

FROM SUPRAMOLECULAR CHEMISTRY TO FUNDAMENTAL ORGANIC
CHEMISTRY: BIS-ROSETTE NANOTUBES AND NOVEL MOLECULAR
FRAMEWORKS

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MOLECULAR FRAMEWORKS**

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ABSTRACT

FROM SUPRAMOLECULAR CHEMISTRY TO FUNDAMENTAL ORGANIC CHEMISTRY: BIS-ROSETTE NANOTUBES AND NOVEL MOLECULAR FRAMEWORKS

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Novel supramolecular structures are inspired by many functional biological systems present in nature. The design of supramolecular components is concerned with the conceptualization of an organized state of matter that possess the steric and functional information necessary to translate complex mixture into ordered structures. The organization of matter brought about through non-covalent forces, and the structures generated are almost impossible to put together from a covalent perspective. Hydrogen bonding as a non-covalent interaction mostly used as a design tool, and the structures expressed have helices, three-dimensional structures, sheet (two-dimensional) structures or cyclic rosettes. One of the first group of structures in supramolecular chemistry area is the cyclic hexameric aggregate based on the melamine-cyanuric acid cocrystal. Bis-rosette derivatives of these structure where assembly of 6 compounds with 36 hydrogen bonding could not be obtained due to steric hindrances and high energy eclipsed conformations of cyanuric acid and melamine units. The other important hydrogen bonding aggregate type molecules includes the use of GAC heterocycles which forms well-ordered hexameric rosettes. Design of the DNA-base hybrid molecule was done in a way that each molecule function exclusively as the corner piece of a hexagon. The combination of the A-A-D (A: acceptor, D: donor) sequence of cytosine and complementary D-D-A sequence of guanine at an angle of 120° to each other in pyrido [4,3-d] pyrimidine, leads to the assembly of independent

hexagonal aggregates in the solid state. This is purely the result of the communication of programmed, 18 hydrogen-bonding information. Even though a variety of derivatives with different properties have been designed and synthesized, there is only one example of a bisrosette structure using GAC heterocycles. This bis-rosette supramolecular cages are formed by taking advantage of hydrophobic effect. However, to date organic solvent based bis-rosette cage structures that only utilizes H-bonding has not been achieved. Here we describe the synthesis of a well-designed precursor that will form supramolecular cage structures using only programmed H-bonding information in organic solvents. The precursor structure was formed by combining two guanine-cytosine units with a rigid bridging group. Synthesis of the compound has been successfully completed in 12 steps. Bis- rosettes are stacked on top of each other to form organic nanotubes. The formation of nanotube structures has been proven by electron microscopy and supported by computational studies.

Synthesis of non-planar aromatic compounds (like fullerene fragments), a class of textbook changing materials, has always attracted great theoretical interest and became important targets for synthesis. Triquinacene and its saturated derivative triquinane have an important place in research. Triquinacene was first synthesized by R. B. Woodward, one of the most prominent organic chemists of his time, and since then many other studies were performed. The main motivation behind the synthesis of triquinacene was the realization of infamous dodecahedrane through an electrocyclic dimerization reaction. Additionally, many discussions related homoaromaticity was based on the experimentation done on the triquinacene structure. Hundreds of triquinacene derivatives were synthesized since then, and many studies were performed addressing their properties: from rearrangement chemistry to metal complexation. Even though many interesting studies were performed on the triquinacene framework, the hetero- analogues of this system were not investigated for years. The nitrogen-containing derivative of the triquinacene was first realized by the Mascall group. Same group has also achieved the synthesis of the non-planar aromatic derivative, azacepentalinide anion and showed that it is remarkably more stable than the carbon counterpart. Theoretical calculations showed that the oxygen and sulfur containing derivatives of it are also non-planar, highly aromatic compounds. Some of the heterotriquinane derivatives that were synthesized toward realization of the non-

planar aromatic compounds showed various unusual and interesting structural properties and reactivity that ultimately pushed the boundaries of our knowledge in organic chemistry. For example, oxotriquinane, an oxonium ion, shows unusual stability. The discovery that oxygen can make more than three covalent bonds was also made using an oxotriquinane derivative. The molecule that contains the world's longest carbon-oxygen bond is an oxotriquinane derivative too. The nitrogen analogue, azatriquinane is the most basic trialkylamine known. Like triquinacene, there are various important studies on different areas of research about tribenzotriquinane. Surprisingly, synthesis of the hetero-analogues of tribenzotriquinane, which also represents the tribenzo derivatives of heterotriquinanes, has not been pursued in the literature. Here, we described the synthesis of tribenzooxotriquinane derivatives and investigation of any unusual reactivity and/or structural property that these structures might reveal. A multi-step but convergent synthetic approach was utilized towards the synthesis of target molecules. Tribenzocyclononatriene, an important core unit in our synthetic approach, has been successfully synthesized. The functionalization of the core unit was carried out towards the synthesis of target compound, tribenzooxotriquinane. The details of the approaches will be discussed in detail.

Keywords: Supramolecular Chemistry, Hydrogen Bonding, Self-Assembly, Rosette Nanotubes, Convex Polycycles, Unusual Reactivity, Aromaticity, Fragments of Fullerenes.

ÖZ

SUPRAMOLEKÜLER KİMYADAN TEMEL ORGANİK KİMYAYA: İKİLİ ROZET NANOTUPLER VE YENİ MOLEKÜLER YAPILAR

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Özgün supramoleküler yapılar, doğada bulunan birçok fonksiyonel biyolojik sistemden esinlenmiştir. Supramoleküler bileşenlerin tasarımı, karmaşık yapıları düzenli yapılara çevirmek için gerekli olan sterik ve fonksiyonel bilgiye sahip olan bir maddenin organize bir haline düzenlenmesi ile ilgilidir. Maddenin organizasyonu kovalent olmayan kuvvetler yoluyla sağlanır ve üretilen yapıların kovalent bir perspektiften bir araya getirilmesi neredeyse imkansızdır. Kendiliğinden düzenlenen moleküller alanında sıklıkta kullanılan ikincil etkileşimler arasında hidrojen bağlanmaları, π - π etkileşimleri, kayton- π etkileşimleri, metal koordinasyonları, van der Waals kuvvetleri ve elektrostatik etkileşimler sayılabilir. Bunların arasında en sıklıkla çalışılmış olan ise kuşkusuz hidrojen bağlanmalarıdır. Hidrojen bağlanmaları kullanılarak birçok supramoleküler mimarisi oluşturulmuştur. Bunların arasında çizgisel yapılar, kıvrımlı bantlar, siklik rozetler ya da 3 boyutlu yapılar sayılabilir. Supramoleküler kimya alanında hidrojen bağlanmaları kullanılarak elde edilen ilk örneklerden biri, melamin-siyanürik asit kokristaline dayanan siklik altılı rozet yapılarıdır. Melamin-siyanürik asit türevinin ikili rozet yapısı ise sterik engeller, yüksek enerjili siyanürik asit ve melamin birimleri konfigürasyonları nedeniyle elde edilememiştir. Diğer önemli hidrojen bağlayıcı supramoleküller, iyi düzenlenmiş heksamerik rozetler oluşturan sitozin-guanin heterosikllerinin kullanımını içerir.

Bu yapılarda, DNA hidrojen bağlanma kodlarından biri olan sitozin-guanin kodu (sırasıyla A-A-D ve D-D-A, A: akseptör, D: donör) aralarında 120° açı olacak şekilde yerleştirilmiştir. Bu bileşik kendi kendine düzenlenerek altılı rozet yapısını net bir şekilde oluşturmuştur. Bu tamamen programlanmış, hidrojen bağlayıcı bilgilerin iletişimi sonucudur. Farklı özelliklere sahip çeşitli türevler tasarlanmış ve sentezlenmiş olsa da guanine-sitozin heterosikleleri kullanan ikili rozet yapısının yalnızca bir örneği bulunmaktadır. Örnekteki ikili rozet supramoleküler kafesler, hidrofobik etkilerden yararlanarak oluşturulur. Ancak, bugüne kadar sadece H-bağlanmasını kullanan organik çözücü bazlı ikili rozet kafes yapıları literatürde bulunmamaktadır. Burada, organik çözücüler içinde yalnızca programlanmış H-bağlama bilgisi kullanılarak supramoleküler kafes yapıları oluşturan iyi tasarlanmış bir öncü yapının sentezini tarif etmekteyiz. Bu öncü yapı, iki guanine-sitozin biriminin sabit bir köprü grubuyla birleşmesiyle oluşturuldu. Bileşiğin sentezi başarıyla 12 adımlı sıralı bir yaklaşımla tamamlandı. İkili rozet yapıların üst üste kümelenerek organik nanotüpler oluşturduğu elektron mikroskopu ile gösterildi ve hesaplamalı çalışmalar ile desteklendi.

Organik kitaplarında tanımları değiştirecek nitelikteki düzlemsel olmayan aromatik bileşiklerin (fuleren fragmanları gibi) sentezi her zaman teorik olarak çok ilgi çekmiş ve sentezleri önemli hedefler olmuştur. Bu alanda yapılan çalışmalarda trikuinasen ve doymuş hali trikuinan molekül platformunun önemli bir yeri vardır. Trikuinasen yapısı ilk olarak organik kimya alanının en önemli isimlerinden R. B. Woodward tarafından 1964 yılında sentezlenmiş ve o zamandan beri üzerinde sıklıkla çalışılmıştır. Bu yapının en önemli sentez motivasyonu ise elektrosiklik dimerleşme reaksiyonu kullanılarak ünlü dodekahedran molekülünün sentezinin gerçekleştirilmesiydi. Buna ek olarak homoaromatiklik konsepti ile ilgili birçok tartışmada trikuinasen yapısı üzerinde yapılan çalışmalar üzerinden gerçekleşmiştir. Şimdiye kadar yüzlerce trikuinasen türevi sentezlenmiş ve düzenlenme kimyasından metal kompleks oluşturma potansiyeline kadar birçok farklı özelliği üzerine araştırmalar yapılmıştır. Bu kadar farklı alanda birçok ilginç çalışmaya konu olmuş bu yapının hetero atom içeren türevlerinin sentezi ise uzun zaman incelenmemiştir. Trikuinasen yapısının azot içeren ilk türevleri Mascall grubu tarafından gerçekleştirilmiştir. Yine aynı grup asepentalenit dianyonunun azot türevi olan azaasepentalenit anyonunda literatüre

kazandırmış ve karbon türevine göre çok daha kararlı olduğunu ispatlamıştır. Bu yapıların oksijen ve sülfür türevlerinin aromatikliklerinin çok yüksek olacağı da teorik çalışmalarla gösterilmiştir. Bu ve benzeri özgün, düzlemsel olmayan aromatik bileşiklerin gerçekleştirilmesi doğrultusunda sentezlenen bazı heterotrikuinan türevleri ise birçok sıradışı reaktivite ve yapı özelliği göstermiş ve temel organik kimya alanındaki bilgi sınırlarımızı genişletmiştir. Örneğin oksonyum iyonlarının trikuinan türevi sıradışı bir kararlılığa sahiptir. Dünyanın en uzun karbon-oksijen bağına içeren molekül yine bir oksatrikuinan türevidir. Oksijenin üç den fazla bağ yapabildiğinin ispatı da yine bir oksatrikuinan türevi kullanarak yapılmıştır. Bilinen en güçlü bazik amin ise azatrikuinandır. Yukarıda bahsedilen trikuinasen yapısında olduğu gibi tribenzotrikuinan yapısı ile ilgili de birçok alanda birbirinden önemli çalışmalar yapılmış. Fakat bu yapıların heteroatom içeren türevlerinin, yani temel organik kimya alanındaki anlayışımızı genişleten heterotrikuinan platformunun benzo türevlerinin sentezi literatürde bulunmamaktadır. Burada, tribenzooxatrikuinan bileşiğinin sentezlemesi ve bu bileşiklerin göstermesi muhtemel yeni sıradışı reaktivite ve yapısal özelliklerin incelenmesidir. Hedef moleküllerin sentezi için çok basamaklı sentetik bir yaklaşım kullanıldı. Sentetik yaklaşımımızda önemli bir çekirdek birim olan Tribenzosiklononatrien başarılı bir şekilde sentezlenmiştir. Bu molekülün fonksiyonlandırılması, hedef bileşiğin yani tribenzooksotrikuinanın sentezi doğrultusunda gerçekleştirildi.

Anahtar Sözcükler: Supramoleküler Kimya, Rozet Supramolekül, Hidrojen Bağlanmaları, Dışbükey Polisiklik Yapılar, Sıradışı Reaktivite, Aromatiklik, Fuleren Fragmanları

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To all chemicals that bind us together...

TABLE OF CONTENTS

ABSTRACT.....	v
ÖZ	viii
ACKNOWLEDGMENTS	xi
TABLE OF CONTENTS.....	xiv
LIST OF FIGURES	xviii
LIST OF SCHEMES	xxiv
LIST OF ABBREVIATIONS	xxvii
PART 1	1
SYNTHESIS AND CHARACTERIZATION OF SELF-ASSEMBLED BIS-ROSETTE SUPRAMOLECULES	1
CHAPTERS	
1.1. INTRODUCTION	1
1.1.1. Supramolecular Chemistry	1
1.1.2. Molecular Recognition and Self-Organization	2
1.1.2.1. Molecular Self-Assembly by Noncovalent Interactions.....	3
1.1.2.2. Hydrogen Bonding	4
1.1.3. Supramolecular Organic Structures	5
1.1.3.1. Cyclic Hexameric Aggregate.....	5
1.1.3.2. Cyclic Bis-Rosette Aggregate	6
1.1.3.3. GAC Hydrogen Bonding Type Rosette Aggregate	8
1.1.3.4. GAC Water Based Type Bis-Rosette Aggregate.....	10
1.1.4. Characterization of Rosette Supramolecules.....	12
1.1.5. Aim of the Study	12
1.2. RESULTS AND DISCUSSION	13
1.2.1. Design of the GAC Bis-Rosette	13
1.2.2. Syntheses of the Precursor Units.....	14
1.2.2.1. Synthesis of the GAC Base	14
1.2.2.2. Synthesis of Bridging Unit	16

1.2.2.3.	Synthesis of GAC Bis-Rosette Units.....	17
1.2.3.	Molecular Modeling of GAC Base Bis-Rosette Nanotubes.....	19
1.2.3.1.	Construction of Initial Motif.....	20
1.2.3.2.	Construction of Initial Bis-Rosette Nanotubes.....	20
1.2.3.3.	Energy Minimization of the RNT Bases Using Molecular Dynamics	21
1.2.3.3.1.	Energy Minimization of the carbon chains as part of the RNT.	23
1.2.3.3.2.	Calculation of the total energy of RNT.....	24
1.2.3.4.	Molecular Dynamic Simulations.....	25
1.2.4.	Microscopy Studies of GAC Base Bis-Rosette Nanotubes.....	26
1.2.4.1.	Sample Preparation for SEM and TEM Imaging studies	27
1.2.4.2.	SEM and TEM Studies	27
1.2.5.	Characterization of the Precursors	28
1.2.5.1.	¹ H-NMR of GC-DR.....	28
1.3.	CONCLUSION.....	31
1.4.	EXPERIMENTAL.....	33
1.4.1.	Materials and Methods.....	33
1.4.2.	Equipment	33
1.4.3.	GAC Base Syntheses.....	34
1.4.3.3.	Synthesis of N-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide	35
1.4.3.4.	Synthesis of 4,7-Diamino-5-methoxypyrido[4,3-d]pyrimidin-2(1H)-one.....	35
1.4.4.	Bridging Group Synthesis	36
1.4.4.1.	Synthesis of Dimethyl 5-iodoisophthalate.....	36
1.4.4.2.	Synthesis of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate	37
1.4.4.3.	Synthesis of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate	38
1.4.4.4.	Synthesis of Dimethyl 5-dodecylisophthalate	38
1.4.4.5.	Synthesis of Dimethyl 5-octadecylisophthalate	39
1.4.4.6.	Synthesis of (5-dodecyl-1,3-phenylene)dimethanol.....	40
1.4.4.7.	Synthesis of (5-octadecyl-1,3-phenylene)dimethanol	40
1.4.4.8.	Synthesis of 1,3-bis(bromomethyl)-5-dodecylbenzene	41
1.4.4.9.	Synthesis of 1,3-bis(bromomethyl)-5-octadecylbenzene	42
1.4.5.	Combination of the Units	42
1.4.5.1.	Synthesis of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-d]pyrimidin-2(1H)-one)	42
1.4.5.2.	Synthesis of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-d]pyrimidin-2(1H)-one)	43

1.4.5.3. Synthesis of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-d]pyrimidine-2,5(1H,6H)-dione)	44
1.4.5.4. Synthesis of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-d]pyrimidine-2,5(1H,6H)-dione)	45
1.4.6. Sample Preparation of SEM	45
1.4.7. Sample Preparation of TEM	46
REFERENCES	47
APPENDICES	
A. NMR SPECTRA	51
B. HRMS DATA	69
PART 2	75
CONVEX POLYCYCLIC STRUCTURES: SYNTHESIS OF TRIBENZOHETEROTRIQUINANES	
75	
CHAPTERS	
2.1. INTRODUCTION	75
2.1.1. Discovery of Fullerene	75
2.1.2. Fragments of Fullerenes	76
2.1.3. Smallest Curved Fragments of C ₂₀	77
2.1.4. Heterotriquinane Molecular Framework	79
2.1.5. Tribenzotriquinane	82
2.1.6. Aim of the Study	83
2.2. RESULTS AND DISCUSSION	85
2.2.1 Design of the Heterobenzotriquinanes and Derivatives	85
2.2.2. The Synthesis of Tribenzooxotriquinane: Retrosynthetic Analysis	88
2.2.3. Synthesis of Tribenzocyclononatriene	90
2.2.4. Towards Synthesis of the Tribenzooxotriquinane	92
2.2.4.1. Oxidation of tribenzocyclononatriene	92
2.2.4.2. Toward Tribenzooxotriquinane: Cyclic Ether Approach	93
2.2.4.3. Toward Tribenzooxotriquinane: Bromination	94
2.2.4.4. Toward Tribenzooxotriquinane: Reduction	96
2.2.5. Synthetic Pathway of Tribenzooxotriquinane	97
2.2.6. Future Work	98
2.3. CONCLUSION	101
2.4. EXPERIMENTAL	103
2.4.1. Materials and Methods	103
2.4.2. Equipment	103

2.4.3.	Core Unit Syntheses	104
2.4.3.1.	Synthesis of 5H-dibenzo[a,d][7]annulene	104
2.4.3.2.	Synthesis of (methylenebis(2,1-phenylene))dimethanol	104
2.4.3.3.	Synthesis of bis(2-(bromomethyl)phenyl)methane	105
2.4.3.4.	Synthesis of 10,15-dihydro-5H-tribenzo[a,d,g][9]annulene.....	106
2.4.4.	Towards Tribenzooxotriquinane Synthesis: Cyclic Ether Approach	106
2.4.4.1.	Synthesis of 10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-5,10-diol	106
2.4.4.2.	(5R,10S)-10,15-dihydro-5H-5,10epoxytribenzo[a,d,g][9]annulene	107
2.4.4.3.	Synthesis of (5R,10S)-5H-5,10-epoxytribenzo[a,d,g][9]annulene-15(10H)-one	108
2.4.5.	Towards Tribenzooxotriquinane Synthesis	108
2.4.5.1.	Synthesis of 10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-5-one	108
2.4.5.2.	Synthesis of 5H-tribenzo[a,d,g][9]annulene-5,10(15H)-dione.....	109
2.4.5.3.	Synthesis of 5H-6,10-(metheno)dibenzo[a,d,][12]annulene-5,11,16-trione	110
2.4.5.4.	Synthesis of 10,15-dibromo-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-5-one	110
2.4.5.5.	Synthesis of 10,15-dibromo-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-5-one	111
2.4.5.6.	Synthesis of 10,15-dibromo-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-5-one	111
2.4.5.7.	Synthesis of 10,15-dibromo-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-5-one	112
2.4.5.8.	Synthesis of 15-bromo-5H-tribenzo[a,d,g][9]annulene-5,10(15H)-dione	113
2.4.5.9.	Synthesis of 15-bromo-10,15-dihydro-5H-5,10-epoxytribenzo[a,d,g][9]annulene-5-ol	113
	REFERENCES	115
	APPENDICES	
	A. NMR SPECTRA	119
	B. HRMS DATA	133

LIST OF FIGURES

FIGURES

Figure 1.1. Formation of target molecules using covalent and noncovalent synthesis	2
Figure 1.2. Complementary base pairing of nucleobases via hydrogen bonding in DNA	4
Figure 1.3. The structure of self-assembled cyanuric acid-melamine molecules into a hexamer	6
Figure 1.4. Schematic representation of bis-rosette supramolecular aggregates based on derivatives of cyanuric acid - melamine compounds	7
Figure 1.5. Schematic representation of supramolecular aggregates based on bis-melamine and bis-isocyanurate derivatives	8
Figure 1.6. The structure of self-assembled pyrido [4,3- <i>d</i>] pyrimidine molecules into a hexamer	9
Figure 1.7. Hydrogen bonding types of cytosine and guanine molecules	9
Figure 1.8. Schematic representation of rosette nanotube formation	10
Figure 1.9. Structure of the precursor to water based type bis-rosette aggregate	11
Figure 1.10. Schematic representation of the bis-rosette nanotube formation	11
Figure 2.1. Schematic representation of initial GC-DR12 motif	20
Figure 2.2. Schematic representation of initial RNT model of GC-DR12 motif	20
Figure 2.3. Schematic representation of GC-DR12 RNT in DMF	21
Figure 2.4. Schematic representation of the parameters to construct RNT	21
Figure 2.5. RMSD of the heavy atoms of the GC bases in the middle three rosettes	22

Figure 2.6. Schematic representation of final GC-DR12 motif and RNT models	23
Figure 2.7. Schematic representation of final GC-DR18 motif and RNT models	24
Figure 2.8. Total energy as a function of motif number.....	25
Figure 2.9. Association free energy as a function of motif number.....	25
Figure 2.10. Association free energy as a function of motif number.....	26
Figure 2.11. SEM images of (a) Compound GC-DR12 (0.4 mg/mL) in DMF, (b) Compound GC-DR18 (0.2 mg/mL) in DMF. TEM images of Compound GC-DR18	27
Figure 2.12. Size distribution of nanobundles formed from (A) Compound GC-DR12 (0.4 mg/mL) in DMF and (B) Compound GC-DR18 (0.2mg/mL) in DMF.....	28
Figure 2.13. NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione).....	29
Figure 2.14. NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione).	30
Figure A.1. ¹ H-NMR spectrum of 2-Amino-1,1,3-propenetricarbonitrile.....	52
Figure A.2. ¹³ C-NMR spectrum of 2-Amino-1,1,3-propenetricarbonitrile.....	52
Figure A.3. ¹ H-NMR spectrum of 4,6-Diamino-2-bromonicotinonitrile.....	53
Figure A.4. ¹³ C-NMR spectrum of 4,6-Diamino-2-bromonicotinonitrile.....	53
Figure A.5. ¹ H-NMR spectrum of <i>N</i> -(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide.....	54
Figure A.6. ¹³ C-NMR spectrum of <i>N</i> -(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide.....	54
Figure A.7. ¹ H-NMR spectrum of 4,7-Diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one.....	55
Figure A.8. ¹³ C-NMR spectrum of 4,7-Diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one	55
Figure A.9. ¹ H-NMR spectrum of Dimethyl 5-iodoisophthalate.....	56
Figure A.10. ¹³ C-NMR spectrum of Dimethyl 5-iodoisophthalate.....	56
Figure A.11. ¹ H-NMR spectrum of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate.....	57

Figure A.12. ^{13}C -NMR spectrum of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate.....	57
Figure A.13. ^1H -NMR spectrum of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate	58
Figure A.14. ^{13}C -NMR spectrum of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate....	58
Figure A.15. ^1H -NMR spectrum of Dimethyl 5-dodecylisophthalate.....	59
Figure A.16. ^{13}C -NMR spectrum of Dimethyl 5-dodecylisophthalate	59
Figure A.17. ^1H -NMR spectrum of Dimethyl 5-octadecylisophthalate.....	60
Figure A.18. ^{13}C -NMR spectrum of Dimethyl 5-octadecylisophthalate.....	60
Figure A.19. ^1H -NMR spectrum of 5-dodecyl-1,3-phenylene)dimethanol.....	61
Figure A.20. ^{13}C -NMR spectrum of 5-dodecyl-1,3-phenylene)dimethanol.....	61
Figure A.21. ^1H -NMR spectrum of (5-octadecyl-1,3-phenylene)dimethanol.....	62
Figure A.22. ^{13}C -NMR spectrum of (5-octadecyl-1,3-phenylene)dimethanol.....	62
Figure A.23. ^1H -NMR spectrum of 1,3-bis(bromomethyl)-5-dodecylbenzene	63
Figure A.24. ^{13}C -NMR spectrum of 1,3-bis(bromomethyl)-5-dodecylbenzene	63
Figure A.25. ^1H -NMR spectrum of 1,3-bis(bromomethyl)-5-octadecylbenzene.....	64
Figure A.26. ^{13}C -NMR spectrum of 1,3-bis(bromomethyl)-5-octadecylbenzene....	64
Figure A.27. ^1H -NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one).	65
Figure A.28. ^{13}C -NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one).	65
Figure A.29. ^1H -NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one).....	66
Figure A.30. ^{13}C -NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one).....	66
Figure A.31. ^1H -NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione).....	67

Figure A.32. ^{13}C -NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione).....	67
Figure A.33. ^1H -NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione)	68
Figure A.34. ^{13}C -NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione)....	68
Figure B.1. HRMS spectrum of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate.....	69
Figure B.2. HRMS spectrum of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate.....	69
Figure B.3. HRMS spectrum of Dimethyl 5-dodecylisophthalate.....	70
Figure B.4. HRMS spectrum of Dimethyl 5-octadecylisophthalate.....	70
Figure B.5. HRMS spectrum of (5-dodecyl-1,3-phenylene)dimethanol.....	70
Figure B.6. HRMS spectrum of (5-octadecyl-1,3-phenylene)dimethanol.....	71
Figure B.7. HRMS spectrum of 1,3-bis(bromomethyl)-5-octadecylbenzene	71
Figure B.8. HRMS spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one).....	72
Figure B.9. HRMS spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one).....	72
Figure B.10. HRMS spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione).....	73
Figure B.11. HRMS spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione).....	73
Figure 1.1. The structures of fullerene and graphene.....	76
Figure 1.2. The structures of corannulene and sumanene.	76
Figure 1.3. The structure of C_{20}	77
Figure 1.4. The structures of acepentalene and acepentalene dianion.....	78
Figure 1.5. The structures of triquinacene and triquinane.....	78

Figure 1.6. The structure of dodecahedrane	78
Figure 1.7. The structures of azatriquinane	79
Figure 1.8. The structures of azaacepentalenide anion and perchloroazaacepentalene.....	80
Figure 1.9. The structures of oxotriquinane and its dervative.....	80
Figure 1.10. Reaction mechanism oxotriquinane derivative with NaN_3	81
Figure 1.11. The structures of oxotriquinane derivatives a-d.....	81
Figure 1.12. The structure of tribenzotriquinane.....	82
Figure 1.13. Synthetic scheme of non-planar nanographene structure.....	83
Figure 1.14. The structure of tribenzoheterotriquinanes.....	83
Figure 2.1. Optimized structure of tribenzooxotriquinane structure with RB3LYP..	85
Figure 2.2. Structure of tribenzoheterotriquinanes.....	86
Figure 2.3. Structure of isolable oxonium ylide.....	86
Figure 2.4. Structure of novel non-planar aromatic unit.....	87
Figure 2.5. Structure of triketotribenzocyclononatriene C3.....	92
Figure 2.6. Structure of 15-bromo-10,15-dihydro-5 <i>H</i> -5,10-epoxytribenzo[<i>a,d,g</i>][9]annulen-5-ol	96
Figure A.1. ^1H -NMR spectrum of 5 <i>H</i> -dibenzo[<i>a,d</i>][7]annulene.....	120
Figure A.2. ^{13}C -NMR spectrum of 5 <i>H</i> -dibenzo[<i>a,d</i>][7]annulene.....	120
Figure A.3. ^1H -NMR spectrum of (methylenebis(2,1-phenylene))dimethanol.....	121
Figure A.4. ^{13}C -NMR spectrum of (methylenebis(2,1-phenylene))dimethanol.....	121
Figure A.5. ^1H -NMR spectrum of bis(2-(bromomethyl)phenyl)methane.....	122
Figure A.6. ^{13}C -NMR spectrum of bis(2-(bromomethyl)phenyl)methane.....	122
Figure A.7. ^1H -NMR spectrum of 10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene..	123
Figure A.8. ^{13}C -NMR spectrum of 10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene.	123

Figure A.9. ^1H -NMR spectrum of 10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulen-5-one.	124
Figure A.10. ^{13}C -NMR spectrum of 10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulen-5-one.	124
Figure A.11. ^1H -NMR spectrum of 5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene-5,10(15 <i>H</i>)-dione.	125
Figure A.12. ^{13}C -NMR spectrum of 5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene-5,10(15 <i>H</i>)-dione.	125
Figure A.13. ^1H -NMR spectrum of 5 <i>H</i> -6,10-(metheno)dibenzo[<i>a,d</i>][12]annulene-5,11,16-trione.	126
Figure A.14. ^{13}C -NMR spectrum of 5 <i>H</i> -6,10-(metheno)dibenzo[<i>a,d</i>][12]annulene-5,11,16-trione.	126
Figure A.15. ^1H -NMR spectrum of 10,15-dibromo-10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulen-5-one.	127
Figure A.16. ^{13}C -NMR spectrum of 10,15-dibromo-10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulen-5-one.	127
Figure A.17. ^1H -NMR spectrum of 15-bromo-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene-5,10(15 <i>H</i>)-dione.	128
Figure A.18. ^{13}C -NMR spectrum of 15-bromo-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene-5,10(15 <i>H</i>)-dione.	128
Figure A.19. ^1H -NMR spectrum of 10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene-5,10-diol.	129
Figure A.20. ^{13}C -NMR spectrum of 10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene-5,10-diol.	129
Figure A.21. ^1H -NMR spectrum of (5 <i>R</i> ,10 <i>S</i>)-10,15-dihydro-5 <i>H</i> -5,10-epoxytribenzo[<i>a,d,g</i>][9]annulene.	130
Figure A.22. ^1H -NMR spectrum of 15-bromo-10,15-dihydro-5 <i>H</i> -5,10-epoxytribenzo[<i>a,d,g</i>][9]annulen-5-ol.	131
Figure A.23. ^{13}C -NMR spectrum of 15-bromo-10,15-dihydro-5 <i>H</i> -5,10-epoxytribenzo[<i>a,d,g</i>][9]annulen-5-ol.	131
Figure B.1. HRMS spectrum of 15-bromo-10,15-dihydro-5 <i>H</i> -5,10-epoxytribenzo[<i>a,d,g</i>][9]annulen-5-ol.	133

LIST OF SCHEMES

SCHEMES

Scheme 2.1. Schematic representation of self-assembly supramolecular structure GC-DR12	13
Scheme 2.2. Synthetic pathway of the GAC base unit.....	14
Scheme 2.3. Synthetic pathway of the bridging unit.....	16
Scheme 2.4. Synthetic pathway of combination 11 and 5.....	18
Scheme 2.5. Synthetic pathway of the corresponding nitrogen alkylation	19
Scheme 4.1. Synthetic route of 2-Amino-1,1,3-propenetricarbonitrile.....	34
Scheme 4.2. Synthetic route of 4,6-Diamino-2-bromonicotinonitrile.....	34
Scheme 4.3. Synthetic route of <i>N</i> -(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide.....	35
Scheme 4.4. Synthetic route of 4,7-Diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one	35
Scheme 4.5. Synthetic route of Dimethyl 5-iodoisophthalate.	36
Scheme 4.6. Synthetic route of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate.....	37
Scheme 4.7. Synthetic route of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate.....	38
Scheme 4.8. Synthetic route of Dimethyl 5-dodecylisophthalate	38
Scheme 4.9. Synthetic route of Dimethyl 5-octadecylisophthalate.....	39
Scheme 4.10. Synthetic route of (5-dodecyl-1,3-phenylene)dimethanol.....	40
Scheme 4.11. Synthetic route of (5-octadecyl-1,3-phenylene)dimethanol.....	40
Scheme 4.12. Synthetic route of 1,3-bis(bromomethyl)-5-dodecylbenzene	41
Scheme 4.13. Synthetic route of 1,3-bis(bromomethyl)-5-octadecylbenzene.....	42

Scheme 4.14. Synthetic route of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one).	42
Scheme 4.15. Synthetic route of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3- <i>d</i>]pyrimidin-2(1 <i>H</i>)-one).	43
Scheme 4.16. Synthetic route of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione).	44
Scheme 4.17. Synthetic route of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3- <i>d</i>]pyrimidine-2,5(1 <i>H</i> ,6 <i>H</i>)-dione).	45
Scheme 1.1. Synthetic scheme of non-planar nanographene structure.	83
Scheme 2.1. Retrosynthetic analysis of tribenzooxotriquinane.	89
Scheme 2.2. Synthetic pathway of tribenzocyclononatriene.	90
Scheme 2.3. Synthetic pathway of oxidation of tribenzocyclononatriene.	92
Scheme 2.4. Synthetic pathway toward tribenzooxotriquinane with cyclic ether approach.	93
Scheme 2.5. Synthetic routes of the bromination reactions.	95
Scheme 2.6. Synthetic pathway of tribenzooxotriquinane.	97
Scheme 2.7. Synthetic pathway of tribenzooxotriquinane.	98
Scheme 2.8. Reactions to investigate the reactivity of the structure of tribenzooxotriquinane.	99
Scheme 4.1. Synthetic route of 5 <i>H</i> -dibenzo[<i>a,d</i>][7]annulene.	104
Scheme 4.2. Synthetic route of (methylenebis(2,1-phenylene))dimethanol.	104
Scheme 4.3. Synthetic route of bis(2-(bromomethyl)phenyl)methane.	105
Scheme 4.4. Synthetic route of 10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene.	106
Scheme 4.5. Synthetic route of 10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene-5,10-diol.	106
Scheme 4.6. Synthetic route of (5 <i>R</i> ,10 <i>S</i>)-10,15-dihydro-5 <i>H</i> -5,10-epoxytribenzo[<i>a,d,g</i>][9]annulene.	107

Scheme 4.7. Synthetic route of (5 <i>R</i> ,10 <i>S</i>)-5 <i>H</i> -5,10-epoxytribenzo[<i>a,d,g</i>][9]annulen-15(10 <i>H</i>)-one	108
Scheme 4.8. Synthetic route of 10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulen-5-one	108
Scheme 4.9. Synthetic route of 5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene-5,10(15 <i>H</i>)-dione	109
Scheme 4.10. Synthetic route of 5 <i>H</i> -6,10-(metheno)dibenzo[<i>a,d</i>][12]annulene-5,11,16-trione	110
Scheme 4.11. Synthetic route of 10,15-dibromo-10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulen-5-one	110
Scheme 4.12. Synthetic route of 10,15-dibromo-10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulen-5-one	111
Scheme 4.13. Synthetic route of 10,15-dibromo-10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulen-5-one	111
Scheme 4.14. Synthetic route of 10,15-dibromo-10,15-dihydro-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulen -5-one	112
Scheme 4.15. Synthetic route of 15-bromo-5 <i>H</i> -tribenzo[<i>a,d,g</i>][9]annulene-5,10(15 <i>H</i>)-dione	113
Scheme 4.16. Synthetic route of 15-bromo-10,15-dihydro-5 <i>H</i> -5,10-epoxytribenzo[<i>a,d,g</i>][9]annulen-5-ol	113

LIST OF ABBREVIATIONS

A-A-D	Acceptor-Acceptor-Donor
ACN	Acetonitrile
ACOH	Acetic acid
AFM	Atomic Force Microscopy
B3LYP	Becke, (3), Lee, Yang, Par
CA	Cyanuric acid
CA.M	Cyanuric acid, Melamine Aggregation
DCM	Dichloromethane
D-D-A	Donor-Donor-Acceptor
DMF	Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOSY	Diffusion- Ordered Spectroscopy
ESI-MS	Electrospray Ionization Mass Spectrometry
EtOAc	Ethyl acetate
GAC	Guanine-Cytosine Aggregation
HRMS	High Resolution Mass Spectroscopy
M	Melamine

MeOH	Methanol
NBS	N-bromosuccinimide
NICS	Nucleus-Independent Chemical Shifts
NMR	Nucleic Magnetic Resonance
PTSA	<i>para</i> -toluenesulfonic acid
RNT	Rosette Nanotube
RT	Room Temperature
SEM	Scanning Electron Microscopy
TAM	Hydrophobic Anticancer Drug
TEM	Transmission Electron Microscopy
TFA	Trifluoroacetic acid
TfOH	Triflic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethyl silane
UV	Ultraviolet
VIS	Visible

PART 1

SYNTHESIS AND CHARACTERIZATION OF SELF-ASSEMBLED BIS-ROSETTE SUPRAMOLECULES

CHAPTER 1.1

INTRODUCTION

1.1.1. Supramolecular Chemistry

Since the mid-nineteenth century, molecular chemistry, especially synthetic chemistry, has resulted in increased skills in covalent synthesis. Now, a parallel evolution is encountered for the assembly for the different molecular structures via non-covalent interactions. Beyond molecular chemistry based on covalent bonds, supramolecular chemistry lies in the aim of controlling intermolecular bonds [1]. One of the leading scientist in the field, Jean-Marie Lehn defined supramolecular chemistry as “chemistry beyond the molecule”, with the presence of high-complexity organizing entities arising from a combination of two or more chemical entities held together by intramolecular forces [2]. The organization of matter brought about through non-covalent forces, and the structures generated are almost impossible to put together from a covalent perspective. The non-covalent interactions, such as π - π stacking, metal-ligand interactions, dipole-dipole interactions, hydrogen bonding etc. make the spontaneous generation of organized structure possible [3]. While most natural products are linked by covalent linkages between adjacent functionalities,

supramolecular complexes are linked to complementary intermolecular interactions (Figure 1.1) [4]. This structure requires the design of molecular components capable of self-assembling into an organized state of matter that possess the steric and functional information necessary to translate complex mixture into ordered structures [5]. Novel supramolecular structures are inspired by many functional biological systems that are present in nature, such as DNA double helix and protein structures [6] [7]. The field of supramolecular chemistry has evolved considerably with the development of numerous subdivisions, including molecular recognition, host guest chemistry, self-assembly and molecular machines.

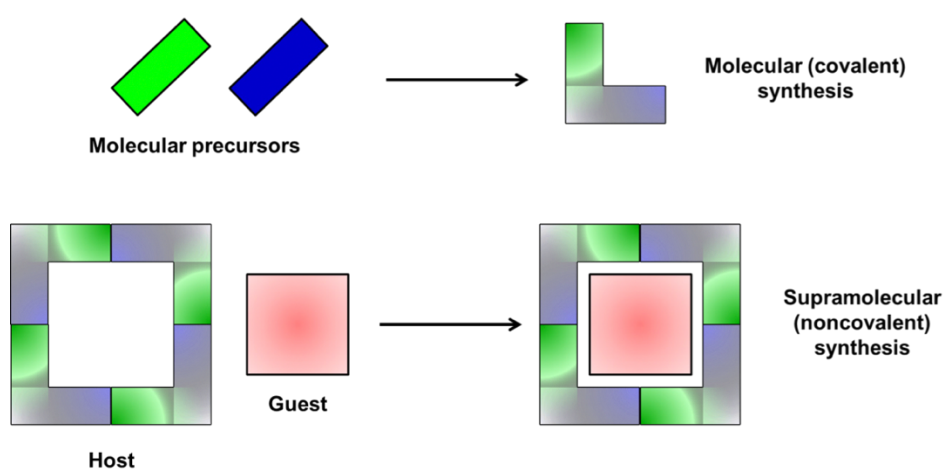


Figure 1.1 Formation of target molecules using covalent and noncovalent synthesis.

1.1.2. Molecular Recognition and Self-Organization

Molecular recognition and molecular self-assembly are the most important approaches of supramolecular chemistry. Molecular recognition is defined as the specific interactions by which molecules can use complementary functions to interact in a well-defined and precise manner via intermolecular forces [8]. Every bimolecular reaction, whether it occurs in the gas phase, dilute solution, or an enzyme's interior, begins with a recognition event that the weak intermolecular forces involved when two molecules encounter each other [9]. It plays an important role in biological systems and mediates interactions between receptors and ligands, enzymes and substrates, nucleic acids and proteins, proteins and proteins, antigens and antibodies, and nucleic acids with each

other [10]. Over the last few decades numerous artificial systems have been synthesized involving molecular recognition approaches by transferring the knowledge learned from biological systems to chemical synthesis [11]. Another process that is integral to the formation of functional supramolecular architectures is molecular self-organization. Self-organization systems are capable of spontaneously generating a well-defined functional supramolecular architecture by self-assembly from their components under a well-defined set of conditions [11]. One of the leading scientist in the field, George Whitesides defined self-assembly as “the spontaneous assembly of molecules into structured, stable, noncovalently joined aggregates” [12]. Molecular self-assembly has a key role in chemistry, biology and materials science as a synthetic strategy. For example, molecular crystals, colloids, lipid bilayers, phase-separated polymers, and self-assembled monolayers have been formed by molecular self-assembly. Even folding of nucleic acids into their functional forms is a form of self-assembly [13].

1.1.2.1. Molecular Self-Assembly by Noncovalent Interactions

The example of non-covalent interactions for molecular self-assembly are π - π stacking, metal-ligand coordination, dipole-dipole interaction, ion-dipole interactions and hydrogen bonding [3]. However, four types of noncovalent interactions are major in biological systems: hydrogen bonds, ionic bonds, van der Waals interactions, and hydrophobic interactions. The bond energies for these intermolecular interactions are between 1 to 5 kcal/mol, much less than the bond energies of single covalent bonds which are between 50 to 110 kcal/mol [14]. While non-covalent bonds are weak, multiple non-covalent bonds determine how molecules will fold or which regions of different molecules will bond together. They provide this characteristic by working together to produce very stable and specific relationships between different parts of a large molecule or between different macromolecules [14].

1.1.2.2. Hydrogen Bonding

Among intermolecular interactions, initial studies of self-assembled structures in literature are based on hydrogen bonds. Hydrogen bonds have a strong directional component hence, it simplifies the design of complementary parts for recognition and binding [15]. It was known that biological systems have already used this information to obtain complex systems from basic units. Well-known scientists in the field such as Rebek, Lehn, Hamilton, and Whitesides studied hydrogen bonding in the organic medium and created the knowledge base for molecular recognition via hydrogen bonds [16] [17]. The most known hydrogen bonding structure in biological systems is DNA which has a double helical form. By the help of hydrogen, oxygen, and nitrogen atoms of the purine and pyrimidine bases, specific hydrogen bonds and π - π stacking favors and stabilizes the double helix formation from two single strands. In the double helix, an adenine (A) or guanine (G) recognizes and interacts with a complementary thymine (T) or cytosine (C) by hydrogen bonding respectively (Figure 1.2) [18].

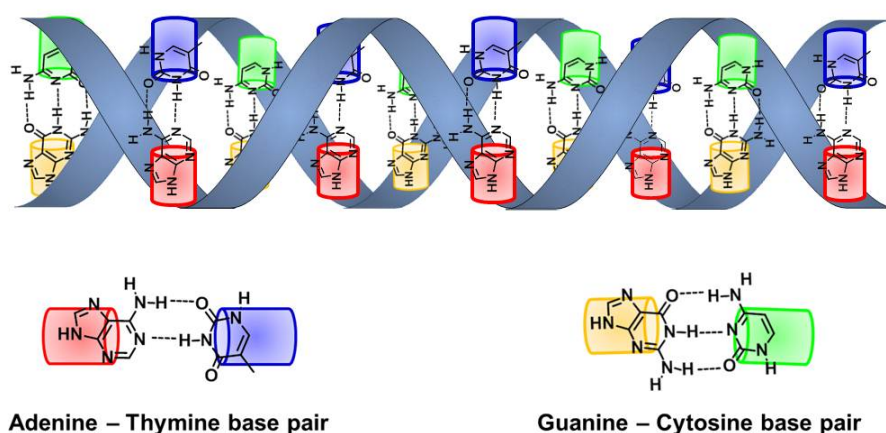


Figure 1.2. Complementary base pairing of nucleobases via hydrogen bonding in DNA.

To create complex structures, both scientists and nature use multiple hydrogen bonds. Increasing the number of sites of hydrogen-bonding is a powerful strategy to enhance the strength of the interactions, stability, directionality and also selectivity [19].

1.1.3. Supramolecular Organic Structures

The synthesis of organic supramolecular structures has been performed in the literature by using design tools like metal ion binding, steric hindrance, covalent pre-organization or pre-programmed hydrogen bonding codes and the structures expressed includes helices, three-dimensional structures, sheets (two-dimensional) structures or cyclic rosettes. These design tools and resulting pre-programmed, self-organized supramolecular structures have a great importance for the identification of biological systems and their further applications such as protein folding or the expression and transfer of genetic information [20] [21].

1.1.3.1. Cyclic Hexameric Aggregate

Initially, in 1990, a two-dimensional hydrogen-bonded molecular network based on the secondary interactions between cyanuric acid and melamine was revealed by Wang et al. [22] The structure of the assembly was proved by the crystal structure derived from the HCl solution [22]. Then, Whitesides and coworkers have enriched this area successfully on this discovery by constructing self-assembled structure from cyanuric acid and melamine derivatives [15], [23]. As the basis for the design of the structure, 1:1 complex(CA.M) was formed from cyanuric acid (CA) and melamine (M). They have described a series of solid state structure based on linear chain (tape) motif, crinkled tape motif and cyclic aggregate (rosette) by taken from CA.M lattice [24]. Formation of these aggregates was achieved by using high density hydrogen bonding and large enthalpy as the driving force for self-assembly [15]. Among these solid-state aggregates, cyclic aggregate crystals were constructed to form a hexagonal rosette through triple hydrogen bonds which include two $N\cdots H-O$ and one $N\cdots H-N$ bonds (Figure 1.3). The rosette arranged with centro-symmetric, 18 hydrogen bonding patterns with 5.9 Å cavity in two-dimensional planar sheets [25].

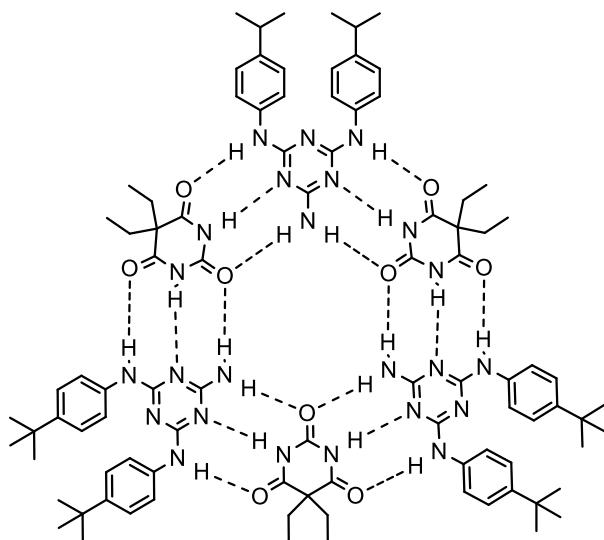


Figure 1.3. The solid-state structure of self-assembled cyanuric acid-melamine molecules into a hexamer.

Even though the assembly of these six independent parts is entropically disfavored these studies showed that the rosette structure is enthalpically favored at a reasonable degree of formation of the rosette in chloroform due to the formation of 18 hydrogen bonds [26].

1.1.3.2. Cyclic Bis-Rosette Aggregate

Whiteside's group further developed their supramolecular structures towards formation of bis-rosette cage structures. Preorganization and peripheral crowding were employed in bis-rosettes as a successful strategy. Preorganization is the main principle of molecular recognition, it provides reduction in the entropic cost by conformational control. However, the bis-rosette aggregation has not only conformational organization of the melamine subunit but also reduction of the number of degrees of rotational and translational freedom to provide self-assembled complexes [27]. Here three bridged melamine units came together with six cyanuric acid counterparts to realize a cage structure via formation of 36 hydrogen bonds (Figure 1.4) [28]. One of the first example of synthesis and characterization of cyclic bis-rosette aggregate was successfully achieved in this study. The reason for the spontaneous aggregation is the decreasing of translational and rotational entropy using the linked melamine

molecules. Thus, less entropic penalties have been paid off by the formation of the new cage compound and the aggregate. And also, the substituent on the melamine and cyanuric acid was selected logically that non-cyclic aggregated structures become energetically less favored than formation of the cyclic assembly for steric reasons [28].

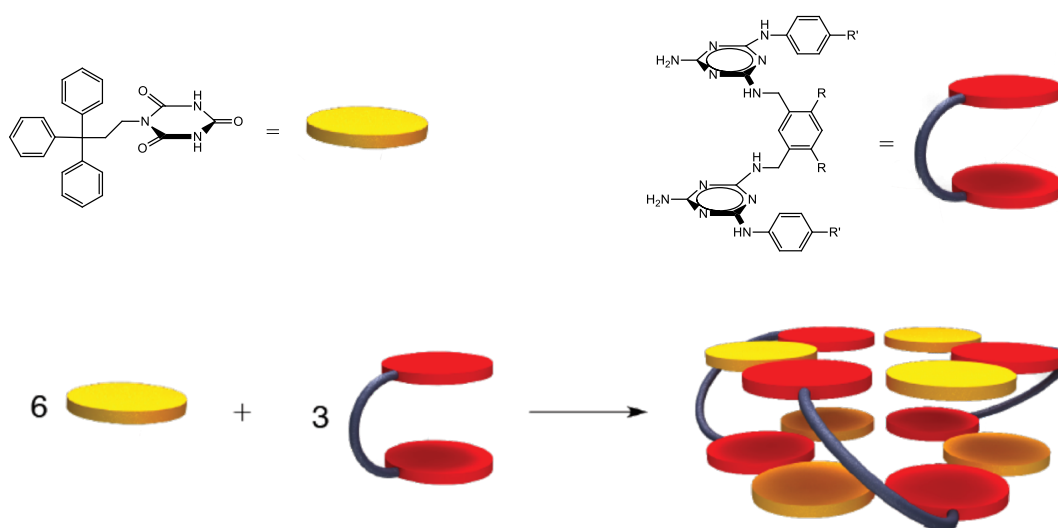


Figure 1.4. Schematic representation of bis-rosette supramolecular aggregates based on derivatives of cyanuric acid - melamine compounds.

