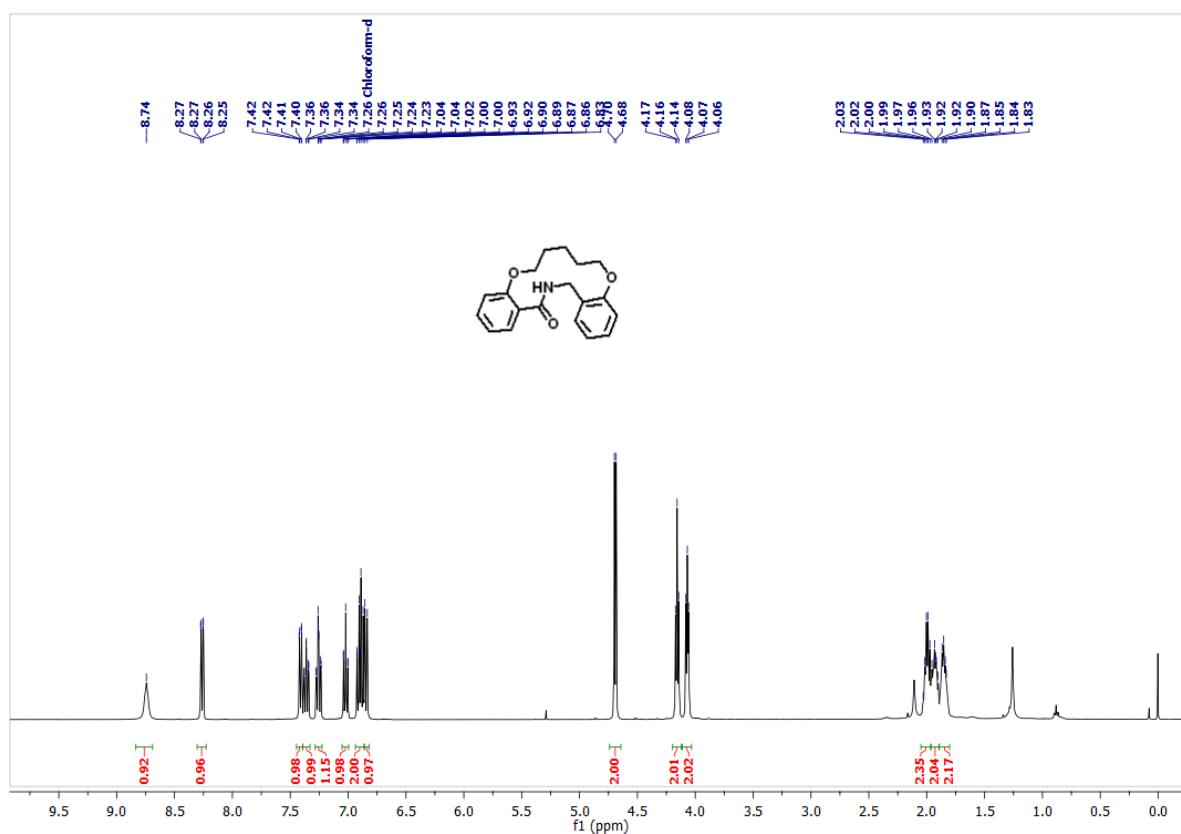


Figure 82. ¹³C NMR spectra for compound **179bb**, 100 MHz, CDCl₃



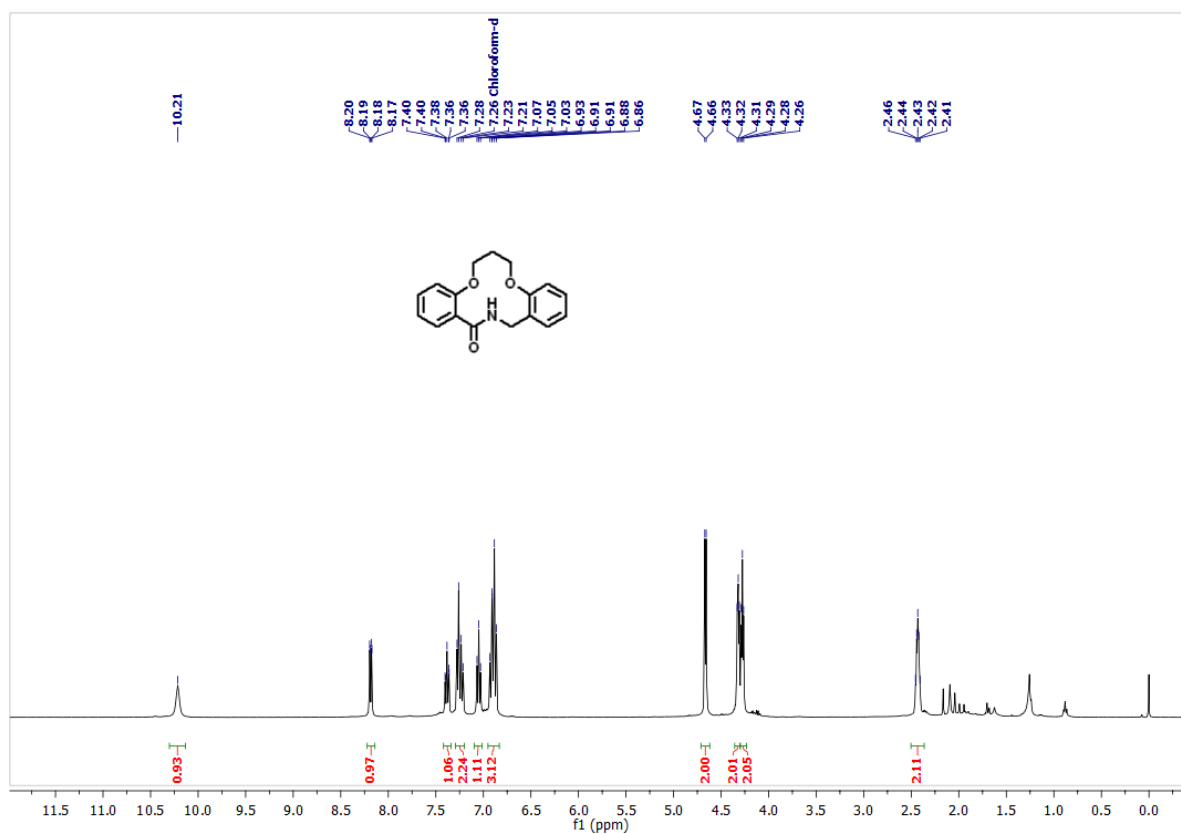


Figure 85. ¹H NMR spectra for compound **180c**, 400 MHz, CDCl₃

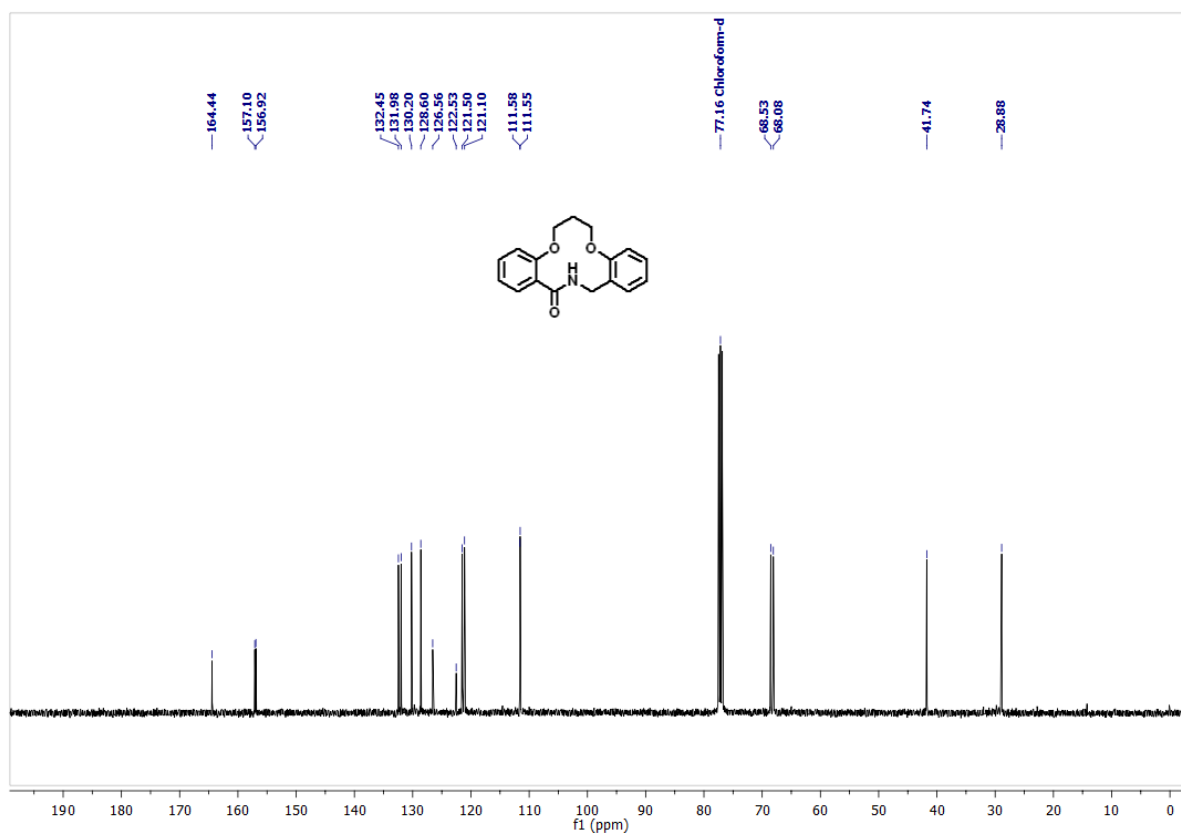


Figure 86. ¹³C NMR spectra for compound **180c**, 100 MHz, CDCl₃

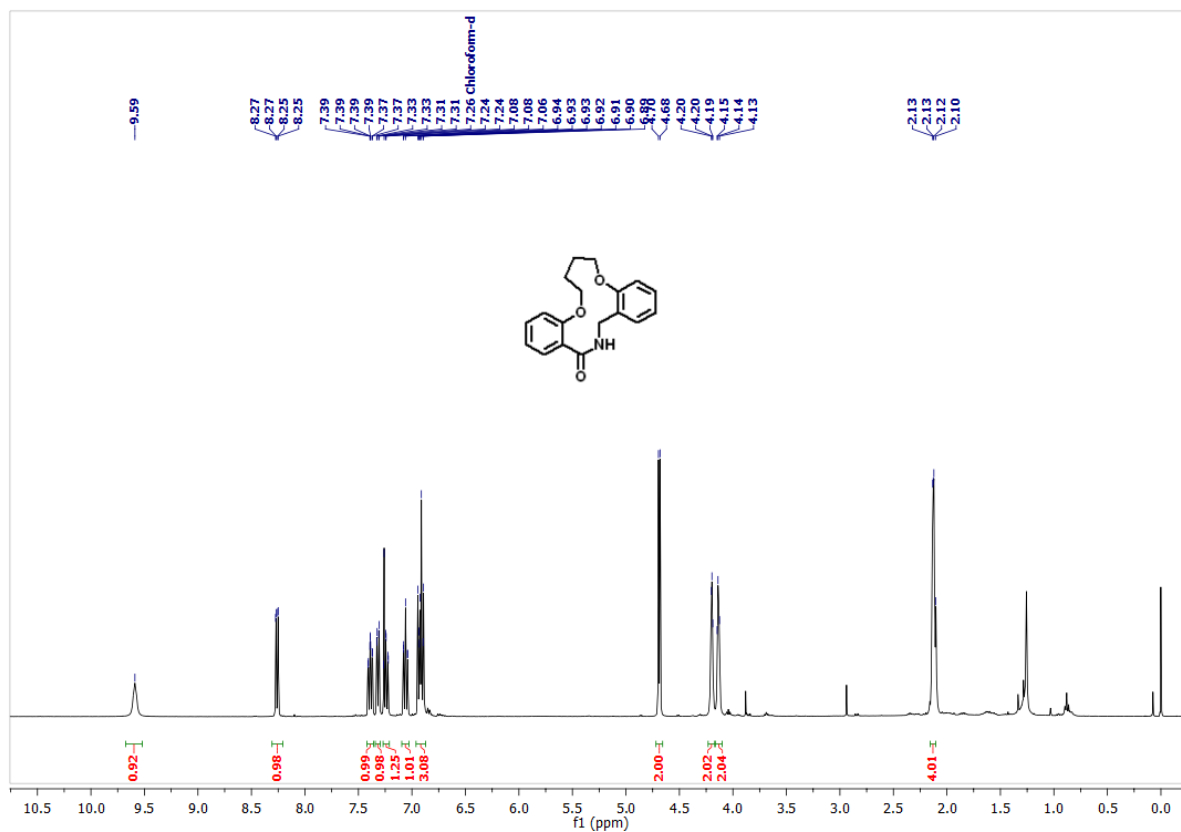


Figure 87. ¹H NMR spectra for compound **180d**, 400 MHz, CDCl₃

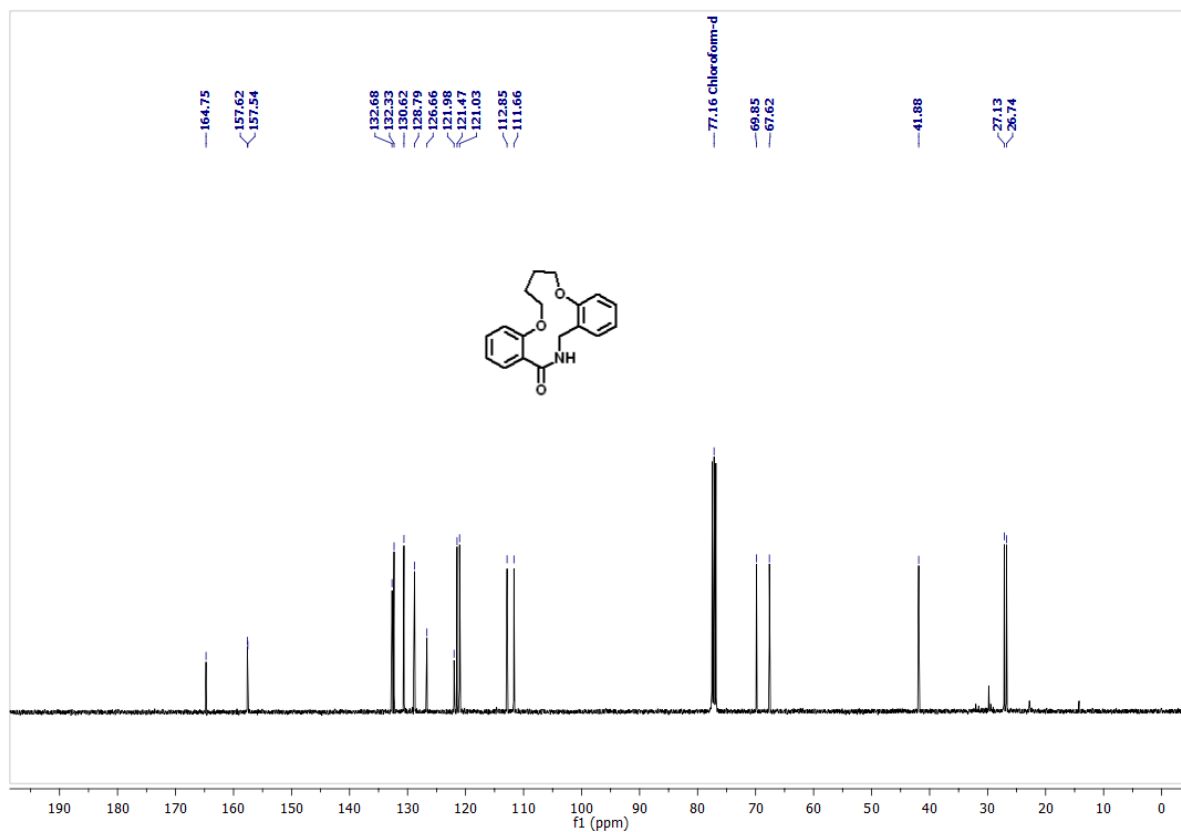


Figure 88. ¹³C NMR spectra for compound **180d**, 100 MHz, CDCl₃

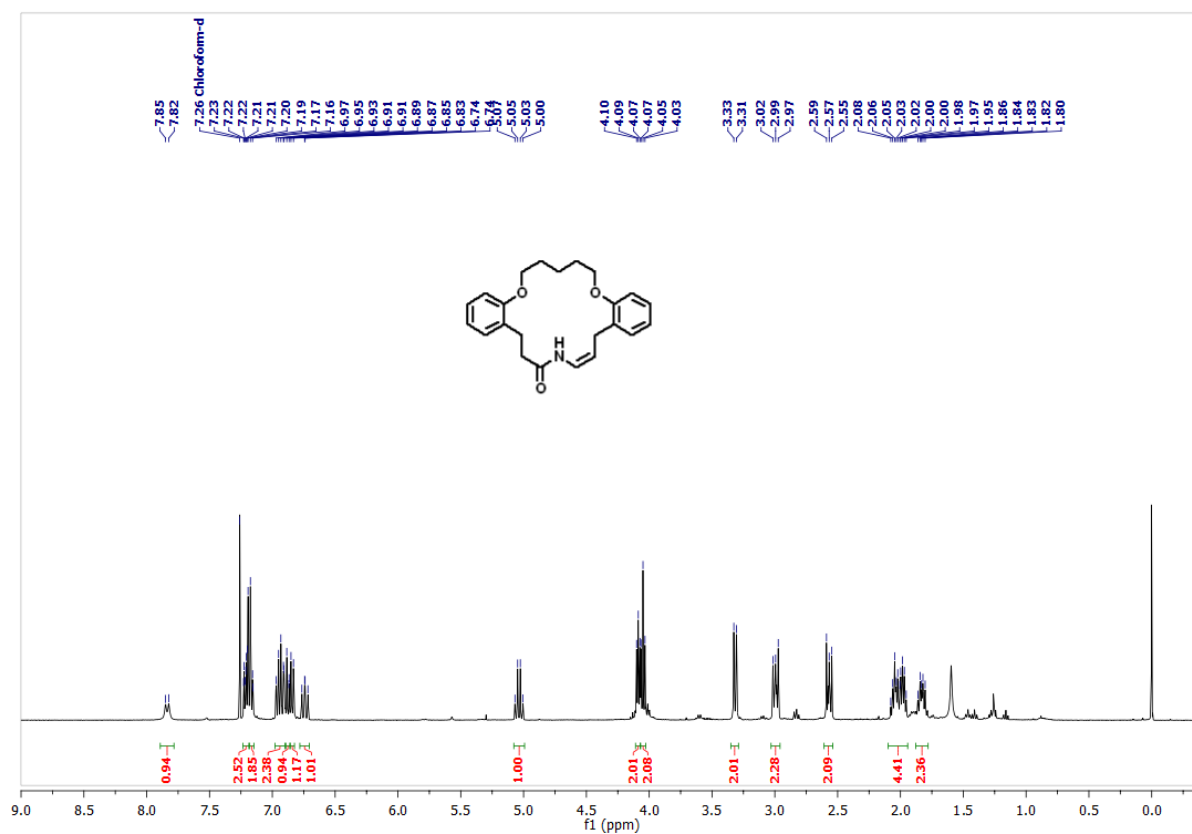


Figure 89. ¹H NMR spectra for compound **180I**, 400 MHz, CDCl₃

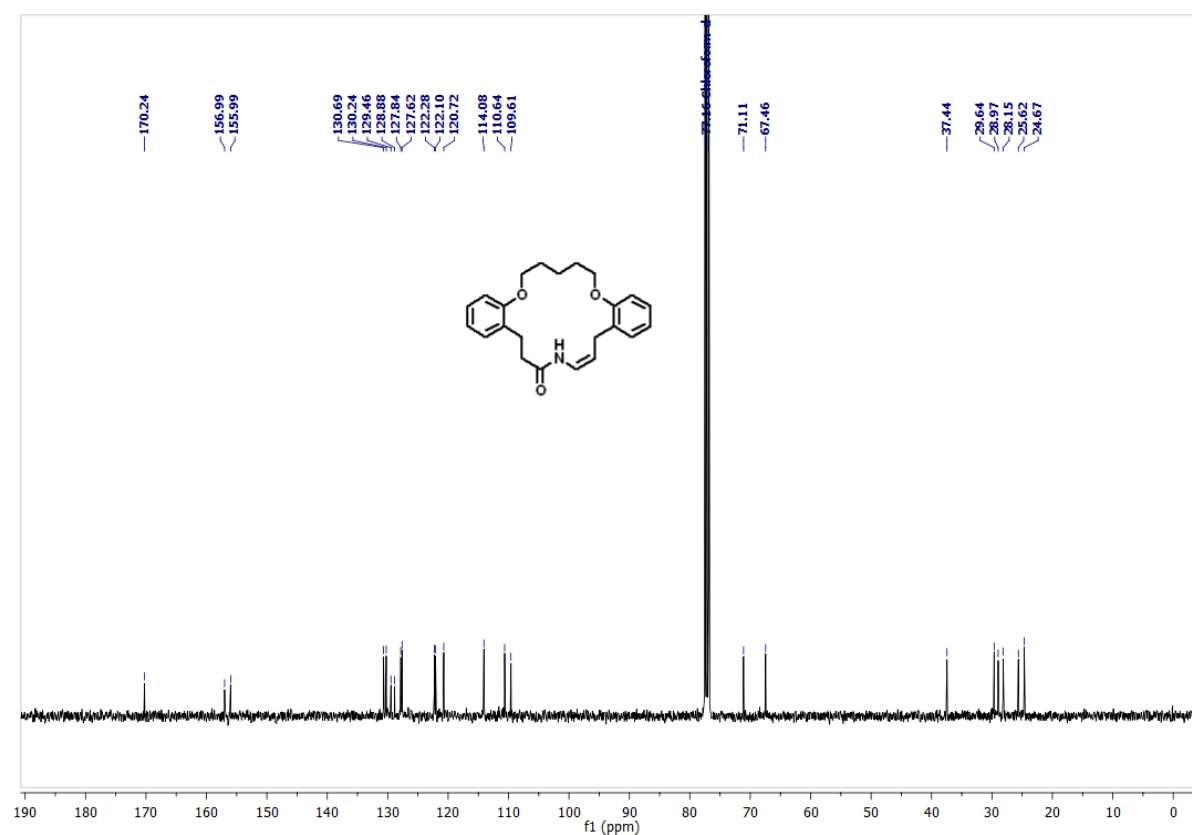
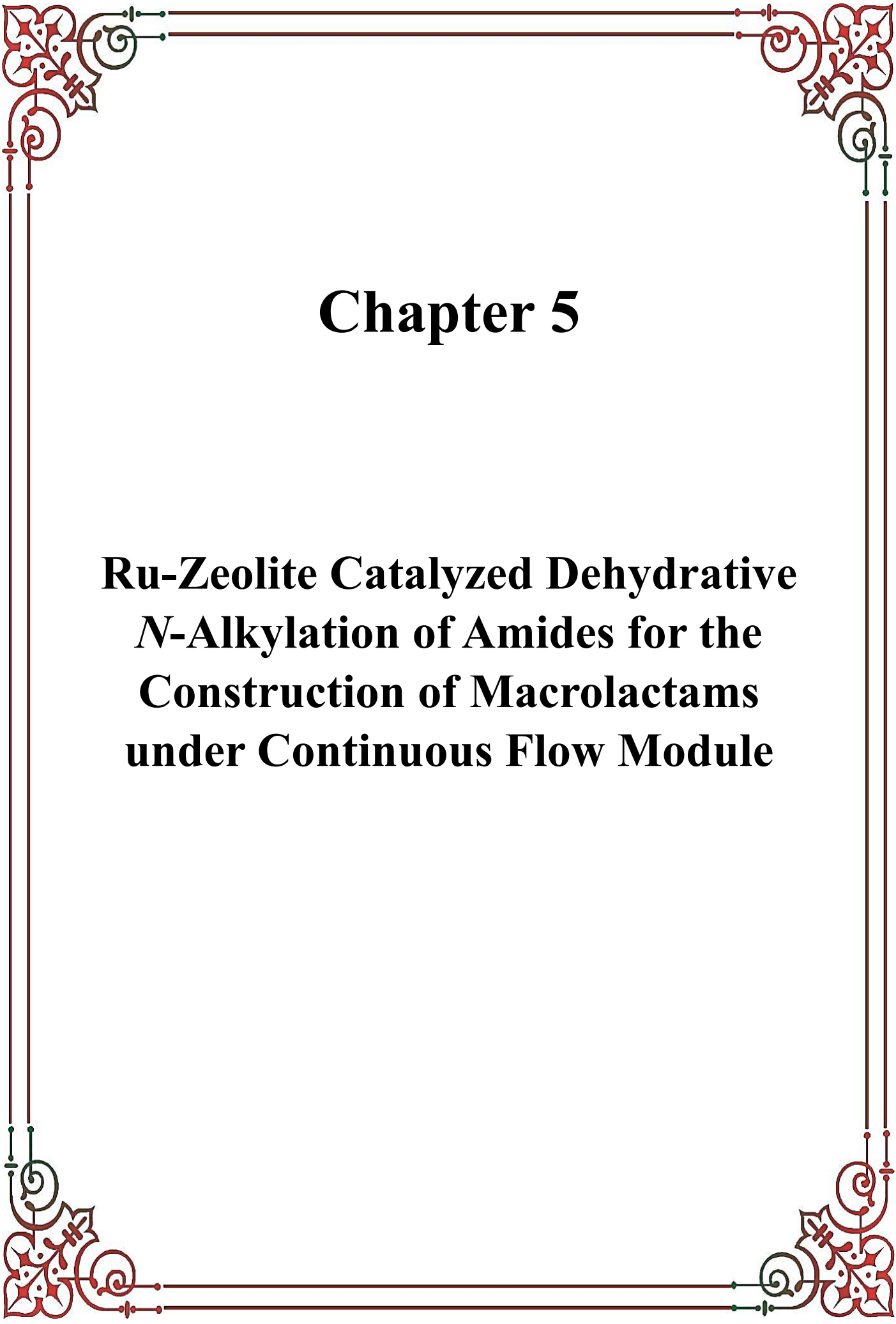


Figure 90. ¹³C NMR spectra for compound **180I**, 100 MHz, CDCl₃



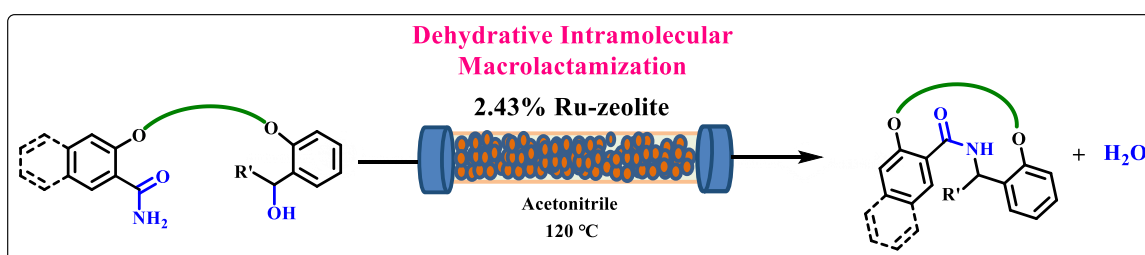
Chapter 5

Ru-Zeolite Catalyzed Dehydrative *N*-Alkylation of Amides for the Construction of Macrolactams under Continuous Flow Module

5. Ru-Zeolite Catalyzed Dehydrative *N*-Alkylation of Amides for the Construction of Macrolactams under Continuous Flow Module

5.1 Abstract:

This chapter explores the continuous flow-mediated synthesis of macrolactams, achieved through the dehydrative *N*-alkylation of amides with alcohols using an economical, reusable, and heterogeneous Ru-Zeolite catalyst. The *N*-alkylative macrolactamization is effectively demonstrated with 15 examples featuring ring sizes ranging from 11 to 15 members. The reusability of heterogeneous catalyst is demonstrated by utilizing it with 16 consecutive reaction cycles. Notably, the scalability issue related to many of the homogeneous catalysis is addressed by performing the macrolactamization reaction on the scale of 2 grams with water as the only benign byproduct generated from the reaction. Finally, a plausible reaction mechanism is elucidated with the support of literature background and a control experiment.



5.2 Introduction:

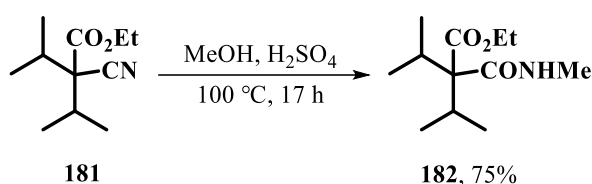
Macrolactams hold significant prominence in the pharmaceutical industry due to their inherent role as components of biologically active molecules such as cyclic peptides and proteins. Consequently, they are integral parts of numerous FDA-approved drugs or combination drugs such as grazoprevir,¹³⁹ polymyxin B,¹⁴⁰ lorlatinib,¹⁴¹ colistin,¹⁴² gramicidin,¹⁴³ bacitracin,¹⁴⁴ etc. Their presence underscores their importance in chemical biology for studying molecular recognition, protein-protein interactions, and drug-target interactions.² Thus, the construction of C-N bonds represents a pivotal process, enabling the synthesis of diverse macrolactams in organic synthesis. Due to their significant relevance, substantial research efforts have been dedicated to advancing methods for constructing C-N bonds. However, methods for constructing C-N bonds mainly explore the synthesis of amides

(acyclic) and the macrolactamization remains relatively underexplored within the domain of macrocyclic compounds.

5.2.1 Literature Background for Amidation:

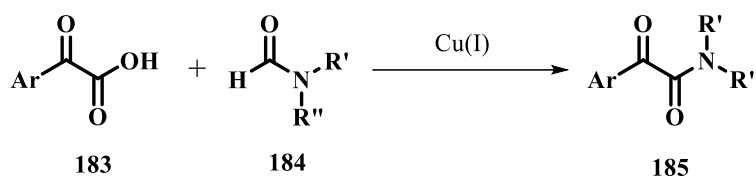
Traditionally, the synthesis of acyclic amides has relied on various methods, including the Ritter reaction,¹⁴⁵ metal-catalyzed oxidative amidation of alcohols,¹⁴⁶ carbonylation of alkyl halides and amines¹⁴⁷ and oxidative coupling of acids with formamides.¹⁴⁸

The reaction of nitrile **181** in the presence of sulphuric acid and methanol efficiently provides the amide **182** with a 75% yield (Scheme 59).



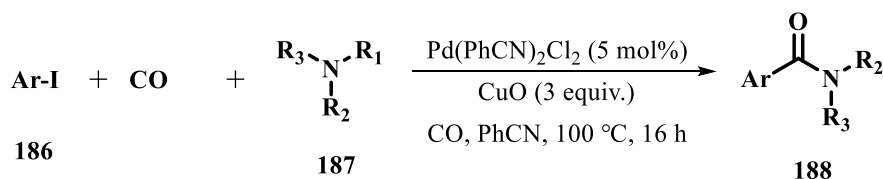
Scheme 59: Ritter reaction for the synthesis of amide

Next, the oxidative coupling of carboxylic acid **183** with formamide **184**, delivers the amide product **185** (Scheme 60).



Scheme 60: Oxidative coupling of acid with formamide for the synthesis of amide

Further, amides can be achieved using the carbonylation of alkyl halides and amines in the presence of a palladium catalyst (Scheme 61).



Scheme 61: Carbonylation of alkyl halides and amines for the synthesis of amide

Moreover, the most common methods used for the synthesis of amides are the coupling of carboxylic acids with amines¹⁴⁹ and *N*-alkylation of amides with alcohols (Figure 44, shown in Chapter 4). The *N*-alkylation of amides with alcohols has been achieved using Bronsted,¹⁵⁰ Lewis acid catalysis (Al,¹⁵¹ Re,¹⁵² Ru,¹⁵³ Au,¹⁵⁴ In,¹⁵⁵ Bi,¹⁵⁶ Fe,¹⁵⁷ Ag,¹⁵⁸ Mo¹⁵⁹), and borrowing hydrogen catalysis (Figure 44).¹⁶⁰ However, these methods are associated with several limitations, including scalability issues, sustainability concerns, and in some cases the

requirement for expensive and specially designed catalysts. Moreover, these approaches often have narrow substrate scopes, typically accommodating only stable amides and strong nucleophiles. Many catalysts used in these methods suffer from reusability challenges due to homogeneous reaction conditions.

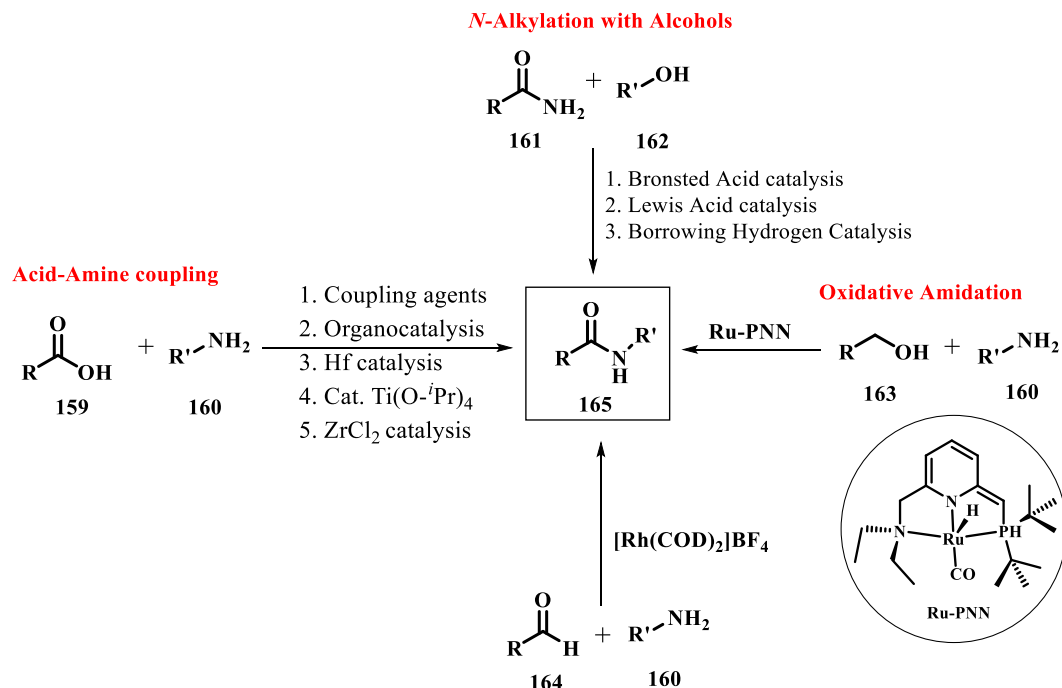
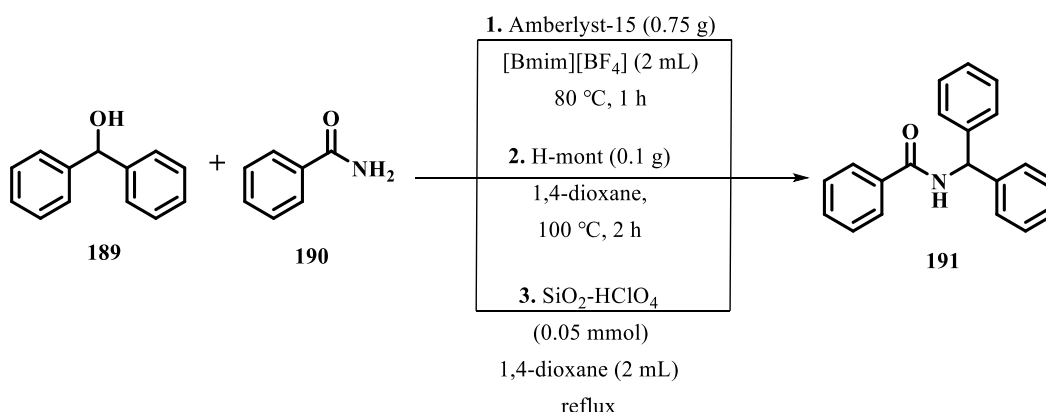


Figure 44: Various strategies for the synthesis of amides

Only a handful of heterogeneous catalytic approaches have been explored for *N*-alkylation of amides, such as Amberlyst-15 in ionic liquid (Scheme 62, reaction condition 1),¹⁶¹ montmorillonite Bronsted acid catalyst for hydroamination (Scheme 62, reaction condition 2),¹⁶² and $\text{HClO}_4\text{-SiO}_2$ (Scheme 62, reaction condition 3).¹⁶³



Scheme 62: *N*-alkylation of amide using heterogeneous catalysts

The aforementioned heterogeneous catalytic methods are predominantly limited to acyclic substrates and have not been extensively investigated for the synthesis of complex and biologi-

cally important macrolactams. The growing emphasis on macrolactamization has attracted much attention from synthetic organic chemists. As a consequence, numerous classical methods followed by a few catalytic approaches have been developed (discussed in Chapter 4). Among all these strategies, catalytic approaches are found to be more productive, atom-economic, environmentally beneficial, and sustainable as compared to classical methods, which use stoichiometric amounts of coupling agents. However, these catalytic methods are associated with a notorious limitation which is scalability.

In pharmaceutical and fine chemical industries, the scalability of organic reactions is paramount. In pharmaceutical industries, a newly discovered drug molecule needs to be synthesized from milligram to gram scale during the initial period. Afterward, kilograms of the drug is required for pre-clinical trials of phases II and III. Subsequently, the amount of the drug increases as the development chain proceeds forward. Such kind of reaction scale is significant in pharmaceutical industries since it covers the scale from milligrams to tons.¹⁶⁴

In chapters 2, 3A and 4, we established new macrocyclization strategies using borrowing hydrogen catalysis and acceptorless dehydrogenation. These methods are efficient in reducing waste formation by producing only water and hydrogen as the byproducts. Despite being proven important, BH catalysis is associated with the scalability challenge. The scale-up of the BH-catalyzed reactions typically necessitates either sealed/ pressure tube setups or reflux arrangements (for acceptorless dehydrogenation). However, when considering scalability, larger reaction setups become imperative and require significant process modifications and optimization which makes the process complicated. Additionally, the reactivity and productivity of a small-scale reaction would not be similar when attempting the same reaction on a large scale. Moreover, precise pressure and temperature control are needed to achieve better heat transfer. Most importantly, issues related to safety may arise.

At the outset, the scalability of the reaction mainly needs improved mass and heat transfer, precise temperature and pressure control, increased safety, and enhanced reaction productivity. An advanced technique needs to be used to fulfill all these parameters and make chemical processes more sustainable.

5.3 Continuous-Flow Chemistry:

Continuous flow chemistry emerged as an imperative tool for organic transformations showcasing its indispensability in modern synthetic methodologies.¹⁶⁵ The name itself defines that, reactants are (dissolved and) passed through a streamline using pumps rather than mixing in the batch to achieve the product formation. Flow chemistry involves the continuous pumping

of reagents into a reaction system, where they interact and react under precisely controlled reaction conditions while passing through a network of interconnected channels or reactors (Figure 91).

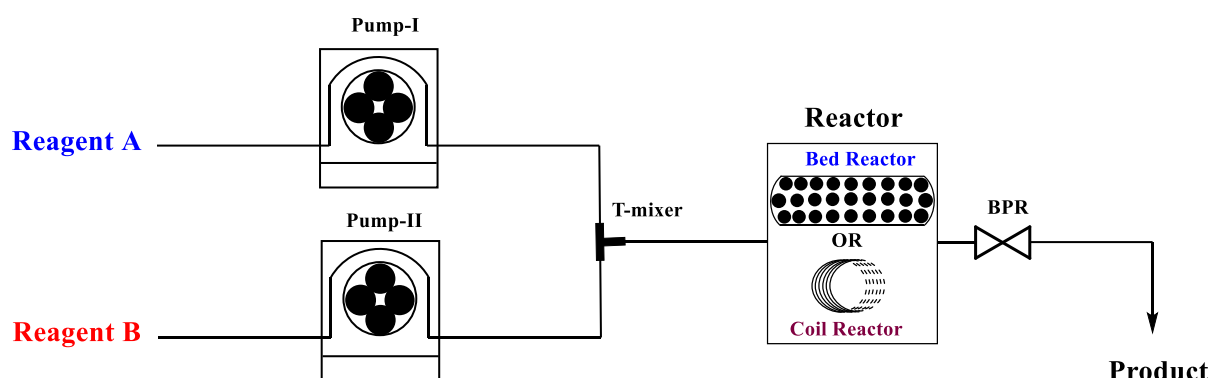


Figure 91: General representation for continuous flow setup

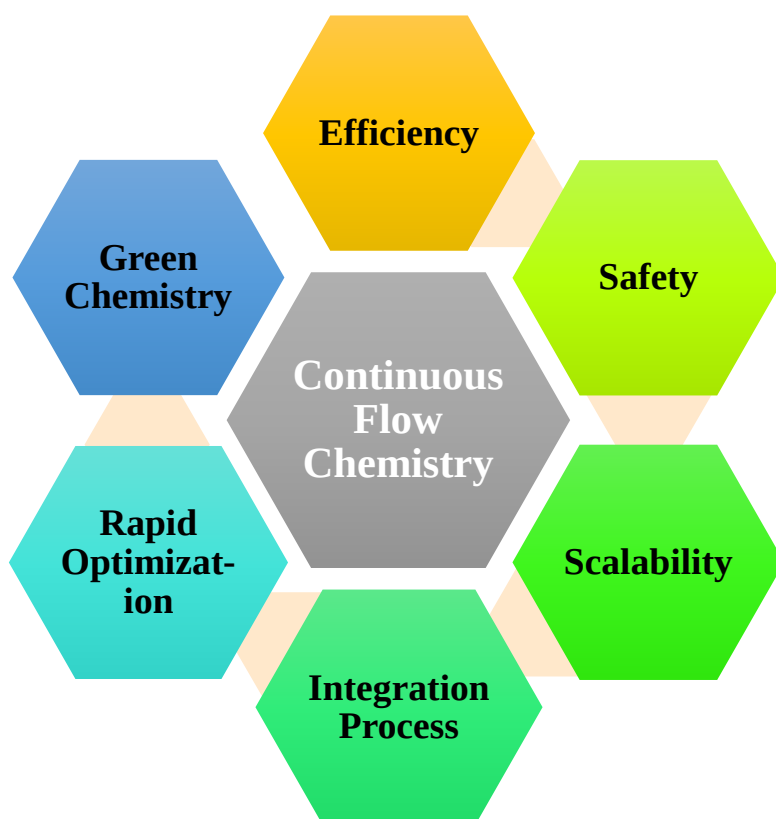


Figure 92: Applications of continuous flow chemistry

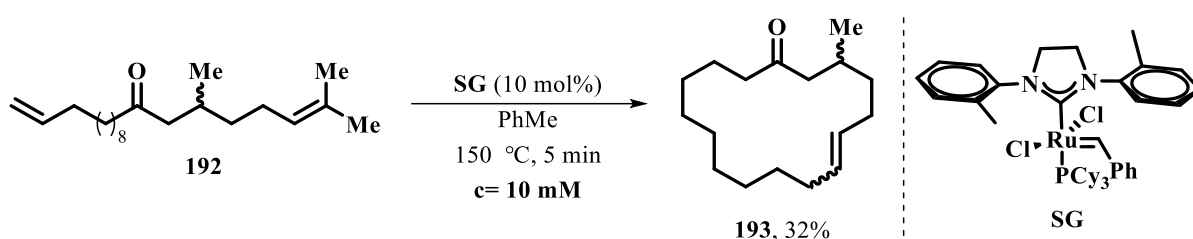
In the last few decades, the use of flow chemistry has substantially increased because of the control over reaction parameters such as temperature and pressure. Thus, the continuous flow technique provides the reaction with higher efficiency, increased safety. As a result, the scalability and the integration of multicomponent reactions become easy. More interestingly, it

also helps in rapid optimization due to control over reaction parameters and collectively contributes to sustainability and green chemistry¹⁶⁶ (Figure 92).

Due to its diverse applications and capabilities, flow chemistry serves as a promising avenue toward achieving sustainability goals for macrocyclization. As a result, continuous flow chemistry has been employed in the synthesis of a diverse range of organic molecules, including macrocycles.

