Synthesis & Characterization of Tripyrrine (furan & selenophene) and Conjugated Furan Macrocycles

A thesis submitted towards partial fulfillment of

BS-MS Dual Degree Programme

by

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Certificate

This is to certify that this dissertation entitled **"Synthesis & Characterization of Tripyrrine (furan & selenophene) and Conjugated furan macrocycles"** towards the partial fulfillment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Pune represents original research carried out by **"Manish kumar at IISER, Pune"** under the supervision of **"Dr. V.G. Anand, Department of Chemistry"** during the academic year 2014-2015.

Supervisor: Dr. V. G. Anand

Date: 25-03-2015

Declaration

I hereby declare that the matter embodied in the report entitled **"Synthesis & Characterization of Tripyrrine (furan & selenophene) and Conjugated furan macrocycles"** are the results of the investigations carried out by me at the Department of Chemistry, Indian Institute of Science Education and Research Pune, under the supervision of Dr. V. G. Anand and the same has not been submitted elsewhere for any other degree.

Manish kumar

Date: 25-03-2015

Dedicated to my beloved family.....

Acknowledgements

I would like to take this opportunity to show my sincere gratitude towards my guide Dr. V. G. Anand for giving me this fascinating project to work on and helping me understand and explore the concepts of chemistry in much interesting way. I would also like to thank my TAC member Dr. R. Boomi Shankar.

I would sincerely like to acknowledge the help given by all my lab mates and colleagues whenever I faced an obstacle during my project work. I would like to thank Santosh Gadekar for helping me throughout my research work, Gopalakrishna Yadagiri to help me understand each and everything that I needed to know, Kiran Reddy for helping me get through all problems that I was facing, Santosh Panchal for being a nice lab mate and senior.

Thanks a lot to Dr. Neelam, Rakesh Gaur, Madan, Ashok and Kaushik for all the great time I had in the lab because of you guys.

Thanks to following people;
Swati for MALDI-TOF, Naina for HRMS, Chinmay and Deepali for NMR and all my undergraduate friends for sharing all good and bad memories & helping me get through everything.

And finally I would like to dedicate all this work to my family who are true pillars of my happiness and strength. Thanks.

Contents

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Abstract

Chapter 1 of this thesis deals with the synthesis of tripyrrine molecule, a subclass of modified porphyrin which was taken into consideration as a noble precursor by *Dr. Martin Broering* in *Institut für Anorganische Chemie, Universität Würzburg* to illustrate its importance [1].

The Thiophene tripyrrine molecule has already been synthesized and characterized and the same procedure/ technique were used to produce the tripyrrine molecules with different subunits such as Furan and Selenophene. The diols were synthesized by lithiating the subunits and these diols were further reacted with pyrrole to give the respective tripyrrine molecules as the product. The mass spectra were done either by MALDI-TOF or ESI-TOF spectrometric techniques for identification of the product and the proton NMRs were recorded for confirming the structure of respective molecules.

The tripyrrines have Amine (NH) groups which act as good hydrogen-bond donors hence making it a good molecular candidate for co-crystals with hydrogen-bond accepting molecules.

Chapter 2 of this thesis describe the products of reaction between furan and pentafluoro-benzaldehyde to give 18π or the 36π conjugated macrocycles. The idea was to synthesize a derivative of modified isophlorin (furan) having benzene and furan subunits in which the difuran and phenyl-diol derivative would be reacted in presence of pentafluoro-benzaldehyde and be oxidized with ferric chloride to obtain the desired product, but the isolation was unsuccessful. The mass spectra were recorded through MALDI-TOF spectrometer and the ^{1}HNMR & ^{1}H-^{1}H COSY confirmed the product. Though the final products were not overwhelming, the results encourage further experimentation.

Chapter 1: Synthesis and characterization of Modified Tripyrrine

1.1 Introduction

Porphyrin [1] is a naturally occurring macrocycle found in several enzymes & proteins of different organisms and has been major focus of research interest mainly due to the π electronic system. These are heterocyclic macrocycles consisting of four pyrrole subunits linked with four methine bridges (=CH-) (figure 1.1).

The macrocyclic cavity of porphyrins can be used for host-guest complexes in several reactions of supramolecular chemistry [2.] The very idea of its interesting features includes something from medicinal chemistry where Wormald R. Evans J et al. described its application for the photodynamic therapy during molecular degeneration from verteporfins [3].