Whiteside's group also attempted the synthesis of another bis-rosette structure via utilizing three bridged melamine and three bridged cyanuric acid units (Figure 1.5) [28]. Bis-rosette structure combine 6 compounds with 36 hydrogen bonding is expected to be more stable than the one in Figure 1.4. However, the expected supramolecular cage did not form because of steric hindrances and high energy eclipsed conformations of cyanuric acid units. They recognized that it required highly electron deficient cyanuric acid rings to be eclipsed [28].

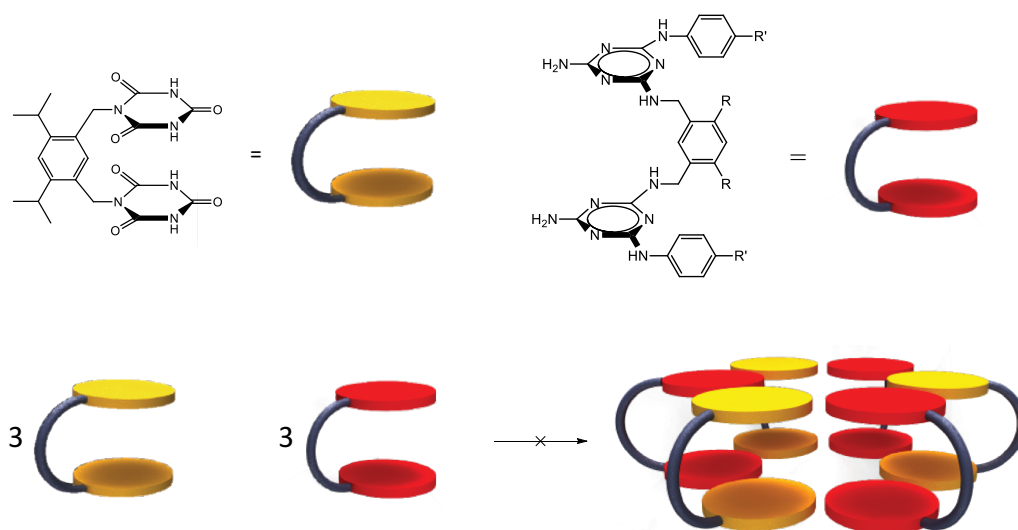


Figure 1.5. Schematic representation of supramolecular aggregates based on bis-melamine and bis-isocyanurate derivatives.

1.1.3.3. GAC Hydrogen Bonding Type Rosette Aggregate

The other important hydrogen bonding aggregate type molecules includes the use of GAC heterocycles which forms well-ordered hexameric rosettes. Six of N-substituted pyrido [4,3-*d*] pyrimidine heterocycles certainly self-organize into a cyclic hexamer with the help of asymmetric hydrogen bonding codes of both guanine and cytosine at 60° angles. In 1996, Mascal group demonstrated the formation of DNA-base hybrid (Figure 1.6) [29]. The assembly of rosette structure was the result of the communication of programmed hydrogen-bonding information. Steric demand had no contribution in the formation of the hexameric rosette structure. As a result, highly strong, cyclic ensemble of 18 intermolecular hydrogen bonds were formed in base hybrid pairings contributed to an association energy of 30 kcal/mol⁻¹ [30].

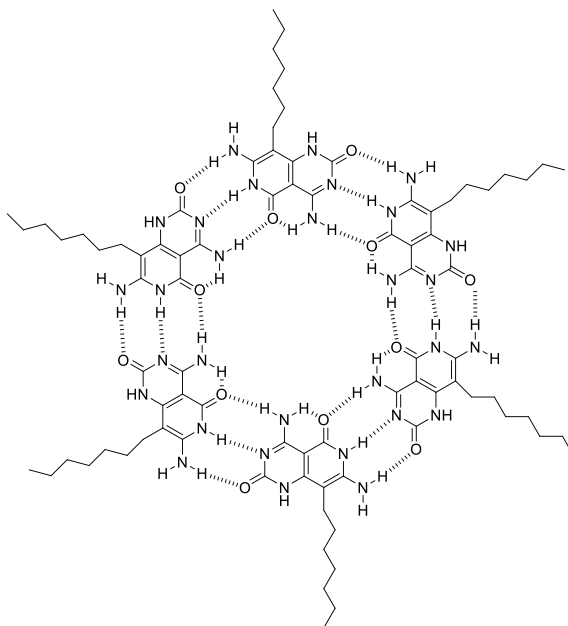


Figure 1.6. The solid-state structure of self-assembled pyrido [4,3-*d*] pyrimidine molecules into a hexamer.

Design of the DNA-base hybrid molecule was done in a way that each molecule functions exclusively as the corner piece of a hexagon. The combination of the A-A-D (A refer to acceptor type hydrogen bond, D refer to donor type hydrogen bond) sequence of cytosine and complementary D-D-A sequence of guanine at an angle of 120° to each other in pyrido [4,3-*d*]pyrimidine, leads to the assembly of independent hexagonal aggregates in the solid states (Figure 1.7). This is purely the result of the communication of programmed, 18 hydrogen bonding information [29].

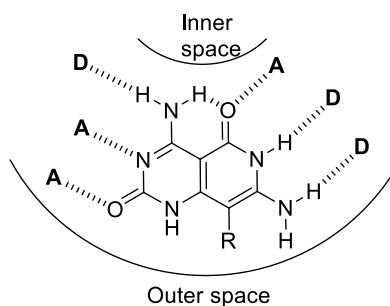


Figure 1.7. Hydrogen bonding scheme of cytosine and guanine molecules.

Later, it was shown by the Fenniri Group that these type of hexameric rosettes can stack up with pi-pi stacking interactions to form very interesting rosette nanotube structures in cyclohexane (Figure 1.10). They provided the formation 1D nanostructures with AFM, SEM and TEM imaging studies. According to results diameter of the 6-membered rosette ring is 4.4 nm. And also, X-ray crystallographic analysis of supramolecular cyclic structure shows that inside cavity of the rosette is 10.5 Å [31].

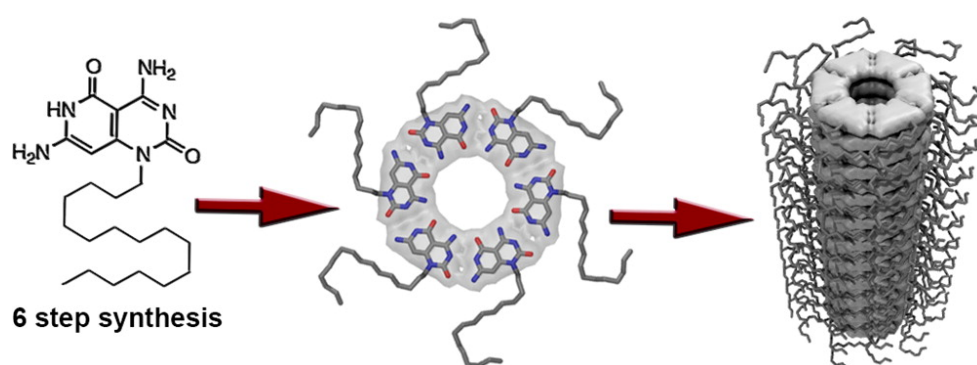


Figure 1.8. Schematic representation of rosette nanotube formation.

1.1.3.4. GAC Water Based Type Bis-Rosette Aggregate

Even though a variety of derivatives with different properties have been designed and synthesized, there is only one example of a bis-rosette structure using GAC heterocycles. Recently, Fenniri group demonstrated that by taking advantage of electrostatic, stacking, and hydrophobic interactions bis-rosette supramolecular cages can be formed. This system organized by hydrogen bonds to direct the hierarchical assembly and helical nanotubular architectures in an aqueous phase [32]. To design the precursor (Figure 1.10), they used an ethylene bridged unit linked the amine component to the chiral center, a methyl group (HNCH₃) to diminish external access of water and also an amino acid moiety to obtain the net charge of the resulting assembly [33].

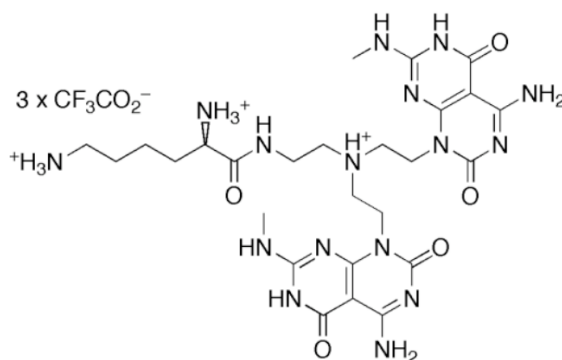


Figure 1.9. Structure of the precursor to water based type bis-rosette aggregate.

Stability of the bis-rosette depends on functional group density which improve steric effects and net charge which provide electrostatic interactions. And also, the thermal stability of the nanotubes has increased due to preorganization and increased amphiphilic character. The presence of 12 hydrogen bonds per module instead of 6 and the corresponding double rosette preorganization by 36 H-bonds instead of 18 resulted in more stable rosette nanotube. TEM and TM-AFM images proved the stable stack formation with a diameter of 4.0 nm with the helical rosette nanotube organization (Figure 1.11) [32].

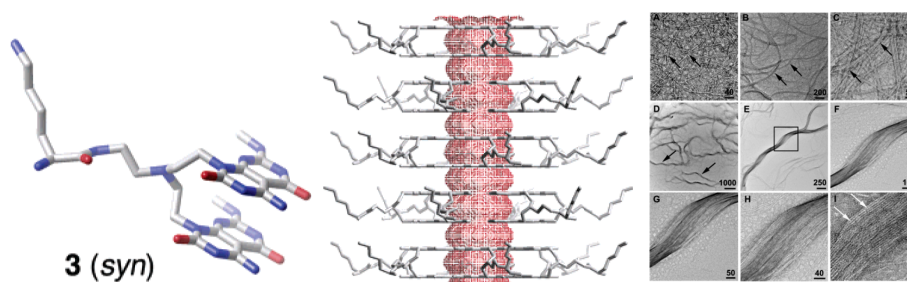


Figure 1.10. Schematic representation of the bis-rosette nanotube formation.

One of the most important application of rosette supramolecular structure is drug delivery. GAC water based rosette nanotubes are able to deliver hydrophobic drugs, because, the self-assembly of the RNTs creates a hydrophobic core and hydrophilic outer surface. With these properties, water-insoluble drugs can integrate into rosette

nanotubes which have tubular structures with hydrophobic interactions. In addition, the hydrophilic outer surface may protect these hydrophobic drugs in a physiological environment. According to literature, GAC water based type bis-rosette aggregates further improved TAM (a hydrophobic anticancer drug) loading. The study revealed that the delivery of hydrophobic pharmaceutical agents can be achieved in a practical and easier way by combining into bis-rosette nanotubes for anticancer treatment purposes [34].

1.1.4. Characterization of Rosette Supramolecules

The characterization methods of rosette supramolecules include X-ray crystallography, electrospray ionization mass spectrometry (ESI-MS), NMR spectroscopy, diffusion-ordered spectroscopy (DOSY), AFM, SEM and TEM measurements.

1.1.5. Aim of the Study

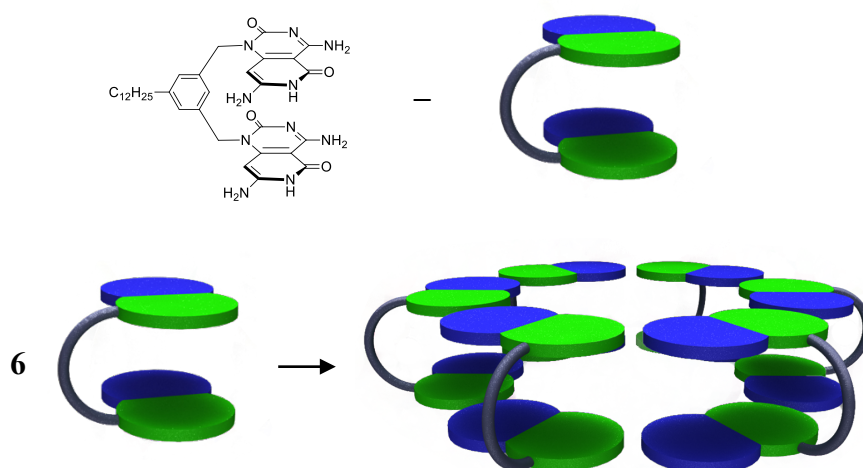
In this study, our aim was the realization of a novel, well-defined GAC based bis-rosette supramolecular aggregate in organic solvents which only uses H-bonding as the for the assembly process. Fenniri group demonstrated that by taking advantage of hydrophobic effect bis-rosette supramolecular cages can be formed. However, to date organic solvent based bis-rosette cage structures that only utilizes H-bonding has not been achieved. Here we describe the synthesis of a well-designed precursor forms supramolecular cage structures using only programmed H-bonding information in organic solvents. Three design principles were used to realize bis-rosette supramolecular aggregate. First, the cage formation designed only by programmed H-Bond coding. Second, eclipsed or close to eclipsed conformations were made possible due to more electron rich structures. Final, a rigid bridging group was introduced that should favor the formation of the cage structure due to entropic reasons. In order to see if our design principle is valid, two different precursors were designed, synthesized, characterized and the computational studies of their corresponding nanotubes were investigated in detail.

CHAPTER 1.2

RESULTS AND DISCUSSION

1.2.1. Design of the GAC Bis-Rosette

The synthesis of the bis-rosette structures depends on the pre-designed hydrogen bonding codes, not on steric requirements. According to that principle, pyrido [4,3-d] pyrimidine structure was chosen as the main aromatic units of GAC precursor units. It is Mascal's original GC design which is less electron deficient than the unit used in Fenniri work with water based bis-rosette structures. It results in significantly lower eclipsing energy [32]. To link two of these units, a rigid bridging group was used. This pre-organization reduced the entropic penalty. Similar bridging group was also used by Whitesides and Reinhoudt [20].



Scheme 2.1. Schematic representation of self-assembly supramolecular structure GC-DR12.

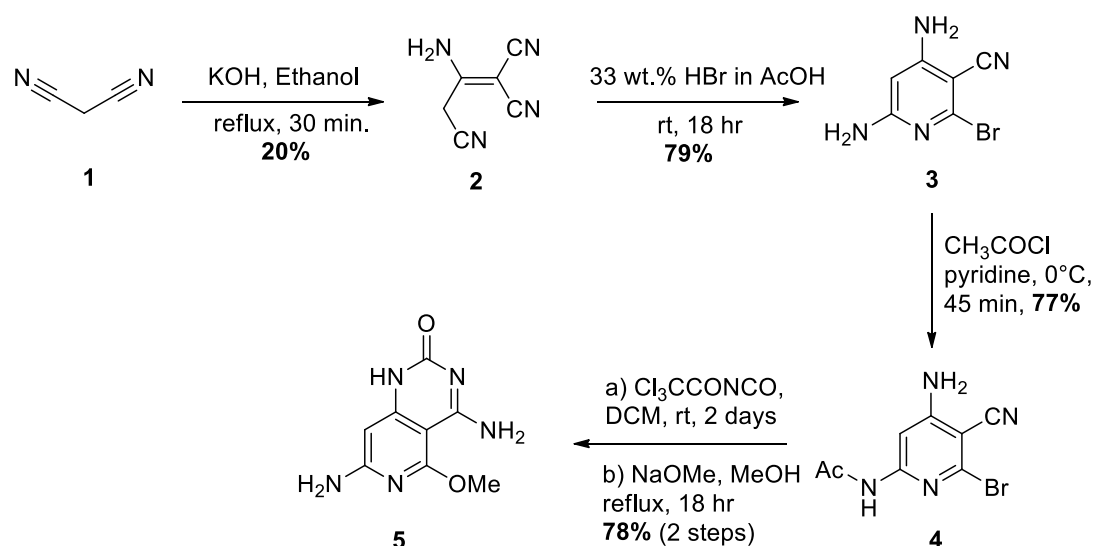
And lastly, long alkyl chains were introduced in the farthest position of the bridging unit to increase solubility in organic solvents. Two different alkyl chains were used to observe the effect of alkyl chain length on solubility which gave **GC-DR12** and **GC-DR18** units. Therefore, stable, self-assembled bis-rosette cage structures can be formed by assembly of six molecules in organic solvent (Scheme 2.1).

1.2.2. Syntheses of the Precursor Units

The precursor units of **GC-DR12** and **GC-DR18** were synthesized with the combination of two different units (Scheme 2.4) according to 12 steps convergent approach. The first unit is pyrido [4,3-*d*]pyrimidine unit which is a literature compound (Scheme 2.2) [31]. This molecule includes all necessary hydrogen bonding code for formation of bis-rosette structure. The second units are 1,3-bis(bromomethyl)-5-octadecylbenzene and 1,3-bis(bromomethyl)-5-dodecylbenzene which are bridging group to link two of the pyrido[4,3-*d*]pyrimidine units (Scheme 2.3). Finally, the two units are combined together in order to obtain the final structure.

1.2.2.1. Synthesis of the GAC Base

Scheme 2.2 shows the synthetic pathway for the GAC base unit.

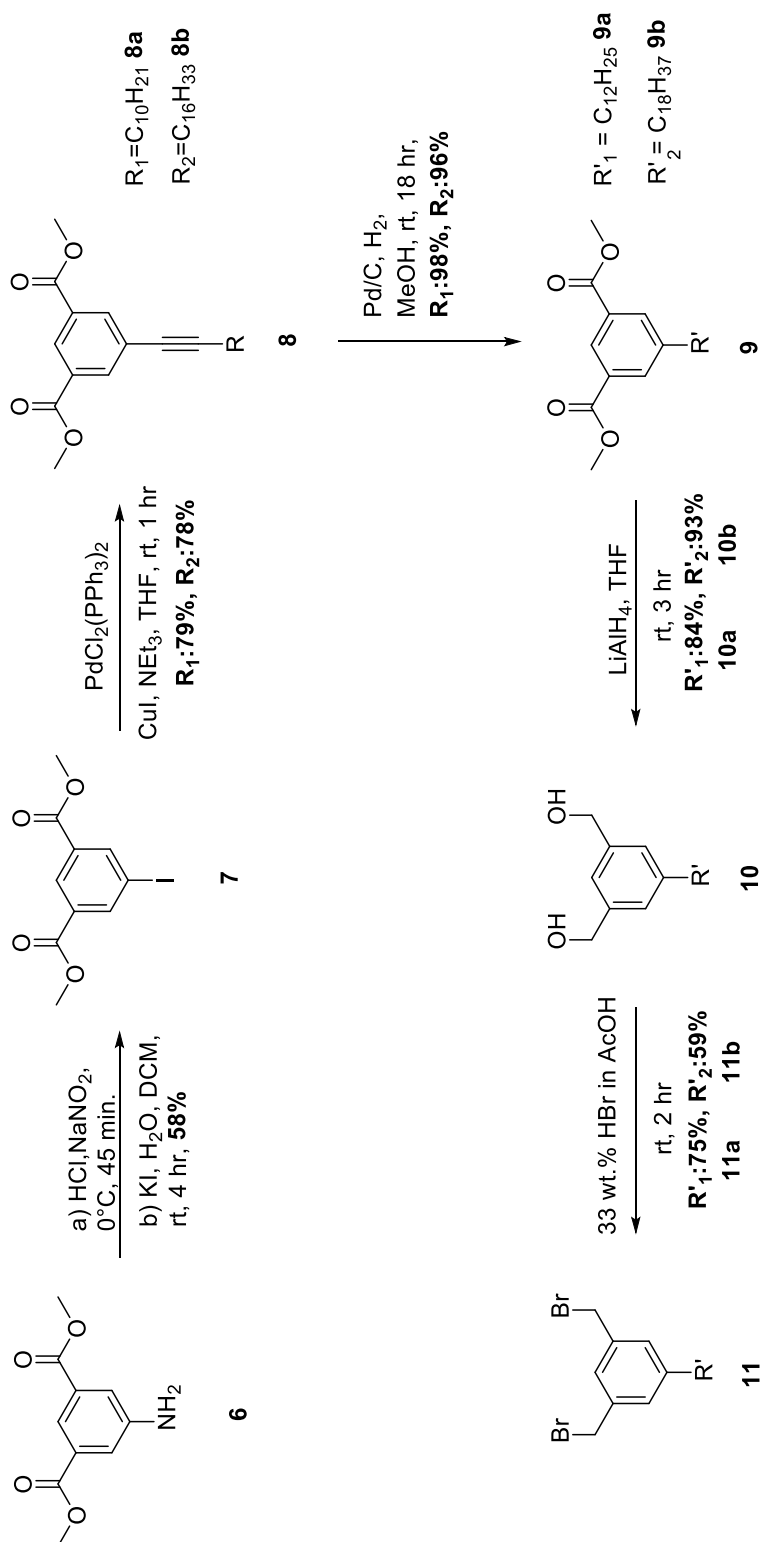


Scheme 2.2. Synthetic pathway of the GAC base unit.

The first step was the dimerization of the malononitrile **1** unit in the presence potassium hydroxide in ethanol [35]. The product of the reaction was purified by recrystallization in water. Recrystallization was performed three times, resulting in low yield, to obtain the pure malonanitrie dimer **2**. Due to the inexpensive of the starting material and the large scale we can perform this reaction, optimization studies were not performed. The next step of the synthesis was the cyclization of malononitrile dimer **2** with hydrobromic acid in acetic acid solution to obtain 4,6-Diamino-2-bromonicotinonitrile (**3**) compound with 79% yield [31]. Then, protection of the the amine group of 4,6-Diamino-2-bromonicotinonitrile (**3**) on the 6th position was performed by addition of acetyl chloride. Acetylation of the compound took place at the most nucleophilic amino group to get *N*-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide (**4**) in 77% yield [31]. The second ring was formed via reaction of pyridine derivative *N*-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide (**4**) and trichloroacetyl isocyanate followed by treatment with NaOMe. According to literature workup procedure, the reaction was quenched first with water and then with saturated aqueous sodium bicarbonate. The layers were then separated and the aqueous phase washed 5 times with 5% isopropyl alcohol/DCM mixture. However, an emulsion was formed in the separation funnel, which makes it difficult to separate the layers. The droplets of the two phases were slow to come together; It took a long time to separate. A method for breaking up the emulsion was to add some NaCl to increase the ionic strength of the aqueous layer. The other method was adding a few milliliters of ethanol. Both methods were tried but emulsion did not break down. We then changed the working procedure to solve this problem. The reaction was stirred with aqueous NaOH solution, then the aqueous phase was washed with a mixture of 5% isopropyl alcohol/DCM (x 5). In this case, a good separation between the two layers was obtained. The product was combined with the sodium methoxide solution to complete the base-induced ring closure and a simultaneous displacement of the bromo group yielded 4,7-Diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one (**5**) with 78% yield [31].

1.2.2.2. Synthesis of Bridging Unit

The synthetic pathway for the bridging unit is as shown in Scheme 2.3.

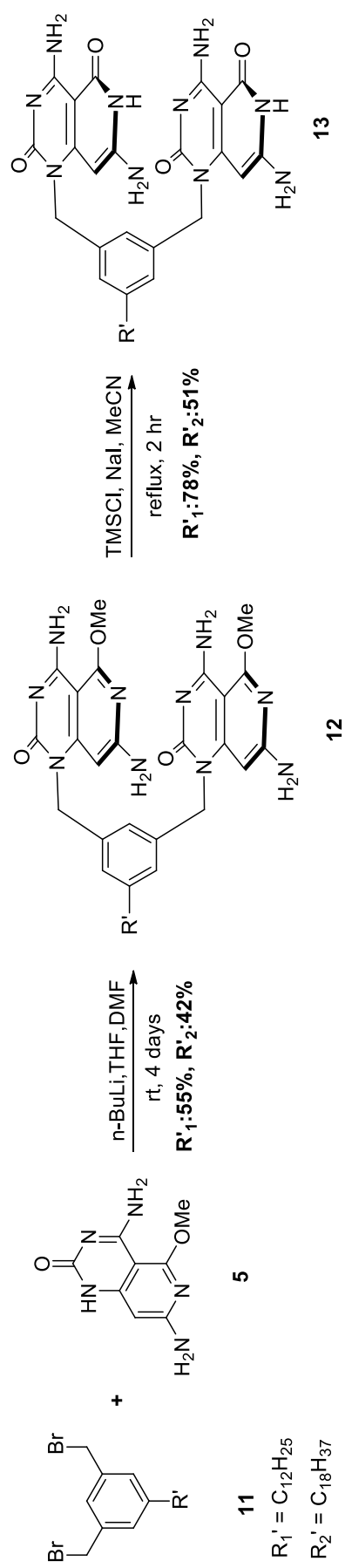


Scheme 2.3. Synthetic pathway of the bridging unit.

For the synthesis of compound 1,3-bis(bromomethyl)-5-dodecylbenzene, the synthetic route shown in the Scheme 2 was followed. The bridging group synthesis was accomplished in five steps starting from commercially available dimethyl 5-aminoisophthalate (**6**). First, the dimethyl 5-aminoisophthalate (**6**) was converted to iodobenzene derivative **7** via Sandmeyer reaction. Sandmeyer reaction is a substitution reaction in which the aryl diazonium salt is reacted with the iodide ion to give the aryl halide product. The primary aryl amine was diazotized to give the aryl diazonium salt. This diazonium salt was then reacted with the halide ion (I^-) [36]. Sonagashira coupling was then performed with two different alkyne units to obtain **8** with 79% and 78% yield. This coupling of the terminal alkynes with the aryl halides was performed with the palladium catalyst $PdCl_2(PPh_3)_2$, the copper(I) co-catalyst CuI , and the amine base NEt_3 [37]. As the third step of the synthetic route, hydrogenation was successfully performed to give **9**. Alkynes **8a** and **8b** was reduced to the compounds **9a** and **9b** via Pd/C and hydrogen with a yield of 98% and 96% respectively [37]. Subsequently, the reduction reaction was obtained by a lithium aluminum hydride solution which reduced the two carboxylic ester units to alcohol. Reduction of these ester groups with this reagent gave the primary alcohols **10a** and **10b** with 84% and 93% yield respectively [38]. The last step in the synthesis of the bridging group was the conversion of benzylic alcohols to benzyl bromides. Compound **10a** and **10b** were treated with HBr in acetic acid solution via nucleophilic substitution reaction the alkyl halides **11a** and **11b** were synthesized with a yield of 75% and 59% respectively [39].

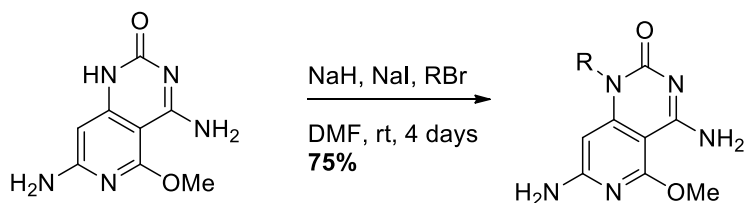
1.2.2.3.Synthesis of GAC Bis-Rosette Units

The synthetic pathway for the combination of the GAC base unit and the bridging unit is as shown in Scheme 2.4.



Scheme 2.4. Synthetic pathway of combination **11** and **5**.

For synthesis of the final product, two units **11** and **5** were combined to obtain the component of the bis-rosette supramolecular structures. Literature reports have shown that the corresponding nitrogen alkylation is provided by NaH deprotonation followed by alkylation with the corresponding alkyl bromide. According to that procedure, 60% sodium hydride was added to the solution of **5** in dry DMF. At the end **11** and sodium iodide were added and the mixture was stirred for 4 days (Scheme 2.5) [31].



Scheme 2.5. Synthetic pathway of the corresponding nitrogen alkylation.

However, this approach did not work for the synthesis of **12a**. Literature search showed that NaH and DMF can react to form sodium dimethyl amine which can then further react with alkyl bromide. This was not an issue when large excess of alkyl bromide was used in literature methods. Nevertheless, in our case half an equivalent of the alkyl chain was used, hence very low yields were observed. To overcome this issue, we changed the coupling procedure. In the new procedure, a 2.5 M n-butyllithium solution was added to a solution of **5** in dry THF at -78 °C, then dry DMF and **11** was added at 10 °C and the mixture was stirred for 4 days at room temperature. The approach worked nicely and the target compounds **12a** and **12b** were successfully synthesized with 55% and 42% yield. Final deprotection was achieved by in situ generated TMSI and final products with a **C12** and **C18** alkyl chain were successfully obtained with 78% and 51% yield respectively [31].

1.2.3. Molecular Modeling of GAC Base Bis-Rosette Nanotubes

The most stable conformation of the **GC-DR12** and **GC-DR18** corresponding rosette nanotubes in organic solvent was obtained using classical molecular modeling techniques. All simulations were done in Schrodinger Materials Science Suite using the OPLS3 force field with collaboration with the Fenniri Group at Northeastern University [40].

1.2.3.1. Construction of Initial Motif

The **GC-DR12** and **GC-DR18** motifs were created using twin GC motifs with a distance of 4.5 Å and offset by an angle of 6°. For each species, the carbon chain was minimized in octanol in MacroModel software package using Polak-Ribier Conjugate Gradient (PRCG) minimization [40].

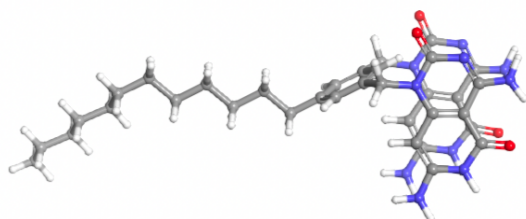


Figure 2.1. Schematic representation of initial **GC-DR12** motif.

1.2.3.2. Construction of Initial Bis-Rosette Nanotubes

The minimized motif (Figure 2.1) was multiplied and arranged to a hexamer rosette, stabilized by a network of 36 hydrogen bonds. Five such rosettes were then stacked with a distance of 4.5 Å and a rotation angle of 15° to form a 30-motif rosette nanotube (Figure 2.2).

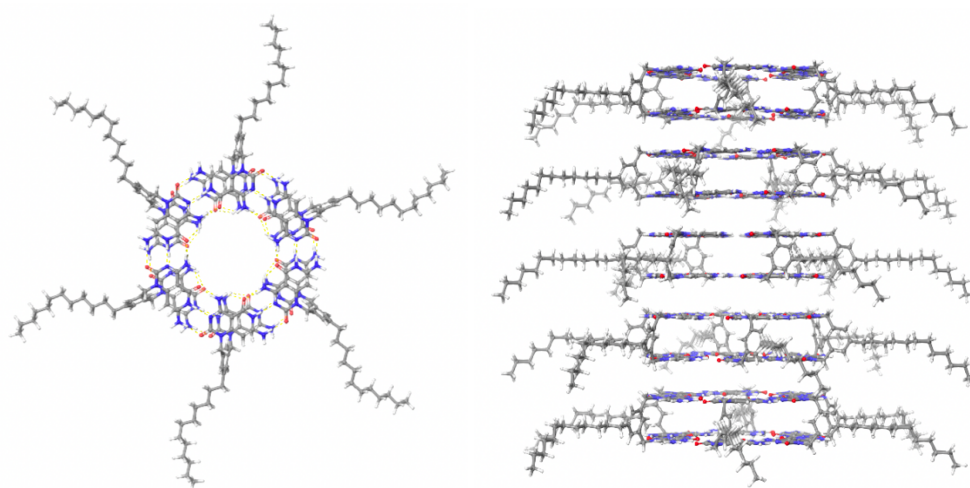


Figure 2.2. Schematic representation of initial RNT model of **GC-DR12** motif.

1.2.3.3. Energy Minimization of the RNT Bases Using Molecular Dynamics

Using Desmond Molecular Dynamics software in Schrödinger Materials Science Suite, Molecular Dynamic, MD, simulations of the RNT's were done in five organic solvents (DMS, octanol, methanol, DMF, and cyclohexane) [40]. The RNTs were placed in a simulation cell with a 10 Å buffer of solvent and part of the solvation box was hidden for clarity (Figure 2.3). The simulations were run at 300 K and 1 atm for 50 ns each.

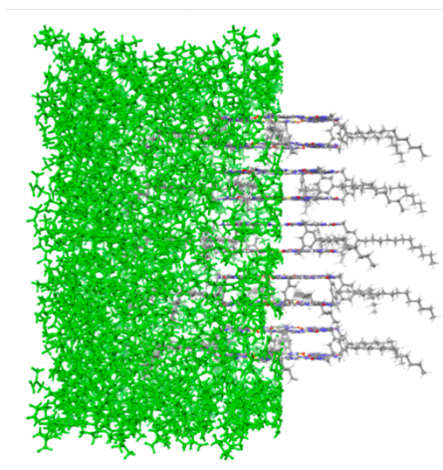
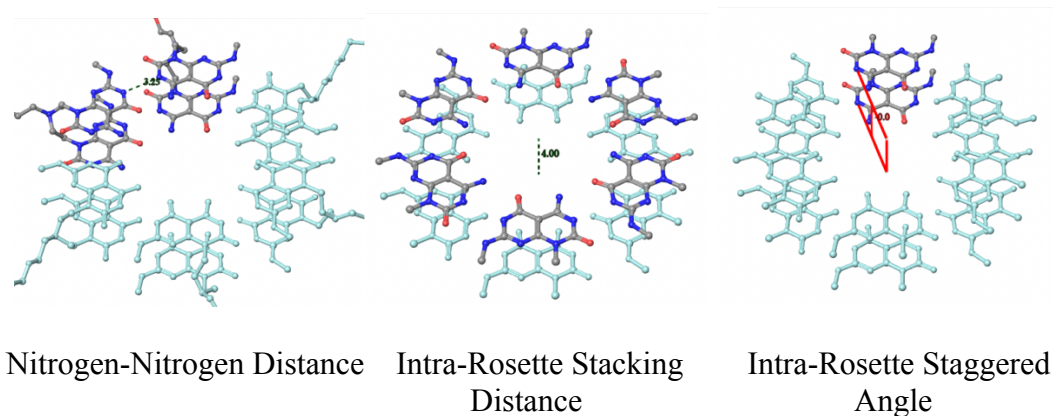
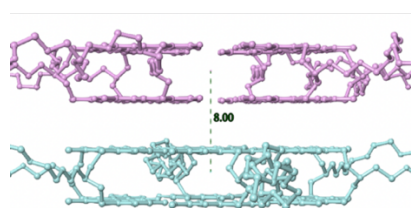


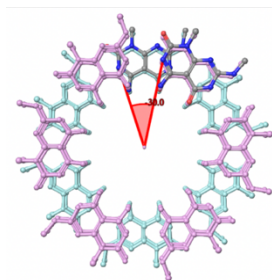
Figure 2.3. Schematic representation of **GC-DR12** RNT in DMF.

The resulting trajectories of the three middle rosettes were then analyzed to comment on stability and obtain the dimensions and conformation of the RNT core. The parameters required to construct the RNT model are nitrogen-nitrogen distance, intra-rosette stacking distance, intra-rosette staggered angle, inter-rosette stacking distance and inter-rosette staggered angle which are described as below (Figure 2.4).





Inter-Rosette Stacking Distance



Inter-Rosette Staggered Angle

Figure 2.4. Schematic representation of the parameters to construct RNT.

Root mean square deviation calculations of the GC bases of the three middle rosettes in all the simulations suggest that the RNT is stable (Figure 2.5). The obtained maximum standard deviation of just 0.13 Å of the RNT bases in DMSO indicates this as well.

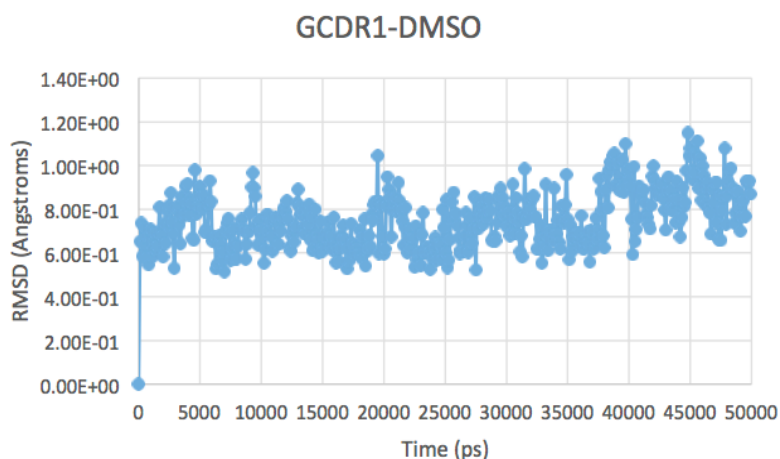


Figure 2.5. RMSD of the heavy atoms of the GC bases in the middle three rosettes.

The following parameters were obtained from the analysis of the trajectories:

Nitrogen-to-nitrogen distance = 2.98 Å

Intra-rosette stacking distance = 4.95 Å

Intra-rosette staggered angle = 6.12°

Inter-rosette stacking distance = 8.15 Å

Inter-rosette staggered angle = -38.08°

1.2.3.3.1. Energy Minimization of the carbon chains as part of the RNT.

Using the dimensions above, the next set of motifs and RNTs were constructed. By again using PRCG minimization in MacroModel, the functional carbon groups were minimized in octanol to obtain their most probable conformation. During minimization, the top and bottom rosettes as well as all the GC bases were fixed to reduce end effects. After minimization, the middle rosette was taken out to construct the final RNT models as shown below (Figure 2.6) (Figure 2.7).

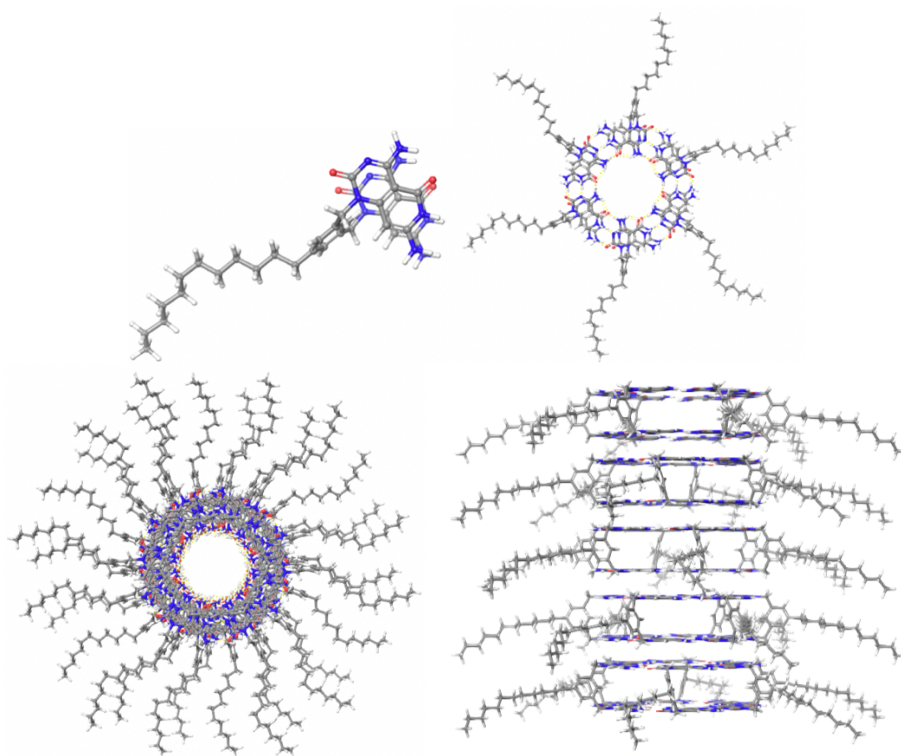


Figure 2.6. Schematic representation of final **GC-DR12** motif and RNT models.

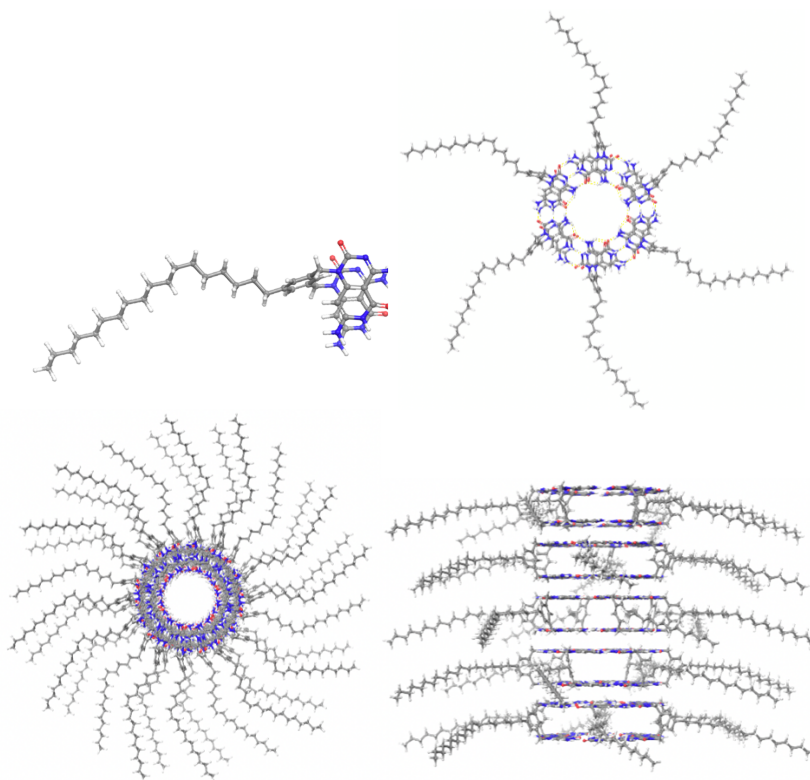


Figure 2.7. Schematic representation of final **GC-DR18** motif and RNT models.

1.2.3.3.2. Calculation of the total energy of RNT.

The total energy of the RNT was determined by using Macro Model as a function of motif number. RNTs composing of $N=1$ to 30 motifs were constructed by symmetric addition of rosettes and stacking to form the nanotube. The association energy, defined as the difference of the total energy of the RNT and the total energy of a single motif multiplied by the number of motifs in the structure, was obtained for each nanotube. Results suggest that both **GC-DR12** and **GC-DR18** are stable in solution (Figure 2.8) (Figure 2.9). The negative trends of both the total energy and association energy further suggest that the formation of nanotubes from free motifs is spontaneous.

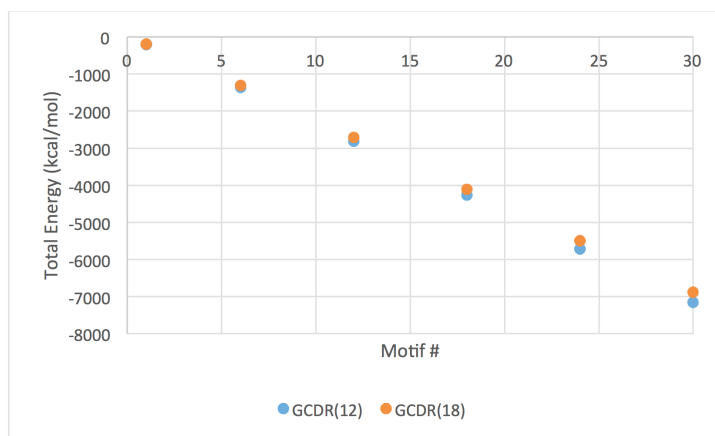


Figure 2.8. Total energy as a function of motif number.

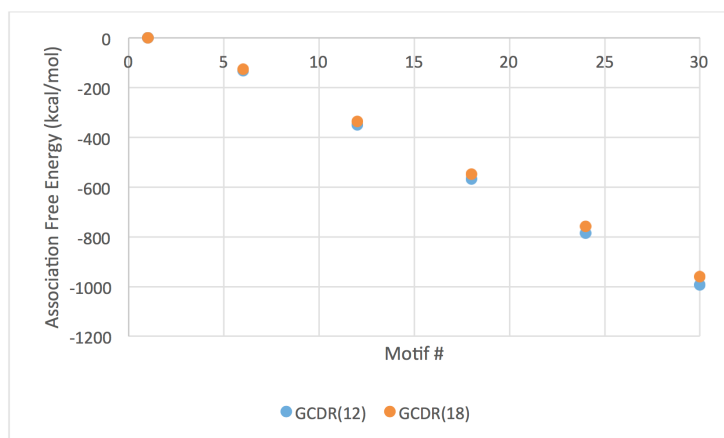


Figure 2.9. Association free energy as a function of motif number.

1.2.3.4. Molecular Dynamic Simulations

To determine the most probable RNT arrangement for **GC-DR 12** and **GC-DR 18**, MD simulations in organic solvent were run using three starting conformations. These are ring stacks; GC bases are offset; and helical coil. The figure shows the before (0 ns) and after (50 ns) snapshots of the three runs. While the ring stack pretty much maintained its structure, the offset structure did not hold and has started to transition to ring stacks. And the helical coil simply switched to a ring stack conformation. after equilibration (around 10 ns). MD simulations in organic solvent showed that the conformation resembles the ring stack more than the other two. Because the ring stack conformation seemed to be the more probable one according to the energetics analysis based on that structure.

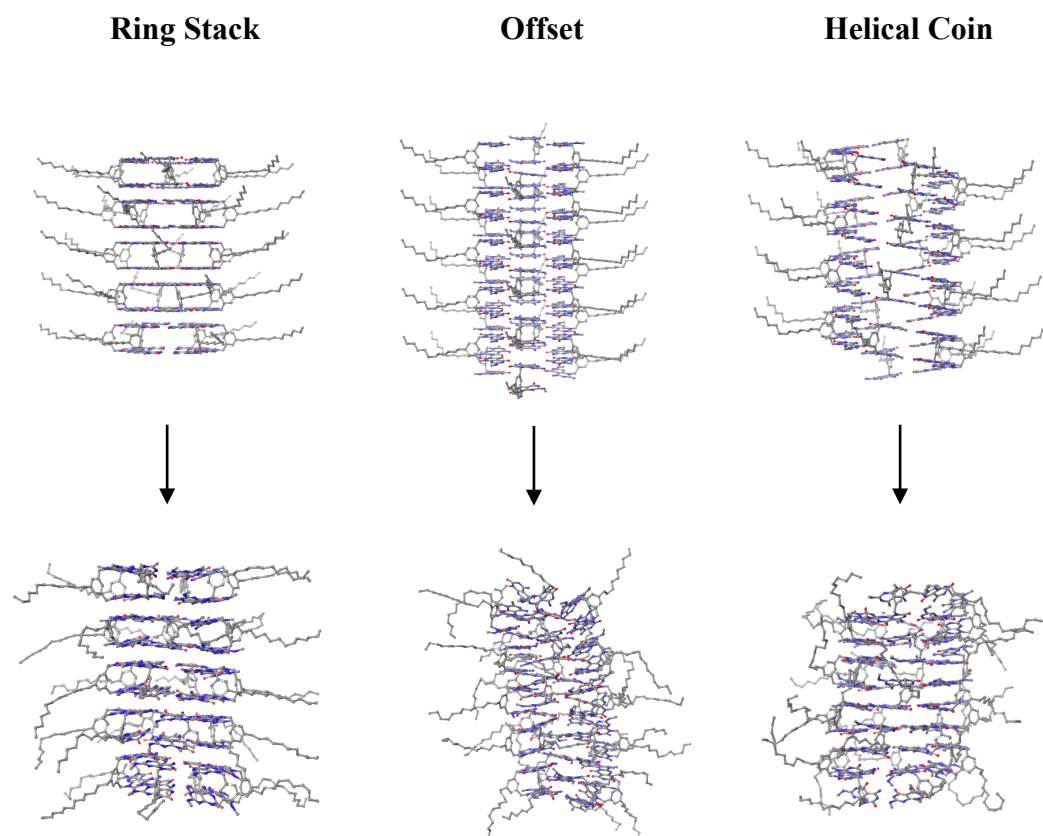


Figure 2.10. Association free energy as a function of motif number.

1.2.4. Microscopy Studies of GAC Base Bis-Rosette Nanotubes

NMR analysis of GAC base bis-rosette structure is not possible due to high aggregation and very low solubility. For this reason, the imaging analysis was performed with SEM and TEM instrument to see if any nanotube formation occurred.

1.2.4.1. Sample Preparation for SEM and TEM Imaging studies

Compound **GC-DR12** and **GC-DR18** were dissolved in dimethylformamide (DMF, 0.4 mg/mL for 1 and 0.2 mg/mL for 2) by sonicating for 30 min at room temperature. The solutions were heated on heating block at 90 °C for 0.5 hour. The result solutions were allowed cool to room temperature followed by 1-day aging. SEM samples were prepared by depositing a droplet of solutions on carbon coated 300 mesh copper grids and blotting after 1 min. All samples were air-dried at least 24 hours prior to imaging. SEM images were obtained without staining at a 5-kV accelerating voltage, 10 μ A, and a working distance of 3-4 mm on Hitatch S4800 coldfield-emission scanning electron microscope. TEM samples were prepared by depositing the solutions on carbon coated 300 mesh copper grids and blotting after 1 min. The samples were stained by uranyl acetate (2% in water). TEM characterization was performed at 80 kV and 60 μ A on JEOL 1010 transmission electron microscope.

1.2.4.2. SEM and TEM Studies

Observed by SEM, both compound **GC-DR12** and **GC-DR18** formed nanobundles (Figure 2.11). The diameter of these nanobundles is about 64.97 ± 2.31 nm for compound **GC-DR12** and 35.22 ± 4.96 nm for compound **GC-DR18** (Figure 2.12) Diameters were measured by ImageJ.