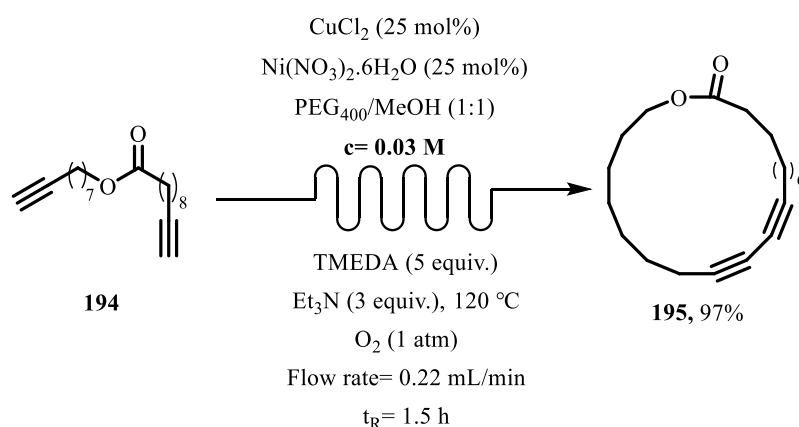
5.3.1 Literature Background for Continuous Flow-Mediated Macrocyclization

Collins and his colleagues attempted the synthesis of macrocyclic musk **193** by using Grubb's metathesis of long-chain alkene **192** with a concentration of 10 mM under continuous flow conditions (Scheme 63).¹⁶⁷



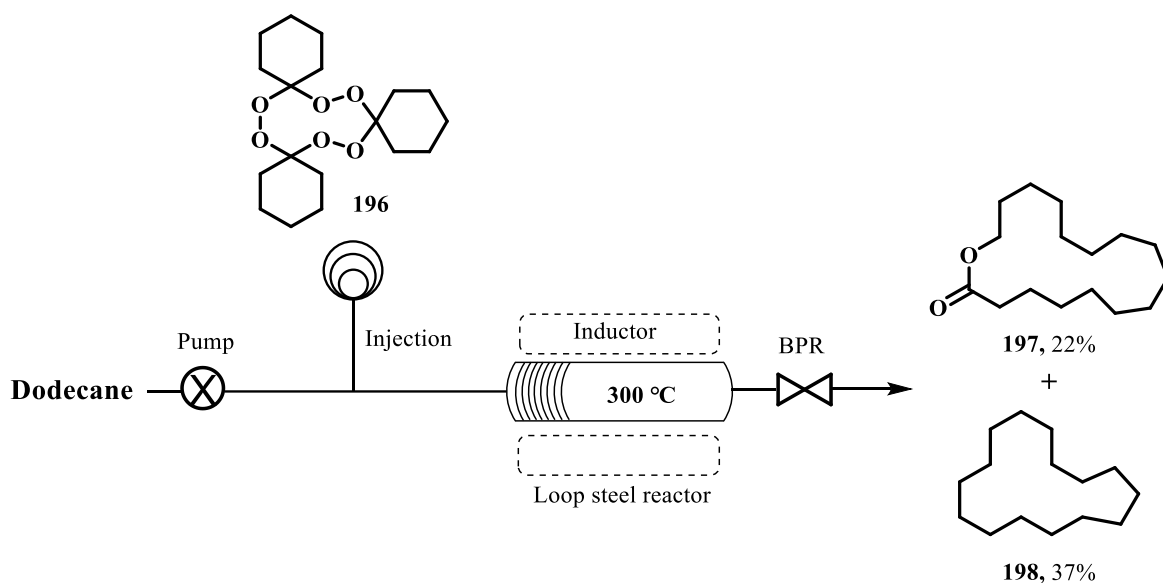
Scheme 63: Grubb's metathesis for synthetic musk

Further, the same research group performed the continuous flow-mediated Glaser–Hay coupling of two alkynes to achieve the macrocyclic product **195** with an excellent yield of 97% (Scheme 64). Notably, this method is also utilized for the synthesis of various macrocyclic lipids.¹⁶⁸



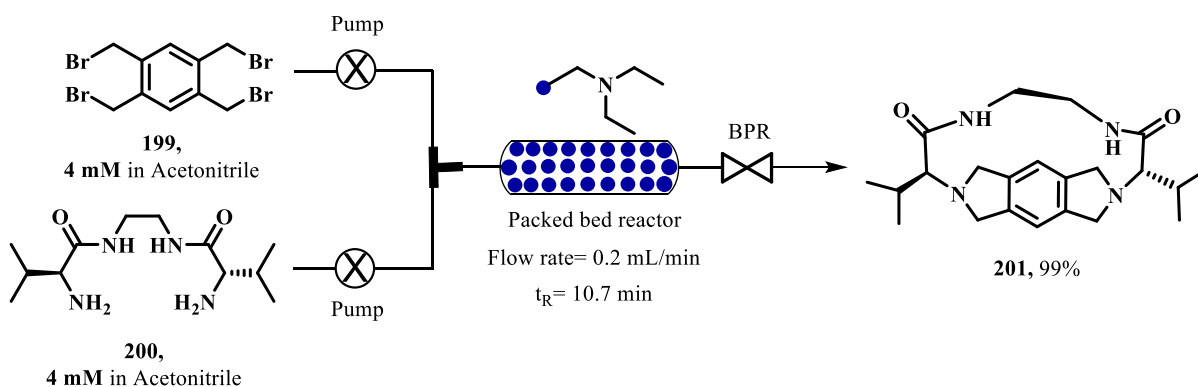
Scheme 64: Continuous flow-mediated Glaser–Hay coupling for macrocyclization

Next, Kirschning and his group achieved macrocyclic musk **197** and macrocyclic alkane **198** via pyrolysis of triperoxide **196** in the presence of dodecane under continuous flow conditions (Scheme 65).¹⁶⁹



Scheme 65: Pyrolysis of triperoxide for synthetic musk

Furthermore, the reaction of alkyl halide **199** and the diamine **200**, using a heterogeneous basic resin in continuous flow afforded a macrocyclic peptide **201** with 99% yield (Scheme 66).¹⁷⁰



Scheme 66: Pyrolysis of triperoxide for synthetic musk

5.4 Aim and Rationale of Current Work:

The earlier developed strategies for macrocyclization, including borrowing hydrogen catalysis (discussed in Chapters 2, 3A, and 4), rely on homogeneous catalysis. However, very few reports are available for macrocyclization using a heterogeneous catalyst under continuous flow conditions. Moreover, there are no reports available on continuous flow-mediated macrolactamization using a metal-zeolite-based heterogeneous catalyst. Hence, there is a compelling need to develop a new approach for the synthesis of biologically important macrolactams, utilizing a cost-effective, environmentally benign, highly reusable, and easily isolable metal-zeolite-based heterogeneous catalyst within a continuous flow module. The

zeolite-based heterogeneous catalysts are known for the dehydration of alcohols. Therefore, they form water as the only benign by-product. This would help to achieve our goal of enhancing scalability while maintaining reaction efficiency by minimizing waste generation under continuous flow conditions.

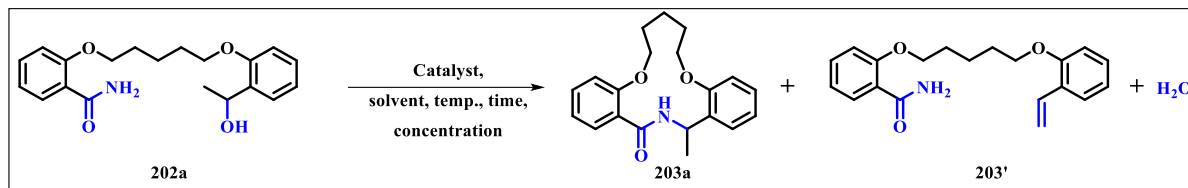
5.5 Results and Discussions:

In response, we sought to develop a new approach for the synthesis of macrolactams via intramolecular *N*-alkylation of amides with alcohols. Initially, we synthesized various metal-zeolite-based heterogeneous catalysts using a reported procedure.¹⁷¹ Next, by using a pre-established method for synthesizing amido-alcohols (discussed in Chapter 4) we synthesized numerous amido-alcohols bearing different substituents on the aromatic rings. Among those amido-alcohols, we selected amide **202a** as a model starting material for the optimization study of *N*-alkylative macrolactamization.

5.5.1 Optimization Studies:

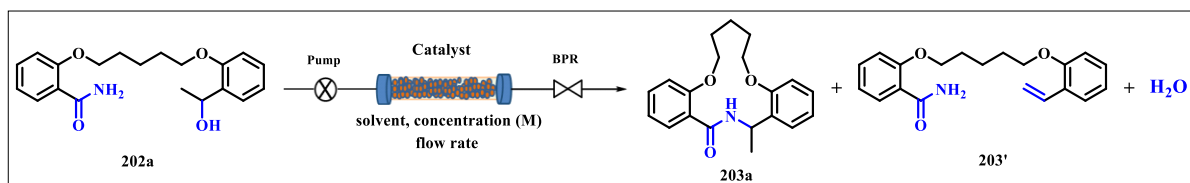
In the beginning, amido-alcohol **202a** (*c*= 0.01 M in 1,4-dioxane) underwent intramolecular reaction in the presence of several homogeneous catalysts, such as NiCl₂·6H₂O, RuCl₃·*x*H₂O, SnCl₂ and ZnCl₂ at 120 °C for 24 h (Table 7, entries 1-4). Among these homogeneous catalysts, SnCl₂ provided the 36% yield of macrolactam **203a** (Table 7, entry 3). Subsequently, we screened a few heterogeneous catalysts such as β -Zeolite, Ni-Zeolite, Fe-Zeolite, 2.43% Ru-Zeolite and Amberlyst-15 (hydrogen form) for macrolactamization (Table 7, entries 5-9). Notably, Fe-Zeolite and 2.43% Ru-Zeolite (% binding of ruthenium on zeolite is checked using ICP analysis) provided 42 and 44% yields of macrolactam product **203a**, respectively, along with an intermediate alkene **203'** (29 and 36 % yields, Table 7, entries 6-7). Extending the reaction time to 48 h, Fe-Zeolite and 2.43% Ru-zeolite furnished 44 and 47% yield of **203a** (Table 7, entries 10 and 11). Further, by employing a 2.43% Ru-zeolite catalyst as an optimal catalyst, reaction temperatures were varied to 100 °C and 140 °C, resulting in 31 and 47% yields of **203a**, respectively (Table 7, entries 12 and 13). These reactions clearly prove that 120 °C is the optimal temperature for this reaction. Moreover, replacing 1,4-dioxane, we screened several other solvents, and among all, acetonitrile provided **203a** with the best yield of 55% accompanied by 24% of alkene intermediate **203'** (Table 7, entries 14-18). Upon achieving optimal reaction condition in batch, we proceeded with the optimization of *N*-alkylative macrolactamization under a continuous flow process.

Table 7: Optimization for Intramolecular Macrolactamization via *N*-alkylation of Amides with Alcohols under Batch Condition:



Entry	Catalyst (mol %)	Solvent (mL)	Conc. (M)	Temp. (°C)	Time (h)	Yield of 203a/203' (%)
1.	NiCl ₂ ·6H ₂ O (20)	1,4-Dioxane (8)	0.01	120	24	Trace/-
2.	RuCl ₃ ·xH ₂ O (20)	1,4-Dioxane (8)	0.01	120	24	31/-
3.	SnCl ₂ (20)	1,4-Dioxane (8)	0.01	120	24	36/-
4.	ZnCl ₂ (20)	1,4-Dioxane (8)	0.01	120	24	-
5.	Ni-Zeolite (w/w)	1,4-Dioxane (8)	0.01	120	24	38/46
6.	Fe-Zeolite (w/w)	1,4-Dioxane (8)	0.01	120	24	42/29
7.	2.43% Ru-Zeolite (w/w)	1,4-Dioxane (8)	0.01	120	24	44/36
8.	β-Zeolite (w/w)	1,4-Dioxane (8)	0.01	120	24	41/18
9.	Amberlyst-15 (w/w)	1,4-Dioxane (8)	0.01	120	24	31/-
10.	Fe-Zeolite (w/w)	1,4-Dioxane (8)	0.01	120	48	44/28
11.	2.43% Ru-Zeolite (w/w)	1,4-Dioxane (8)	0.01	120	48	47/33
12.	2.43% Ru-Zeolite (w/w)	1,4-Dioxane (8)	0.01	100	24	31/30
13.	2.43% Ru-Zeolite (w/w)	1,4-Dioxane (8)	0.01	140	24	47/35
14.	2.43% Ru-Zeolite (w/w)	Toluene (8)	0.01	120	24	39/46
15.	2.43% Ru-Zeolite (w/w)	ACN (8)	0.01	120	24	55/24
16.	2.43% Ru-Zeolite (w/w)	THF (8)	0.01	120	24	47/35
17.	2.43% Ru-Zeolite (w/w)	DMSO (8)	0.01	120	24	-/51
18.	2.43% Ru-Zeolite (w/w)	DMF (8)	0.01	120	24	-

Reaction Condition: Amide **202a** (0.08 mmol, 1 equiv.), catalyst (see table) and solvent (see table) were heated at temperature (see table) for time (see table) to get the macrolactam **203a** and alkene **203'**. Mentioned yields are isolated yields.

Table 8: Continuous Flow Optimization for *N*-alkylative Macrolactamization^a

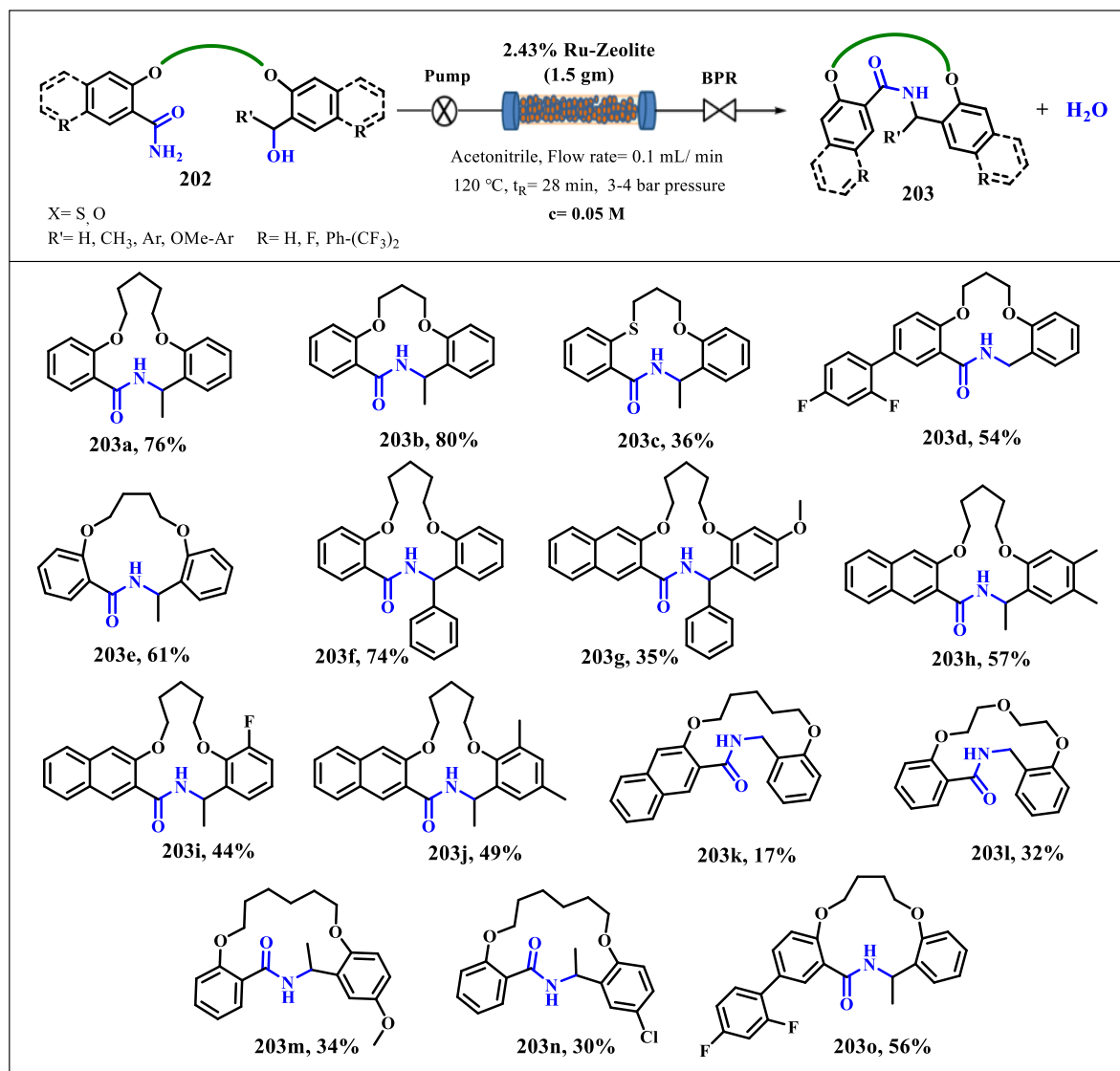
Sr. No.	Conc. (M)	Catalysts	Residence Time t_R (min)/ No. of runs	Yield of 203a/203' (%)
1 ^b	0.01	Ru-Zeolite	28/1	68/ trace
2 ^b	0.01	Fe-Zeolite	28/1	37/41
3	0.01	Ru-Zeolite	28/1	76/ trace
4	0.01	β -Zeolite	28/1	41/28
5	0.03	Ru-Zeolite	28/1	74/trace
6	0.05	Ru-Zeolite	28/1	76/ trace
7	0.1	Ru-Zeolite	28/1	50/ 31
8	0.05	Ru-Zeolite	28/1	77/ trace
9 ^c	0.05	Ru-Zeolite	14/1	70/ trace
10 ^d	0.05	Ru-Zeolite	22/1	60/25

^a**Reaction Conditions:** The solution of **202a** in acetonitrile was flown through an Omnifit® column reactor bed (6.6 mm bore and 150 mm length) containing fresh 2.43% Ru-Zeolite at 120 °C for residence time (t_R) (see table) (Bed height= 8 cm, Catalyst wt.= 1.5 gm). ^b1,4-Dioxane is used as a solvent. ^c0.2 mL/min flow rate. ^dBed height= 7 cm (1.3 gm catalyst) to get the product **203a**.

Amido-alcohol **202a** was dissolved in 1,4-dioxane ($c = 0.01$ M) and passed through PTFE tubing at a flow rate of 0.1 mL/min, where it reacted with a 2.43% Ru-zeolite catalyst packed in an Omnifit® column (6.6 mm bore and 150 mm length). This reaction afforded 68% yield of product **203a** and trace amounts of alkene intermediate **203'** with a residence time of 28 minutes (Table 8, entry 1). Next, amide **202a** afforded 37% of **203a** and 41% of alkene **203'** when Fe-Zeolite was used as a catalyst (Table 8, entry 2). Further, 1,4-dioxane was replaced by acetonitrile to afford a 76% yield of **203a** (Table 8, entry 3). Moreover, a reaction with only β -Zeolite afforded a 41% yield of product **203a** (Table 8, entry 4). Furthermore, utilizing 2.43% Ru-Zeolite as an optimal catalyst and acetonitrile as the optimal solvent, we conducted a

concentration study. Amido-alcohol **202a** was diluted to 0.03, 0.05, and 0.1 M, resulting in 74, 76 and 50 % yields of **203a**, respectively (Table 8, entries 5-7). Two consecutive runs yielded similar results (Table 8, entry 8). Subsequently, increasing the flow rate to 0.2 mL/min and reducing the bed height resulted in a decreased yield of **203a** (Table 8, entries 9 and 10). After screening all the parameters, we achieved the best-optimized reaction condition (Table 8, entry 8).

5.5.2 Substrate Scope:

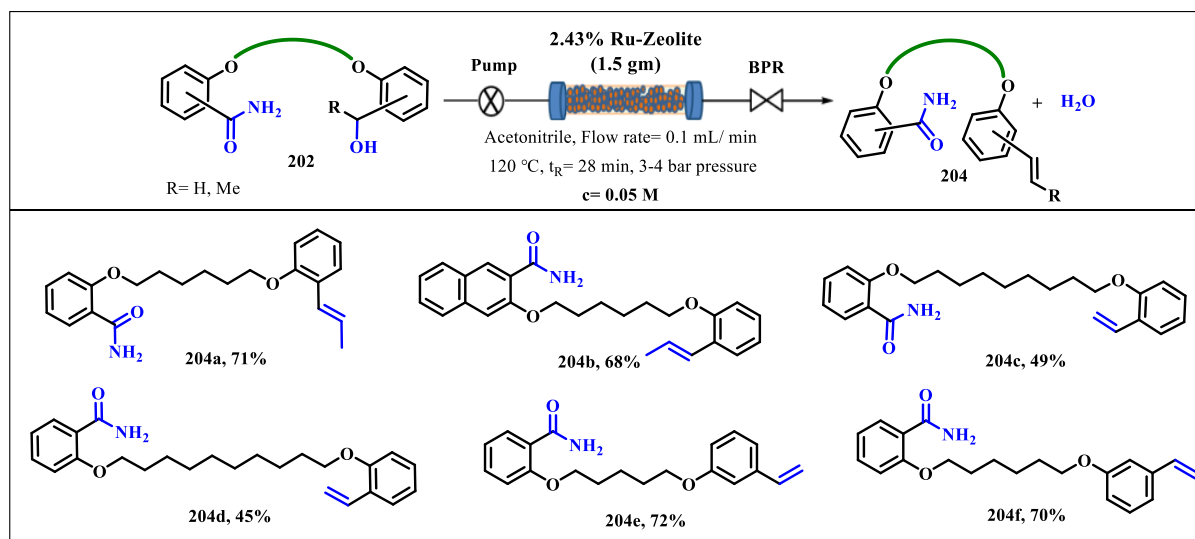


Scheme 67: Substrate scope for the intramolecular *N*-alkylation of amides with alcohols

Reaction Condition: The solution of **202** (0.08 mmol, c = 0.05 M) in 2 mL acetonitrile was flown through an Omnifit® column reactor bed (6.6 mm bore and 150 mm length) containing fresh 2.43% Ru-Zeolite (bed height = 8 cm, catalyst weight = 1.5 gm) at 120 °C for residence time t_R = 28 min with 3-4 bar pressure to achieve the macrolactams **203**.

The established optimized reaction conditions were employed for the synthesis of macrolactams **203a- 203o** (Scheme 67). Macrolactams with the 14- and 12-membered ring sizes (**203a** and **203b**) were obtained with yields of 76 and 80%, respectively (Scheme 67). Additionally, sulfur-containing and difluoro-substituted amides (**202c** and **202d**) yielded macrolactams **203c** and **203d** with yields of 36 and 54%, respectively. Next, a 13-membered macrolactam **203e** was achieved in 61% yield. Further, the methyl group of the alcohol was replaced with a phenyl group, which led to the formation of macrolactams **203f** and **203g** with yields of 74 and 35%, respectively (Scheme 67). Later, introducing dimethyl and fluoro-substituents on the aromatic ring afforded compounds **203h**, **203i**, and **203j** with yields ranging from 57 to 44% (Scheme 67). Moreover, the *N*-alkylation using primary alcohols provided macrolactams **203k** and **203l** with yields of 17 and 32%, respectively (Scheme 67). Furthermore, methoxy-, chloro-, and difluorophenyl substitutions on the aromatic ring resulted in products **203m**, **203n**, and **203o** with yields of 34, 30 and 56%, respectively (Scheme 67).

In addition to successful outcomes, several unsuccessful results were obtained (Scheme 68). Amido-alcohols bearing nonyl (**202n**) and decyl (**202o**) spacers failed to afford products. Moreover, ethyl substitution adjacent to the alcohol (**202p**), meta-substituted alcohol (**202q**)



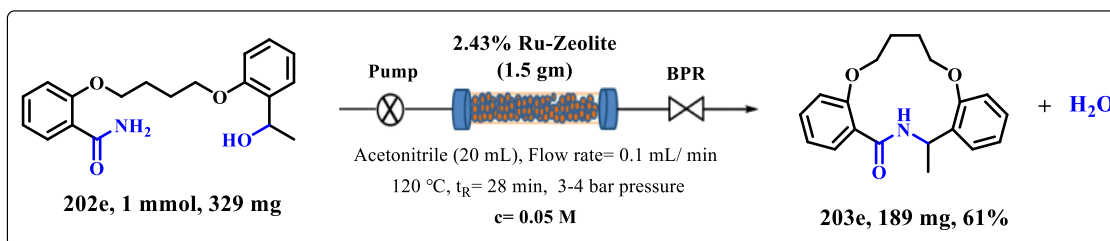
Scheme 68: Unsuccessful substrates with alkene formation

Reaction condition: The solution of **202** (0.08 mmol, c= 0.05 M) in 2 mL acetonitrile was flown through an Omnifit® column reactor bed (6.6 mm bore and 150 mm length) containing fresh 2.43% Ru-Zeolite (bed height= 8 cm, catalyst weight= 1.5 gm) at 120 °C for residence time t_R = 28 min with 3-4 bar pressure.

and non-benzylic amide (**202r**) failed to provide the desired products under the optimized reaction conditions. These amides, upon reaction, provided only the alkene product via the E1 reaction (Scheme 68). The *N*-alkylation process for these intramolecular reactions is challenging due to the inaccessible nature of the reaction centers (the alkene and amide functionalities). Moreover, the reaction with amide **202s** was not successful by virtue of solubility concern.

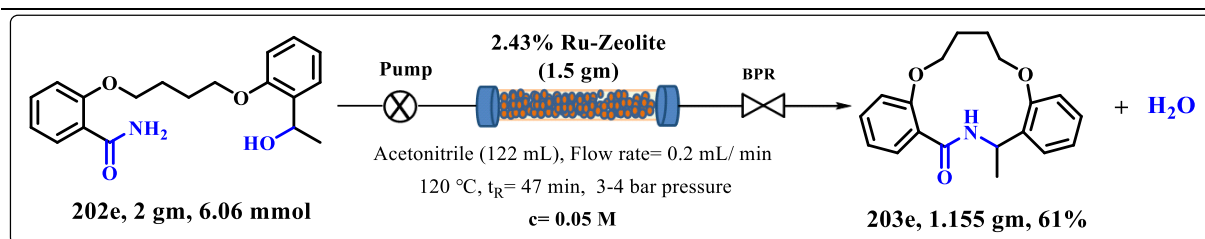
5.5.3 Scalability and Reusability:

To assess scalability, we conducted experiments on both millimole (mmol) and gram scales (2 gm) using amide **202e**, yielding **203e** in 61% yield in both instances (Schemes 69 and 70).



Scheme 69: Scale-up reaction for 1 millimole of **202e**

Reaction condition: The solution of **202e** (1 mmol, c = 0.05 M) in 20 mL acetonitrile was flown through an Omnifit® column reactor bed (6.6 mm bore and 150 mm length) containing fresh 2.43% Ru-Zeolite (bed height = 8 cm, catalyst wt. = 1.5 gm) at 120 °C for residence time t_R = 28 min with 3-4 bar pressure.

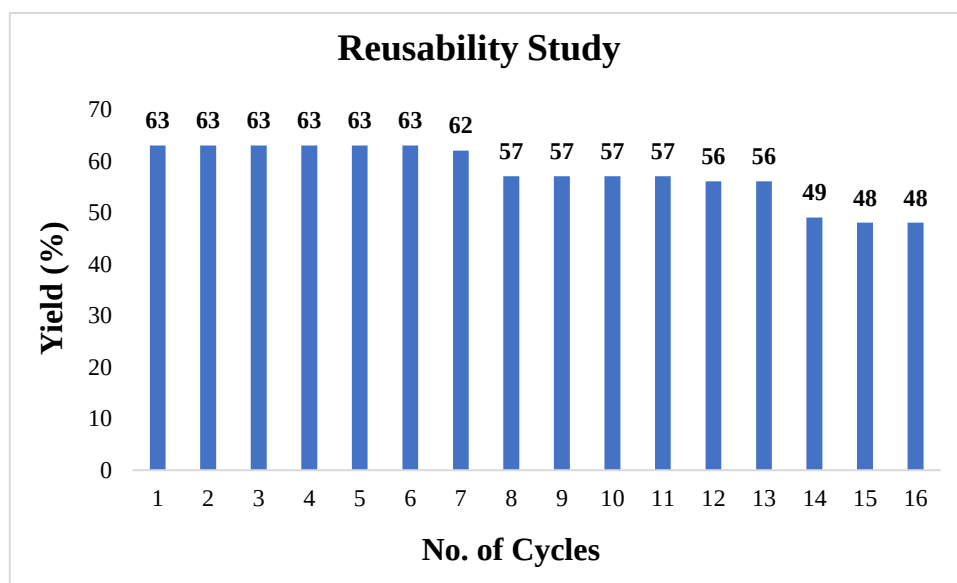
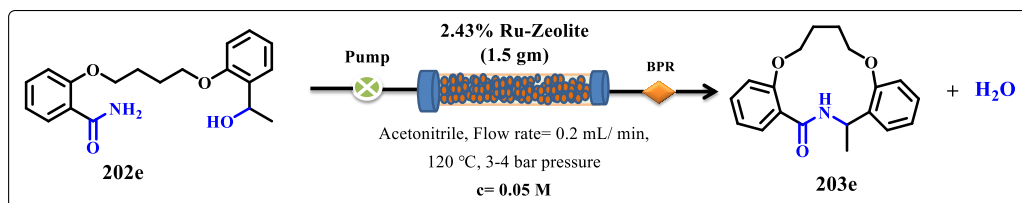


Scheme 70: Scale-up reaction for 2 gm of **202e**

Reaction condition: The solution of **202e** (1 mmol, c = 0.05 M) in 122 mL acetonitrile was flown through an Omnifit® column reactor bed (10 mm bore x 150 mm length) containing fresh 2.43% Ru-Zeolite (bed height = 10 cm, catalyst wt. = 5 gm) at 120 °C for residence time t_R = 28 min with 3-4 bar pressure.

Moreover, to assess the catalyst's reusability, we conducted 16 consecutive reaction cycles using a single batch of a one-time packed bed of 2.43% Ru-zeolite catalyst (5 grams).

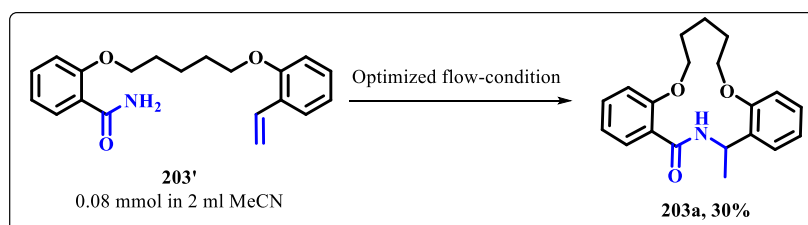
Even after 16 cycles, the catalyst was found to be active (Scheme 71). After the 16th cycle, we achieved the product **203e** with 48% yield.



Scheme 71: Catalyst reusability study

5.6 Mechanistic Investigation:

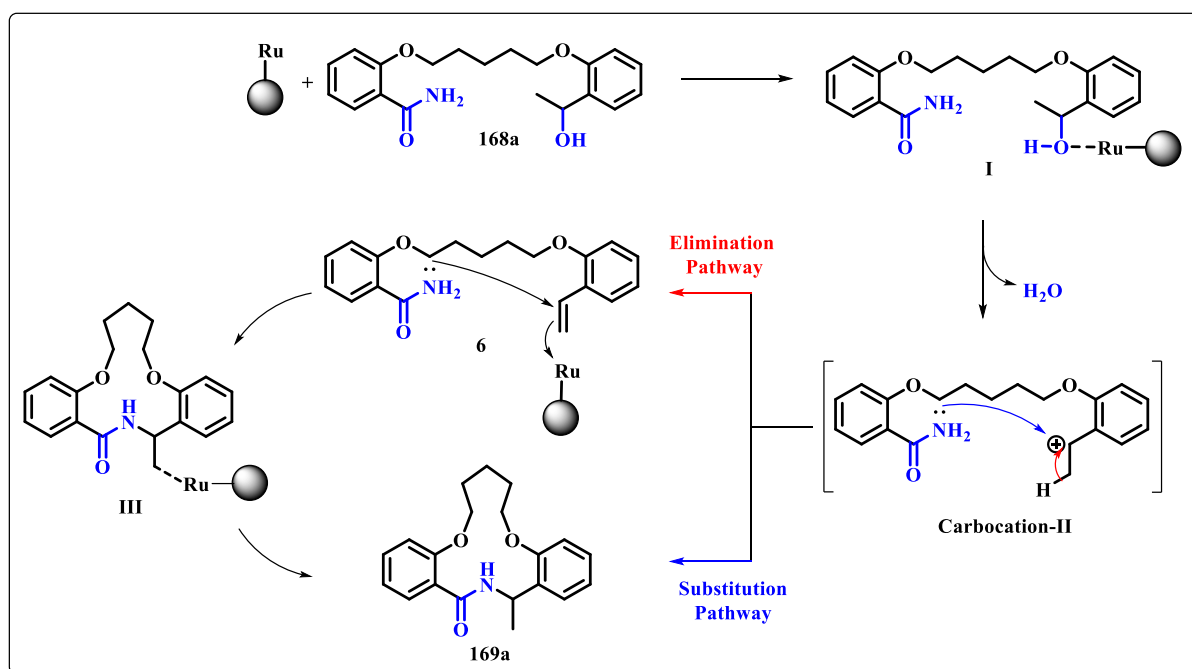
The formation of an alkene as an intermediate in the reaction via dehydration of alcohols indicates that there are two possible routes to the reaction through which it proceeds. The dehydration of alcohol in the presence of 2.43% Ru-Zeolite, leads to the formation of a carbocation (benzylic carbocation). Afterwards, the carbocation either directly reacts intramolecularly with the amide-NH₂ (S_N1 reaction) or undergoes an E1 elimination reaction to form an alkene intermediate. The possibility of alkene **203'** as an intermediate in the reaction



Scheme 72: Control experiment for mechanism

was cross-checked with a control experiment. Alkene **203'** was synthesized and subjected to optimized flow conditions, resulting in a 30% yield of compound **203a** (Scheme 72). This

outcome clearly confirms the role of alkene as the intermediate in the reaction mechanism. However, the possibility of S_N1 reaction cannot be ruled out since the reaction of amides **202f** and **202g** (no α -CH₂ for E1 reaction) both have afforded the macrolactone products under the



Scheme 73: Plausible reaction mechanism for dehydrative macrolactamization

optimized reaction condition (Scheme 67). Therefore, based on the literature survey¹⁷² and the control experiment (Scheme 72), we depicted the plausible reaction mechanism (Scheme 73). Initially, amide **202a** interacts with the 2.43% Ru-Zeolite catalyst to generate intermediate **I**, followed by dehydration to form carbocation species **II**. Subsequently, carbocation **II** undergoes S_N1 and E1-elimination reactions, yielding product **203a** and intermediate **203'**, respectively. The intermediate **203'** undergoes intramolecular hydroamination to furnish the macrolactam product **203a** (as shown in Scheme 72).

5.7 Conclusion:

In conclusion, we have developed a new synthetic approach for the synthesis of macrolactams via intramolecular *N*-alkylation of amides using alcohols, employing a heterogeneous 2.43% Ru-Zeolite catalyst under continuous flow conditions. This is the first study to demonstrate the synthesis of diverse macrolactams with variable ring sizes. Notably, this study leverages the advantages of a cost-effective, atom-efficient, highly reusable heterogeneous Ru-Zeolite catalyst, generating water as the sole benign byproduct. Furthermore, the mechanistic pathway involves the formation of a carbocation intermediate, followed by S_N1 (when primary alcohol is used) and E1-elimination reactions (when secondary

alcohol is used). After the elimination reaction, subsequent hydroamination leads to the formation of the desired product. We have validated this protocol through the synthesis of 15 distinct macrolactams, demonstrating its robustness and versatility in organic synthesis. More interestingly, a significant advancement in addressing the scalability challenges related to macrocyclization is evidenced by successfully demonstrating reactions from milligrams to 2 grams.

5.8 Experimental Section and Characterization Data

5.8.1 General information and data collection:

The Zeolite beta, hydrogen (CAS number- 1318-02-1, Thermo Fisher Scientific), Ruthenium (III) chloride hydrate (CAS number- 14898-67-0, Sigma-Aldrich), all starting material alcohols and amides were purchased from Sigma-Aldrich and BLD pharm. All the solvents used were dry grade and purchased from FINAR. The column chromatographic separations were performed over 60-120 mesh and 100-200 mesh size Silica-gel. Visualization was accomplished with UV light, PMA, DNP, and KMnO₄ stains. ¹H and ¹³C NMR spectra were recorded on 400 and 100 MHz, respectively, using Bruker spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiple. High-Resolution Mass Spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATIR) spectra were obtained with a Bruker Alpha-E infrared spectrometer.

5.8.2. Experimental section:

I) Experimental procedure for 2.43% Ru-Zeolite:¹⁷¹

Zeolite (10 g) was suspended in 20 mL of deionized water. A 10% metal chloride (RuCl₃.xH₂O) solution was prepared in deionized water. Metal loading of 2%-3% over zeolite samples was achieved by using the corresponding amounts of stock solution. This suspension was stirred for 6 h in a rotary evaporator for uniform dispersion. Water was removed under vacuum, and the metal-loaded samples were dried in an oven at 120 °C for 2 h. The dried samples were calcined at 600 °C for 6 h. The ICP-MS data indicated that 2.43% of Ruthenium bound on the zeolite.

A. Experimental procedure of sample preparation for ICP-MS analysis:

In a Teflon beaker, 0.1 gm (100 mg) of RuCl₃.xH₂O, 4 mL of conc. nitric acid (HNO₃), 2 mL of conc. hydrochloric acid (HCl) and 4 mL of hydrofluoric acid (HF) were added. The Teflon beaker was covered by a Teflon lid, and the resulting mixture was heated at 100 °C for 3-4 h. Then the acids from the mixture evaporated to a drop. Next, 4 mL of HCl and 2 mL of HNO₃

were added to the one-drop mixture and again heated at 100 °C for 3-4 h to get a clear solution (if clear solution is not obtained, repeat the same procedure until getting clear solution). To that clear solution was added 0.25 mL HNO₃ and then heated to evaporate all acids completely. After evaporation of all acids, 1 ml of HNO₃ was added and the resulting mixture was refluxed for 5 minutes. After that, the resulting mixture was diluted to 20 ppb using 2% HNO₃: water.

II) General experimental procedure for esterification:¹⁷³

In a 250 mL round bottom flask, were added carboxylic acid (1 equiv.) and catalytic amount of sulphuric acid in the ethanol. The resulting reaction mixture was refluxed overnight. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the reaction mixture was extracted with saturated solution of sodium bicarbonate (NaHCO₃) solution and ethyl acetate. The organic fraction was evaporated under vacuum and subjected for the purification by silica gel chromatography (*n*-hexane).

III) General experimental procedure for mono- and di-alkylation of ethyl 2-hydroxybenzoate:⁸⁴

In a 100 mL round bottom flask, were added ester (1 equiv.), dibromoalkanes (1.2 equiv.), and potassium carbonate (K₂CO₃) (1.3 equiv.) in acetonitrile. The solution was refluxed for 16-24 h. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the mixture of products (mono- and di-alkylated) was extracted in water and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane).

IV) General experimental procedure for alkylation of 2/3-hydroxy acetophenones or 2-hydroxybenzylalcohol or 2-(3-hydroxypropyl)phenol or 2-(2-hydroxyethyl)phenol with mono-bromo-ethyl-2-hydroxybenzoates:⁸⁴

In a 100 mL round bottom flask, added 2/3-hydroxy acetophenones or 2-hydroxy benzyl alcohol/ 2-hydroxy acetophenone/ 2-hydroxy benzophenone (1 equiv.), mono-bromo-ester (1 equiv.), and potassium carbonate (K₂CO₃) (1.5 equiv.) in acetonitrile. The solution was refluxed for 16-24 h. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the product was extracted in water and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane).

V) General experimental procedure for reduction of ketone using sodium borohydride:¹⁷⁴

In a 100 mL round bottom flask, were added ketone (1 equiv.) and sodium borohydride slowly (3 equiv.) in ethanol at 0 °C. The solution was stirred at room temperature overnight. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the reaction mixture was extracted in an aqueous saturated solution of ammonium chloride and ethyl acetate. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane).

VI) General experimental procedure for ring opening of various macrolactones using Ruthenium catalyst and hydrazine hydrate:¹⁶⁰

In a 25 mL long neck round bottom flask were added $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (0.15 equiv. (15 mol%)), ester (1 equiv.), and hydrazine hydrate in the presence of 1,4-dioxane as a solvent. The reaction mixture was refluxed at 120 °C in a preheated oil bath for 24 hrs. After completion of the reaction, the reaction mixture was diluted and extracted with ethyl acetate and water. Further, a volatile component was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (40-90% EtOAc: *n*-hexane).

VII) General experimental procedure for intramolecular ring closure of hydroxyalkylamides to macrolactam using 2.43% Ru-Zeolite catalyst via dehydrative *N*-alkylation of amides

In a 20 mL vial was added amide (0.08 mmol, 1 equiv.), in the presence of acetonitrile (2 mL, 0.05 M) as a solvent. Amides were dissolved by sonication, followed by heating in a water bath to get a clear solution. The resulting reaction mixture was flown using PTFE tubing through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with 2.43% Ru-Zeolite catalyst and heated at 120 °C. The progress of the reaction was monitored by the thin-layer chromatography technique. Further, a volatile component was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane).

A) General experimental procedure for 1 mmol Scale Reaction:

In a 25 mL RB flask was added amide **202e** (329 mg, 1 mmol, 1 equiv.), in the presence of acetonitrile (20 mL, 0.05M) as a solvent. Amide was dissolved by sonication followed by heating in water bath to get clear solution. The resulting reaction mixture was flown using PTFE tubing through Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with 2.43% Ru-Zeolite catalyst and heated at 120 °C. The progress of the reaction was monitored by the thin-layer chromatography technique. Further, a volatile component was

evaporated under a vacuum. The residue was directly purified by silica gel chromatography to afford 61% yield of **203e** (189 mg) (20% EtOAc in *n*-hexane).

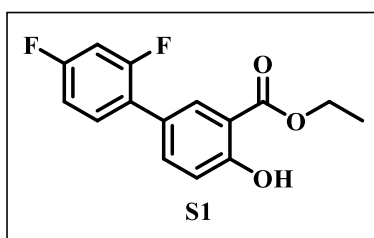
B) General experimental procedure for gram scale reaction:

In a 250 mL RB flask was added amide **202e** (2 gm, 6.06 mmol, 1 equiv.), in the presence of acetonitrile (122 mL, 0.05M) as a solvent. Amides were dissolved by sonication, followed by heating in a water bath to get a clear solution. The resulting reaction mixture was flowed using PTFE tubing through Omnifit® column reactor bed (10 mm bore x 150 mm length) loaded with 2.43% Ru-Zeolite catalyst and heated at 120 °C. The progress of the reaction was monitored by the thin-layer chromatography technique. Further, a volatile component was evaporated under a vacuum. The residue was directly purified by silica gel chromatography to afford 61% yield of **203e** (1.155 gm) (20% EtOAc in *n*-hexane).

5.8.3. Analytical Data of Compounds:

A) Characterization Data for Starting Materials:

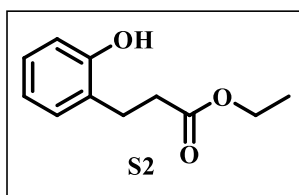
ethyl 2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylate (S1): Prepared according to



general procedure **5.8.2.II**, using 2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid (1.72 gm, 6.8 mmol, 1 equiv.), sulphuric acid (1.5 mL) in ethanol (50 mL) to afford desired ethyl 2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylate **S1** (1.6 gm, 84% yield) as a white solid compound

(isolated in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 10.93 (s, 1H), 7.98 (dd, *J* = 2.1, 1.2 Hz, 1H), 7.59 (dt, *J* = 8.6, 1.9 Hz, 1H), 7.37 (td, *J* = 8.7, 6.4 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.98 – 6.86 (m, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 170.1, 163.5 (d, *J* = 11.9 Hz), 161.4, 161.1 (d, *J* = 11.8), 160.9, 158.6, 158.5 (d, *J* = 11.8), 136.2, 136.1, 131.2 (dd, *J* = 9.4, 4.8), 130.2 (d, *J* = 2.7), 126.1, 124.4 (d, *J* = 3.9), 124.2 (d, *J* = 3.8), 117.9, 112.8, 111.8 (d, *J* = 3.8), 111.6 (d, *J* = 3.8), 104.7, 104.5 (m), 104.2, 61.7, 14.3. **IR** (neat): 2998, 2943, 1677, 1597, 1210, 1143 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₅H₁₃F₂O₃ 279.0833 found: 279.0829.

ethyl 3-(2-hydroxyphenyl)propanoate (S2): Prepared according to general procedure

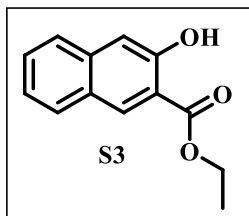


5.8.2.II, using 3-(2-hydroxyphenyl)propanoic acid (3 gm, 18 mmol, 1 equiv.), sulphuric acid (3 mL) in ethanol (80 mL) to afford desired ethyl 3-(2-hydroxyphenyl)propanoate **S2** (2.8 gm, 80% yield) as a white crystalline solid compound (isolated in 2% ethyl acetate in *n*-hexane).

¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, *J* = 1.4 Hz, 1H), 7.12 (m, 2H), 6.92 – 6.83 (m,

2H), 4.17 (q, $J = 7.1$ Hz, 2H), 2.96 (t, $J = 6.8$ Hz, 2H), 2.74 (t, $J = 6.9$ Hz, 2H), 1.26 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 175.4, 154.3, 130.4, 127.8, 127.2, 120.6, 116.6, 61.1, 34.9, 25.0, 14.0. IR (neat): 3342, 2970, 1723, 1462, 1304, 1118 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{15}\text{O}_3$, 195.1021 found: 195.1010.

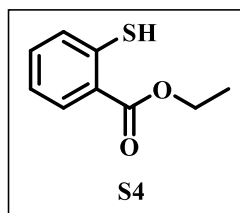
ethyl 3-hydroxy-2-naphthoate (S3): Prepared according to general procedure 5.8.2.II, using



3-hydroxy-2-naphthoic acid (3 gm, 16 mmol, 1 equiv.), sulphuric acid (3 mL) in ethanol (80 mL) to afford desired ethyl 3-hydroxy-2-naphthoate **S3** (3.2 gm, 93% yield) as a faint yellowish liquid compound (isolated in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 10.56 (d, $J = 0.8$ Hz, 1H), 8.46 (s, 1H), 7.78 (d, $J = 8.3$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 1H),

7.48 (t, $J = 7.6$ Hz, 1H), 7.34 – 7.28 (m, 2H), 4.46 (q, $J = 7.1, 3.6$ Hz, 2H), 1.47 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 169.9, 156.4, 137.9, 132.3, 129.2, 129.1, 127.0, 126.3, 123.8, 114.4, 111.6, 61.8, 14.2. IR (neat): 3229, 2993, 1680, 1514, 1284, 1143 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{O}_3$, 217.0864 found: 217.0852.

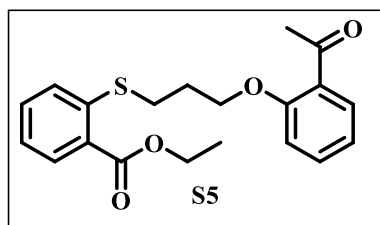
ethyl 2-mercaptobenzoate (S4): Prepared according to general procedure 5.8.2.II, using 2-



mercaptobenzoic acid (5 gm, 16 mmol, 1 equiv.), sulphuric acid (5 mL) in ethanol (80 mL) to afford desired ethyl 2-mercaptobenzoate **S4** (4.8 gm, 81% yield) as a colourless liquid compound (isolated in *n*-hexane).

^1H NMR (400 MHz, CDCl_3) δ 8.00 (d, $J = 7.9$ Hz, 1H), 7.31 – 7.24 (m, 2H), 7.17 – 7.08 (m, 1H), 4.70 (s, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 1.38 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 138.1, 132.3, 131.5, 130.8, 126.0, 124.5, 61.1, 14.2. IR (neat): 2995, 1703, 1256, 1060 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{S}$, 182.0480 found: 183.0293.

ethyl 2-((3-(2-acetylphenoxy)propyl)thio)benzoate (S5): Prepared according to general

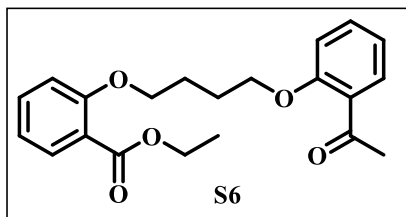


procedure 5.8.2.IV, using ethyl 2-((3-bromopropyl)thio)benzoate (287 mg, 1 mmol, 1 equiv.), 2-hydroxy acetophenone (136 mg, 1 mmol, 1 equiv.) and K_2CO_3 (217 mg, 1.5 mmol, 1.5 equiv.) to afford desired product ethyl 2-((3-(2-acetylphenoxy)propyl)thio)benzoate **S5** (100 mg,

28% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.97 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.72 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.47 – 7.40 (m, 2H), 7.34 (d, $J = 7.7$ Hz, 1H), 7.20 – 7.13 (m, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 6.94 (d, $J = 8.3$ Hz, 1H),

4.38 (q, $J = 7.1$ Hz, 2H), 4.23 (t, $J = 6.0$ Hz, 2H), 3.15 (t, $J = 7.1$ Hz, 2H), 2.62 (s, 3H), 2.28 (p, $J = 6.6$ Hz, 2H), 1.39 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 199.8, 166.6, 158.0, 140.9, 133.7, 132.4, 131.4, 130.5, 128.5, 128.4, 125.7, 124.2, 120.8, 112.4, 67.0, 61.3, 32.1, 28.8, 28.2, 14.4. IR (neat): 2930, 1715, 1600, 1204, 1150 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{NaO}_4\text{S}$, 381.1134 found: 381.1134.