In addition to the normal porphyrins with N4 units, there have been wider researches based on replacement of these pyrrolic nitrogens with different hetero-atoms known as core-modified porphyrins which provide an attractive aspect to the physiological properties of these compounds. These replacements are majorly based upon group 16 hetero-atoms such as oxygen, sulphur, selenium and tellurium or on phosphorus. These changes in pyrrolic nitrogen with various hetero-atoms have resulted in notable changes in the electronic structures, spectroscopic, physiochemical properties as well as in metal-binding/H-bonding ability [4].

Also these alternations of nitrogen with various hetero-atoms have resulted in being a successful competitive candidate for the photodynamic therapy as in case of water-soluble thiaporphyrins and selenaporphyrins [5].

Dipyrrin and tripyrrin are a subclass of modified porphyrin. Dipyrrin consists of two pyrroles and one meso carbon, where as tripyrrine have three pyrroles & two meso carbons with respect to parent porphyrin framework (figure 1.1).

The various derivatives of tripyrrines can be synthesized by replacing the central pyrrolic nitrogen with hetero-atoms such as O, P, S, Se, Te etc.
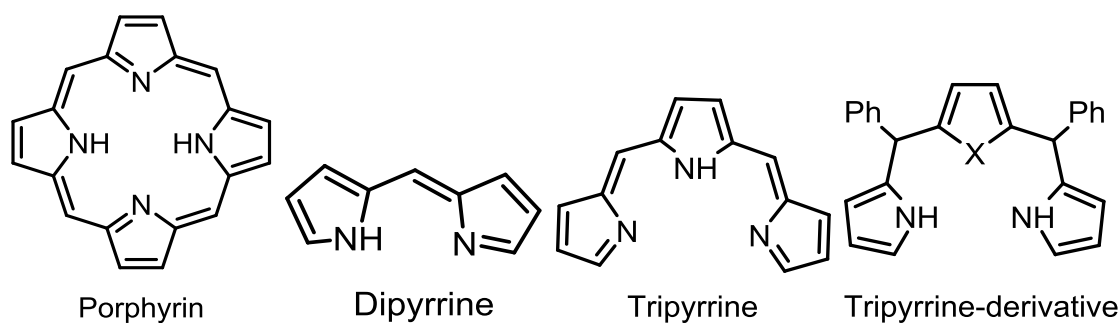
Figure 1.1 Chemical structures of Porphyrin, Dipyrrine, Tripyrrine and its derivative

Although tripyrrine molecule was illustrated by *Dr. Martin Broering* in 2001 but Sessler *et al* in 1996 did produce tripyrrane and subjected it to oxidizing conditions to observe an unexpected formation of tripyrrinone-Cu (II) complex [6]. After that, many groups experimented around the modified subclasses i.e. tripyrrine derivatives for synthesizing core-modified expanded porphyrins, core modified porphyrinogens [7] [8] with different substituent at the meso-positions but not many studies have been done exclusively on tripyrrines and its derivatives. The experiments carried were majorly contributed from Dr. Grazynski and co-workers such as different metals complexes of the core-modified porphyrins [9] as in 1997 oxaporphyrins and dioxaporphyrins were synthesized and complexed with nickel. Similar experiments were carried out by Dr. Chandrashekhar and co-workers for core-modified porphyrins [7] in process of synthesizing sapphyrins and rubyrins containing hetero-atoms such as S, O, Se in addition to the pyrrole nitrogens. These structures showed planarity of small deviation resulting from different hydrogen bondings.

Very recently, the different derivatives of tripyrrine and its subclasses have been described by Uno and co-workers synthesizing triphyrins and thia-tryphyrins [10] where the core-modification of porphyrins was utilized. The unique reactivity along with structural and optical properties were discussed and the modified structure was shown to be aiding in tuning the electronic properties of the macrocycle.

In 2011, carboxylate group functionalized oxaporphyrins and its zinc complex were studied by C.H.Hung and coworkers [11] where a series of new modified porphyrins were synthesized from furan diol and aldehyde reactions. These isolated derivatives are said be an important discovery as it can be used in research related to energy as well as in biology.

Chauhan and co-workers [8] have described Porphyrinogens (calixpyrroles), as a class of tetrapyrrolic macrocycles having the four pyrrole rings are linked through

meso-carbon atoms. The selenium and tellurium N_2Te_2, N_2Se_2, N_3Te and N_3Se meso-unsubstituted core-modified porphyrinogens and N_2Te_2, N_2Se_2, N_2TeSe meso-substituted core-modified porphyrinogens were synthesized for the first time. In contrast to vast interest on core-modification of porphyrins, the role of tripyrrins is not well explored as a synthon for suparmolecular chemistry. The pyrrole rings can act as good h-bond acceptors with suitable hosts. So in this project the role of core-modification and its effects on non-covalent interactions will be described.