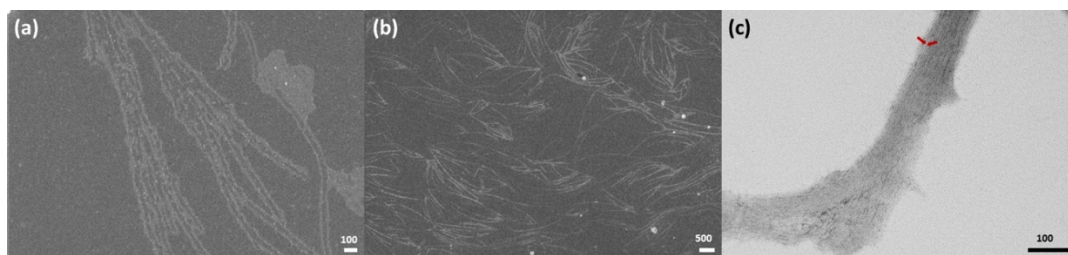


Figure 2.11. SEM images of (a) Compound **GC-DR12** (0.4 mg/mL) in DMF, (b) Compound **GC-DR18** (0.2 mg/mL) in DMF. TEM images of compound **GC-DR18**. (0.4 mg/mL) in DMF. Scale bars are given in nm.

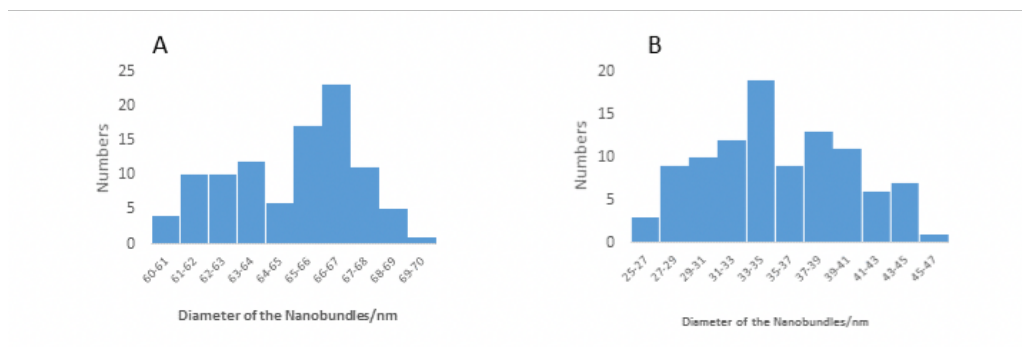


Figure 2.12. Size distribution of nanobundles formed from (A) Compound **GC-DR12** (0.4 mg/mL) in DMF and (B) Compound **GC-DR18** (0.2mg/mL) in DMF.

TEM images indicated that in the compound, the nanobundles consisted of rosette nanotubes (Figure 2.11.c). Literature examples showed that the GC derivatives self-assemble into single rosette nanotubes through Watson–Crick base pairs and π - π stacking [31]. Here we have investigated that the rosette nanotubes interweave to form larger nanobundles presumably due to strong van der Waals interactions between the long alkyl chains.

1.2.5. Characterization of the Precursors

For the characterization of the **GC-DR 12** and **GC-DR 18** precursors, ^1H -NMR, ^{13}C -NMR and HRMS measurements were performed.

1.2.5.1. ^1H -NMR of GC-DR

Solubility due to high aggregation in organic solvent by hydrogen bonding was a problem for the NMR analysis of the precursors **GC-DR 12** and **GC-DR 18**. They did not dissolve in DMSO, so a few drops of d-TFA were added to obtain NMR data. This strong acid was breaking up the aggregate as it is a Brønsted acid donor. Although ^1H -NMR data have been obtained this way, there are some difficulties to using d-TFA. Firstly, when d-TFA was used a number of protons were exchanged with deuterium. A broad singlet that was expected for four protons around 7-8 ppm are buried in the baseline for **GC-DR 12** and **GC-DR 18** precursors (Figure 2.13) (Figure 2.14).

Secondly, as the amount of d-TFA increases, the peak in the spectrum shifts to up field and at the same time the broadening and the intensity increases. For the **GC-DR 12** precursor's ^1H -NMR data, just one drop d-TFA was used and moderately small peak was shown around 9.50 ppm (Figure 2.13). At this point, the peak at 9.69 ppm is still visible. However, for the **GC-DR 18** precursor's ^1H -NMR data, three drops d-TFA was used and very broad and intense peak was shown at 5.00 ppm and it covered peaks of the product (Figure 2.14).

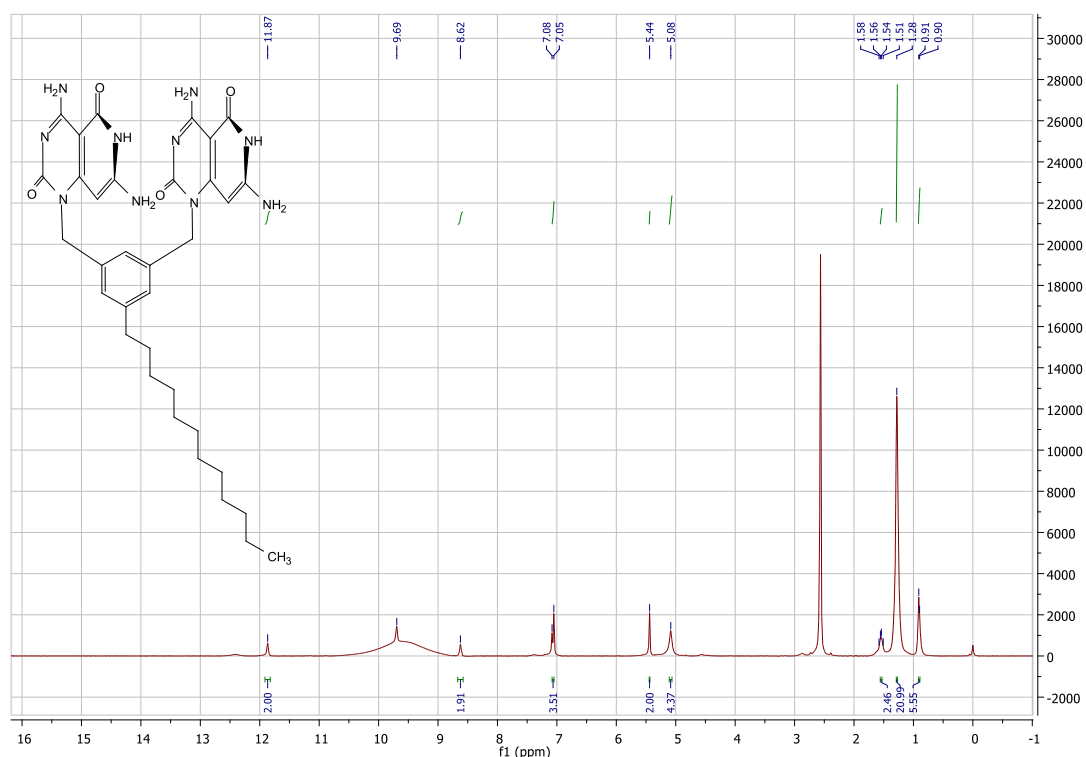


Figure 2.13. ^1H -NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione).

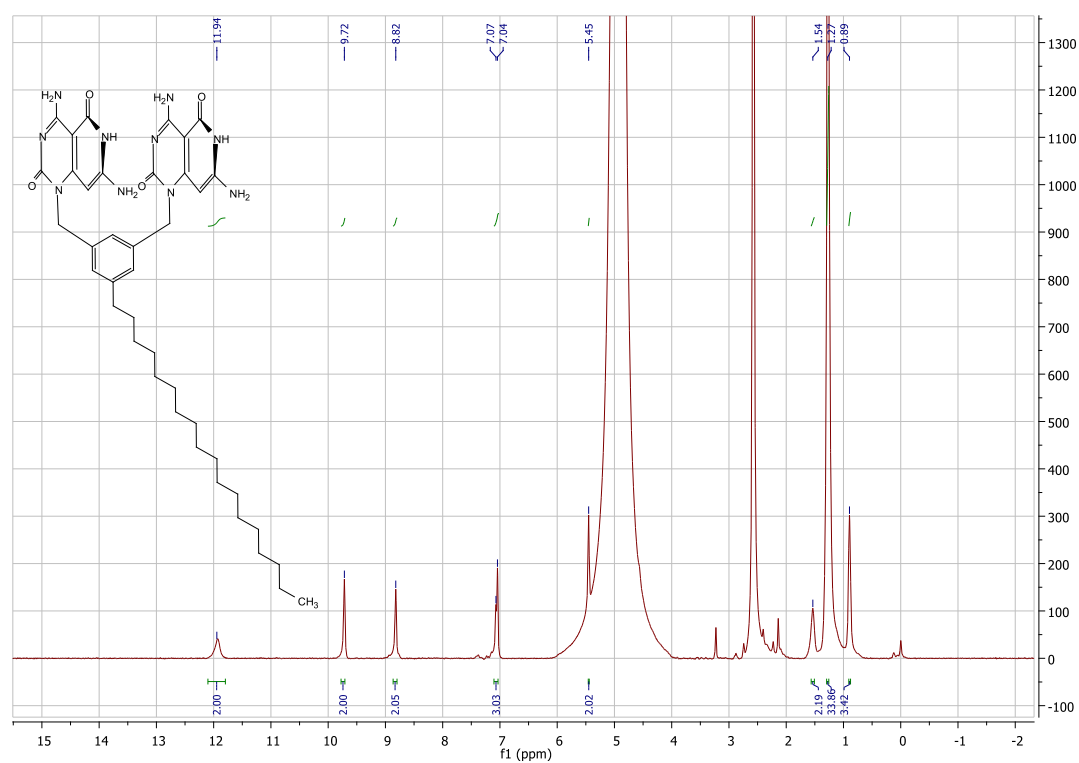


Figure 2.14. ¹H-NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione).

CHAPTER 1.3

CONCLUSION

A synthetic approach has been described for the preparation of G $\wedge$ C nucleobase hybrids in the form of self-assembling by hydrogen bonding, pyrido[4,3-d]pyrimidine derivatives which are only 5 steps from the commercially available malononitrile. Protected pyrido[4,3-d]pyrimidine unit was synthesized according to literature methods with minor modifications. Then, the synthesis of rigid bridging group structure was pursued. The synthetic approach was convergent in 5 steps and in good overall yield. The 3 intermediate step products and the final product in the synthesis are novel in the literature and characterized by nuclear magnetic resonance and high-resolution mass spectroscopy. Finally, the two units G $\wedge$ C base and rigid bridging group were combined and the final deprotection step was performed to yield the **GC-DR 12** and **GC-DR 18** precursors which were also fully characterized by NMR and Mass Analyses. After syntheses of **GC-DR 12** and **GC-DR 18** motifs were achieved, bis-rosette and nanotube formations were proved by imaging and computational analyses. Molecular dynamic simulations and computational optimizations studies have shown that formation of bis-rosette cage structures and Ring Stack RNT arrangement is favorable in organic solvent. On the other hand, the supramolecular nanotube formation was investigated in detail via SEM and TEM studies. **GC-DR 12** and **GC-DR 18** precursors are subjected to rapid self-assembly into RNTs in DMF solvent. And formed nanotubes comes together to give large nanobundles. SEM and TEM imaging studies showed the formation 1D nanostructures of **GC-DR 12** and **GC-DR 18** with average cross sections in 64.97 nm and 35.22 nm respectively. As a result, this study shows that **GC-DR 12** and **GC-DR 18** are the first organic-solvent based bis-rosette GAC cage molecule in literature.

CHAPTER 1.4

EXPERIMENTAL

1.4.1. Materials and Methods

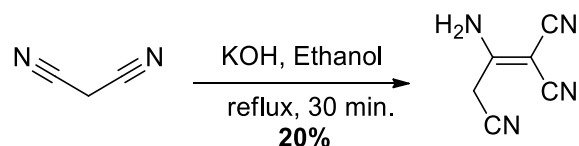
The ^1H and ^{13}C -NMR spectra were recorded on a Bruker Avance III Ultrashield (400 MHz) spectrometer. The chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (J) are reported in hertz (Hz), and the spin multiplicities were specified by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), td (triplet of doublet), and m (multiplet). NMR spectrums were processed with MestReNova program. Column chromatography was performed by using thick walled glass columns and silica Gel 60 (Merck 230-400 mesh). Thin layer chromatography (TLC Merck Silica Gel 60 F254) was performed by using commercially prepared 0.25 mm silica gel plates and visualization was provided by UV lamp. The relative proportions of solvents in chromatography solvent mixtures refer to the volume: volume ratio. All commercially available reagents and starting materials were purchased from Aldrich Chemical and used directly without further purification. All dry solvents used in reactions were directly obtained from the Mbraun MBSPS5 solvent drying system. The inert atmosphere was obtained by Argon.

1.4.2. Equipment

CDCl_3 and d_6 -DMSO was used as the solvents for the ^1H and ^{13}C -NMR analyses on Bruker Spectrospin Avance DPX-400 Spectrometer and tetramethylsilane was used as the internal reference. High resolution mass spectroscopy was performed in order to determine the exact masses of the novel synthesized compounds using Waters Synapt MS System.

1.4.3. GAC Base Syntheses

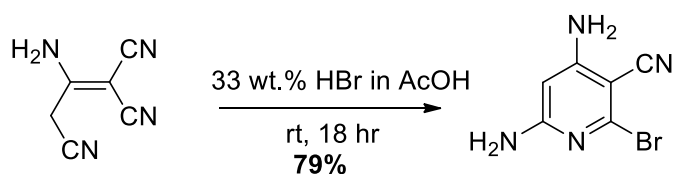
1.4.3.1. Synthesis of 2-Amino-1,1,3-propenetricarbonitrile



Scheme 4.1. Synthetic route of 2-Amino-1,1,3-propenetricarbonitrile.

2-Amino-1,1,3-propenetricarbonitrile was synthesized according to the literature with small modifications [35]. To a cooled solution of KOH (7.01 g, 0.125 mol) in ethanol (50 mL), malononitrile (16.5 g, 0.250 mol) was added, and the mixture was slowly heated to 80 °C for 30 min and then cooled to room temperature. The resulting precipitate was filtered, washed with cold ethanol and dried. The alkali salt was dissolved with small amount of water, and acidified to pH 4 using conc. hydrochloric acid. The resulting mixture was recrystallized with water and colorless needles were obtained (6.60 g, 20%): ^1H NMR (400 MHz, DMSO- d_6) δ 8.99 (d, J = 20.5 Hz, 2H), 3.83 (s, 2H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 164.8, 115.3, 114.6, 114.2, 49.7, 22.1.

1.4.3.2. Synthesis of 4,6-Diamino-2-bromonicotinonitrile

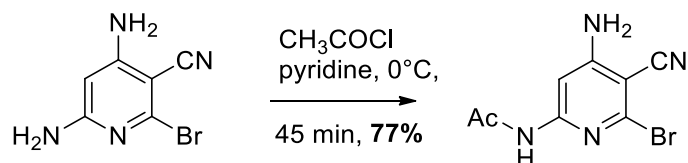


Scheme 4.2. Synthetic route of 4,6-Diamino-2-bromonicotinonitrile.

4,6-Diamino-2-bromonicotinonitrile was synthesized according to the literature with small modifications [31]. The mixture of 2-Amino-1,1,3-propenetricarbonitrile (4.05 g, 30.7 mmol) and 33% HBr in acetic acid (40 mL) was stirred at room temperature for overnight. Then the reaction was quenched with a mixture of saturated aqueous sodium bicarbonate (360 mL) and EtOAc (12 mL). The resulting precipitate was filtered off, washed with water and dried to give a light yellow solid (5.59 g, 79%): ^1H NMR (400 MHz, DMSO- d_6) δ 6.66(s, 2H), 6.54(s, 2H), 5.60(s, 1H). ^{13}C NMR (100

MHz, DMSO-*d*₆) δ 160.7, 157.5, 143.8, 117.1, 86.5, 85.2.

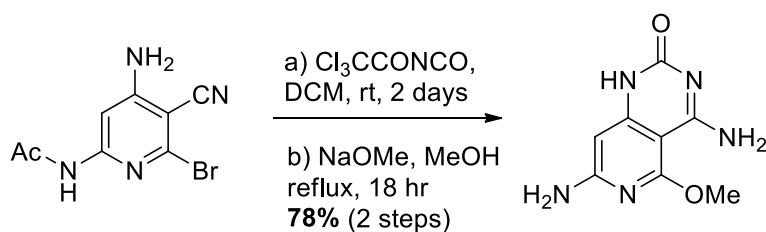
1.4.3.3. Synthesis of *N*-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide



Scheme 4.3. Synthetic route of *N*-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide.

N-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide was synthesized according to the literature with small modifications [31]. 4,6-Diamino-2-bromonicotinonitrile (1.02 g, 4.40 mmol) was dissolved in dry pyridine (10 mL), and acetyl chloride (0.900 mL, 11.5 mmol) was added dropwise at 0°C . The solution was stirred for 45 min while maintaining the temperature at 0°C and then quenched with cold water (50 mL). The resulting precipitate was filtered and washed with cold water to yield *N*-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide as a light brown solid (0.870 g, 78%): ^1H NMR (400 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 7.52 (s, 1H), 7.33 (s, 2H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d*₆) δ 169.8, 159.2, 152.9, 142.7, 115.6, 95.0, 90.2, 23.6.

1.4.3.4. Synthesis of 4,7-Diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one



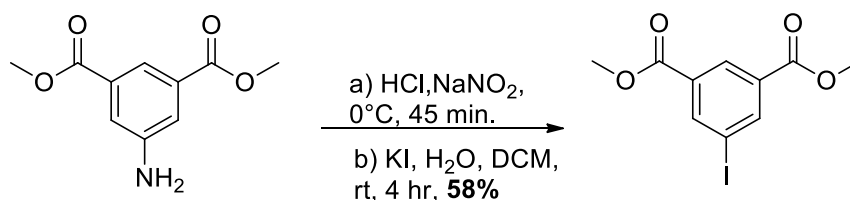
Scheme 4.4. Synthetic route of 4,7-Diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one.

4,7-Diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one was synthesized according to the literature with small modifications [31]. To a solution of *N*-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide (1.06 g, 4.16 mmol) in dry DCM (200 mL) at room temperature, trichloroacetyl isocyanate (1.00 mL, 1.58 g, 8.40 mmol) was added. The solution was stirred for 2 days at room temperature. Then, the reaction was quenched

with water (15 mL) and 5% NaOH (15 mL) respectively and the mixture was stirred for an additional 2 h. The aqueous layer was extracted with a 5% isopropyl alcohol/DCM mixture (5 × 30 mL). The combined organic layers were successively washed with brine and dried over magnesium sulfate. The solvent was evaporated and the resulting solid was dissolved in dry methanol (80 mL), and a solution of sodium methoxide prepared from sodium (0.840 g, 36.6 mmol) and dry methanol (120 mL) was then added. The reaction mixture was stirred for 1 h at room temperature followed by under reflux for overnight. The solvent was concentrated under reduced pressure, and the resulting residue was treated with acetic acid (6 mL). The resulting precipitate was filtered, washed with water and dried to obtain 4,7-Diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one as a light yellow solid (0.670 g, 78%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.03 (br s, 1H), 8.70 (br s, 1H), 7.93 (s, 1H), 6.99 (s, 2H), 5.73 (s, 1H), 3.95 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.8, 160.9, 160.1, 153.6, 150.9, 83.3, 82.4, 53.8.

1.4.4. Bridging Group Synthesis

1.4.4.1. Synthesis of Dimethyl 5-iodoisophthalate

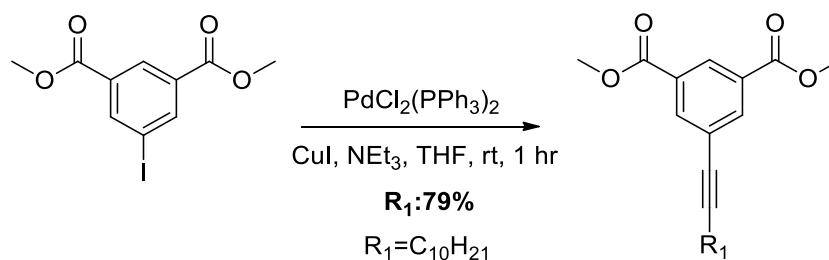


Scheme 4.5. Synthetic route of Dimethyl 5-iodoisophthalate.

Dimethyl 5-iodoisophthalate was synthesized according to the literature with small modifications [36]. To stirred solution of dimethyl 5-iodoisophthalate (1.50 g, 7.17 mmol) in 2M hydrochloric acid (6.8 mL) at 0°C was added a solution of NaNO₂ (0.530 g, 7.65 mmol) in water (4.5 mL). Then, the mixture was stirred at for 45 min to obtain a clear solution and ice-cold KI (1.70 g, 10.3 mmol) in water (16 mL) was added at 0°C. When the color turned dark red, CH₂Cl₂ (23 mL) was added and the mixture was allowed to stir at room temperature for 4 h. The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over magnesium sulfate. The

solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel with CH_2Cl_2 as eluent, to yield the target product with a white solid (1.33 g, 58%): ^1H NMR (400 MHz, CDCl_3) δ 8.56 (t, $J = 1.5$ Hz, 1H), 8.47 (d, $J = 1.5$ Hz, 2H), 3.88 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 163.5, 141.3, 130.9, 128.5, 92.3, 51.3.

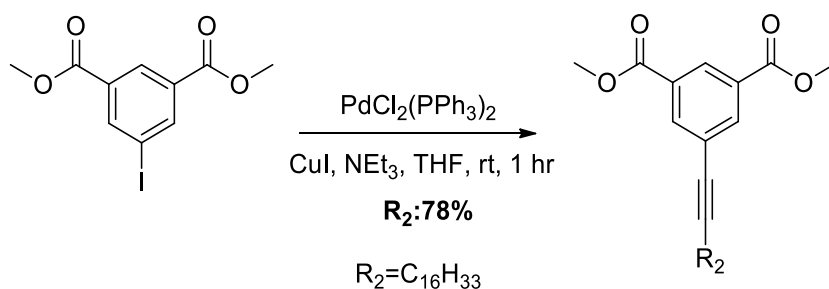
1.4.4.2. Synthesis of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate



Scheme 4.6. Synthetic route of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate.

Dimethyl-5-(dodec-1-yn-1-yl)isophthalate was synthesized according to a literature method for that was used for a related starting material [37]. Dimethyl-5-iodoisophthalate (0.560 g, 1.75 mmol), 1-Dodecyne (0.72 g, 0.94 mL, 4.4 mmol), and Et_3N (0.45 g, 0.60 mL, 4.4 mmol) was stirred in dry THF (13 mL) and then, $\text{PdCl}_2(\text{PPh}_3)_2$ (60 mg, 0.087 mmol) and CuI (30 mg, 0.18 mmol) was added respectively. The reaction mixture was stirred for 2 hours under argon atmosphere at room temperature. The resulting ammonium salt was filtered and the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1:6 EtOAc/hexane) to yield target product as a brown solid (0.495 g, 79% yield): ^1H NMR (400 MHz, CDCl_3) δ 8.48 (t, $J = 1.6$ Hz, 1H), 8.14 (d, $J = 1.6$ Hz, 2H), 3.87 (s, 6H), 2.34 (t, $J = 7.1$ Hz, 2H), 1.58 – 1.48 (m, 2H), 1.42 – 1.33 (m, 2H), 1.31 – 1.13 (m, $J = 11.5$ Hz, 12H), 0.80 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.1, 134.8, 129.0, 127.7, 123.6, 91.3, 77.2, 50.8, 30.3, 27.9, 27.9, 27.7, 27.5, 27.3, 26.9, 21.0, 17.7, 12.4. HRMS calculated for $\text{C}_{22}\text{H}_{31}\text{O}_4$: 359.2222, found: 359.2234.

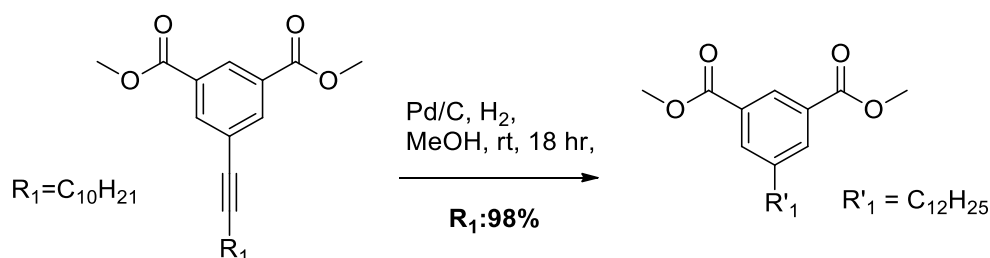
1.4.4.3. Synthesis of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate



Scheme 4.7. Synthetic route of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate.

Dimethyl 5-iodoisophthalate (1.03 g, 3.21 mmol), 1-Octadecyne (2.01 g, 2.50 mL, 8.03 mmol), and Et_3N (0.81 g, 1.1 mL, 8.0 mmol) was stirred in dry THF (25 mL) and then, $\text{PdCl}_2(\text{PPh}_3)_2$ (0.11 g, 0.16 mmol) and CuI (60 mg, 0.32 mmol) was added respectively. The reaction mixture was stirred for 2 hours under argon atmosphere at room temperature. The resulting ammonium salt was filtered and the solvent was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1:6 EtOAc/hexane) to yield a brown solid (1.11 g, 78% yield): ^1H NMR (400 MHz, CDCl_3) δ 8.56 (t, $J = 1.6$ Hz, 1H), 8.22 (d, $J = 1.6$ Hz, 2H), 3.94 (s, 6H), 2.42 (t, $J = 7.1$ Hz, 2H), 1.67 – 1.56 (m, 2H), 1.51 – 1.37 (m, 2H), 1.38 – 1.16 (m, 24H), 0.88 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 136.4, 130.7, 129.3, 125.0, 92.8, 78.8, 52.4, 31.9, 29.7, 29.5, 29.3, 29.1, 28.9, 28.5, 22.7, 19.3, 14.1. HRMS calculated for $\text{C}_{28}\text{H}_{43}\text{O}_4$: 443.3161, found: 443.3156.

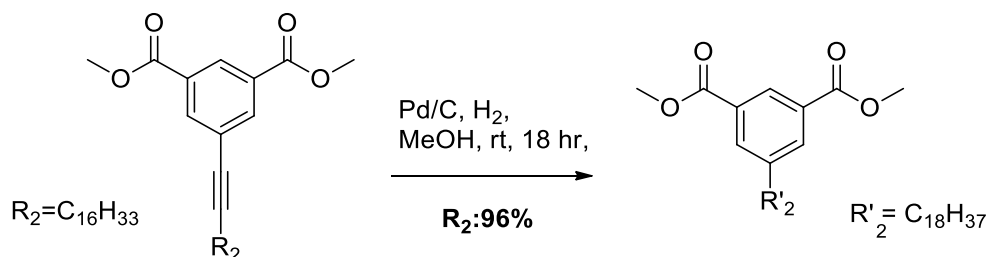
1.4.4.4. Synthesis of Dimethyl 5-dodecylisophthalate



Scheme 4.8. Synthetic route of Dimethyl 5-dodecylisophthalate.

To the solution of dimethyl-5-(dodec-1-yn-1-yl)isophthalate (0.440 g, 1.23 mmol) in methanol (15 mL) was added Pd/C catalyst (10 wt. %, 0.05 g) under argon atmosphere. Then, the flask was evacuated under vacuum and flushed with H₂ (3x) and the reaction was stirred under a H₂ balloon at room temperature for 24 h. The mixture was filtered through a bed of Celite, washed with methanol, and concentrated to yield the target product as a white solid (0.440 g, 99%): ¹H NMR (400 MHz, CDCl₃) δ 8.43 (t, *J* = 1.6 Hz, 1H), 7.97 (d, *J* = 1.6 Hz, 2H), 3.87 (s, 6H), 2.64 (t, *J* = 7.7 Hz, 2H), 1.61 – 1.52 (m, 2H), 1.28 – 1.14 (m, 18H), 0.81 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 143.8, 133.8, 130.5, 128.1, 52.2, 35.5, 31.9, 31.2, 29.6, 29.5, 29.4, 29.3, 29.1, 22.6, 14.1. HRMS calculated for C₂₂H₃₅O₄: 363.2535, found: 363.2538.

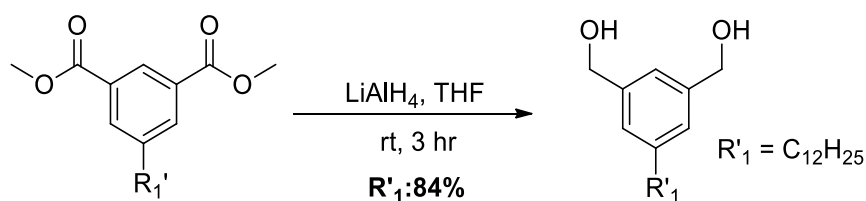
1.4.4.5. Synthesis of Dimethyl 5-octadecylisophthalate



Scheme 4.9. Synthetic route of Dimethyl 5-octadecylisophthalate.

To the solution of dimethyl-5-(octadec-1-yn-1-yl)isophthalate (1.12 g, 2.53 mmol) in methanol (25 mL) was added Pd/C catalyst (10 wt. %, 0.110 g) under argon atmosphere. Then, the flask was evacuated under vacuum and flushed with H₂ (3x) and the reaction was stirred under a H₂ balloon at room temperature for 24 h. The mixture was filtered through a bed of Celite, washed with methanol, and concentrated to yield the target compound as an off-white solid (1.08 g, 96%): ¹H NMR (400 MHz, CDCl₃) δ 8.43 (t, *J* = 1.6 Hz, 1H), 7.97 (d, *J* = 1.6 Hz, 2H), 3.87 (s, 6H), 2.62 (t, *J* = 7.7 Hz, 2H), 1.69 – 1.55 (m, 2H), 1.23 – 1.18 (m, 30H), 0.80 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 143.8, 133.8, 130.5, 128.1, 52.2, 35.5, 31.9, 31.2, 29.6, 29.6, 29.5, 29.4, 29.3, 29.1, 22.6, 14.1. HRMS calculated for C₂₈H₄₇O₄: 447.3474, found: 447.3479.

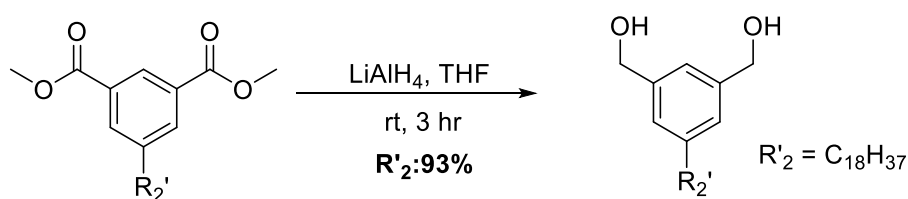
1.4.4.6. Synthesis of (5-dodecyl-1,3-phenylene)dimethanol



Scheme 4.10. Synthetic route of (5-dodecyl-1,3-phenylene)dimethanol.

(Dimethyl 5-dodecylisophthalate (0.217 g, 0.599 mmol) dissolved in anhydrous THF (50 mL) and the solution was added dropwise to the cooled 0°C solution of Lithium aluminum hydride (76.0 mg, 2.00 mmol) in anhydrous THF (3 mL). The mixture was stirred at room temperature for 2 h. 0.1 mL water and 0.1 mL 15% (w/w) NaOH solution was sequentially added at 0°C to resulting mixture to quench reaction. Then 0.3 mL water was added again and the mixture was dried with anhydrous MgSO_4 . The residue was filtered and washed with THF (20 mL), then concentrated to obtain white solid (0.154 g, 84%): ^1H NMR (400 MHz, CDCl_3) δ 7.09 (t, $J = 1.6$ Hz, 1H), 7.02 (d, $J = 1.6$ Hz, 2H), 4.57 (s, 4H), 2.52 (t, $J = 7.7$ Hz, 2H), 1.96 (t, $J = 7.7$ Hz, 2H), 1.55 – 1.49 (m, 2H), 1.23 – 1.18 (m, 18H), 0.81 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 141.7, 139.1, 124.3, 120.8, 63.2, 33.8, 29.8, 29.4, 27.6, 27.5, 27.5, 27.4, 27.3, 27.3, 20.6, 12.0. HRMS calculated for $\text{C}_{20}\text{H}_{34}\text{O}_2\text{Na}$: 329.2457, found: 329.2466.

1.4.4.7. Synthesis of (5-octadecyl-1,3-phenylene)dimethanol

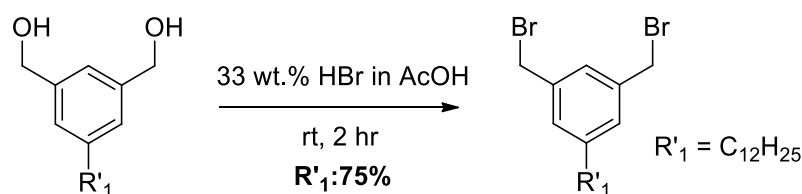


Scheme 4.11. Synthetic route of (5-octadecyl-1,3-phenylene)dimethanol.

Dimethyl 5-octadecylisophthalate (1.09 g, 2.44 mmol) dissolved in anhydrous THF (60 mL) and the solution was added dropwise to the cooled 0°C solution of Lithium aluminum hydride (0.310 g, 8.17 mmol) in anhydrous THF (12 mL). The mixture was stirred at room temperature for 2 h. 0.3 mL water and 0.3 mL 15% (w/w) NaOH

solution was sequentially added at 0°C to resulting mixture to quench reaction. Then 0.9 mL water was added again and the mixture was dried with anhydrous MgSO₄. The residue was filtered and washed with THF (80 mL) solvent, then concentrated to obtain white solid (0.887 g, 93%): ¹H NMR (400 MHz, CDCl₃) δ 7.12 (t, *J* = 1.7 Hz, 1H), 7.05 (d, *J* = 1.6 Hz, 2H), 4.61 (s, 4H), 2.54 (t, *J* = 7.6 Hz, 2H), 1.65 – 1.50 (m, 4H), 1.23 – 1.18 (m, 30H), 0.81 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 143.8, 141.1, 126.4, 122.9, 65.3, 35.9, 31.9, 31.5, 30.3, 29.7, 29.7, 29.6, 29.5, 29.4, 29.4, 22.7, 14.1. HRMS calculated for C₂₆H₄₆O₂Na: 413.3396, found: 413.3416.

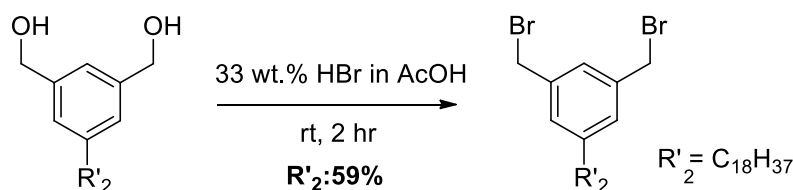
1.4.4.8. Synthesis of 1,3-bis(bromomethyl)-5-dodecylbenzene



Scheme 4.12. Synthetic route of 1,3-bis(bromomethyl)-5-dodecylbenzene.

The mixture of (5-dodecyl-1,3-phenylene)dimethanol (0.160 g, 0.523 mmol) and 33% HBr in acetic acid (2 mL) was stirred at room temperature for 2 h. After addition of DCM (10 mL), the organic solvent was washed with water and saturated bicarbonate solution and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel (1:4 EtOAc/hexane) to yield white solid (0.168 g, 75%): ¹H NMR (400 MHz, CDCl₃) δ 7.16 (t, *J* = 1.6 Hz, 1H), 7.06 (d, *J* = 1.6 Hz, 2H), 4.38 (s, 4H), 2.51 (t, *J* = 7.6 Hz, 2H), 1.57 – 1.49 (m, 2H), 1.23 – 1.19 (m, 18H), 0.81 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 144.4, 138.2, 129.2, 126.9, 77.3, 77.0, 76.7, 35.6, 33.1, 31.9, 31.2, 29.7, 29.6, 29.5, 29.4, 29.3, 22.7, 14.1.

1.4.4.9. Synthesis of 1,3-bis(bromomethyl)-5-octadecylbenzene

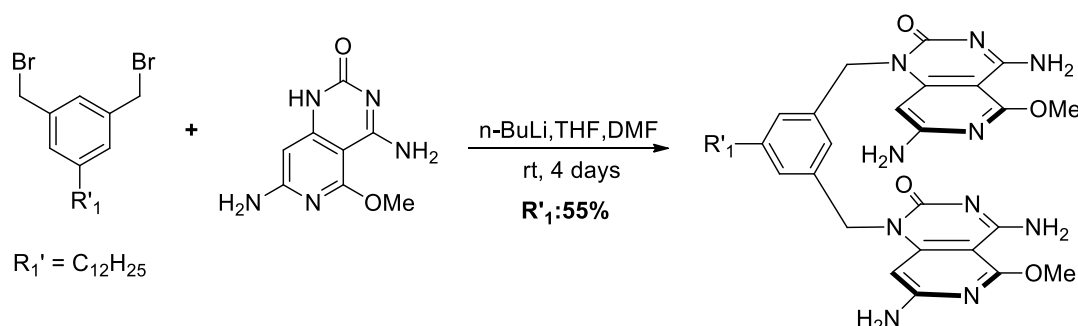


Scheme 4.13. Synthetic route of 1,3-bis(bromomethyl)-5-octadecylbenzene.

The mixture of (5-octadecyl-1,3-phenylene)dimethanol (0.887 g, 2.27 mmol) and 33% HBr in acetic acid (6 mL) was stirred at room temperature for 2 h. After addition of DCM (10 mL), the organic solvent was washed with water and saturated bicarbonate solution and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel (1:4 EtOAc/hexane) to yield white solid (0.689 g, 59%): ^1H NMR (400 MHz, CDCl_3) δ 7.16 (t, J = 1.6 Hz, 1H), 7.07 (d, J = 1.6 Hz, 2H), 4.38 (s, 4H), 2.51 (t, J = 7.6 Hz, 2H), 1.57 – 1.49 (m, 2H), 1.24 – 1.18 (m, 30H), 0.81 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 144.3, 138.2, 129.2, 126.9, 77.3, 77.0, 76.7, 35.6, 33.1, 31.9, 31.2, 29.7, 29.6, 29.5, 29.4, 29.3, 22.7, 14.1. HRMS calculated for $\text{C}_{26}\text{H}_{44}\text{Na}^{79}\text{Br}^{81}\text{Br}$: 539.1687, found: 539.1716.

1.4.5. Combination of the Units

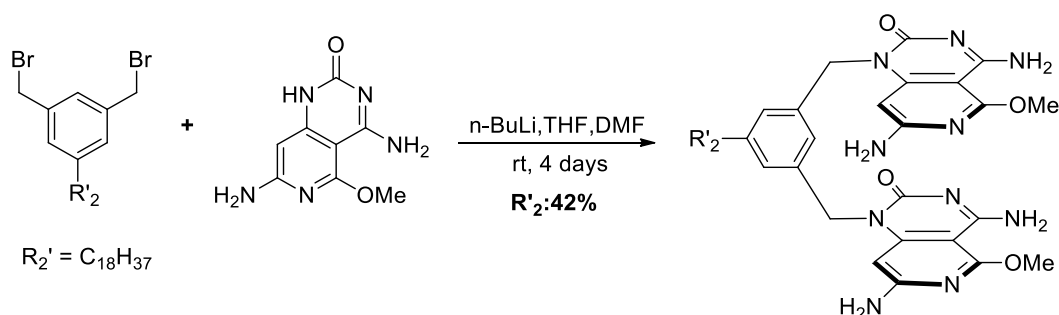
1.4.5.1. Synthesis of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one)



Scheme 4.14. Synthetic route of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one).

To a solution of 4,7-Diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one (0.213 g, 1.03 mmol) in dry THF (3.00 mL), 2.5 M *n*-Buthyllithium (0.450 mL, 1.13 mmol, in hexanes) was added dropwise at -78 °C, and the mixture was stirred until -10 °C was reached. Then, 1,3-bis(bromomethyl)-5-dodecylbenzene (0.216 g, 0.500 mmol) in dry DMF (25 mL) were added, and the mixture was stirred for 4 days. The reaction was quenched with MeOH (20 mL), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (1:9 methanol/DCM) to yield off-white solid (0.190 g, 55%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.62 (s, 2H), 7.37 (s, 2H), 6.97 (s, 1H), 6.72 (s, 2H), 6.66 (s, 2H), 5.61(s, 2H), 5.02 (br s, 4H), 3.93 (s, 6H), 2.40 (t, *J* = 7.7 Hz, 2H), 1.42 – 1.35 (m, 2H), 1.22 – 1.15 (m, 18H), 0.84 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.6, 161.3, 160.3, 155.3, 151.9, 142.7, 137.3, 124.2, 122.4, 84.7, 82.4, 53.7, 45.9, 34.9, 31.3, 30.8, 28.98, 28.9, 28.9, 28.7, 28.7, 28.5, 22.0, 13.9. HRMS calculated for C₃₆H₄₉N₁₀O₄: 685.3938, found: 685.3939.

1.4.5.2. Synthesis of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one)

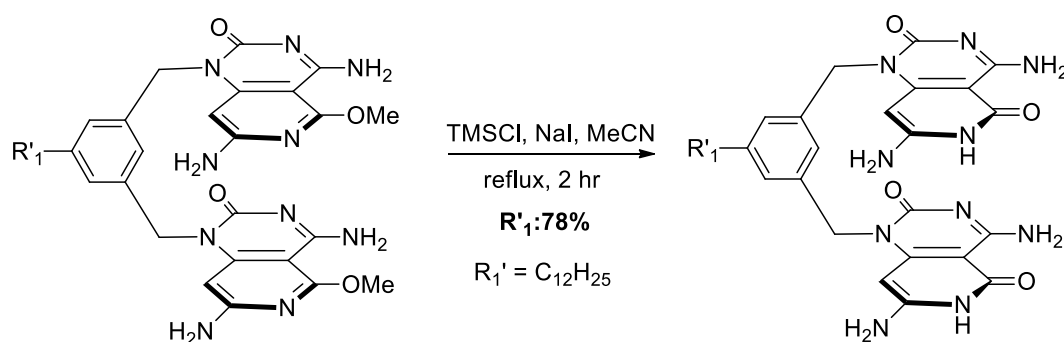


Scheme 4.15. Synthetic route of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one).

To a solution of 4,7-Diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one (0.200 g, 0.970 mmol) in dry THF (3.00 mL), 2.5 M *n*-Buthyllithium (0.400 mL, 1.06 mmol, in hexanes) was added dropwise at -78 °C, and the mixture was stirred until -10 °C was reached. Then, 1,3-bis(bromomethyl)-5-octadecylbenzene (0.240 g, 0.460 mmol) in dry DMF (30 mL) were added, and the mixture was stirred for 4 days. The reaction was quenched with MeOH (20 mL), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (1:9

methanol/DCM) to yield off-white solid (0.150 g, 42%): ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.62 (s, 2H), 7.38 (s, 2H), 6.97 (s, 1H), 6.72 (s, 2H), 6.66 (s, 2H), 5.61 (s, 2H), 5.04 (br s, 4H), 3.93 (s, 6H), 2.41 (t, $J = 7.7$ Hz, 2H), 1.42 – 1.35 (m, 2H), 1.23 – 1.16 (m, 18H), 0.85 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 161.6, 161.3, 160.3, 155.3, 152.0, 142.7, 137.3, 124.2, 122.3, 84.8, 82.4, 53.7, 45.9, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 31.2, 28.9, 28.8, 28.6, 28.5, 22.0, 13.9. HRMS calculated for $\text{C}_{42}\text{H}_{61}\text{N}_{10}\text{O}_4$: 769.4877, found: 769.4841.

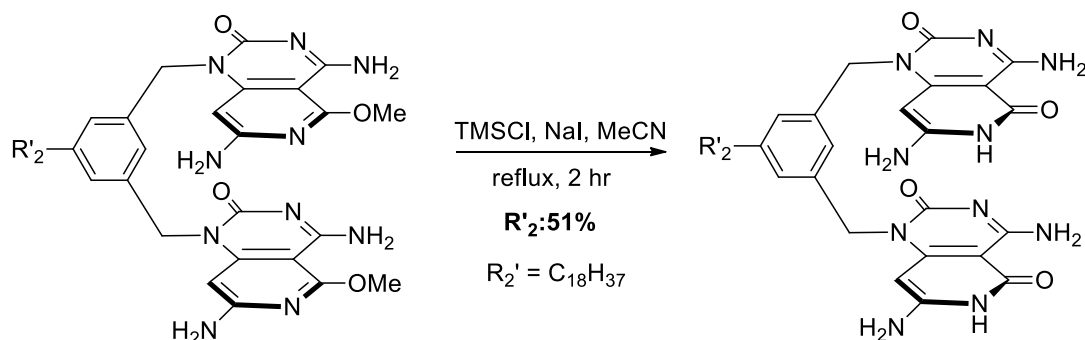
1.4.5.3. Synthesis of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione)



Scheme 4.16. Synthetic route of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione).

To a solution of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one) (60.0 mg, 0.0876 mmol) in dry acetonitrile (14 mL) were added sodium iodide (0.974 g, 0.650 mmol) and chlorotrimethylsilane (0.0600 mL, 0.0450 g, 0.430 mmol). The reaction flask was protected from light and the mixture was heated at reflux for 3 h. The mixture was poured into pH 7 aqueous phosphate buffer (0.5 M, 15.0 mL). The resulting precipitate was filtered, washed with EtOAc, and then with MeOH to give an off-white solid (45.0 mg, 78%): ^1H NMR (400 MHz, $\text{DMSO-}d_6$, 1 drop of *d*-TFA) δ 11.87 (s, 2H), 9.69 (s, 2H), 8.62 (s, 2H), 7.07 (d, $J = 12.0$ Hz, 3H), 5.44 (s, 2H), 5.09 (s, 4H), 1.58–1.51 (m, 2H), 1.33–1.22 (m, 20H), 0.91 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 161.3, 156.2, 155.7, 152.2, 147.9, 143.5, 135.3, 125.2, 121.2, 82.6, 77.9, 46.1, 34.7, 31.1, 30.6, 28.8, 28.5, 28.3, 21.9, 13.7. HRMS calculated for $\text{C}_{34}\text{H}_{45}\text{N}_{10}\text{O}_4$: 657.3625, found: 657.3600.

1.4.5.4. Synthesis of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione)



Scheme 4.17. Synthetic route of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione).

To a solution of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one) (80.0 mg, 0.104 mmol) in dry acetonitrile (16 mL) were added sodium iodide (0.174 g, 1.16 mmol) and chlorotrimethylsilane (0.100 mL, 83.0 mg, 0.766 mmol). The reaction flask was protected from light and the mixture was heated at reflux for 3 h. The mixture was poured into pH 7 aqueous phosphate buffer (0.5 M, 15.0 mL). The resulting precipitate was filtered, washed with EtOAc, and then with MeOH to give an off-white solid (39.0 mg, 51%): ¹H NMR (400 MHz, DMSO-*d*₆, 3 drop of *d*-TFA) δ 11.88 (s, 2H), 9.65 (s, 2H), 8.81 (s, 2H), 7.01 (d, *J* = 12.1 Hz, 3H), 5.39 (s, 2H), 5.02 (s, 4H), 1.51–1.46 (m, 2H), 1.26–1.20 (m, 32H), 0.84 (t, *J* = 6.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 161.3, 156.4, 155.9, 152.2, 147.9, 143.5, 135.3, 125.1, 121.6, 82.7, 77.8, 46.3, 34.9, 31.2, 30.8, 28.9, 28.7, 28.6, 22.0, 13.8. HRMS calculated for C₄₀H₅₇N₁₀O₄: 741.4564, found: 741.4566.

1.4.6. Sample Preparation of SEM

Compound **GC-DR12** and **GC-DR18** were dissolved in dimethylformamide (DMF, 0.4 mg/mL for 1 and 0.2 mg/mL for 2) by sonicating for 30 min at room temperature. The solutions were heated on heating block at 90 °C for 0.5 hour. The result solutions were allowed cool to room temperature followed by 1-day aging. SEM samples were prepared by depositing a droplet of solutions on carbon coated 300 mesh copper grids

and blotting after 1 min. All samples were air-dried at least 24 hours prior to imaging. SEM images were obtained without staining at a 5-kV accelerating voltage, 10 μ A, and a working distance of 3-4 mm on Hitachi S4800 coldfield-emission scanning electron microscope.

1.4.7. Sample Preparation of TEM

TEM samples were prepared by depositing the solutions on carbon coated 300 mesh copper grids and blotting after 1 min. The samples were stained by uranyl acetate (2% in water). TEM characterization was performed at 80 kV and 60 μ A on JEOL 1010 transmission electron microscope.

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APPENDIX A

NMR SPECTRA

NMR measurements were performed with Bruker Avance III Ultrashield 400 Hz using CDCl_3 , or *d*-DMSO as the solvents.

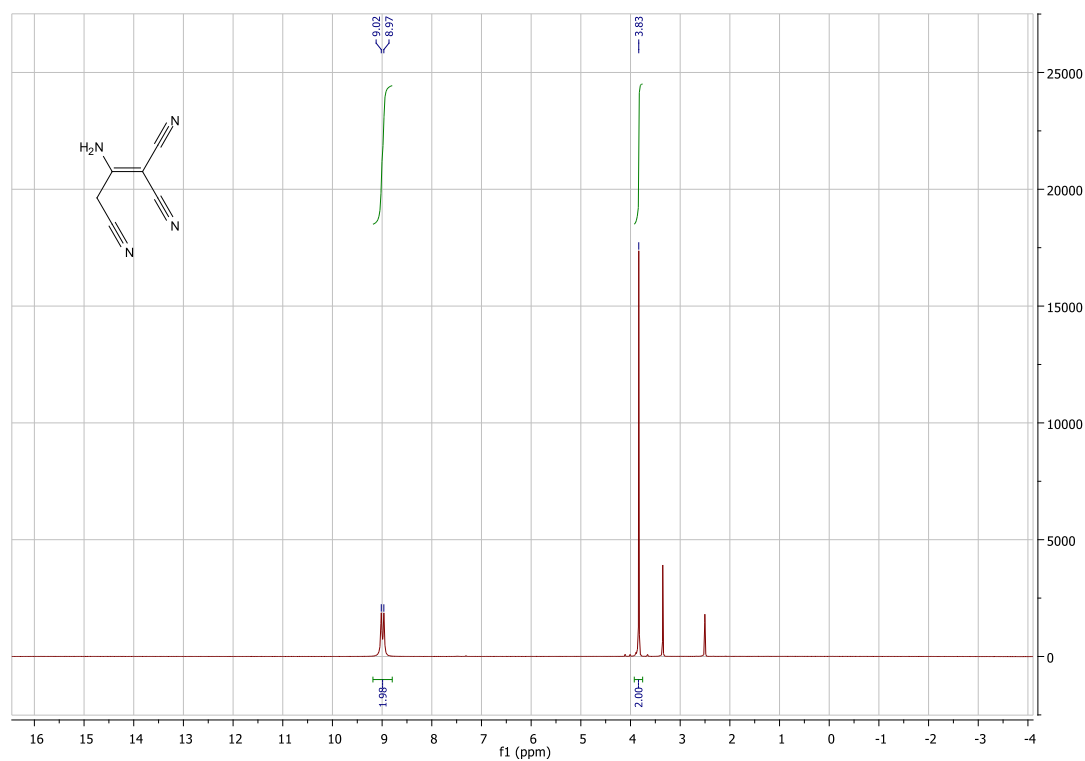


Figure A.1. ¹H-NMR spectrum of 2-Amino-1,1,3-propenetricarbonitrile.