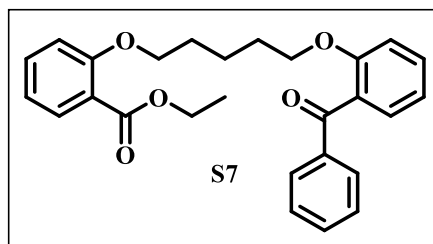
ethyl 2-(4-(2-acetylphenoxy)butoxy)benzoate (S6): Prepared according to general procedure



5.8.2.IV, using ethyl 2-(4-bromobutoxy)benzoate (752 mg, 2.5 mmol, 1 equiv.), 2-hydroxyacetophenone (340 mg, 2.5 mmol, 1 equiv.) and K_2CO_3 (518 mg, 3.75 mmol, 1.5 equiv.) to afford the desired product ethyl 2-(4-(2-acetylphenoxy)butoxy)benzoate **S6** (760 mg, 85% yield) as

a white solid compound (15% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.78 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.72 (dd, $J = 7.9, 1.8$ Hz, 1H), 7.43 (ddd, $J = 8.4, 7.5, 1.8$ Hz, 2H), 7.00 – 6.93 (m, 4H), 4.33 (q, $J = 7.1$ Hz, 2H), 4.15 (t, $J = 6.1$ Hz, 2H), 4.11 (t, $J = 5.8$ Hz, 2H), 2.62 (s, 3H), 2.12 (m, 2H), 2.08 – 1.99 (m, 2H), 1.35 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 199.90, 166.40, 158.41, 158.34, 133.72, 133.33, 131.62, 130.43, 128.34, 120.85, 120.54, 120.31, 113.08, 112.40, 68.18, 60.79, 32.12, 26.18, 14.43. IR (neat): 2928, 1710, 1650, 1587, 1210, 1145 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{NaO}_5$, 379.1521 found: 379.1523.

ethyl 2-((5-(2-benzoylphenoxy)pentyl)oxy)benzoate (S7): Prepared according to general

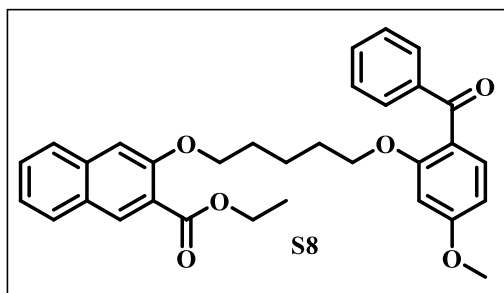


procedure **5.8.2.IV**, using ethyl 2-((5-bromopentyl)oxy)benzoate (480 mg, 1.5 mmol, 1 equiv.), (2-hydroxyphenyl)(phenyl)methanone (230 mg, 1.2 mmol, 1 equiv.) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv.) to afford desired product ethyl 2-((5-(2-benzoylphenoxy)pentyl)oxy)benzoate **S7** (395 mg, 60% yield) as a yellowish sticky liquid

(20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.81 – 7.72 (m, 3H), 7.48 – 7.39 (m, 4H), 7.36 (t, $J = 7.5$ Hz, 2H), 7.03 (t, $J = 7.5$ Hz, 1H), 6.95 (t, $J = 8.0$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 3.89 (t, $J = 6.1$ Hz, 2H), 3.83 (t, $J = 6.4$ Hz, 2H), 1.69 – 1.58 (m, 2H), 1.55 – 1.45 (m, 2H), 1.34 (t, $J = 7.1$ Hz, 3H), 1.27 – 1.15 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 196.8, 166.5, 158.4, 156.8, 138.4, 133.1, 132.5, 132.0, 131.4, 129.6, 129.4, 129.0, 128.1, 120.7, 120.5, 120.0, 113.0, 112.1, 68.4, 67.9, 60.6, 28.6, 28.5, 22.1,

14.3. **IR** (neat): 2994, 1717, 1663, 1593, 1485, 1246, 1077 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{28}\text{NaO}_5$, 455.1834 found: 455.1830.

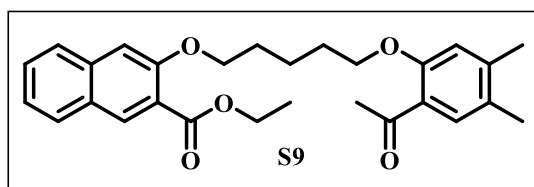
ethyl 3-((5-(2-benzoyl-5-methoxyphenoxy)pentyl)oxy)-2-naphthoate (S8): Prepared



according to general procedure 5.8.2.IV, using ethyl 3-((5-bromopentyl)oxy)-2-naphthoate (365 mg, 1 mmol, 1 equiv.), (2-hydroxy-4-methoxyphenyl)(phenyl)methanone (198 mg, 1 mmol, 1 equiv.) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv.) to afford desired product ethyl 3-((5-(2-benzoyl-5-methoxyphenoxy)pentyl)oxy)-2-naphthoate **S8** (302 mg, 59% yield) as a colourless

oily compound (20% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.26 (s, 1H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.76 – 7.70 (m, 3H), 7.54 – 7.45 (m, 2H), 7.43 – 7.39 (m, 1H), 7.39 – 7.37 (m, 1H), 7.37 – 7.33 (m, 2H), 7.13 (s, 1H), 6.56 (dd, $J = 8.5, 2.2$ Hz, 1H), 6.47 (d, $J = 2.2$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.95 (t, $J = 6.5$ Hz, 2H), 3.91 – 3.83 (m, 5H), 1.76 – 1.66 (m, 2H), 1.54 – 1.46 (m, 2H), 1.40 (t, $J = 7.1$ Hz, 3H), 1.29 – 1.18 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 196.2, 166.6, 163.6, 159.1, 155.1, 139.6, 136.1, 132.4, 132.2, 132.1, 129.4, 128.7, 128.3, 128.0, 127.6, 126.5, 124.3, 122.7, 121.9, 107.6, 105.0, 99.3, 68.4, 68.1, 61.1, 55.6, 28.7, 28.6, 22.3, 14.4. **IR** (neat): 2927, 2859, 1721, 1599, 1500, 1202 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{33}\text{O}_6$, 513.2277 found: 513.2270

ethyl 3-((5-(2-acetyl-4,5-dimethylphenoxy)pentyl)oxy)-2-naphthoate (S9): Prepared

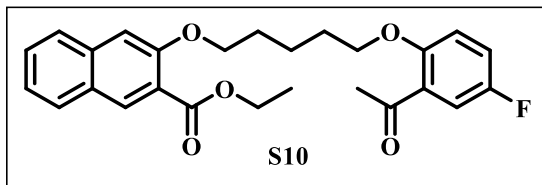


according to general procedure 5.8.2.IV, using ethyl 3-((5-bromopentyl)oxy)-2-naphthoate (365 mg, 1 mmol, 1 equiv.), 1-(2-hydroxy-4,5-dimethylphenyl)ethan-1-one (164 mg, 1 mmol, 1

equiv.) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv.) to afford desired product ethyl 3-((5-(2-acetyl-4,5-dimethylphenoxy)pentyl)oxy)-2-naphthoate **S9** (186 mg, 42% yield) as a colourless liquid (20% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.26 (s, 1H), 7.80 (d, $J = 8.2$ Hz, 1H), 7.71 (d, $J = 8.2$ Hz, 1H), 7.49 (t, $J = 7.5$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 1H), 7.19 (s, 2H), 7.12 (s, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 4.15 (t, $J = 6.3$ Hz, 2H), 3.79 (t, $J = 6.6$ Hz, 2H), 2.61 (s, 3H), 2.28 (d, $J = 1.9$ Hz, 6H), 2.01 – 1.92 (m, 2H), 1.92 – 1.84 (m, 2H), 1.78 – 1.68 (m, 2H), 1.41 (t, $J = 7.1$ Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 201.8, 166.6, 155.1, 154.3, 136.1, 135.5, 133.6, 133.3, 132.4, 131.9, 128.7, 128.2, 127.6, 127.5, 126.4, 124.3, 122.7, 107.6, 75.0, 68.5, 61.1, 31.9, 30.6, 30.1, 29.1, 22.7, 20.6, 16.1, 14.4, 14.2. **IR** (neat): 2942, 1722, 1689,

1595, 1263, 1212 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{32}\text{NaO}_5$, 471.2147 found: 471.2144.

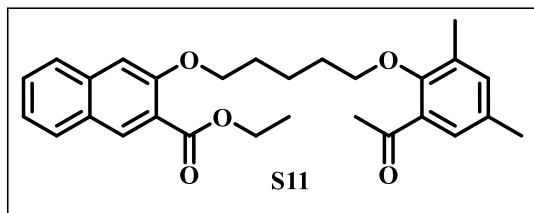
ethyl 3-((5-(2-acetyl-4-fluorophenoxy)pentyl)oxy)-2-naphthoate (S10): Prepared



according to general procedure **5.8.2.IV**, using ethyl 3-((5-bromopentyl)oxy)-2-naphthoate (548 mg, 1.5 mmol, 1 equiv.), 1-(4-fluoro-2-hydroxyphenyl)ethan-1-one (232 mg, 1.5 mmol, 1 equiv.) and K_2CO_3 (311 mg, 2.25 mmol, 1.5 equiv.) to afford desired product ethyl 3-((5-(2-acetyl-4-fluorophenoxy)pentyl)oxy)-2-naphthoate **S10** (590 mg, 89% yield) as a yellowish liquid (20% ethyl acetate in *n*-hexane).

^1H NMR (400 MHz, CDCl_3) δ 8.27 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.45 (dd, J = 9.0, 3.3 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.18 (s, 1H), 7.13 (ddd, J = 9.1, 7.4, 3.3 Hz, 1H), 6.89 (dd, J = 9.1, 4.1 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 4.16 (t, J = 6.2 Hz, 2H), 4.07 (t, J = 6.4 Hz, 2H), 2.63 (s, 3H), 2.05 – 1.91 (m, 4H), 1.83 – 1.73 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 198.4, 166.4, 157.9, 155.5, 155.1, 154.7 (d, J = 1.8), 136.1, 132.5, 129.1, 129.0, 128.7, 128.3, 127.6, 126.5, 124.4, 122.6, 120.2, 120.0 (d, J = 23.4), 116.7, 116.5 (d, J = 24), 113.8, 113.6 (d, J = 7.8), 107.7, 69.1, 68.4, 61.1, 32.0, 29.1, 28.9, 23.0, 14.4. **IR** (neat): 2945, 1709, 1685, 1595, 1220, 1185 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{27}\text{FNaO}_5$, 461.1740 found: 461.1742.

ethyl 3-((5-(2-acetyl-4,6-dimethylphenoxy)pentyl)oxy)-2-naphthoate (S11): Prepared

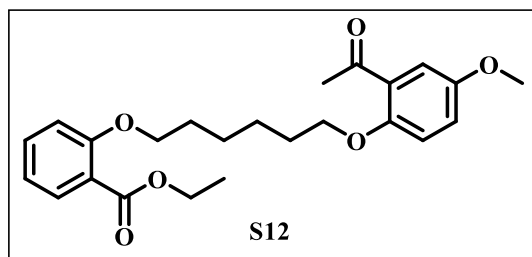


according to general procedure **5.8.2.IV**, using ethyl 3-((5-bromopentyl)oxy)-2-naphthoate (731 mg, 2 mmol, 1 equiv.), 1-(2-hydroxy-4,6-dimethylphenyl)ethan-1-one (269 mg, 2 mmol, 1 equiv.) and K_2CO_3 (415 mg, 3 mmol, 1.5 equiv.)

to afford desired product ethyl 3-((5-(2-acetyl-4,6-dimethylphenoxy)pentyl)oxy)-2-naphthoate **S11** (290 mg, 32% yield) as a colourless oily compound (20% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.26 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.39 – 7.33 (m, 1H), 7.19 (d, J = 3.6 Hz, 2H), 7.12 (d, J = 1.5 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.15 (t, J = 6.3 Hz, 2H), 3.78 (t, J = 6.6 Hz, 2H), 2.61 (s, 3H), 2.28 (d, J = 2.3 Hz, 6H), 2.02 – 1.92 (m, 2H), 1.92 – 1.83 (m, 2H), 1.79 – 1.68 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 201.8, 166.6, 155.1, 154.3, 136.1, 135.5, 133.6, 133.3, 132.4, 131.9, 128.7, 128.2, 127.6, 127.5, 126.4, 124.3, 122.7, 107.6, 75.0, 68.5, 61.1,

30.6, 30.1, 29.1, 22.7, 20.6, 16.1, 14.4. **IR** (neat): 2995, 2941, 1721, 1631, 1596, 1265, 1210 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{32}\text{NaO}_5$, 471.2147 found: 471.2148.

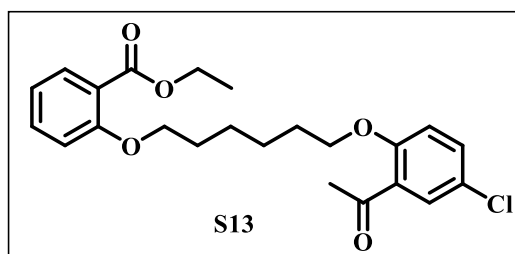
ethyl 2-((6-(2-acetyl-4-methoxyphenoxy)hexyl)oxy)benzoate (S12): Prepared according to



general procedure **5.8.2.IV**, using ethyl 2-((6-bromohexyl)oxy)benzoate (493 mg, 1.5 mmol, 1 equiv.), 1-(2-hydroxy-5-methoxyphenyl)ethan-1-one (250 mg, 1.5 mmol, 1 equiv.) and K_2CO_3 (311 mg, 2.25 mmol, 1.5 equiv.) to afford desired

product ethyl 2-((6-(2-acetyl-4-methoxyphenoxy)hexyl)oxy)benzoate **S12** (502 mg, 81% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 7.75 (dd, J = 7.6, 1.7 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.27 (d, J = 3.2 Hz, 1H), 6.98 (dd, J = 9.0, 3.2 Hz, 1H), 6.93 (t, J = 8.4 Hz, 2H), 6.87 (d, J = 9.0 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.01 (q, J = 6.5 Hz, 4H), 3.76 (s, 3H), 2.61 (s, 3H), 1.93 – 1.78 (m, 4H), 1.64 – 1.50 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 199.4, 166.5, 158.4, 153.2, 153.0, 133.2, 131.5, 128.3, 120.8, 120.4, 120.0, 113.9, 113.7, 113.1, 68.9, 68.5, 60.7, 55.8, 32.1, 29.3, 29.1, 25.9, 25.7, 14.3. **IR** (neat): 2941, 1717, 1680, 1597, 1489, 1244 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{30}\text{NaO}_6$, 437.1939 found: 437.1935.

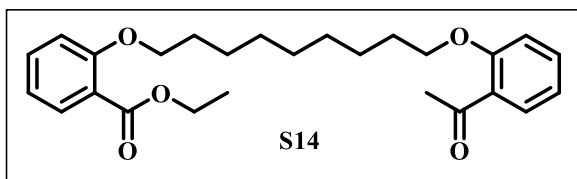
ethyl 2-((6-(2-acetyl-4-chlorophenoxy)hexyl)oxy)benzoate (S13): Prepared according to



general procedure **5.8.2.IV**, using ethyl 2-((6-bromohexyl)oxy)benzoate (658 mg, 2 mmol, 1 equiv.), 1-(5-chloro-2-hydroxyphenyl)ethan-1-one (342 mg, 2 mmol, 1 equiv.) and K_2CO_3 (415 mg, 3 mmol, 1.5 equiv.) to afford desired product ethyl 2-

((6-(2-acetyl-4-chlorophenoxy)hexyl)oxy)benzoate **S13** (540 mg, 64% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 7.76 (dd, J = 7.7, 1.7 Hz, 1H), 7.69 (d, J = 2.7 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.36 (dd, J = 8.8, 2.8 Hz, 1H), 6.99 – 6.91 (m, 2H), 6.88 (d, J = 8.9 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.04 (td, J = 6.3, 4.4 Hz, 4H), 2.59 (s, 3H), 1.93 – 1.82 (m, 4H), 1.65 – 1.50 (m, 4H), 1.35 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 198.4, 166.5, 158.5, 157.1, 133.3, 133.2, 131.6, 130.1, 129.3, 125.8, 120.8, 120.1, 113.9, 113.1, 68.9, 68.6, 60.8, 32.0, 29.1, 29.1, 25.9, 25.7, 14.4. **IR** (neat): 2943, 1655, 1586, 1232, 921 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{27}\text{ClNaO}_5$, 441.1445 found: 441.2065.

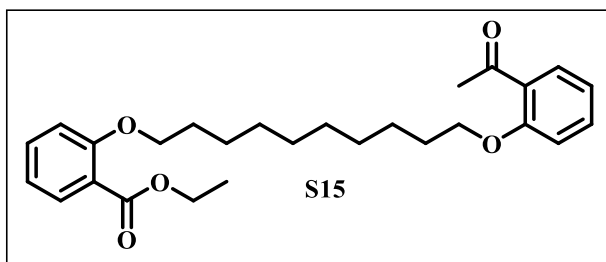
ethyl 2-((9-(2-acetylphenoxy)nonyl)oxy)benzoate (S14): Prepared according to general



procedure **5.8.2.IV**, using ethyl 2-((9-bromononyl)oxy)benzoate (371 mg, 1 mmol, 1 equiv.), 2-hydroxyacetophenone (136 mg, 1 mmol, 1 equiv.) and K_2CO_3 (207 mg, 1.5

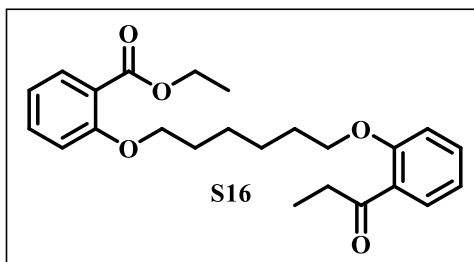
mmol, 1.5 equiv.) to afford desired product ethyl 2-((9-(2-acetylphenoxy)nonyl)oxy)benzoate **S14** (405 mg, 95% yield) as a colourless liquid (20% ethyl acetate in *n*-hexane). 1H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.70 (m, 2H), 7.41 (ddd, J = 13.4, 4.5, 1.0 Hz, 2H), 6.98 – 6.89 (m, 4H), 4.34 (q, J = 7.1 Hz, 2H), 4.06 – 3.97 (m, 4H), 2.62 (s, 3H), 1.89 – 1.77 (m, 4H), 1.55 – 1.43 (m, 4H), 1.36 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 166.7, 158.5, 158.5, 133.6, 133.2, 131.5, 130.4, 128.2, 120.8, 120.3, 120.0, 113.1, 112.3, 68.8, 68.5, 60.7, 32.1, 29.4, 29.3, 29.2, 26.2, 26.0, 14.3. IR (neat): 2935, 2857, 1679, 1594, 1243 cm^{-1} . HRMS (ESI-TOF) m/z : $[M+Na]^+$ calcd for $C_{26}H_{34}NaO_5$, 449.2303 found: 449.2303.

ethyl 2-((10-(2-acetylphenoxy)decyl)oxy)benzoate (S15): Prepared according to general



procedure **5.8.2.IV**, using ethyl 2-((10-bromodecyl)oxy)benzoate (385 mg, 1 mmol, 1 equiv.), 2-hydroxyacetophenone (136 mg, 1 mmol, 1 equiv.) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv.) to afford desired product ethyl 2-((10-(2-

acetylphenoxy)decyl)oxy)benzoate **S15** (290 mg, 66% yield) as a colourless liquid (20% ethyl acetate in *n*-hexane). 1H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.71 (m, 2H), 7.42 (tdd, J = 7.6, 5.8, 1.8 Hz, 2H), 6.99 – 6.90 (m, 4H), 4.35 (q, J = 7.1 Hz, 2H), 4.07 – 3.98 (m, 4H), 2.63 (s, 3H), 1.89 – 1.78 (m, 4H), 1.48 (d, J = 5.0 Hz, 4H), 1.36 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 166.8, 158.6, 158.5, 133.7, 133.2, 131.5, 130.4, 128.3, 120.9, 120.4, 120.0, 113.1, 112.3, 68.9, 68.5, 60.8, 32.1, 29.5, 29.5, 29.4, 29.4, 29.3, 26.3, 26.0, 14.4. IR (neat): 2934, 2857, 1709, 1679, 1596, 1242 cm^{-1} . HRMS (ESI-TOF) m/z : $[M+Na]^+$ calcd for $C_{27}H_{36}NaO_5$, 463.2460 found: 463.2465.

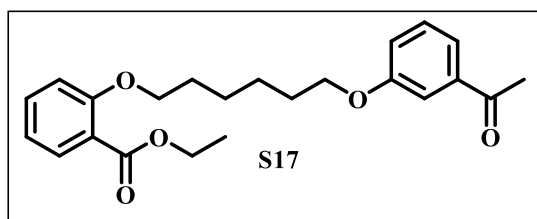


ethyl 2-((6-(2-propionylphenoxy)hexyl)oxy)benzoate (S16):

Prepared according to general procedure **5.8.2.IV**, using ethyl 2-((6-bromohexyl)oxy)benzoate (329 mg, 1 mmol, 1 equiv.), 1-(2-hydroxyphenyl)propan-1-one

(150 mg, 1 mmol, 1 equiv.) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv.) to afford desired product ethyl 2-((6-(2-propionylphenoxy)hexyl)oxy)benzoate **S16** (343 mg, 64% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.76 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.66 (dd, $J = 7.7$, 1.7 Hz, 1H), 7.40 (td, $J = 7.8$, 1.7 Hz, 2H), 7.02 – 6.89 (m, 4H), 4.32 (q, $J = 7.1$ Hz, 2H), 4.04 (q, $J = 6.2$ Hz, 4H), 2.99 (q, $J = 7.3$ Hz, 2H), 1.97 – 1.80 (m, 4H), 1.66 – 1.50 (m, 4H), 1.35 (t, $J = 7.1$ Hz, 3H), 1.15 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 203.6, 166.5, 158.4, 158.0, 133.2, 133.1, 131.5, 130.2, 128.5, 120.8, 120.4, 120.0, 113.1, 112.2, 68.6, 68.3, 60.7, 37.1, 29.1, 25.9, 25.7, 14.3, 8.6. IR (neat): 2934, 1824, 1678, 1590, 1488, 1249, 1181 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{30}\text{NaO}_5$, 421.1990 found: 421.1989.

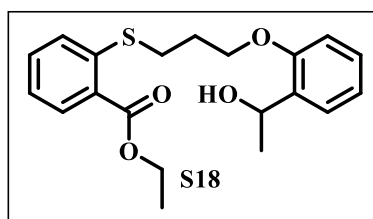
ethyl 2-((6-(3-acetylphenoxy)hexyl)oxy)benzoate (S17): Prepared according to general



procedure **5.8.2.IV**, using ethyl ethyl 2-((6-bromohexyl)oxy)benzoate (286 mg, 0.87 mmol, 1 equiv.), 3-hydroxyacetophenone (118 mg, 0.87 mmol, 1 equiv.) and K_2CO_3 (182 mg, 1.32 mmol, 1.5 equiv.) to afford desired product ethyl 2-((6-

(3-acetylphenoxy)hexyl)oxy)benzoate **S17** (192 mg, 57% yield) as a colourless liquid (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.75 (dd, $J = 7.8$, 1.4 Hz, 1H), 7.50 (d, $J = 7.6$ Hz, 1H), 7.46 (s, 1H), 7.43 – 7.37 (m, 1H), 7.33 (t, $J = 7.9$ Hz, 1H), 7.11 – 7.05 (m, 1H), 6.94 (dd, $J = 11.1$, 4.4 Hz, 2H), 4.32 (q, $J = 7.1$ Hz, 2H), 4.01 (dd, $J = 14.7$, 6.5 Hz, 4H), 2.56 (s, 3H), 1.84 (tt, $J = 13.0$, 6.5 Hz, 4H), 1.63 – 1.50 (m, 4H), 1.35 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 198.0, 166.6, 159.3, 158.4, 138.4, 133.2, 131.5, 129.5, 120.9, 120.8, 120.0, 119.9, 113.1, 113.1, 68.6, 68.0, 60.7, 29.1, 29.1, 26.7, 25.8, 14.3. IR (neat): 2993, 2940, 1819, 1686, 1591, 1485, 1254 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{NaO}_5$, 407.1834 found: 407.1831.

ethyl 2-((3-(2-(1-hydroxyethyl)phenoxy)propyl)thio)benzoate (S18): Prepared according to

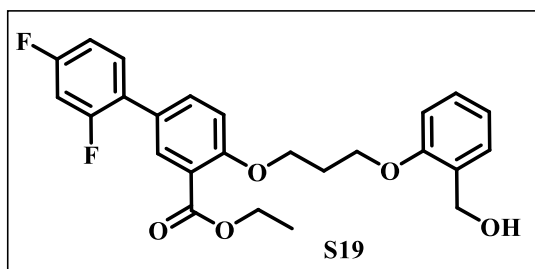


the general procedure **5.8.2.V**, using ethyl 2-((3-(2-acetylphenoxy)propyl)thio)benzoate (300 mg, 0.083 mmol, 1 equiv.), sodium borohydride (93 mg, 2.5 mmol, 3 equiv.) to afford the desired product ethyl 2-((3-(2-(1-

hydroxyethyl)phenoxy)propyl)thio)benzoate **S18** (250 mg, 82% yield) as colourless sticky compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.97 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.38 (dd, $J = 7.5$, 1.5 Hz,

1H), 7.35 (d, $J = 7.5$ Hz, 1H), 7.21 (td, $J = 8.0, 1.7$ Hz, 1H), 7.18 – 7.14 (m, 1H), 6.96 (td, $J = 7.5, 0.6$ Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 5.17 (q, $J = 6.5$ Hz, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 4.15 (t, $J = 5.8$ Hz, 2H), 3.13 (t, $J = 7.2$ Hz, 2H), 2.61 (s, 1H), 2.28 – 2.19 (m, 2H), 1.50 (d, $J = 6.5$ Hz, 3H), 1.39 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 155.4, 141.1, 133.7, 132.3, 131.3, 128.2, 128.2, 126.0, 125.5, 124.0, 121.0, 111.2, 66.4, 66.0, 61.2, 28.7, 28.2, 23.2, 14.3. **IR** (neat): 3541, 2985, 1703, 1594, 1452, 1238 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{NaO}_4\text{S}$, 383.1292 found: 383.1291.

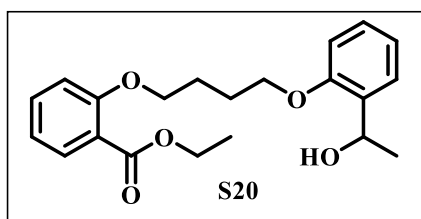
ethyl 2',4'-difluoro-4-(3-(2-(hydroxymethyl)phenoxy)propoxy)-[1,1'-biphenyl]-3-



carboxylate (S19): Prepared according to general procedure **5.8.2.IV**, using ethyl 2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylate (500 mg, 1.8 mmol, 1 equiv.), ethyl 2-(3-bromopropoxy)benzoate (300 mg, 1 mmol, 2 equiv.) and K_2CO_3 (373 mg, 2.7 mmol, 1.5

equiv.) to afford desired product ethyl 2',4'-difluoro-4-(3-(2-(hydroxymethyl)phenoxy)propoxy)-[1,1'-biphenyl]-3-carboxylate **S19** (770 mg, 96% yield) as a colourless oily compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, $J = 1.2$ Hz, 1H), 7.61 – 7.54 (m, 1H), 7.36 (td, $J = 8.7, 6.5$ Hz, 1H), 7.31 – 7.21 (m, 2H), 7.04 (d, $J = 8.7$ Hz, 1H), 6.97 – 6.83 (m, 4H), 4.68 (d, $J = 5.2$ Hz, 2H), 4.37 – 4.31 (m, 2H), 4.30 – 4.23 (m, 4H), 2.47 (s, 1H), 2.34 (p, $J = 5.9$ Hz, 2H), 1.34 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.1, 163.5, 163.4 (d, $J = 11.8$), 161.0 (dd, $J = 11.8, 3.9$), 160.9, 160.9, 158.5, 158.4 (d, $J = 11.9$), 157.9, 156.6, 133.7 (d, $J = 3.3$), 132.0 (d, $J = 2.2$), 131.2 (dd, $J = 9.4, 4.8$), 129.3, 128.9, 128.7, 127.2, 124.1 (d, $J = 3.9$), 124.0 (d, $J = 3.8$), 120.9, 120.8, 113.3, 111.7 (d, $J = 3.7$), 111.5 (d, $J = 3.8$), 111.3, 104.4 (m), 65.5, 64.5, 61.8, 61.0, 29.3, 14.3. **IR** (neat): 3503, 2992, 2945, 1705, 1605, 1242, 1153, 973 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{24}\text{F}_2\text{NaO}_5$, 465.1489 found: 465.1478.

ethyl 2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzoate (S20): Prepared according to the

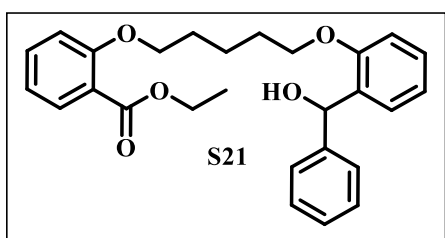


general procedure **5.8.2.V**, using ethyl 2-(4-(2-acetylphenoxy)butoxy)benzoate (600 mg, 1.68 mmol, 1 equiv.), sodium borohydride (192 mg, 5 mmol, 3 equiv.) to afford the desired product ethyl 2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzoate **S20** (310 mg,

51% yield) as colourless liquid compound (25% ethyl acetate in *n*-hexane). ^1H NMR (400

MHz, CDCl₃) δ 7.79 (dd, J = 7.7, 1.8 Hz, 1H), 7.43 (td, J = 8.4, 1.8 Hz, 1H), 7.36 (dd, J = 7.5, 1.5 Hz, 1H), 7.22 (td, J = 8.0, 1.6 Hz, 1H), 7.00 – 6.92 (m, 3H), 6.88 (d, J = 8.2 Hz, 1H), 5.12 (q, J = 6.5 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 4.11 (dd, J = 10.6, 5.4 Hz, 4H), 2.97 – 2.52 (s, 1H), 2.13 – 2.00 (m, 4H), 1.49 (d, J = 6.5 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.5, 158.3, 155.8, 133.6, 133.3, 131.6, 128.2, 126.0, 120.8, 120.7, 120.2, 113.1, 111.2, 68.2, 67.5, 66.3, 60.8, 26.1, 26.1, 23.1, 14.4. **IR** (neat): 3510, 2980, 1715, 1600, 1204, 1150 cm⁻¹. **HRMS** (ESI-TOF) m/z : [M+Na]⁺ calcd for C₂₁H₂₆NaO₅, 381.1677 found: 381.1674.

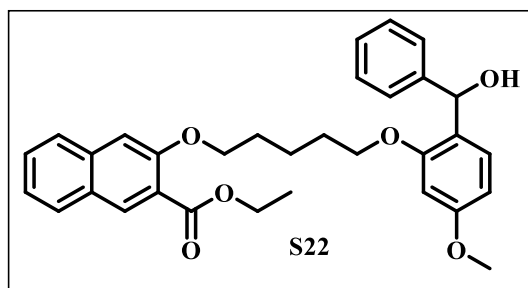
ethyl 2-((5-(2-(hydroxy(phenyl)methyl)phenoxy)pentyl)oxy)benzoate (S21): Prepared



according to the general procedure 5.8.2.V, using ethyl 2-((5-(2-benzoylphenoxy)pentyl)oxy)benzoate (360 mg, 0.83 mmol, 1 equiv.), sodium borohydride (95 mg, 2.5 mmol, 3 equiv.) to afford the desired product ethyl 2-((5-(2-(hydroxy(phenyl)methyl)phenoxy)pentyl)oxy)

benzoate **S21** (275 mg, 76% yield) as yellowish liquid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.76 (dd, J = 7.7, 1.4 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.31 – 7.15 (m, 5H), 6.94 (dd, J = 15.3, 7.9 Hz, 3H), 6.84 (d, J = 8.1 Hz, 1H), 6.04 (d, J = 3.5 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.01 – 3.92 (m, 4H), 3.21 (s, 1H), 1.87 – 1.73 (m, 4H), 1.59 – 1.48 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.6, 158.5, 156.1, 143.7, 133.3, 132.1, 131.6, 128.7, 128.1, 127.9, 127.1, 126.6, 120.8, 120.7, 120.1, 113.1, 111.5, 72.4, 68.5, 67.8, 60.8, 28.9, 28.9, 22.6, 14.4. **IR** (neat): 3502, 2994, 2943, 1696, 1594, 1246, 1178 cm⁻¹. **HRMS** (ESI-TOF) m/z : [M+Na]⁺ calcd for C₂₇H₃₀NaO₅, 457.1990 found: 457.1985.

ethyl 3-((5-(2-(hydroxy(phenyl)methyl)-5-methoxyphenoxy)pentyl)oxy)-2-naphthoate (S22): Prepared according to the general

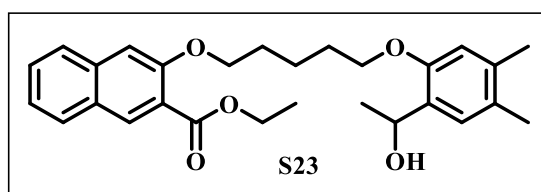


procedure 5.8.2.V, using ethyl 3-((5-(2-benzoyl-5-methoxyphenoxy)pentyl)oxy)-2-naphthoate (270 mg, 0.52 mmol, 1 equiv.), sodium borohydride (60 mg, 1.58 mmol, 3 equiv.) to afford the desired product ethyl 3-((5-(2-(hydroxy(phenyl)methyl)-

5-methoxyphenoxy)pentyl)oxy)-2-naphthoate **S22** (225 mg, 83% yield) as colourless oily compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.51 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.42 – 7.34

(m, 3H), 7.32 – 7.25 (m, 2H), 7.23 – 7.10 (m, 3H), 6.45 (dd, $J = 6.7, 2.3$ Hz, 2H), 6.01 (d, $J = 4.0$ Hz, 1H), 4.39 (q, $J = 7.1$ Hz, 2H), 4.09 (t, $J = 6.3$ Hz, 2H), 4.04 – 3.91 (m, 2H), 3.78 (s, 3H), 3.09 (s, 1H), 1.95 – 1.86 (m, 2H), 1.85 – 1.76 (m, 2H), 1.59 (m, 2H), 1.40 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 160.4, 157.2, 155.1, 144.0, 136.1, 132.5, 128.7, 128.7, 128.3, 128.1, 127.6, 127.0, 126.5, 126.5, 124.9, 124.3, 122.6, 107.6, 104.2, 99.5, 72.0, 68.4, 67.9, 61.1, 55.4, 28.9, 28.8, 22.7, 14.4. IR (neat): 3503, 2993, 2942, 1711, 1600, 1501, 1266, 1201 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{32}\text{H}_{34}\text{NaO}_6$, 537.2252 found: 537.2247.

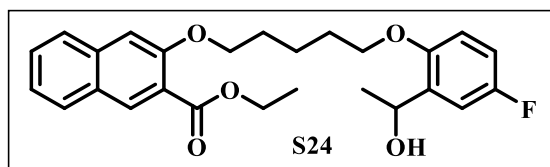
ethyl 3-((5-(2-(1-hydroxyethyl)-4,5-dimethylphenoxy)pentyl)oxy)-2-naphthoate (S23):



Prepared according to the general procedure 5.8.2.V, using ethyl 3-((5-(2-acetyl-4,5-dimethylphenoxy)pentyl)oxy)-2-naphthoate (120 mg, 0.27 mmol, 1 equiv.), sodium

borohydride (86 mg, 2.25 mmol, 3 equiv.) to afford the desired product ethyl 3-((5-(2-(1-hydroxyethyl)-4,5-dimethylphenoxy)pentyl)oxy)-2-naphthoate **S23** (105 mg, 87% yield) as colourless liquid compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (s, 1H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 1H), 7.53 – 7.47 (m, 1H), 7.40 – 7.33 (m, 1H), 7.20 (s, 1H), 7.08 (d, $J = 1.5$ Hz, 1H), 6.91 (s, 1H), 5.19 (q, $J = 6.4$ Hz, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 4.18 (t, $J = 6.3$ Hz, 2H), 3.84 (td, $J = 6.4, 3.9$ Hz, 2H), 2.43 (d, $J = 10.9$ Hz, 1H), 2.28 (s, 3H), 2.26 (s, 3H), 2.00 (dd, $J = 14.3, 7.2$ Hz, 2H), 1.96 – 1.87 (m, 2H), 1.83 – 1.73 (m, 2H), 1.50 (d, $J = 6.5$ Hz, 3H), 1.42 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 155.1, 152.5, 138.0, 136.1, 133.7, 132.5, 131.2, 130.8, 128.7, 128.3, 127.6, 126.5, 124.4, 124.3, 122.7, 107.7, 73.5, 68.6, 65.1, 61.2, 30.2, 29.2, 23.9, 22.9, 21.0, 16.3, 14.4. IR (neat): 3502, 2928, 1710, 1631, 1459, 1266, 1208 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{34}\text{NaO}_5$, 473.2303 found: 473.2296.

ethyl 3-((5-(4-fluoro-2-(1-hydroxyethyl)phenoxy)pentyl)oxy)-2-naphthoate (S24):

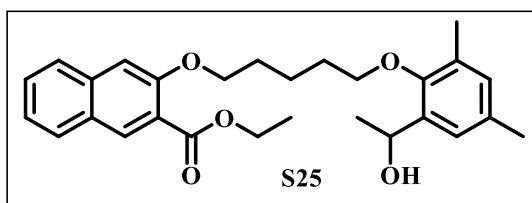


Prepared according to the general procedure 5.8.2.V, using ethyl 3-((5-(2-acetyl-4-fluorophenoxy)pentyl)oxy)-2-naphthoate (500 mg, 1.14 mmol, 1 equiv.), sodium borohydride

(130 mg, 3.42 mmol, 3 equiv.) to afford the desired product ethyl 3-((5-(4-fluoro-2-(1-hydroxyethyl)phenoxy)pentyl)oxy)-2-naphthoate **S24** (445 mg, 88% yield) as colourless sticky liquid compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.26 (s, 1H),

7.81 (d, $J = 8.1$ Hz, 1H), 7.71 (d, $J = 8.2$ Hz, 1H), 7.53 – 7.46 (m, 1H), 7.39 – 7.33 (m, 1H), 7.18 (s, 1H), 7.11 (dd, $J = 9.2, 3.1$ Hz, 1H), 6.87 (td, $J = 8.4, 3.1$ Hz, 1H), 6.76 (dd, $J = 8.9, 4.4$ Hz, 1H), 5.12 (q, $J = 6.4$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 4.16 (t, $J = 6.2$ Hz, 2H), 4.01 (td, $J = 6.3, 3.3$ Hz, 2H), 2.70 (s, 1H), 2.03 – 1.86 (m, 4H), 1.80 – 1.70 (m, 2H), 1.46 (d, $J = 6.5$ Hz, 3H), 1.41 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 158.5, 156.1, 155.1, 151.8, 151.8, 136.1, 135.8 (d, $J = 6.4$), 132.5, 128.7, 128.3, 127.6, 126.5, 124.4, 122.6, 113.9, 113.7, 113.2, 113.0, 112.1 (d, $J = 8$), 107.6, 68.4, 68.4, 65.7, 61.1, 29.1, 28.9, 23.1, 22.9, 14.4. IR (neat): 3479, 2991, 1704, 1632, 1260, 1198 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{29}\text{FNaO}_5$, 463.1896 found: 463.1895.

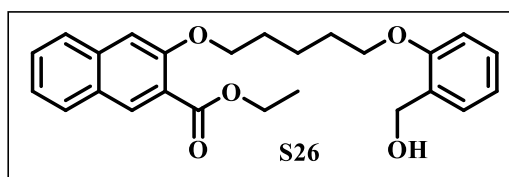
ethyl 3-((5-(2-(1-hydroxyethyl)-4,6-dimethylphenoxy)pentyl)oxy)-2-naphthoate (S25):



Prepared according to the general procedure 5.8.2.V, using ethyl 3-((5-(2-acetyl-4,6-dimethylphenoxy)pentyl)oxy)-2-naphthoate (260 mg, 0.58 mmol, 1 equiv.), sodium borohydride (66 mg, 1.74 mmol, 3 equiv.) to

afford the desired product ethyl 3-((5-(2-(1-hydroxyethyl)-4,6-dimethylphenoxy)pentyl)oxy)-2-naphthoate **S25** (170 mg, 65% yield) as colourless oily compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (s, 1H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 1H), 7.50 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 7.36 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 7.20 (s, 1H), 7.08 (d, $J = 1.6$ Hz, 1H), 6.91 (d, $J = 1.4$ Hz, 1H), 5.19 (q, $J = 6.4$ Hz, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 4.18 (t, $J = 6.3$ Hz, 2H), 3.85 (m, 2H), 2.50 (s, 1H), 2.29 (s, 3H), 2.26 (s, 3H), 2.04 – 1.88 (m, 4H), 1.78 (m, 2H), 1.50 (d, $J = 6.5$ Hz, 3H), 1.42 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 155.1, 152.5, 138.0, 136.1, 133.6, 132.4, 131.1, 130.7, 128.7, 128.3, 127.6, 126.5, 124.4, 124.3, 122.7, 107.7, 73.5, 68.5, 65.0, 61.1, 30.2, 29.1, 23.9, 22.9, 21.0, 16.3, 14.4. IR (neat): 3505, 2932, 1712, 1640, 1485, 1250, 1190 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{34}\text{NaO}_5$, 473.2303 found: 473.2296.

ethyl 3-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoate (S26):

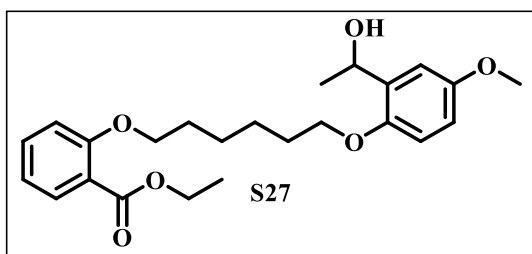


according to general procedure 5.8.2.IV, using ethyl 3-((5-bromopentyl)oxy)-2-naphthoate (731 mg, 2 mmol, 1 equiv.), 2-hydroxy benzyl alcohol (248 mg, 1 mmol, 2 equiv.) and K_2CO_3 (415 mg, 3

mmol, 1.5 equiv.) to afford desired product ethyl 3-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoate **S26** (725 mg, 88% yield) as a colourless

oily compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.50 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.36 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.29 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.18 (s, 1H), 6.93 (td, *J* = 7.5, 0.8 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 4.71 (d, *J* = 3.2 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.16 (t, *J* = 6.3 Hz, 2H), 4.07 (t, *J* = 6.3 Hz, 2H), 2.52 (s, 1H), 2.03 – 1.88 (m, 4H), 1.76 (m, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.6, 156.9, 155.1, 136.1, 132.4, 129.3, 128.9, 128.7, 128.7, 128.3, 127.6, 126.5, 124.3, 122.6, 120.6, 111.1, 107.6, 68.4, 67.8, 62.1, 61.1, 29.1, 28.9, 22.9, 14.4. **IR** (neat): 3519, 2929, 2860, 1704, 1595, 1239 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₅H₂₈NaO₅, 431.1834 found: 431.1829.

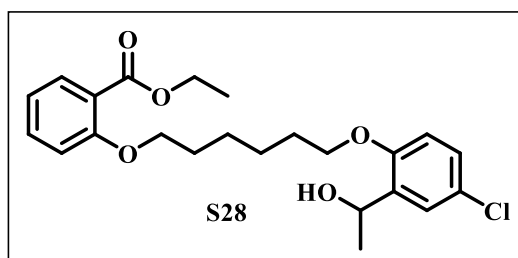
ethyl 2-((6-(2-(1-hydroxyethyl)-4-methoxyphenoxy)hexyl)oxy)benzoate (S27): Prepared



according to the general procedure 5.8.2.V, using ethyl 2-((6-(2-acetyl-4-methoxyphenoxy)hexyl)oxy)benzoate (414 mg, 1 mmol, 1 equiv.), sodium borohydride (114 mg, 3 mmol, 3 equiv.) to afford the desired product ethyl

2-((6-(2-(1-hydroxyethyl)-4-methoxyphenoxy)hexyl)oxy)benzoate **S27** (390 mg, 93% yield) as colourless sticky liquid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.76 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.45 – 7.38 (m, 1H), 6.98 – 6.91 (m, 3H), 6.78 (d, *J* = 8.9 Hz, 1H), 6.72 (dd, *J* = 8.8, 3.0 Hz, 1H), 5.06 (q, *J* = 6.5 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.99 – 3.93 (m, 2H), 3.76 (s, 3H), 2.81 (s, 1H), 1.93 – 1.78 (m, 4H), 1.57 (m, 4H), 1.48 (d, *J* = 6.5 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.6, 158.5, 153.7, 150.1, 134.9, 133.2, 131.5, 120.8, 120.1, 113.1, 112.4, 112.3, 68.6, 68.4, 66.6, 60.8, 55.7, 29.4, 29.2, 26.0, 25.8, 23.1, 14.4. **IR** (neat): 3521, 2992, 2940, 1698, 1596, 1491, 1251 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₄H₃₂NaO₆, 439.2096 found: 439.2089.

ethyl 2-((6-(4-chloro-2-(1-hydroxyethyl)phenoxy)hexyl)oxy)benzoate (S28): Prepared

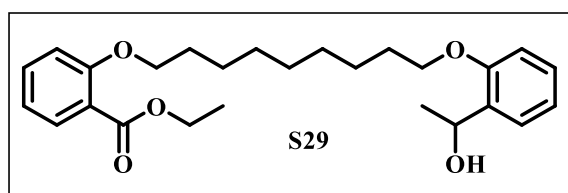


according to the general procedure 5.8.2.V, using ethyl 2-((6-(2-acetyl-4-chlorophenoxy)hexyl)oxy)benzoate (500 mg, 1.28 mmol, 1 equiv.), sodium borohydride (145 mg, 3.84 mmol, 3 equiv.) to afford the desired product ethyl

ethyl 2-((6-(4-chloro-2-(1-hydroxyethyl)phenoxy)hexyl)oxy)benzoate **S28** (480 mg, 95% yield) as colourless liquid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400

MHz, CDCl₃) δ 7.76 (dd, J = 7.7, 1.7 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.34 (d, J = 2.6 Hz, 1H), 7.14 (dd, J = 8.7, 2.6 Hz, 1H), 7.00 – 6.90 (m, 2H), 6.76 (d, J = 8.7 Hz, 1H), 5.06 (q, J = 6.3 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.03 (t, J = 6.3 Hz, 2H), 3.98 (td, J = 6.3, 1.3 Hz, 2H), 2.65 (s, 1H), 1.94 – 1.79 (m, 4H), 1.64 – 1.49 (m, 4H), 1.45 (d, J = 6.5 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.6, 158.5, 154.4, 135.6, 133.3, 131.5, 127.7, 126.1, 125.7, 120.8, 120.1, 120.1, 113.1, 112.4, 68.6, 68.1, 65.8, 60.8, 29.1, 25.9, 25.7, 23.0, 14.4. **IR** (neat): 3501, 2936, 1703, 1596, 1240, 1078 cm⁻¹. **HRMS** (ESI-TOF) m/z : [M+Na]⁺ calcd for C₂₃H₂₉ClNaO₅, 443.1601 found: 443.1596.