1.2 Synthesis, Results & Discussion

The thia-tripyrrine molecule has already been synthesized in our group [12] and was reacted with different solvents. The idea behind the reaction with different solvents was to dissolve the molecule as well as to co-crystallize them with amine groups of thia-tripyrrine through hydrogen bonding. The same reaction was reproduced and characterized in order to understand the concept in more depth, and hence was applied during synthesis of furan-tripyrrine and selenophene-tripyrrine.

Thiophene **1** was lithiated with n-BuLi to give lithiated solution **2** which was further reacted with benzaldehyde to give the diol **3**. Then the thiophenediol **3** was reacted to pyrrole (excess) in the acidic condition to give thiatripyrrine **4** (figure 1.2) in good yield and was confirmed through ^{1}H NMR and mass spectra**.**
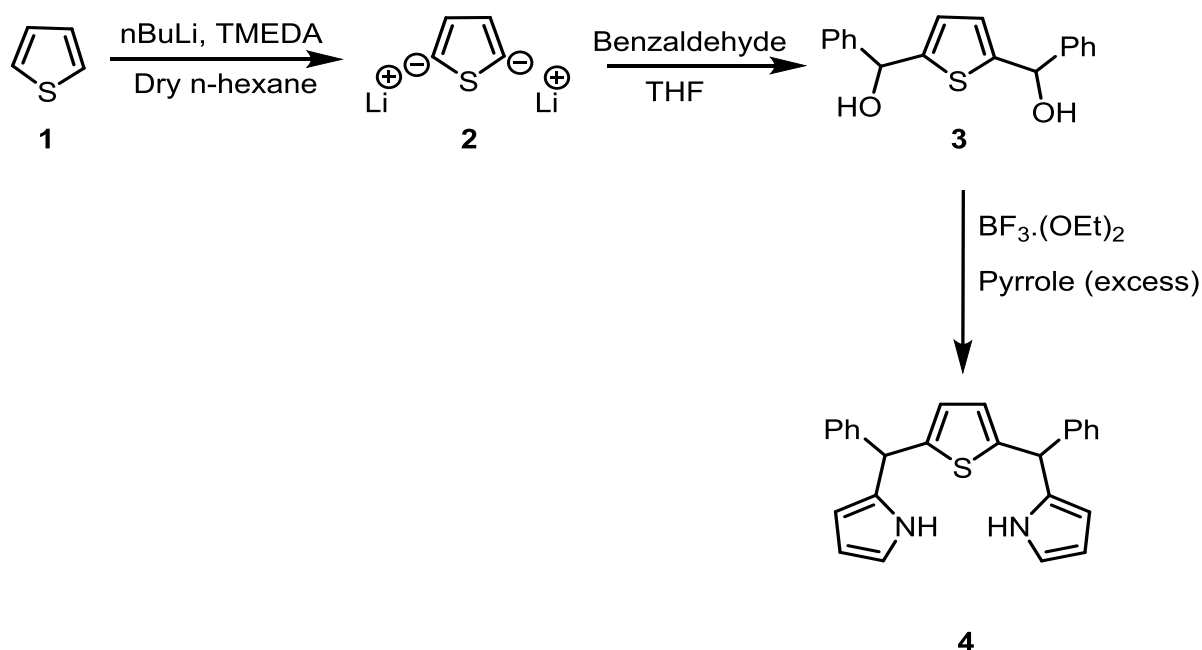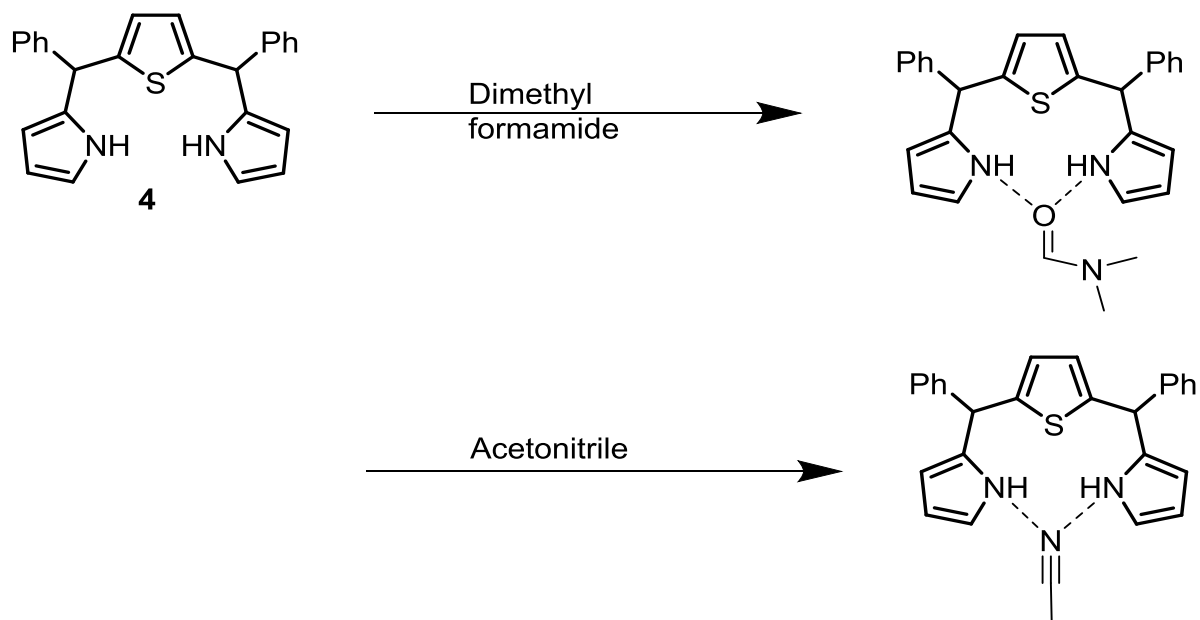