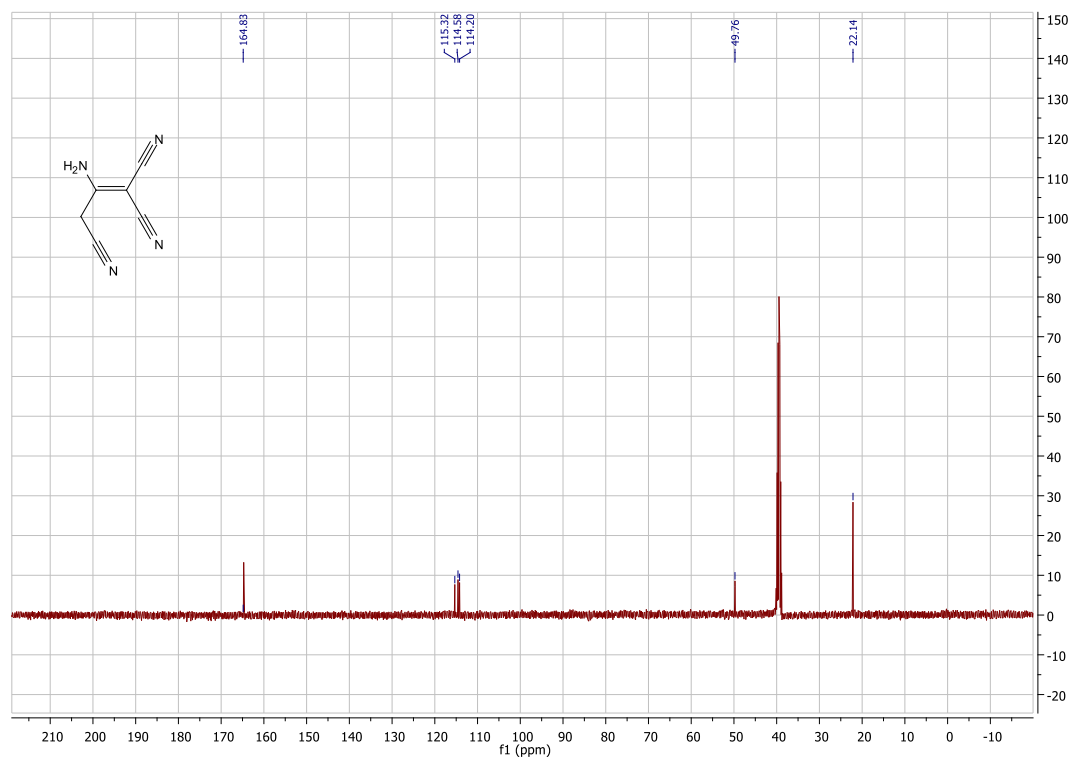


Figure A.2. ¹³C-NMR spectrum of 2-Amino-1,1,3-propenetricarbonitrile.

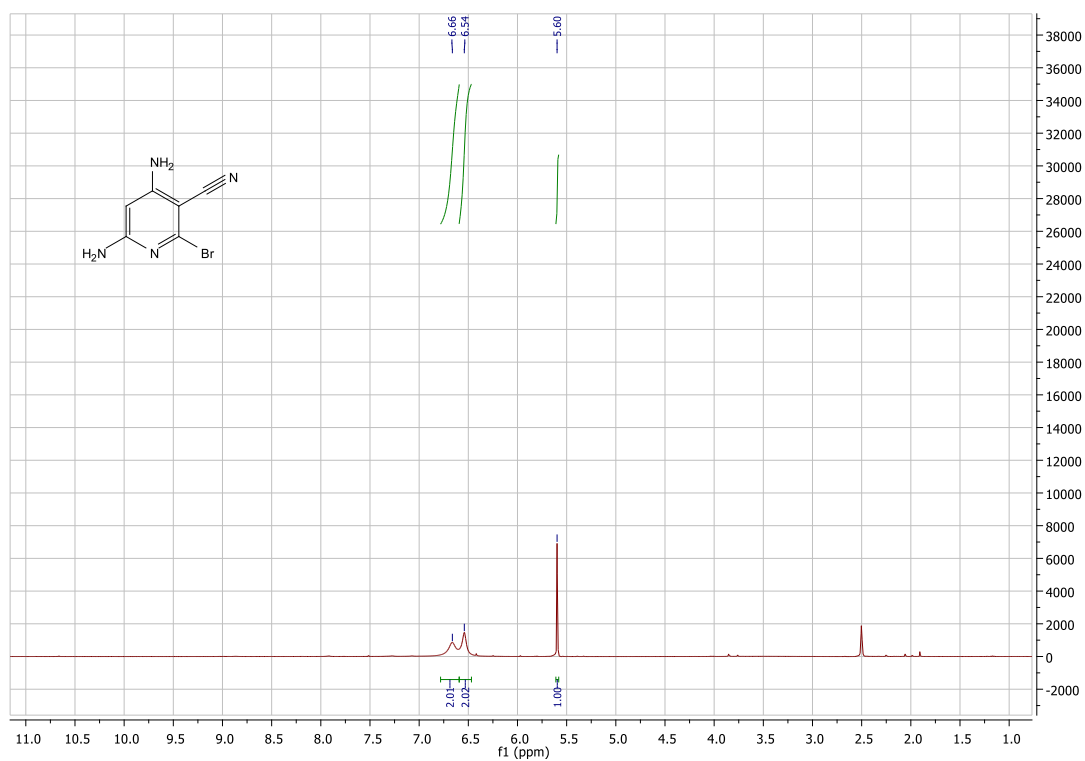


Figure A.3. ¹H-NMR spectrum of 4,6-Diamino-2-bromonicotinonitrile.

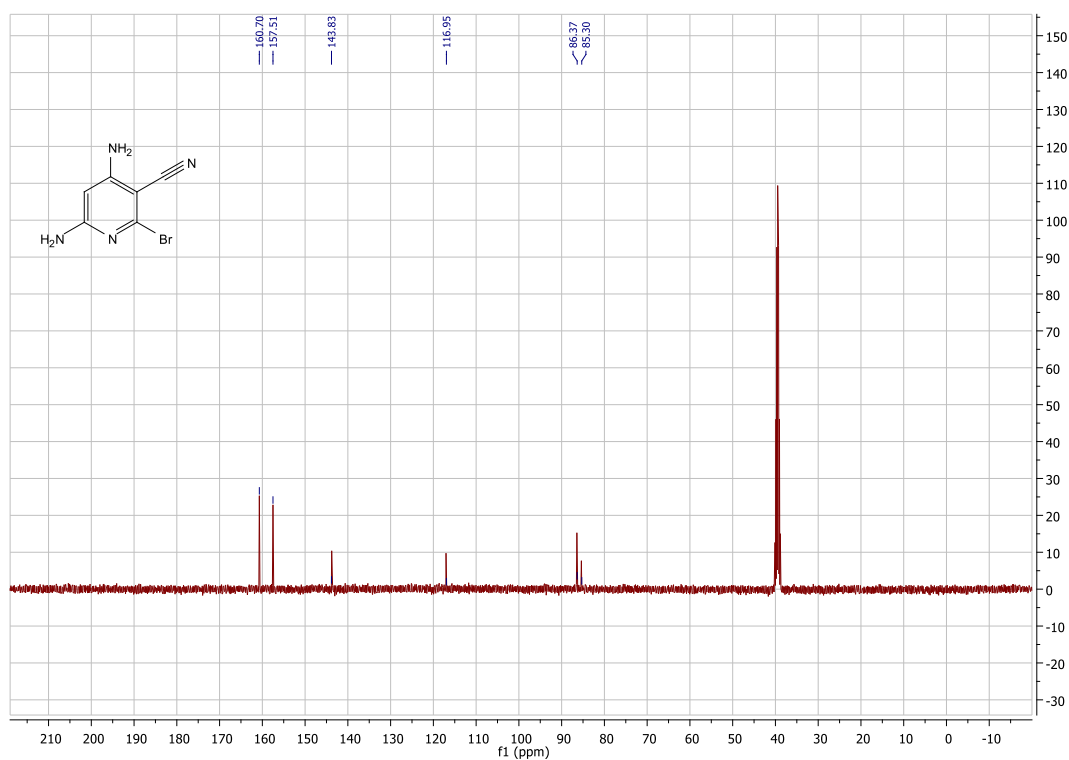


Figure A.4. ¹³C-NMR spectrum of 4,6-Diamino-2-bromonicotinonitrile.

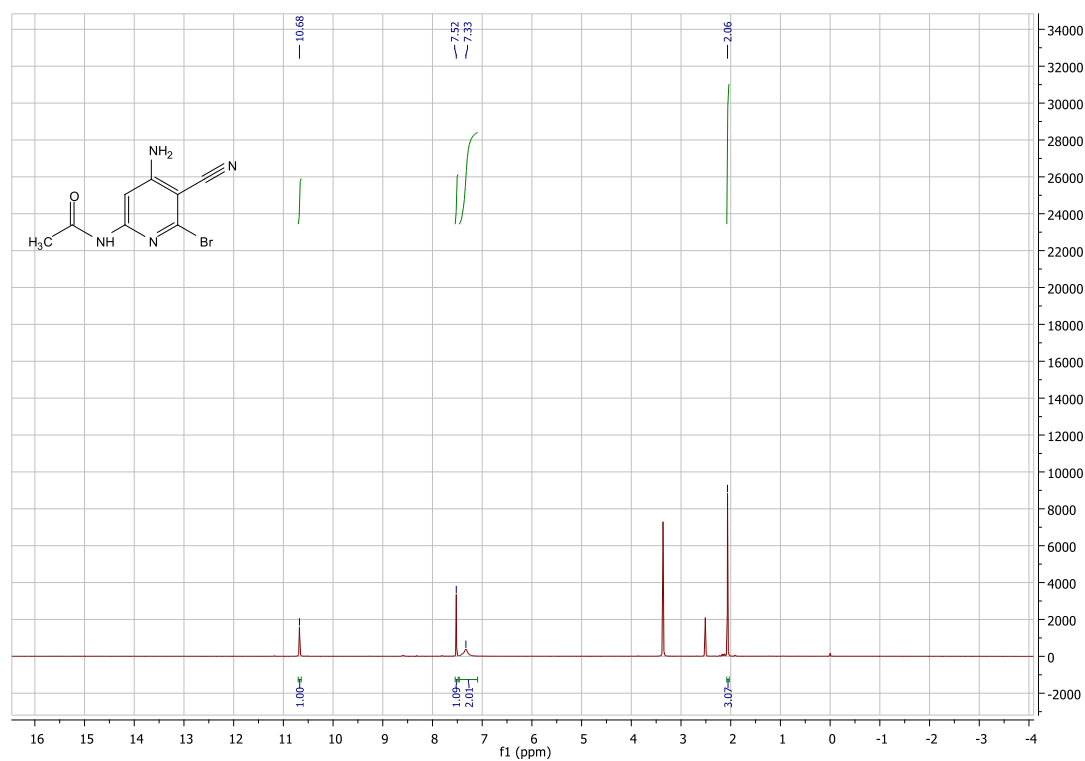


Figure A.5. ^1H -NMR spectrum of *N*-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide.

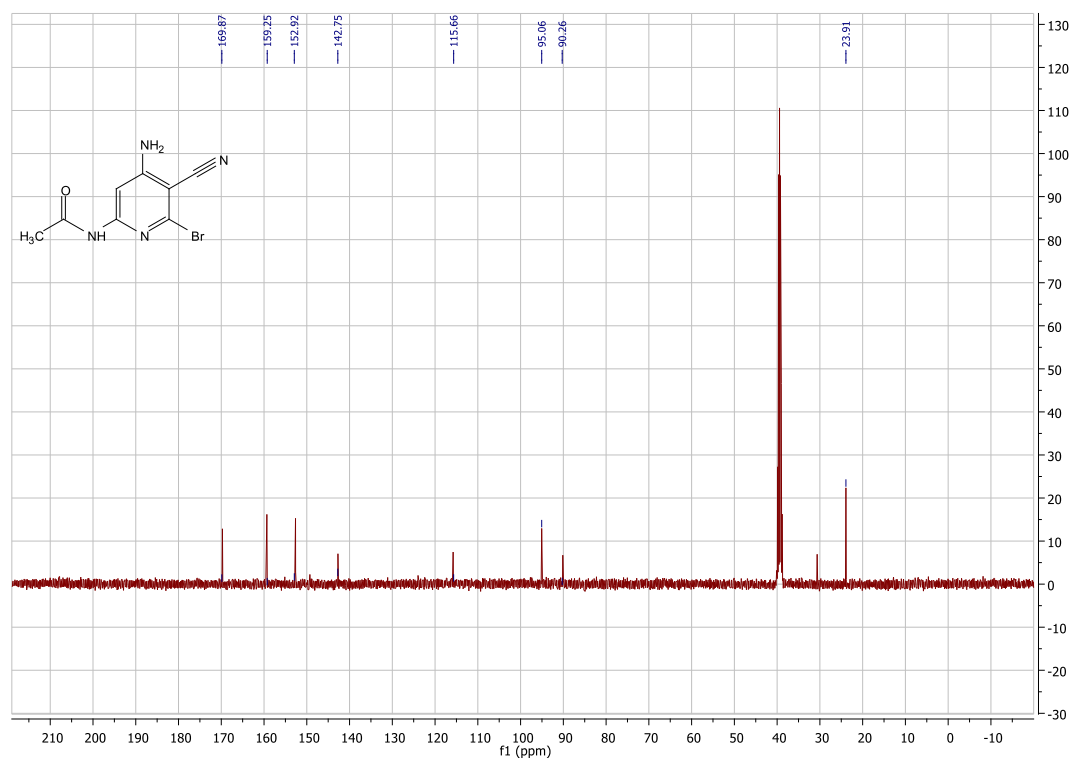


Figure A.6. ^{13}C -NMR spectrum of *N*-(4-Amino-6-bromo-5-cyanopyridin-2-yl)acetamide.

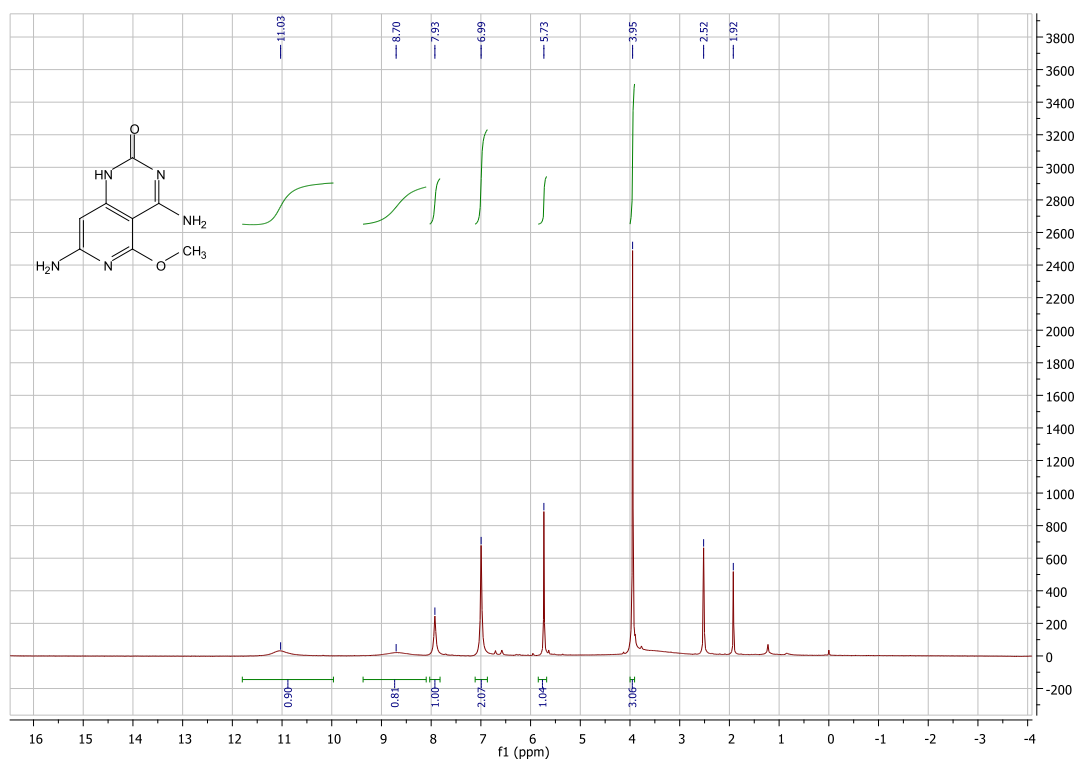


Figure A.7. ^1H -NMR spectrum of 4,7-Diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one.

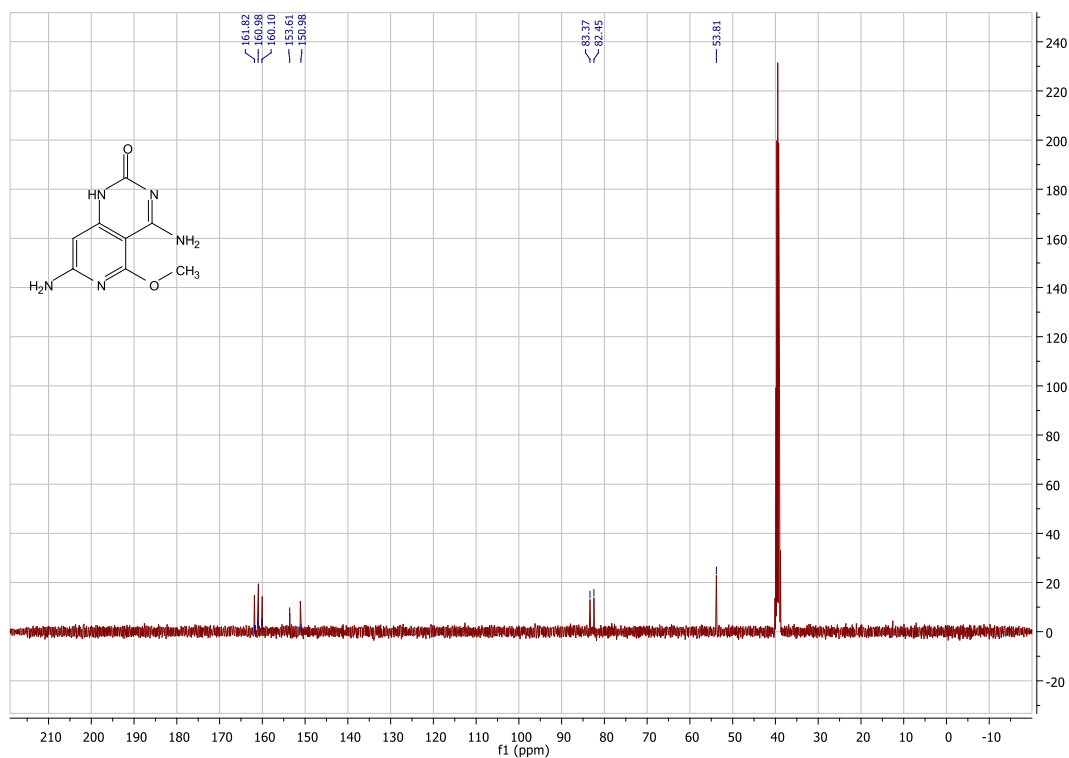


Figure A.8. ^{13}C -NMR spectrum of 4,7-Diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one.

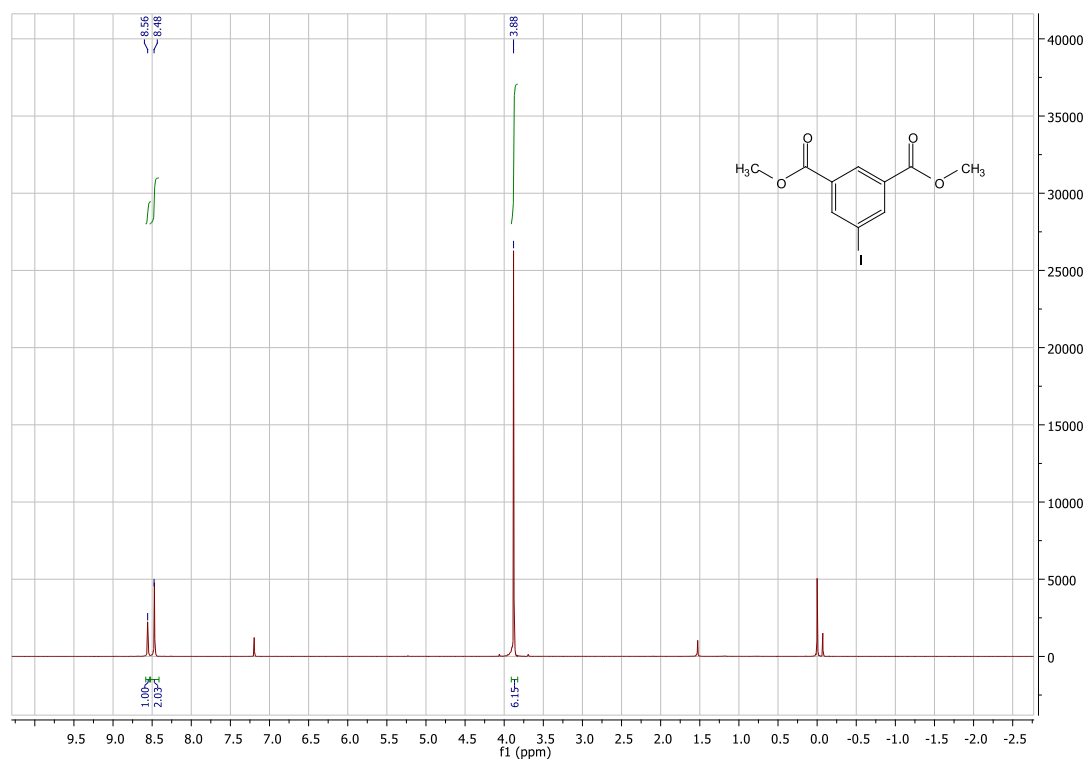


Figure A.9. ^1H -NMR spectrum of Dimethyl 5-iodoisophthalate.

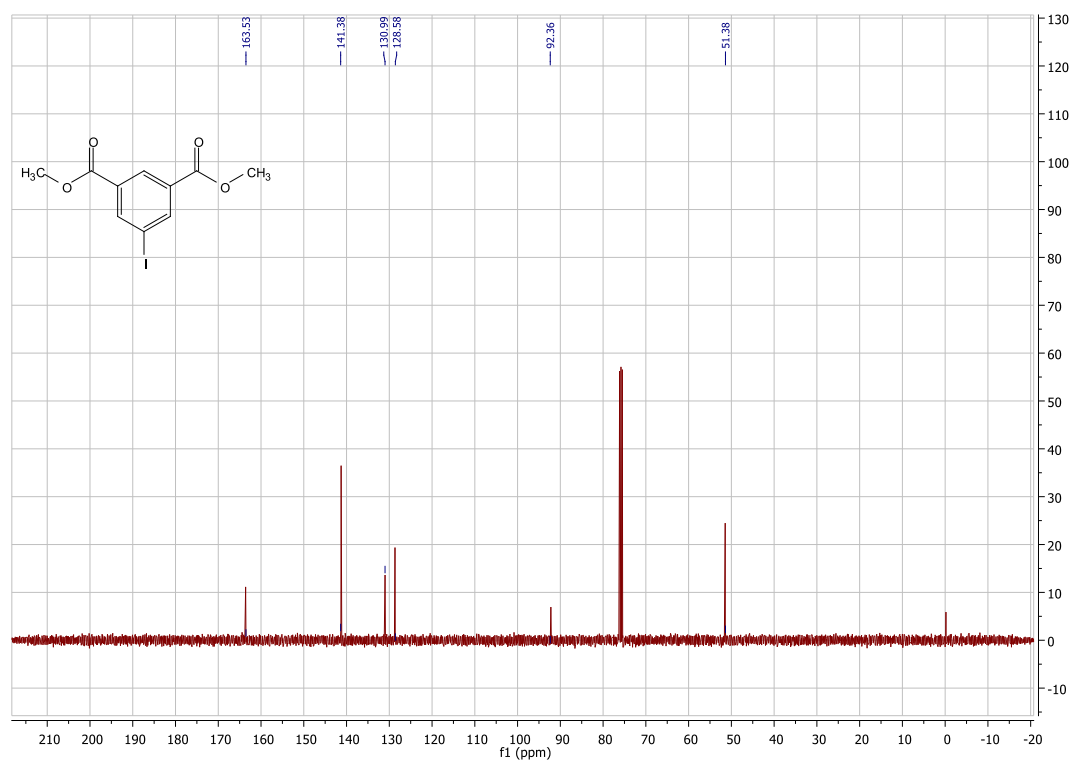


Figure A.10. ^{13}C -NMR spectrum of Dimethyl 5-iodoisophthalate.

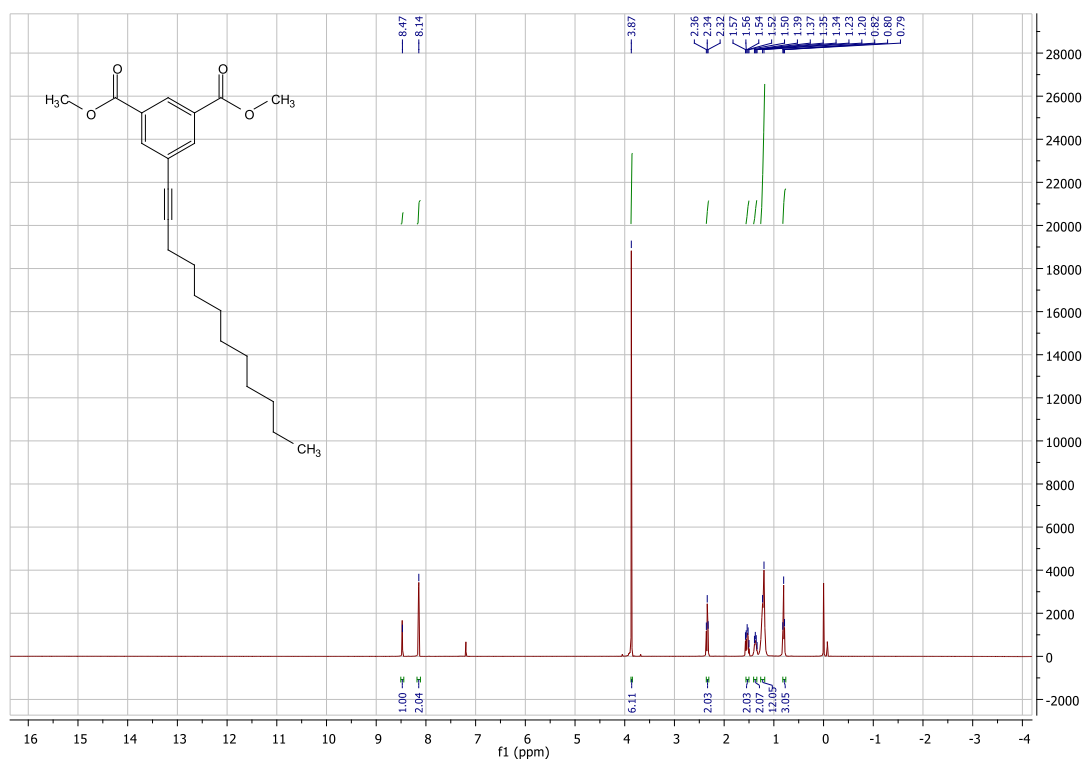


Figure A.11. ^1H -NMR spectrum of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate.

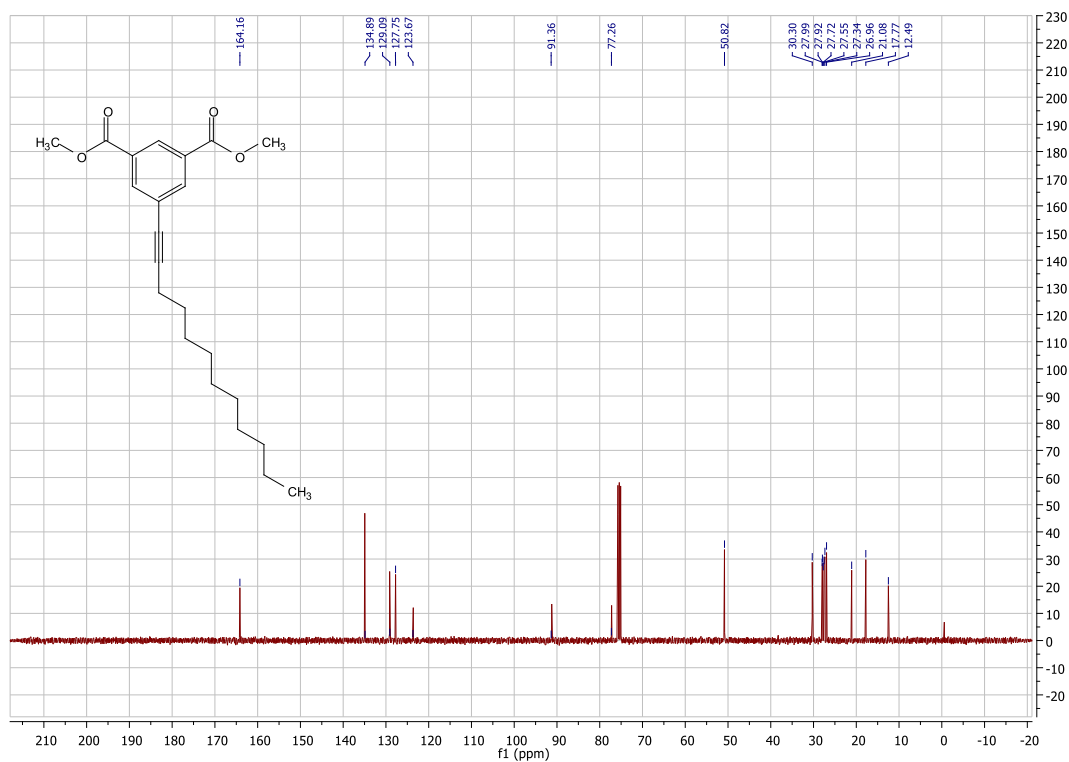


Figure A.12. ^{13}C -NMR spectrum of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate.

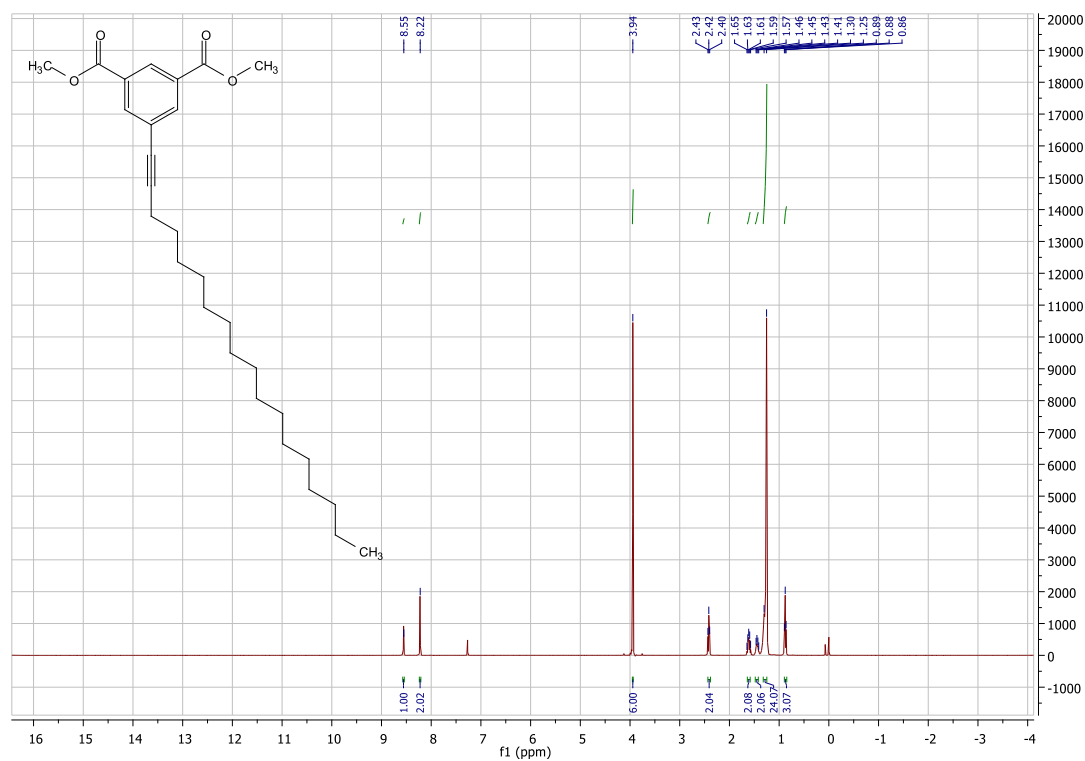


Figure A.13. ¹H-NMR spectrum of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate.

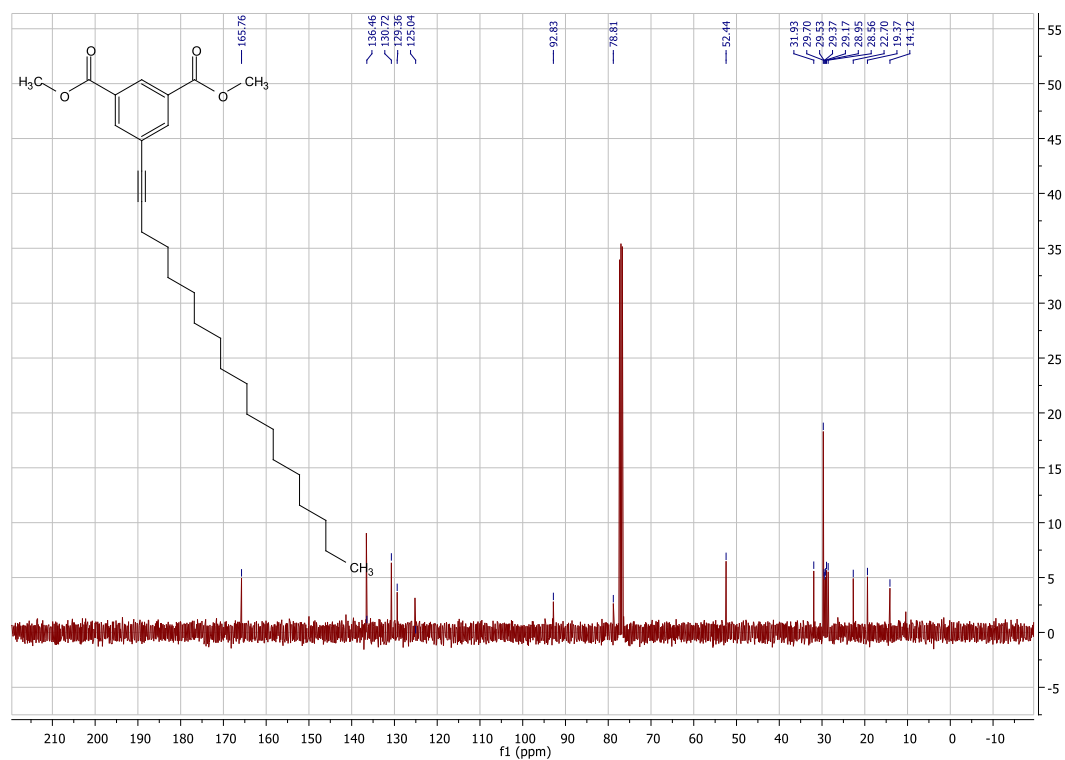


Figure A.14. ¹³C-NMR spectrum of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate.

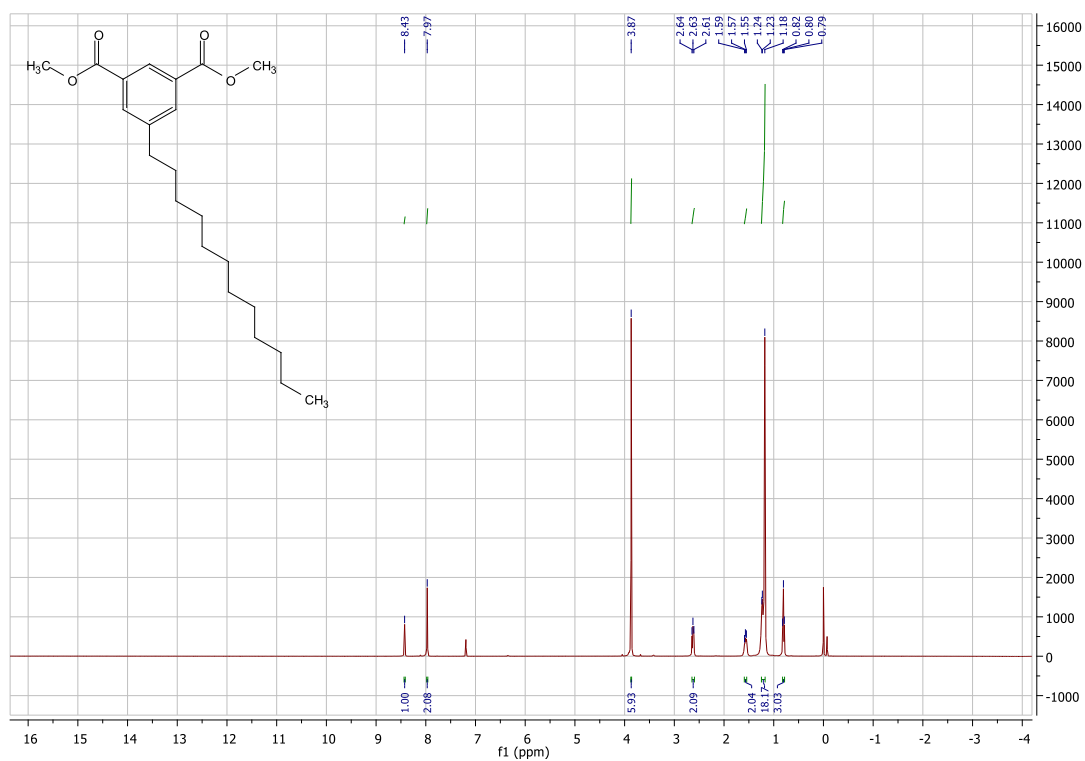


Figure A.15. ¹H-NMR spectrum of Dimethyl 5-dodecylisophthalate.

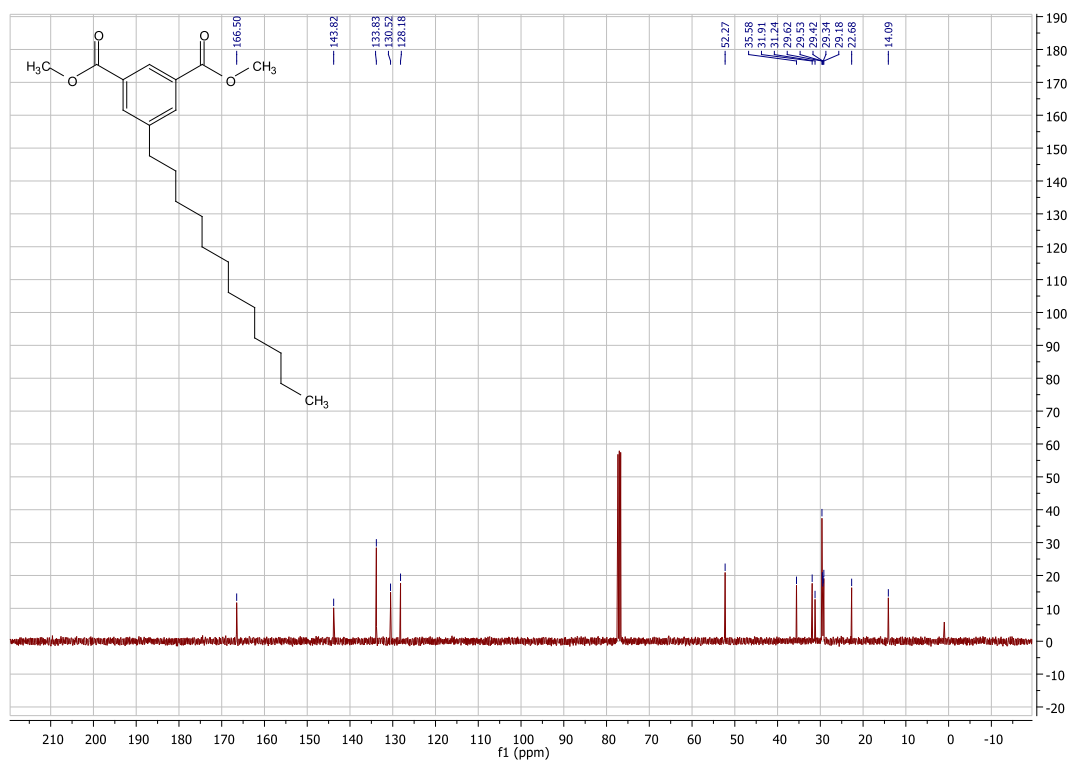


Figure A.16. ¹³C-NMR spectrum of Dimethyl 5-dodecylisophthalate.

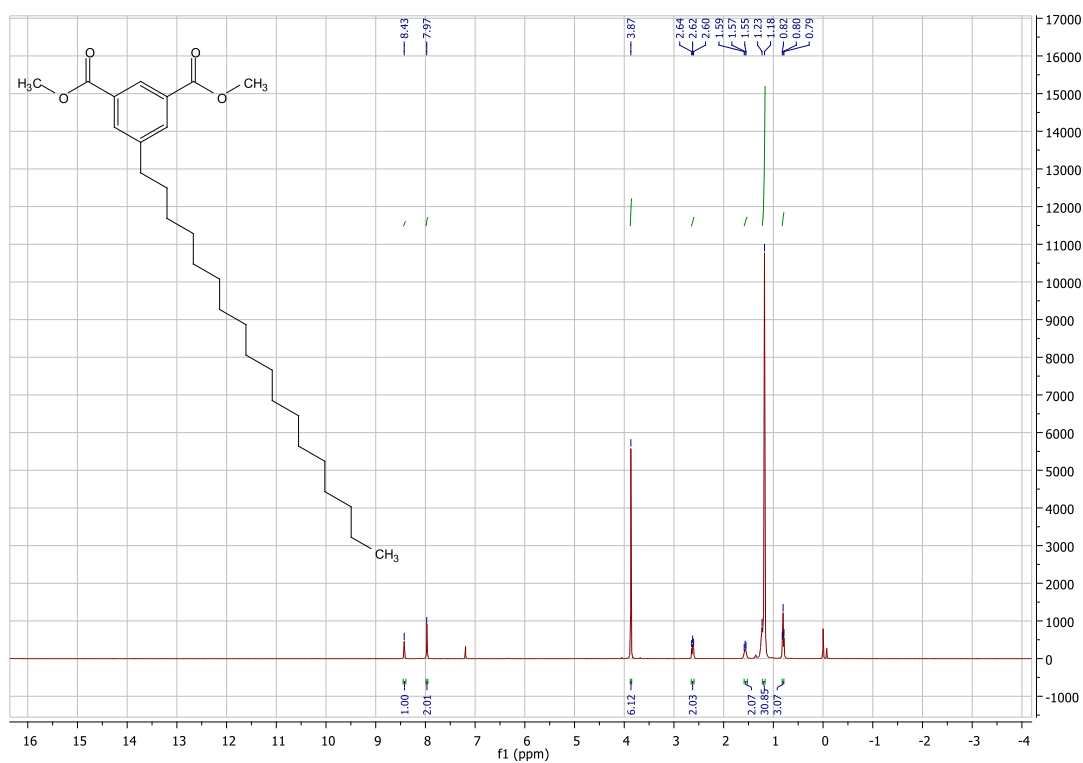


Figure A.17. ¹H-NMR spectrum of Dimethyl 5-octadecylisophthalate.

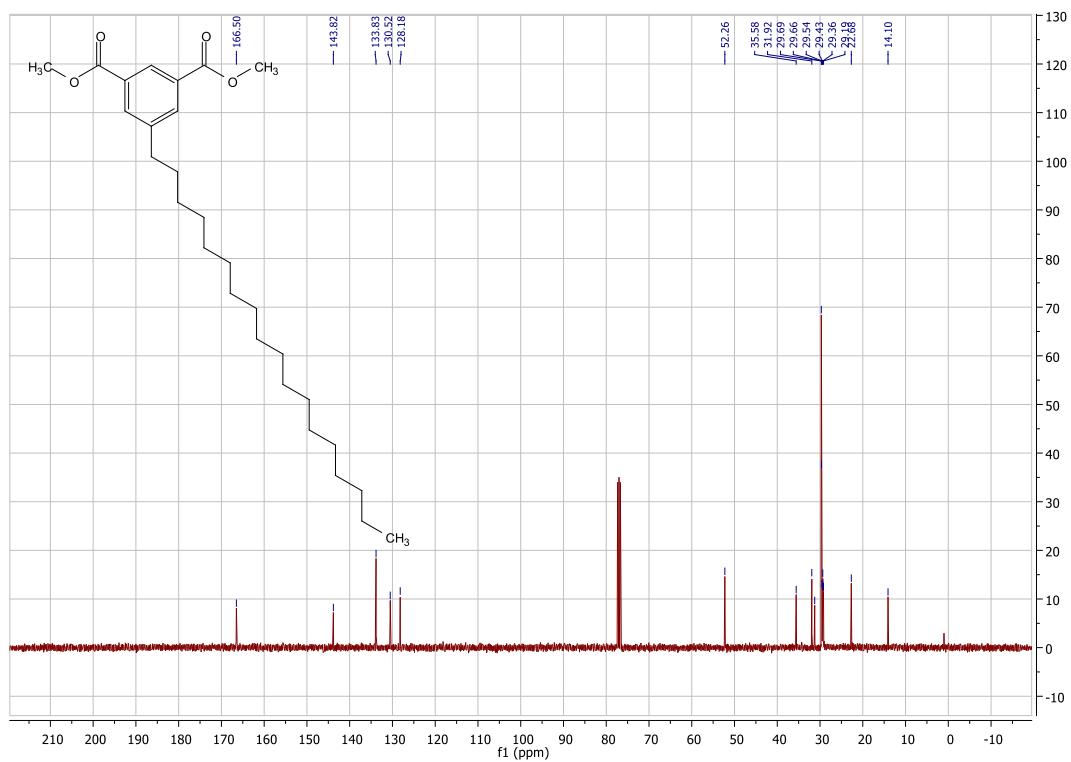


Figure A.18. ¹³C-NMR spectrum of Dimethyl 5-octadecylisophthalate.

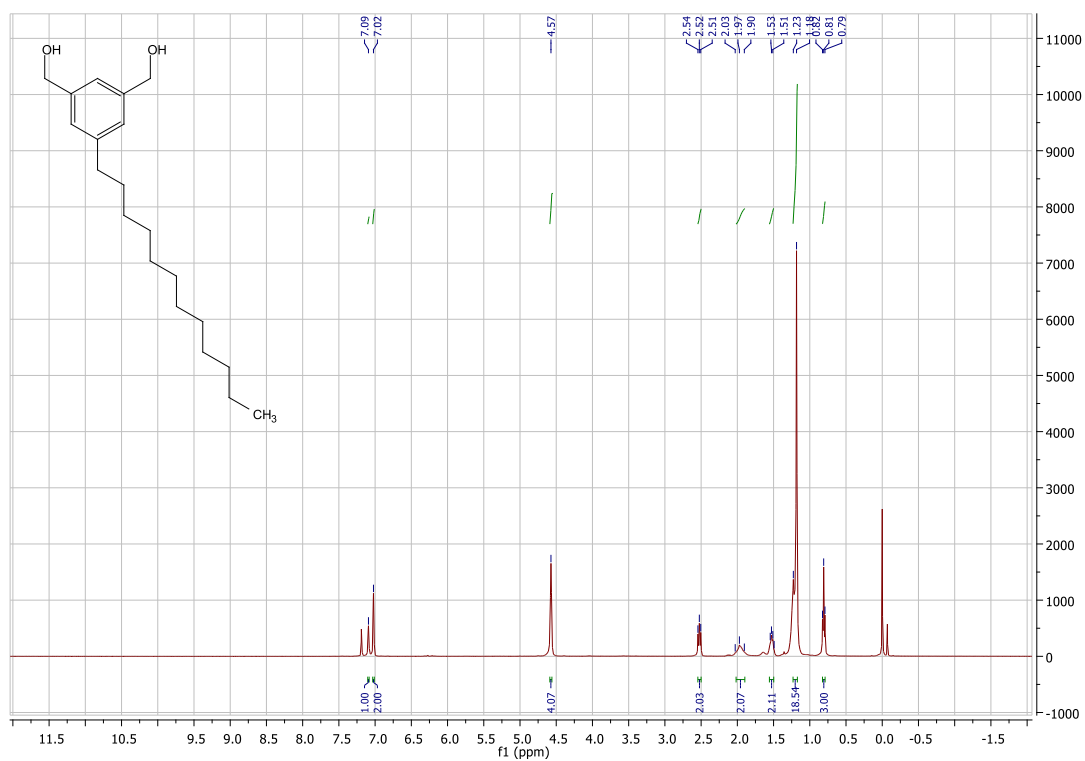


Figure A.19. ^1H -NMR spectrum of 5-dodecyl-1,3-phenylene)dimethanol.