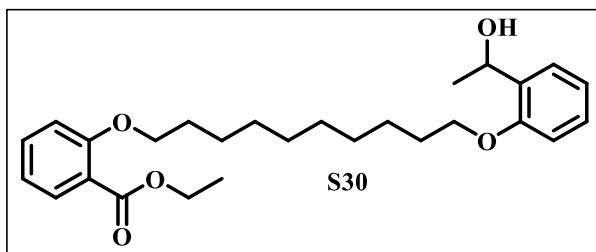
ethyl 2-((9-(2-(1-hydroxyethyl)phenoxy)nonyl)oxy)benzoate (S29): Prepared according to



the general procedure **5.8.2.V**, using ethyl 2-((9-(2-acetylphenoxy)nonyl)oxy)benzoate (370 mg, 0.87 mmol, 1 equiv.), sodium borohydride (99 mg, 2.6 mmol, 3 equiv.) to

afford the desired product ethyl 2-((9-(2-(1-hydroxyethyl)phenoxy)nonyl)oxy)benzoate **S29** (275 mg, 74% yield) as colourless liquid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.76 (dd, J = 8.0, 1.8 Hz, 1H), 7.41 (td, J = 8.4, 1.8 Hz, 1H), 7.33 (dd, J = 7.5, 1.5 Hz, 1H), 7.21 (td, J = 8.0, 1.7 Hz, 1H), 6.94 (dt, J = 6.7, 5.1 Hz, 3H), 6.86 (d, J = 8.2 Hz, 1H), 5.09 (q, J = 6.2 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 4.01 (q, J = 6.5 Hz, 4H), 2.85 (s, 1H), 1.88 – 1.76 (m, 4H), 1.56 – 1.42 (m, 7H), 1.37 (m, 9H). **¹³C NMR** (100 MHz, CDCl₃) δ 166.7, 158.5, 156.1, 133.5, 133.2, 131.5, 128.2, 126.1, 120.9, 120.6, 120.0, 113.1, 111.2, 68.8, 67.9, 66.8, 60.8, 29.5, 29.3, 29.3, 29.2, 26.2, 26.0, 23.0, 14.3. **IR** (neat): 3495, 2929, 2860, 1704, 1595, 1454, 1239, 1079 cm⁻¹. **HRMS** (ESI-TOF) m/z : [M+Na]⁺ calcd for C₂₆H₃₆NaO₅, 451.2460 found: 451.2454.

ethyl 2-((10-(2-(1-hydroxyethyl)phenoxy)decyl)oxy)benzoate (S30): Prepared according to

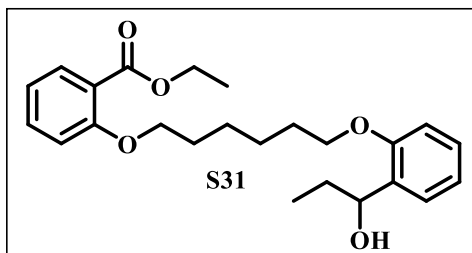


the general procedure **5.8.2.V**, using ethyl 2-((10-(2-acetylphenoxy)decyl)oxy)benzoate (220 mg, 0.5 mmol, 1 equiv.), sodium borohydride (57 mg, 1.5 mmol, 3 equiv.) to afford the desired

product ethyl 2-((10-(2-(1-hydroxyethyl)phenoxy)decyl)oxy)benzoate **S30** (130 mg, 59% yield) as colourless liquid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 7.76 (dd, J = 8.0, 1.8 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.32 (dd, J = 7.5, 1.5 Hz, 1H), 7.22 (td, J = 8.0, 1.7 Hz, 1H), 6.94 (dt, J = 6.7, 5.0 Hz, 3H), 6.86 (d, J = 8.2 Hz, 1H), 5.09 (d,

$J = 3.1$ Hz, 1H), 4.35 (q, $J = 7.1$ Hz, 2H), 4.01 (dd, $J = 11.6, 6.4$ Hz, 4H), 2.81 (s, 1H), 1.88 – 1.77 (m, 4H), 1.57 – 1.42 (m, 7H), 1.37 (dd, $J = 14.1, 7.0$ Hz, 11H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 158.6, 156.1, 133.5, 133.2, 131.5, 128.3, 126.2, 120.9, 120.7, 120.0, 113.2, 111.2, 68.9, 68.0, 66.9, 60.8, 29.6, 29.4, 29.4, 29.4, 29.3, 26.3, 26.0, 22.9, 14.4. IR (neat): 3346, 2971, 2927, 1692, 1599, 1260, 1082 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{38}\text{NaO}_5$, 465.2616 found: 465.2609.

ethyl 2-((6-(2-(1-hydroxypropyl)phenoxy)hexyl)oxy)benzoate (S31): Prepared according to

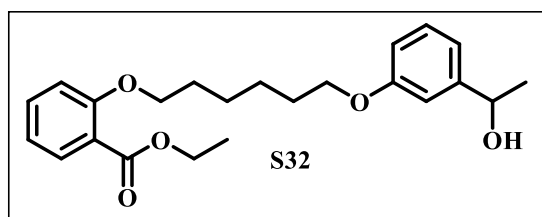


the general procedure 5.8.2.V, using ethyl 2-((6-(2-propionylphenoxy)hexyl)oxy)benzoate (300 mg, 0.75 mmol, 1 equiv.), sodium borohydride (86 mg, 2.25 mmol, 3 equiv.) to afford the desired product ethyl 2-

((6-(2-(1-

hydroxypropyl)phenoxy)hexyl)oxy)benzoate **S31** (258 mg, 85% yield) as colourless liquid compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.77 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.42 (td, $J = 8.1, 1.8$ Hz, 1H), 7.29 (dd, $J = 7.5, 1.6$ Hz, 1H), 7.20 (td, $J = 8.1, 1.7$ Hz, 1H), 6.98 – 6.90 (m, 3H), 6.86 (d, $J = 8.1$ Hz, 1H), 4.79 (t, $J = 6.6$ Hz, 1H), 4.33 (q, $J = 7.1$ Hz, 2H), 4.07 – 3.97 (m, 4H), 2.73 (s, 1H), 1.93 – 1.76 (m, 6H), 1.66 – 1.52 (m, 4H), 1.36 (t, $J = 7.1$ Hz, 3H), 0.94 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 158.5, 156.0, 133.2, 132.5, 131.5, 128.1, 127.1, 120.8, 120.6, 120.1, 113.1, 111.3, 72.5, 68.6, 67.7, 60.8, 30.3, 29.3, 29.2, 26.0, 25.8, 14.3, 10.5. IR (neat): 3523, 2939, 1700, 1596, 1487, 1245, 1082 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{30}\text{NaO}_5$, 423.2147 found: 423.2136.

ethyl 2-((6-(3-(1-hydroxyethyl)phenoxy)hexyl)oxy)benzoate (S32): Prepared according to

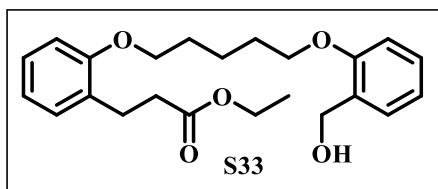


the general procedure 5.8.2.V, using ethyl 2-((6-(3-acetylphenoxy)hexyl)oxy)benzoate (190 mg, 0.5 mmol, 1 equiv.), sodium borohydride (57 mg, 1.5 mmol, 3 equiv.) to afford the desired product ethyl 2-((6-(3-(1-

hydroxyethyl)phenoxy)hexyl)oxy)benzoate **S32** (139 mg, 73% yield) as colourless liquid compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.76 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.42 (td, $J = 9.2, 7.7, 1.8$ Hz, 1H), 7.23 (t, $J = 7.8$ Hz, 1H), 6.99 – 6.89 (m, 4H), 6.82 – 6.76 (m, 1H), 4.84 (q, $J = 6.4$ Hz, 1H), 4.33 (q, $J = 7.1$ Hz, 2H), 4.03 (t, $J = 6.4$ Hz, 2H), 3.97 (t, $J = 6.4$ Hz, 2H), 2.21 (s, 1H), 1.91 – 1.77 (m, 4H), 1.66 – 1.52 (m, 4H), 1.47 (d, $J = 6.5$ Hz, 3H), 1.36 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 159.3, 158.5, 147.7,

133.2, 131.5, 129.5, 120.8, 120.0, 117.6, 113.3, 113.1, 111.5, 70.3, 68.7, 67.7, 60.8, 29.2, 29.2, 25.8, 25.8, 25.2, 14.3. **IR** (neat): 3510, 2935, 1701, 1599, 1204 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{NaO}_5$, 409.1990 found: 409.1986.

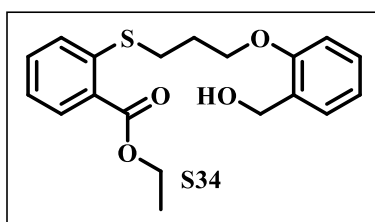
ethyl 3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propanoate (S33): Prepared



according to general procedure **5.8.2.IV**, using ethyl 3-(2-((5-bromopentyl)oxy)phenyl)propanoate (600 mg, 1.75 mmol, 1 equiv.), 2-hydroxybenzyl alcohol (217 mg, 1.75 mmol, 1 equiv.) and K_2CO_3 (362 mg, 2.6 mmol, 1.5

equiv.) to afford desired product ethyl 3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propanoate **S33** (377 mg, 56% yield) as a colourless liquid (20% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 7.29 (d, J = 7.3 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.16 (dd, J = 13.5, 7.2 Hz, 2H), 6.93 (t, J = 7.4 Hz, 1H), 6.89 – 6.79 (m, 3H), 4.70 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 4.04 (t, J = 6.3 Hz, 2H), 3.99 (t, J = 6.2 Hz, 2H), 2.94 (t, J = 7.8 Hz, 2H), 2.61 (dd, J = 10.6, 4.8 Hz, 2H), 1.95 – 1.83 (m, 4H), 1.74 – 1.64 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 173.6, 156.9, 156.8, 130.0, 129.3, 129.0, 128.8, 128.6, 127.6, 120.6, 120.4, 111.1, 111.0, 67.8, 67.5, 61.9, 60.4, 34.3, 29.1, 29.1, 26.2, 23.0, 14.3. **IR** (neat): 3512, 2958, 1685, 1605, 1178 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{NaO}_5$, 409.1990 found: 409.1989.

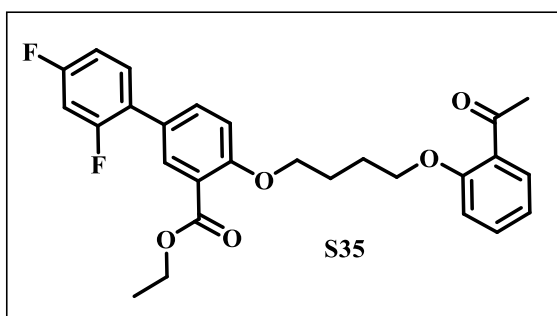
ethyl 2-((3-(2-(hydroxymethyl)phenoxy)propyl)thio)benzoate (S34): Prepared according to



general procedure **5.8.2.IV**, using ethyl 2-((3-bromopropyl)thio)benzoate (200 mg, 0.69 mmol, 1 equiv.), 2-hydroxy benzyl alcohol (87 mg, 0.69 mmol, 1 equiv.) and K_2CO_3 (217 mg, 1.5 mmol, 1.5 equiv.) to afford desired product ethyl 2-((3-(2-

(hydroxymethyl)phenoxy)propyl)thio)benzoate **S34** (210 mg, 87% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 7.96 (dd, J = 7.8, 1.4 Hz, 1H), 7.48 – 7.40 (m, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.30 (dd, J = 7.3, 1.2 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.20 – 7.13 (m, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.72 (s, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.17 (t, J = 5.9 Hz, 2H), 3.14 (t, J = 7.1 Hz, 2H), 2.31 (s, 1H), 2.24 (t, J = 6.5 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 166.6, 156.4, 141.0, 132.3, 131.3, 129.3, 128.9, 128.7, 128.3, 125.6, 124.0, 120.9, 111.2, 66.4, 61.8, 61.2, 28.7, 28.2, 14.3. **IR** (neat): 3524, 2994, 1699, 1596, 1249 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{NaO}_4\text{S}$, 369.1136 found: 369.1139.

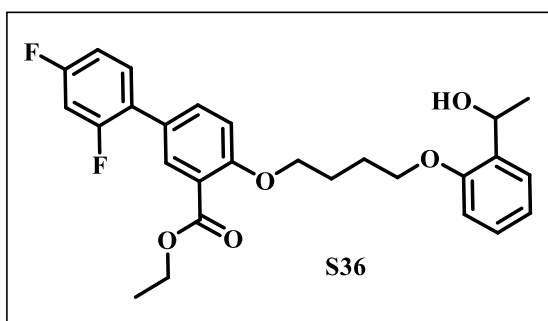
ethyl 4-(4-(2-acetylphenoxy)butoxy)-2',4'-difluoro-[1,1'-biphenyl]-3-carboxylate (S35):



Prepared according to general procedure 5.8.2.IV, using ethyl 2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylate (300 mg, 1.07 mmol, 1 equiv.), 1-(2-(4-bromobutoxy)phenyl)ethan-1-one (290 mg, 1.07 mmol, 1 equiv.) and K₂CO₃ (221 mg, 1.6

mmol, 1.5 equiv.) to afford desired product ethyl 4-(4-(2-acetylphenoxy)butoxy)-2',4'-difluoro-[1,1'-biphenyl]-3-carboxylate **S35** (330 mg, 66% yield) as a yellow liquid (20% ethyl acetate in *n*-hexane). ¹H NMR (400 MHz, CDCl₃) δ 7.91 (dd, *J* = 2.3, 1.1 Hz, 1H), 7.73 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.44 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.38 (td, *J* = 8.7, 6.5 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.99 (dd, *J* = 7.5, 6.7 Hz, 2H), 6.96 – 6.87 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.21 – 4.15 (m, 4H), 2.63 (s, 3H), 2.18 – 2.03 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 200.0, 166.1, 158.4, 158.0, 133.7, 132.0, 131.3, 131.3, 131.2 (dd, *J* = 9.4, 4.9 Hz), 130.5, 128.4, 127.1, 121.0, 120.6, 113.2, 112.4, 104.5 (m), 77.4, 77.3, 76.8, 68.4, 68.2, 61.0, 32.1, 26.2, 26.2, 14.5. IR (neat): 3544, 2992, 1710, 1695, 1555, 1223 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₇H₂₆F₂NaO₅ 491.1646 found: 491.1640.

ethyl 2',4'-difluoro-4-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)-[1,1'-biphenyl]-3-carboxylate (S36):



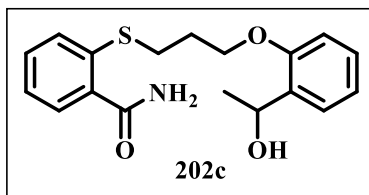
Prepared according to general procedure 5.8.2.V, using ethyl 4-(4-(2-acetylphenoxy)butoxy)-2',4'-difluoro-[1,1'-biphenyl]-3-carboxylate (300 mg, 0.62 mmol, 1 equiv.), and NaBH₄ (70.5 mg, 1.8 mmol, 3 equiv.) to afford desired product ethyl 2',4'-

difluoro-4-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)-[1,1'-biphenyl]-3-carboxylate **S36** (289 mg, 96% yield) as a pale yellow liquid compound (20% ethyl acetate in *n*-hexane). ¹H NMR (400 MHz, CDCl₃) δ 7.91 (dd, *J* = 2.3, 1.0 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.43 – 7.32 (m, 2H), 7.23 (td, *J* = 8.0, 1.7 Hz, 1H), 7.07 – 6.85 (m, 5H), 5.12 (dd, *J* = 6.0, 3.7 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.21 – 4.08 (m, 4H), 2.61 (d, *J* = 4.2 Hz, 1H), 2.15 – 2.06 (m, 4H), 1.51 (d, *J* = 6.5 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 166.2, 158.0, 155.9, 133.7 (dd, *J* = 3.5 Hz), 133.6, 132.0, 131.3, 131.2 (m), 128.4, 127.1, 126.2, 121.1, 120.9, 113.2, 111.8, 111.6, 111.3, 104.5 (m), 68.5, 67.6, 66.5, 61.1, 26.2, 26.2, 23.1, 14.4. IR (neat): 3534, 2996,

1691, 1549, 1248 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{28}\text{F}_2\text{NaO}_5$ 493.1802 found: 493.1800.

Characterization Data for Starting Material Amides:

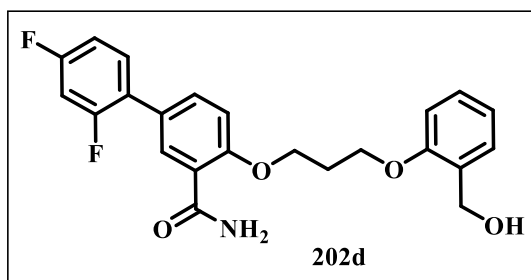
2-((3-(2-(1-hydroxyethyl)phenoxy)propyl)thio)benzamide (202c): Prepared according to



general procedure **5.8.VI**, using ethyl 2-((3-(2-(1-hydroxyethyl)phenoxy)propyl)thio)benzoate **S18** (180 mg, 0.5 mmol, 1 equiv.), Hydrazine hydrate (3.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15.5 mg, 0.075 mmol, 0.15 equiv.) in 1,4-dioxane (2 mL) as

a solvent to afford desired product 2-((3-(2-(1-hydroxyethyl)phenoxy)propyl)thio)benzamide **202c** (68 mg, 41% yield) as a white solid compound (60% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 7.69 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.46 (dd, $J = 7.9, 0.9$ Hz, 1H), 7.37 (td, $J = 7.7, 1.5$ Hz, 2H), 7.29 – 7.23 (m, 1H), 7.20 (td, $J = 8.1, 1.7$ Hz, 1H), 6.96 (dd, $J = 10.9, 4.1$ Hz, 1H), 6.82 (d, $J = 8.2$ Hz, 1H), 6.73 (s, 1H), 6.10 (s, 1H), 5.12 (q, $J = 6.5$ Hz, 1H), 4.11 (t, $J = 5.8$ Hz, 2H), 3.13 (td, $J = 7.1, 2.0$ Hz, 2H), 2.77 (s, 1H), 2.13 (m, 2H), 1.47 (d, $J = 6.5$ Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 169.9, 155.5, 135.9, 134.2, 133.8, 131.2, 131.2, 129.6, 128.3, 126.9, 126.2, 121.1, 111.3, 66.1, 65.8, 31.6, 28.8, 23.3. **IR** (neat): 3385, 2928, 1644, 1576, 1237 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{21}\text{NNaO}_3\text{S}$, 381.1134 found: 381.1134.

2',4'-difluoro-4-(3-(2-(hydroxymethyl)phenoxy)propoxy)-[1,1'-biphenyl]-3-carboxamide (202d): Prepared according to general procedure

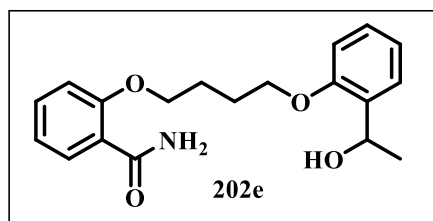


5.8.2.VI, using ethyl 2',4'-difluoro-4-(3-(2-(hydroxymethyl)phenoxy)propoxy)-[1,1'-biphenyl]-3-carboxylate **S19** (442 mg, 1 mmol, 1 equiv.), Hydrazine hydrate (6 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (31 mg, 0.15 mmol, 0.15 equiv.) in

1,4-dioxane (3 mL) as a solvent to afford desired 2',4'-difluoro-4-(3-(2-(hydroxymethyl)phenoxy)propoxy)-[1,1'-biphenyl]-3-carboxamide **202d** (210 mg, 51% yield) as a brownish white solid compound (60% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.31 (d, $J = 1.9$ Hz, 1H), 7.71 (s, 1H), 7.62 (dt, $J = 8.5, 2.0$ Hz, 1H), 7.41 (td, $J = 8.7, 6.6$ Hz, 1H), 7.33 (d, $J = 7.3$ Hz, 1H), 7.30 – 7.24 (m, 1H), 7.08 (d, $J = 8.6$ Hz, 1H), 6.97 (t, $J = 7.4$ Hz, 1H), 6.95 – 6.85 (m, 3H), 6.20 (s, 1H), 4.71 (s, 2H), 4.41 (t, $J = 6.1$ Hz, 2H), 4.23 (t, $J = 5.9$ Hz, 2H), 2.53 – 2.37 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 166.9, 156.6, 156.3, 133.9, 133.8 (d, $J = 4$ Hz), 132.9, 131.4 (dd, $J = 9.4, 4.8$ Hz), 129.4, 129.1, 129.0, 128.4, 121.4,

121.3, 112.7, 111.8 (d, $J = 3.8$ Hz) 111.6, 111.4, 104.4 (m), 66.4, 64.7, 61.6, 29.3. **IR** (neat): 3463, 2999, 1661, 1588, 1237 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{21}\text{F}_2\text{NNaO}_4$, 436.1336 found: 436.1330.

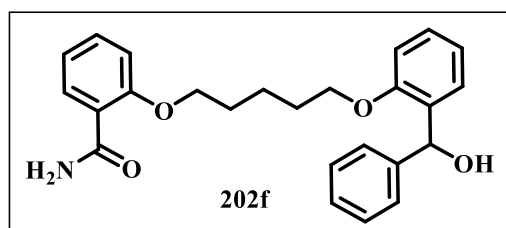
2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzamide (202e): Prepared according to general



procedure **5.8.2.VI**, using ethyl 2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzoate **S20** (100 mg, 0.27 mmol, 1 equiv.), Hydrazine hydrate (2 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (8.7 mg, 0.0418 mmol, 0.15 equiv.) in 1,4-

dioxane (1 mL) as a solvent to afford desired product 2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzamide **202e** (60 mg, 65 % yield) as a white crystalline solid (50% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.19 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.75 (s, 1H), 7.45 (ddd, $J = 8.4, 7.4, 1.9$ Hz, 1H), 7.39 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.22 (td, $J = 8.0, 1.7$ Hz, 1H), 7.09 – 7.04 (m, 1H), 6.97 (dt, $J = 6.6, 2.8$ Hz, 2H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.39 (s, 1H), 5.14 (q, $J = 6.5$ Hz, 1H), 4.21 (t, $J = 5.9$ Hz, 2H), 4.09 (t, $J = 5.7$ Hz, 2H), 2.15 – 1.98 (m, 4H), 1.49 (d, $J = 6.5$ Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.5, 157.2, 155.5, 133.7, 133.4, 132.6, 128.3, 126.2, 121.3, 121.0, 121.0, 112.3, 111.2, 68.7, 67.1, 66.0, 26.3, 26.3, 23.3. **IR** (neat): 3455, 3381, 2940, 1647, 1590, 1229 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{NNaO}_4$, 352.1524 found: 352.1521.

2-((5-(2-(hydroxy(phenyl)methyl)phenoxy)pentyl)oxy)benzamide (202f): Prepared

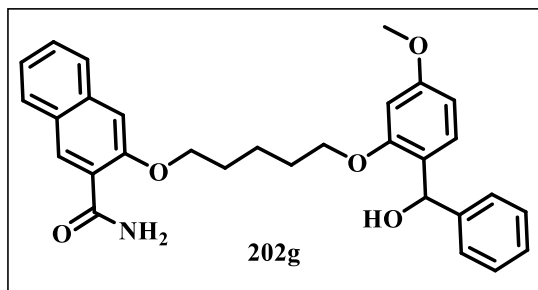


according to general procedure **5.8.2.VI**, using ethyl 2-((5-(2-(hydroxy(phenyl)methyl)phenoxy)pentyl)oxy)benzoate **S21** (210 mg, 0.48 mmol, 1 equiv.), Hydrazine hydrate (3 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (15 mg, 0.073 mmol, 0.15 equiv.) in 1,4-dioxane (2 mL) as

a solvent to afford desired product 2-((5-(2-(hydroxy(phenyl)methyl)phenoxy)pentyl)oxy)benzamide **202f** (110 mg, 56 % yield) as a white crystalline solid (60% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.18 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.71 (s, 1H), 7.51 – 7.41 (m, 1H), 7.34 (dd, $J = 8.1, 4.5$ Hz, 3H), 7.25 (dt, $J = 9.5, 4.5$ Hz, 3H), 7.18 (t, $J = 7.3$ Hz, 1H), 7.06 (dd, $J = 11.1, 4.0$ Hz, 1H), 7.00 – 6.93 (m, 2H), 6.86 (d, $J = 8.1$ Hz, 1H), 6.03 (d, $J = 3.7$ Hz, 2H), 4.08 (t, $J = 6.4$ Hz, 2H), 4.04 – 3.91 (m, 2H), 1.91 – 1.81 (m, 2H), 1.81 – 1.74 (m, 2H), 1.51 (dt, $J = 15.1, 7.5$ Hz, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.40, 157.3, 155.9, 143.8, 133.4, 132.6, 132.0, 128.8, 128.2, 128.0, 127.2, 126.6, 121.3, 121.0, 120.9, 112.4, 111.4,

72.4, 68.9, 67.4, 28.9, 28.9, 22.8. **IR** (neat): 3460, 2999, 2944, 1659, 1591, 1238 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{27}\text{NNaO}_4$, 428.1837 found: 428.1830.

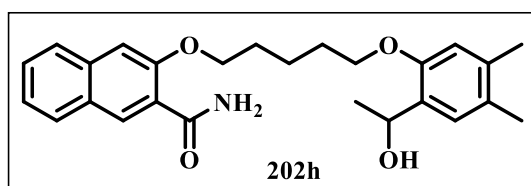
3-((5-(2-(hydroxy(phenyl)methyl)-5-methoxyphenoxy)pentyl)oxy)-2-naphthamide



(202g): Prepared according to general procedure **5.8.2.VI**, using ethyl 3-((5-(2-(hydroxy(phenyl)methyl)-5-methoxyphenoxy)pentyl)oxy)-2-naphthoate **S22** (190 mg, 0.37 mmol, 1 equiv.), Hydrazine hydrate (2.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (11.5 mg,

0.055 mmol, 0.15 equiv.) in 1,4-dioxane (2 mL) as a solvent to afford desired product 3-((5-(2-(hydroxy(phenyl)methyl)-5-methoxyphenoxy)pentyl)oxy)-2-naphthamide **202g** (88 mg, 49 % yield) as a white crystalline solid (60% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.74 (s, 1H), 7.87 (d, $J = 7.8$ Hz, 2H), 7.72 (d, $J = 8.1$ Hz, 1H), 7.56 – 7.48 (m, 1H), 7.37 (ddd, $J = 7.4, 6.6, 2.5$ Hz, 3H), 7.26 (dd, $J = 8.3, 6.8$ Hz, 2H), 7.23 – 7.14 (m, 3H), 6.63 (s, 1H), 6.50 – 6.41 (m, 2H), 6.00 (s, 1H), 4.13 (td, $J = 6.8, 4.8$ Hz, 2H), 3.95 (tdd, $J = 9.3, 5.9, 3.2$ Hz, 2H), 3.77 (s, 3H), 1.94 – 1.85 (m, 2H), 1.85 – 1.73 (m, 2H), 1.54 (dt, $J = 15.3, 7.7$ Hz, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.6, 160.3, 157.0, 154.3, 144.1, 136.1, 134.3, 129.3, 128.7, 128.5, 128.1, 127.0, 126.5, 126.3, 124.8, 124.6, 121.7, 107.4, 104.2, 99.4, 71.8, 68.8, 67.4, 55.4, 28.8, 28.8, 22.8. **IR** (neat): 3456, 2998, 2942, 1663, 1592, 1500, 1236, 1115 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{31}\text{NNaO}_5$, 508.2100 found: 508.2106.

3-((5-(2-(1-hydroxyethyl)-4,5-dimethylphenoxy)pentyl)oxy)-2-naphthamide (202h):

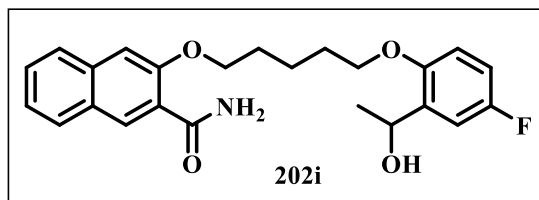


Prepared according to general procedure **5.8.2.VI**, using ethyl 3-((5-(2-(1-hydroxyethyl)-4,5-dimethylphenoxy)pentyl)oxy)-2-naphthoate **S23** (74 mg, 0.165 mmol, 1 equiv.), Hydrazine hydrate

(1.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (5.1 mg, 0.024 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 3-((5-(2-(1-hydroxyethyl)-4,5-dimethylphenoxy)pentyl)oxy)-2-naphthamide **202h** (28 mg, 41 % yield) as a yellowish sticky compound (60% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.76 (s, 1H), 7.94 (s, 1H), 7.88 (d, $J = 8.2$ Hz, 1H), 7.73 (d, $J = 8.3$ Hz, 1H), 7.55 – 7.49 (m, 1H), 7.39 (t, $J = 7.5$ Hz, 1H), 7.23 (s, 1H), 7.08 (s, 1H), 6.91 (s, 1H), 6.39 (s, 1H), 5.17 (q, $J = 6.4$ Hz, 1H), 4.27 (t, $J = 6.5$ Hz, 2H), 3.89 – 3.79 (m, 2H), 2.28 (s, 3H), 2.25 (s, 3H), 2.03 (m, 2H), 1.97 – 1.87 (m, 2H), 1.78 (m, 2H), 1.50 (d, $J = 6.5$ Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.4, 154.3, 152.3, 137.9, 136.1, 134.4, 133.8,

131.2, 130.7, 129.3, 128.6, 128.2, 126.3, 124.7, 124.5, 121.8, 107.6, 73.2, 69.0, 65.0, 30.1, 29.1, 24.0, 23.1, 21.0, 16.3. **IR** (neat): 3453, 3045, 2929, 1665, 1595, 1225, 1184 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{31}\text{NNaO}_4$, 444.2150 found: 444.2144.

3-((5-(4-fluoro-2-(1-hydroxyethyl)phenoxy)pentyl)oxy)-2-naphthamide (202i): Prepared



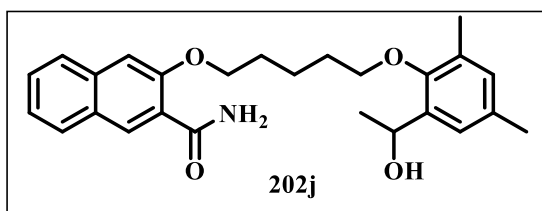
according to general procedure **5.8.2.VI**, using ethyl

3-((5-(4-fluoro-2-(1-hydroxyethyl)phenoxy)pentyl)oxy)-2-naphthoate

S24 (400 mg, 0.9 mmol, 1 equiv.), Hydrazine

hydrate (6 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (28.2 mg, 0.136 mmol, 0.15 equiv.) in 1,4-dioxane (3 mL) as a solvent to afford desired product 3-((5-(4-fluoro-2-(1-hydroxyethyl)phenoxy)pentyl)oxy)-2-naphthamide **202i** (212 mg, 57% yield) as a white solid compound (60% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.75 (s, 1H), 7.88 (d, $J = 7.9$ Hz, 2H), 7.72 (d, $J = 8.2$ Hz, 1H), 7.56 – 7.48 (m, 1H), 7.44 – 7.36 (m, 1H), 7.21 (s, 1H), 7.14 (dd, $J = 9.2, 3.1$ Hz, 1H), 6.91 – 6.83 (m, 1H), 6.75 (dd, $J = 8.9, 4.4$ Hz, 1H), 6.40 (s, 1H), 5.12 (q, $J = 6.4$ Hz, 1H), 4.26 (t, $J = 6.3$ Hz, 2H), 4.01 (td, $J = 6.1, 2.8$ Hz, 2H), 2.97 (s, 1H), 2.01 (dq, $J = 12.8, 6.4$ Hz, 2H), 1.92 (dt, $J = 13.5, 3.8$ Hz, 2H), 1.81 – 1.68 (m, 2H), 1.46 (d, $J = 6.5$ Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 167.4, 158.6, 156.2, 154.2, 151.6, 151.6, 136.1, 135.9, 135.8 (d, $J = 6.3$ Hz), 134.3, 129.3, 128.6, 128.2, 126.3, 124.7, 121.9, 113.9, 113.7, 113.3, 113.1, 112.0, 111.9 (d, $J = 8.1$ Hz), 107.5, 68.9, 68.0, 65.5, 29.1, 28.9, 23.3, 23.2. **IR** (neat): 3455, 2943, 1657, 1590, 1238 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{26}\text{FNNaO}_4$, 434.1743 found: 434.1746.

3-((5-(2-(1-hydroxyethyl)-4,6-dimethylphenoxy)pentyl)oxy)-2-naphthamide (202j):



Prepared according to general procedure **5.8.2.VI**,

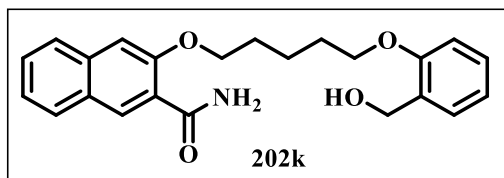
using ethyl 3-((5-(2-(1-hydroxyethyl)-4,6-dimethylphenoxy)pentyl)oxy)-2-naphthoate **S25**

(140 mg, 0.03 mmol, 1 equiv.), Hydrazine

hydrate (3 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (9.3 mg, 0.045 mmol, 0.15 equiv.) in 1,4-dioxane (2 mL) as a solvent to afford desired product 3-((5-(2-(1-hydroxyethyl)-4,6-dimethylphenoxy)pentyl)oxy)-2-naphthamide **202j** (60 mg, 46% yield) as a white solid compound (60% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.78 (s, 1H), 7.93 (s, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 7.74 (d, $J = 8.2$ Hz, 1H), 7.52 (t, $J = 7.1$ Hz, 1H), 7.40 (t, $J = 7.1$ Hz, 1H), 7.25 (s, 1H), 7.08 (s, 1H), 6.92 (s, 1H), 6.04 (s, 1H), 5.17 (q, $J = 6.4$ Hz, 1H), 4.30 (t, $J = 6.4$ Hz, 2H), 3.85 (dd, $J = 12.5, 6.2$ Hz, 2H), 2.38 (s, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 2.05

(m, 2H), 1.98 – 1.88 (m, 2H), 1.79 (m, 2H), 1.50 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.2, 154.3, 152.4, 137.9, 136.1, 134.4, 133.8, 131.3, 130.7, 129.3, 128.6, 128.2, 126.3, 124.7, 124.5, 107.6, 73.2, 69.0, 65.1, 30.2, 29.2, 23.9, 23.1, 21.0, 16.3. IR (neat): 3451, 3010, 2930, 1665, 1590, 1215, 1175 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{31}\text{NNaO}_4$, 444.2150 found: 444.2152.

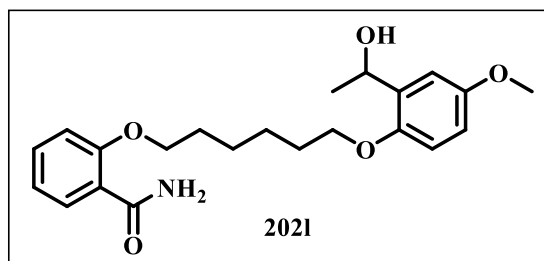
3-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthamide (202k): Prepared according



to general procedure 5.8.2.VI, using ethyl 3-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoate **S26** (408 mg, 1 mmol, 1 equiv.), Hydrazine hydrate (6 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (31 mg,

0.15 mmol, 0.15 equiv.) in 1,4-dioxane (3 mL) as a solvent to afford desired 3-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthamide **202k** (254 mg, 67% yield) as a white solid compound (60% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.75 (s, 1H), 7.87 (d, $J = 8.1$ Hz, 2H), 7.72 (d, $J = 8.1$ Hz, 1H), 7.51 (ddd, $J = 8.2, 6.9, 1.2$ Hz, 1H), 7.42 – 7.35 (m, 1H), 7.32 (dd, $J = 7.4, 1.6$ Hz, 1H), 7.24 (dt, $J = 7.9, 2.3$ Hz, 1H), 7.20 (s, 1H), 6.94 (td, $J = 7.4, 0.8$ Hz, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.49 (s, 1H), 4.71 (s, 2H), 4.24 (t, $J = 6.4$ Hz, 2H), 4.06 (t, $J = 6.0$ Hz, 2H), 2.06 – 1.96 (m, 2H), 1.96 – 1.88 (m, 2H), 1.80 – 1.70 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 156.6, 154.3, 136.1, 134.3, 129.3, 129.3, 128.8, 128.7, 128.5, 128.2, 126.3, 124.7, 121.9, 120.8, 111.0, 107.5, 68.9, 67.4, 61.7, 29.1, 29.0, 23.2. IR (neat): 3455, 3053, 2940, 1662, 1589, 1236, 1184 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{25}\text{NNaO}_4$, 402.1681 found: 402.1675.

2-((6-(2-(1-hydroxyethyl)-4-methoxyphenoxy)hexyl)oxy)benzamide (202l): Prepared

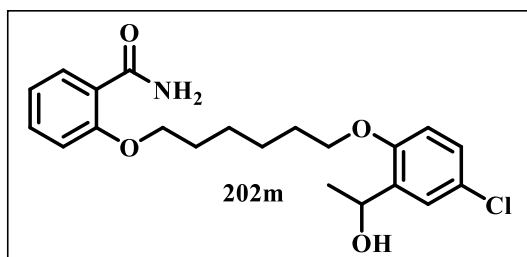


according to general procedure 5.8.2.VI, using ethyl 2-((6-(2-(1-hydroxyethyl)-4-methoxyphenoxy)hexyl)oxy)benzoate **S27** (340 mg, 0.81 mmol, 1 equiv.), Hydrazine hydrate (5.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (25 mg, 0.12 mmol, 0.15

equiv.) in 1,4-dioxane (3 mL) as a solvent to afford desired product 2-((6-(2-(1-hydroxyethyl)-4-methoxyphenoxy)hexyl)oxy)benzamide **202l** (185 mg, 58% yield) as a white solid compound (60% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.18 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.79 (s, 1H), 7.47 – 7.39 (m, 1H), 7.04 (t, $J = 7.5$ Hz, 1H), 6.97 – 6.93 (m, 2H), 6.77 (d, $J = 8.8$ Hz, 1H), 6.71 (dd, $J = 8.8, 3.0$ Hz, 1H), 6.41 (s, 1H), 5.07 (q, $J = 6.5$ Hz, 1H), 4.12 (t, $J = 6.5$ Hz, 2H), 3.95 (t, $J = 6.3$ Hz, 2H), 3.75 (s, 3H), 3.00 (s, 1H), 1.96 – 1.85 (m,

2H), 1.85 – 1.77 (m, 2H), 1.55 (dt, $J = 7.0, 3.4$ Hz, 4H), 1.47 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 157.3, 153.8, 149.9, 135.0, 133.3, 132.5, 121.1, 120.9, 112.4, 112.3, 112.3, 68.9, 68.2, 66.3, 55.7, 29.3, 29.1, 26.0, 25.9, 23.2. IR (neat): 3456, 2937, 1660, 1590, 1215, 1161 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{29}\text{NNaO}_4$, 410.1943 found: 410.1930.

2-((6-(4-chloro-2-(1-hydroxyethyl)phenoxy)hexyl)oxy)benzamide (202m): Prepared

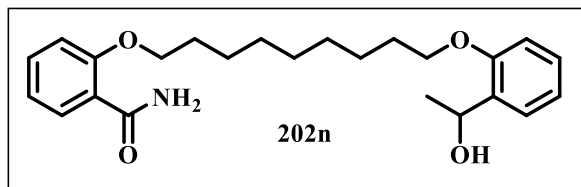


according to general procedure 5.8.2.VI, using ethyl

2-((6-(4-chloro-2-(1-hydroxyethyl)phenoxy)hexyl)oxy)benzoate **S28** (450 mg, 1.15 mmol, 1 equiv.), Hydrazine hydrate (7 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (35.7 mg, 0.17 mmol, 0.15 equiv.) in 1,4-dioxane (3 mL) as a

solvent to afford desired 2-((6-(4-chloro-2-(1-hydroxyethyl)phenoxy)hexyl)oxy)benzamide **202m** (147 mg, 35% yield) as a brownish white solid compound (60% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.19 (d, $J = 7.8$ Hz, 1H), 7.79 (s, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.35 (d, $J = 2.6$ Hz, 1H), 7.15 (d, $J = 8.7$ Hz, 1H), 7.06 (t, $J = 7.6$ Hz, 1H), 6.96 (d, $J = 8.3$ Hz, 1H), 6.75 (d, $J = 8.6$ Hz, 1H), 6.25 (s, 1H), 5.07 (q, $J = 6.4$ Hz, 1H), 4.14 (t, $J = 6.4$ Hz, 2H), 3.98 (t, $J = 5.9$ Hz, 2H), 2.76 (s, 1H), 1.98 – 1.87 (m, 2H), 1.87 – 1.78 (m, 2H), 1.56 (m, 4H), 1.45 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.5, 157.3, 154.3, 135.7, 133.4, 132.6, 127.7, 126.2, 125.8, 121.2, 120.9, 112.4, 69.0, 68.1, 65.7, 29.2, 26.0, 23.2. IR (neat): 3344, 2971, 1658, 1464, 1119 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{ClNNaO}_4$, 414.1448 found: 414.1437.

2-((9-(2-(1-hydroxyethyl)phenoxy)nonyl)oxy)benzamide (202n): Prepared according to

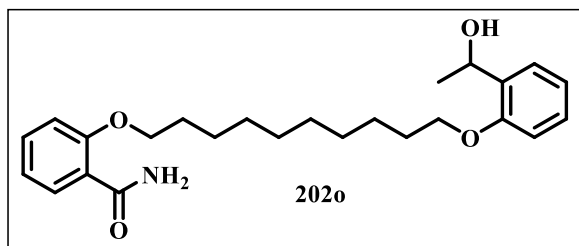


general procedure 5.8.2.VI, using ethyl 2-((9-(2-(1-hydroxyethyl)phenoxy)nonyl)oxy)benzoate **S29** (225 mg, 0.52 mmol, 1 equiv.), Hydrazine

hydrate (4 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (16 mg, 0.075 mmol, 0.15 equiv.) in 1,4-dioxane (2 mL) as a solvent to afford desired product 2-((9-(2-(1-hydroxyethyl)phenoxy)nonyl)oxy)benzamide **202n** (74 mg, 35 % yield) as a white solid (50% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.20 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.84 (s, 1H), 7.49 – 7.39 (m, 1H), 7.33 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.24 – 7.16 (m, 1H), 7.05 (t, $J = 7.5$ Hz, 1H), 6.94 (dd, $J = 14.1, 7.6$ Hz, 2H), 6.85 (d, $J = 8.2$ Hz, 1H), 6.24 (s, 1H), 5.09 (q, $J = 6.5$ Hz, 1H), 4.11 (t, $J = 6.4$ Hz, 2H), 4.00

(t, $J = 6.3$ Hz, 2H), 1.92 – 1.76 (m, 4H), 1.49 (m, 7H), 1.37 (m, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 157.4, 156.0, 133.5, 133.4, 132.6, 128.2, 126.1, 121.1, 120.8, 120.7, 112.3, 111.2, 69.1, 67.9, 66.7, 29.4, 29.3, 29.2, 29.2, 29.2, 26.2, 26.1, 23.0. IR (neat): 3336, 2995, 2930, 1672, 1598, 1525, 1244 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{33}\text{NNaO}_4$, 422.2307 found: 422.2301.

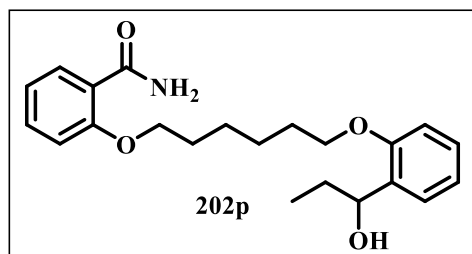
2-((10-(2-(1-hydroxyethyl)phenoxy)decyl)oxy)benzamide (202o): Prepared according to



general procedure **5.8.2.VI**, using ethyl 2-((10-(2-(1-hydroxyethyl)phenoxy)decyl)oxy)benzoate **S30** (100 mg, 0.225 mmol, 1 equiv.), Hydrazine hydrate (2 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (8

mg, 0.033 mmol, 0.15 equiv.) in 1,4-dioxane (1 mL) as a solvent to afford desired product 2-((10-(2-(1-hydroxyethyl)phenoxy)decyl)oxy)benzamide **202o** (45 mg, 48% yield) as a brownish white solid compound (60% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.20 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.86 (s, 1H), 7.44 (ddd, $J = 8.4, 7.5, 1.8$ Hz, 1H), 7.33 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.21 (td, $J = 8.1, 1.6$ Hz, 1H), 7.09 – 7.02 (m, 1H), 6.99 – 6.90 (m, 2H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.33 (s, 1H), 5.09 (q, $J = 6.5$ Hz, 1H), 4.11 (t, $J = 6.5$ Hz, 2H), 4.00 (t, $J = 6.4$ Hz, 2H), 1.91 – 1.76 (m, 4H), 1.55 – 1.43 (m, 7H), 1.34 (m, 8H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.5, 157.3, 156.1, 133.5, 133.4, 132.6, 128.2, 126.1, 121.1, 120.7, 120.6, 112.3, 111.2, 69.1, 67.9, 66.8, 29.4, 29.4, 29.3, 29.3, 29.3, 29.2, 26.2, 26.1, 23.0. IR (neat): 3336, 2994, 2856, 1671, 1597, 1455, 1243 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{35}\text{NNaO}_4$, 436.2463 found: 436.2465.