Figure 1.2 Synthetic scheme of Thiatripyrrine (4)

Co-crystals were grown by dissolving the tripyrrine into the solvent and, passing the resulting solution through the syringe or cannula leading to immediate formation of co-crystals suitable enough for single crystal X-ray diffraction.

Figure 1.3 Synthetic schemes of Thiatripyrrine-solvent Co-crystals

The tripyrrine with DMF co-crystals were later oxidized in presence of Fecl$_3$ to synthesize modified expanded porphyrin molecule named Rubyrin. But the reaction was unsuccessful as monitored through MALDI-TOF mass analysis and UV spectra.

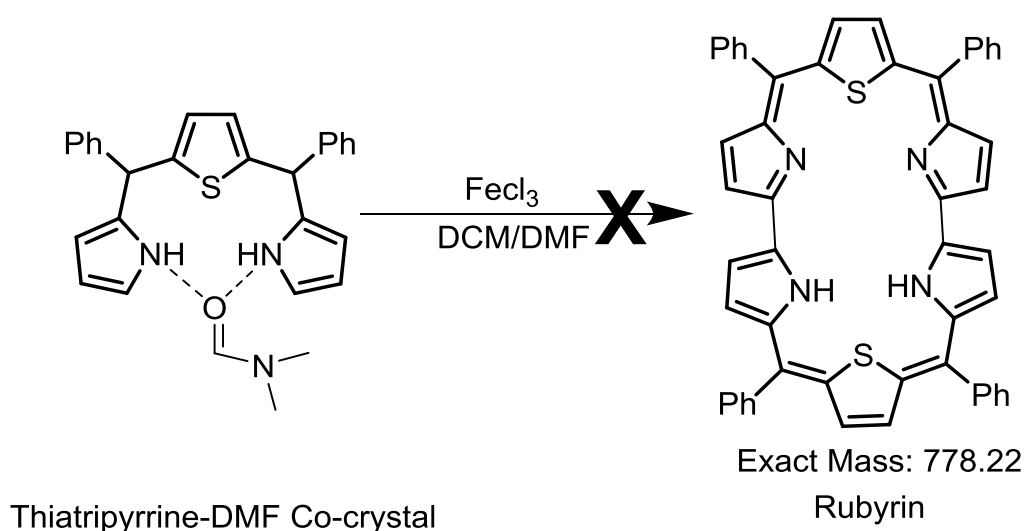Thiatripyrrine-DMF Co-crystal

Exact Mass: 778.22
Rubyrin

Figure 1.4 Proposed synthetic scheme of Rubyrin

In one set of reactions, the thiatripyrrine-DMF Co-crystal (50 mg) was dissolved in DMF (50 ml) and the oxidising agent ($FeCl_3$) was added to it. In the other set of reactions, the Co-crystal (100 mg) was dissolved in dichloromethane (100 ml) and the oxidising agent ($FeCl_3$) was added. The m/z value obtained from the product of first reaction was 393.21 and from the second reaction, it was 649.28 which were nowhere near to the expected value of 778.22, so it was not pursued further.