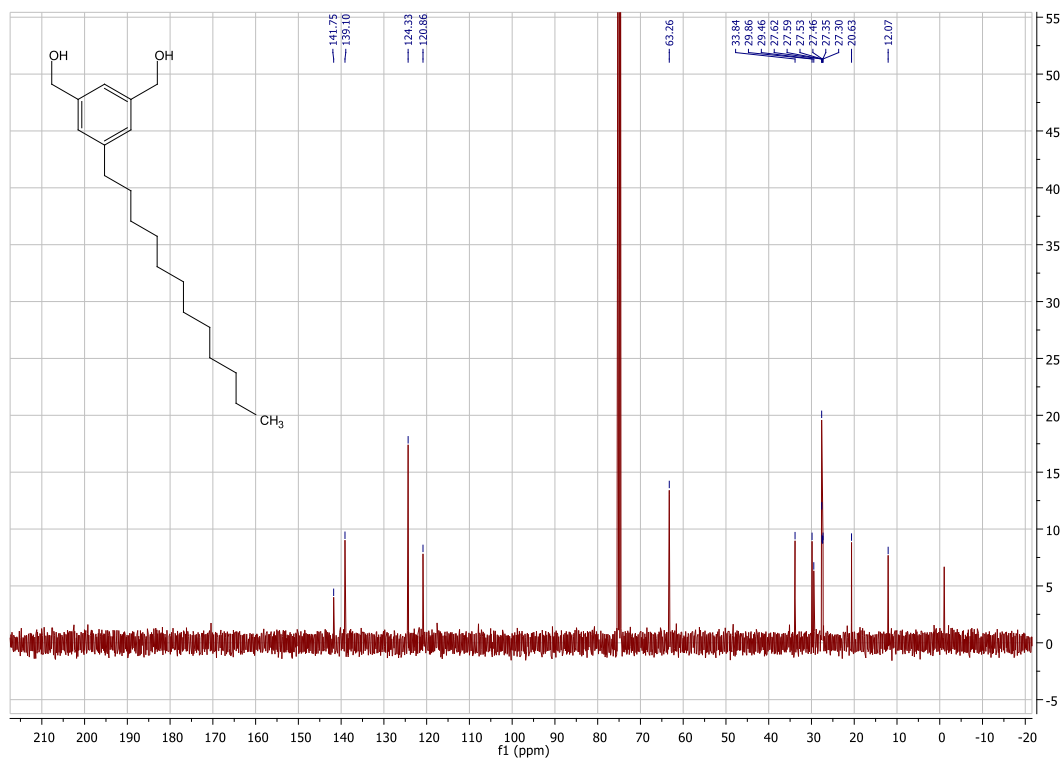


Figure A.20. ^{13}C -NMR spectrum of 5-dodecyl-1,3-phenylene)dimethanol.

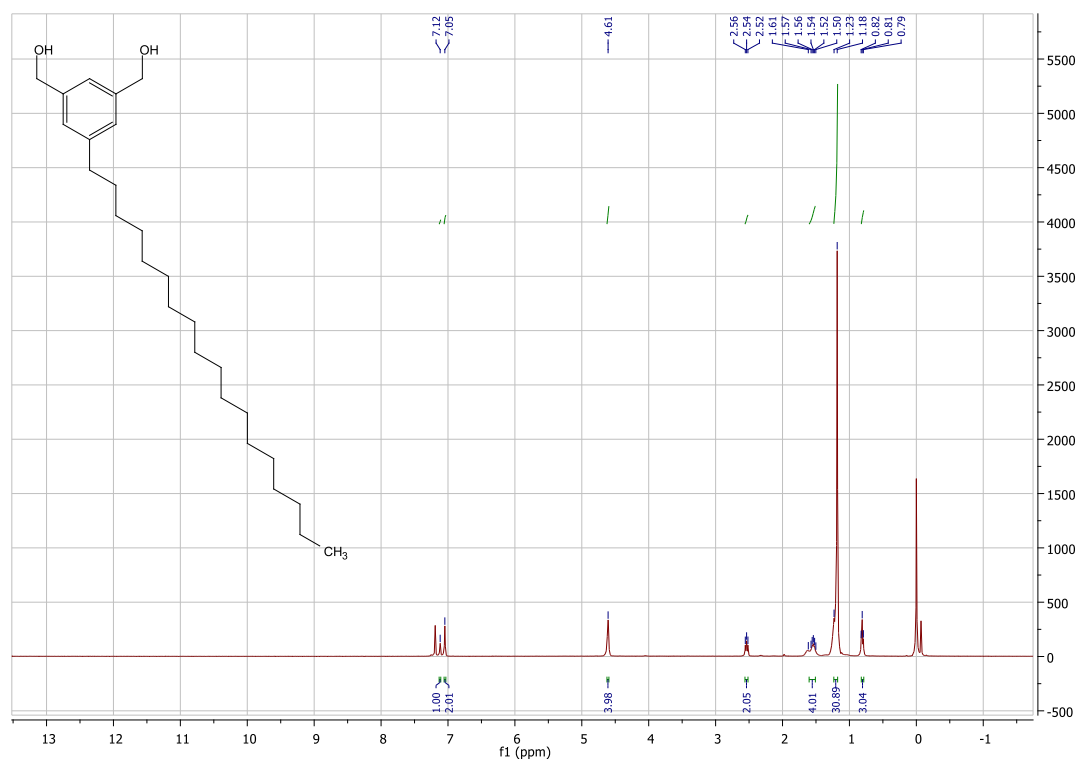


Figure A.21. ^1H -NMR spectrum of (5-octadecyl-1,3-phenylene)dimethanol.

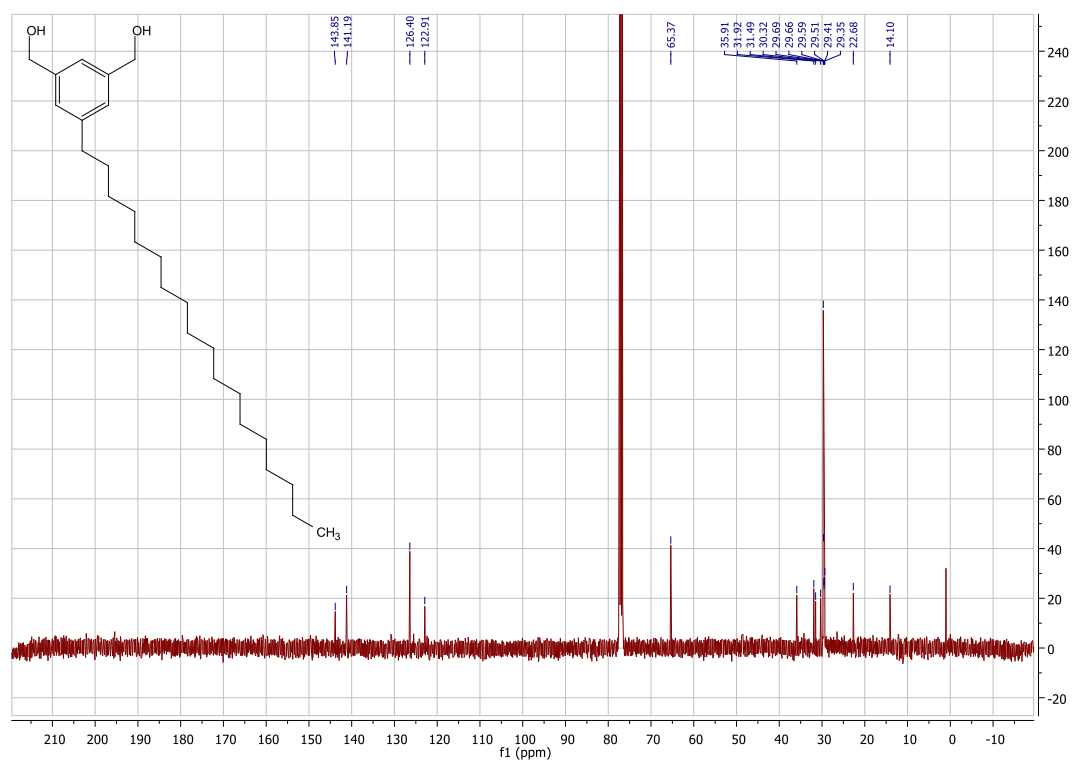


Figure A.22. ^{13}C -NMR spectrum of (5-octadecyl-1,3-phenylene)dimethanol.

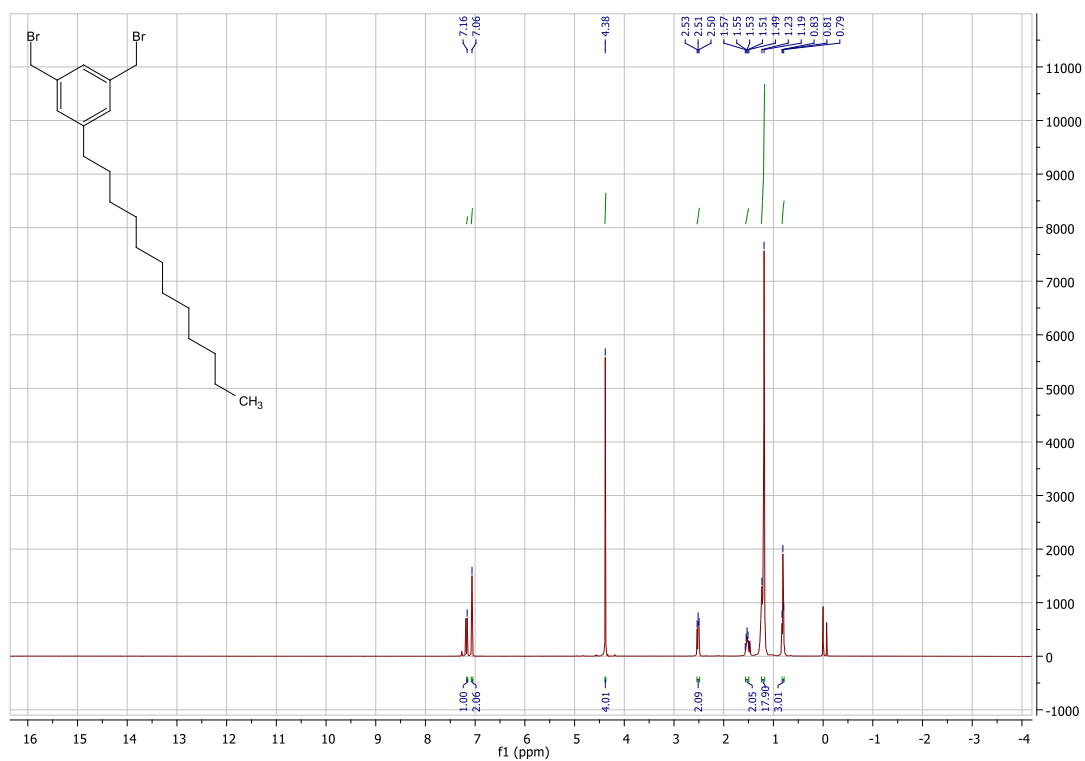


Figure A.23. ¹H-NMR spectrum of 1,3-bis(bromomethyl)-5-dodecylbenzene.

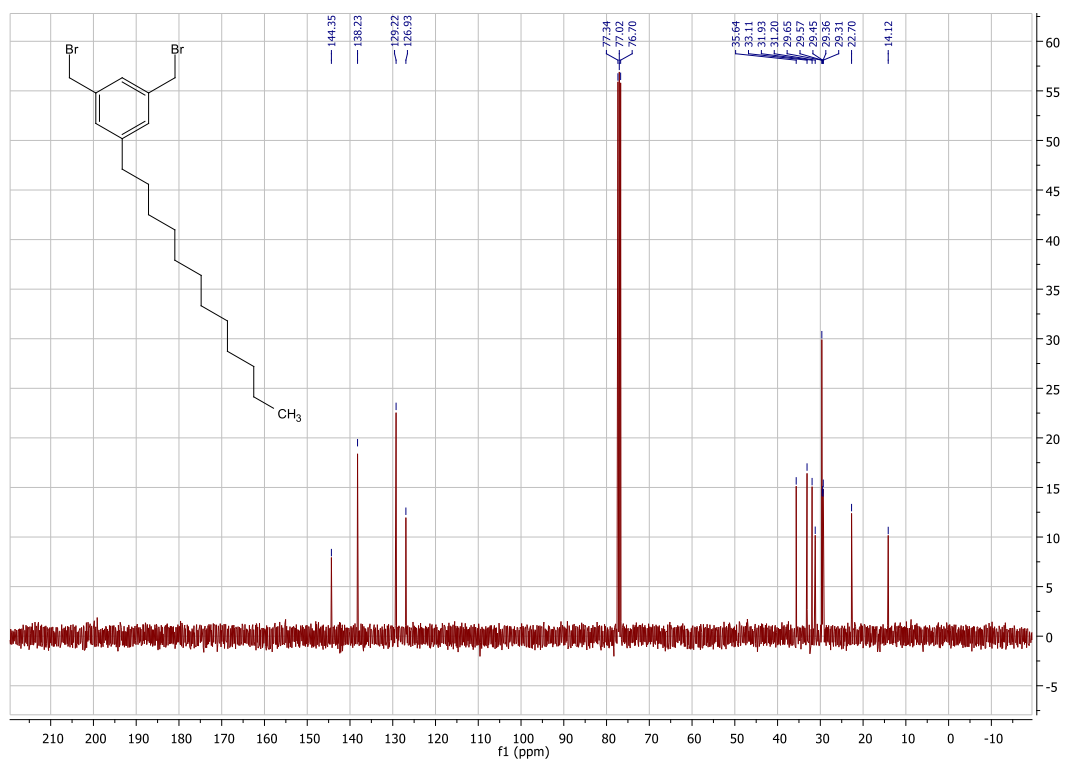


Figure A.24. ¹³C-NMR spectrum of 1,3-bis(bromomethyl)-5-dodecylbenzene.

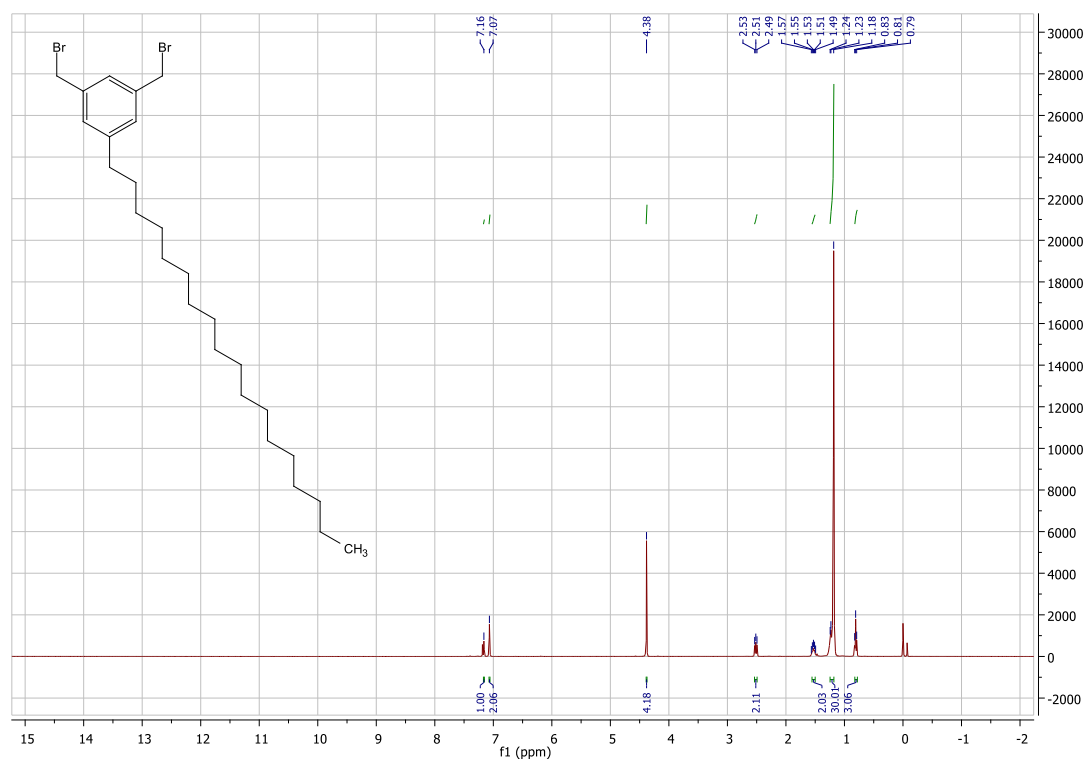


Figure A.25. ^1H -NMR spectrum of 1,3-bis(bromomethyl)-5-octadecylbenzene.

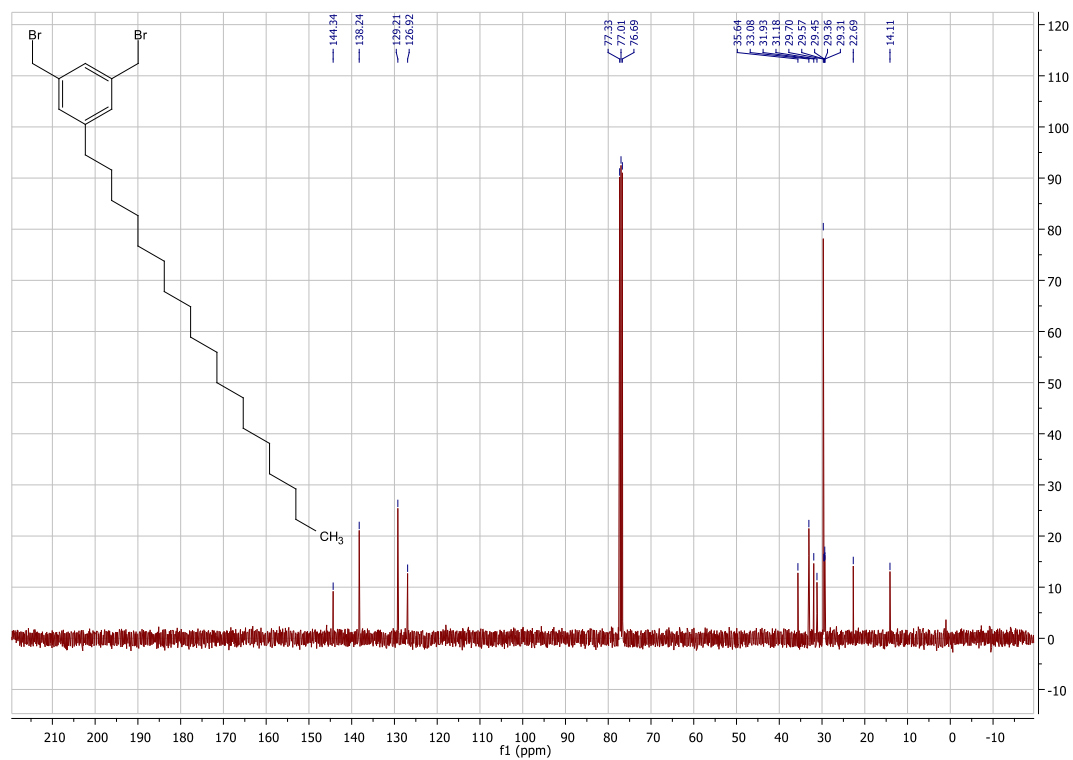


Figure A.26. ^{13}C -NMR spectrum of 1,3-bis(bromomethyl)-5-octadecylbenzene.

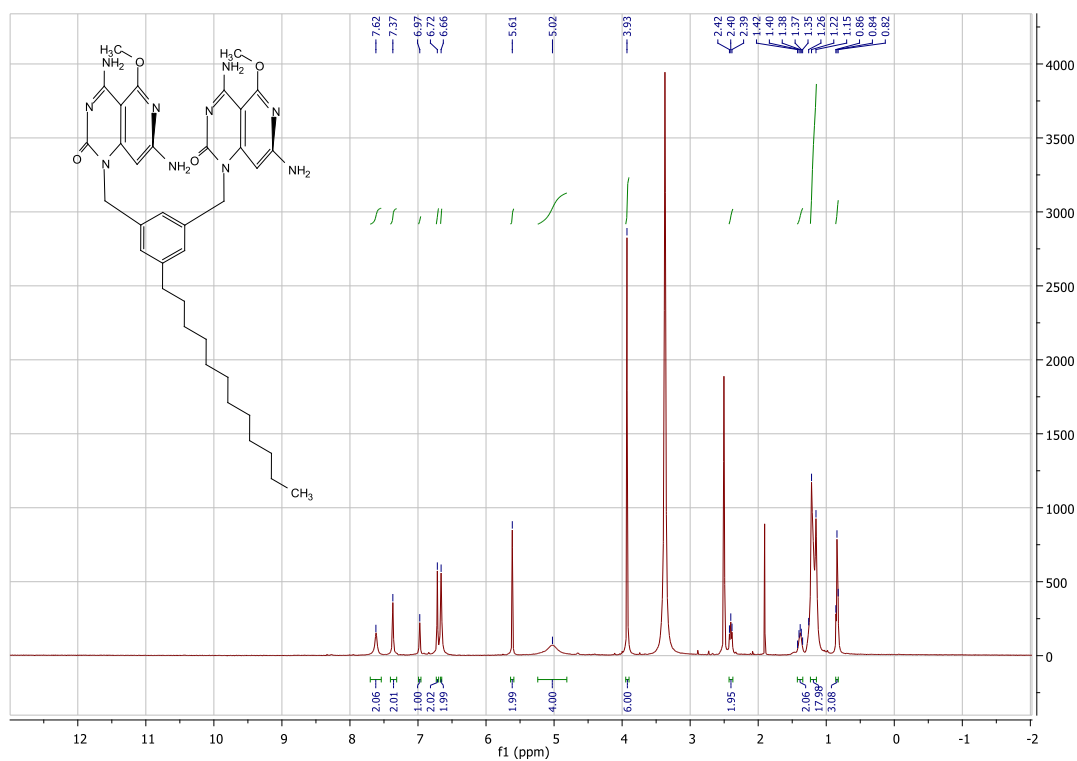


Figure A.27. ^1H -NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one).

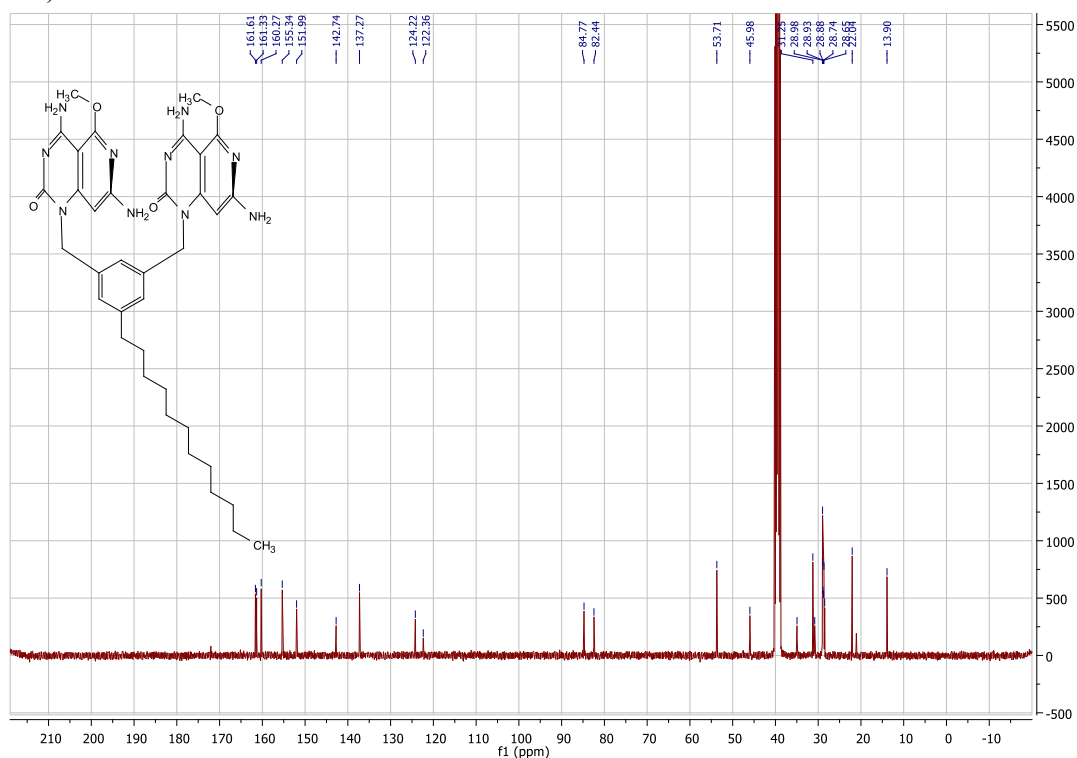


Figure A.28. ^{13}C -NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one).

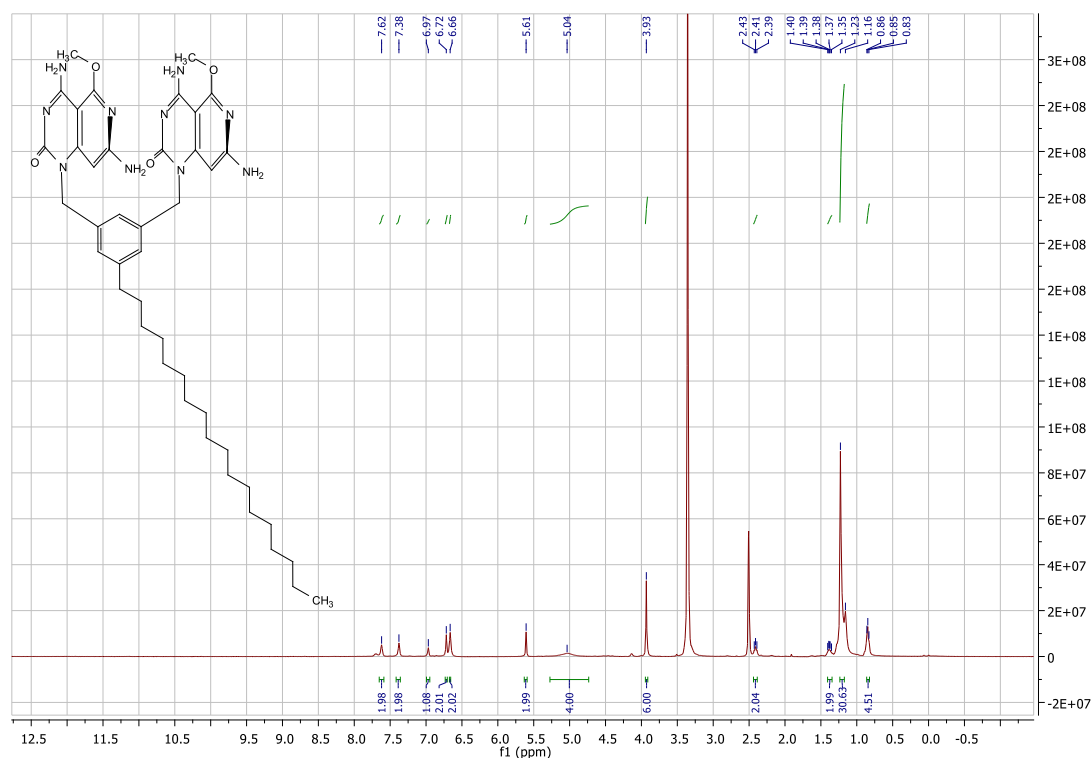


Figure A.29. ^1H -NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one).

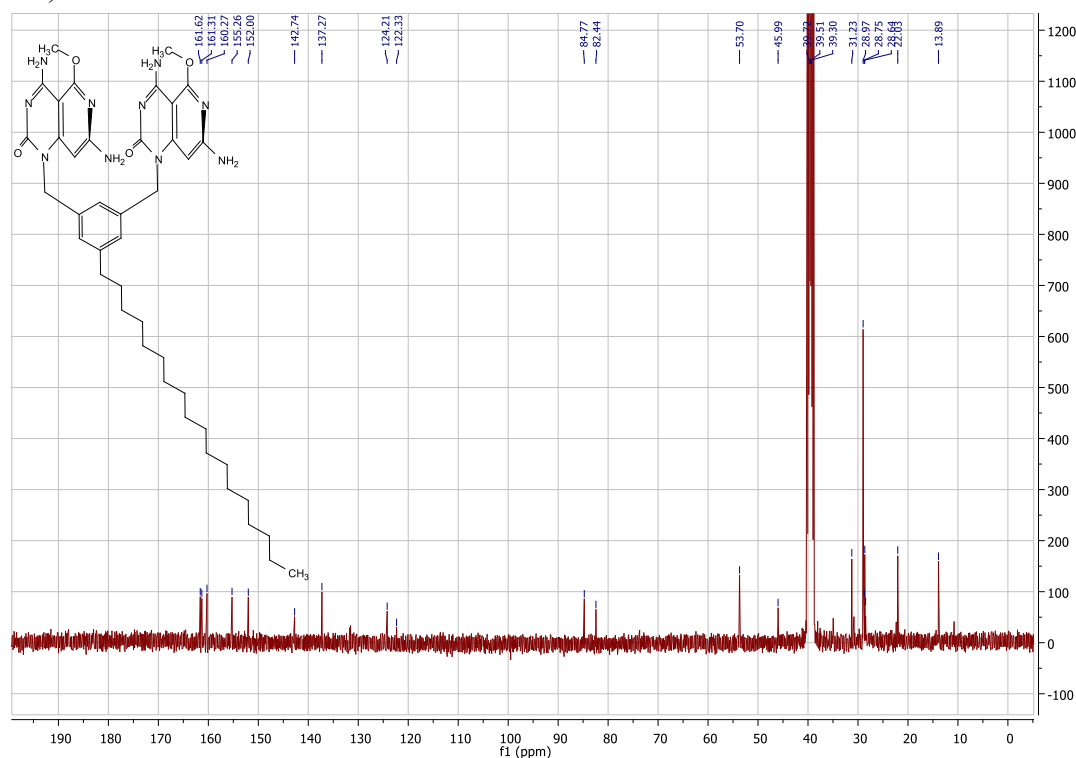


Figure A.30. ^{13}C -NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one).

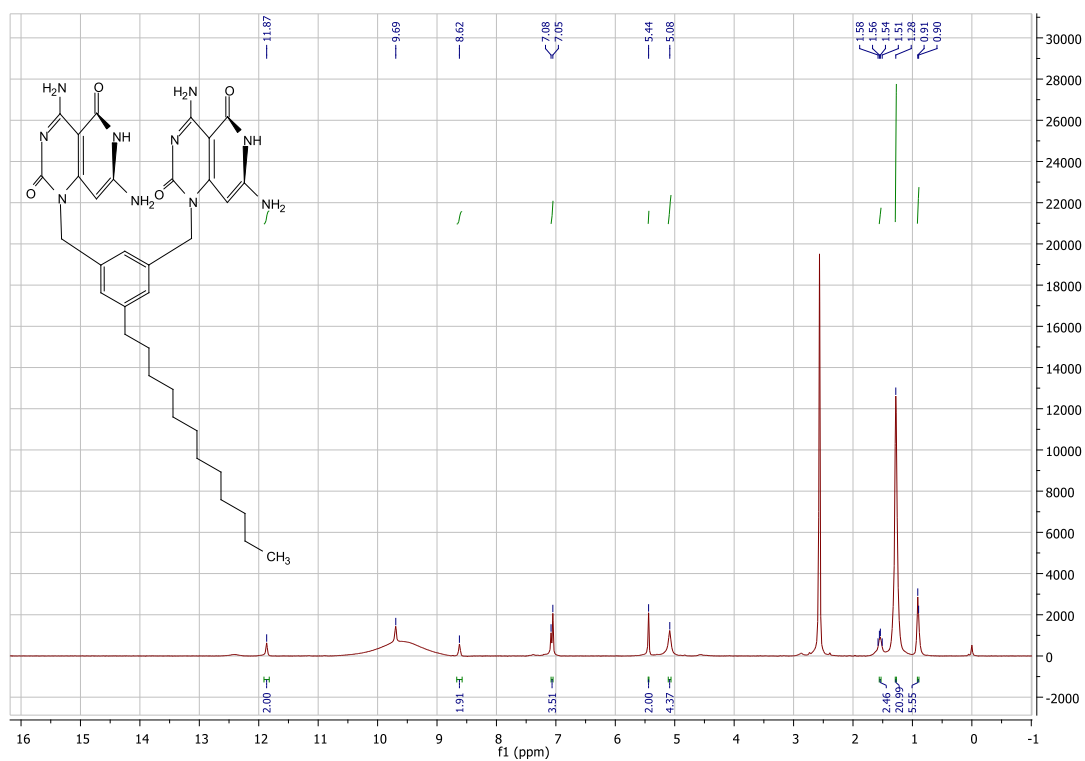


Figure A.31. ^1H -NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene)) bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione)

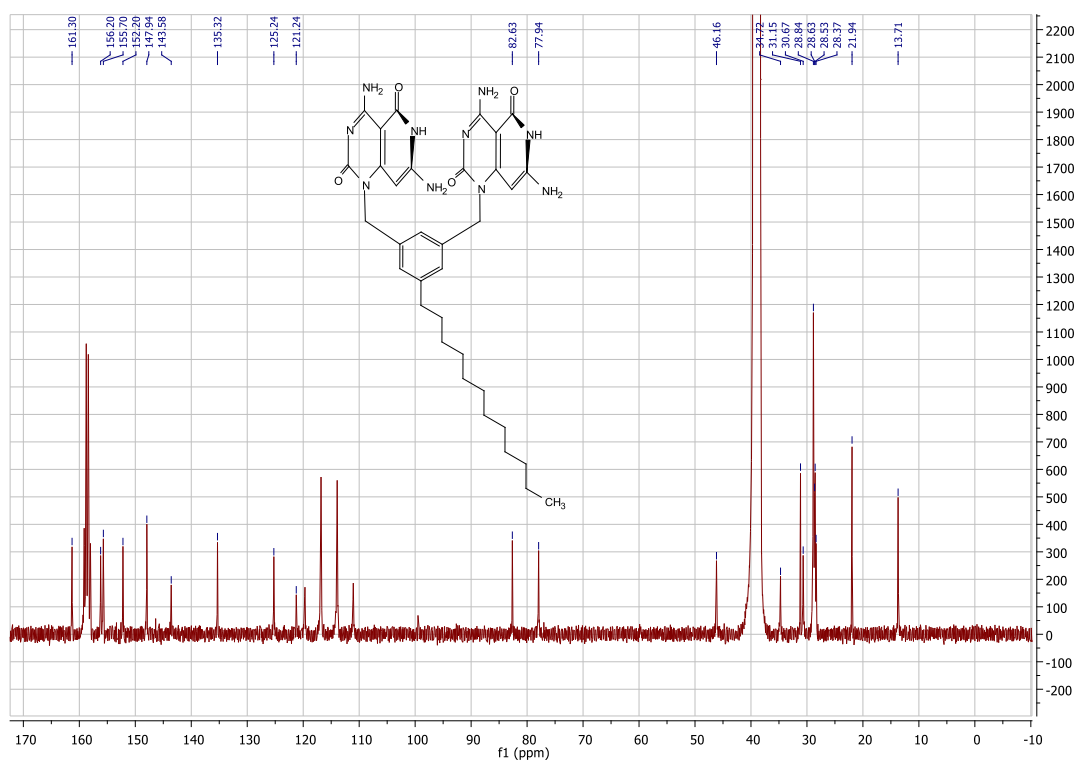


Figure A.32. ^{13}C -NMR spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene)) bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione).

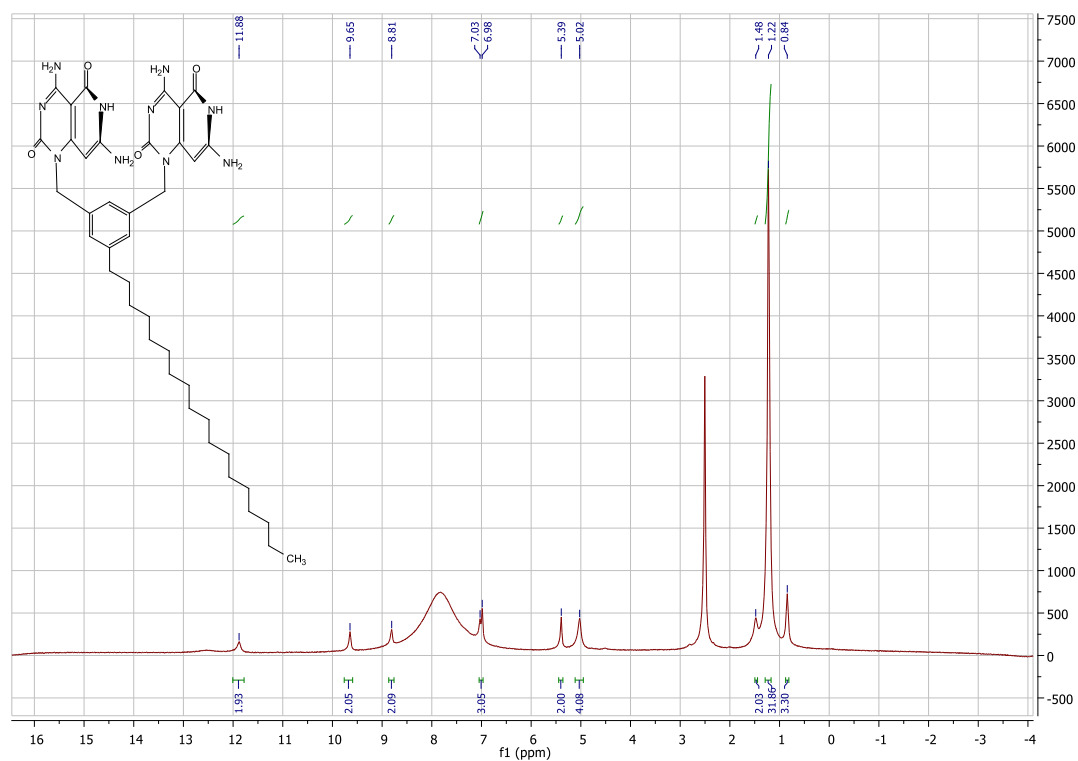


Figure A.33. ^1H -NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione).

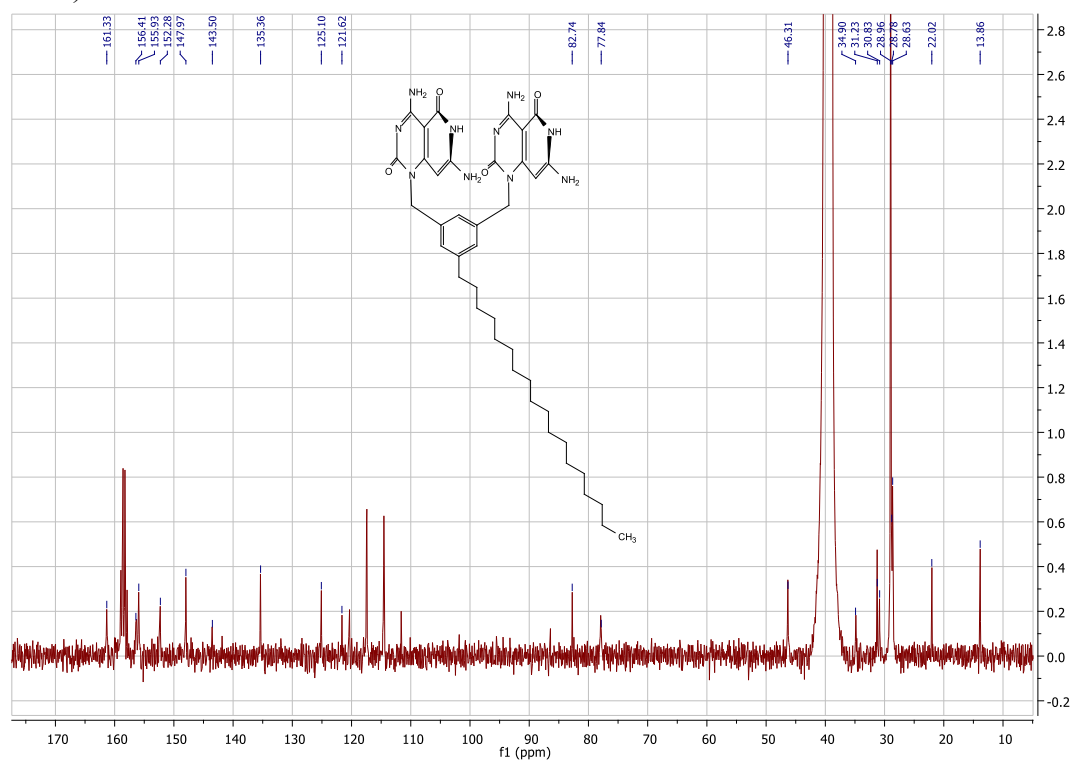
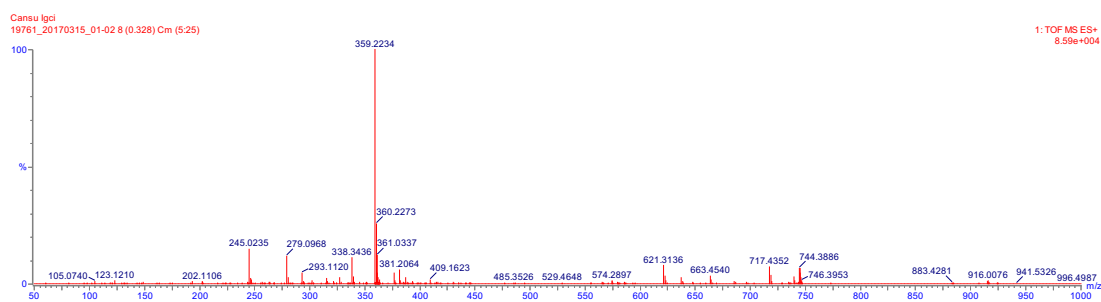


Figure A.34. ^{13}C -NMR spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione).

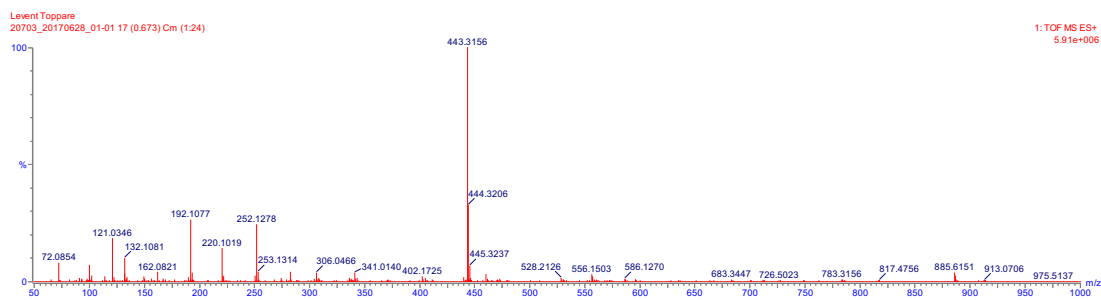
APPENDIX B

HRMS DATA



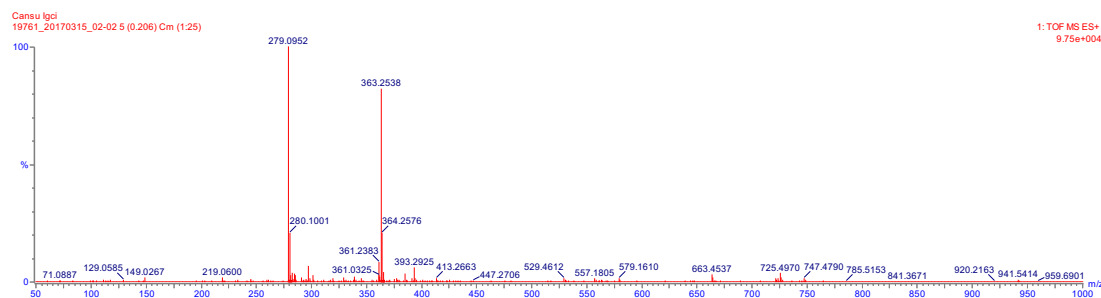
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
359.2234	359.2222	1.2	3.3	7.5	465.1	0.0	C ₂₂ H ₃₁ O ₄

Figure B.1. HRMS spectrum of Dimethyl 5-(dodec-1-yn-1-yl)isophthalate.



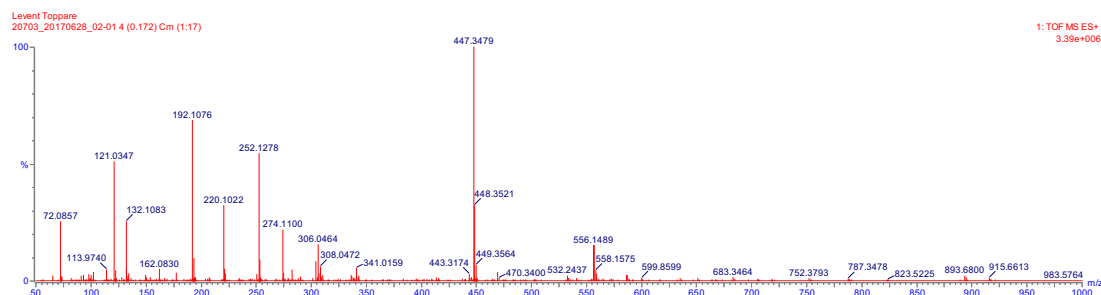
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
443.3156	443.3161	-0.5	-1.1	7.5	879.5	0.0	C ₂₈ H ₄₃ O ₄

Figure B.2. HRMS spectrum of Dimethyl 5-(octadec-1-yn-1-yl)isophthalate.



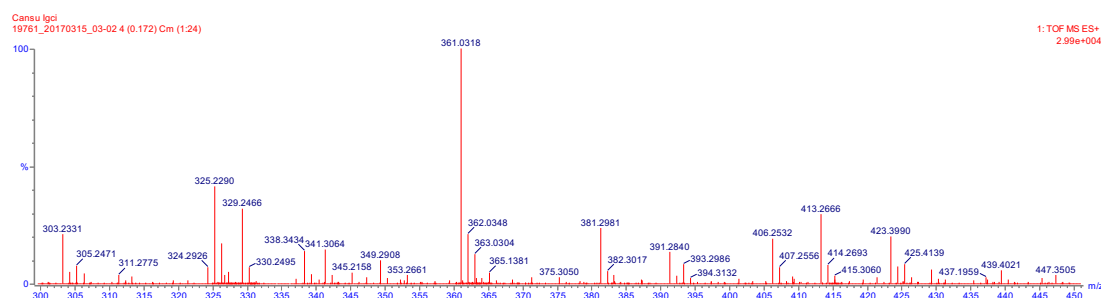
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
363.2538	363.2535	0.3	0.8	5.5	523.0	0.0	C ₂₂ H ₃₅ O ₄

Figure B.3. HRMS spectrum of Dimethyl 5-dodecylisophthalate.



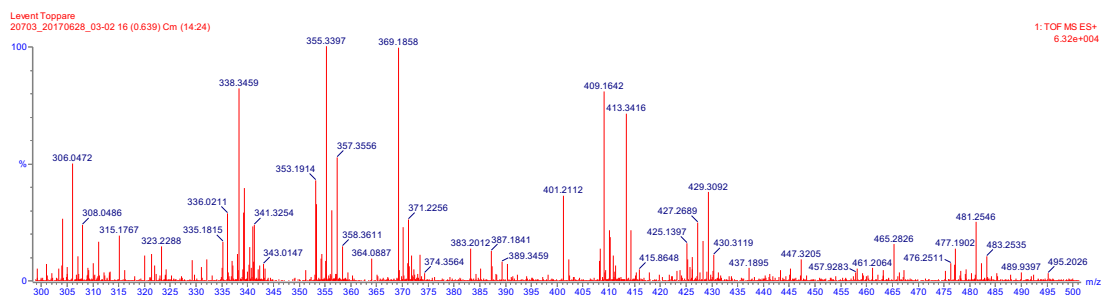
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
447.3479	447.3474	0.5	1.1	5.5	756.7	0.0	C ₂₈ H ₄₇ O ₄

Figure B.4. HRMS spectrum of Dimethyl 5-octadecylisophthalate.



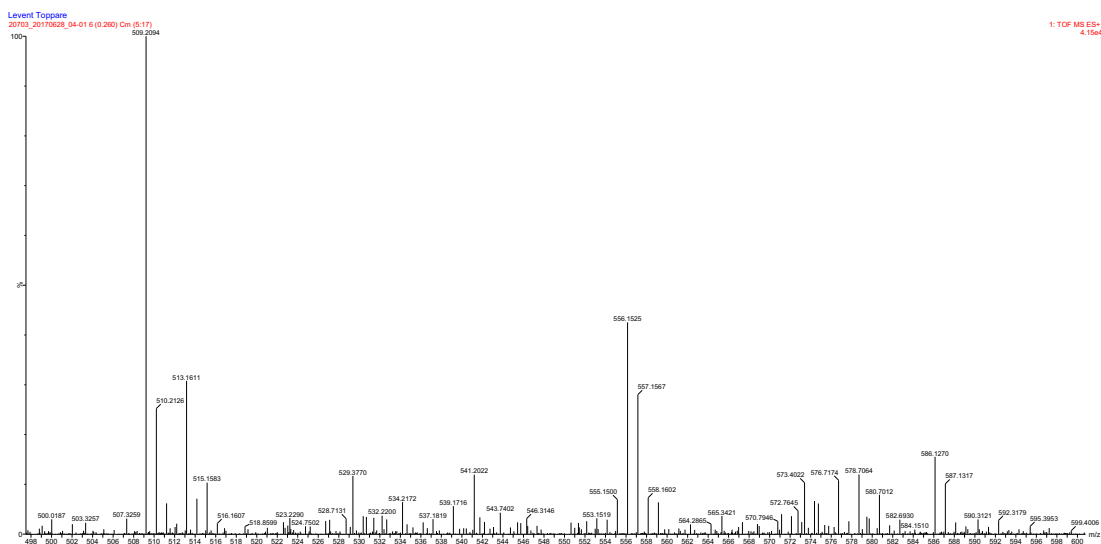
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
329.2466	329.2457	0.9	2.7	3.5	384.9	0.0	C ₂₀ H ₃₄ O ₂ Na

Figure B.5. HRMS spectrum of (5-dodecyl-1,3-phenylene)dimethanol.