2-((6-(2-(1-hydroxypropyl)phenoxy)hexyl)oxy)benzamide (202p): Prepared according to

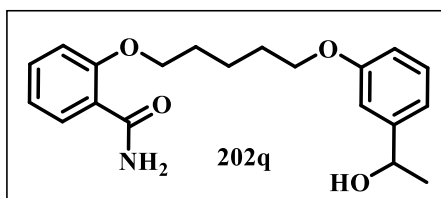


general procedure **5.8.2.VI**, using ethyl 2-((6-(2-(1-hydroxypropyl)phenoxy)hexyl)oxy)benzoate **S31** (220 mg, 0.55 mmol, 1 equiv.), Hydrazine hydrate (3 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (17 mg, 0.082 mmol, 0.15 equiv.) in 1,4-dioxane (2 mL) as a solvent to afford

desired product 2-((6-(2-(1-hydroxypropyl)phenoxy)hexyl)oxy)benzamide **202p** (67 mg, 33% yield) as a brownish sticky compound (60% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.19 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.81 (s, 1H), 7.43 (ddd, $J = 8.4, 7.4, 1.9$ Hz, 1H), 7.30 (dd, $J = 7.5, 1.6$ Hz, 1H), 7.20 (td, $J = 8.1, 1.7$ Hz, 1H), 7.07 – 7.02 (m, 1H), 6.98 – 6.89 (m, 2H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.53 (s, 1H), 4.81 (t, $J = 6.5$ Hz, 1H), 4.12 (dd, $J = 8.3, 4.7$ Hz,

2H), 3.99 (td, $J = 6.2, 1.9$ Hz, 2H), 1.96 – 1.75 (m, 7H), 1.63 – 1.49 (m, 4H), 0.93 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 157.4, 155.9, 133.4, 132.5, 128.1, 127.0, 121.1, 120.8, 120.6, 112.3, 111.2, 72.2, 68.9, 67.5, 30.4, 29.2, 29.1, 25.9, 25.9, 10.5. IR (neat): 3455, 2936, 2867, 1658, 1589, 1230, 1163 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{29}\text{NNaO}_4$, 394.1994 found: 394.1988.

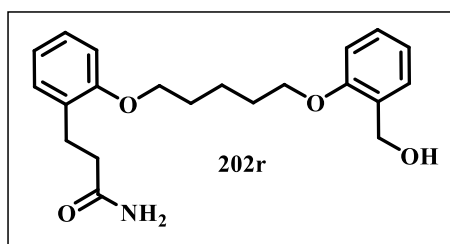
2-((5-(3-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzamide (202q): Prepared according to



general procedure **5.8.2.VI**, using ethyl 2-((5-(3-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoate (372 mg, 1 mmol, 1 equiv.), Hydrazine hydrate (6 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (31 mg, 0.015 mmol, 0.015 equiv.) in 1,4-

dioxane (3 mL) as a solvent to afford desired product 2-((5-(3-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzamide **202q** (260 mg, 75% yield) as a white solid compound (50% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 7.8$ Hz, 1H), 7.76 (s, 1H), 7.48 – 7.39 (m, 1H), 7.28 – 7.20 (m, 1H), 7.05 (t, $J = 7.5$ Hz, 1H), 6.94 (t, $J = 9.0$ Hz, 3H), 6.81 – 6.74 (m, 1H), 6.08 (s, 1H), 4.86 (q, $J = 6.2$ Hz, 1H), 4.15 (t, $J = 6.2$ Hz, 2H), 4.01 (t, $J = 6.0$ Hz, 2H), 2.62 (s, 1H), 2.01 – 1.90 (m, 2H), 1.86 (dt, $J = 13.4, 6.6$ Hz, 2H), 1.74 – 1.62 (m, 2H), 1.48 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 159.1, 157.4, 148.0, 133.4, 132.6, 129.6, 121.2, 120.9, 117.9, 113.2, 112.3, 111.8, 70.2, 68.9, 67.3, 28.9, 28.8, 25.3, 22.8. IR (neat): 3456, 2937, 2868, 1657, 1590, 1238, 1162 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{NNaO}_4$, 395.1834 found: 395.1840.

3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propenamide (202r): Prepared

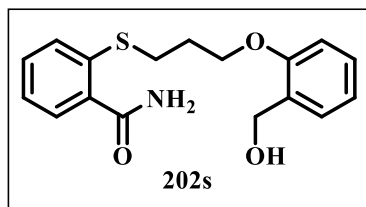


according to general procedure **5.8.2.VI**, using ethyl 3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propanoate **S33** (330 mg, 0.85 mmol, 1 equiv.), Hydrazine hydrate (6 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (26.4 mg, 0.127 mmol, 0.15 equiv.) in 1,4-dioxane (3 mL) as a solvent to afford

desired product 3-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propenamide **202r** (195 mg, 44% yield) as a brownish white solid compound (60% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.30 (dd, $J = 7.3, 1.1$ Hz, 1H), 7.24 (td, $J = 7.9, 1.5$ Hz, 1H), 7.20 – 7.13 (m, 2H), 6.93 (t, $J = 7.2$ Hz, 1H), 6.90 – 6.81 (m, 3H), 5.79 (d, $J = 46.3$ Hz, 2H), 4.69 (s, 2H), 4.05 (t, $J = 6.0$ Hz, 2H), 4.00 (t, $J = 6.0$ Hz, 2H), 2.99 – 2.89 (m, 2H), 2.54 – 2.46 (m, 2H), 1.95 – 1.84 (m, 4H), 1.76 – 1.66 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 175.7, 156.8, 156.7, 130.0, 129.2, 129.1, 128.8, 128.6, 127.6, 120.6, 120.6, 111.1, 67.8, 67.6, 61.7, 35.9,

29.3, 29.1, 26.3, 23.4. **IR** (neat): 3455, 3189, 2938, 1664, 1599, 1284, 1234 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{27}\text{NNaO}_4$, 358.2018 found: 358.2024.

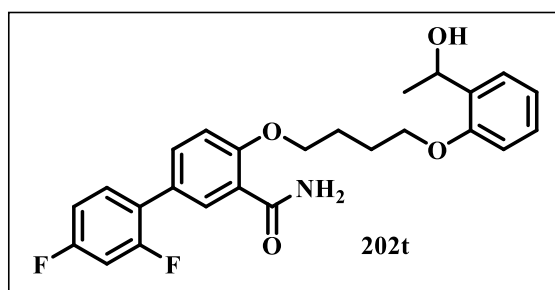
2-((3-(2-(hydroxymethyl)phenoxy)propyl)thio)benzamide (202s): Prepared according to



general procedure **5.8.2.VI**, using ethyl 2-((3-(2-(hydroxymethyl)phenoxy)propyl)thio)benzoate **S34** (150 mg, 0.43 mmol, 1 equiv.), Hydrazine hydrate (3 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (13.5 mg, 0.065 mmol, 0.15 equiv.) in 1,4-dioxane (2 mL) as a solvent to afford desired product 2-((3-(2-(hydroxymethyl)phenoxy)propyl)thio)benzamide **202s** (65 mg, 46% yield) as a white solid compound (60% ethyl acetate in *n*-hexane).

^1H NMR (400 MHz, CDCl_3 +DMSO (d^6)) δ 7.56 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.16 (dd, J = 15.2, 7.7 Hz, 2H), 6.97 (s, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.27 (s, 1H), 4.61 (d, J = 5.6 Hz, 2H), 4.05 (t, J = 5.7 Hz, 2H), 3.09 (t, J = 7.1 Hz, 2H), 2.13 – 2.02 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3 +DMSO (d^6)) δ 169.6, 155.4, 135.6, 134.2, 130.0, 129.3, 129.2, 128.2, 127.7, 125.4, 120.0, 110.4, 65.4, 59.8, 30.1, 28.0. **IR** (neat): 3418, 2996, 2945, 1663, 1493, 1240 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{NNaO}_3\text{S}$, 340.0983 found: 340.0976.

2',4'-difluoro-4-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)-[1,1'-biphenyl]-3-carboxamide (202t): Prepared according to general procedure



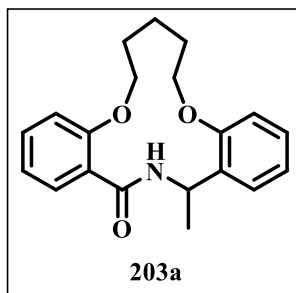
5.8.2.VI, using ethyl 2-((3-(2-(hydroxymethyl)phenoxy)propyl)thio)benzoate **S36** (290 mg, 0.61 mmol, 1 equiv.), Hydrazine hydrate (3.5 mL) and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (19.2 mg, 0.065 mmol, 0.15 equiv.) in 1,4-dioxane (2 mL)

as a solvent to afford desired product 2',4'-difluoro-4-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)-[1,1'-biphenyl]-3-carboxamide **202t** (29 mg, 11% yield) as a pale yellow solid compound (70% ethyl acetate in *n*-hexane). **^1H NMR** (400 MHz, CDCl_3) δ 8.33 (d, J = 1.9 Hz, 1H), 7.76 (s, 1H), 7.63 (dt, J = 8.6, 2.2 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.25 – 7.18 (m, 1H), 7.05 (d, J = 8.7 Hz, 1H), 7.01 – 6.83 (m, 4H), 6.48 (s, 1H), 5.15 (q, J = 6.5 Hz, 1H), 4.26 (t, J = 6.0 Hz, 2H), 4.11 (dd, J = 9.5, 3.8 Hz, 2H), 2.15 – 2.02 (m, 4H), 1.50 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 171.3, 167.2, 163.5 (d, J = 11.8 Hz), 161.1, 161.0 (dd, J = 11.8, 5.4 Hz), 160.9, 158.5 (d, J = 11.9 Hz), 156.8, 155.5, 133.8, 133.8, 133.7, 132.9, 131.4 (dd, J = 9.5, 4.8 Hz), 130.7, 129.0, 128.3, 128.18, 126.1, 124.5, 124.1 (d, J = 3.8 Hz), 123.9 (d, J = 3.8 Hz), 121.1, 121.1, 116.2, 116.0, 112.6, 111.8 (d, J = 3.7 Hz), 111.5 (d, J = 3.7 Hz), 111.2, 104.6, 104.4 (m),

104.1, 69.0, 67.1, 65.9, 65.9, 60.5, 29.7, 26.3, 26.3, 26.1, 23.3, 21.1, 14.2. **IR** (neat): 3420, 2985, 2942, 1668, 1495, 1210, 748 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{25}\text{F}_2\text{NNaO}_4$ 464.1649 found: 464.1649.

C) Characterization data for Macrolactams:

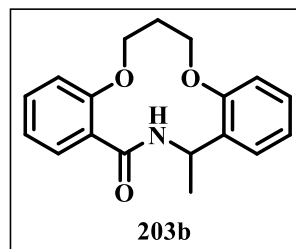
18-methyl-7,8,9,10,17,18-hexahydro-6*H*,16*H*-



dibenzo[*b,g*][1,9]dioxo[5]azacyclotetradecin-16-one (203a):

Prepared according to general procedure 5.8.2.VII, using 2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzamide **179cc** (28.2 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05M) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 18-methyl-7,8,9,10,17,18-hexahydro-6*H*,16*H*-dibenzo[*b,g*][1,9]dioxo[5]azacyclotetradecin-16-one **203a** (20 mg, 76% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl_3) δ 8.89 (d, J = 8.9 Hz, 1H), 8.30 (dd, J = 7.9, 1.8 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.32 (dd, J = 7.3, 1.4 Hz, 1H), 7.23 (td, J = 8.1, 1.7 Hz, 1H), 7.05 – 7.00 (m, 1H), 6.94 – 6.84 (m, 3H), 5.56 (dq, J = 14.0, 7.0 Hz, 1H), 4.23 – 4.13 (m, 3H), 4.04 – 3.95 (m, 1H), 2.32 – 2.09 (m, 2H), 2.07 – 1.95 (m, 1H), 1.92 – 1.72 (m, 3H), 1.66 (d, J = 7.0 Hz, 3H). **¹³C NMR** (100 MHz, CDCl_3) δ 164.1, 157.2, 157.1, 132.8, 132.6, 130.8, 130.2, 128.7, 121.3, 120.9, 120.7, 111.4, 111.0, 67.7, 63.7, 50.1, 26.0, 25.3, 20.7, 20.7. **IR** (neat): 3355, 2990, 2929, 1657, 1601, 1550, 1240 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{NNaO}_3$, 348.1576 found: 348.1579.

16-methyl-7,8,15,16-tetrahydro-6*H*,14*H*-dibenzo[*f,k*][1,5]dioxo[9]azacyclododecin-14-

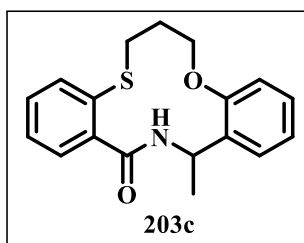


one (203b): Prepared according to general procedure 5.8.2.VII, using 2-(3-(2-(1-hydroxyethyl)phenoxy)propoxy)benzamide **179aa** (25.2 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05M) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with

heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 16-methyl-7,8,15,16-tetrahydro-6*H*,14*H*-dibenzo[*f,k*][1,5]dioxo[9]azacyclododecin-14-one **203b** (19 mg, 80% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl_3) δ 10.58 (d, J = 8.9

Hz, 1H), 8.23 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.38 (td, $J = 8.2, 1.8$ Hz, 1H), 7.21 (ddd, $J = 9.6, 5.4, 1.5$ Hz, 2H), 7.06 (dd, $J = 11.1, 3.9$ Hz, 1H), 6.91 (td, $J = 8.2, 2.1$ Hz, 3H), 5.40 – 5.27 (m, 1H), 4.58 (ddd, $J = 12.6, 9.1, 3.9$ Hz, 2H), 4.08 – 3.96 (m, 2H), 2.74 – 2.58 (m, 1H), 2.28 – 2.18 (m, 1H), 1.56 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 163.3, 156.9, 156.2, 132.3, 132.0, 131.3, 129.6, 128.2, 122.3, 121.4, 121.2, 111.9, 111.3, 68.3, 67.8, 49.6, 28.9, 22.8. **IR** (neat): 3365, 2997, 2935, 1662, 1598, 1535, 1220 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{NNaO}_3$, 320.1262 found: 320.1263.

16-methyl-7,8,15,16-tetrahydro-6*H*,14*H*-dibenzo[*f,k*][1]oxa[5]thia[9]azacyclododecin-14-one (203c):

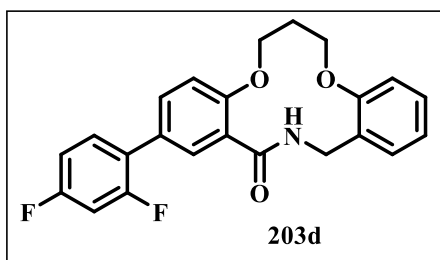


14-one (203c): Prepared according to general procedure 5.8.2.VII, using 2-((3-(2-(1-hydroxyethyl)phenoxy)propyl)thio)benzamide **202c** (26.5mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43%

Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 16-methyl-7,8,15,16-tetrahydro-6*H*,14*H*-dibenzo[*f,k*][1]oxa[5]thia[9]azacyclododecin-14-one

203c (9 mg, 36% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.98 (d, $J = 6.4$ Hz, 1H), 8.08 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.56 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.40 (td, $J = 7.6, 1.4$ Hz, 1H), 7.37 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 7.00 – 6.88 (m, 2H), 5.38 – 5.27 (m, 1H), 4.39 – 4.27 (m, 2H), 3.17 (ddd, $J = 10.8, 6.1, 4.6$ Hz, 1H), 3.07 – 2.96 (m, 1H), 2.31 (ddd, $J = 9.9, 7.8, 3.9$ Hz, 1H), 2.10 – 1.99 (m, 1H), 1.68 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 156.3, 137.6, 136.5, 131.9, 131.2, 130.7, 130.6, 129.4, 129.1, 128.8, 121.2, 112.5, 64.6, 49.3, 34.0, 25.5, 19.8. **IR** (neat): 3348, 2992, 2928, 1660, 1600, 1555, 1250 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{19}\text{NNaO}_2\text{S}$ 336.1034 Found: 336.1031.

12-(2,4-difluorophenyl)-7,8,15,16-tetrahydro-6*H*,14*H*-

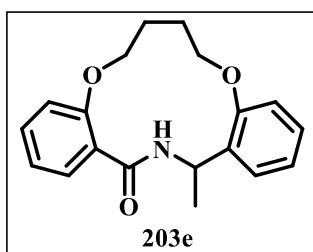


dibenzo[*f,k*][1,5]dioxo[9]azacyclododecin-14-one (203d): Prepared according to general procedure 5.8.2.VII, using 2',4'-difluoro-4-(3-(2-(hydroxymethyl)phenoxy)propoxy)-[1,1'-biphenyl]-3-carboxamide **202d** (46 mg, 0.1 mmol, 1 equiv.) dissolved

in acetonitrile (2.5 mL) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 12-(2,4-difluorophenyl)-7,8,15,16-

tetrahydro-6*H*,14*H*-dibenzo[*f,k*][1,5]dioxo[9]azacyclododecin-14-one **203d** (22 mg, 54% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 10.24 (d, *J* = 5.1 Hz, 1H), 8.35 – 8.28 (m, 1H), 7.55 (dt, *J* = 8.5, 2.1 Hz, 1H), 7.40 (td, *J* = 8.7, 6.5 Hz, 1H), 7.25 (td, *J* = 9.3, 4.5 Hz, 2H), 7.01 – 6.84 (m, 5H), 4.68 (d, *J* = 5.8 Hz, 2H), 4.32 (dd, *J* = 9.1, 4.3 Hz, 4H), 2.46 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.0, 157.0, 156.4, 132.8 (d, *J* = 4.1 Hz), 132.2, 131.5, 131.4 (dd, *J* = 9.4, 4.9 Hz), 130.2, 128.6, 128.2, 126.4, 122.7, 121.1, 111.8, 111.7, 111.7, 111.5, 111.5, 104.4 (m), 68.8, 68.0, 41.8, 28.8. **IR** (neat): 3361, 2994, 2927, 1655, 1603, 1546, 1238, 966 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₃H₂₀F₂NO₃, 396.1411 found: 396.1407.

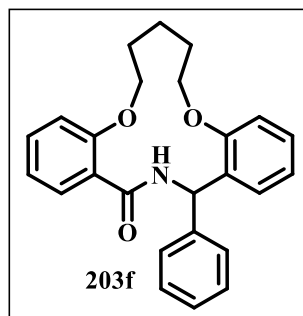
17-methyl-6,7,8,9,16,17-hexahydro-15*H*-dibenzo[*b,g*][1,9]dioxo[5]azacyclotridecin-15-



one (203e): Prepared according to general procedure 5.8.2.VII, using 2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzamide **202e** (26.4 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05 M) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous

2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 17-methyl-6,7,8,9,16,17-hexahydro-15*H*-dibenzo[*b,g*][1,9]dioxo[5]azacyclotridecin-15-one **203e** (17 mg, 61% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 9.89 (d, *J* = 9.1 Hz, 1H), 8.30 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.40 (ddd, *J* = 8.3, 7.4, 1.9 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.24 – 7.19 (m, 1H), 7.11 – 7.02 (m, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.92 (ddd, *J* = 7.4, 3.7, 1.0 Hz, 2H), 5.44 (dq, *J* = 9.2, 6.9 Hz, 1H), 4.24 – 4.13 (m, 4H), 2.42 – 2.19 (m, 2H), 2.10 – 1.94 (m, 2H), 1.53 (d, *J* = 6.9 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 163.8, 157.6, 156.9, 132.6, 132.5, 131.6, 129.9, 128.3, 122.0, 121.4, 121.4, 113.0, 112.7, 69.9, 67.8, 50.0, 27.2, 26.7, 23.0. **IR** (neat): 3351, 2995, 2922, 1663, 1604, 1555, 1220 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₁₉H₂₁NNaO₃, 334.1418 found: 334.1421.

18-phenyl-7,8,9,10,17,18-hexahydro-6*H*,16*H*-

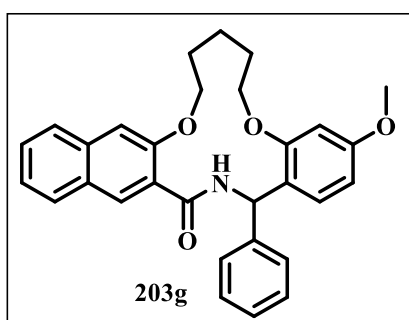


dibenzo[*b,g*][1,9]dioxo[5]azacyclotetradecin-16-one (203f):

Prepared according to general procedure 5.8.2.VII, using 2-(4-(2-(1-hydroxyethyl)phenoxy)butoxy)benzamide **202f** (32.5 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05 M) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43% Ru-

Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 18-phenyl-7,8,9,10,17,18-hexahydro-6*H*,16*H*-dibenzo[*b,g*][1,9]dioxo[5]azacyclotetradecin-16-one **203f** (23 mg, 74% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 9.31 (d, *J* = 9.3 Hz, 1H), 8.37 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.54 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.30 (td, *J* = 8.0, 1.7 Hz, 1H), 7.27 – 7.19 (m, 4H), 7.15 (t, *J* = 6.8 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.99 (td, *J* = 7.4, 0.8 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 9.4 Hz, 1H), 4.28 – 4.18 (m, 1H), 4.03 (dd, *J* = 11.8, 7.3 Hz, 2H), 3.78 (dt, *J* = 8.9, 4.4 Hz, 1H), 2.11 – 1.88 (m, 2H), 1.80 – 1.67 (m, 2H), 1.66 – 1.58 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.8, 157.4, 156.8, 142.2, 133.1, 132.9, 131.8, 129.3, 129.2, 127.8, 126.1, 125.8, 121.0, 120.9, 120.6, 111.5, 111.3, 67.8, 63.6, 56.1, 25.5, 25.1, 20.4. **IR** (neat): 3395, 2994, 1641, 1493, 1252, 1180 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₅H₂₅NNaO₃, 388.1912 found: 388.1916.

3-methoxy-20-phenyl-7,8,9,10,19,20-hexahydro-6*H*,18*H*-benzo[*b*]naphtho[2,3-

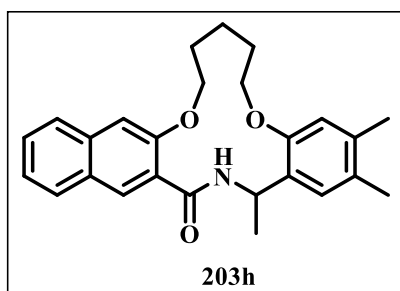


g][1,9]dioxo[5]azacyclotetradecin-18-one (203g):

Prepared according to general procedure 5.8.2.VII, using 3-((5-(2-(hydroxy(phenyl)methyl)-5-methoxyphenoxy)pentyl)oxy)-2-naphthamide **202g** (41 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05 M) as a solvent and flowed through the Omnifit® column

reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 3-methoxy-20-phenyl-7,8,9,10,19,20-hexahydro-6*H*,18*H*-benzo[*b*]naphtho[2,3-*g*][1,9]dioxo[5]azacyclotetradecin-18-one **203g** (14 mg, 35% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 9.36 (d, *J* = 9.3 Hz, 1H), 8.92 (s, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.40 – 7.33 (m, 1H), 7.32 – 7.08 (m, 7H), 6.72 (d, *J* = 9.3 Hz, 1H), 6.50 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 4.38 – 4.27 (m, 1H), 4.12 (dd, *J* = 11.7, 5.9 Hz, 1H), 4.01 (td, *J* = 9.4, 5.0 Hz, 1H), 3.86 – 3.74 (m, 4H), 2.13 – 1.91 (m, 2H), 1.62 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.59, 160.92, 157.85, 154.77, 142.51, 135.93, 134.88, 132.25, 129.43, 128.33, 128.30, 127.84, 126.17, 126.11, 125.85, 124.44, 122.10, 122.04, 106.71, 103.61, 99.83, 77.16, 68.06, 63.78, 55.72, 55.55, 25.52, 25.16, 20.60. **IR** (neat): 3386, 2994, 1648, 1504, 1252, 1177 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₃₀H₃₀NO₄, 468.2175 found: 468.2177.

2,3,20-trimethyl-7,8,9,10,19,20-hexahydro-6*H*,18*H*-benzo[*b*]naphtho[2,3-

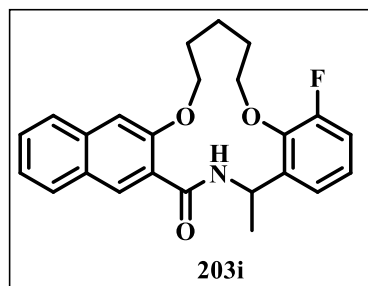


***g*][1,9]dioxo[5]azacyclotetradecin-18-one (203h):**

Prepared according to general procedure 5.8.2.VII, using 3-((5-(2-(1-hydroxyethyl)-4,5-dimethylphenoxy)pentyl)oxy)-2-naphthamide **202h** (20 mg, 0.047 mmol, 1 equiv.) dissolved in acetonitrile (1 mL, 0.05 M) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm

bore x 150 mm length) loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 2,3,20-trimethyl-7,8,9,10,19,20-hexahydro-6*H*,18*H*-benzo[*b*]naphtho[2,3-*g*][1,9]dioxo[5]azacyclotetradecin-18-one **203h** (11 mg, 57% yield) as a brownish sticky compound (20% ethyl acetate in *n*-hexane). ¹H NMR (400 MHz, CDCl₃) δ 9.55 (d, *J* = 8.7 Hz, 1H), 8.82 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.52 – 7.43 (m, 1H), 7.36 (dd, *J* = 11.1, 3.9 Hz, 1H), 7.19 (s, 1H), 6.94 (d, *J* = 15.6 Hz, 2H), 5.50 (dq, *J* = 14.1, 7.0 Hz, 1H), 4.38 – 4.30 (m, 1H), 4.25 – 4.10 (m, 3H), 2.31 (s, 3H), 2.26 (s, 3H), 2.02 (dd, *J* = 14.1, 8.7 Hz, 6H), 1.64 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 154.9, 153.7, 135.7, 135.0, 134.1, 133.4, 131.6, 131.2, 129.2, 128.7, 128.2, 128.0, 126.2, 124.3, 123.0, 106.7, 73.7, 69.5, 50.4, 28.1, 27.8, 24.9, 24.5, 20.6, 16.9. IR (neat): 3371, 2985, 2921, 1661, 1605, 1545, 1232 cm⁻¹. HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₆H₃₀NO₃, 404.2225 found: 404.2221.

4-fluoro-20-methyl-7,8,9,10,19,20-hexahydro-6*H*,18*H*-benzo[*b*]naphtho[2,3-

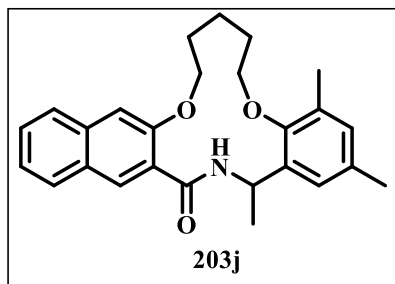


***g*][1,9]dioxo[5]azacyclotetradecin-18-one (203i):** Prepared according to general procedure 5.8.2.VII, using 3-((5-(4-fluoro-2-(1-hydroxyethyl)phenoxy)pentyl)oxy)-2-naphthamide **202i** (35.2 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05 M) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length)

loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 4-fluoro-20-methyl-7,8,9,10,19,20-hexahydro-6*H*,18*H*-benzo[*b*]naphtho[2,3-*g*][1,9]dioxo[5]azacyclotetradecin-18-one **203i** (15 mg, 44% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). ¹H NMR (400 MHz, CDCl₃) δ 8.98 (d, *J* = 9.2 Hz, 1H), 8.85 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.16 – 7.07 (m, 2H), 6.95 – 6.87 (m, 1H), 6.81 (dd, *J* = 8.9, 4.4 Hz, 1H), 5.55 (dq, *J* = 9.1, 7.0 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.13 (dd, *J* = 8.1, 3.1 Hz, 3H),

2.30 – 2.12 (m, 2H), 1.94 – 1.72 (m, 4H), 1.68 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.1, 157.9, 155.5, 154.5, 153.4, 153.3, 135.8, 134.5, 131.6 (d, $J = 6.6$ Hz) 129.4, 128.4, 126.1, 124.4, 122.3, 117.7 (d, $J = 23.2$ Hz), 114.2 (d, $J = 22.5$ Hz), 111.5 (d, $J = 8$ Hz), 106.6, 67.9, 64.3, 49.8, 26.0, 25.3, 20.8, 20.5. **IR** (neat): 3345, 2990, 2930, 1655, 1597, 1210, 985 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{25}\text{FNO}_3$, 394.1818 found: 394.1813.

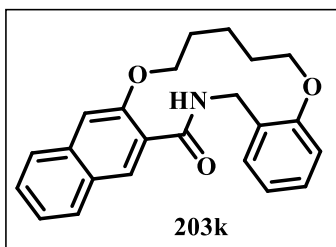
2,4,20-trimethyl-7,8,9,10,19,20-hexahydro-6H,18H-benzo[b]naphtho[2,3-



g][1,9]dioxo[5]azacyclotetradecin-18-one (203j): Prepared according to general procedure **5.8.2.VII**, using 3-((5-(2-(1-hydroxyethyl)-4,6-dimethylphenoxy)pentyl)oxy)-2-naphthamide **202j** (33.7 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05M) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm bore x

150 mm length) loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 2,4,20-trimethyl-7,8,9,10,19,20-hexahydro-6H,18H-benzo[b]naphtho[2,3-g][1,9]dioxo[5]azacyclotetradecin-18-one **203j** (14 mg, 49% yield) as a colourless oily compound (20% ethyl acetate in *n*-hexane). ^1H NMR (400 MHz, CDCl_3) δ 9.55 (d, $J = 8.7$ Hz, 1H), 8.82 (s, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 7.70 (d, $J = 8.1$ Hz, 1H), 7.52 – 7.44 (m, 1H), 7.41 – 7.30 (m, 1H), 7.19 (s, 1H), 6.94 (d, $J = 15.1$ Hz, 2H), 5.50 (dq, $J = 14.1, 7.0$ Hz, 1H), 4.38 – 4.31 (m, 1H), 4.26 – 4.12 (m, 3H), 2.31 (s, 3H), 2.26 (s, 3H), 2.12 – 1.93 (m, 6H), 1.63 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.2, 154.9, 153.7, 135.8, 135.0, 134.1, 133.5, 131.6, 131.2, 129.3, 128.7, 128.2, 128.0, 126.2, 124.3, 123.0, 106.7, 73.7, 69.5, 50.4, 28.1, 27.9, 24.9, 24.5, 20.7, 17.0. **IR** (neat): 3368, 2982, 2923, 1662, 1604, 1548, 1235 cm^{-1} . **HRMS** (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{NO}_4$, 370.2018 found: 370.2017.

7,8,9,10,19,20-hexahydro-6H,18H-benzo[b]naphtho[2,3-

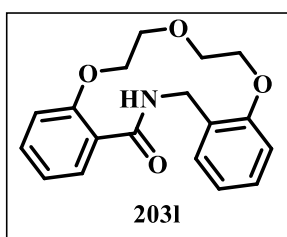


g][1,9]dioxo[5]azacyclotetradecin-18-one (203k): Prepared according to general procedure **5.8.2.VII**, using 3-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthamide **202k** (30.4 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05M) as a solvent and flowed through the Omnifit® column

reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 7,8,9,10,19,20-hexahydro-6H,18H-benzo[b]naphtho[2,3-g][1,9]dioxo[5]azacyclotetradecin-18-one **203k** (5

mg, 17% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 8.87 (s, 1H), 8.82 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.40 – 7.33 (m, 1H), 7.28 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.12 (s, 1H), 6.96 – 6.88 (m, 2H), 4.75 (d, *J* = 6.0 Hz, 2H), 4.19 (dd, *J* = 7.5, 4.2 Hz, 4H), 2.04 – 1.97 (m, 4H), 1.94 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.6, 157.4, 154.5, 135.8, 134.2, 131.4, 129.4, 129.2, 128.3, 128.2, 126.7, 126.1, 124.4, 122.4, 120.7, 110.4, 106.6, 68.1, 63.6, 40.2, 26.2, 25.6, 20.8. **IR** (neat): 3345, 2995, 1653, 1526, 1181 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₃H₂₄NO₃, 362.1756 found: 362.1751.

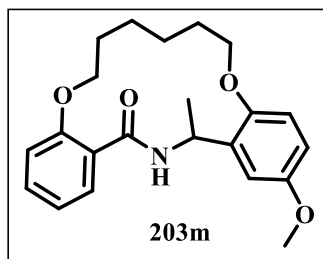
6,7,9,10,17,18-hexahydro-16*H*-dibenzo[*h,m*][1,4,7]trioxa[11]azacyclotetradecin-16-one



(203l): Prepared according to general procedure 5.8.2.VII, using 2-(2-(2-(2-(hydroxymethyl)phenoxy)ethoxy)ethoxy)benzamide **179s** (26.5 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05 M) as a solvent and flowed through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43%

Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 6,7,9,10,17,18-hexahydro-16*H*-dibenzo[*h,m*][1,4,7]trioxa[11]azacyclotetradecin-16-one **203l** (8 mg, 32% yield) as a yellowish sticky compound (30% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 8.77 (s, 1H), 8.23 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.44 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.37 (td, *J* = 7.1, 1.8 Hz, 1H), 7.23 (td, *J* = 8.0, 1.7 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.91 (td, *J* = 7.5, 0.7 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 4.71 (d, *J* = 6.2 Hz, 2H), 4.19 (dd, *J* = 4.2, 2.6 Hz, 4H), 4.02 – 3.98 (m, 2H), 3.97 – 3.92 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.8, 157.3, 156.8, 132.8, 132.5, 131.2, 128.9, 127.5, 121.8, 121.2, 120.9, 111.5, 110.6, 69.4, 68.7, 67.5, 66.0, 39.7. **IR** (neat): 3443, 2930, 1665, 1595, 1201, 1165 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₁₈H₁₉NNaO₄, 336.1211 found: 336.1213.

2-methoxy-19-methyl-6,7,8,9,10,11,18,19-octahydro-17*H*-



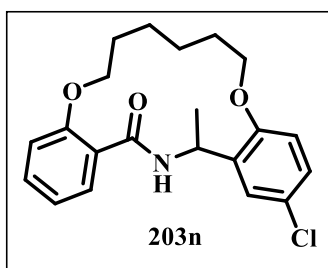
dibenzo[*b,g*][1,9]dioxo[5]azacyclopentadecin-17-one (**203m**):

Prepared according to general procedure 5.8.2.VII, using 2-((6-(2-(1-hydroxyethyl)-4-methoxyphenoxy)hexyl)oxy)benzamide **202l** (31 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05 M) as a solvent and flowed through the Omnifit® column

reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 2-methoxy-19-methyl-6,7,8,9,10,11,18,19-octahydro-17*H*-dibenzo[*b,g*][1,9]dioxo[5]azacyclopentadecin-17-

one **203m** (6 mg, 34% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 8.61 (d, *J* = 8.7 Hz, 1H), 8.20 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.37 (ddd, *J* = 8.4, 7.4, 1.9 Hz, 1H), 7.03 – 6.98 (m, 1H), 6.95 (d, *J* = 3.1 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 8.9 Hz, 1H), 6.72 (dd, *J* = 8.9, 3.1 Hz, 1H), 5.38 (dq, *J* = 14.3, 7.1 Hz, 1H), 4.21 (t, *J* = 5.0 Hz, 2H), 4.06 (t, *J* = 3.8 Hz, 2H), 3.76 (s, 3H), 2.01 – 1.89 (m, 4H), 1.88 – 1.77 (m, 4H), 1.70 (d, *J* = 7.1 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.3, 157.0, 153.5, 151.9, 132.7, 132.5, 132.1, 121.9, 120.9, 116.5, 113.7, 113.2, 111.7, 69.9, 68.7, 55.8, 49.9, 28.0, 28.0, 26.7, 26.0, 20.5. **IR** (neat): 3403, 2992, 1644, 1598, 1221, 1173 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₂H₂₈NO₄, 370.2018 found: 370.2017.

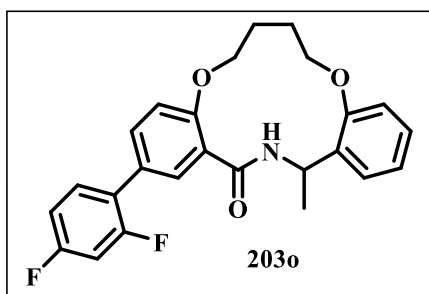
2-chloro-19-methyl-6,7,8,9,10,11,18,19-octahydro-17H-



dibenzo[*b,g*][1,9]dioxo[5]azacyclopentadecin-17-one (**203n**):

Prepared according to general procedure **5.8.2.IVIII**, using 2-((6-(4-chloro-2-(1-hydroxyethyl)phenoxy)hexyl)oxy)benzamide **202m** (31 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05 M) as a solvent and flowed through the Omnitfit® column reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 2-chloro-19-methyl-6,7,8,9,10,11,18,19-octahydro-17H-dibenzo[*b,g*][1,9]dioxo[5]azacyclopentadecin-17-one **203n** (9 mg, 30% yield) as a white solid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 8.59 (d, *J* = 7.8 Hz, 1H), 8.20 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 2H), 7.14 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.35 (dd, *J* = 15.5, 7.4 Hz, 1H), 4.24 (t, *J* = 5.0 Hz, 2H), 4.07 (ddd, *J* = 17.5, 9.1, 3.2 Hz, 2H), 2.00 – 1.73 (m, 8H), 1.69 (d, *J* = 7.2 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 164.4, 156.9, 156.3, 132.8, 132.7, 132.6, 130.8, 128.1, 125.5, 121.7, 121.0, 113.5, 111.7, 69.3, 68.5, 49.4, 27.9, 26.4, 25.9, 20.1. **IR** (neat): 3400, 2940, 1650, 1585, 1204 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₁H₂₆ClNO₃ 374.1523 found: 374.1530.

13-(2,4-difluorophenyl)-17-methyl-6,7,8,9,16,17-hexahydro-15H-



dibenzo[*b,g*][1,9]dioxo[5]azacyclotridecin-15-one (**203o**):

Prepared according to general procedure **5.8.2.VII**, using 2',4'-difluoro-4-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)-[1,1'-biphenyl]-3-carboxamide (**202t**) (28 mg, 0.08 mmol, 1 equiv.) dissolved in acetonitrile (2 mL, 0.05 M) as a solvent and

flowed through the Omnifit® column reactor bed (6.6 mm bore x 150 mm length) loaded with heterogeneous 2.43% Ru-Zeolite (1.5 gm, 8 cm bed height) with 0.1 mL/min flow rate to afford desired product 13-(2,4-difluorophenyl)-17-methyl-6,7,8,9,16,17-hexahydro-15*H*-dibenzo[*b,g*][1,9]dioxo[5]azacyclotridecin-15-one **203o** (15 mg, 56% yield) as a yellowish liquid compound (20% ethyl acetate in *n*-hexane). **¹H NMR** (400 MHz, CDCl₃) δ 9.91 (d, *J* = 9.2 Hz, 1H), 8.42 (d, *J* = 2.0 Hz, 1H), 7.58 (dt, *J* = 8.5, 2.3 Hz, 1H), 7.43 (td, *J* = 8.7, 6.5 Hz, 1H), 7.28 (d, *J* = 1.5 Hz, 1H), 7.22 (dd, *J* = 11.6, 4.1 Hz, 1H), 7.02 – 6.85 (m, 4H), 5.45 (dd, *J* = 9.2, 6.9 Hz, 1H), 4.31 – 4.15 (m, 4H), 2.48 – 2.20 (m, 2H), 2.14 – 1.97 (m, 2H), 1.54 (d, *J* = 6.9 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 163.5, 157.1, 156.9, 133.1, 132.8, 131.5, 130.0, 128.4, 128.2, 122.2, 121.5, 113.0, 112.8, 111.6 (m), 11.4 (m), 104.6, 104.4, 104.1 (m), 70.2, 67.8, 50.1, 27.1, 26.7, 23.0. **IR** (neat): 3405, 2945, 1656, 1580, 1215 cm⁻¹. **HRMS** (ESI-TOF) *m/z*: [M+H]⁺ calcd for C₂₁H₂₆ClNO₃ 374.1523 found: 374.1530.