The main objective of this reaction was since the two pyrroles in the thiatripyrrine molecule are not in the same plane and orientation; so the formation of co-crystals where the solvent molecule is bonded with tripyrrine will bring out the planarity into the complex and hence the product yield would be much greater compared to what already has been reported. However the reaction was found to be unsuccessful probably due to the steric hindrance upon binding DMF through pyrrole rings.

The synthesis of thiatripyrrine and its co-crystals were used as the basis for synthesizing furan-tripyrrine and selenophene-tripyrrine. The furan **5** was lithiated with n-BuLi to give lithiated solution **6** which was further reacted with benzaldehyde to give the diol **7**. The furan-diol **7** was reacted to pyrrole (excess) in the acidic condition to give furan-tripyrrine **8** in good yield as described in figure 1.5 and confirmed through ^{1}H NMR and Mass spectra.
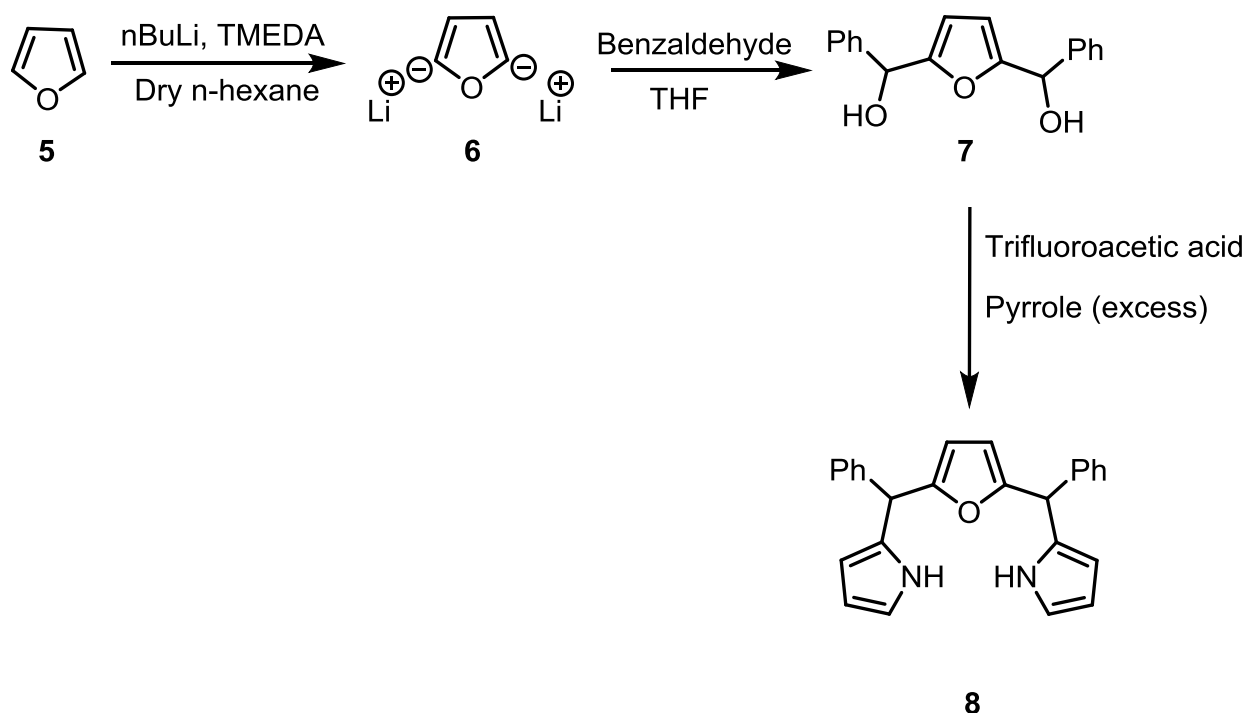

Figure 1.5 Synthetic scheme of Furan-tripyrrine (8)