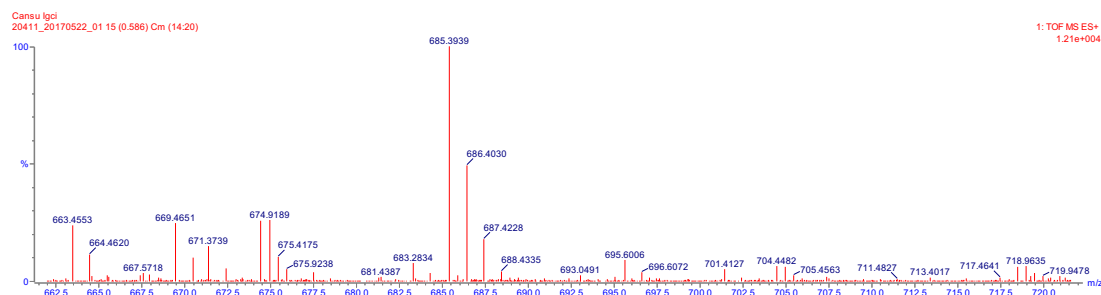
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
413.3416	413.3396	2.0	4.8	3.5	352.3	0.0	C ₂₈ H ₄₆ O ₂ Na

Figure B.6. HRMS spectrum of (5-octadecyl-1,3-phenylene)dimethanol.



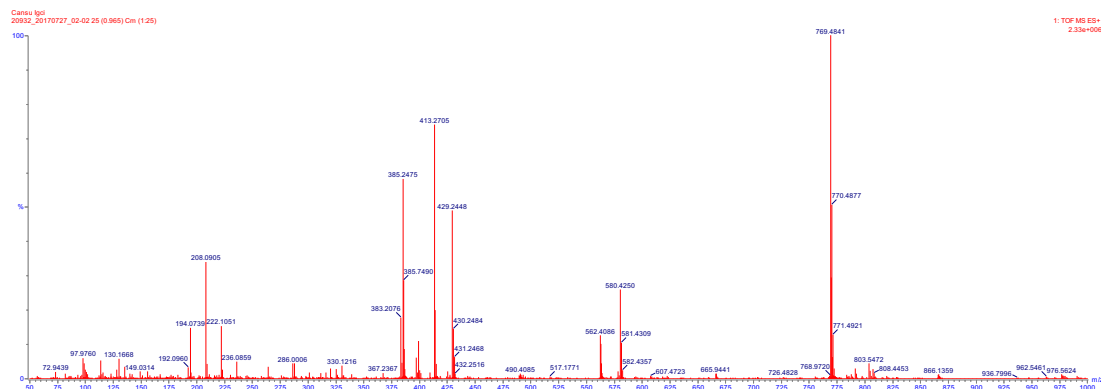
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
539.1716	539.1687	2.9	5.4	3.5	208.6	0.0	C ₂₆ H ₄₄ Na ⁷⁹ Br ⁸¹ Br

Figure B.7. HRMS spectrum of 1,3-bis(bromomethyl)-5-octadecylbenzene.



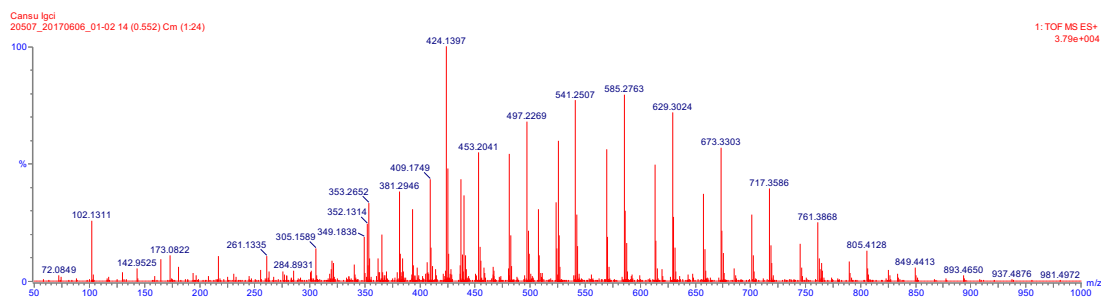
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
685.3939	685.3938	0.1	0.1	17.5	219.0	0.0	C ₃₆ H ₄₉ N ₁₀ O ₄

Figure B.8. HRMS spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one).



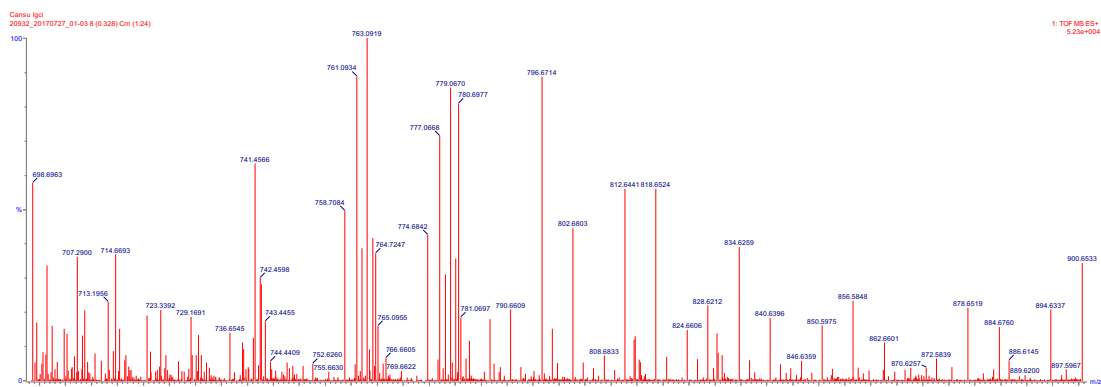
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT(Norm)	Formula
769.4841	769.4877	-3.6	-4.7	17.5	432.8	0.0	C ₄₂ H ₆₁ N ₁₀ O ₄

Figure B.9. HRMS spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diamino-5-methoxypyrido[4,3-*d*]pyrimidin-2(1*H*)-one).



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
657.3600	657.3625	-2.5	-3.8	17.5	334.6	0.0	C ₃₄ H ₄₅ N ₁₀ O ₄

Figure B.10. HRMS spectrum of 1,1'-((5-dodecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione).



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
741.4566	741.4564	0.2	0.3	17.5	264.6	0.0	C ₄₀ H ₅₇ N ₁₀ O ₄

Figure B.11. HRMS spectrum of 1,1'-((5-octadecyl-1,3-phenylene)bis(methylene))bis(4,7-diaminopyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione).

PART 2

CONVEX POLYCYCLIC STRUCTURES: SYNTHESIS OF TRIBENZOHETEROTRIQUINANES

CHAPTER 2.1

INTRODUCTION

2.1.1. Discovery of Fullerene

Many scientific studies that have been awarded the Nobel Prize have had a major impact on science outside of their fields and have the potential to provide significant contributions to human life in the long run. But among these studies, the discovery of new carbon allotrope fullerene (1996 Chemistry Nobel Prize) [1] and graphene (2010 Physics Nobel Prize) [2] have a special place (Figure 2.1). Interest on Convex polycyclic structures drastically increased after discovery of fullerene. As being a new form of carbon, the immense fundamental interest on fullerenes was inevitable. In addition to discovery of many fundamentally interesting properties, fullerenes were also found to be useful for a number of applications ranging from medical chemistry to renewable energy. Especially the synthesis of fullerenes has created profound effects in many areas of science and has pioneered the formation of many new research fields in the field of fundamental science [3,4].

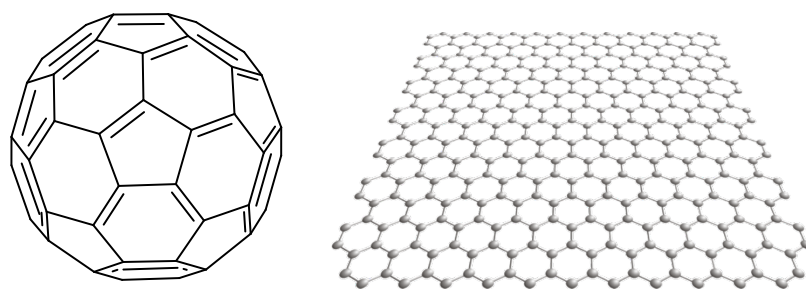


Figure 1.1. The structures of fullerene and graphene.

In addition, many important application areas of fullerene structures have emerged. Among them, the most important ones are the medical applications such as anti-viral activity, antioxidant activity and drug delivery system [5] and organic solar battery applications, one of the most important candidates addressing for today's energy problem [6]. Synthesis of fullerene C_{60} fragments and investigation of their chemical and electronic properties became a lively research area. Fullerene-based materials have interesting charge conducting properties and ionic mobility higher than standard ionic conductors and are expected to be the materials of the next-generation electronic devices [7].

2.1.2. Fragments of Fullerenes

Synthesis of non-planar aromatic compounds like fullerene fragments, a class of textbook changing materials, has always attracted great theoretical interest and became important targets for synthesis. Among these corannulene, sumanene and their derivatives were actively investigated [8] (Figure 2.2).

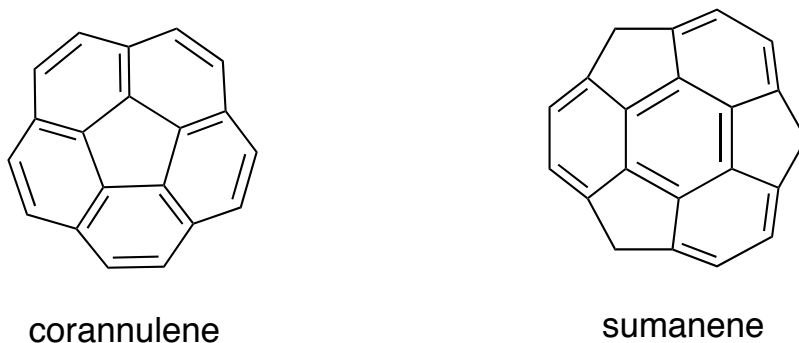


Figure 1.2. The structures of corannulene and sumanene.

Sumanene is a key partial C_{5v} symmetric structure of fullerenes. It has three benzylic positions that make possible further functionalization to create new bowl-shaped species via the corresponding radicals, cations, anions, carbenes, etc. On the other hand, corannulenes, compounds with also C_{5v} symmetry, was synthesized in 1966 by the groups of Barth and Lawton which marks the realization of the first bowl-shaped polycyclic aromatic hydrocarbon fragment of fullerenes [9].

2.1.3. Smallest Curved Fragments of C_{20}

Theoretically the smallest possible fullerene is C_{20} (Figure 2.3) and this structure consists of entirely five-membered rings. It has only been produced as a short lived intermediate in the gas-phase. The synthesis of C_{20} is much more difficult than that of C_{60} , because the highly curved fullerene C_{20} is so reactive that it cannot be produced by carbon condensation or cluster annealing processes due to its high reactivity [10].

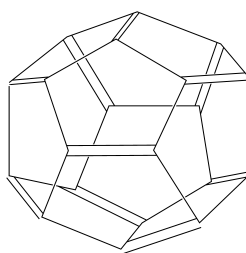


Figure 1.3. The structure of C_{20} .

Acepentalene (Figure 2.4), the smallest non-planar fragment of C_{20} , has long been a source of interest in the theoretical chemistry community and important amount of work on its synthesis was performed [11]. Since acepentalene has an anti-aromatic structure, it can only be observed in mass spectroscopy experiments [12]. Its dianion, acepentalene dianion (Figure 2.4) is a relatively stable and an isolable non-planar aromatic species. The structure was synthesized by de Meijere et al. via dehydrogenation of triquinacene under the influence of a super-base system [13].

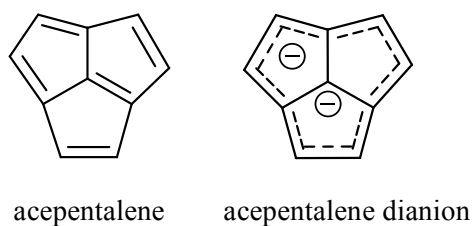


Figure 1.4. The structures of acepentalene and acepentalene dianion.

Triquinacene (Figure 2.5), which is used in the synthesis of this very important non-planar aromatic compound, has been investigated in detail for many different properties, ranging from regeneration chemistry [14] to metal complex formation [15]. And more than 150 derivatives have been synthesized up to now. In addition, many discussions about the concept of homoaromaticity have been carried out through the structure of triquinacene [16].

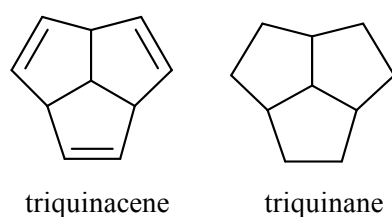


Figure 1.5. The structures of triquinacene and triquinane.

The most important synthetic motivation for the synthesis of triquinacene was to investigate the possibility of its dimerization to one of the most significant synthetic target in organic chemistry, docehadrane (Figure 2.6) by using the electro cyclic dimerization reaction [17]. Despite many different attempts, however, the desired result has not been achieved.

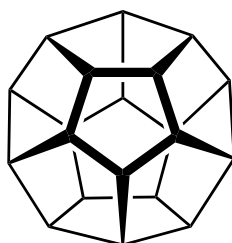


Figure 1.6. The structure of docehadrane.

Docehadrane was first synthesized by the Paquette group in a linear 26-step effort starting from cyclopentadiene. Then, docehadrane used as a precursor to produce the gas-phase cage C_{20} fullerene by replacing the hydrogen atoms with bromine atoms, and followed by debromination [18], [19].

2.1.4. Heterotriquinane Molecular Framework

Although lots of triquinacene derivatives are known in literature, heteroatom containing derivatives were not studied until the work of Mascal et. al. [20]. Mascal group found out that the nitrogen analogue of the triquinane, azatriquinane (Figure 2.7) is the most powerful trialkyl amine base [21].

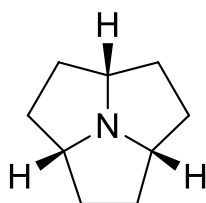


Figure 1.7. The structures of azatriquinane.

The group also successfully synthesized nitrogen derivative of acepentalenide dianion, azaacepentalenide anion (Figure 2.8), a highly aromatic non-planar compound. The carbon derivative acepentalenide is a molecule with low kinetic stability, because of its dianion structure. The nitrogen derivative contains only one anion and proves to be much more stable than the carbon derivative. For example, the THF solution of this aromatic compound is completely stable at room temperature. The perchloro derivative of the compound (Figure 2.8) is a very stable compound and can be isolated as the tetrabutylammonium salt or even purified by column chromatograph [22].

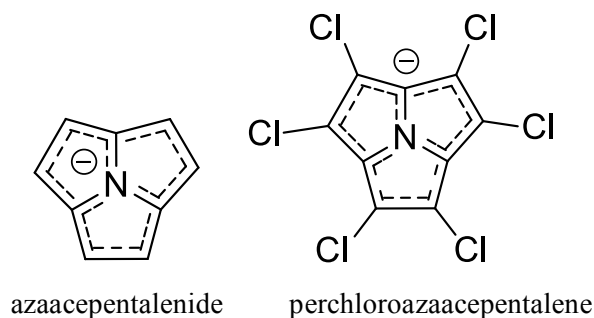


Figure 1.8. The structures of azaaceptalenide anion and perchloroazaaceptalene.

Besides these, although oxygen and sulfur derivatives of azaaceptalenide anion are not known in literature, theoretical studies (NICS calculations) show that the aromaticity of oxygen and sulfur derivatives of these structures are very high. It has been shown that is even more aromatic than benzene [23]. Oxygen derivatives of the parent triquinane, oxotriquinanes, showed unusual properties for oxonium ion. Even though oxonium ions are generally highly reactive species, this compound (Figure 2.9) can be boiled in water for a week and can be purified by column chromatography [24].

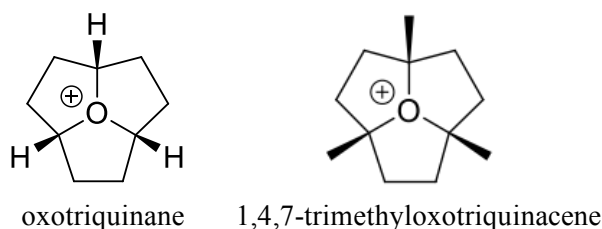


Figure 1.9. The structures of oxotriquinane and its derivative.

Furthermore, oxotriquinane compound does not give any reactions with weak nucleophiles like thiols and alcohols. In order to synthesize more stable oxotriquinane derivatives, methyl groups were attached to α position of oxotriquinane (Figure 2.9) to prevent displacement reaction. However, it was shown that the product reacts with nucleophilic NaN_3 via $\text{S}_\text{N}2$ mechanism (Figure 2.10). This was the first clear demonstration of an $\text{S}_\text{N}2$ on a tertiary center [25].

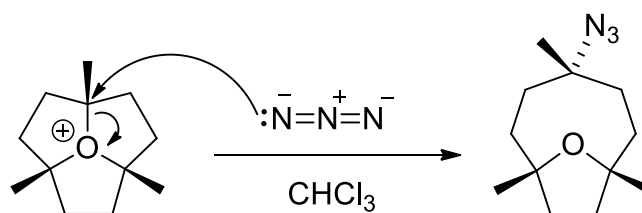


Figure 1.10. Reaction mechanism oxotriquinane derivative with NaN_3 .

It is believed that oxotriquinane derivative should possess some basic property due to its similarity in structure to azatriquinane. This concept was proven with detailed protonation studies with super acids. It was clearly demonstrated by IR studies that oxygen can make more than three covalent bonds, for the first time in the literature. Unexpected properties of compounds are important to broaden horizon of chemistry. Therefore, Mascall group have studied crystal structure of oxotriquinanes and found out that their C-O bond lengths are longer than usual. In order to figure out the limits of C-O bond length series of oxotriquinane derivatives were synthesized (Figure 2.11). Average C-O single bond length is known to be a 1.43 Å. However, C-O bond length in compound **b** was reported as 1.622 Å and it was the longest C-O bond length in the literature [26] until it was shown that compound **d** has C-O bond length of 1.658 Å [27]. Theoretical studies were conducted to explain the bond length difference revealed that while steric hindrance is the main driving force for the elongated bond length in compound **b**, interaction between the lone pair of hydroxyl group and antibonding orbital of adjacent C-O bond was responsible for the bond elongation in compound **d**.

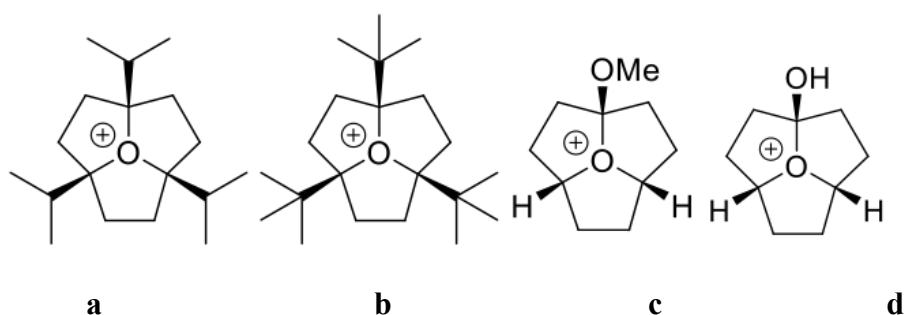


Figure 1.11. The structures of oxotriquinane derivatives **a-d**.

As can be seen from the summary given above, research starting from the synthesis of the triquinane structure of heteroatom-containing derivatives have pioneered the synthesis of many new structures and have led to many firsts in fundamental chemistry.

2.1.5. Tribenzotriquinane

Tribenzotriquinane (Figure 2.12) is a structural interesting molecule which contains three isolated aromatic rings that are posed nearly orthogonal to each other in the three-dimensional space [28].

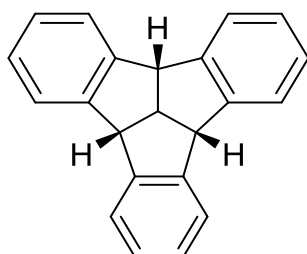
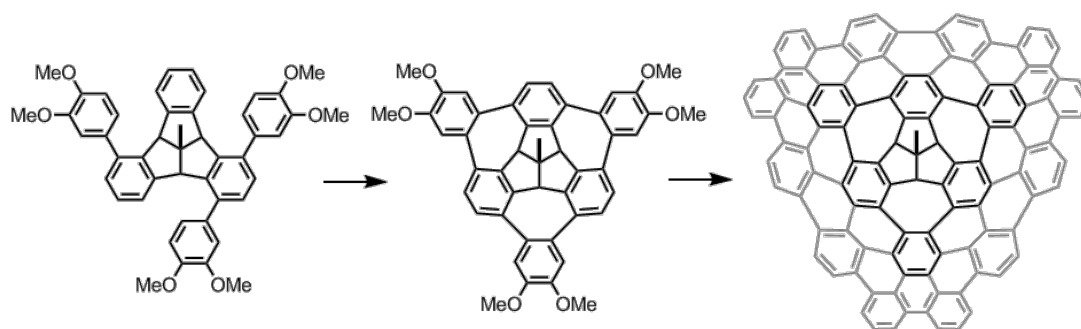


Figure 1.12. The structure of tribenzotriquinane.

Tribenzotriquinane skeleton has been studied extensively only on the carbon derivative, and many articles have been published in leading journals on this structure and important results have been obtained. Among these studies, the synthesis of non-planar aromatic anion has an important place [13]. The supramolecular cube constructed using the tribenzotriquinane structure is one of the most important studies recently published [29]. In addition to number of interesting research articles based on tribenzotriquinane structure, one new example is the π -expanded molecule, a non-planar nanographene analogue (Figure 2.13) [30].



Scheme 1.1. Synthetic scheme of non-planar nanographene structure.

The wizard hat-shaped molecule was synthesized by using a Scholl oxidative cyclization method. The three isolated aromatic rings on the tribenzotriquinane became conjugated by the addition of three aromatic rings [30].

2.1.6. Aim of the Study

Heterotriquinane and heterotriquinacene derivatives were synthesized. They have exhibited many unusual reactivity and structural properties and broadened our knowledge in the field of fundamental organic chemistry. However, hetero analogues of tribenzotriquinane core has never been synthesized in the literature and it is expected that tribenzoheterotriquinanes (Figure 2.14) might show similar unusual structural properties and reactivity. The main aim of this project is the synthesis of tribenzoheterotriquinane derivatives and investigation of any unusual reactivity and structural property that these structures might reveal. In the long run, synthesis of novel, non-planar aromatic derivatives of tribenzoheterotriquinanes will be pursued and their chemistry and electronic properties will be investigated in order to determine their potential applications in nanotechnology and organic electronics.

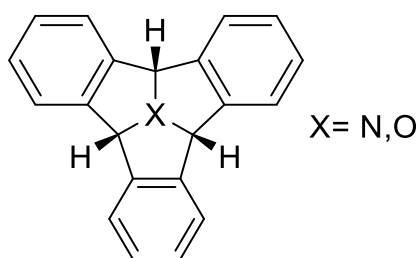


Figure 1.14. The structure of tribenzoheterotriquinanes.

A core design principle was built in order to realize the first bis-benzylic oxonium ion and first stable oxonium ylide in the literature. Additionally, presence of the benzene rings provides additional positions for structural modification, which could potentially be used for the synthesis of new derivatives with desired properties. A multi-step but convergent synthetic approach was utilized towards the synthesis of target molecules. Tribenzocyclononatriene, an important core unit in our synthetic approach, has been successfully synthesized. The functionalization of the core unit was carried out towards the synthesis of target compound, tribenzooxotriquinane and tribenzoazatriquinane. .

CHAPTER 2.2

RESULTS AND DISCUSSION

2.2.1 Design of the Heterobenzotriquinanes and Derivatives

The structural properties of the targeted compounds were evaluated first by using theoretical calculations (Gaussian). As a preliminary study, the structure of tribenzoxotriquinane was clarified using theoretical methods. When examined in detail, the length of the C-O bonds is similar but even shorter than that of the oxotriquinane C-O bonds. This is a promising result for the design of the structures.

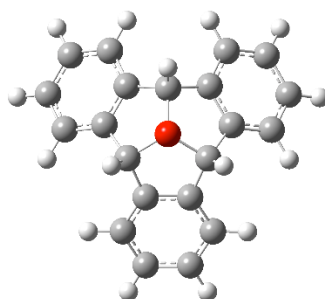


Figure 2.1. Optimized structure of tribenzoxotriquinane structure with RB3LYP method and 6-31 + G (d, p) basis set.

Then a multi-step but convergent synthetic approach has been utilized towards the synthesis of target molecules. The incorporation of benzene ring to the heterotriquinane framework opens up range of possibilities (Figure 2.1).

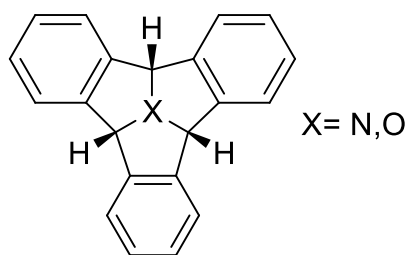


Figure 2.2. Structure of tribenzoheterotriquinanes.

First of all, the electronic structure of the heterotriquinane will be completely different which means a new series of novel convex polycyclic species will be attained. Additionally, presence of the benzene rings provides additional positions for structural modification, which could potentially be used for the synthesis of new derivatives with desired properties. The synthesis of the tribenzooxotriquinane structure will mean the realization of the first known bis-benzylic oxonium ion. There is no such compound synthesized and studied before in the literature. In addition to the specificity of the structure, it will be a unique compound in the sense of functional group. This compound will expand our fundamental knowledge in the name of oxonium chemistry which has great theoretical importance. The aromatic rings involved in the structure of tribenzooxotriquinane provide a significant advantage over the previously synthesized oxotriquinane structure. This advantage comes from the additional position richness and aromatic ring chemistry so that the structure can be modified in accordance with the desired properties. Using this new framework, realization of the first stable oxonium ylide in the literature will also be pursued (Figure 2.2).

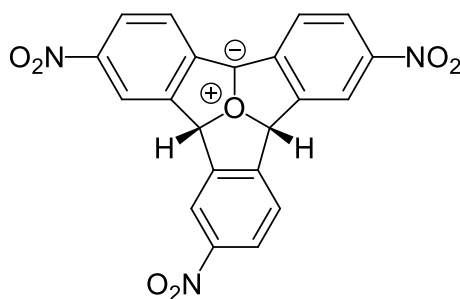


Figure 2.3. Structure of isolable oxonium ylide.

Despite being an intermediate in many reactions, there are no oxonium ylide compounds isolated in the literature or characterized by spectroscopic methods at low temperatures. The phosphonium and sulphonium ylides have an important place in the organic chemistry literature. The phosphonite ylides have many uses in synthetic chemistry, but the earliest and most prevalent is the olefin synthesis from ketones, Wittig reaction [31]. Sulphonium ylides are also the preferred reagents in many synthetic methods. The most common use is epoxide synthesis from ketones, that is, Corey-Chaykovsky reaction [32]. There are many stable, isolated phosphonium and sulphonium ylides in the literature, and detailed analyzes of these structures provide important information on their reactivity. However, there are no oxonium ylide compounds isolated in the literature or characterized by spectroscopic methods at low temperatures [33], although it is claimed to be an intermediate in a range of reactions. There are important reasons for expecting this compound to be stable. The first one is the general stability expected of the tribenzoxotriquinane skeleton. The second is that the compound will become stable with the addition of many resonance structures that can be obtained with the anion on it. Another significant novelty for this molecular framework is synthesis of the non-planar aromatic derivatives and investigation of their chemistry and electronic properties.

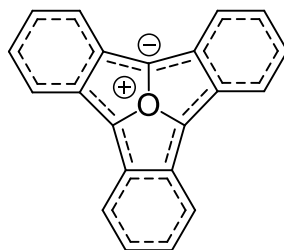


Figure 2.4. Structure of novel non-planar aromatic unit.

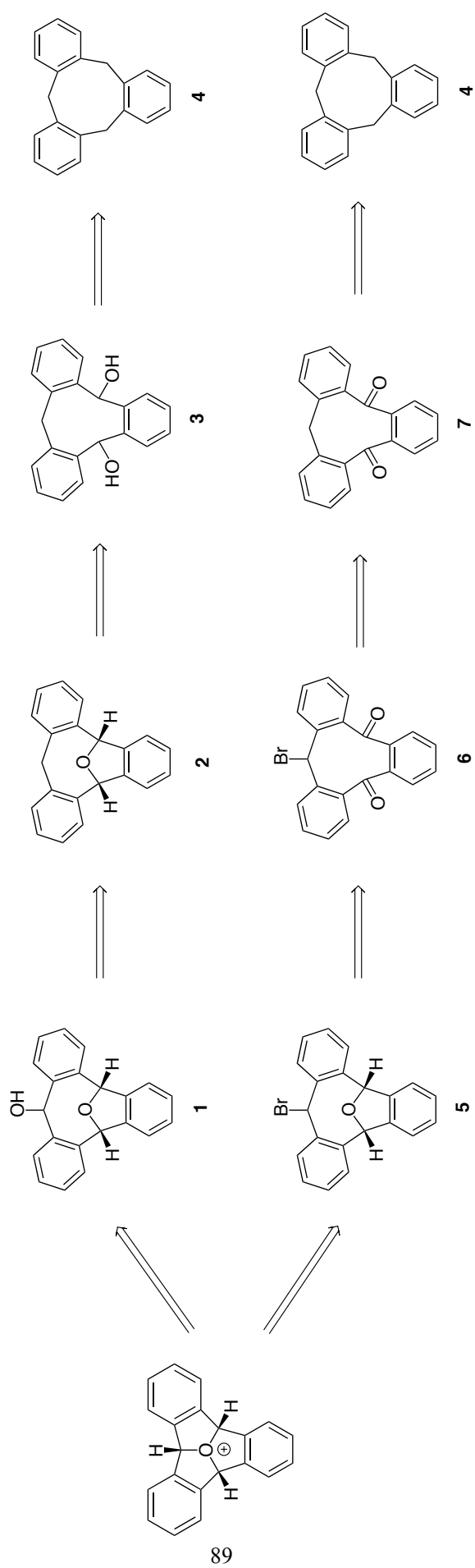
Once the synthesis of tribenzoxotriquinane is complete, the synthesis of the aromatic derivative of this compound will proceed. The compound will be the synthesis of the first aromatic tribenzoheterotriquinane derivative in the literature. After synthesis, detailed crystallization studies will be performed to clarify the crystal structure of the compound. The clarification of the crystal structure will give detailed information on the aromatic structure of the compound. There is no doubt that the fullerene

compound and its derivatives have opened a major breakthrough in science. The synthesis of classical and non-classical fragments of these structures is a field of study that is attracting more and more interest. The compound will also be a new addition to a few non-classical fragments of fullerene and electronic properties of these structures will be examined.

2.2.2. The Synthesis of Tribenzooxotriquinane: Retrosynthetic Analysis

The retrosynthetic analyses for the synthesis of tribenzooxotriquinane was shown (Scheme 2.1). To obtain the target product two different synthetic approaches were designed. First, the final C-O bond can be formed via addition of a strong acid to alcohol **1**. Alcohol **1** can come from the oxidation of the ether **2** to the corresponding ketone followed by reduction with NaBH₄. The ether **2** can be realized from diol **3** which can come from literature compound tribenzocyclononatriene (**4**). Second, tribenzooxotriquinane can be also be synthesized via Ag mediated substitution reaction of bromide **5**. Bromo compound **5** can be realized from diketobromo compound **6**, via reduction followed by acid catalyzed cyclization. Compound **6** can be synthesized from tribenzocyclononatriene via oxidation and radical bromination reactions.

Scheme 2.1. shows the retrosynthetic analysis for the tribenzooxotriquinane.

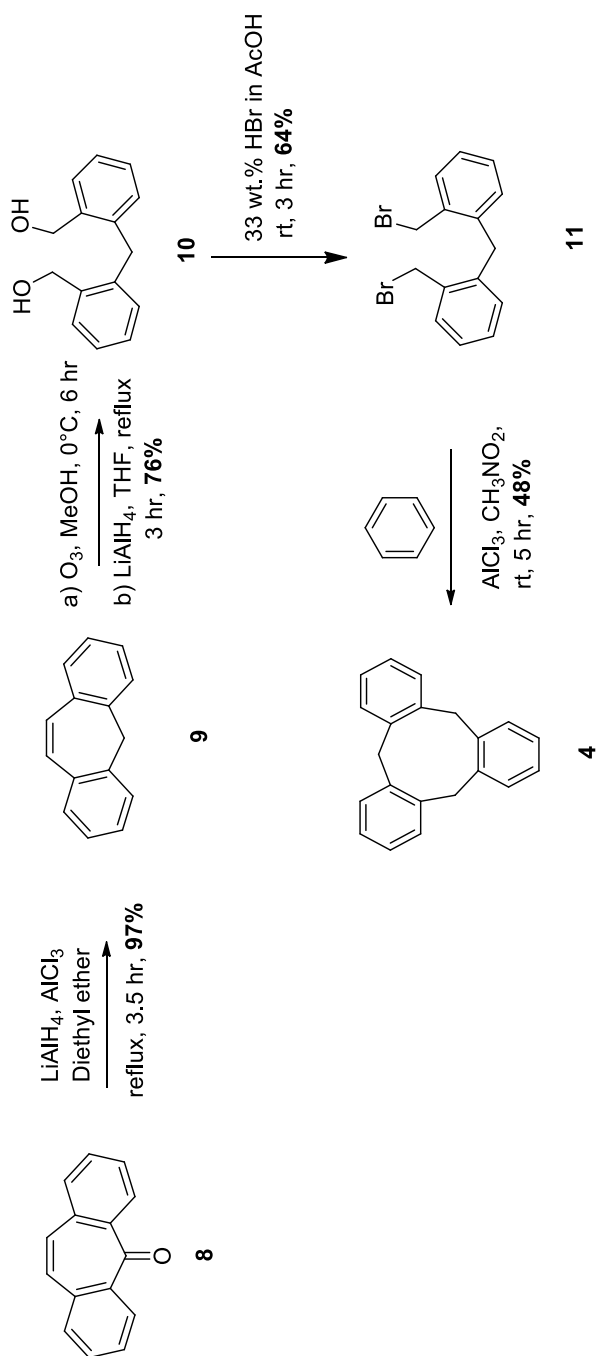


Scheme 2.1. Retrosynthetic analysis of tribenzooxotriquinane.

2.2.3. Synthesis of Tribenzocyclononatriene

Synthesis of tribenzocyclononatriene is also important in the two synthetic approaches to tribenzooxotriquinane. Literature method for the synthesis of tribenzocyclononatriene was followed with small modifications [34].

The synthetic pathway for the tribenzocyclononatriene is as shown in Scheme 2.2.



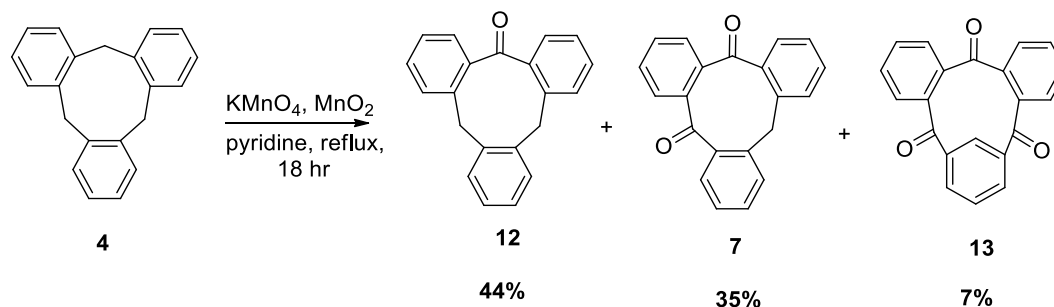
Scheme 2.2. Synthetic pathway of tribenzocyclononatriene.

The first step was the reductively removed of the carbonyl group of 5-dibenzosuberone (**8**) in the presence LiAlH_4 and AlCl_3 in dry Et_2O [34]. After performing workup step, the product of the reaction was successfully obtained without further purification with a yield of 97%. The next step of the synthesis was the ozonolysis reaction of corresponding dibenzosuberene precursor **9**. The reaction mixture was purged with stream of O_2/O_3 in methanol for 6 h to complete 1,3-dipolar cycloaddition of ozone to the alkene and followed by a reductive workup with LiAlH_4 in THF under reflux. Cleavage of the alkene **9** to diol **10** was successfully achieved with 76% yield [34]. Literature search showed that tribenzocyclononatriene **4** was first synthesized by Sato et al. in 1973 by Friedel-Craft cyclocondensation of a bis-benzylic alcohol **10** with benzene in the presence of concentrated sulfuric acid as catalyst using high dilution conditions. To obtain high yield from this procedure, the compound and benzene mixture should be added dropwise to a mixture of H_2SO_4 and benzene using syringe pump for 30 h [35]. Due to the lack of instrumentation, we decided to change the procedure with first nucleophilic bromination substitution and then double Friedel-Craft alkylation reaction. The next step of the synthesis was dibromination of the alcohol groups of (methylenebis(2,1-phenylene))dimethanol (**10**) with the addition of HBr in AcOH . Without further purification, this nucleophilic substitution reaction was generated the alkyl halide **11** with a yield of 64% [36]. Finally, the target compound **4** was synthesized by double Friedel-Craft alkylation reaction of bis(2-(bromomethyl)phenyl)methane (**11**) in the presence CH_3NO_2 and AlCl_3 in dry benzene [37]. Although, the bis(2-benzylphenyl)methane structure emerges as an undesirable byproduct, the use of a high dilution condition has been observed to increase the yield 48% of the target product, tribenzocyclononatriene.

2.2.4. Towards Synthesis of the Tribenzooxotriquinane

2.2.4.1. Oxidation of tribenzocyclononatriene

The synthetic pathway for the oxidation of tribenzocyclononatriene is as shown in Scheme 2.3.



Scheme 2.3. Synthetic pathway of oxidation of tribenzocyclononatriene.

Oxidation of tribenzocyclononatriene is known in the literature [38] albeit low yields 25% were observed for the target diketotribenzocyclononatriene (7). The main purpose here was to increase the efficiency of this step. Detailed studies have been carried out in the literature on the oxidation of cyclotrimeratrylene (CVT) compound, which is very similar in structure to compound 4. Recently, a new method of oxidation of the CVT compound has resulted in much higher yields for diketo derivative of it [39]. When this new method was applied to compound 4, we obtained much better results than the method known at present. Tribenzocyclononatriene was oxidized to compound 12, 7 and 13 in the presence KMnO_4 and MnO_2 in dry pyridine [39]. After performing workup, the products were yielded by column chromatography with a yield of 44%, 35% and 7% sequentially (Scheme 2.3). The triketotribenzocyclononatriene C3 (Figure 2.4) is unknown in the literature and we were excited to see a small third spot in the TLC during the oxidation reaction. However detailed characterization of this spot revealed that it is the triketone 13.

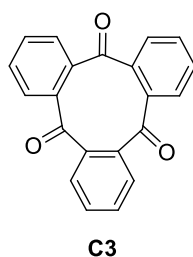
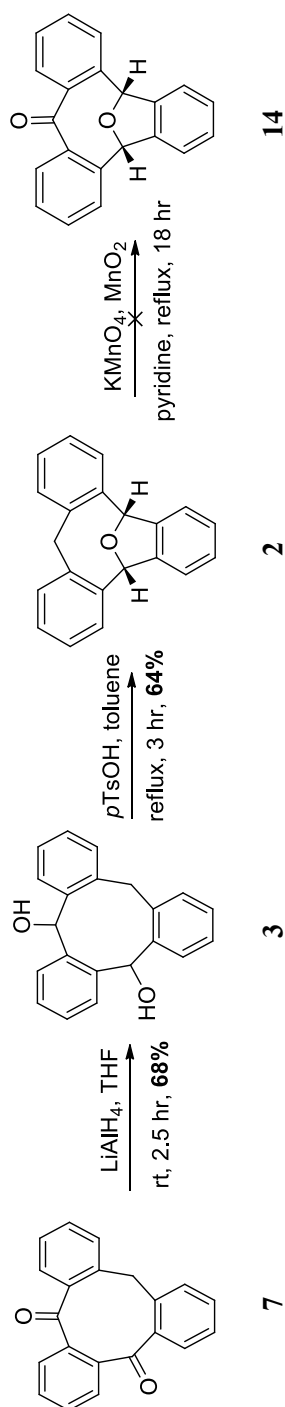


Figure 2.5. Structure of triketotribenzocyclononatriene C3.

2.2.4.2. Toward Tribenzooxotriquinane: Cyclic Ether Approach

As mentioned above, one approach to the synthesis of tribenzooxotriquinane is cyclic ether approach (Scheme 2.4). After the successful synthesis of the diketotribenzocyclononatriene (**7**), reduction to diol **3** with LAH in dry THF was achieved with 68% yield [40].



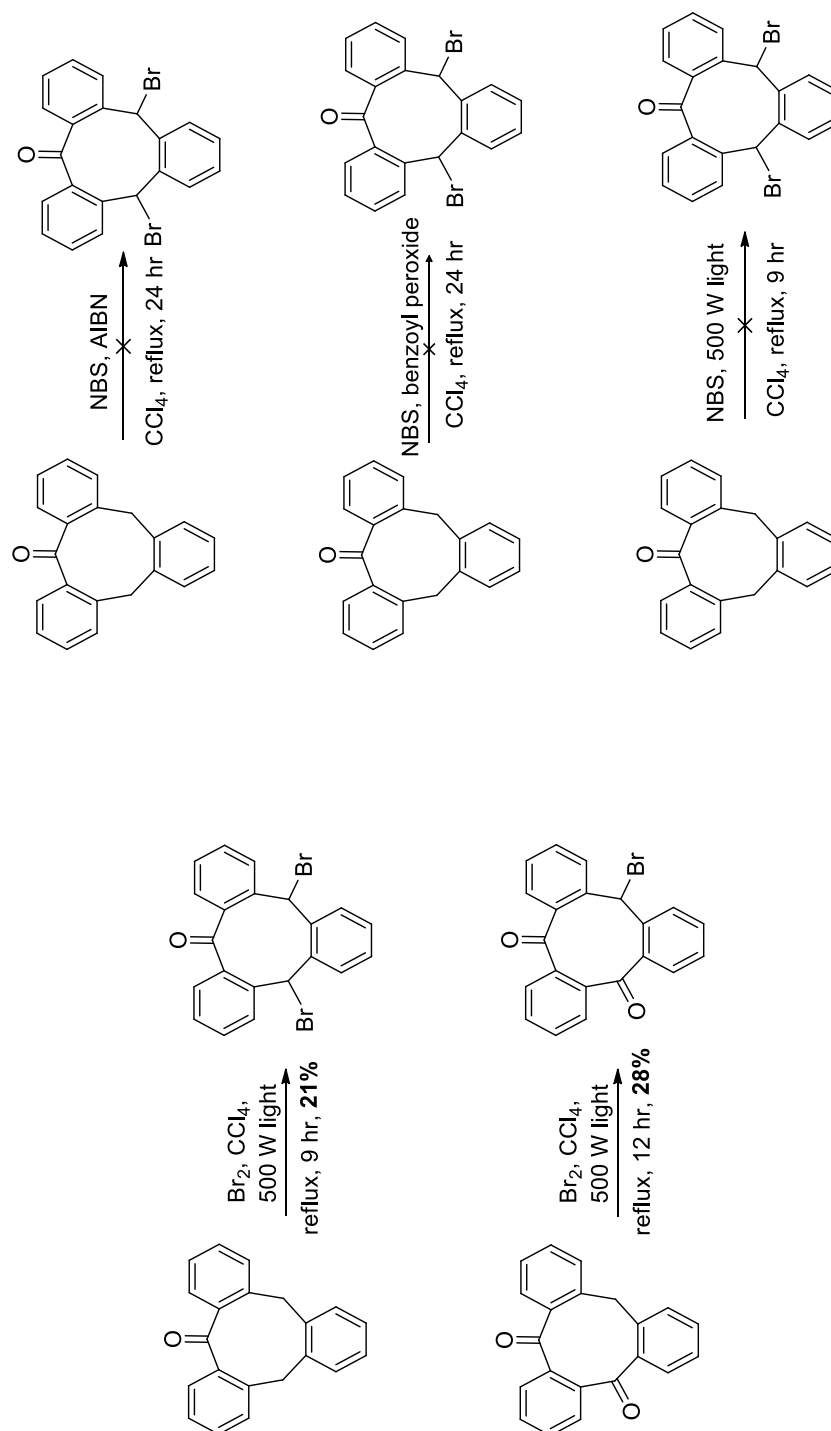
Scheme 2.4. Synthetic pathway toward tribenzooxotriquinane with cyclic ether approach.

The next step of the synthesis was the cyclization reaction of diol **3** with PTSA in toluene to obtain the corresponding ether **2** with 64% [41]. Then the treatment of ether **2** with KMnO_4 and MnO_2 in pyridine was attempted to get compound **14**. Unfortunately, allylic oxidation did not give the expected product and it was observed that under these reaction condition diketotribenzocyclononatriene (**7**) was produced quantitatively [39].

2.2.4.3. Toward Tribenzooxotriquinane: Bromination

Since we got a decent yield of the monoketone **12** during the oxidation reaction, the preliminary studies of benzylic bromination were performed on the monoketotribenzocyclononatriene (**12**). A number of conditions were investigated using NBS as the bromine source however none of these reactions gave the expected product. In the first unsuccessful trial, NBS was used with AIBN as a radical initiator for the bromination of **12**. Then the radical initiator was changed with benzoyl peroxide [42]. And the last failed attempt was performed with NBS in the presence 500 W light [43]. When the source of bromine was changed from NBS to bromine the product was formed [44]. The photochemical reaction between **12** and bromine was performed in dry CCl_4 with 500 W light. It was observed that dry solvent prevented side products. The dibromo derivative was successfully synthesized in 21% yield. Similar conditions also worked for the diketotribenzocyclononatriene derivative **13** and bromination was achieved with 28% yield. Although the yields were quite low, the remaining part of the reaction was starting material, which was successfully recovered by column chromatography and had been reused.

The synthetic routes for the bromination of tribenzocyclononatriene derivatives are as shown in Scheme 2.5.



Scheme 2.5. Synthetic routes of the bromination reactions.

2.2.4.4. Toward Tribenzooxotriquinane: Reduction

The reduction of 5*H*-tribenzo[*a,d,g*][9]annulene-5,10(15*H*)-dione **7** is a very important step for the synthesis of tribenzooxotriquinane. According to the designed synthetic pathway, the predicted target compound of the reduction reaction in LiAlH₄ and dry ether was diol **15**. Although the synthesis of compound **15** could not be completed yet, it has been showed that the reduction experiment gives different results in different reaction times. When the reduction reaction was carried out with 2.0 equivalents of LiAlH₄, the starting material was finished within 2 hours, but the characterization of the resulting product was inconclusive. The same reaction was performed by adding four times the reductant (a total of 2.2 equivalents of LiAlH₄). The reaction was continued for 10 hours and HRMS and NMR data showing that 15-bromo-10,15-dihydro-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulen-5-ol **17** (Figure 2.4) was obtained.

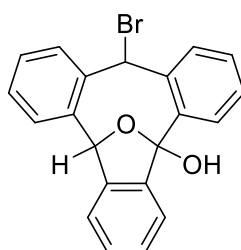
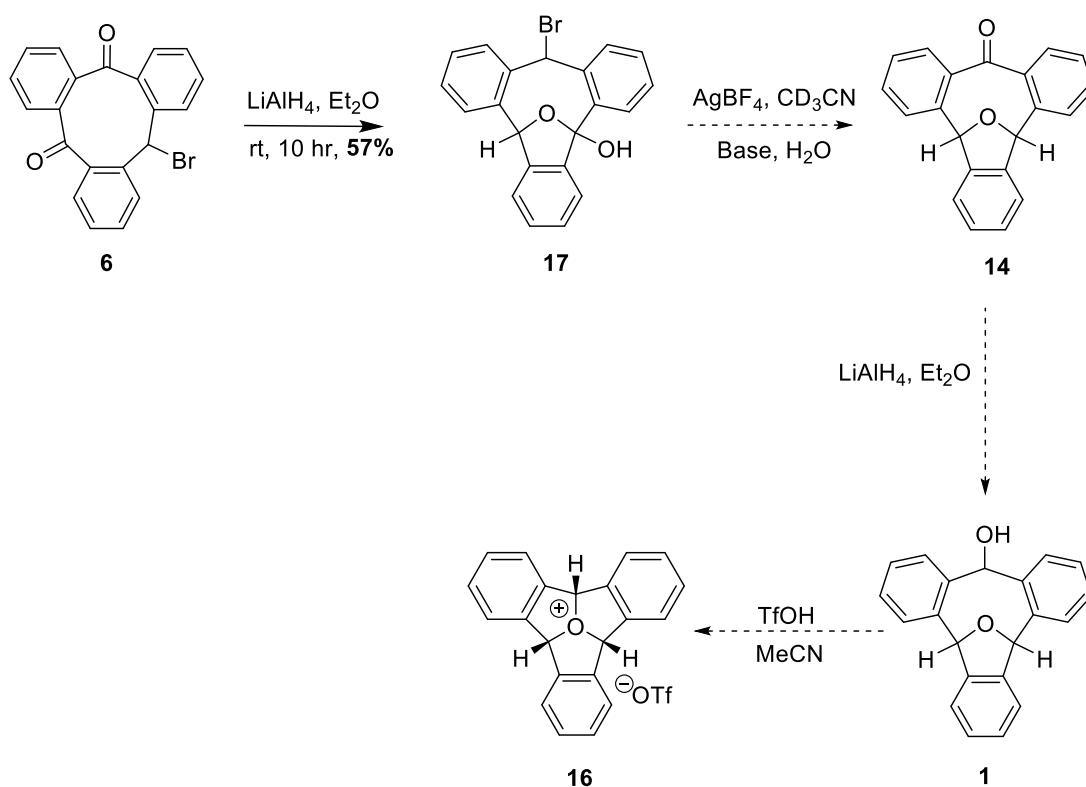


Figure 2.6. Structure of 15-bromo-10,15-dihydro-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulen-5-ol.