5.9 Appendix V: Copies of ^1H and ^{13}C NMR spectra and crystal structure of representative compounds

Entry	Figure No.	Data	Page No.
S1	93 and 94	^1H and ^{13}C	270
S8	95 and 96	^1H and ^{13}C	271
S22	97 and 98	^1H and ^{13}C	272
202c	99 and 100	^1H and ^{13}C	273
202d	101, 102 and 103	^1H , ^{13}C and ^{19}F	274, 275
203a	104 and 105	^1H and ^{13}C	275, 276
203b	106 and 107	^1H and ^{13}C	276, 277
203c	108 and 109	^1H and ^{13}C	277, 278
203e	110 and 111	^1H and ^{13}C	278, 279
203f	112 and 113	^1H and ^{13}C	279, 280
203g	114 and 115	^1H and ^{13}C	280, 281

5.9.1 Copies of NMR Spectra:

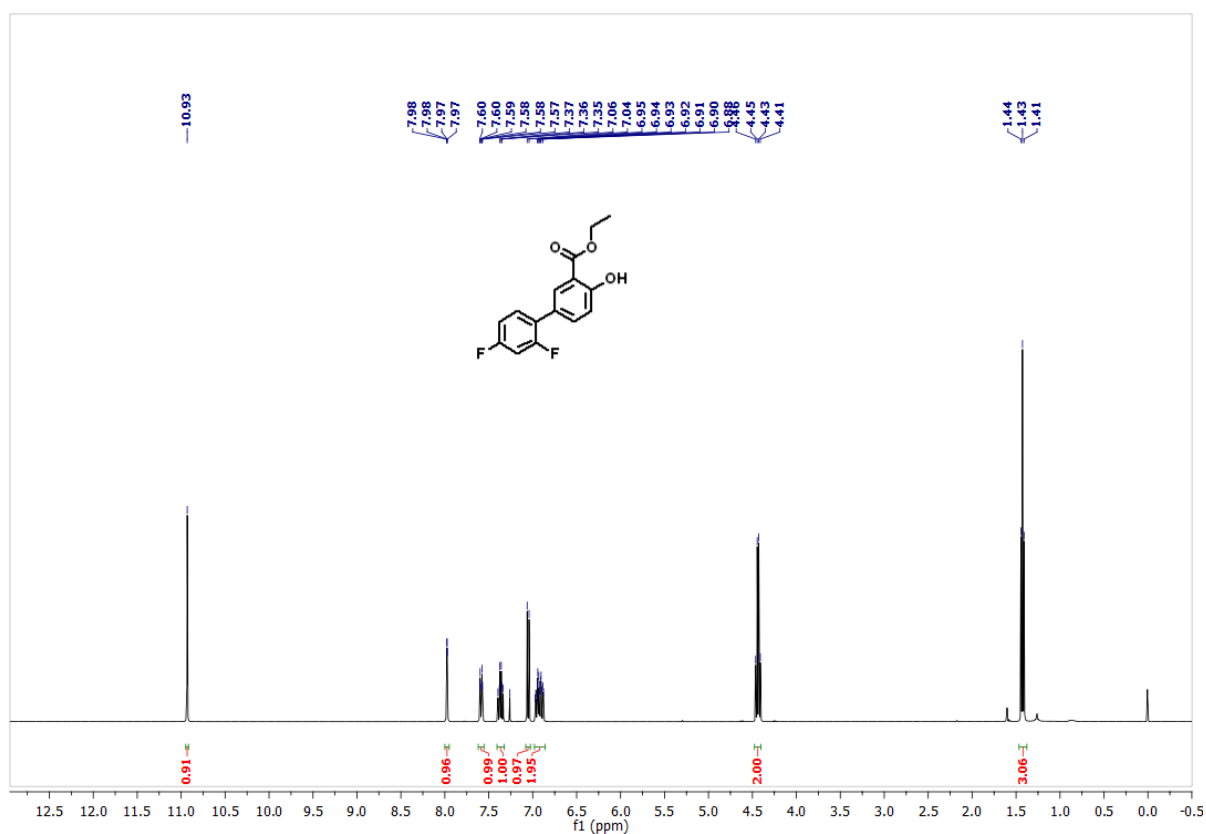


Figure 93. ¹H NMR spectra for compound S1, 400 MHz, CDCl₃

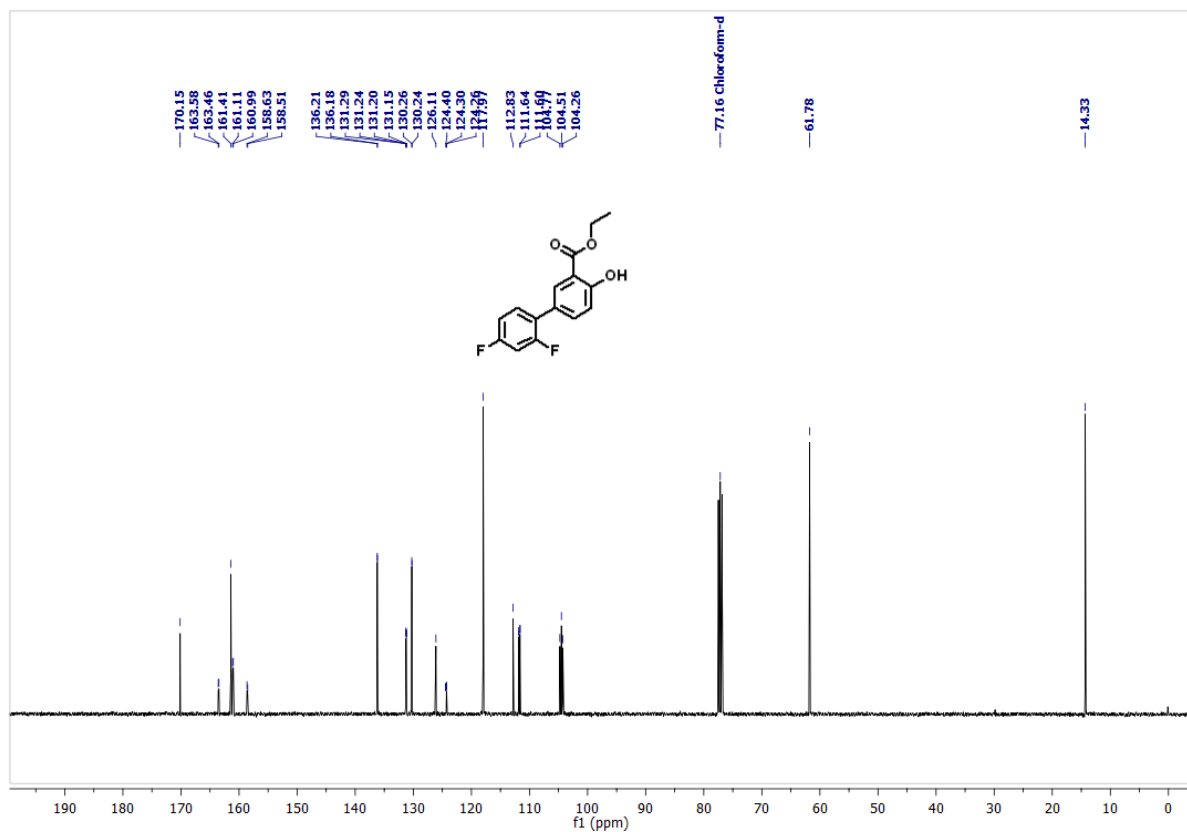


Figure 94. ¹³C NMR spectra for compound S1, 100 MHz, CDCl₃

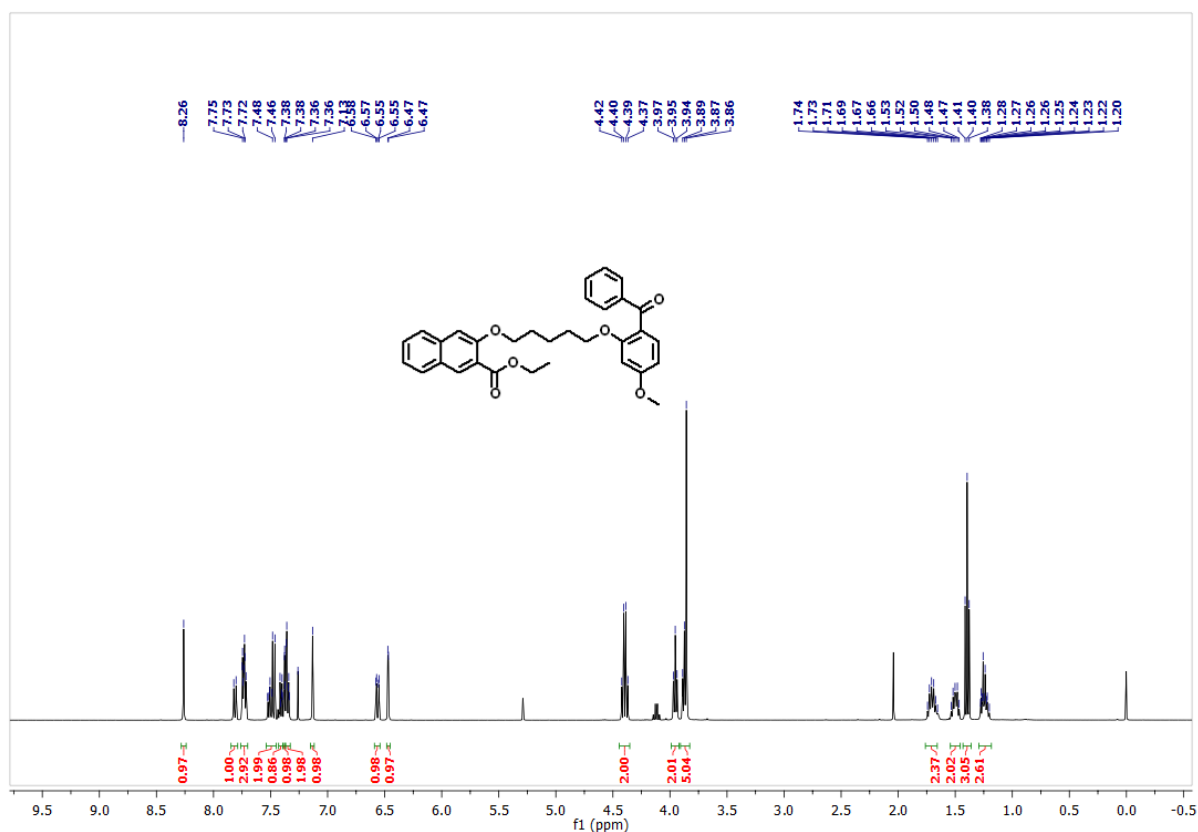


Figure 95. ¹H NMR spectra for compound **S8**, 400 MHz, CDCl₃

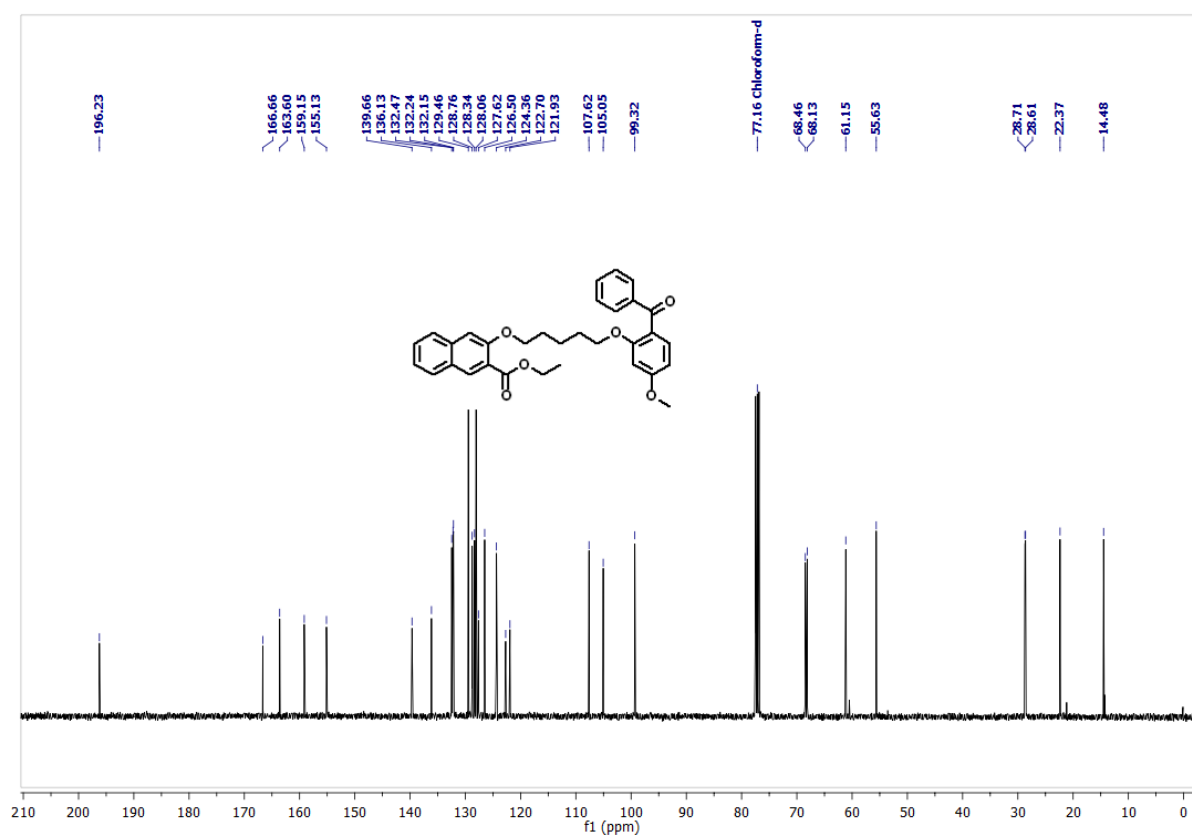


Figure 96. ¹³C NMR spectra for compound **S8**, 100 MHz, CDCl₃

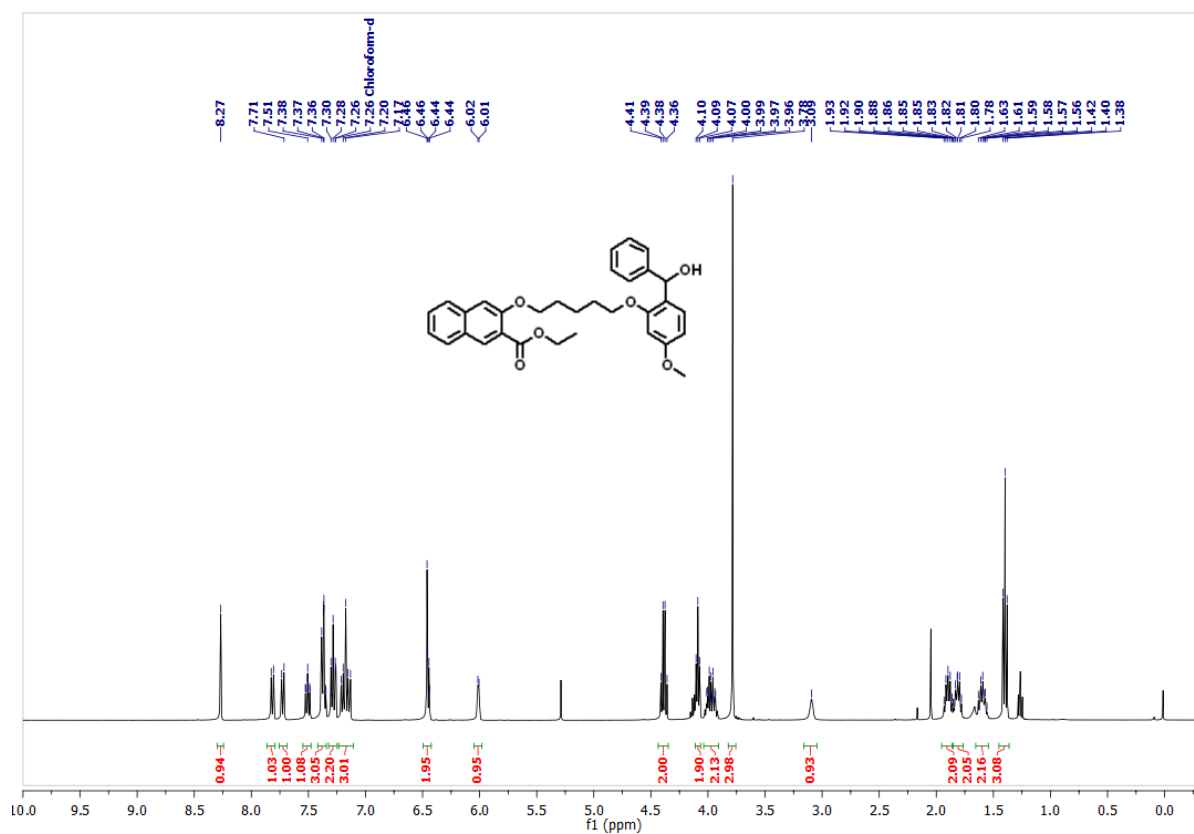


Figure 97. ¹H NMR spectra for compound S22, 400 MHz, CDCl₃

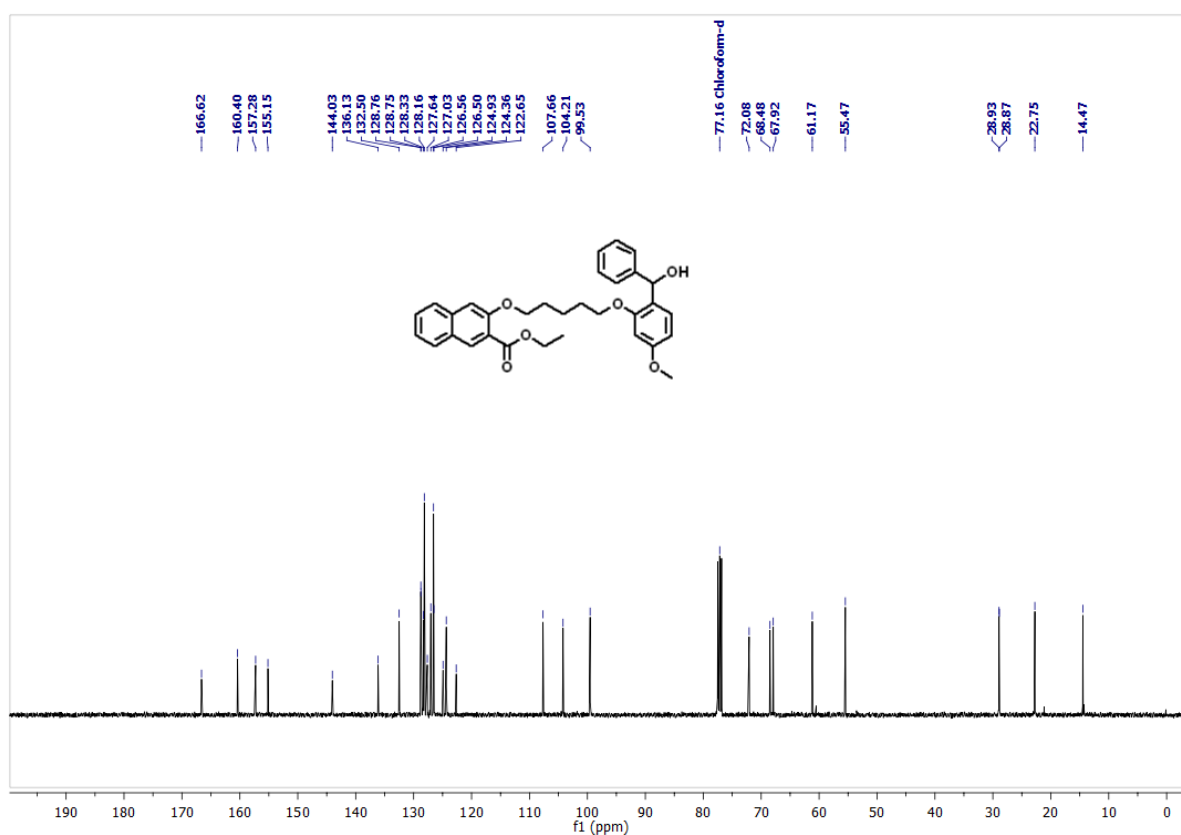


Figure 98. ¹³C NMR spectra for compound S22, 100 MHz, CDCl₃

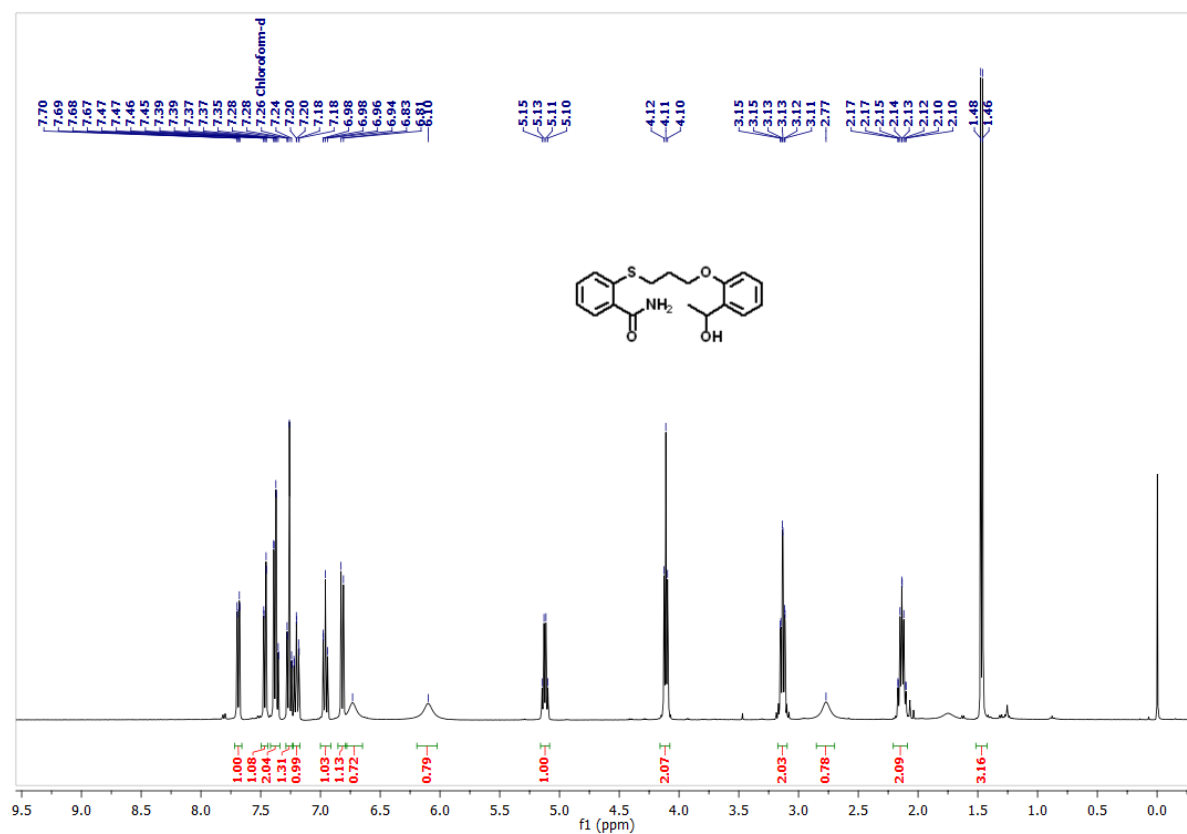


Figure 99. ^1H NMR spectra for compound 202c, 400 MHz, CDCl_3

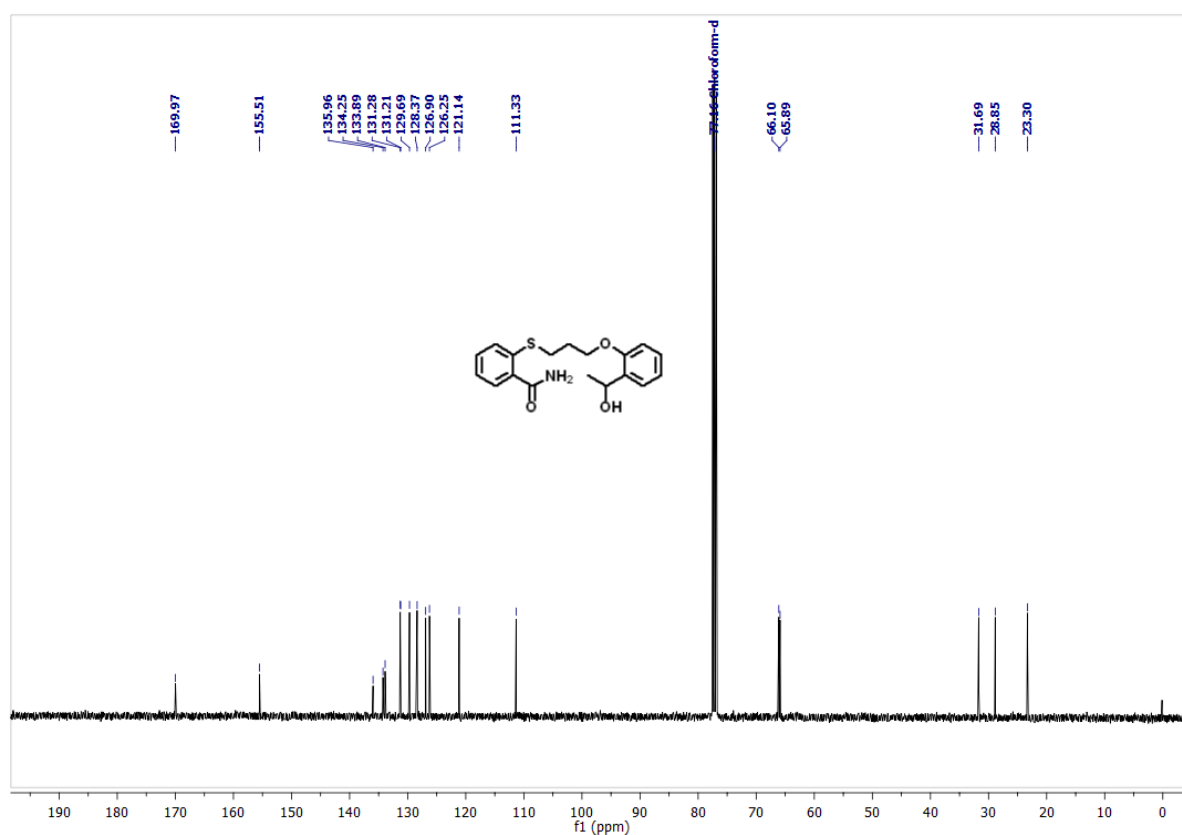


Figure 100. ^{13}C NMR spectra for compound 202c, 100 MHz, CDCl_3

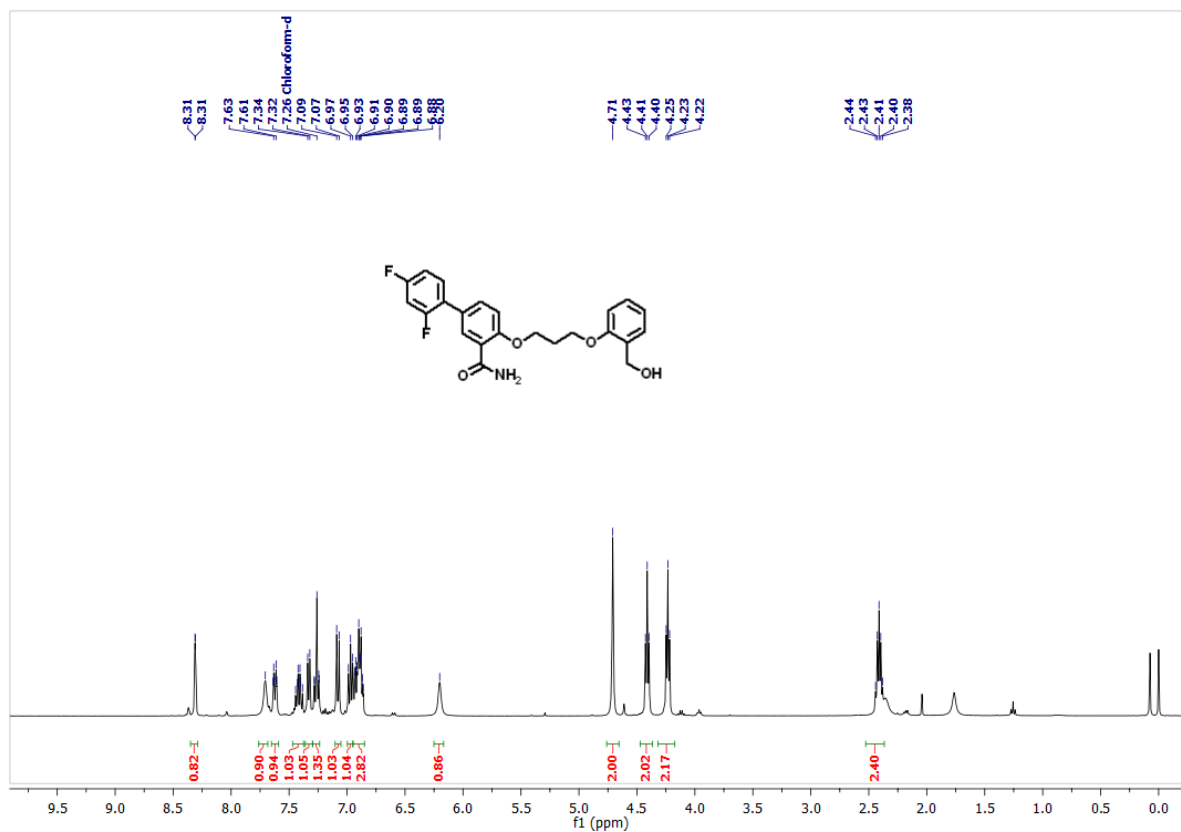


Figure 101. ¹H NMR spectra for compound **202d**, 400 MHz, CDCl₃

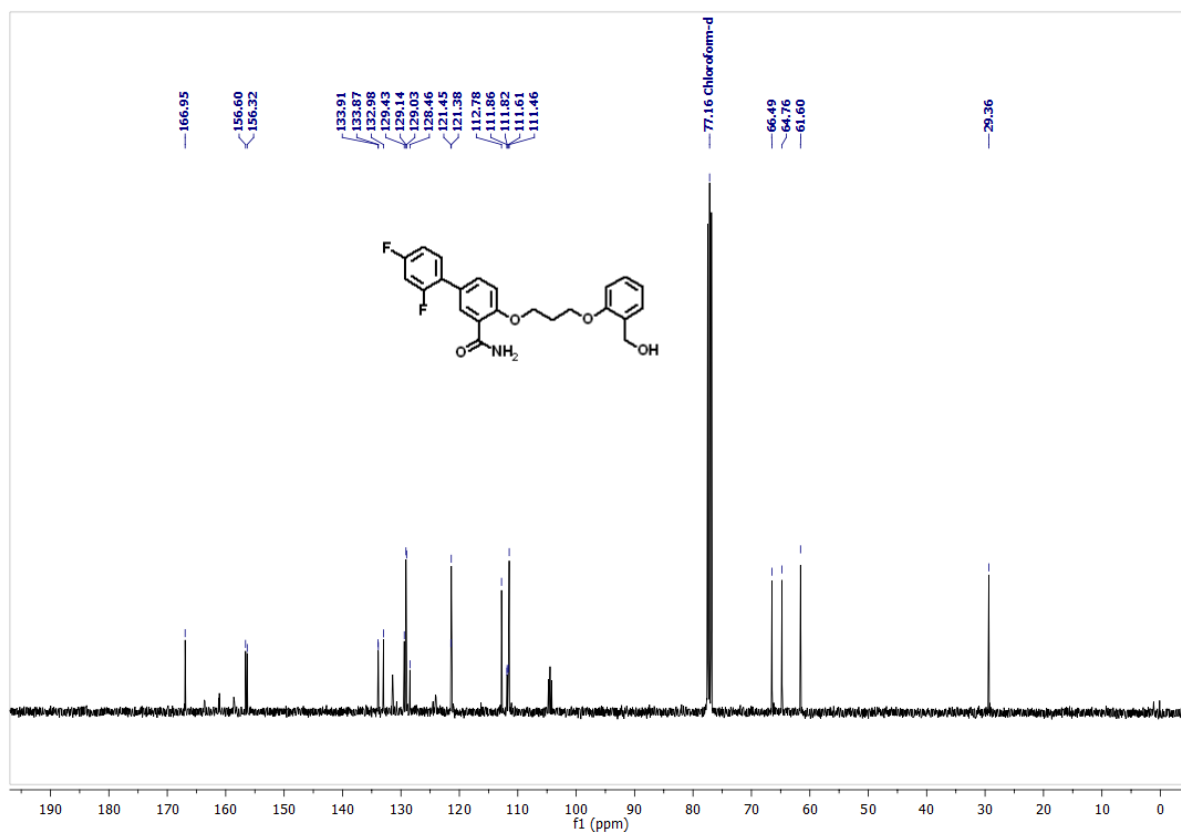


Figure 102. ¹³C NMR spectra for compound **202d**, 100 MHz, CDCl₃

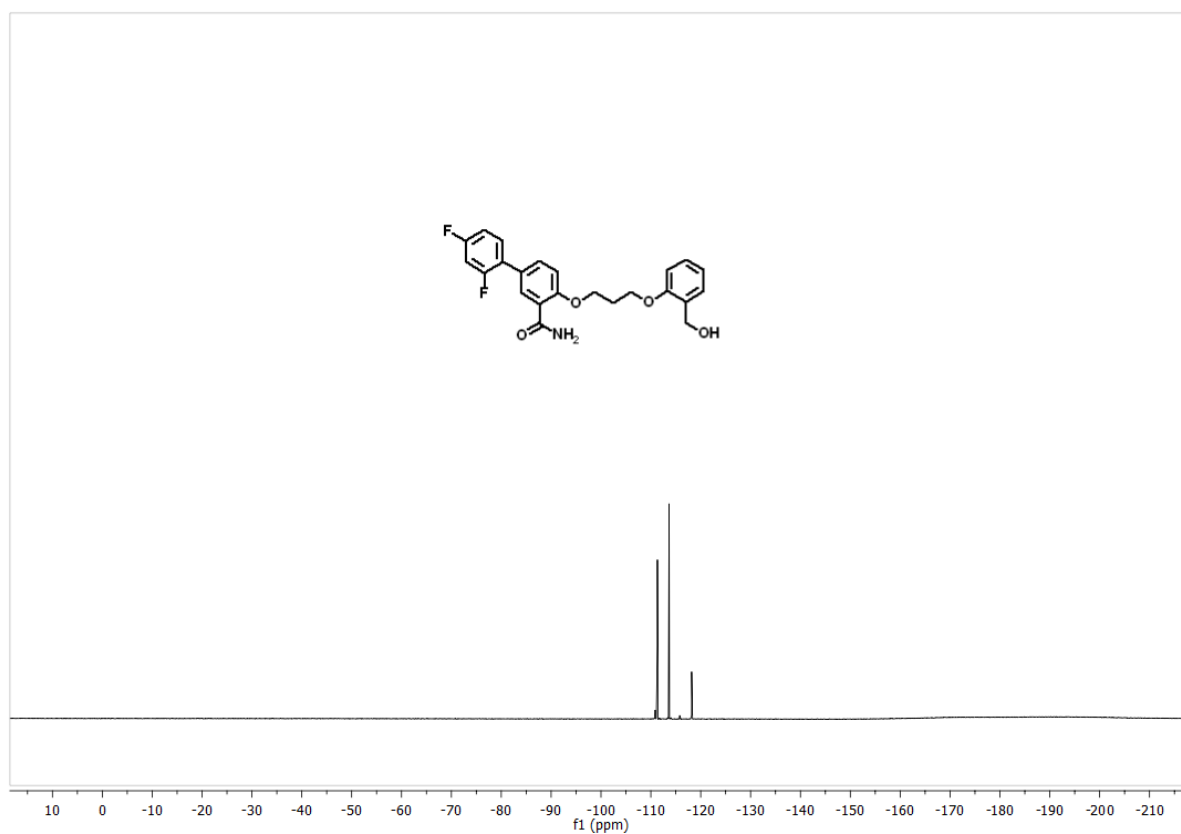


Figure 103. ^{19}F NMR spectra for compound **202d**, 400 MHz, CDCl_3

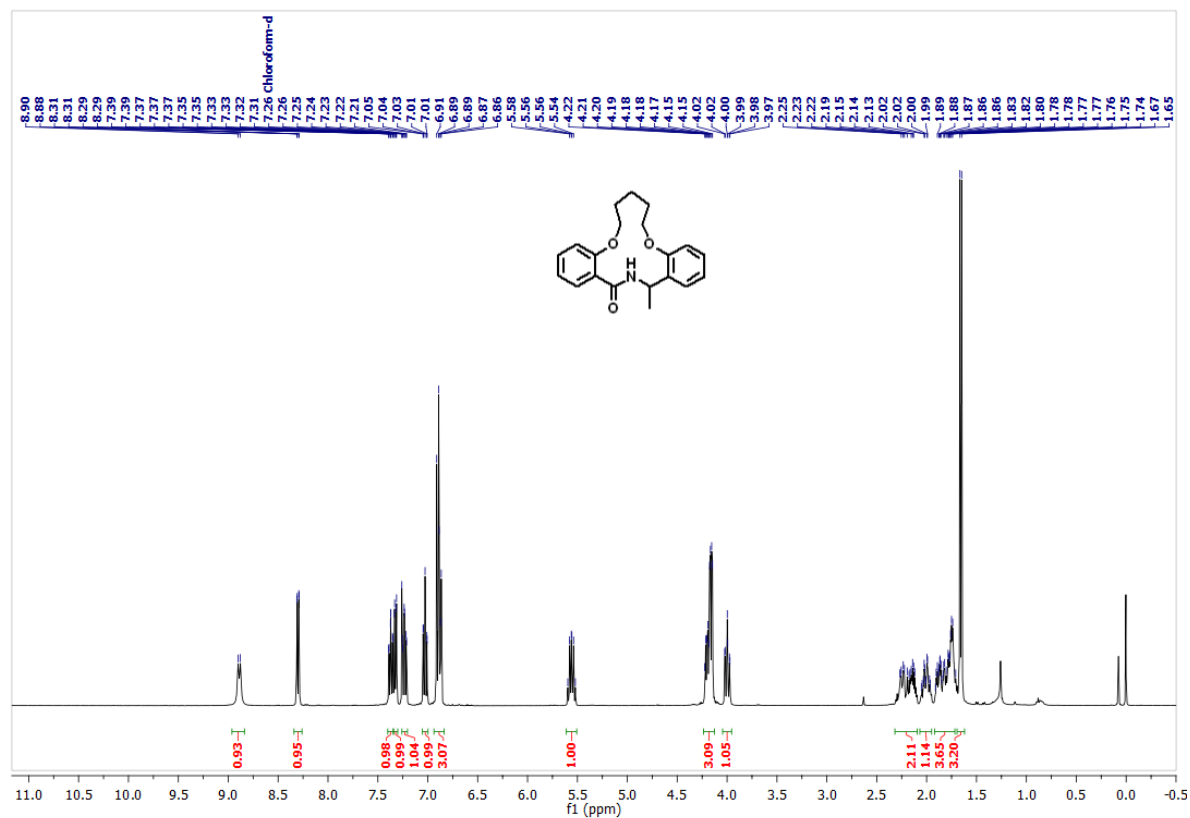


Figure 104. ^1H NMR spectra for compound **203a**, 400 MHz, CDCl_3

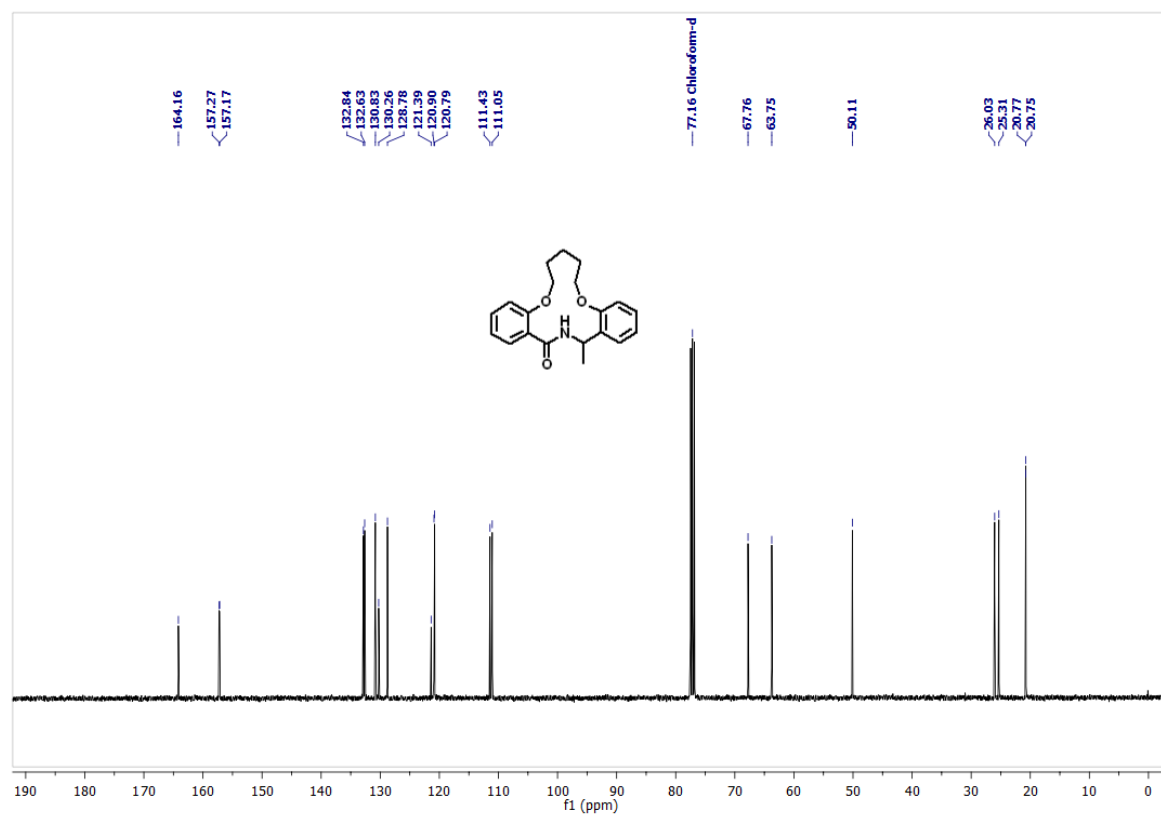


Figure 105. ¹³C NMR spectra for compound **203a**, 100 MHz, CDCl₃

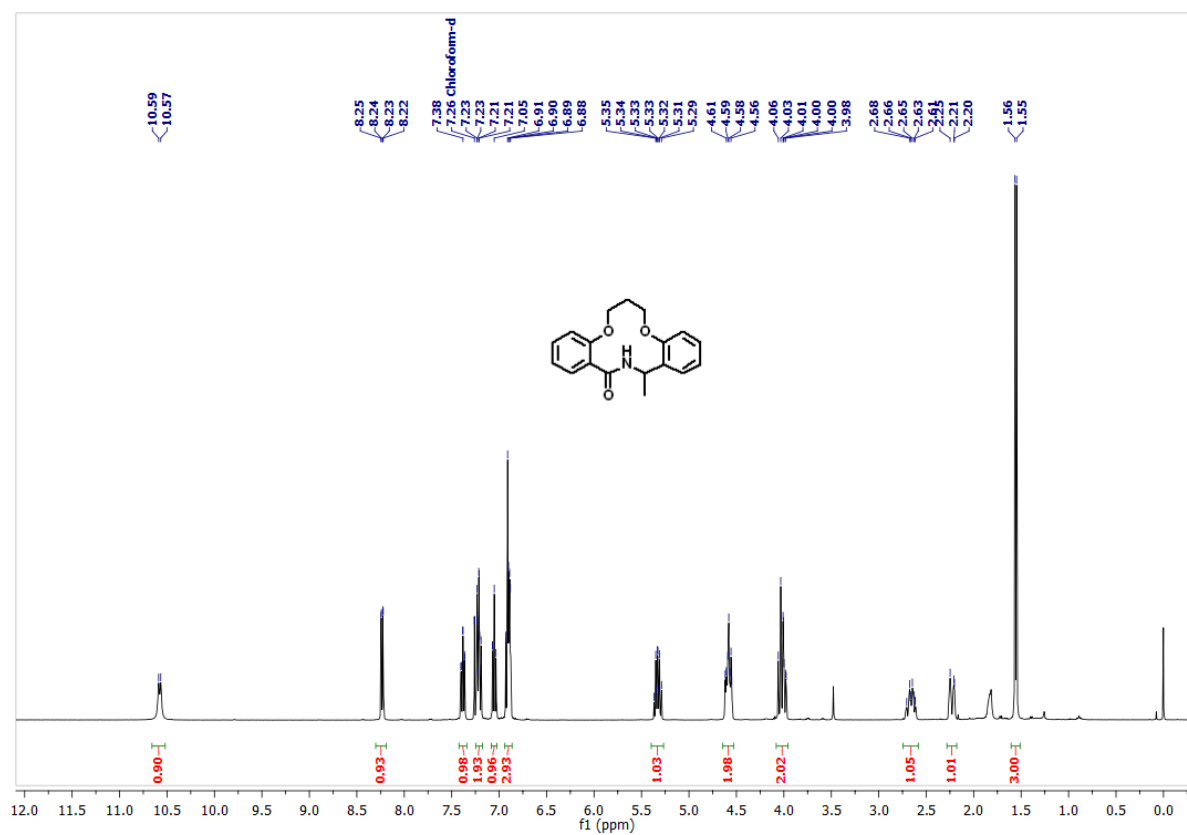


Figure 106. ¹H NMR spectra for compound **203b**, 400 MHz, CDCl₃

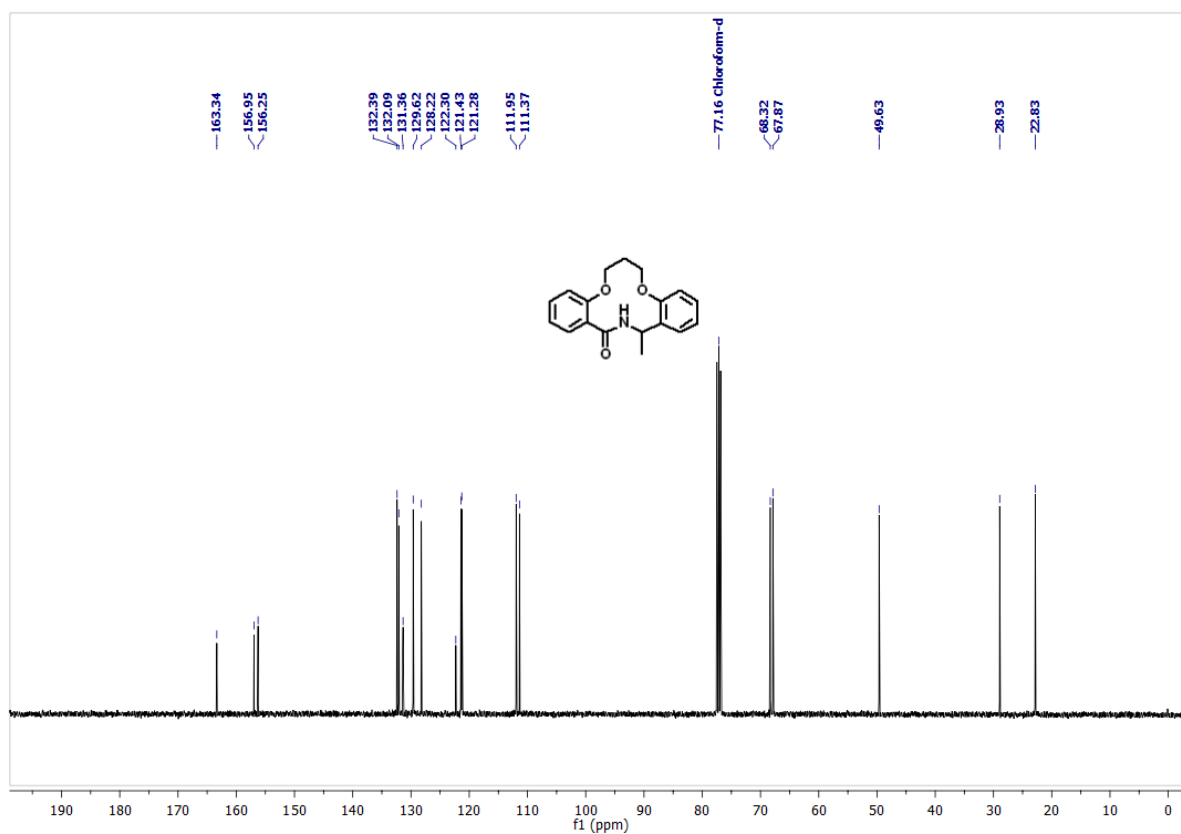


Figure 107. ¹³C NMR spectra for compound **203b**, 100 MHz, CDCl₃

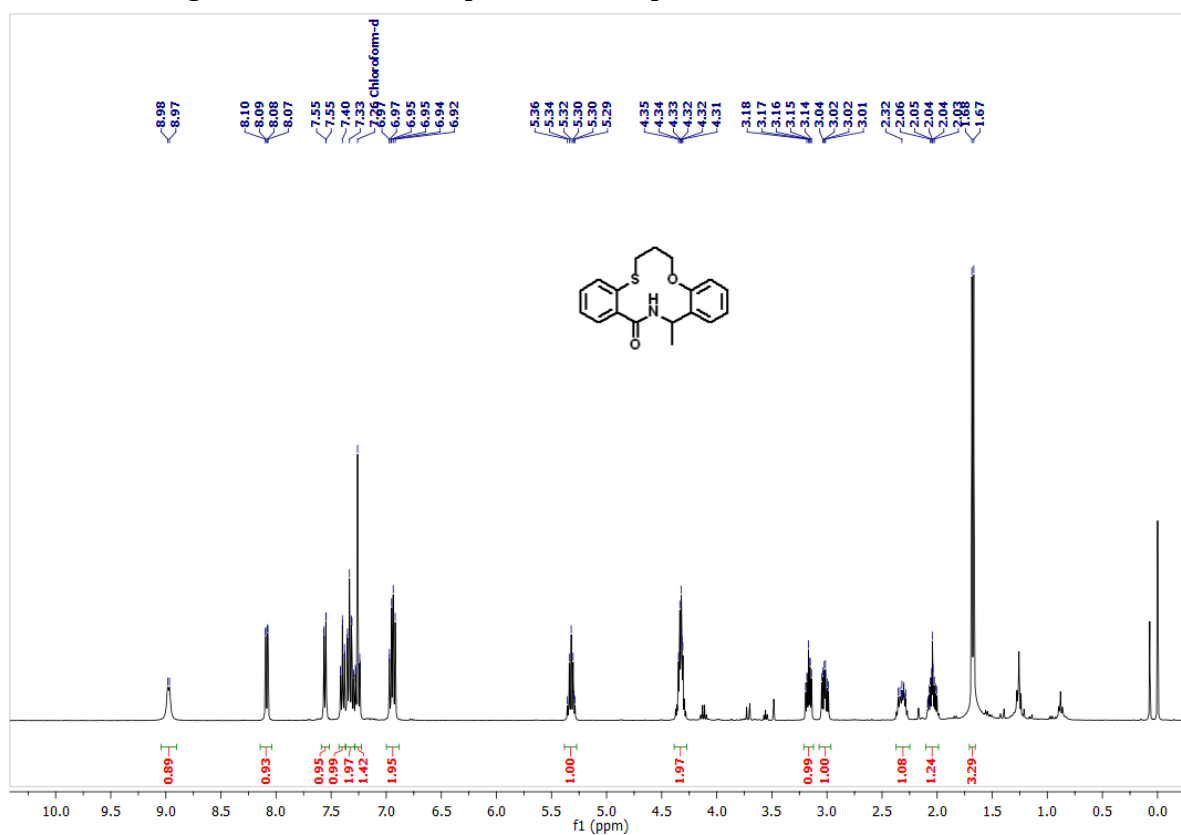


Figure 108. ¹H NMR spectra for compound **203c**, 400 MHz, CDCl₃

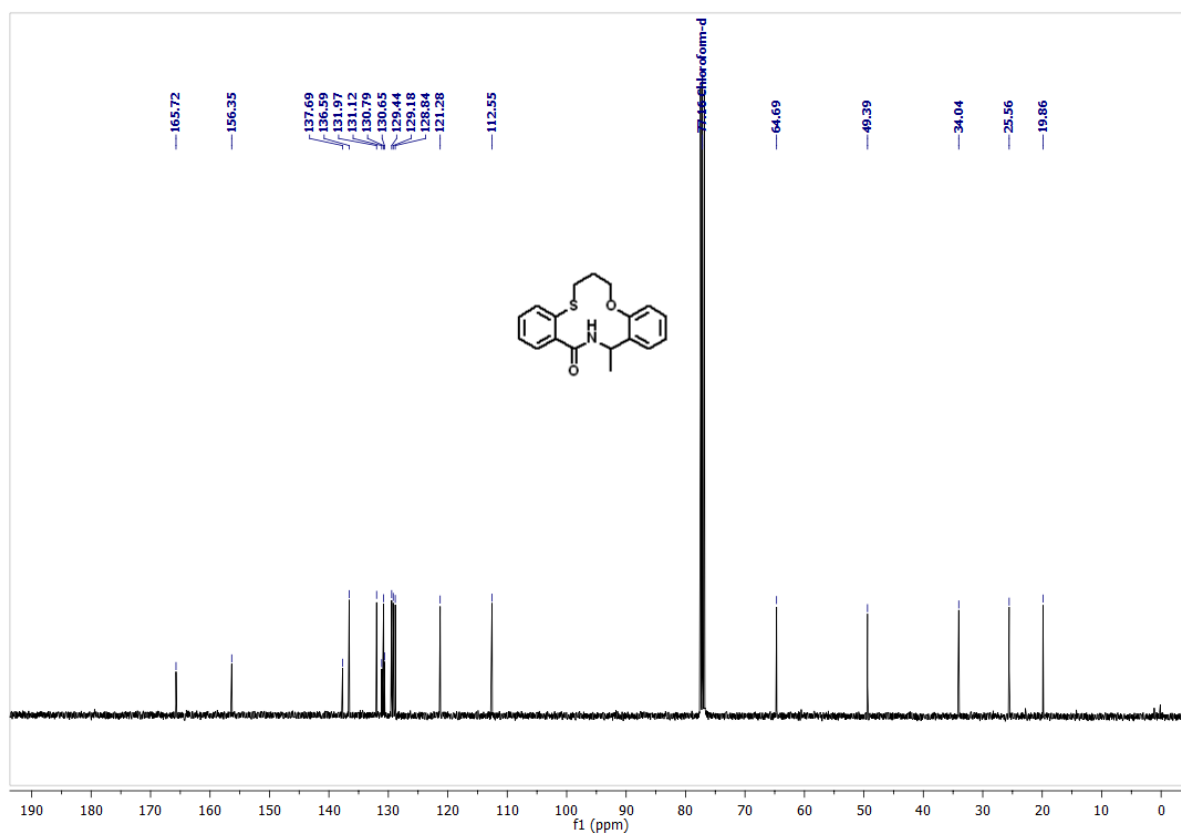


Figure 109. ¹³C NMR spectra for compound **203c**, 100 MHz, CDCl₃

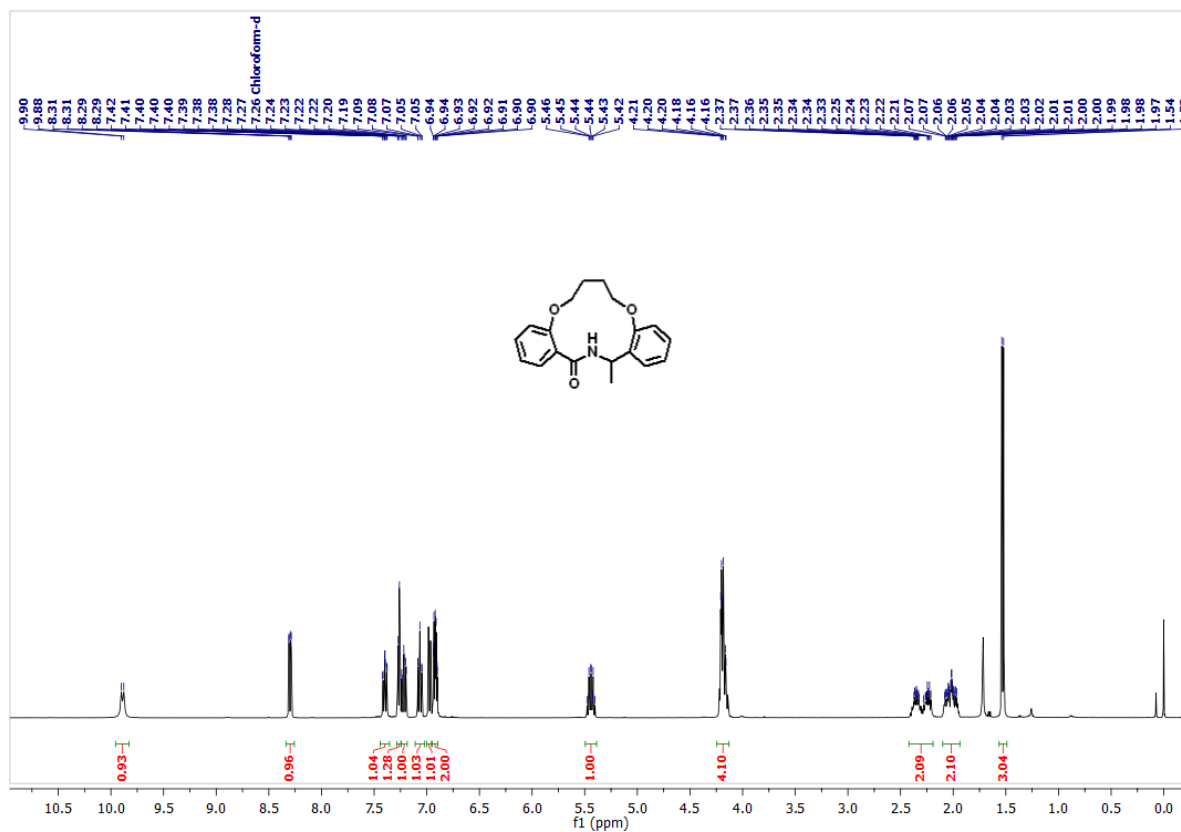


Figure 110. ¹H NMR spectra for compound **203e**, 400 MHz, CDCl₃

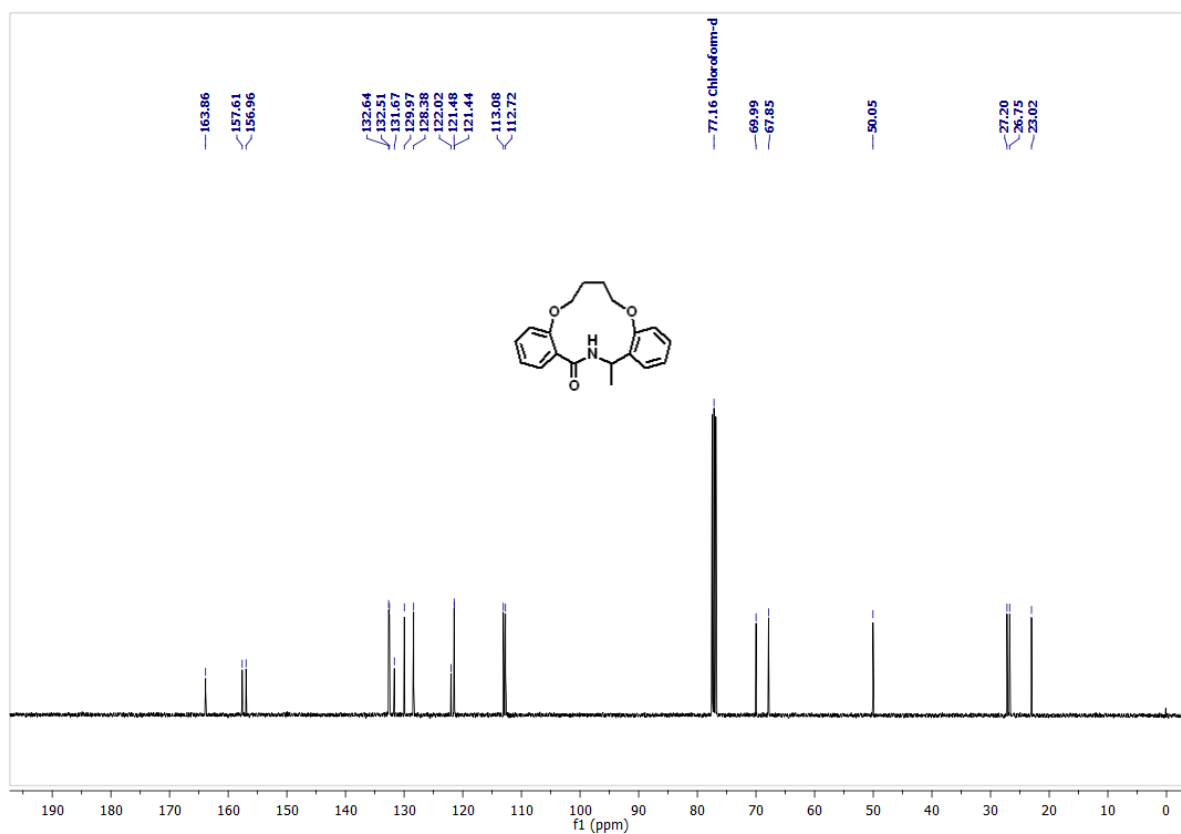


Figure 111. ¹³C NMR spectra for compound **203e**, 100 MHz, CDCl₃

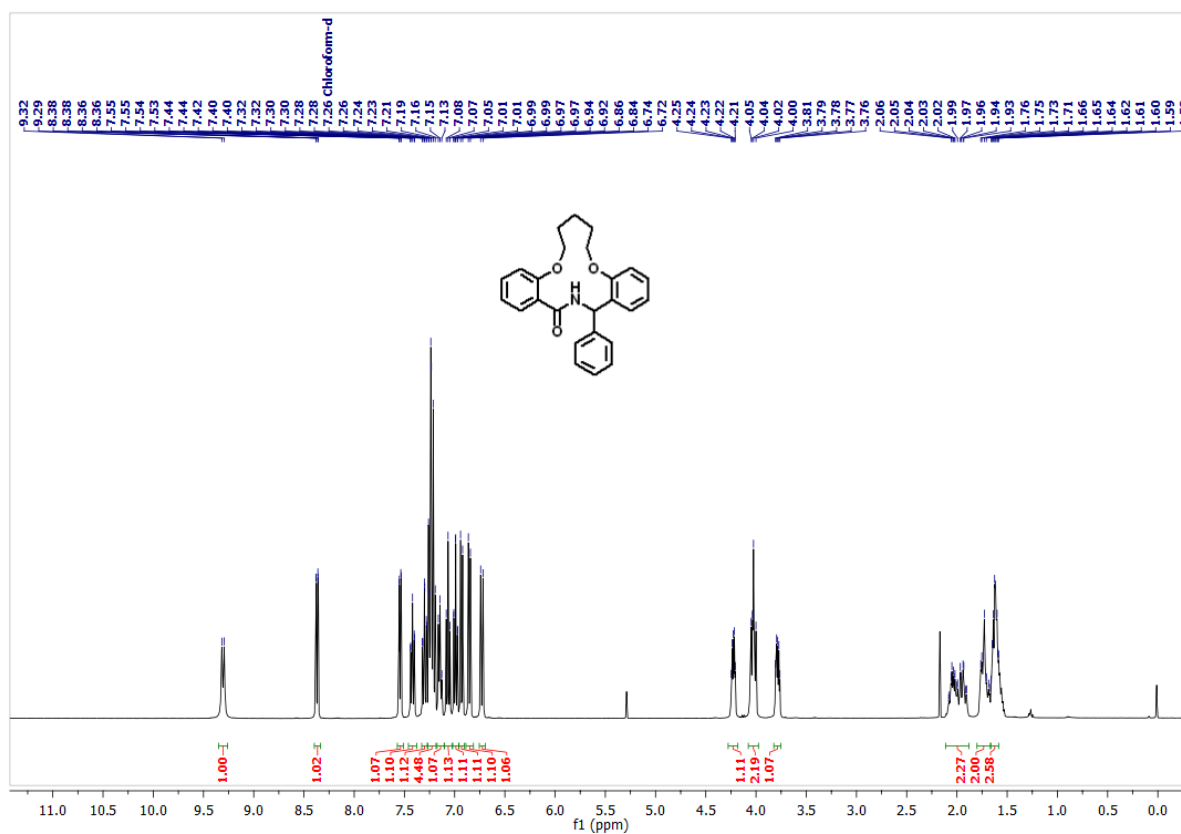


Figure 112. ¹H NMR spectra for compound **203f**, 400 MHz, CDCl₃

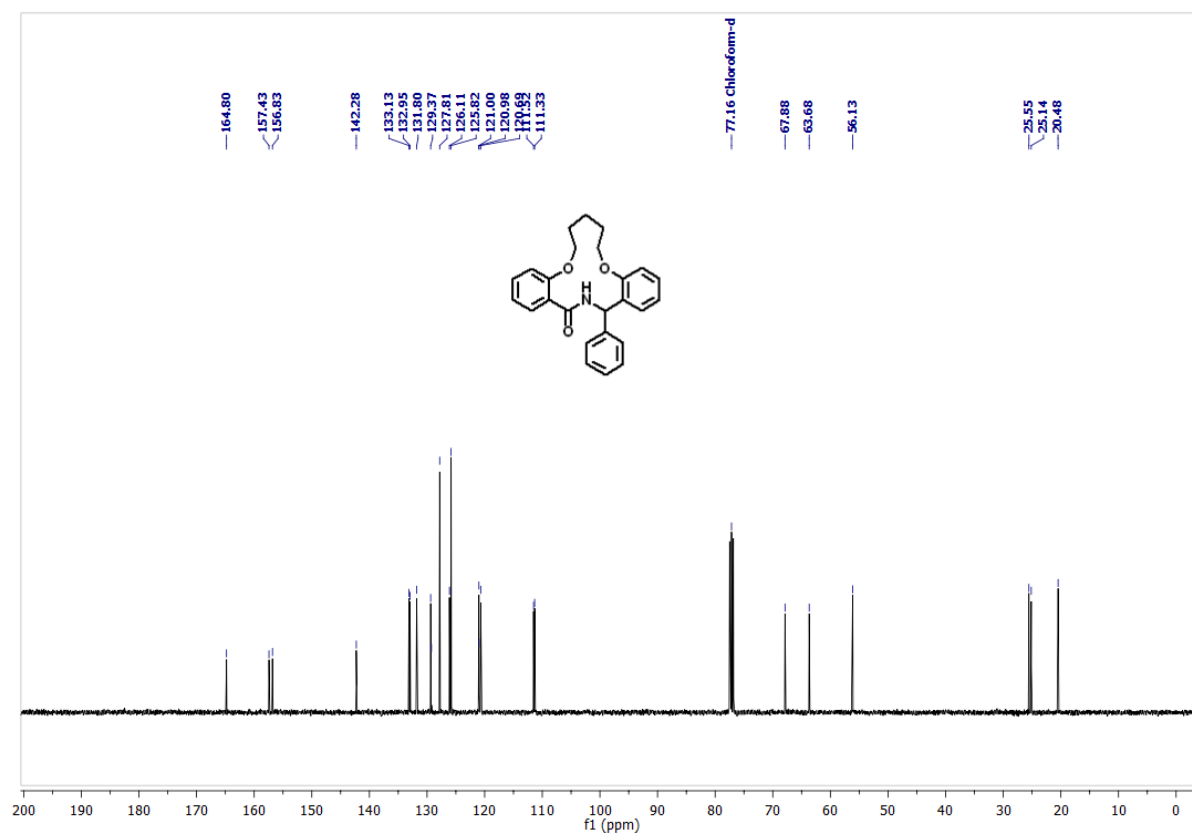


Figure 113. ¹³C NMR spectra for compound **203f**, 100 MHz, CDCl₃

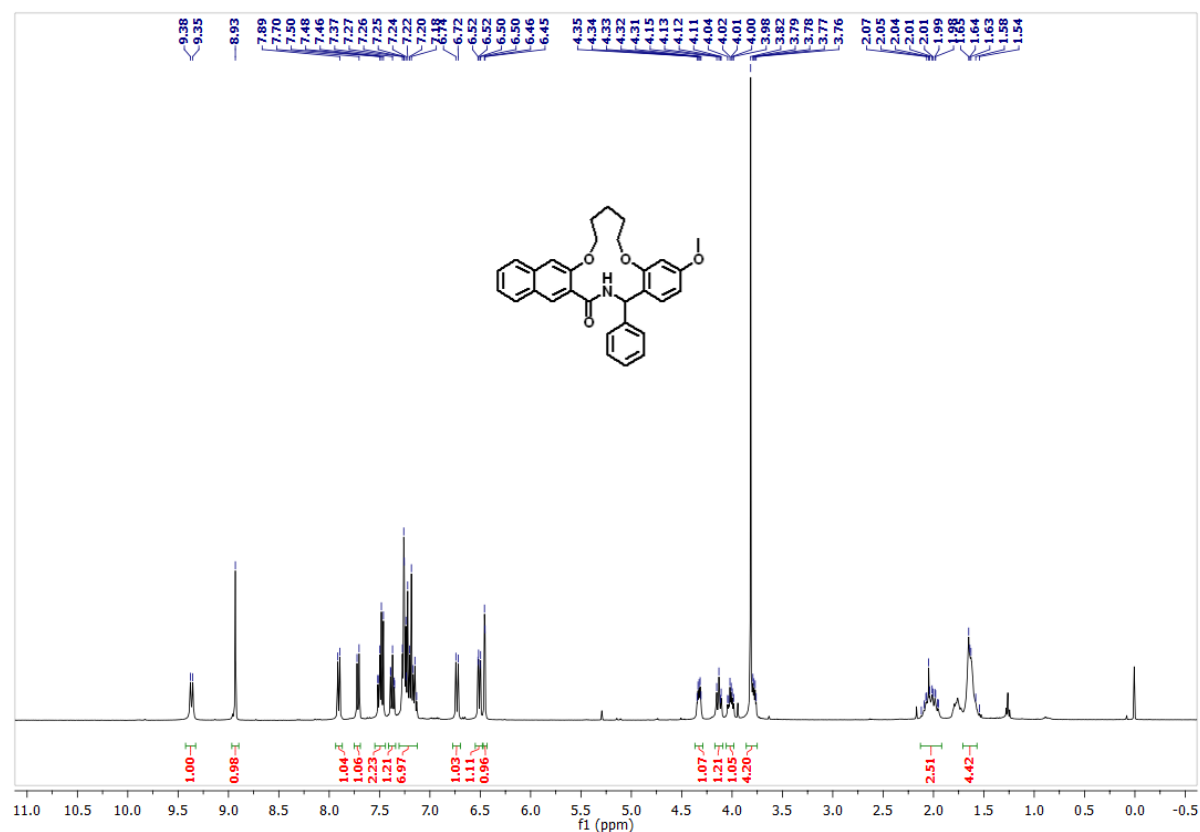


Figure 114. ¹H NMR spectra for compound **203g**, 400 MHz, CDCl₃

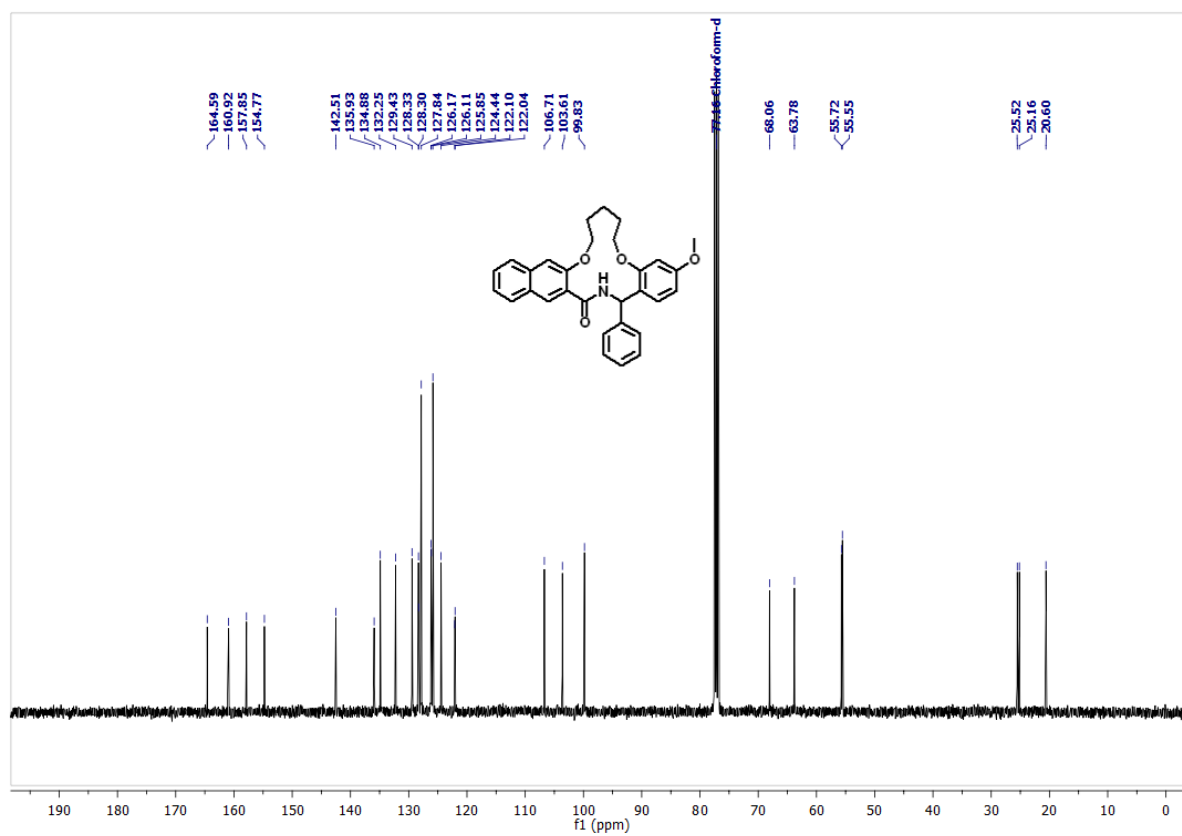


Figure 115. ¹³C NMR spectra for compound **203g**, 100 MHz, CDCl₃

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List Of Publications

1. Pandey, A. M.; Digrawal, N. K.; Mohanta, N.; **Jamdade, A. B.**; Chaudhari, M. B.; Bisht, G. S. and Gnanaprakasam, B. Catalytic Acceptorless Dehydrogenation of Amino Alcohols and 2-Hydroxybenzyl Alcohols for Annulation Reaction under Neutral Condition. *J. Org. Chem.*, **2021**, *86*, 8805-8828.
2. **Jamdade, A. B.**; Sutar, D. S.; Bisht, G. S.; Gnanaprakasam, B. Ru-MACHO Catalyzed Direct Inter/Intramolecular Macrocyclization of Alcohols and Ketones. *Org. Lett.* **2021**, *23*, 7386–7390.
3. **Jamdade, A. B.**; Sutar, D. S.; Gnanaprakasam, B. Dehydrogenative Intramolecular Macrolactonization of Dihydroxy Compounds Using Ru-MACHO Catalyst. *Org. Lett.* **2022**, *24*, 4394–4398.
4. Sutar, D. S.; Sarang, N. U.; **Jamdade, A. B.**; Gnanaprakasam, B. Continuous Flow Inter- and Intramolecular Macrolactonization under High Dilution Condition. *J. Org. Chem.* **2023**, *88*, 3740–3759.
5. **Jamdade, A. B.**; Sutar, D. S.; Gnanaprakasam, B. Synthesis of Macrolactams from Macrolactones Using Ru-/Ir-Catalytic System under Neutral Conditions. *Org. Lett.* **2023**, *25*, 9058–9063.
6. Sutar, D. S.; Swami, G. B.; **Jamdade, A. B.**; Gnanaprakasam, B. Direct Intramolecular Coupling of Primary/Secondary Alcohols with Secondary Alcohols for Macrocyclic Alkenylation Using Ni-Zeolite Catalyst Under Continuous-Flow Conditions. *Adv. Synth. Catal.* **2024**, *366*, 1 – 11.
7. **Jamdade, A. B.**; Swami, G. B.; Sutar, D. S.; Gnanaprakasam, B. Ru-zeolite Catalyzed Dehydrative N-Alkylation of Amides for the Construction of Macrolactams under Continuous Flow Module. *Manuscript Submitted to Wiley- European Journal of Organic Chemistry*.
8. Sutar, D. S.; **Jamdade, A. B.**; Swami, G. B.; Gnanaprakasam, B. Continuous-Flow Ni- or Ru-Zeolite Catalyzed Intramolecular Dehydration of Diols and Seco-acids for Macrocyclic Ethers and Lactones. *Manuscript Submitted to ACS-Journal of Organic Chemistry*.

Ru-MACHO-Catalyzed Direct Inter/Intramolecular Macrocyclization of Alcohols and Ketones

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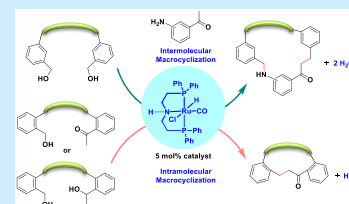


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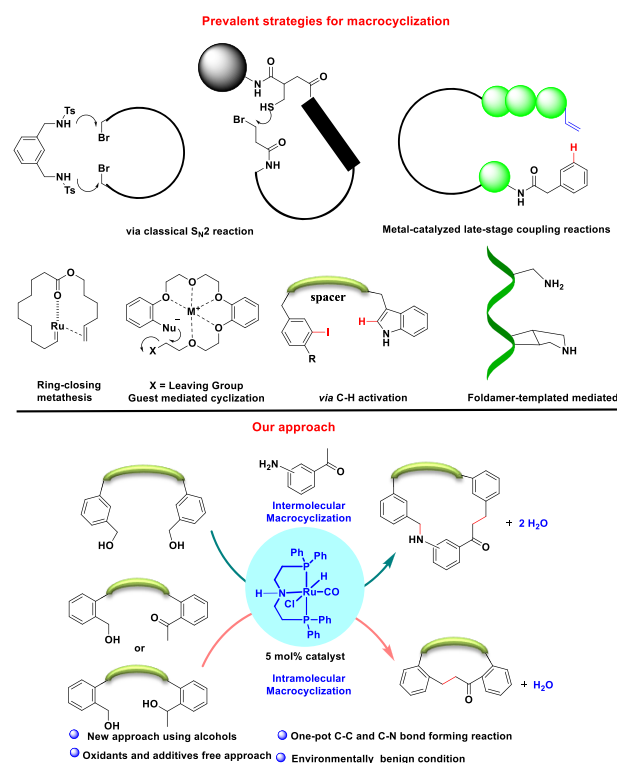
Supporting Information

ABSTRACT: Herein we describe a new approach for end-to-end cyclization to construct macrocycles through the inter/intramolecular dehydrogenative coupling of alcohols and ketones in the presence of a Ru-MACHO catalyst. This method is highly atom economical and sustainable and can be used for many substrates. Additionally, this method results in the generation of only water as the byproduct. Moreover, in this approach, high dilution of the reactants is crucial for cyclization and high-yield macrocycle synthesis.



In chemistry, macrocycles constitute a special class of chemical compounds with ubiquitous structural motifs. Macrocycles of 12 or more atoms form a cyclic ring system in many natural products,¹ and they are widely used in pharmaceutical,² material,³ and supramolecular chemistry.⁴ However, the synthesis of macrocycles through the ring closure of end groups of linear long chains is challenging because of the highly complex entropy process⁵ involved, which possibly leads to competing undesired intermolecular reactions and oligomerization.⁶ Selectivity during macrocyclization is difficult because of possible side reactions, which decrease the yield of the desired product. Despite various challenges in macrocyclization, a significant number of approaches have been developed for the construction of macrocycles. In classical approaches, stoichiometric reagents are required to activate the functional group, and toxic halogenated reagents are used for inter/intramolecular macrocyclization.⁷ These approaches thus result in the generation of a considerable amount of waste byproducts and are unsustainable.⁸ In contemporary macrocyclization approaches, transition-metal-catalyzed reactions have been reported with various end-group functionalities. These approaches have gained considerable attention because of their advantages such as their selectivity, efficiency, high atom economy, low byproduct generation, and sustainability.⁹ Thus numerous approaches have been developed for inter/intramolecular macrocyclization using transition metals as catalysts. Notable synthesis strategies include ring-closing metathesis (RCM),¹⁰ cycloaddition reactions using alkyne–azide,¹¹ the guest-mediated synthesis of the macrocycle,¹² the foldamer-templated-mediated reaction,¹³ the multicomponent reaction,¹⁴ cross-coupling reactions,¹⁵ and C–H activation¹⁶ (Scheme 1). However, the development of a novel synthesis method for efficient macrocyclization with high selectivity and sustainability is highly desirable. In the 21st century, metal-catalyzed transformations proceeding through the borrowing hydrogen concept (BHC) have emerged as a superlative approach for the C–C and C–N bond-forming reactions¹⁷ because of advantages

Scheme 1. State-of-the-Art Schematics of Various Macrocyclization Strategies



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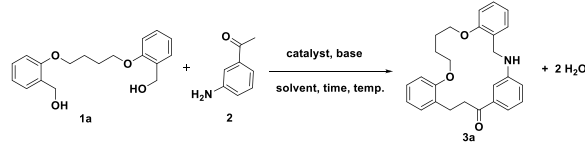


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Table 1. Optimization of Reaction Conditions^a


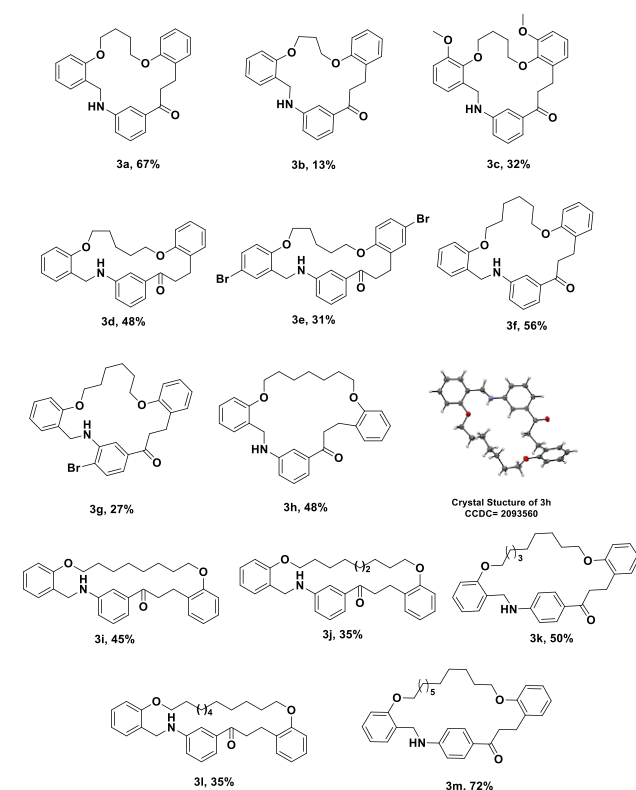
entry	catalyst (5 mol %)	base (equiv)	conc. (1:2) in toluene (M)	time (h)	yield of 3a (%)
1		KOH (2)	0.1:0.1	16	trace
2	Ru-MACHO		0.1:0.1	16	
3	Ru-MACHO	NaOH (1)	0.1:0.1	16	17
4	Ru-MACHO	NaOH (2)	0.1:0.1	16	13
5 ^b	Ru-MACHO	NaOH (1)	0.1:0.1	16	14
6 ^c	Ru-MACHO	NaOH (1)	0.1:0.1	16	30
7 ^c	Ru-MACHO	NaOH (1)	0.08:0.04	24	36
8 ^c	Ru-MACHO	NaOH (2)	0.08:0.04	24	38
9 ^c	Ru-MACHO	KO ^t Bu (2)	0.08:0.04	24	40
10 ^c	Ru-MACHO	KOH (2)	0.08:0.04	24	42
11 ^c	Ru-MACHO	KOH (2)	0.05:0.02	24	49
12 ^c	Ru-MACHO	KOH (2)	0.05:0.02	48	54
13 ^{c,d}	Ru-MACHO	KOH (2)	0.05:0.02	48	44
14 ^c	RuCl ₃ ·xH ₂ O	KOH (2)	0.05:0.02	48	trace
15 ^c	Ru-PNN	KOH (2)	0.05:0.02	48	28
16 ^c	RuH ₂ (CO)(PPh ₃) ₃	KOH (2)	0.05:0.02	48	30
17 ^c	Ru-NHC	KOH (2)	0.05:0.02	48	34
18 ^c	Ru-MACHO	KOH (2)	0.01:0.01	48	67
19 ^c		KOH (2)	0.01:0.01	48	trace

^aReaction conditions: Compounds **1a** and **2** (M solution in toluene, see table), Ru-MACHO (5 mol %), and base (see table) were stirred in an oil bath preheated to 160 °C for different time periods (see table). ^bReaction conditions: Reaction mixture heated to 140 °C. ^cReaction conditions: Reaction mixture heated to 180 °C. ^dReaction conditions: 1,4-Dioxane was used as a solvent.

such as minimal byproduct formation, mutagenic-reagent-free reactions, low *E* factor, and sustainability. Although fundamental reactions for BHC with several catalytic systems have been investigated, the application of this approach toward macrocycle synthesis has not been studied until now.

In this study, we report a novel approach for end-to-end cyclization toward the synthesis of macrocycles by using BHC. This study is the first to describe an approach for the synthesis of macrocycles by using alcohols and ketones through inter- and intramolecular borrowing alkylation.

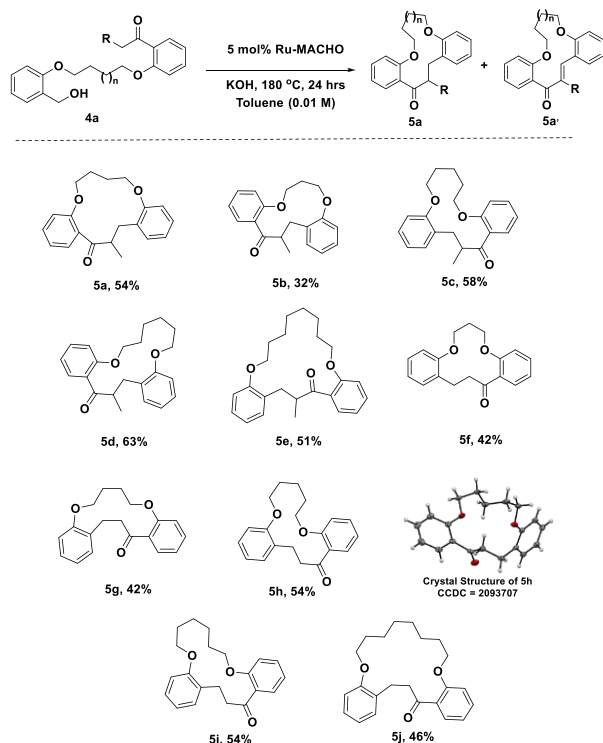
We initiated our investigation by performing dehydrogenative coupling of compound **1a** and 1-(3-aminophenyl)ethan-1-one as a model reaction. In addition, we performed a controlled experiment, which revealed that both the catalyst and the base are essential for this transformation (Table 1, entries 1 and 2). Notably, 5 mol % of Ru-MACHO [carbonylchlorohydrido{bis-[2-(diphenylphosphinomethyl)ethyl]amino}ethyl]amino}-ruthenium(II)]¹⁸ catalyst and 1 equiv of NaOH base provided a 17% isolated yield of product **3a** (Table 1, entry 3). The use of 2 equiv of NaOH base resulted in a decrease in the product yield (Table 1, entry 4). A yield enhancement was observed upon increasing the reaction temperature up to 180 °C (Table 1, entry 6). Moreover, when the concentrations of both starting materials were reduced, the product yield increased. Macrocyclization was found to be highly dependent on dilution (Table 1, entry 7). Furthermore, the use of 2 equiv of the base resulted in a slight increase in the product yield. Bases KO^tBu and KOH