And the proposed synthetic scheme (figure 1.6) for growing co-crystals of furan-tripyrrine with different solvents was same as for the thiatripyrrine molecule. The tripyrrine molecule was taken in a 5 ml one neck round bottomed flask and dissolved in DMF under inert atmosphere. The dissolved compound was kept undisturbed for few hours and then little amount of the dissolved mixture was taken out through a 1 ml syringe. The mixture was taken out of the RB and then injected back into the original mixture after color change. But the results were not successful as no crystals were observed after going through the same procedure. The reaction was repeated with different set of conditions to the get the desired result, such as change in molar concentrations, reaction conditions etc. but the results weren't productive as for thiophene derivative.
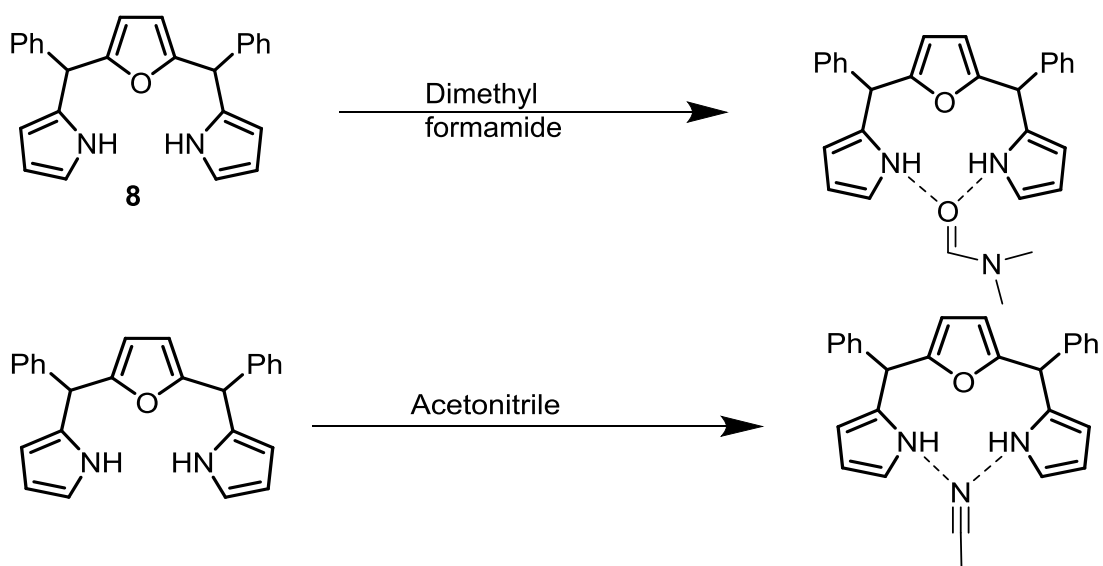

Figure1.6 Proposed Synthetic schemes of Furan-tripyrrine - solvent Co-crystals

Some of the noticeable repetitions and changes in condition for the getting the desired result were:

a) Compound was dissolved in minimum solvent to make it concentrated. Then it was sonificated and the expected changes were monitored i.e. change in color from yellow to black.

b) The compound was dissolved in minimum amount of solvent and another solvent (immiscible) layered on top of it to recrystallize, but no crystals were formed.

c) Compound was dissolved in minimum of solvent and transferred into a vial and the small vial was kept in much bigger vial with non-miscible solvent for vapor interactions to occur but no visible result were found.

So the next set of reactions was carried out with selenophene, keeping in mind that this molecule has very similar properties to thiophene. Selenophene **9** was lithiated with n-BuLi to give lithiated solution **10** which was further reacted with benzaldehyde to give the diol **11**. Then the Selenophene-diol **11** was reacted with pyrrole (excess) in the acidic condition to give Selenophene-tripyrrine **12** and confirmed through 1-H NMR and Mass spectra**s.**
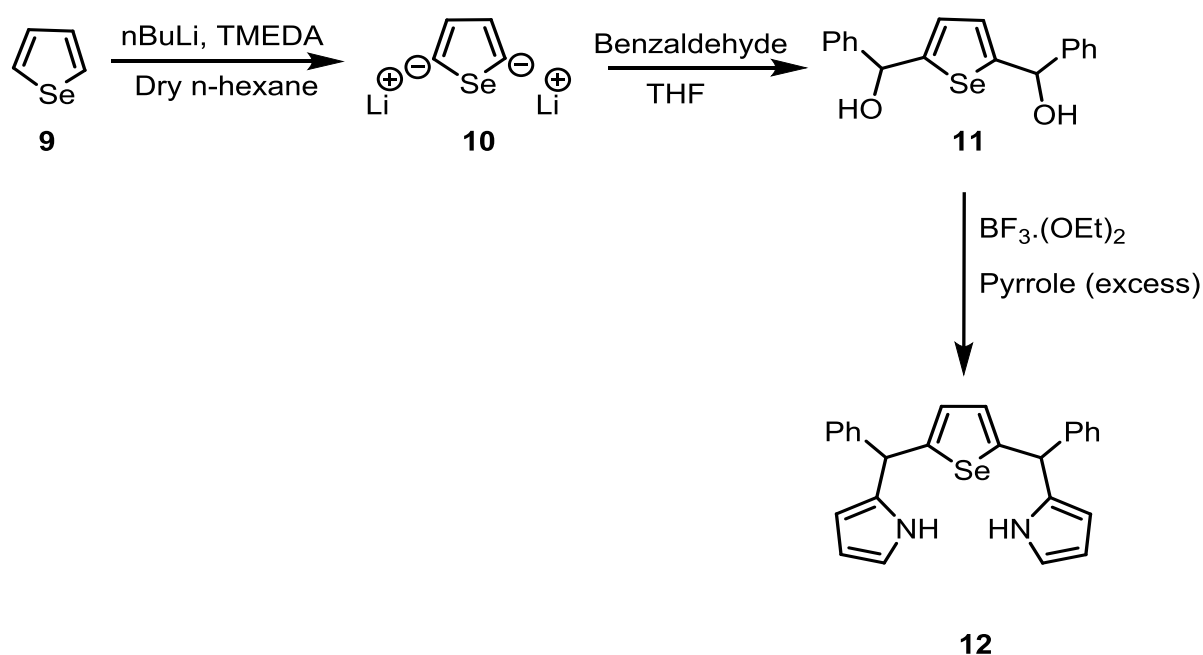