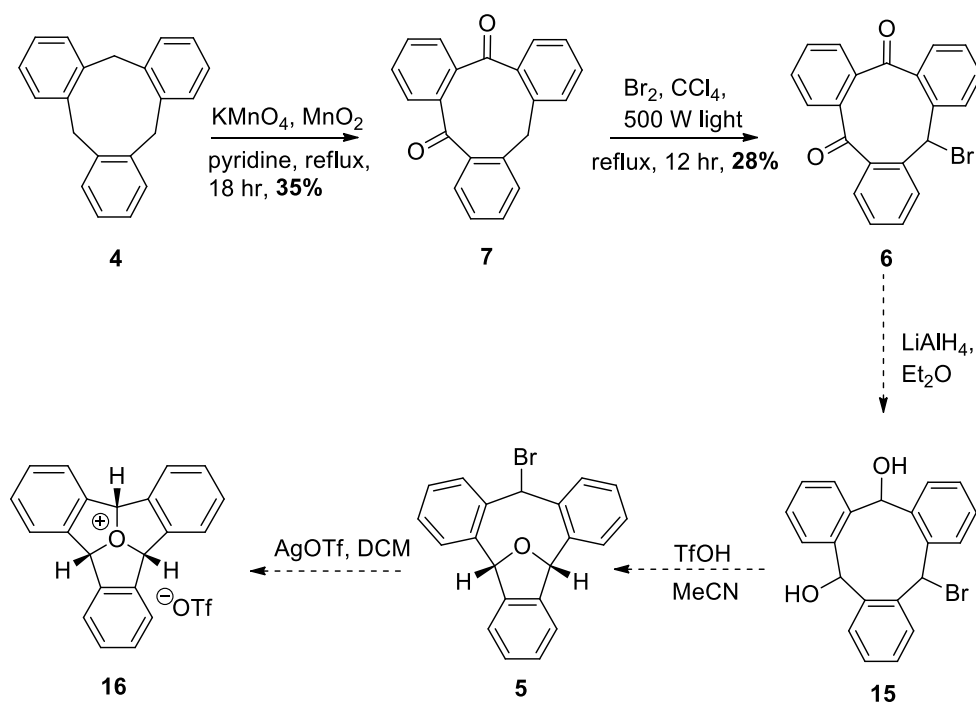
A new synthetic route has emerged with this product obtained. According to the route, compound **14** will be yielded via silver mediated substitution reaction of bromide **17** followed by base treatment. Then LiAlH₄ reduction reaction will be carried out to obtained compound **1**. The final C-O bond of tribenzooxotriquinane can be formed via addition of a strong acid to alcohol **1**.



Scheme 2.6. Synthetic pathway of tribenzooxotriquinane.

2.2.5. Synthetic Pathway of Tribenzooxotriquinane

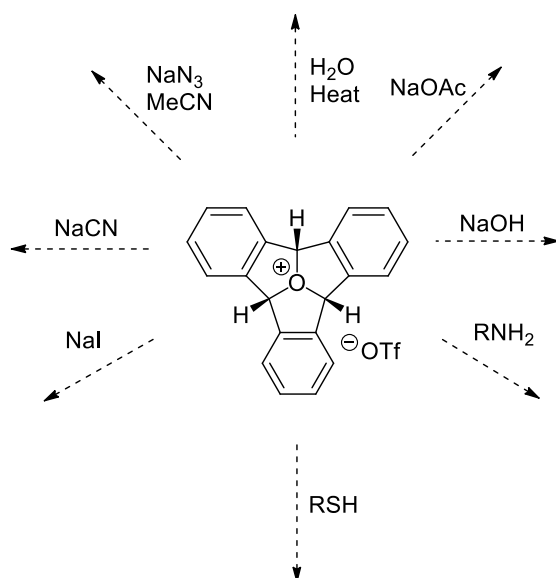
The first designed synthetic approach of tribenzooxotriquinane is still important as an alternative way. Synthesis of Compound **6** was completed as outlined above, the synthetic route to obtain the target product in Scheme 2.7 will be followed. When compound **15** is reacted with a strong acid, TfOH, ether **5** will be readily synthesized via the resulting carbocation intermediate [24]. Ether **5** will then be exposed to benzylic bromination conditions and compound **5** will be obtained. Conversion of compound **5** to target molecule **16** will be carried out silver mediated displacement of the bromide with the silver salt AgOTf [45].



Scheme 2.7. Synthetic pathway of tribenzooxotriquinane.

2.2.6. Future Work

After we successfully synthesize tribenzooxotriquinane the first order of business would be to investigate its reactivity thoroughly. The compound represents the first bis-benzylic oxonium ion known in the literature. As mentioned before, oxonium ions are normally very strong alkylating agents and they do not exhibit stability under any conditions (Scheme 2.7). The first example of a stable oxonium structure in the literature is the oxotriquinane compound. The reactivity of a benzene derivative of it is an important question in terms of fundamental chemistry. The following reactions will be examined to clarify the reactivity of this interesting molecular framework. We are hoping to see that this special oxonium ion will survive most of these conditions even though it is a bis-benzylic oxonium ion. In particular, if the compound does not react with the strong nucleophiles N_3^- , OH^- and CN^- , it is going to be a breakthrough because it will mean the realization of the first oxonium derivative which is resistant to strong nucleophiles. In addition, the tribenzooxotriquinane will be modified with nitro groups to obtain the first isolable oxonium ylide. Additionally, synthesis of the non-planar aromatic derivatives and investigation of their chemistry and electronic properties will be pursued.



Scheme 2.7. Reactions to investigate the reactivity of the structure of tribenzooxotriquinane.

CHAPTER 2.3

CONCLUSION

Two different synthetic approaches have been described for the preparation of tribenzooxotriquinane **16**. First of all, this project concentrated on the synthesis of a pivotal intermediate toward the synthesis of tribenzooxotriquinane in both approaches. Tribenzocyconatriene intermediate **4** was successfully synthesized from commercially available compound, 5- dibenzosuberone (8), with good overall yield in 5 steps. All products were characterized by NMR analysis in detail. After that, tribenzocyconatriene derivatives were synthesized with cyclic ether approach towards tribenzooxotriquinane synthesis. However, the product obtained after 4 steps showed that this approach failed. The second approach, the first step was the oxidation, which was successfully performed. The second step was the bromination reaction. Although many different procedures have been tried and failed for the bromination reaction, the desired product was finally synthesized and the structure was proven by NMR spectroscopy. The next synthetic step, reduction, has been investigated, but the optimizations of the synthesis step is still ongoing. Having large amounts of this compound will open the way for the synthesis of tribenzooxotriquinanes. The synthetic route to obtain the target product will be followed by acid catalyzed cyclization and Ag mediated substitution reaction. After the successful synthesis of tribenzooxotriquinane, the first order of business would be to investigate its reactivity thoroughly. We hope that this special bis-benzylic oxonium ion will have an unexpected chemistry like literature known heterotriquinane and heterotriquinacene derivatives.

CHAPTER 2.4

EXPERIMENTAL

2.4.1. Materials and Methods

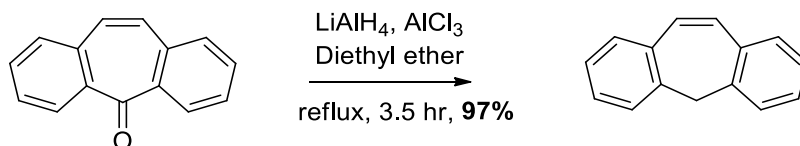
The ^1H and ^{13}C -NMR spectra were recorded on a Bruker Avance III Ultrashield (400 MHz) spectrometer. The chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (J) are reported in hertz (Hz), and the spin multiplicities were specified by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), td (triplet of doublet), and m (multiplet). NMR spectrums were processed with MestReNova program. Column chromatography was performed by using thick walled glass columns and silica Gel 60 (Merck 230-400 mesh). Thin layer chromatography (TLC Merck Silica Gel 60 F254) was performed by using commercially prepared 0.25 mm silica gel plates and visualization was provided by UV lamp. The relative proportions of solvents in chromatography solvent mixtures refer to the volume: volume ratio. All commercially available reagents and starting materials were purchased from Aldrich Chemical and used directly without further purification. All dry solvents used in reactions were directly obtained from the Mbraun MBSPS5 solvent drying system. The inert atmosphere was obtained by Argon.

2.4.2. Equipment

CDCl_3 and d_6 -DMSO was used as the solvents for the ^1H and ^{13}C -NMR analyses on Bruker Spectrospin Avance DPX-400 Spectrometer. High resolution mass spectroscopy was performed in order to determine the exact masses of the novel synthesized compounds using Waters Synapt MS System.

2.4.3. Core Unit Syntheses

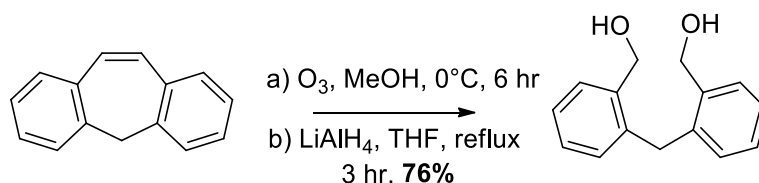
2.4.3.1. Synthesis of 5*H*-dibenzo[*a,d*][7]annulene



Scheme 4.1. Synthetic route of 5*H*-dibenzo[*a,d*][7]annulene.

5*H*-Dibenzo[*a,d*][7]annulene was synthesized according to the literature with small modifications [34]. To a solution of AlCl₃ (3.55 mg, 26.7 mmol) in dry Et₂O (13 mL), LiAlH₄ (1.00 g, 26.4 mmol) in dry Et₂O (19 mL) was added at room temperature and the resulting mixture was stirred for 30 min. Then, the mixture was added dropwise at 0 °C to 5-Dibenzosuberone (5.00 g, 24.2 mmol) in dry THF (28 mL). The reaction mixture was heated to reflux for 3 h followed by stirring at room temperature overnight. To decompose excess of LiAlH₄, 1.0 mL water and 1.0 mL 15% (w/w) NaOH solution was sequentially added to the resulting mixture to quench the reaction. Then 3.0 mL water was added again and the mixture was dried with anhydrous MgSO₄. The residue was filtered and washed with THF (200 mL), then concentrated to obtain off-white solid (4.51 g, 97%): ¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.18 (m, 6H), 7.15 – 7.10 (m, 2H), 6.94 (s, 2H), 3.66 (s, 2H). ¹³C-NMR (100 MHz, CDCl₃): δ 138.1, 135.2, 131.5, 128.4, 128.1, 127.9, 126.0, 41.6.

2.4.3.2. Synthesis of (methylenebis(2,1-phenylene))dimethanol

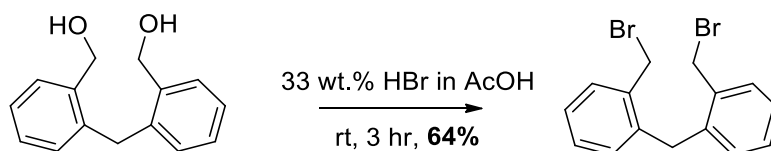


Scheme 4.2. Synthetic route of (methylenebis(2,1-phenylene))dimethanol.

(Methylenebis(2,1-phenylene))dimethanol was synthesized according to the literature with small modifications [34]. The suspension solution of 5*H*-dibenzo[*a,d*][7]annulene

(4.68 g, 24.3 mmol) in dry MeOH (140 mL) was cooled to 0 °C and a stream of O₂/O₃ was passed through for 6 h. Then, Argon gas was bubbled through the reaction mixture at room temperature for 30 min. The solvent was evaporated under reduced pressure at 30 °C and the remaining yellow oil was dissolved in dry Et₂O (120 mL) followed by slow addition to a suspension of LiAlH₄ (4.70 g, 0.124 mmol) in dry Et₂O (190 mL) at 0 °C. To complete the reaction, the mixture was heated to reflux for 3 h and then stirred at room temperature overnight. The excess of LiAlH₄ was decomposed by adding 4.7 mL water and 4.7 mL 15% (w/w) NaOH solution was sequentially added to resulting mixture to quench the reaction. Then 14.0 mL water was added again and the mixture was dried with anhydrous MgSO₄. The residue was filtered and washed with THF (200 mL), The solvent was evaporated and the resulting solid was recrystallized from benzene to yield a white powder (4.20 g, 76%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.18 (dt, *J* = 27.3, 6.9 Hz, 4H), 6.86 (d, *J* = 7.3 Hz, 2H), 5.11 (br s, 2H), 4.49 (s, 4H), 3.99 (s, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 140.2, 137.2, 128.8, 126.8, 126.6, 125.9, 60.6, 33.4.

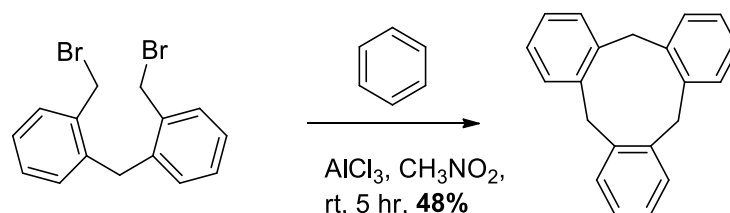
2.4.3.3.Synthesis of bis(2-(bromomethyl)phenyl)methane



Scheme 4.3. Synthetic route of bis(2-(bromomethyl)phenyl)methane.

Bis(2-(bromomethyl)phenyl)methane was synthesized according to the literature with small modifications [36]. (methylenebis(2,1-phenylene))dimethanol (0.100 g, 0.430 mmol) and 33% HBr in acetic acid (2 mL) was stirred at room temperature for 3h. Then the reaction was quenched with a mixture of saturated aqueous sodium bicarbonate (50 mL) and DCM (15 mL). The aqueous layer was extracted with a DCM (3 × 30 mL). The combined organic layers were dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give an off-white solid (0.107 g, 64% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.32 (dd, *J* = 5.6, 3.5 Hz, 2H), 7.20 – 7.15 (m, 4H), 6.88 (dd, *J* = 5.1, 3.8 Hz, 2H), 4.43 (s, 4H), 4.22 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 138.7, 136.0, 130.6, 130.3, 129.2, 127.2, 34.6, 31.8.

2.4.3.4. Synthesis of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene

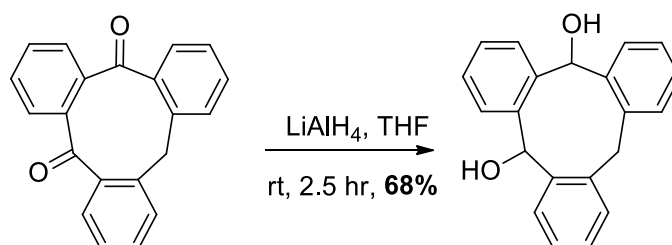


Scheme 4.4. Synthetic route of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene.

10,15-Dihydro-5*H*-tribenzo[*a,d,g*][9]annulene was synthesized according to the literature with small modifications [37]. To a solution of bis(2-(bromomethyl)phenyl)methane (1.44 g, 4.07 mmol) in dry Benzene (60 mL) was slowly added to a mixture of AlCl_3 (1.10 g, 8.30 mmol), CH_3NO_2 (2.70 mL) in Benzene (40 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h and was quenched with 1% HCl (200 mL). The mixture was extracted with Et_2O (3 x 50 mL). The combined organic layer was washed with water (2 x 40 mL) and dried over MgSO_4 . The solvent was evaporated and the resulting residue was purified by column chromatography on silica gel (1:6 DCM/hexane) to yield an off-white solid (0.527 g, 48 %): ^1H NMR (400 MHz, CDCl_3) δ 7.30 (dd, $J = 5.3, 3.7$ Hz, 6H), 7.01 (dd, $J = 5.4, 3.5$ Hz, 6H), 4.83 (d, $J = 13.4$ Hz, 3H), 3.68 (d, $J = 13.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 139.5, 130.1, 127.0, 37.2.

2.4.4. Towards Tribenzooxotriquinane Synthesis: Cyclic Ether Approach

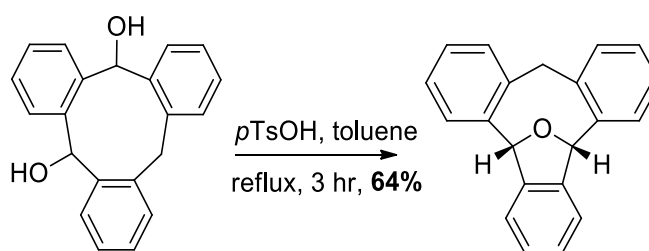
2.4.4.1. Synthesis of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene-5,10-diol



Scheme 4.5. Synthetic route of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene-5,10-diol.

5*H*-tribenzo[*a,d,g*][9]annulene-5,10(15*H*)-dione (0.30 g, 1.01 mmol)) was dissolved in anhydrous THF (50 mL) and the solution was added dropwise to the cooled (0°C) solution of LiAlH₄ (0.115 g, 3.02 mmol) in anhydrous THF (6 mL). The mixture was stirred at room temperature for 2.5 h. To decompose excess of LiAlH₄, 0.1 mL water and 0.1 mL 15% (w/w) NaOH solution was sequentially added to resulting mixture to quench reaction. Then 0.3 mL water was added again and the mixture was dried with anhydrous MgSO₄. The residue was filtered and washed with THF, then concentrated to obtain a yellow oil (0.206 g, 68%): ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 7.5 Hz, 2H), 7.48 (dt, *J* = 6.9, 3.5 Hz, 2H), 7.25 – 7.19 (m, 4H), 7.14 (td, *J* = 7.4, 1.1 Hz, 2H), 7.07 (d, *J* = 7.4 Hz, 2H), 5.93 (s, 2H), 3.95 (d, *J* = 14.8 Hz, 1H), 3.45 (d, *J* = 14.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 141.5, 140.8, 136.7, 130.5, 128.3, 127.6, 127.5, 126.8, 126.3, 70.3, 39.0.

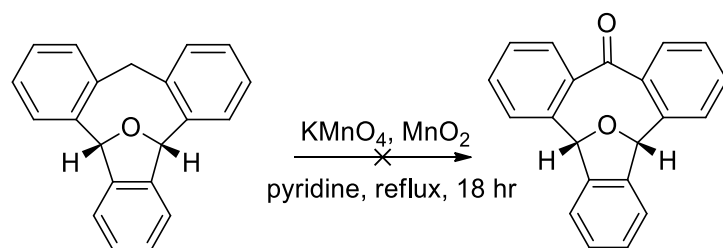
2.4.4.2. (5*R*,10*S*)-10,15-dihydro-5*H*-5,10epoxytribenzo[*a,d,g*][9]annulene



Scheme 4.6. Synthetic route of (5*R*,10*S*)-10,15-dihydro-5*H*-5,10epoxytribenzo[*a,d,g*][9]annulene.

To a solution of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene-5,10-diol (10 mg, 0.0330 mmol) in Toluene (14 mL), *p*-toluenesulfonic acid (3.00 mg, 0.0160 mmol) was added. The reaction mixture was heated to reflux for 3 h, then distilled water was added (30 mL) at room temperature. After stirred for 30 min, the mixture was washed with toluene and with saturated aq. Na₂CO₃ solution. The combined organic layer was dried (MgSO₄) and the solvent was evaporated to yield a colorless oil (6.00 mg, 64%): ¹H NMR (100 MHz, CDCl₃) δ 7.36 – 7.31 (m, 2H), 7.27 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.20 – 7.12 (m, 8H), 6.20 (s, 2H), 3.25 (d, *J* = 14.1 Hz, 1H), 3.13 (s, 1H).

2.4.4.3. Synthesis of (5*R*,10*S*)-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulen-15(10*H*)-one

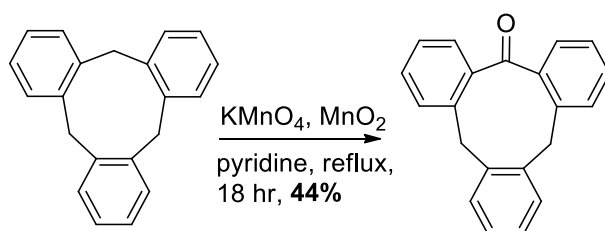


Scheme 4.7. Synthetic route of (5*R*,10*S*)-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulen-15(10*H*)-one.

To a solution of (5*R*,10*S*)-10,15-dihydro-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulene (10 mg, 0.0352 mmol) in Pyridine (7 mL) were added a finely ground uniform mixture of potassium permanganate (350 mg, 2.21 mmol) and activated manganese dioxide (380 mg, 0.437 mmol). The reaction mixture was stirred vigorously under reflux for 72 h. The reaction mixture was filtered while hot through a bed of Celite bed and it were rinsed with EtOAc (50 mL) followed by DCM (50 mL). The organic solvent was removed under reduced pressure and crude material was further dried in vacuo at 100 °C. The crude NMR of the reaction showed no expected product peaks.

2.4.5. Towards Tribenzooxotriquinane Synthesis

2.4.5.1. Synthesis of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one

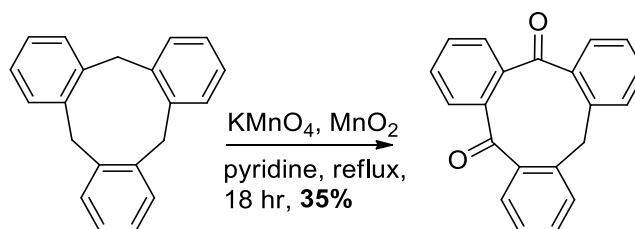


Scheme 4.8. Synthetic route of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one.

To a solution of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene (0.350 g, 1.29 mmol) in pyridine (16 mL) were added a finely ground uniform mixture of potassium permanganate (8.19 g, 51.8 mmol) and activated manganese dioxide (9.00 g, 104

mmol). The reaction mixture was stirred vigorously under reflux for 72 h. The reaction mixture was filtered while hot through a bed of Celite bed and it were rinsed with EtOAc (200 mL) followed by DCM (200 mL). The organic solvent was removed under reduced pressure and crude material was further dried in vacuo at 100 °C. Then, the crude product was purified by column chromatography on silica gel with CH₂Cl₂ as eluent, then a yellow solid was obtained (0.162 g, 44%): ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 7.7 Hz, 2H), 7.31 – 7.21 (m, 4H), 7.16 – 7.08 (m, 4H), 7.02 (d, *J* = 7.5 Hz, 2H), 3.74 (s, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 195.9, 140.6, 139.8, 137.9, 132.6, 131.4, 130.4, 129.8, 127.2, 126.9, 37.7.

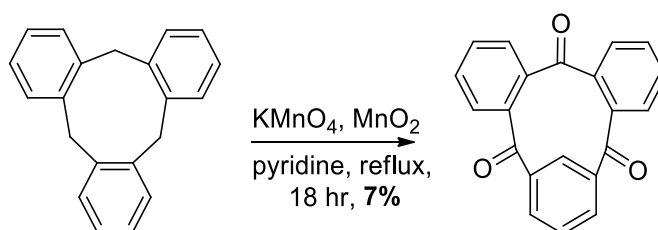
2.4.5.2. Synthesis of 5*H*-tribenzo[*a,d,g*][9]annulene-5,10(15*H*)-dione



Scheme 4.9. Synthetic route of 5*H*-tribenzo[*a,d,g*][9]annulene-5,10(15*H*)-dione.

5*H*-tribenzo[*a,d,g*][9]annulene-5,10(15*H*)-dione was synthesized according to the literature with small modifications [39]. To a solution of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene (0.350 g, 1.29 mmol) in Pyridine (16 mL) were added a finely ground uniform mixture of potassium permanganate (8.19 g, 51.8 mmol) and activated manganese dioxide (9.00 g, 104 mmol). The reaction mixture was stirred vigorously under reflux for 72 h. The reaction mixture was filtered while hot through a bed of Celite bed and it were rinsed with EtOAc (200 mL) followed by DCM (200 mL). The organic solvent was removed under reduced pressure and crude material was further dried in vacuo at 100 °C. Then, the crude product was purified by column chromatography on silica gel with CH₂Cl₂ as eluent, then a yellow solid was obtained (0.135 g, 35%): ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.45 (ddd, *J* = 30.7, 5.8, 3.4 Hz, 4H), 7.23 (dt, *J* = 14.3, 7.4 Hz, 4H), 7.00 (d, *J* = 7.5 Hz, 2H), 3.84 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 198.0, 140.3, 139.9, 139.2, 132.3, 130.8, 130.3, 129.0, 127.9, 127.3, 37.7.

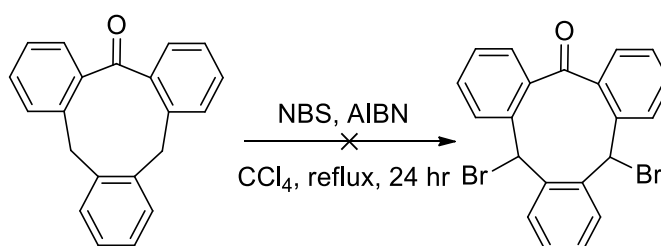
2.4.5.3. Synthesis of 5*H*-6,10-(metheno)dibenzo[*a,d*][12]annulene-5,11,16-trione



Scheme 4.10. Synthetic route of 5*H*-6,10-(metheno)dibenzo[*a,d*][12]annulene-5,11,16-trione.

To a solution of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene (0.350 g, 1.29 mmol) in pyridine (16 mL) were added a finely ground uniform mixture of potassium permanganate (8.19 g, 51.8 mmol) and activated manganese dioxide (9.00 g, 104 mmol). The reaction mixture was stirred vigorously under reflux for 72 h. The reaction mixture was filtered while hot through a bed of Celite bed and it were rinsed with EtOAc (200 mL) followed by DCM (200 mL). The organic solvent was removed under reduced pressure and crude material was further dried in vacuo at 100 °C. Then, the crude product was purified by column chromatography on silica gel with EtOAc as eluent, then a yellow solid was obtained (28 mg, 7%): ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 7.2 Hz, 2H), 7.60 – 7.33 (m, 6H), 7.29 (t, *J* = 7.7 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 195.6, 194.7, 139.9, 137.7, 135.9, 131.9, 130.0, 129.6, 128.8, 128.7, 127.9, 127.2.

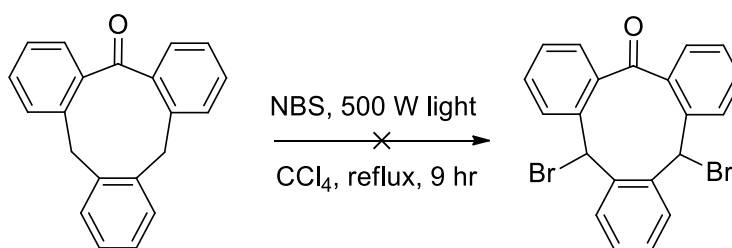
2.4.5.4. Synthesis of 10,15-dibromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene-5-one



Scheme 4.11. Synthetic route of 10,15-dibromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulene-5-one.

A solution of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one (0.100 g, 0.352 mmol) in dry CCl₄ (7 mL) was treated with AIBN (6.00 mg, 0.0360 mmol) and NBS (0.128 g, 0.720 mmol). The resulted mixture was heated to reflux for 24h. After filtered, the reaction mixture was quenched with aqueous NaHSO₃ (5%) and the organic layer was extracted with water. The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The crude NMR of the reaction showed no product peaks.

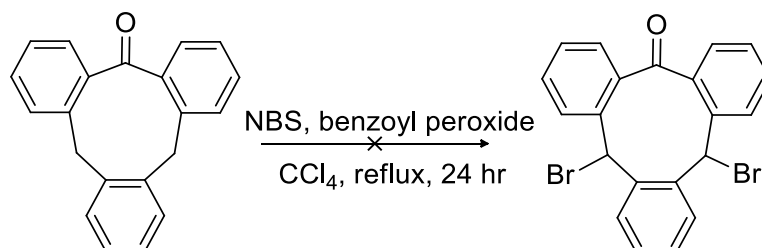
2.4.5.5. Synthesis of 10,15-dibromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen 5-one



Scheme 4.12. Synthetic route of 10,15-dibromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one.

A solution of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one (50.0 mg, 0.176 mmol) in dry CCl₄ (3 mL) was treated NBS (63.0 mg, 0.352 mmol). The resulted mixture was exposed to 500 W light for 8h. The reaction mixture was evaporated under reduced pressure. The crude NMR of the reaction showed no product peaks.

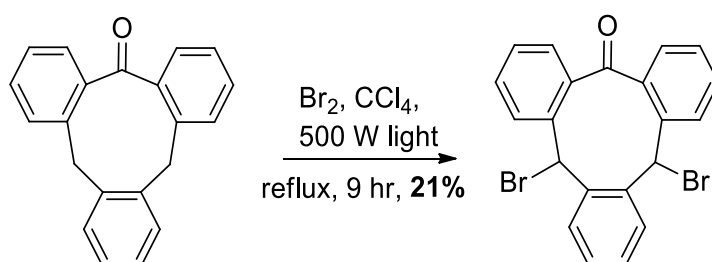
2.4.5.6. Synthesis of 10,15-dibromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen 5-one



Scheme 4.13. Synthetic route of 10,15-dibromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one.

A solution of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one (50.0 mg, 0.176 mmol) in dry CCl₄ (10 mL) was treated with benzoyl peroxide (8.00 mg, 0.0330 mmol) and NBS (60.0 mg, 0.360 mmol). The resulted mixture was heated to reflux for 12h. After filtered, the reaction mixture was evaporated under reduced pressure. The crude NMR of the reaction showed no product peaks.

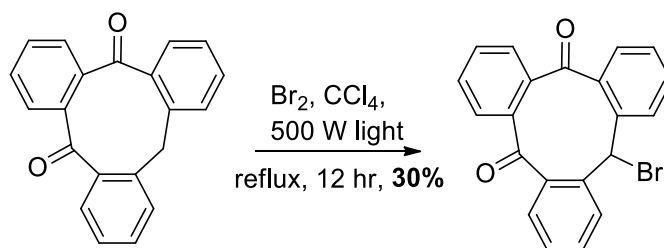
2.4.5.7. Synthesis of 10,15-dibromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen 5-one



Scheme 4.14. Synthetic route of 10,15-dibromo-10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen -5-one.

A solution of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one (100 mg, 0.352 mmol) in dry CCl₄ (18 mL) was treated dropwise at 50 °C with Br₂ solution (1.0 M, 0.112 g, 0.703 mmol) in dry CCl₄. The resulted mixture was irradiated with 500 W light for 9 h. The solvent was removed under reduced pressure. Then, the crude product was purified by column chromatography on silica gel (1:3 DCM/hexane) to yield a white solid (33.0 mg, 21%): ¹H NMR (400 MHz, CDCl₃) δ 7.86 (dd, *J* = 5.6, 3.5 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 5.7 Hz, 4H), 7.34 (dt, *J* = 5.1, 1.8 Hz, 4H), 6.47 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 194.0, 139.3, 137.9, 136.9, 133.1, 131.6, 129.5, 129.1, 129.0, 128.8, 48.6.

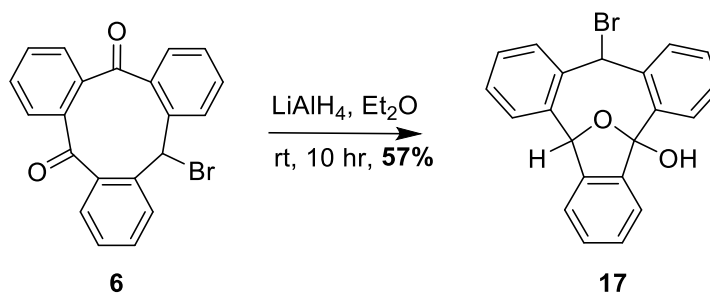
2.4.5.8. Synthesis of 15-bromo-5*H*-tribenzo[*a,d,g*][9]annulene-5,10(15*H*)-dione



Scheme 4.15. Synthetic route of 15-bromo-5*H*-tribenzo[*a,d,g*][9]annulene-5,10(15*H*)-dione.

A solution of 5*H*-tribenzo[*a,d,g*][9]annulene-5,10(15*H*)-dione (100 mg, 0.336 mmol) in dry CCl_4 (15 mL) was treated dropwise at 50 °C with solution of Br_2 (1.0 M, 0.53 g, 0.336 mmol) in dry CCl_4 . The resulted mixture was irradiated with 500 W light for 9 h. The solvent was removed under reduced pressure. Then, the crude product was purified by column chromatography on silica gel (1:3 DCM/hexane) to yield a white solid (45.0 mg, 30%): ^1H NMR (400 MHz, CDCl_3) δ 7.60 (dd, $J = 5.8, 3.3$ Hz, 2H), 7.50 (dt, $J = 6.3, 3.5$ Hz, 6H), 7.42 (td, $J = 7.7, 1.4$ Hz, 2H), 7.31 (td, $J = 7.5, 1.0$ Hz, 2H), 6.71 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 196.6, 140.3, 139.5, 138.1, 132.5, 131.4, 129.7, 128.6, 128.3, 47.8.

2.4.5.9. Synthesis of 15-bromo-10,15-dihydro-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulene-5-ol



Scheme 4.16. Synthetic route of 15-bromo-10,15-dihydro-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulene-5-ol.

15-bromo-10,15-dihydro-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulen-5-ol (45.0 mg, 0.121 mmol) was dissolved in anhydrous ether (5 mL) and the solution was added dropwise to the cooled 0°C solution of LiAlH₄ (2.5 mg, 0.066 mmol) and the mixture was stirred at room temperature for 2h. LiAlH₄ was added three more times at 0°C in the same portion and the mixture was stirred again at room temperature for 2 h each time. Then, to decompose excess of LiAlH₄, 0.01 mL water and 0.01 mL 15% (w/w) NaOH solution was sequentially added to resulting mixture to quench reaction. Then 0.03 mL water was added again and the mixture was dried with anhydrous MgSO₄. The residue was filtered and washed with THF, then concentrated to obtain a yellow solid (22.0 mg, 57%): ¹H NMR (400 MHz, CDCl₃) δ 8.00 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.95 – 7.89 (m, 3H), 7.46 – 7.42 (m, 3H), 7.41 (t, *J* = 2.1 Hz, 1H), 7.30 – 7.19 (m, 8H), 7.19 – 7.11 (m, 3H), 6.15 (s, 1H), 6.12 (s, 1H), 4.43 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 140.9, 139.9, 139.4, 138.9, 137.7, 136.7, 130.1, 129.9, 129.6, 129.1, 128.9, 128.0, 127.9, 126.4, 126.1, 123.6, 121.3, 120.6, 106.4, 85.6, 45.9. HRMS calculated for C₂₁H₁₅O₂Na⁸¹Br [*M* + Na] 403.0192, found 403.0133.

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APPENDIX A

NMR SPECTRA

NMR measurements were performed with Bruker Avance III Ultrashield 400 Hz using CDCl_3 , or *d*-DMSO as the solvents.

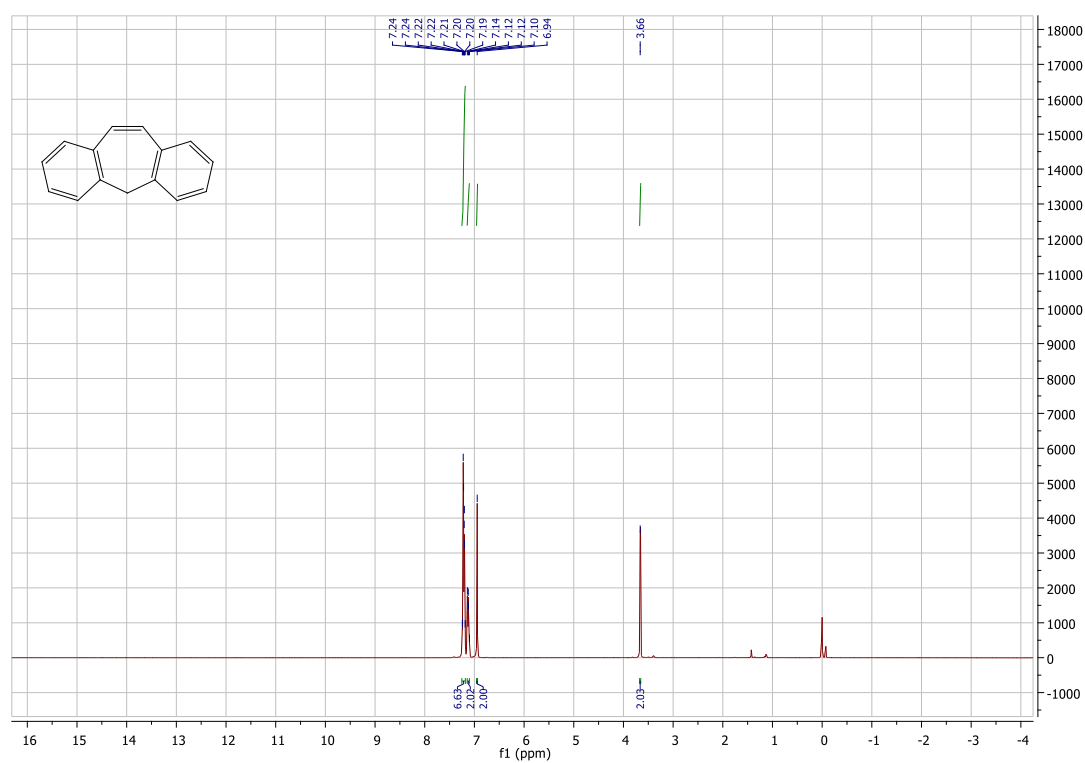


Figure A.1. ^1H -NMR spectrum of 5H-dibenzo[*a,d*][7]annulene.

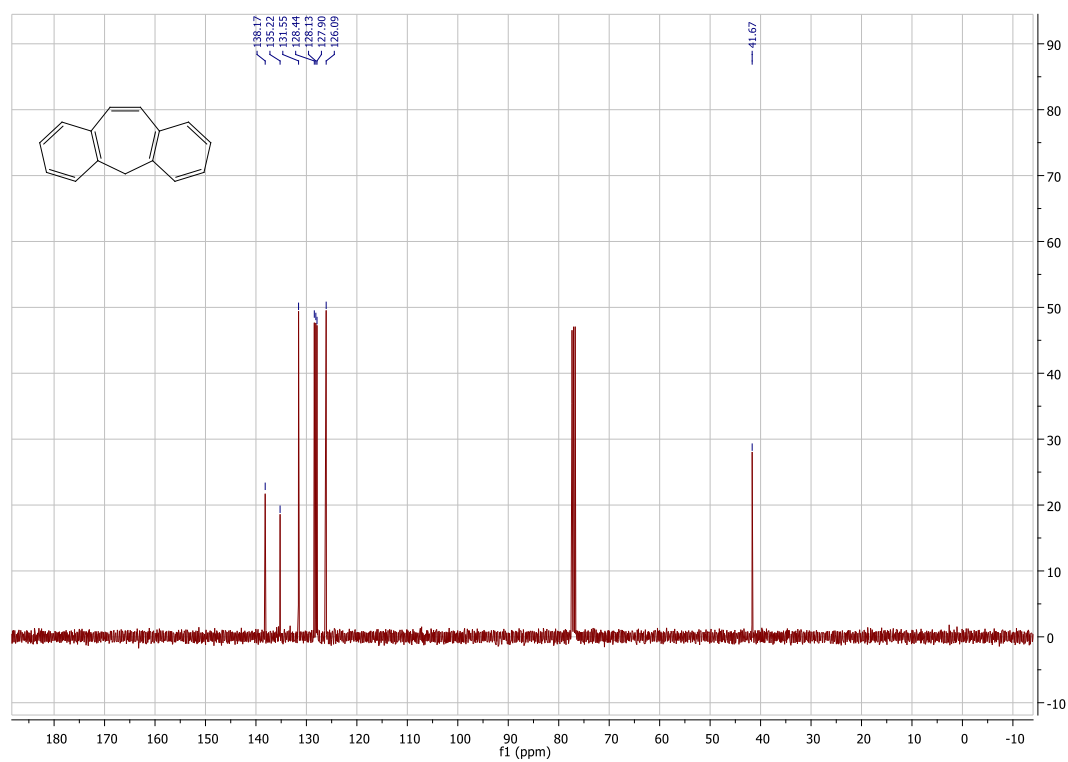


Figure A.2. ^{13}C -NMR spectrum of 5H-dibenzo[*a,d*][7]annulene.

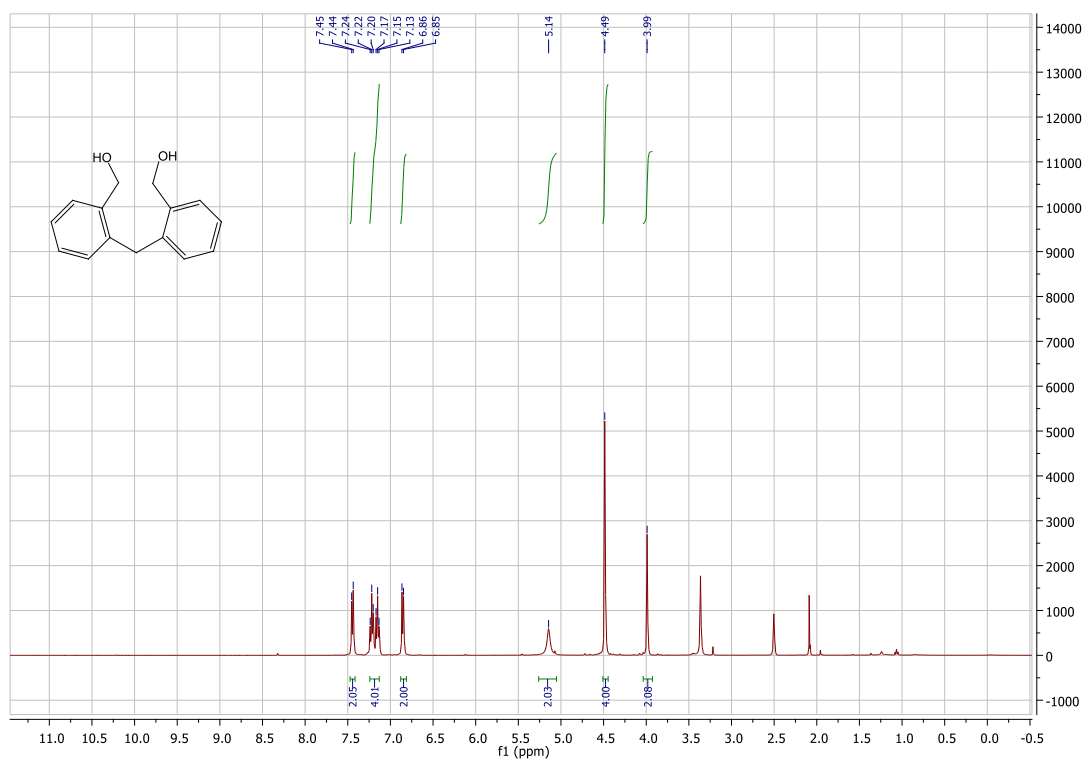


Figure A.3. ¹H-NMR spectrum of (methylenebis(2,1-phenylene))dimethanol.

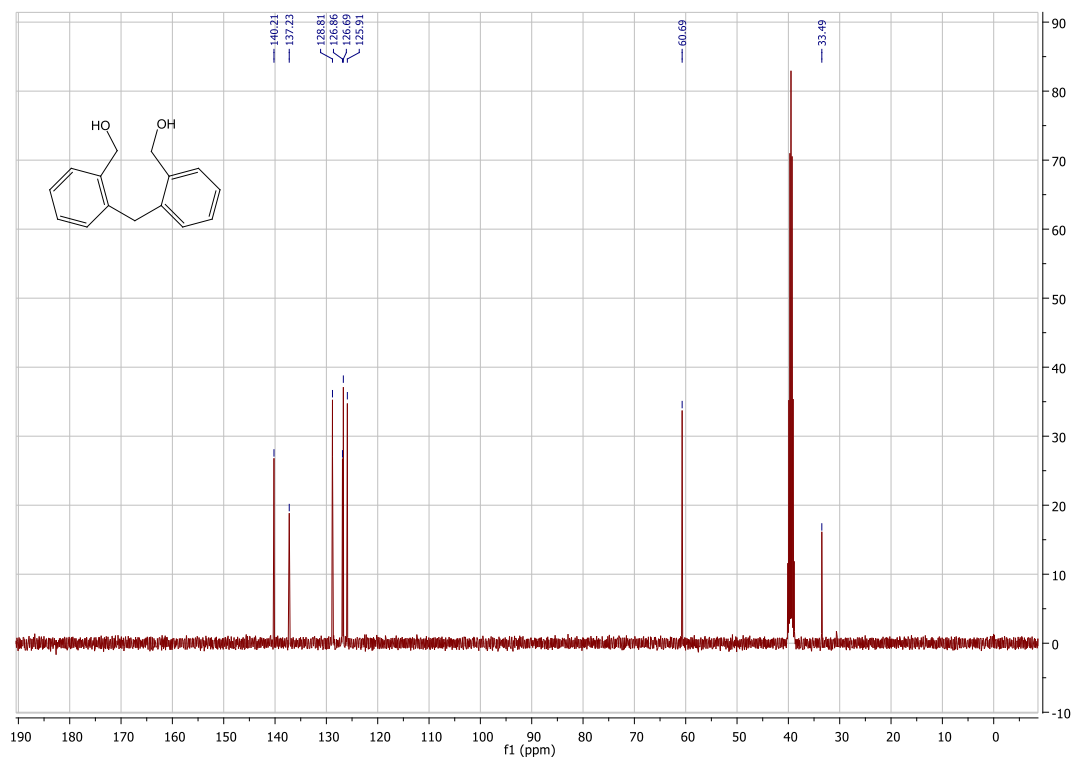


Figure A.4. ¹³C-NMR spectrum of (methylenebis(2,1-phenylene))dimethanol.

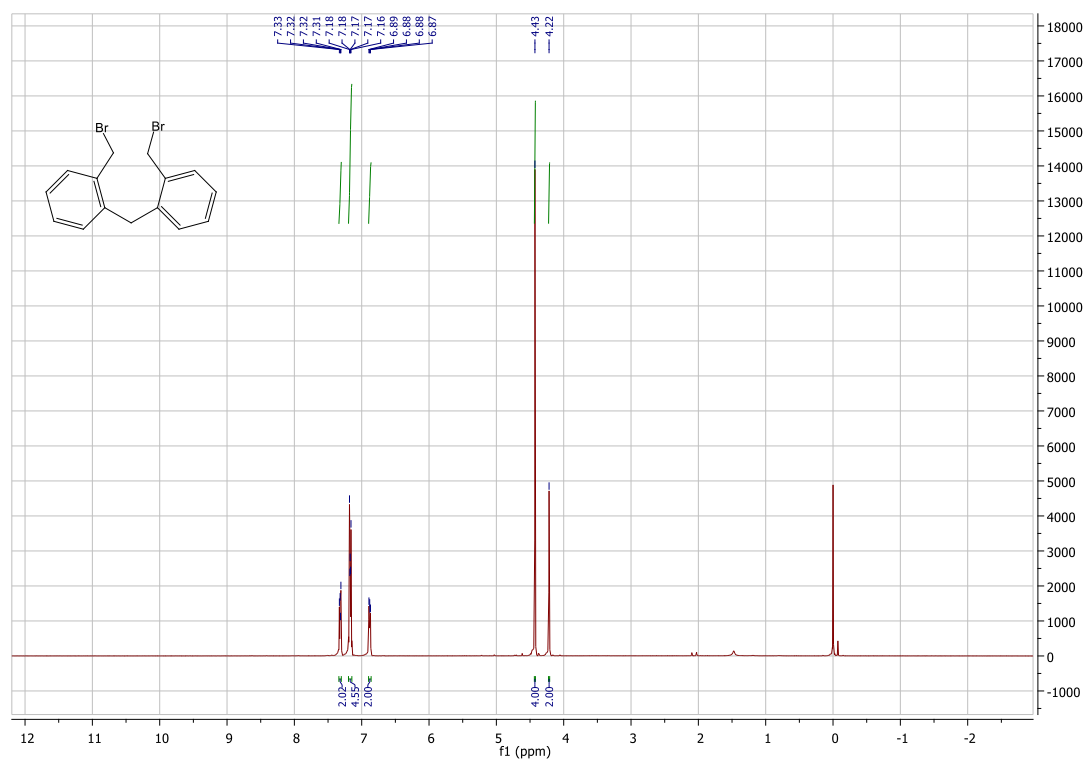


Figure A.5. ^1H -NMR spectrum of bis(2-(bromomethyl)phenyl)methane.