Scheme 2. Substrate Scope for Intermolecular Macrocyclization^a

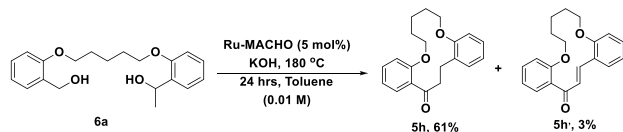
^aReaction conditions: Diphenyldimethanol derivatives (0.01 M in toluene), aminoacetophenone (0.01 M in toluene), Ru-MACHO (5 mol %), and KOH (0.166 mmol) were taken in a sealed tube. The reaction mixture was heated to 180 °C for 48 h.

resulted in a 40 and 42% yield, respectively (Table 1, entries 9 and 10). High dilution of both starting materials up to 0.05:0.02 M substantially increased the product yield (Table 1, entry 11). When the reaction was maintained for a long time period, a slight increment in the product yield was observed (Table 1, entry 12). Furthermore, other solvents, such as 1,4-dioxane, were found to be inefficient for this transformation after screening. Subsequently, various Ru catalysts such as RuCl₃·xH₂O, Ru-PNN, RuH₂(CO)(PPh₃)₃, and Ru-NHC used for the formation of this macrocycle resulted in a poor-to-moderate yield (Table 1, entries 14–17). The product yield increased substantially when the concentration of the starting material was decreased to 0.01 M (Table 1, entry 18). The absence of catalyst resulted in no reaction (Table 1, entry 19).

Inspired by the optimized results, we investigated the substrate scope for this method with various diphenyldimethanol derivatives. The experimental results revealed that the macrocycle yield depends on the chain length of the spacer. The diphenyldimethanol containing butyl spacer in **3a** resulted in a 67% yield. The propyl-substituted spacer resulted in **3b** in a poor yield (13%). However, diphenyldimethanols with ethyl and methyl spacers could not promote macrocyclization. Other substrates exhibiting a long spacer length resulted in a 45–56% yield of macrocycles **3c–i**, with the exception of bromo-substituted derivatives, **3e** and **3g**, and methoxy derivative **3c**, whose yield percentages were 31, 27, and 32%, respectively (Scheme 2). However, diols with nonyl and undecyl spacers with 4-amino acetophenone resulted in macrocycles **3k** (50%)

Scheme 3. Substrate Scope for Intramolecular Macrocyclization^a

^aReaction conditions: Alcohol–ketone derivatives (0.01 M solution in toluene), Ru-MACHO (5 mol %), and KOH (1 equiv) were taken in a sealed tube and heated to 180 °C in an oil bath for 24 h.

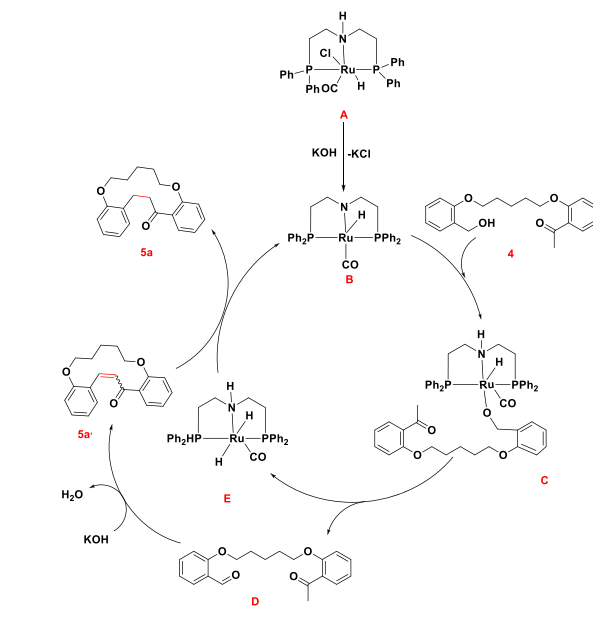
Scheme 4. Intramolecular Macrocyclization Using Primary and Secondary Alcohols^a

^aReaction conditions: Compound 6a (0.01 M solution in toluene), Ru-MACHO (5 mol %), and KOH (1 equiv) were taken in a sealed tube. The reaction mixture was heated to 180 °C in an oil bath for 24 h.

and 3m (72%), respectively. Positional isomers (para- and meta-substituted) of diphenyldimethanols did not react with 3-aminoacetophenone or 4-amino acetophenone.

Next, we applied this strategy for the intramolecular macrocyclization reaction. Although the Ru-MACHO-catalyzed alkylation of ketones and amides using alcohols was reported,¹⁹ applications in macrocyclization were not studied. We used 1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)propan-1-one 4a as a model substrate. A controlled experiment revealed that the catalyst and base were crucial for this transformation because in the absence of the catalyst and base in the reaction mixture, no reaction was observed. (See the SI, Table 1, entries 1 and 2.) Notably, heating of the reaction mixture containing 1 mol % of Ru-MACHO catalyst and stoichiometry KOH as a base yielded macrocycle 5a (30%) along with (*E*)-16-methyl-6,7,8,9-tetrahydro-15*H*-dibenzo[*g,l'*][1,6]dioxacyclotridecin-15-one 5a' as a minor product. (See the SI, Table 1, entry 3.) When this reaction mixture was heated to 160 and 180 °C, 40 and 46%

Scheme 5. Plausible Mechanism for Macrocyclization



yields of product 5a (see the SI, Table 1, entries 4 and 5), respectively, were obtained. When NaOH was used as a base, the product yield decreased. (See the SI, Table 1, entry 6.) Notably, upon an increase in the amount of catalyst (5 mol %), an increase in the yield of product 5a was observed. A two-fold decrease in the concentration of starting material 4a increased the yield of product 5a. (See the SI, Table 1, entry 7.) Other catalysts such as RuH₂CO(PPh₃)₃ and [Ru-(COD)Cl₂]_n were found to be inefficient for macrocyclization. (See the SI, Table 1, entries 8 and 9.)

Next, we investigated the generality of this transformation with other ketone–alcohol derivatives. A propyl spacer compound resulted in a 32% yield of macrocycle 5b. Moderate yields of macrocycles 5c–e were obtained using respective alcohols having ethyl ketone through the intramolecular BHC reaction. An increase in the chain length in the spacer of ketone–alcohol 4 directly influenced the yield of the macrocycle. Thus with four to six chain spacers, the yield of macrocycles 5f–i increased to 54%. An octyl spacer resulted in a 46% yield of macrocycle 5j (Scheme 3). Furthermore, in most of these reactions, traces of the alkene macrocycle were observed. To expand the scope of the application of this strategy, we performed intramolecular macrocyclization with unsymmetric diols (Scheme 4). Thus the macrocyclization was successfully achieved through the intramolecular coupling of 6 with primary and secondary alcohols, following which products 5h and 5h' were obtained (Scheme 4). This reaction was allowed with another substrate 6b to obtain product 5g (56%).

On the basis of literature reports,²⁰ a plausible mechanism for this transformation is depicted in Scheme 5. At the outset, KOH and Ru-MACHO catalyst A were used to generate active catalyst B.²¹ Furthermore, active catalyst B reacted with alcohol 4 to produce alkoxy-coordinated intermediate C. Subsequently, β -hydride elimination in intermediate C formed aldehyde D and hydride intermediate E. Next, compound D underwent an intramolecular aldol condensation reaction to generate compound 5a'. Finally, the hydrogenation of compound 5a' resulted in the desired macrocycle 5a. A plausible mechanism for

intermolecular cyclization to form **3** based on literature²⁰ is also depicted. (See the SI.)

In conclusion, we developed a novel approach for the synthesis of macrocycles through inter- and intramolecular cyclization by using dimethanol and ketone–alcohol in the presence of a Ru-MACHO catalyst. Moderate yields of numerous macrocycles with 12- to 26-membered rings were obtained using this approach. We also found that high dilution and the spacer length are pivotal to efficient macrocyclization. The proposed approach is highly sustainable, atom economical, and easily synthesizable and results in the generation of water as the only byproduct. The feasibility of this approach for the synthesis of natural products and drugs is being investigated in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c02569>.

Experimental procedures, compound characterization data, copies of NMR for the compounds, and X-ray crystallographic data (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a–j**, **3a–m**, **4a–j**, **5a–j**, and **6a,b** (ZIP)

Accession Codes

CCDC 2093560 and 2093707 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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Dehydrogenative Intramolecular Macrolactonization of Dihydroxy Compounds Using Ru-MACHO Catalyst

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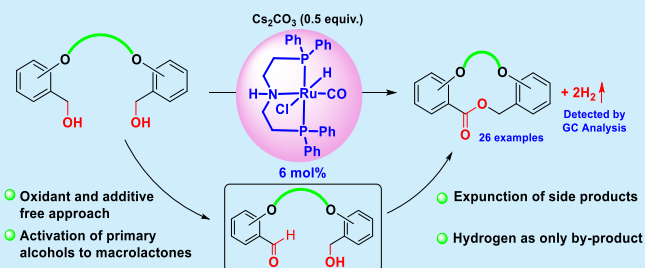


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Supporting Information

ABSTRACT: Herein, we have developed a new approach for the synthesis of 11 to 21-membered macrolactones via intramolecular dehydrogenative coupling of primary alcohols by using Ru-MACHO as a catalyst and Cs_2CO_3 as a base. This protocol generated 11–21-ring-sized macrocycles (26 derivatives), free from an external oxidant or an additive, eliminating stoichiometric reagents and producing only hydrogen as a byproduct.



Macrolactones are ubiquitous structural motifs in biologically active natural products,¹ drugs,² and perfumes.³ Medium- to large-sized macrocyclic lactones has broad applications in the area of perfumes, cosmetics, and pharmaceutical industries. As a result, a range of synthetic methods were developed using various strategies typically employing stoichiometric reagents to catalysis in the past few decades. Moreover, selective macrolactonization is a formidable and long-standing challenge for organic chemists, as it is an entropically forbidden process^{4a–c} and leads to a competitive intermolecular reaction to form a dimer as a side-product.^{4d} The task of bringing two reacting ends of a linear, long-chain molecule to close proximity is quite challenging, and the system must have an excellent combination of both enthalpy and entropy in order to facilitate macrolactonization. Conventional approaches include the use of seco-acids via either activation of acid or activation of alcohols toward the synthesis of macrolactones. These approaches mainly focus on Yamaguchi reaction,⁵ Shiina macrolactonization,⁶ Corey–Nicolaou strategy,⁷ Stenglich–Boden–Keck reaction,⁸ use of Mukaiyama salt,⁹ use of pentafluorobenzoyl chloride,¹⁰ and ynamide mediated macrolactonization¹¹ through activation of the carboxylic acids (Figure 1A). In contrast, the Mitsunobu reaction¹² proceeds through the activation of alcohol (Figure 1A). Industrially, the Yamaguchi reaction has been used more frequently for macrolactonization. However, these approaches are associated with several limitations such as the use of halogenated reagents and generating an equivalent amount of halogenated waste in the reaction. To overcome these limitations, White and co-workers developed a strategy that relied on the sulfoxide-promoted palladium acetate catalyzed macrolactonization of ω -alkenoic acids¹³ where benzoquinone was used as an external oxidant (Figure 1B). Further, in 2011 Breit and co-workers rendered an elegant approach for the macrolactonization based on the coupling of terminal alkynes

and carboxylic acids via a redox neutral process including $[\text{Rh}(\text{COD})\text{Cl}]_2$ as a catalyst and DPEphos as a ligand (Figure 1B).¹⁴ Moreover, in this approach, high dilution with a prolonged reaction time has a direct impact on the yields of the products. Recently, Li and co-workers successfully performed intramolecular macrolactonization of alcohols with terminal alkynes by using $[\text{Rh}(\text{COD})\text{Cl}]_2$ as a catalyst along with the use of an external oxidant (Figure 1B).¹⁵

However, very few numbers of methods are available in the literature toward the activation of alcohols that avoid the use of external oxidants. Indeed, the development of a new approach toward the activation of alcohols to provide an atom-economic, sustainable, and highly efficient pathway toward the synthesis of macrolactones is highly desirable.