Figure 1.7 Synthetic scheme of Selenophene-tripyrrine (12)

Again, the proposed synthetic scheme for growing co-crystals of selenophene-tripyrrine with different solvents was same, as for the thiatripyrrine molecule. But the results could not be reproduced in this case too even though repeated for many times with different set of conditions and concentrations.

The set conditions and parameters mentioned for the furan tripyrrine were tried exactly for the selenophene-tripyrrine too, during the repetitions of this reaction (figure 1.8) but none of them were successful in providing the desired product.
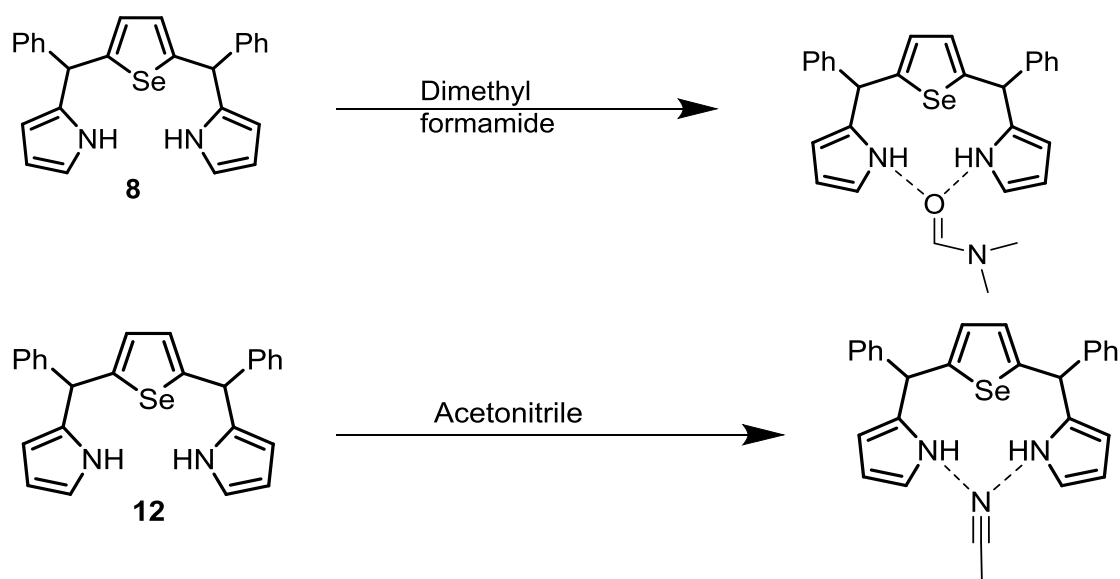
Figure 1.8 Proposed Synthetic schemes of Selenophene-tripyrrine-solvent Co-crystals

The most plausible reason that could be given for unsuccessful synthesis of selenophene co-crystals is that even though the selenophene has very similar properties compared to thiophene, the steric hindrance of selenium could have prevented the formation of co-crystals.

1.3 Summary

In this chapter, we have synthesized, characterized and featured tripyrrine molecules with different hetero-atoms in solid as well as solution state and attempted to reproduce the co-crystals as reported for thiatripyrrine. We also employed thiatripyrrine co-crystal to synthesize rubyrin in greater yield. Although, the final results were not as successful as hoped to be but were promising enough to continue much more research in this field. The successful results could have been used for much greater purpose such as CO_2 trapping etc.