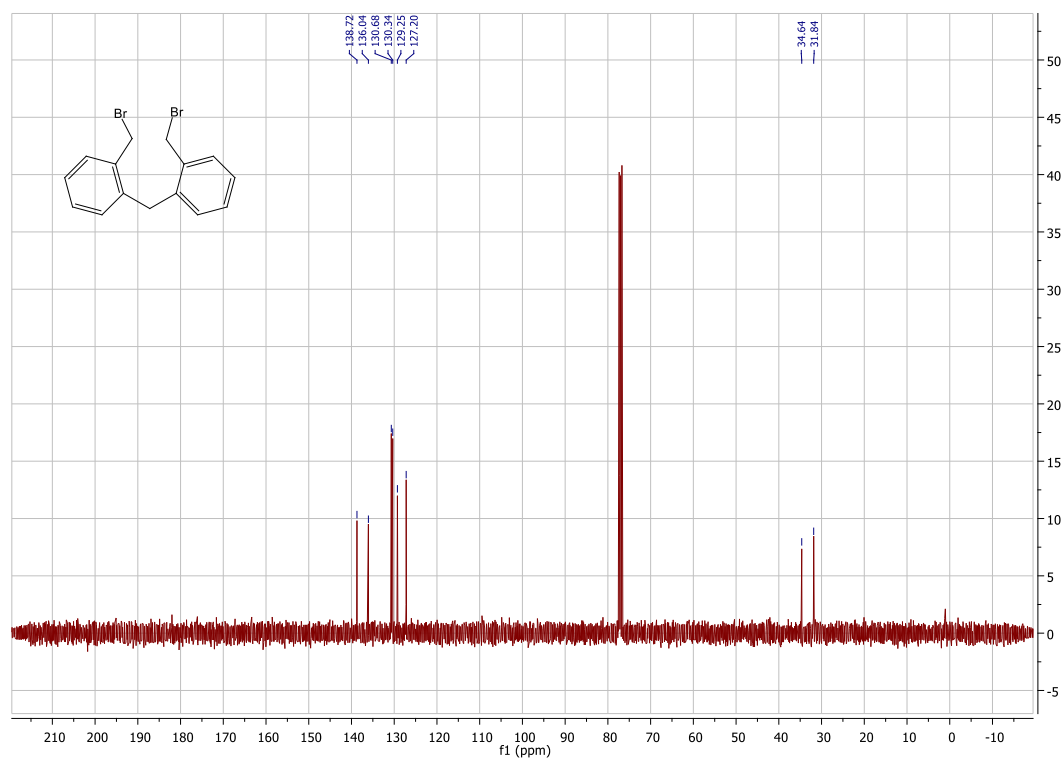


Figure A.6. ^{13}C -NMR spectrum of bis(2-(bromomethyl)phenyl)methane.

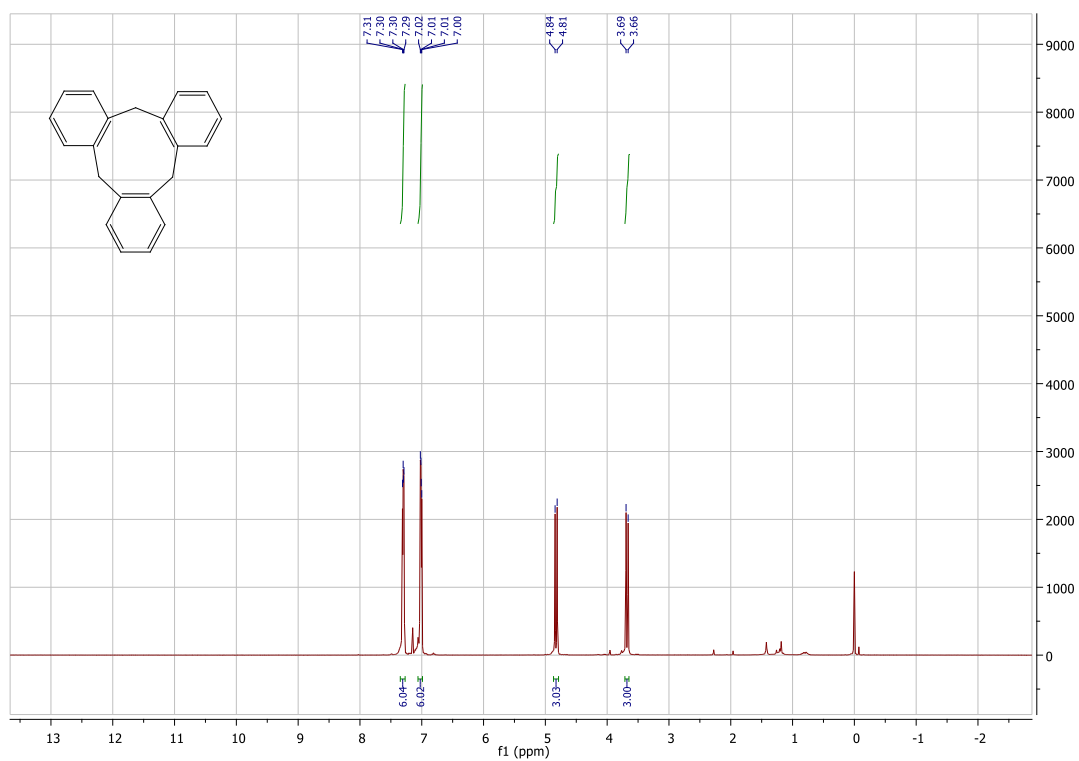


Figure A.7. ¹H-NMR spectrum of 10,15-dihydro-5H-tribenzo[*a,d,g*][9]annulene.

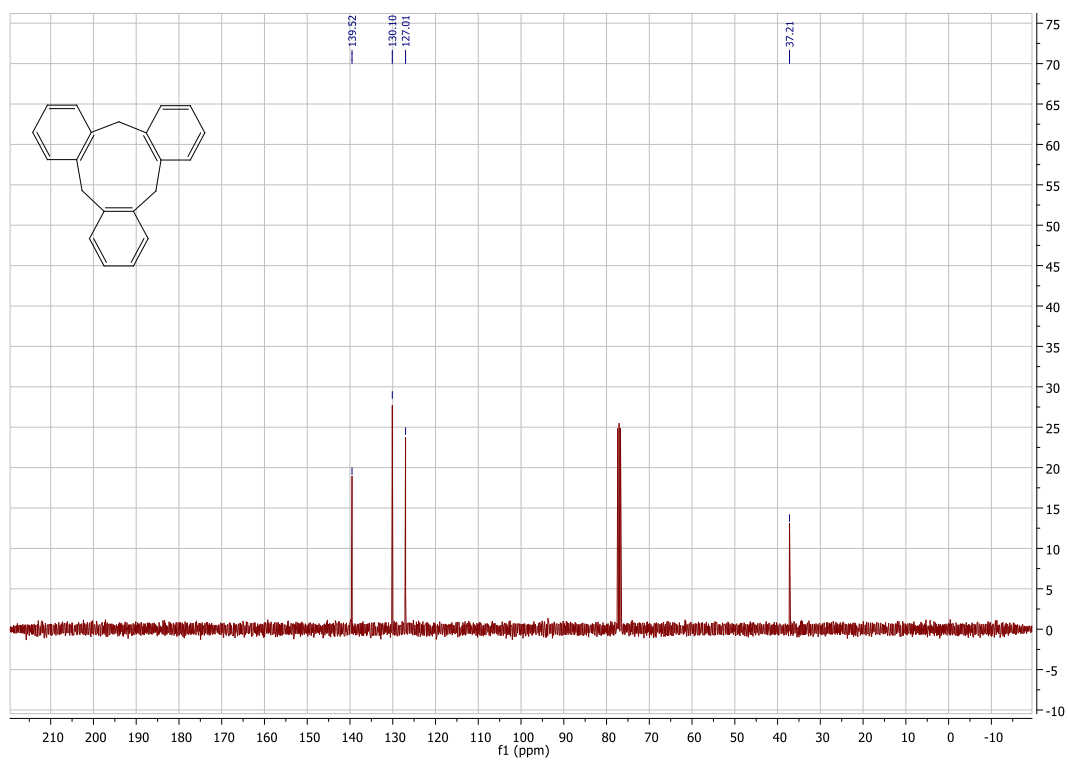


Figure A.8. ¹³C-NMR spectrum of 10,15-dihydro-5H-tribenzo[*a,d,g*][9]annulene.

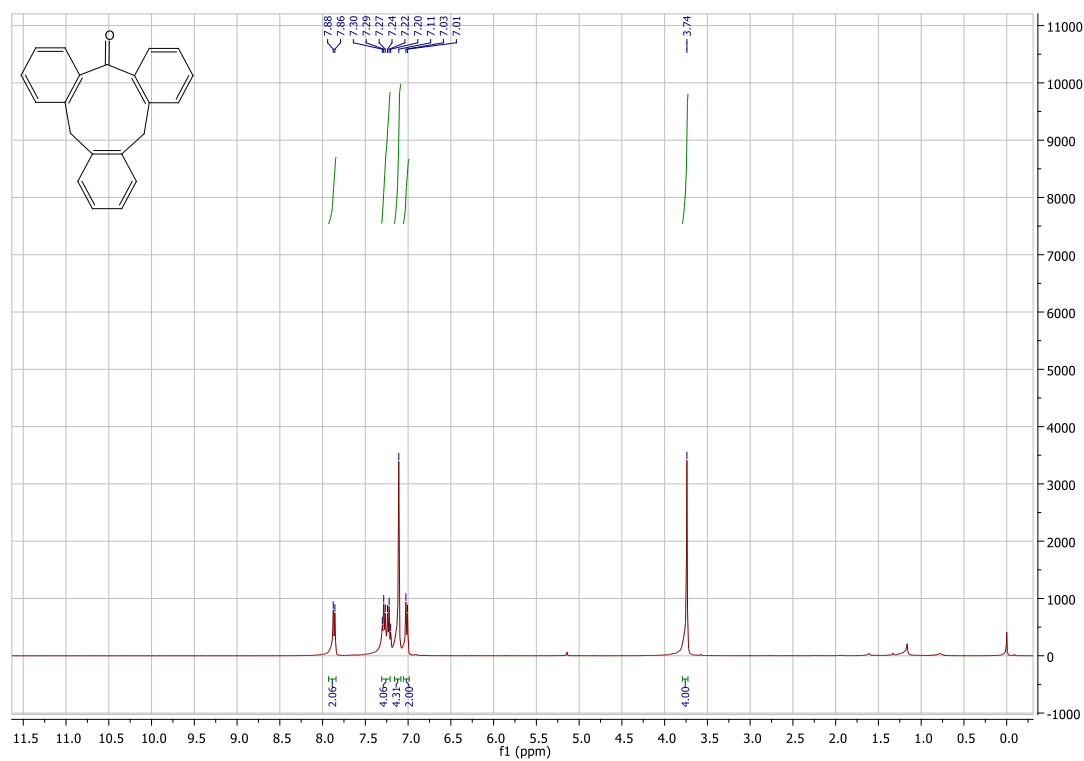


Figure A.9. ¹H-NMR spectrum of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one.

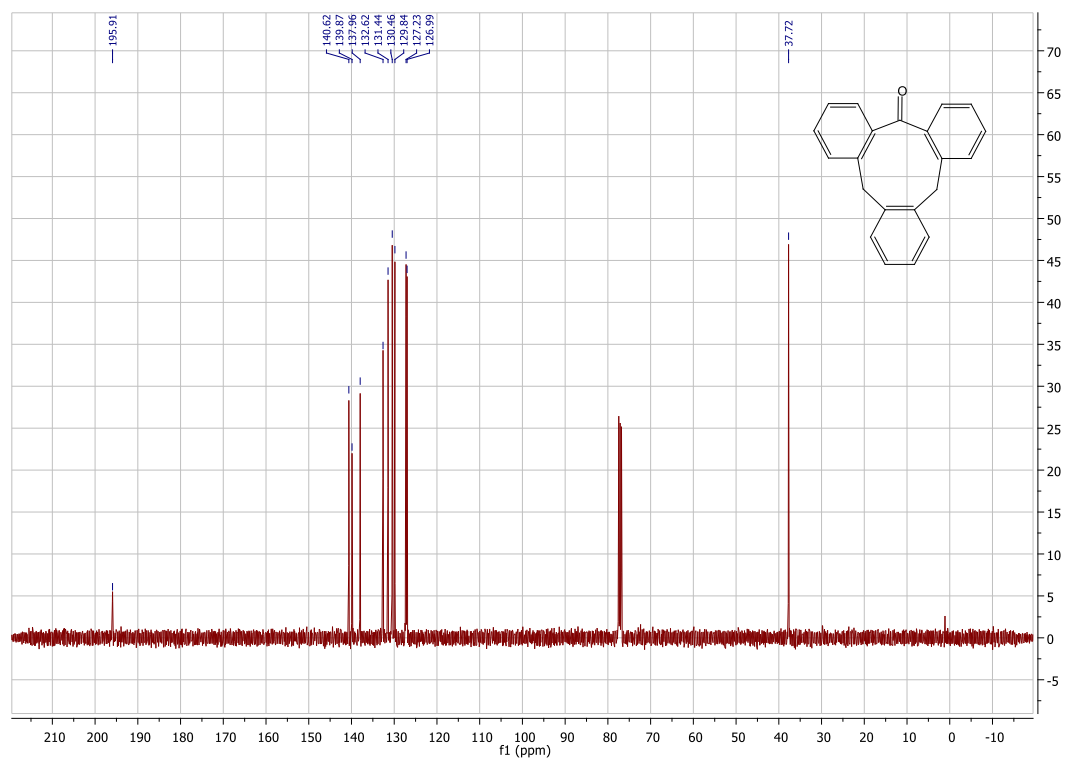


Figure A.10. ¹³C-NMR spectrum of 10,15-dihydro-5*H*-tribenzo[*a,d,g*][9]annulen-5-one.

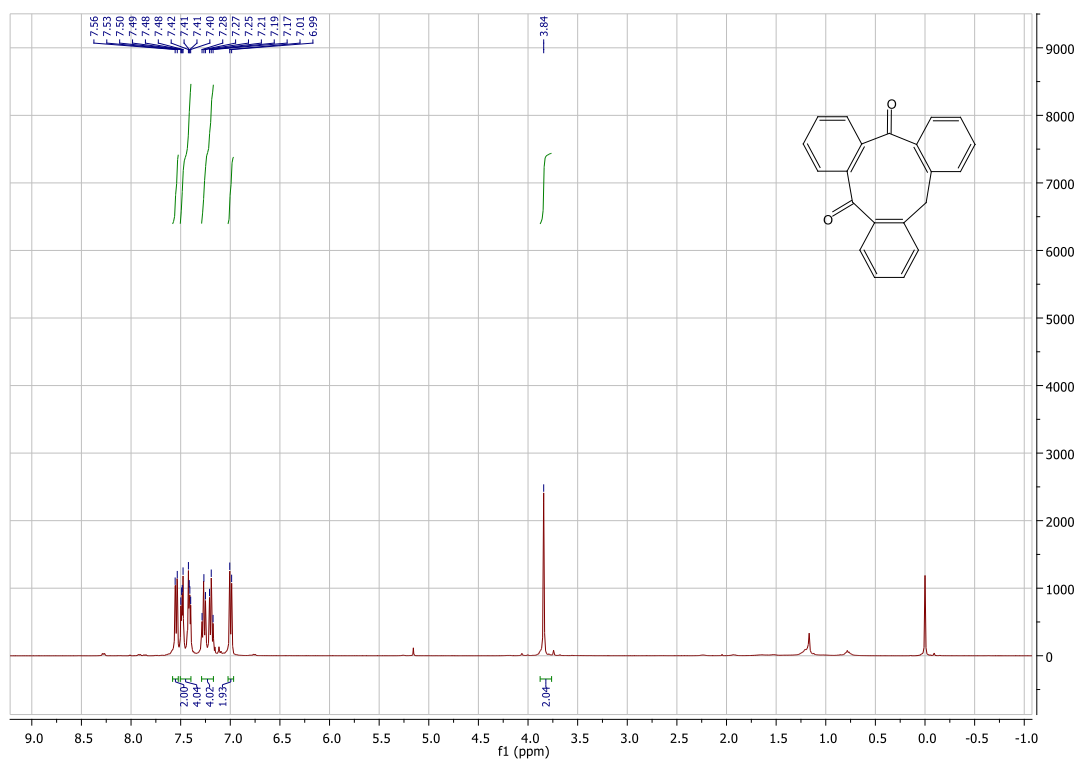


Figure A.11. ¹H-NMR spectrum of 5H-tribenzo[*a,d,g*][9]annulene-5,10(15H)-dione.

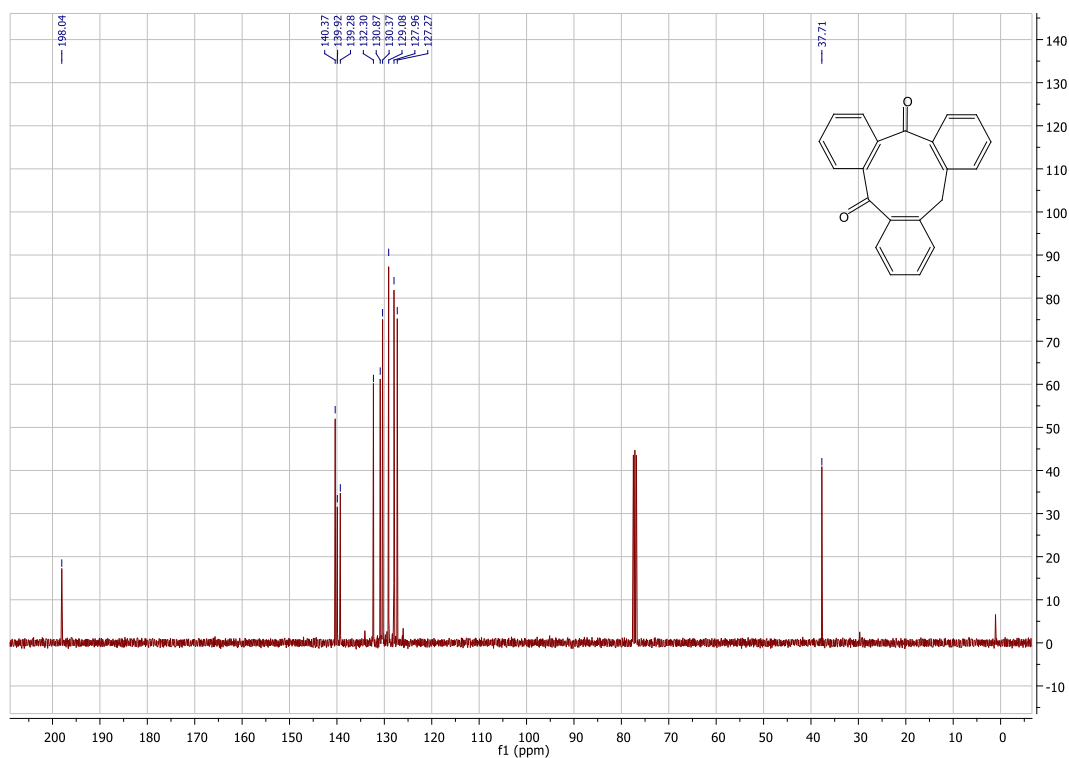


Figure A.12. ¹³C-NMR spectrum of 5H-tribenzo[*a,d,g*][9]annulene-5,10(15H)-dione.

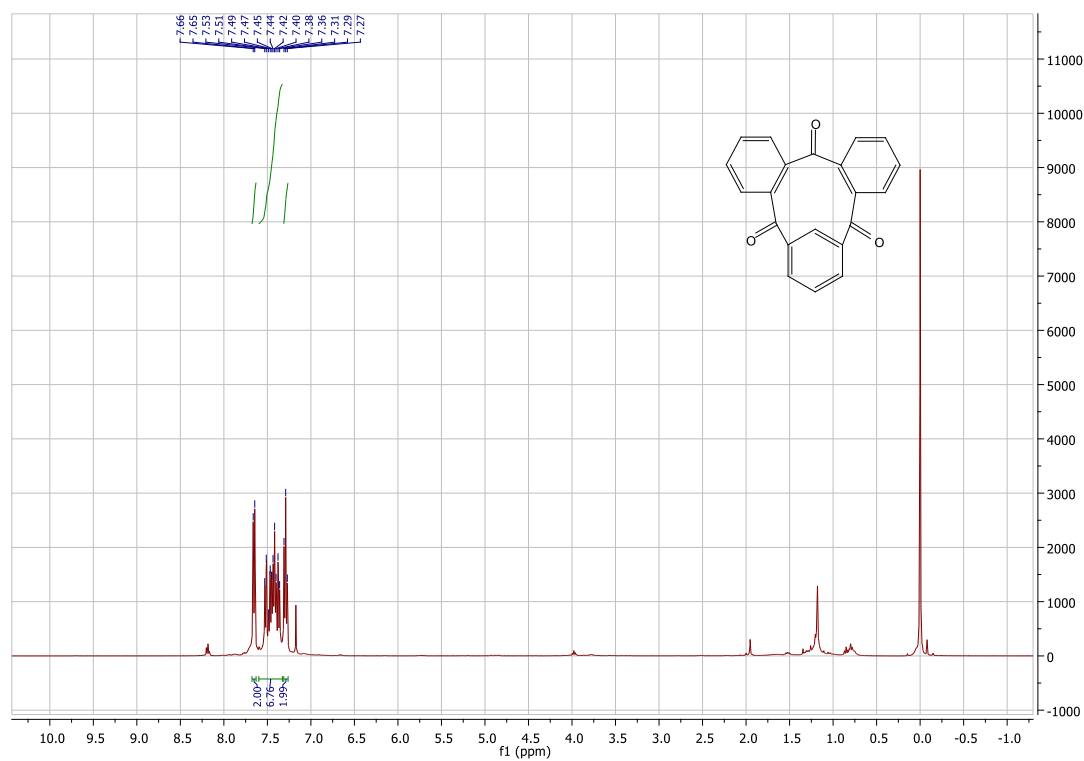


Figure A.13. ¹H-NMR spectrum of 5H-6,10-(metheno)dibenzo[*a,d*][12]annulene-5,11,16-trione.

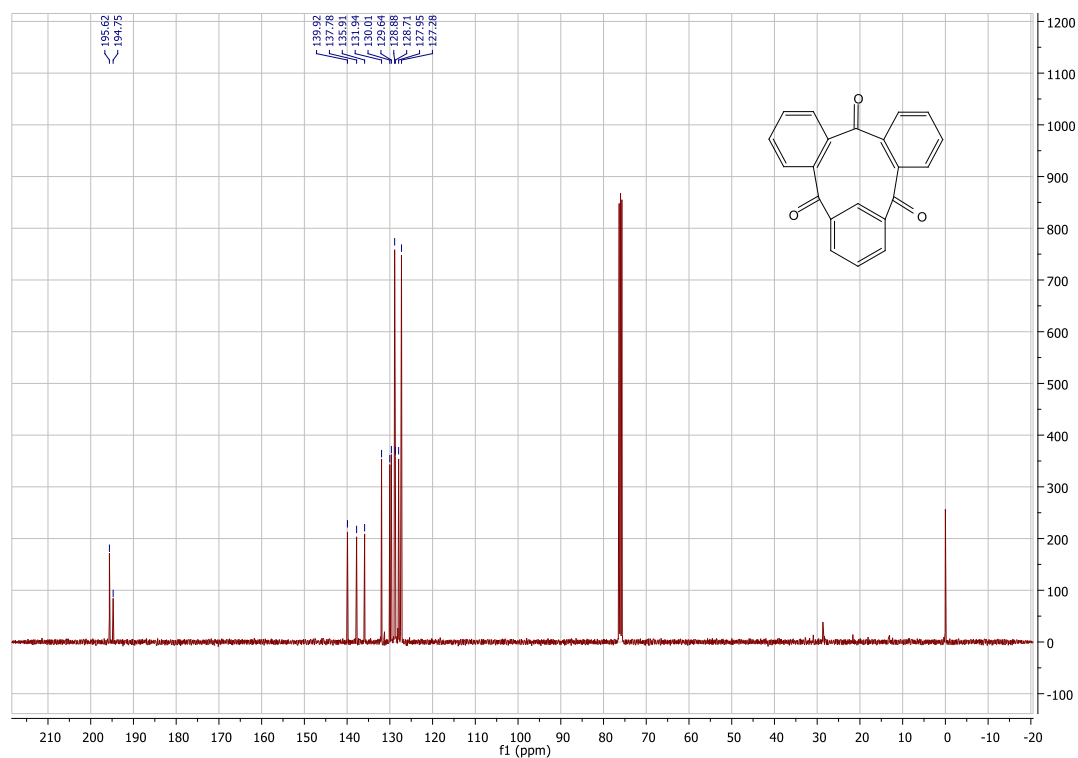


Figure A.14. ¹³C-NMR spectrum of 5H-6,10-(metheno)dibenzo[*a,d*][12]annulene-5,11,16-trione.

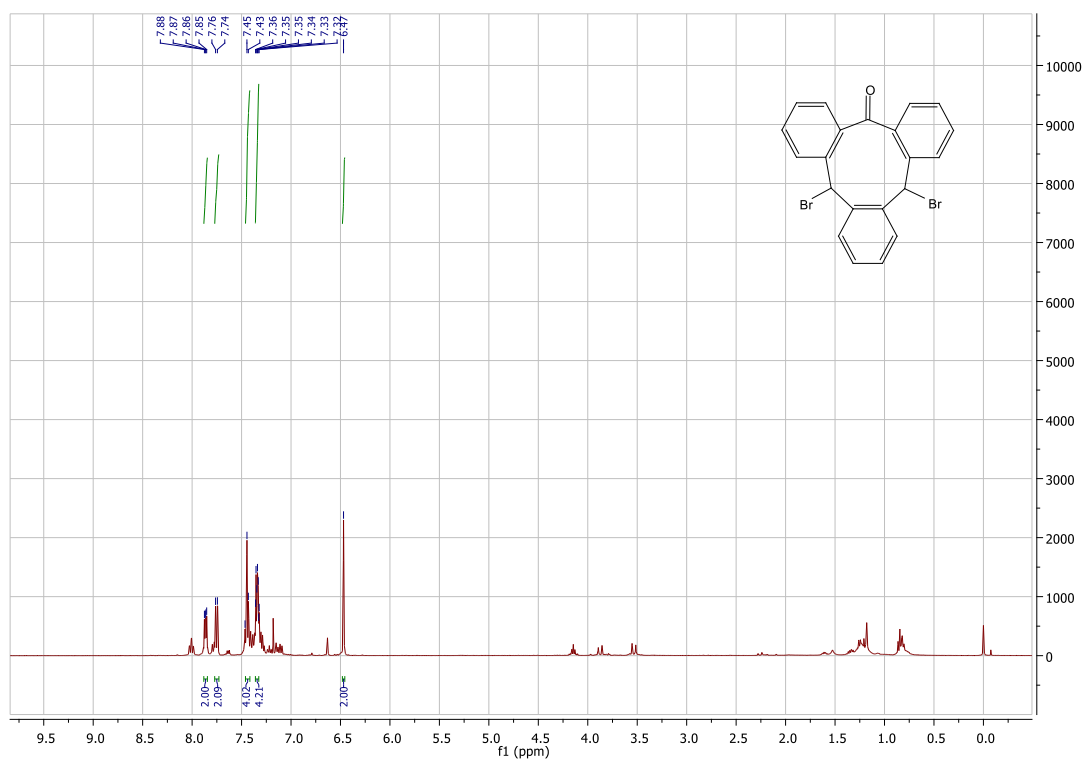


Figure A.15 ¹H-NMR spectrum of 10,15-dibromo-10,15-dihydro-5H-tribenzo[*a,d,g*][9]annulen-5-one.

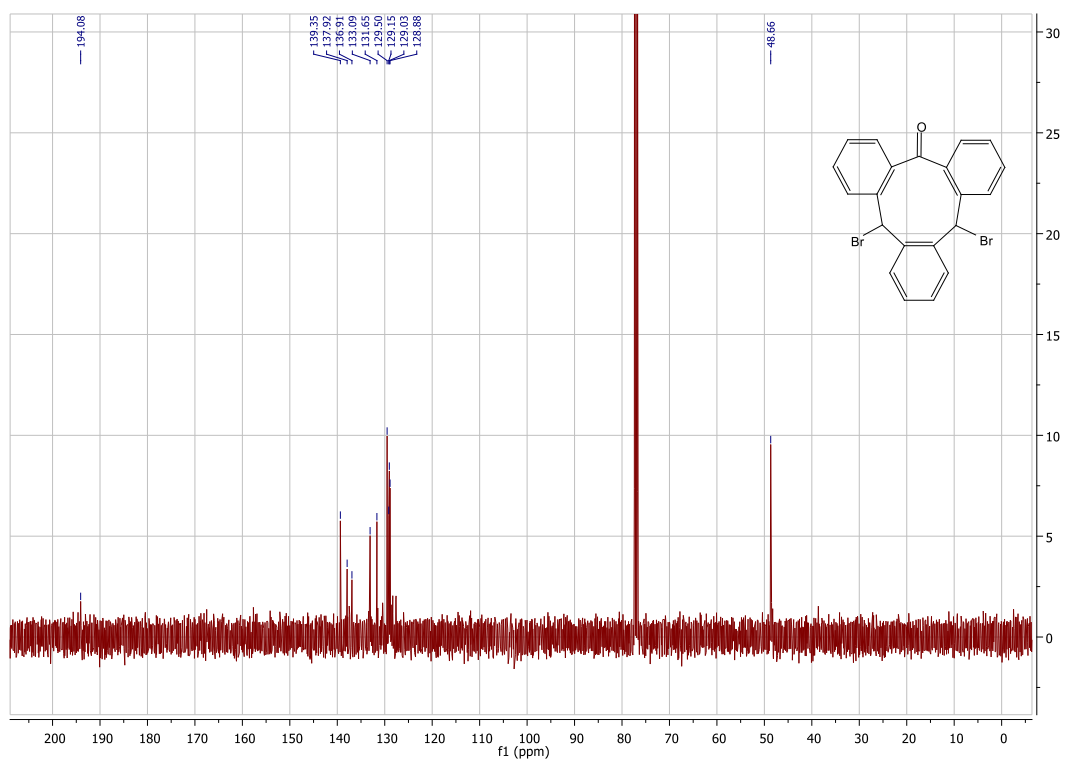


Figure A.16. ¹³C-NMR spectrum of 10,15-dibromo-10,15-dihydro-5H-tribenzo[*a,d,g*][9]annulen-5-one.

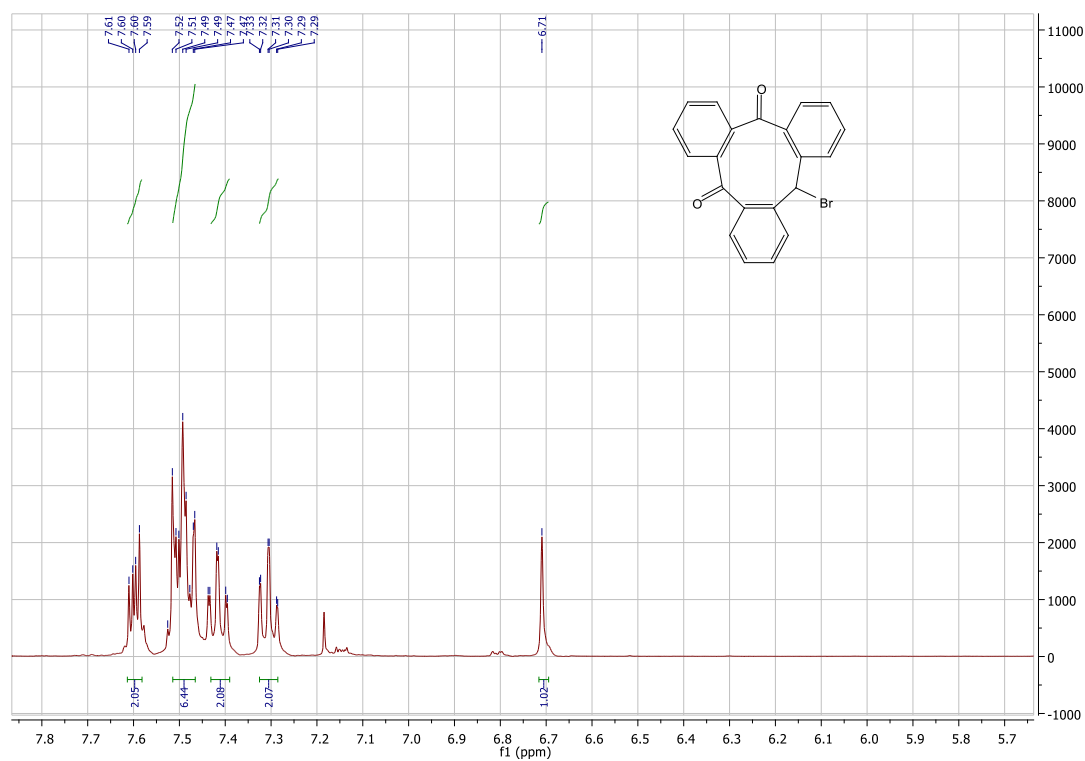


Figure A.17. ¹H-NMR spectrum of 15-bromo-5H-tribenzo[*a,d,g*][9]annulene-5,10(15H)-dione.

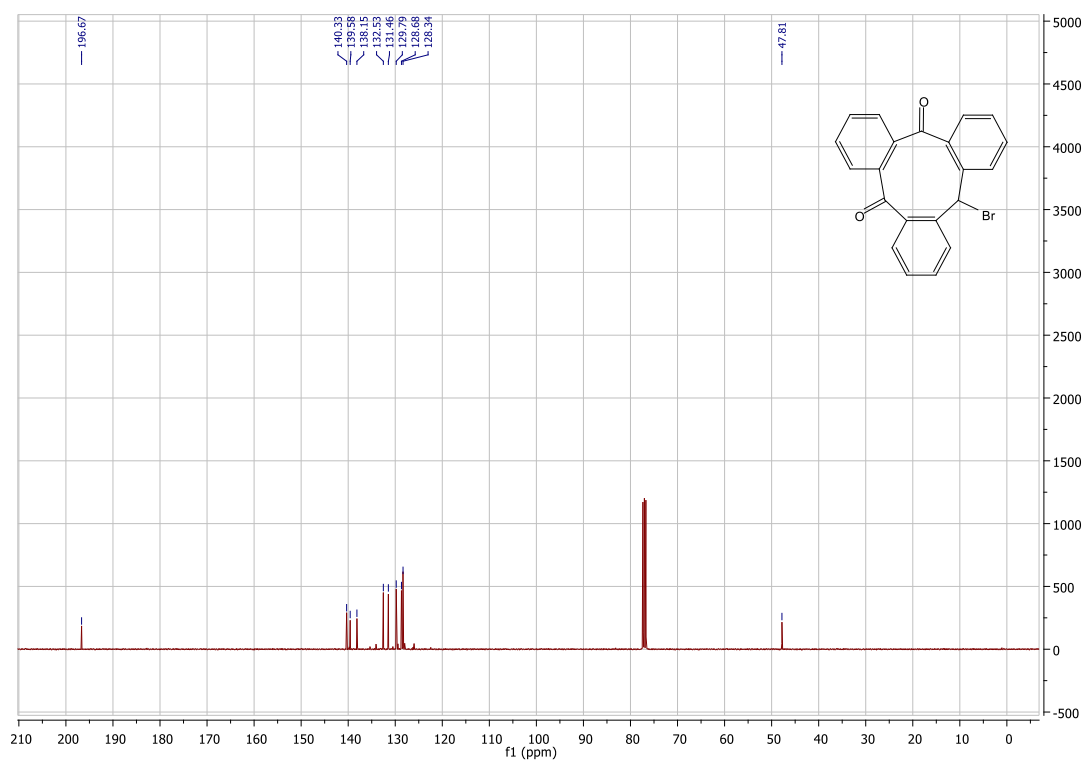


Figure A.18. ¹³C-NMR spectrum of 15-bromo-5H-tribenzo[*a,d,g*][9]annulene-5,10(15H)-dione.

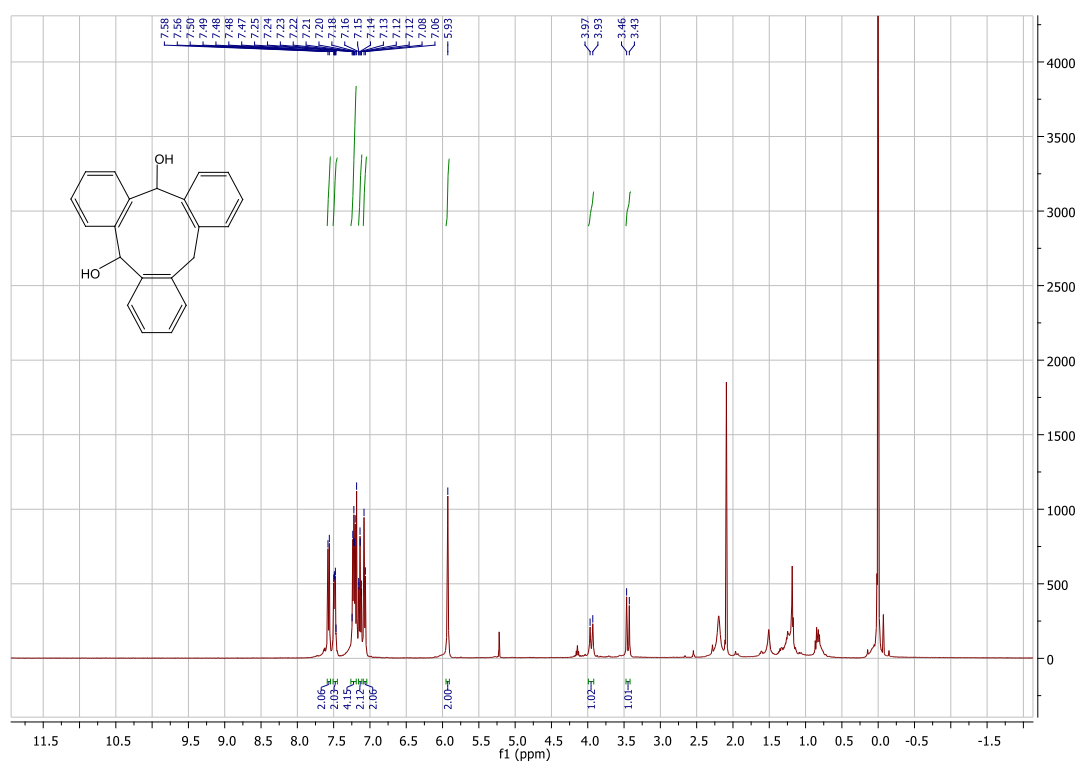


Figure A.19. ¹H-NMR spectrum of 10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-5,10-diol.

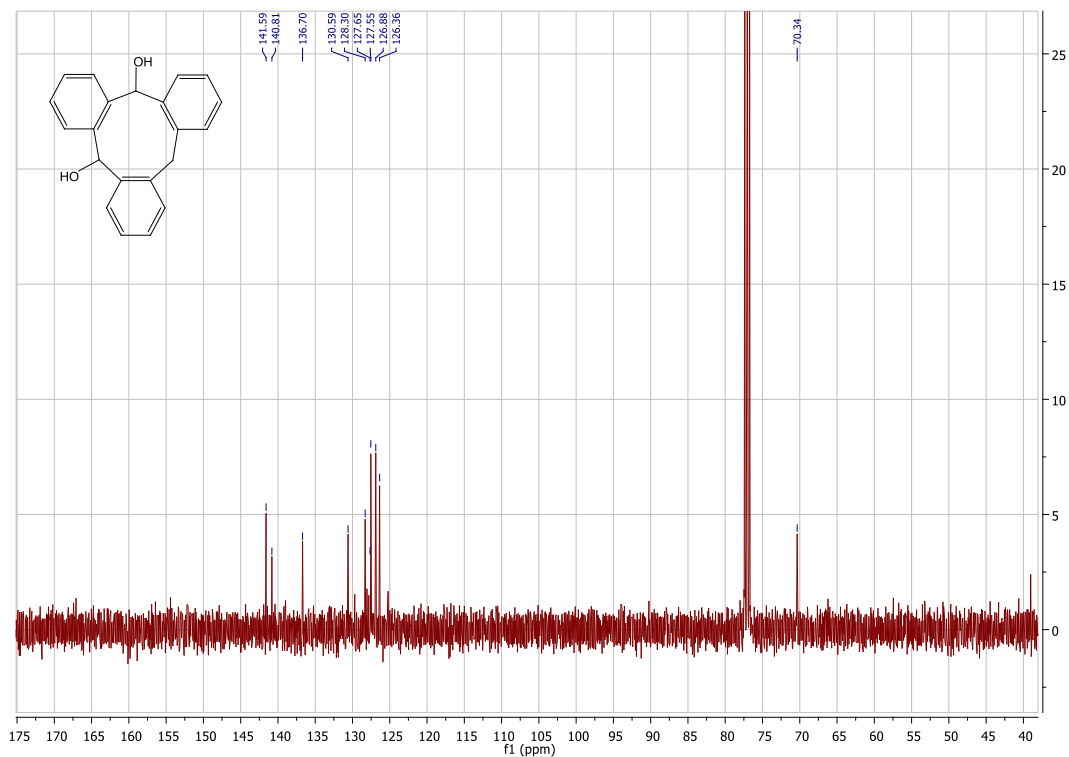


Figure A.20. ¹³C-NMR spectrum of 10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-5,10-diol.

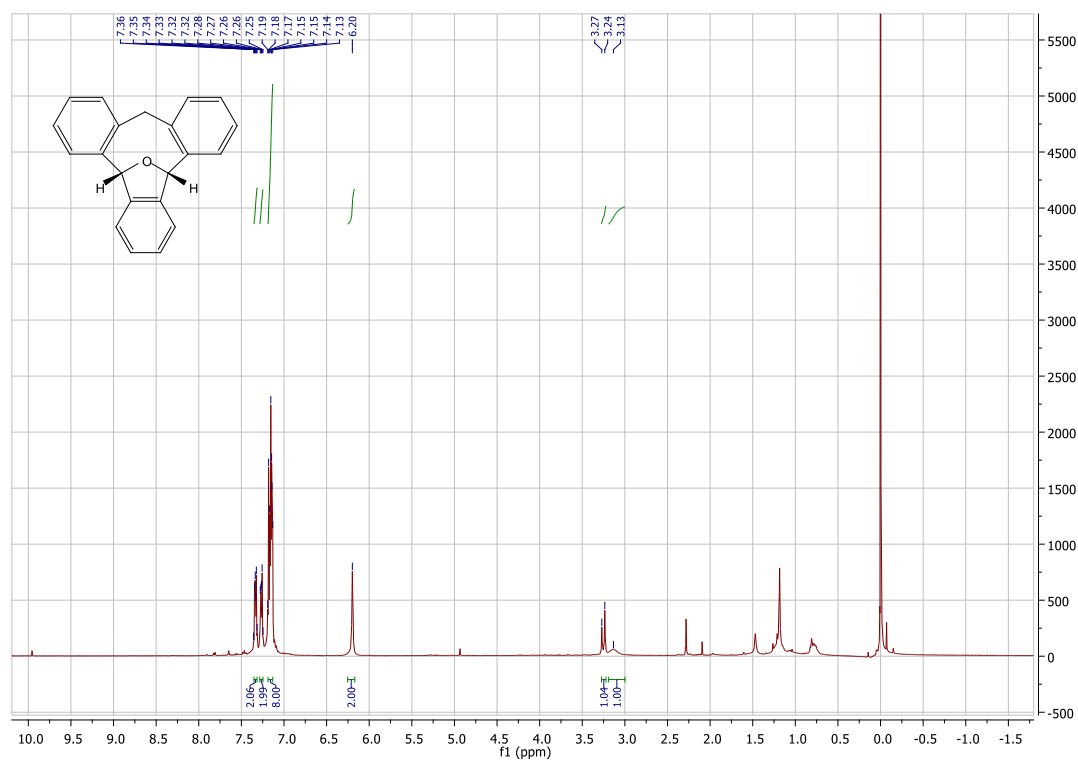


Figure A.21. ¹H-NMR spectrum of (5*R*,10*S*)-10,15-dihydro-5*H*-5,10epoxytribenzo[*a,d,g*][9]annulene..

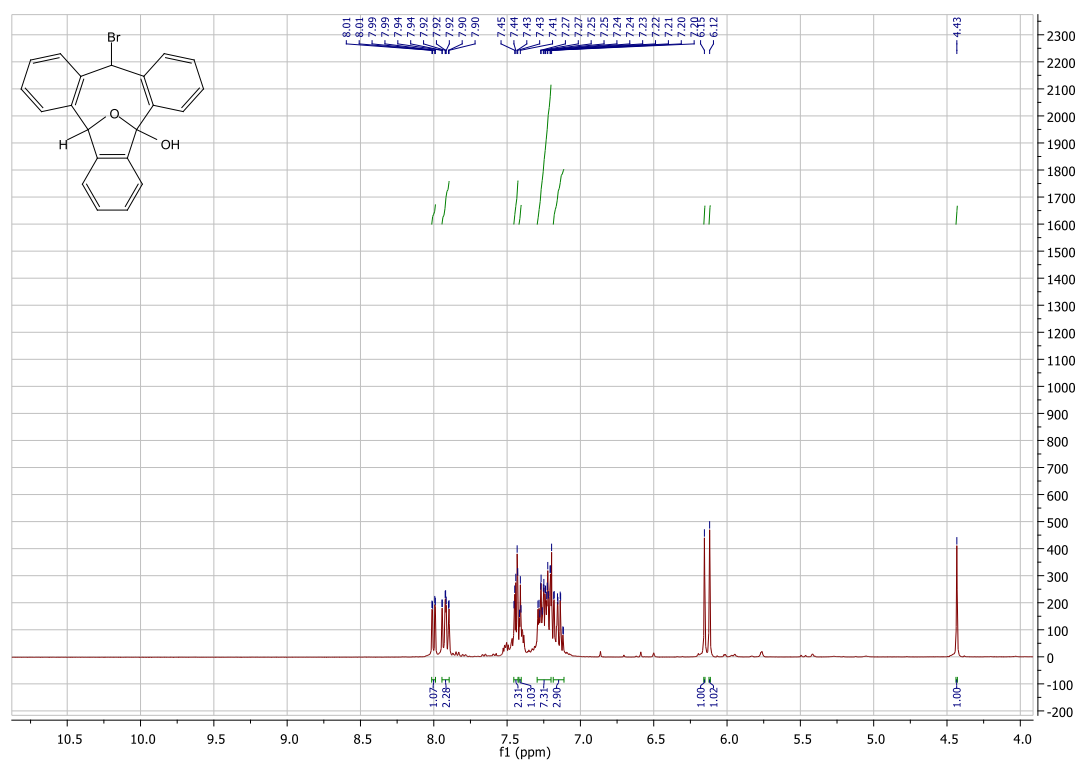


Figure A.22. ¹H-NMR spectrum of 15-bromo-10,15-dihydro-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulene-5-ol.

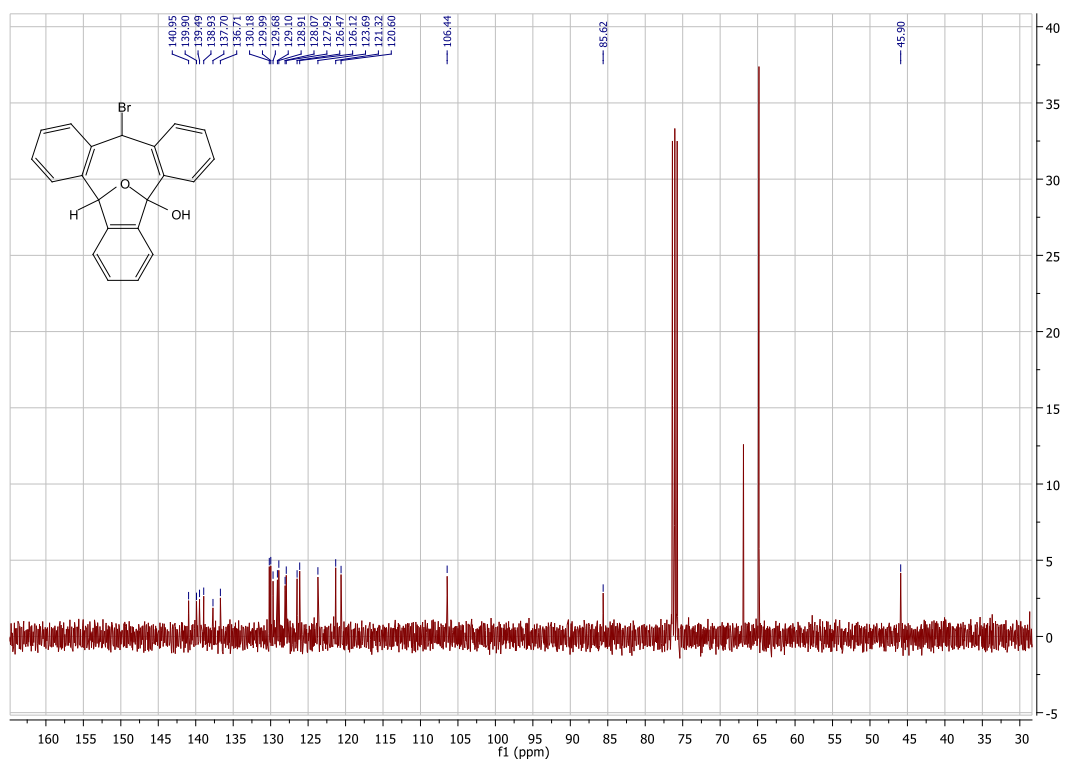
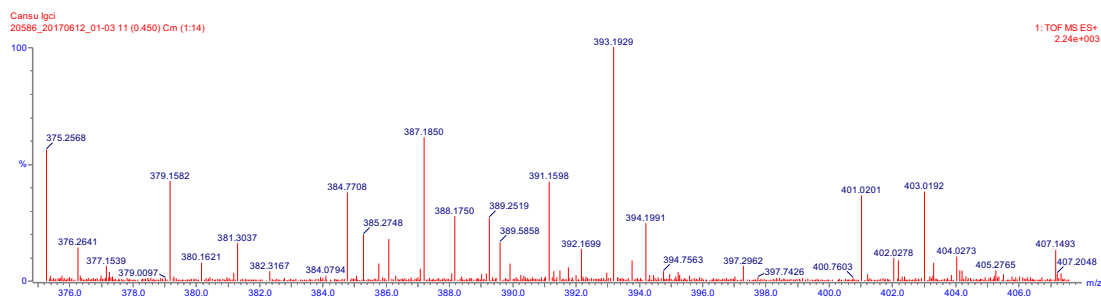


Figure A.23. ^{13}C -NMR spectrum of 15-bromo-10,15-dihydro-5H-5,10-epoxytribenzo[*a,d,g*][9]annulen-5-ol.

APPENDIX B

HRMS DATA



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
403.0192	403.0133	5.9	14.6	13.5	282.9	0.0	C ₂₁ H ₁₅ O ₂ Na ₈₁ Br

Figure B.1. HRMS spectrum of 15-bromo-10,15-dihydro-5*H*-5,10-epoxytribenzo[*a,d,g*][9]annulen-5-ol.