In the 21st century, borrowing hydrogen catalysis (BHC) has emerged as a superlative approach for C–O, C–N, and C–C coupling reactions¹⁶ due to advantages such as sustainability, producing minimal waste, avoiding the use of halogenated reagents as well as reactants, and having a low E-factor. In 2005, Milstein and co-workers reported the coupling of primary alcohols to afford esters by using Ru-PNN as a catalyst.^{17a,b} Subsequently, a series of catalysts were reported for the ester and lactone formation using alcohols.^{17c–e} However, macrolactonization via dehydrogenative coupling of alcohols using a metal catalyst is not reported.

Herein, we have developed a new strategy toward the synthesis of macrolactones via activation of primary alcohols.

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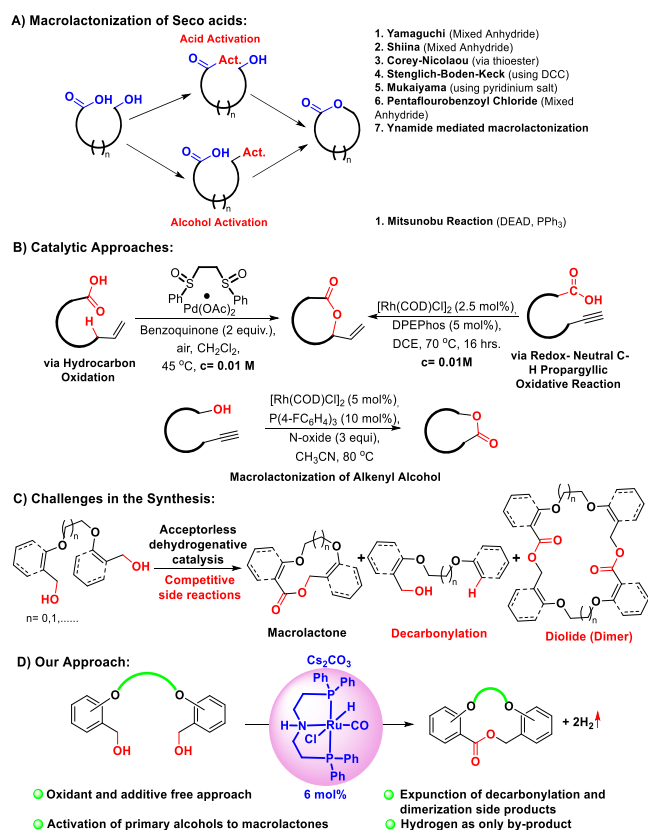


Figure 1. State of the art for the synthesis of macrolactones.

This is the first study to describe the macrolactonization of primary alcohols by using Ru-MACHO [carbonylchlorohydrido{bis-[2-(diphenylphosphinomethyl)ethyl]-amino}ethyl]amino-ruthenium(II)]¹⁸ as a catalyst (Figure 2) and Cs₂CO₃ as a base where toluene is used as the reaction media and produces hydrogen as the only byproduct.

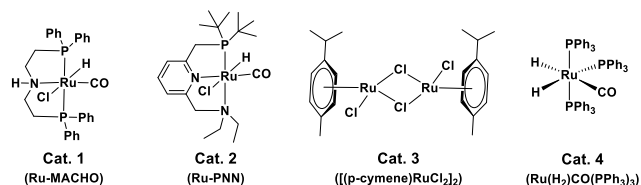


Figure 2. Ru-catalysts used for the optimization.

We commenced optimization for the intramolecular dehydrogenative coupling of diphenyldimethanol **3a** bearing a pentyl spacer. Initial control experiments revealed that both the catalyst and the base are crucial for the transformation of **3a** to macrolactone product **4a** (Table 1, entries 1 and 2). Further, 1 mol % Ru-MACHO afforded the macrolactone **4a** in 12% yield (Table 1, entry 3); apart from the main product, partially oxidized dimethanol (monoaldehyde **F**) and mono-decarbonylation¹⁹ product (20% and 11% respectively) were observed as side products in the reaction. Variation in the KOH loading to 10 mol % and 2 equiv afforded 25% and 21% yield of **4a** respectively (Table 1, entries 4 and 5). Notably, Ru-MACHO (6 mol %) in the presence of KOH (1 equiv) afforded 39% of product **4a** (Table 1, entry 6). Other bases such as NaOH and *t*-BuOK in this reaction afforded 10% and 48% yields respectively (Table 1, entries 7 and 8). However,

Table 1. Optimization of Reaction Conditions^a

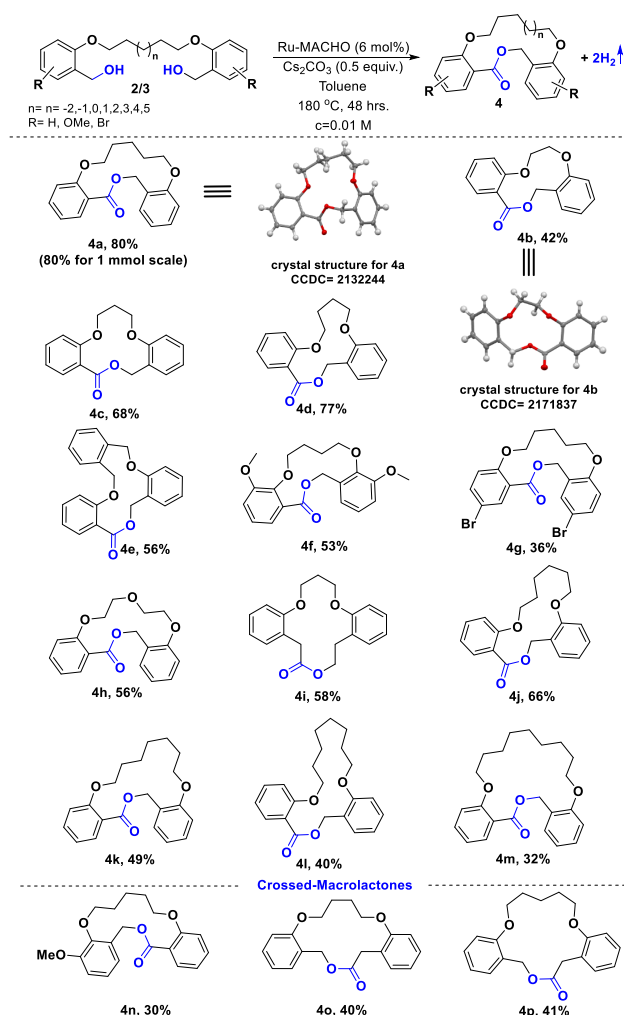
Sr. No.	Catalyst (mol %)	Base (equiv)	Yield (%)
1	1 (6)	—	—
2	—	KOH (2)	—
3	1 (1)	KOH (1)	12
4	1 (1)	KOH (10 mol %)	25
5	1 (6)	KOH (2)	21
6	1 (6)	KOH (1)	39
7	1 (6)	NaOH (1)	10
8	1 (6)	<i>t</i> -BuOK (1)	48
9	1 (6)	<i>t</i> -BuOK (1)	— ^b /37 ^c
10	1 (6)	Cs ₂ CO ₃ (1)	69
11	1 (6)	Cs ₂ CO ₃ (0.5)	70
12	1 (6)	Cs ₂ CO ₃ (0.5)	57 ^d /63 ^e /71 ^f
13 ^g	1 (6)	Cs ₂ CO ₃ (0.5)	17
14	3 (6)	Cs ₂ CO ₃ (0.5)	21
15	2 (6)	Cs ₂ CO ₃ (0.5)	49
16	4 (6)	Cs ₂ CO ₃ (0.5)	—
17	4 (6)	—	Trace
18	RuCl ₃ ·xH ₂ O (10)	Cs ₂ CO ₃ (0.5)	11

^aReaction conditions: Diphenyldimethanol derivative **3a** (0.166 mmol), catalyst (6 mol %), and base (see table) in toluene (5 mL) were stirred in a preheated parallel synthesizer at 180 °C. ^b140 °C. ^c160 °C for 48 h. ^d24 h. ^e40 h. ^f72 h. ^g1,4-Dioxane used as a solvent. The mentioned yields are isolated yields.

both the side products were reduced to trace amounts in the case of *t*-BuOK. Moreover, a temperature study revealed 140 and 160 °C were not optimal toward the conversion of **3a** into product **4a** (Table 1, entry 9). Furthermore, the reaction with Cs₂CO₃ (1 equiv) afforded a 69% yield of **4a** (Table 1, entry 10), which clearly proves that Cs₂CO₃ is efficient for this transformation. Interestingly 0.5 equiv of Cs₂CO₃ provided a 70% yield of **4a** (Table 1, entry 11). Consequently, all the side products (monoaldehyde and monodecarbonylation product) were found to be minimized successfully by the use of Cs₂CO₃.

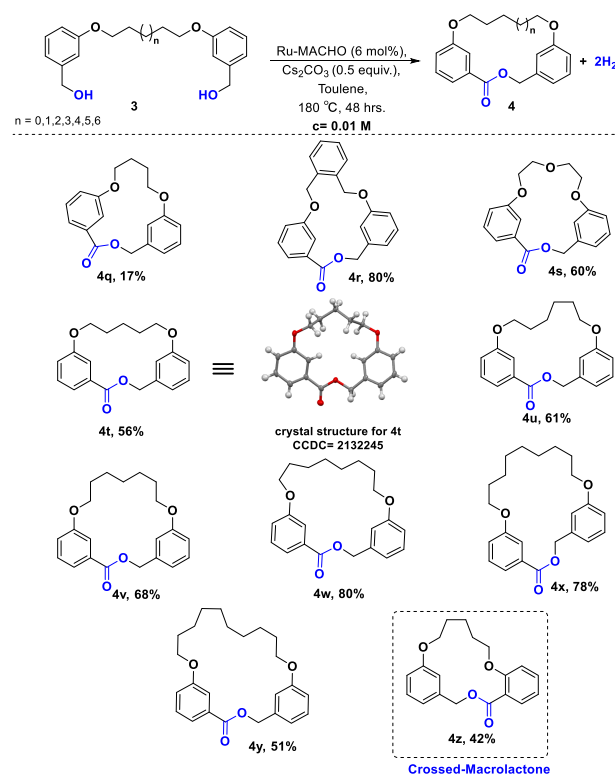
Later, the reactions performed for 24, 40, and 72 h using Cs₂CO₃ as an optimal base afforded 57%, 63%, and 71% yields of product **4a** respectively (Table 1, entry 12). Another solvent, 1,4-dioxane, rendered only 17% of **4a** (Table 1, entry 13). Other Ru-catalysts, such as [Ru(Cl₂)(*p*-cymene)₂], Ru-PNN, RuCl₃·xH₂O, and Ru(H₂)(CO)(PPh₃)₃, were found to be inefficient for the transformation of **3a** to the macrolactone **4a** (Table 1, entries 14 to 18). Next, to check the effect of the concentration, dilution experiments were performed by diluting **3a** in toluene to a 0.01 M concentration, in the presence of 6 mol % of Ru-MACHO as a catalyst and Cs₂CO₃ (0.5 equiv) as a base which afforded a good yield (80%) of macrolactone **4a** (see Supporting Information (SI)). Dilution up to 0.02 M furnished a 73% yield of **4a**. Whereas, with 0.03 and 0.06 M concentrations of **3a**, a substantial decrease in the yield of product **4a** (70%, 58% respectively) was observed (see SI). The dilution study clearly proves that the dilution of starting material has a direct impact on the yield of the macrolactone product.

Subsequently, we explored the scope of the reaction with various *ortho*-diphenyldimethanols (Scheme 1) and *meta*-diphenyldimethanols (Scheme 2) bearing different alkyl, aryl,

Scheme 1. Substrate Scope for Macrolactonization of *o*-Diphenyldimethanols^a

^aReaction conditions: *o*-diphenyldimethanol derivatives (0.069 mmol, 1 equiv), Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv. (6 mol %)), and Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv) in toluene (7 mL) were stirred in preheated parallel synthesizer at 180 °C for 48 h.

and ether spacers by diluting to 0.01 M. Initially, we attempted syntheses of 11- and 12-membered macrolactones, which are likely to be difficult to synthesize as compared to other macrolactones. Surprisingly, 11-membered macrolactone **4b** furnished a 42% yield and 12-membered macrolactone **4c** afforded a 68% yield. Whereas 13-membered macrolactone **4d** has provided a 77% yield (Scheme 1). However, replacing the alkyl spacers with an aryl spacer (**2d**, see SI) provided no product formation because of the lower flexibility of the molecule due to the aryl spacer. In contrast, **2e** (the positional isomer of **2d**) rendered a 56% yield of **4e**. Moreover, the methoxy- and bromo-substituted macrolactones **4f** and **4g** afforded 53% and 36% yields respectively (Scheme 1). A change in spacer by the diethylene glycol spacer afforded a 56% yield of **4h**. To explore the scope of the reaction with nonbenzylic alcohols, a diphenyldiethanol was subjected to macrolactonization to furnish **4i** in a 58% yield (Scheme 1). Diphenyldimethanols bearing spacer lengths from hexyl to nonyl (**4j–4m**) rendered 66%, 49%, 40%, and 32% yields respectively (Scheme 1). This might be due to the increasing probability of unfavorable conformations of long-chain

Scheme 2. Substrate Scope for Macrolactonization of *m*-Diphenyldimethanols^a

^aReaction conditions: *m*-diphenyldimethanol derivatives (0.069 mmol, 1 equiv), Ru-MACHO (2.5 mg, 0.0042 mmol, 0.06 equiv. (6 mol %)), and Cs₂CO₃ (11.4 mg, 0.035 mmol, 0.5 equiv) in toluene (7 mL) were stirred in preheated parallel synthesizer at 180 °C for 48 h.

diphenylmethanols leading to an inefficient macrolactonization. Furthermore, unsymmetrical monomethoxy-diphenyldimethanol (**2a**, see SI) was subjected to crossed-macrolactonization to yield product **4n** in 30% yield (Scheme 1), where the carbonyl moiety was obtained from less sterically hindered alcohol.

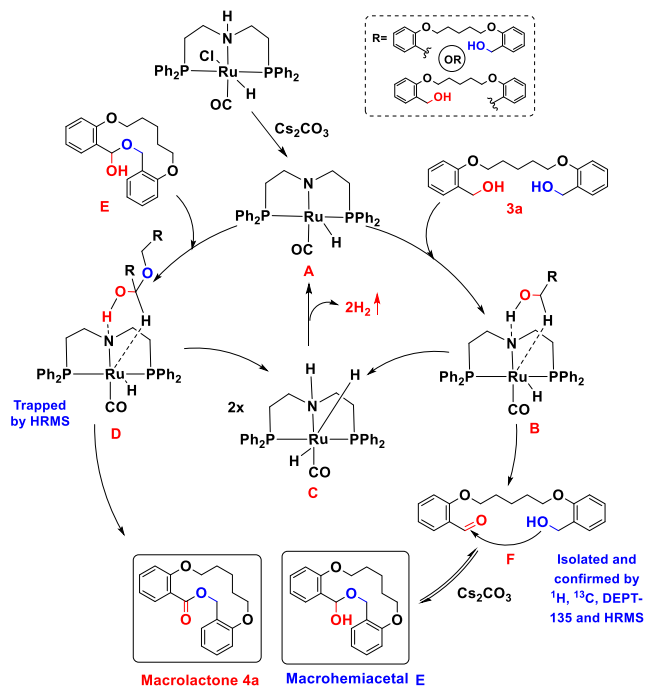
Surprisingly, benzyl alcohols were treated intramolecularly with the linear nonbenzylic alcohol by using diols **2b** and **2c** (see SI) to furnish two new crossed-macrolactone products **4o** and **4p** with 40% and 41% yields respectively (Scheme 1). In these two examples, the linear nonbenzylic alcohol was oxidized rather than benzylic alcohol. This might be due to the less sterically hindered nature of the nonbenzylic terminal alcohol relative to the benzylic alcohol. The exploration of substrate scope disclosed that the yields of macrolactones solely depend upon the spacer length and the substituents attached to phenyl rings.

Next, we applied the same strategy to *meta*-diphenyldimethanols (Scheme 2) towards the synthesis of 15–21-membered macrolactones. Diphenyldimethanol bearing a butyl spacer afforded a 17% yield of **4q** in the presence of *t*-BuOK (1 equiv) whereas in the case of Cs₂CO₃ no product formation was observed. Further, the diphenyldimethanol bearing an aryl spacer (**3r**, see SI) and a diethylene glycol spacer afforded 80% of product **4r** and 60% of **4s** respectively (Scheme 2). Interestingly, with increasing spacer lengths from the pentyl to nonyl spacer, a substantial increase in the yields of the products **4t–4x** was observed with yields ranging from 56% to 80% (Scheme 2). Moreover, macrolactone **4y** was achieved by

treating the diol-bearing decyl spacer with a 51% yield. Eventually, a crossed macrolactone **4z** was synthesized with a 42% yield (Scheme 2) by taking the *ortho-meta* diphenyldimethanol derivative (**3z**, see SI) where the carbonyl group was obtained from *ortho*-substituted benzyl alcohol which is electronically rich in nature. This substrate study reveals that by increasing the spacer length from a butyl spacer to a decyl spacer, an increase in the yield of macrolactone products was observed.

On the basis of literature reports²⁰ and the intermediate (**D**) trapping experiment, we depicted the plausible reaction mechanism for the macrolactonization (Scheme 3). Initially,

Scheme 3. A Plausible Mechanism



Ru-MACHO in the presence of Cs_2CO_3 creates an active species **A**. An active species **A** undergoes a reaction with **3a** to form species **B**. Further, **B** undergoes β -hydride elimination to furnish Ru-H intermediate **C** and monoaldehyde intermediate **F**, which was isolated and confirmed by NMR and HRMS analysis (see SI). Later, intermediate **F** undergoes a reaction with Cs_2CO_3 to get macrocyclic hemiacetal intermediate **E**. Next, intermediate **E** undergoes a reaction with active species **A** to form intermediate **D** (trapped by HRMS, see SI). Subsequently, intermediate **D** undergoes β -hydride elimination to give macrolactone product **4a** and Ru-H intermediate **C**. Finally, intermediate **C** regenerates active species **A** in the catalytic cycle with the removal of hydrogen gas (detected by gas chromatography, see SI). The reversible reaction from **4a** to **3a** is not feasible under this experimental condition due to very low hydrogen pressure generated in the reaction.¹⁸

In conclusion, we have disclosed a new protocol to achieve valuable macrolactones through the intramolecular dehydrogenative coupling of primary alcohols with various long-chain diphenyldimethanols in the presence of Ru-MACHO as a catalyst to furnish 11–21-membered macrolactones (26 examples) with good to moderate yields. The cross-coupling of benzylic alcohols with nonbenzylic linear alcohols was successfully implemented to achieve new crossed-macro-

lactones. The high yield of macrolactone completely depends on the spacer lengths and high dilution of starting materials. This is a simple, atom economic, and sustainable protocol for the synthesis of macrolactones which excludes the use of an external oxidant and produces hydrogen as the only byproduct.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.2c01617>.

Experimental procedures, compound characterization data, copies of NMR for the compounds, and X-ray crystallographic data (PDF)

FAIR data, including the primary NMR FID files, for compounds **1**, **2a–h**, **3q–z**, **4a–z** (ZIP)

■ Accession Codes

CCDC 2132244–2132245 and 2171837 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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■ Notes

The authors declare no competing financial interest.

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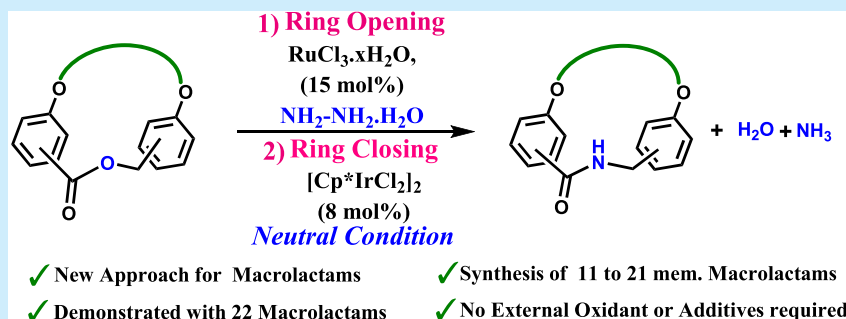
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ABSTRACT: Herein, we report the Ru-/Ir-catalyzed synthesis of valuable macrolactams from macrolactones and esters. The ring-opening of the macrolactones was efficaciously facilitated by the Ru catalyst to generate 32 amides in the first step. In the second step, intramolecular *N*-alkylative ring closure of amides with alcohols was succeeded by Ir catalyst to provide a series of 22 macrolactams and gave water as a byproduct. Moreover, this approach proceeded under neutral conditions and avoided the use of external additives.

Macrocycles are known to be pivotal in drug discoveries because of their ability to interact with proteins by providing structural preorganization and flexibility.¹ Although macrocycles have significant importance, their synthesis is an enduring problem for chemists by virtue of entropic factors.² Amides and macrolactams are ubiquitous structural cores that contribute a major part to organic synthesis. More interestingly, numerous natural products especially macrolactams (having an amide core) and macrolactones exhibit their prevalence in drug discovery and pharmaceutical industry because of their biological activities such as antibiotic, anticancer, antimicrobial, antifungal, etc.³ In recent years, macrocyclic amides like rifaximin,⁴ viridenomycin,⁵ vice-nistatin,⁶ and cyclomenal A,⁷ etc. have attracted much attention because of their wide range of biological applications. Owing to the significance of amides and macrolactams, several methods have been developed for their synthesis. Construction of amide bonds can be done by the coupling of carboxylic acids and amines using various coupling reagents,⁸ oxidative amidation of alcohol and amines,⁹ organocatalysis¹⁰ and metal catalysis,¹¹ etc. Subsequently, macrolactams can be achieved using a ring expansion process,¹² imine formations for ring closure,¹³ coupling of amines with acids,¹⁴ esters,¹⁵ and the use of the Mukaiyama salt for ring closure.¹⁶ Despite traditional approaches for macrolactams, fewer catalytic methods such as Sn-catalyzed double activation strategy¹⁷ (Figure 1A) and Cu-catalyzed intramolecular coupling of phenol and aryl halide to synthesize vancomycin¹⁸ (Figure 1B)

are described. Recently, Loh and co-workers developed two catalytic methods for macrolactams via intramolecular oxidative cross-coupling of alkenes¹⁹ and ring-closing alkene–alkene cross-coupling reactions,²⁰ respectively, using [Cp*RhCl₂]₂ as a catalyst, Cu(OAc)₂.H₂O as an external oxidant, and NaBARF as an external additive (Figure 1C).

Despite the extensiveness of amide and macrolactam synthesis, no catalytic approach is available for the direct ring-opening amidation of macrolactones and the subsequent *N*-alkylative ring closure of amides with alcohols to synthesize macrolactams. Thus, developing a new catalytic method for the direct ring opening of macrolactones to amides and subsequent *N*-alkylative ring closure is highly challenging.

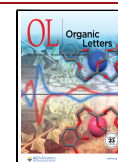
Previously, our group reported the macrocyclization of alcohols for the synthesis of macrocyclic ketone and lactones using Ru-MACHO as a catalyst via borrowing hydrogen catalysis^{21a} and acceptorless dehydrogenation, respectively.^{21b} Consequently, we sought to develop a simple catalytic approach for the synthesis of macrolactams from macrolactones, which could avoid the halogenated toxic reagents, as

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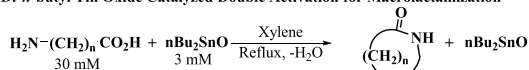
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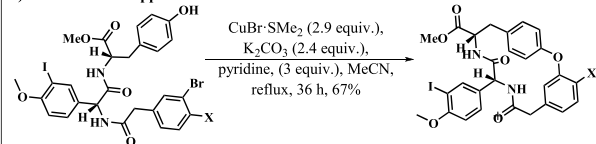


Catalytic Approaches:

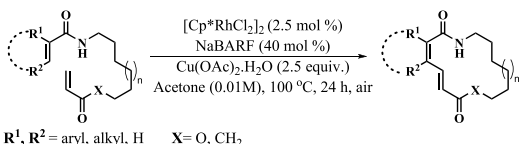
A) *Di-n*-butyl Tin Oxide Catalyzed Double Activation for Macrolactamization



B) K.C.Nicolaou's approach for Macrolactamization

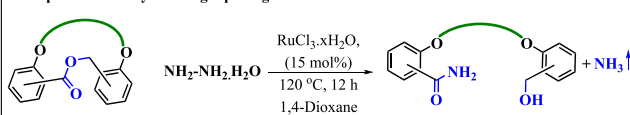


C) Intramolecular Oxidative Cross-Coupling of Alkenes

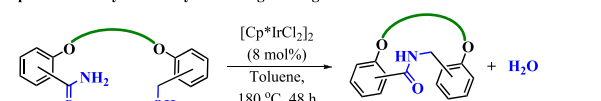

$$R^1, R^2 = \text{aryl, alkyl, H} \quad X = O, CH_2$$

D) This Work:

● **Step- I: Ru-Catalyzed Ring Opening to Amides**



● Step- II: Ir-Catalyzed N-alkylative Ring Closing to Macrolactams



- ✓ Macrocyclic ring opening and closing strategy
- ✓ Coupling of amides with alcohol
- ✓ Synthesis of macrocycle from another macrocycle
- ✓ Ammonia and water are byproducts

E) Challenges in Borrowing Hydrogen Catalysis:

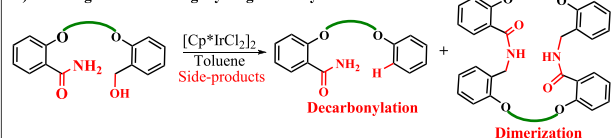


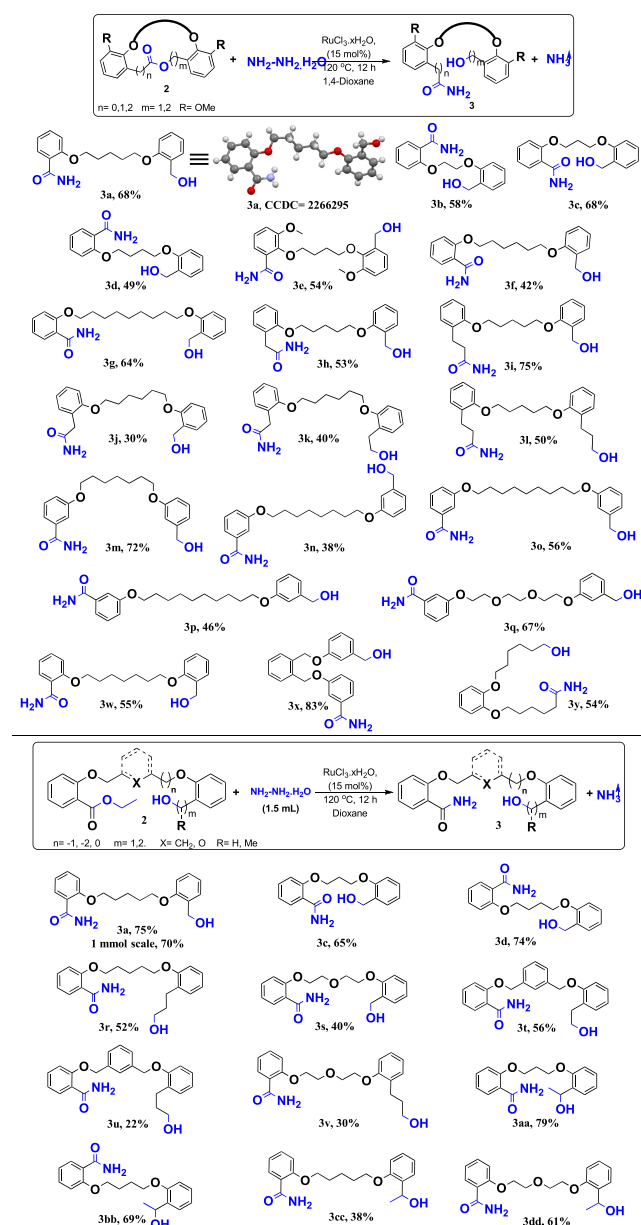
Figure 1. State of the art for macrolactamization.

well as avoid the use of external oxidants or additives. Hence, we wondered whether borrowing hydrogen catalysis²² could be employed to achieve valuable macrolactams via intramolecular *N*-alkylative ring closure of amides with alcohols.

Herein, we developed a Ru- and Ir-catalysis strategy that efficiently converts macrolactones to macrolactams in two steps with the removal of ammonia and water as byproducts. This approach describes (i) $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ catalyzed ring opening of macrolactones to form amides in the presence of hydrazine hydrate in the first step, and (ii) $[\text{Cp}^*\text{IrCl}_2]_2$ (η^5 -pentamethylcyclopentadienyliidium chloride dimer)²³ catalyzed intramolecular *N*-alkylation of amides with alcohols to achieve macrolactams under the neutral condition in the second step (Figure 1D).

To probe the concept of ring-opening and ring-closing macrocyclization, initially, we synthesized various macrolactones by utilizing the acceptorless dehydrogenation of primary alcohols.^{21b} Next, to investigate the ring-opening of macrolactone **2a** to achieve amide **3a**, we started an optimization study by varying different reaction parameters (for optimization, see [Supporting Information](#) (SI), Table S1). After the optimized reaction conditions for ring-opening were established, several macrocyclic lactones were transformed to acyclic amides **3a–3q** ([Scheme 1](#)). Macrolactones bearing an ethyl to pentyl spacer afforded products **3a–3d** with yields ranging from 68 to 49%. Moreover, the methoxy-substituted

Scheme 1. Substrate Scope for Direct Amidation from Macrolactones and Esters^a



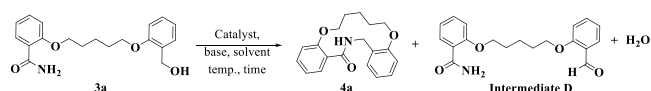
^aReaction conditions: macrolactones/esters (**2**) (0.165 mmol, 1 equiv), RuCl₃·xH₂O (15 mol %), and NH₂–NH₂·H₂O (1–1.5 mL) were refluxed at 120 °C for 24 h in 1,4-dioxane (1 mL) to get amide **3**.

macrolactone cleaved to amide **3e** with 54% yield. Lactones with hexyl, nonyl, and heptyl spacers afforded products **3f**, **3g**, and **3w** with 42, 64, and 55% yields, respectively. In addition, amides **3h**, **3i**, **3j**, **3k**, and **3l** were achieved with 75–40% yields. Further, we cleaved the *meta*-isomers of macrolactones bearing heptyl to decyl and an ether spacer to amides **3m–3q** with yields 72–38%. Next, amides **3x** and **3y** were synthesized with yields 83 and 54%, respectively (Scheme 1). Furthermore, acyclic ethyl esters were subjected to amidation to achieve amides **3a**, **3c**, and **3d** with 75, 65, and 74% yields, respectively. One mmol of **2a'** afforded 70% yield of **3a**. Later the esters with nonbenzylic alcohol bore ethers and aryl spacers furnished amides **3r–3v** with yields 52, 40, 56, 22, 30%, respectively.

More interestingly, esters with secondary benzyl alcohols were well tolerated to provide amides **3aa–3dd** with 79–38% yields (Scheme 1).

Later, amides **3** were subjected to intramolecular *N*-alkylation to achieve macrolactam **4**. More interestingly, macrocyclization has been associated with several challenges (Figure 1E), such as (i) the formation of a dimer/oligomers, (ii) Ir-catalyzed decarbonylation,²⁴ and (iii) obtaining a good yield due to the unfavorable conformation of two reaction centers. To overcome these limitations associated with macrocyclization, different reaction parameters were screened to get the best-optimized condition for a better yield of macrolactam by reacting amide **3a** with catalyst [Cp*IrCl₂]₂ (5 mol %) and Cs₂CO₃ (1 equiv) at 160 °C in toluene (7.6 mL) for 48 h to afford 13% of desired product macrolactam **4a** and 50% of partially oxidized intermediate **D** (Table 1, entry 1).

Table 1. Optimization for *N*-Alkylative Macrolactamization^a



Sr. No.	Catalyst (mol %)	Base (equiv)	Temp. (°C)	Yield of 4a (%)
1.	[Cp*IrCl ₂] ₂	Cs ₂ CO ₃	160	13
2.	[Cp*IrCl ₂] ₂	KOH	160	25
3.	[Cp*IrCl ₂] ₂	<i>t</i> -BuOK	160	25
4.	[Cp*IrCl ₂] ₂	K ₃ PO ₄	160	-
5.	[Cp*IrCl ₂] ₂	KOAc	160	-
6.	[Cp*IrCl ₂] ₂	-	160	31
7.	[Cp*IrCl ₂] ₂	-	140/180	-/70
8.	[Cp*IrCl ₂] ₂	-	180	Trace ^b
9.	[(COD)IrCl] ₂	-/ Cs ₂ CO ₃	180	20/-
10.	H ₂ ClIrPNP	-	180	-
11.	[Cp*RuCl ₂] ₂	-	180	-
12.	[Cp*IrCl ₂] ₂	-	180	54 ^c
13.	[Cp*IrCl ₂] ₂	-	180	70 ^d
14.	[Cp*IrCl ₂] ₂	-	180	73 ^e
15.	[Cp*IrCl ₂] ₂	-	180	75 ^f
16.	[Cp*IrCl ₂] ₂	-	180	67 ^g /70 ^h /75 ⁱ
17.	[Cp*IrCl ₂] ₂	-	180	62 ^j /58 ^k
18.	-	-	180	-

^aReaction conditions: hydroxyalkylbenzamide derivative **3a** (*c* = 0.01 M, 0.075 mmol), catalyst (5 mol %), and base (1 equiv.) in toluene (7.6 mL) were stirred in a preheated parallel synthesizer at 160 °C. ^b1,4-Dioxane as a solvent. ^c2.5 mol %. ^d6 mol %. ^e7 mol %. ^f8 mol % of catalyst loading for 48 h. ^g24 h. ^h38 h. ⁱ72 h. ^j*c* = 0.03 M. ^k*c* = 0.06 M. The mentioned yields are isolated yields.

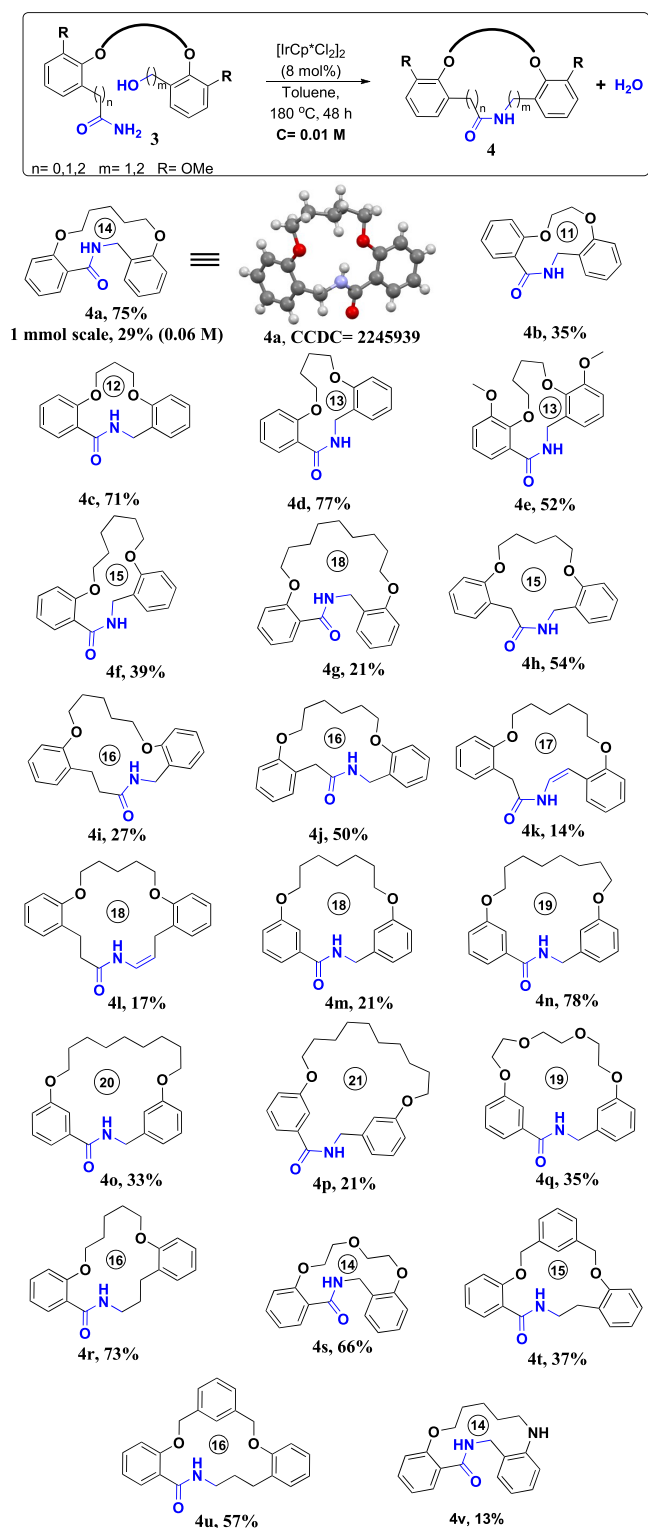
Next, by retaining the same concentration (0.01 M) of **3a**, we screened bases such as KOH and *t*-BuOK to obtain 25% yield of **4a** in both cases (Table 1, entries 2 and 3), whereas K₃PO₄ and KOAc afforded no product formation (Table 1, entries 4 and 5).

Interestingly, the reaction in the absence of a base afforded 31% yield of **4a** and 40% of intermediate **D**, which indicates that the system does not require a base for product formation (Table 1, entry 6). Surprisingly, an increased yield of product **4a** (70%) and a reduced amount of aldehyde **D** (10%) were observed at 180 °C. However, no product formation was observed when the reaction was performed at 140 °C (Table 1, entry 7). The reaction afforded a trace amount of product when 1,4-dioxane was used as a solvent (Table 1, entry 8). The

catalyst [(COD)IrCl]₂ afforded 20% of **4a** under neutral conditions and no product was observed in the presence of a base (Table 1, entry 9). Other catalysts such as H₂ClIrPNP and [Cp*RuCl₂]₂ were found to be inefficient for this transformation (Table 1, entries 10 and 11). The catalyst screening allowed us to use [Cp*IrCl₂]₂ as an optimal catalyst for this transformation. Furthermore, 2.5 mol %, 6 mol %, 7 mol %, and 8 mol % of catalyst loading afforded 54%, 70%, 73%, and 75% yield of **4a**, respectively (Table 1, entries 12 to 15).

With 8 mol % of catalyst loading, we checked the reaction for 24, 38, and 72 h of reaction time to achieve 67%, 70%, and 75% yield of **4a** respectively (Table 1, entry 16). This study proves that 48 h of reaction time is required for this transformation. Subsequently, **3a** was subjected to react intramolecularly with different concentrations (0.03 and 0.06 M) to afford 62% and 58% yield of **4a**, respectively (Table 1, entry 17), which clearly proves that 0.01 M **3a** provides the best yield (75%) of **4a** with a trace amount of aldehyde. Finally, a blank experiment was performed in the absence of a catalyst, where only starting material **3a** was observed in the reaction mixture (Table 1, entry 18). With the best-optimized conditions (Table 1, entry 15), *o*-hydroxymethylbenzamides (**3a–3g**) bearing different alkyl spacers such as **3a** afforded a 75% yield of **4a** (1 mmol of **3a** (0.06 M in toluene) afforded a 29% yield). **3b** afforded 35% yield of 11-membered macrolactam **4b** (Scheme 2). Next, amides bearing propyl and butyl spacers **3c** and **3d** afforded 71% and 77% of products **4c** and **4d**, respectively (Scheme 2). Moreover, methoxy-substituted compound **3e** afforded a 52% yield of product **4e**. Further, amide **3f** afforded 39% yield of **4f** (Scheme 1). Later, amide **3w** bearing a heptyl spacer resulted in no product formation, affording only an oxidized product. Amide **3g** bearing a nonyl spacer afforded a lower yield (21%) of product **4g**. Furthermore, *o*-hydroxymethylphenylacetamide **3h** and *o*-hydroxymethylphenylpropanamide **3i** afforded product **4h** and **4i** in 54% and 27% yields, respectively, whereas **3j** bearing hexyl spacer provided 50% yield of **4j** (Scheme 2). Moreover, we investigated the *N*-alkylation with *o*-hydroxyethylphenylacetamide **3k**, and *o*-hydroxypropylphenylpropanamide **3l** afforded product **4k** and **4l** in 14% and 17% yields, respectively (Scheme 2). Interestingly, in these two macrolactams, we observed an enamine kind of carbon–carbon double bond that resulted after the isomerization of the intermediate imine bond. Then we performed macrolactamization with *meta*-hydroxymethylbenzamides **3m–3q**, bearing heptyl to decyl spacer and an ether spacer, which afforded 21%, 78%, 33%, 21%, and 35% yields of products **4m–4q**, respectively. Amides **3x** and **3y** failed to give the product due to the unapproachable reaction centers.

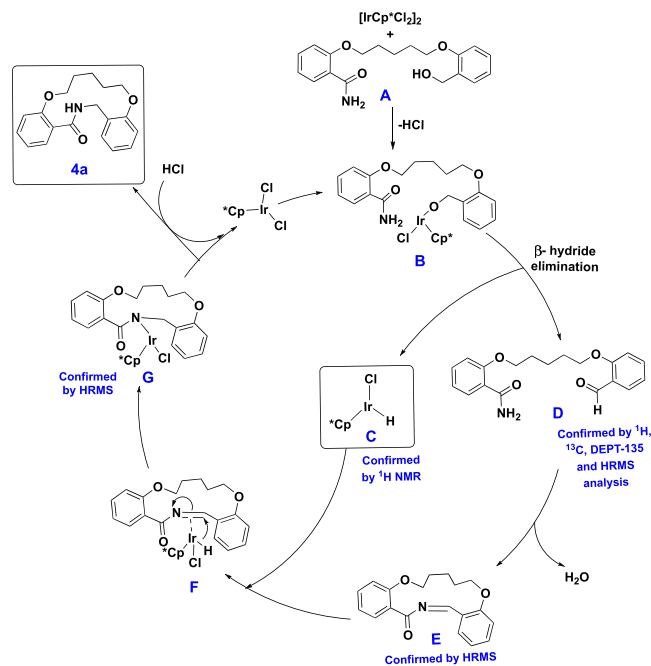
In addition, we explored the intramolecular *N*-alkylative ring closure of amides **3r–3u** to get new macrolactams **4r–4u** (Scheme 2). Amide **3r** afforded 73% of **4r** (Scheme 2). Next, amide bearing ether spacer **3s** afforded 66% of **4s**. Later, amides **3t** and **3u** having aryl spacers reacted with nonbenzylic alcohol to furnish 37% and 57% of products **4t** and **4u**, respectively (Scheme 2). However, amide **3v** afforded a trace amount of product formation. Next, amide **3hh** having amine in the spacer afforded a 13% yield of **4v**. Moreover, the reaction of benzamides with secondary alcohols (**3aa–3dd**) provided only oxidized products rather than macrolactams whereas amides **3ee**, **3ff**, **3gg**, and **3ii** bearing alkene, alkyne, and amine spacer failed to provide macrolactams (see SI).

Scheme 2. Substrate Scope for *N*-Alkylative Ring Closure of Amides to Macrolactams^a

^aReaction conditions: amides (**3**) (0.075 mmol, 1 equiv), [Cp*IrCl₂]₂ (4.8 mg, 0.006 mmol, 8 mol %), were heated at 180 °C in a preheated oil bath/parallel synthesizer for 48 h in toluene (7.6 mL) in a sealed tube to achieve macrolactams **4**.

Based on the trapped intermediates and literature background,²⁵ we depicted a plausible mechanism for the macrolactamization (Scheme 3) (for ring-opening amidation

Scheme 3. Plausible Reaction Mechanism for the Macrolactamization



mechanism, see SI). Initially, amide **A** reacts with the catalyst [Cp*IrCl₂]₂ to give iridium alkoxy species **B** with the loss of a proton. Subsequently, **B** underwent β -hydride elimination to give the Ir–H species **C** (confirmed by ¹H NMR at δ = –13.8 ppm, see SI) and intermediate **D** aldehyde, which was isolated and confirmed by ¹H, ¹³C, DEPT-135, and HRMS analysis. In the next step, aldehyde **D** reacted intramolecularly with amide-NH₂ to provide macrocyclic imine **E** (confirmed using HRMS analysis) with the removal of water. Further, iridium hydride bound coordinatively to the imine to form intermediate **F**. Furthermore, **F** underwent a hydride shift followed by the *N*-coordination with iridium to give intermediate **G** (confirmed by HRMS analysis) (Scheme 3). In the last step, **G** abstracted protons from the reaction to afford the desired macrolactam **4a** by pushing iridium back into the catalytic cycle.

In conclusion, we developed a new method for the synthesis of macrolactams from macrolactones and esters using Ru- and Ir-catalytic systems. This study illustrated 32 examples of amides and 22 examples of macrolactams with good to low yields. This is the first study to describe the synthesis of a macrocycle from another macrocycle. The intramolecular *N*-alkylative ring closure reaction with primary alcohols works well under higher dilution conditions. This is a very simple protocol that works well under neutral conditions and produces water as the only byproduct by avoiding external additives and oxidants. The mechanism has been supported by the trapping of intermediate **C** (Ir–H), intermediate **E**, and **G** by HRMS and the direct isolation of intermediate **D**.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c03885>.

Experimental procedures, compound characterization data, copies of NMR for the compounds, and X-ray crystallographic data for compounds **3a** and **4a** (PDF)

FAIR data, including the primary NMR FID files, for compounds **H**, **1**, **1a–1d**, **2i–2l**, **2q–2v**, **2y**, **3a–y**, **3aa–3ii'**, **4a–v**, and **D'** (ZIP)

Accession Codes

CCDC 2245939 and 2266295 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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