1.4 Experimental Methods and Techniques

1.4.1 Chemicals used for Synthesis:

Normal solvent used for synthesis were purified and dried according to known procedures. Thiophene, pyrrole, Furan and benzaldehyde were distilled before use. TMEDA, $BF_3.(OEt)_2$,Selenophenewere used from Aldrich chemicals, USA. n-Butyllithium (1.6M in hexane) and $FeCl_3$ were used from E. Merck, Germany. Pyrrole, Furan, Benzaldehyde, TFA were used from Spectrochem chemicals, India. Thiophene and anhydrous sodium sulphate were obtained from Rankem Fine chemicals, India.

1.4.2 Spectral characterization techniques

Electronic spectra were recorded on a Perkin Elmer-Lambda 20 UV-Vis spectrophotometer. The data analyses were done using the UV-winlab software package. ^{1}H-NMR spectra were obtained either from 500 MHz Bruker Advance DPX spectrometer or 400 MHz Jeol machine in $CDCl_3$ using tetramethylsilane (TMS) as integral standard. ESI HRMS data were recorded on Waters Synapt G2 spectrometer. MALDI-TOF was carried out on Voyager-De-STR (Applied Biosystems).

1.4.3 Synthesis of Chemical Compounds

Furan-2,5-diylbis(phenylmethanol) (7)

Dry and freshly distilled n-hexane (200 mL) was added to a two-necked, round bottomed flask (500 mL) that was under inert atmosphere for 10 min. A solution of n-BuLi (78 ml of 1.6M solution in hexane) and tetramethylethylenediamine (TMEDA) (15 ml, 0.100 mol) was added to it under inert atmosphere. Furan (3.63 ml, 3.4 gm, 0.050mol) was added slowly via syringe and the resulting solution was warmed to reflux for 1 hr then cooled to ambient temperature. The lithiated Furan solution was cooled to 0°c in an ice bath and added slowly to a solution of benzaldehyde (11.78 ml, 0.116 mol) indry THF (120 ml).The ice bath was removed and the reaction was allowed to room temperature. The reaction was quenched by a cold, saturated NH_4Cl solution (200 ml) and the organic layer was washed, separated with water, brineand dried over Na_2SO_4. The desired compound was isolated via column chromatography on silica gel eluted with ethyl acetate/hexane (10:90). The product was collected as

white powder (yield: 82%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.25 (m, 10H), δ 5.95-5.94 (d, 2H), δ 5.78 (s, 2H), δ 2.60 (s, 2H).

HRMS: C$_{18}$H$_{16}$O$_3$; 280.109, observed 303.0996 (M+Na)$^+$

2,5-bis(phenyl(1H-pyrrol-2-yl)methyl)furan (8)

Compound **7** (0.56 g, 0.002mol) was taken in a two-necked, round-bottomed flask (100 ml) under inert atmosphere and was dissolved in excess pyrrole (5.54 ml). TFA (0.0154 ml) was added to it and the resulting mixture was allowed to stir for 1 hr. Then the reaction was quenched by the addition of dichloromethane (50 ml) followed by 40% NaOH (15 ml). The Organic layer was separated, washed with water and brine then dried over sodium sulphate. The residual oily solution was purified via chromatography on silica gel eluted with ethyl acetate/hexane (5:95) and the desired product was collected as yellow oil (yield: 84%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96(s, 2H), 7.32- 7.17(m, 10H), 6.63(s, 2H), 6.12(s, 2H), 5.97- 5.91(d, 4H), 5.40(s, 2H).

HRMS: C$_{26}$H$_{22}$N$_2$O; 378.173, observed 379.181 (M+H)$^+$

Selenophene-2,5-diylbis(phenylmethanol) (11)

Dry and freshly distilled n-hexane (80 mL) was added to a two-necked, round-bottomed flask (250 mL) that was under inert atmosphere for 10 min. A solution of n-BuLi (25.44 ml, 0.03816 mol) and tetramethylethylenediamine (TMEDA) (5.74 ml, 0.03816mol) was added to it under inert atmosphere. Selenophene (1.4 ml, 2 gm, 0.152mol) was added slowly via syringe and the resulting solution was warmed to reflux for 1 hr then cooled to ambient temperature. The lithiated Selenophene solution was cooled to 0°c in an ice bath and added slowly to a solution of benzaldehyde (3.86 ml, 0.03816 mol) in dry THF (30 ml). The ice bath was removed and the reaction was allowed to room temperature. The reaction was quenched by a cold, saturated NH$_4$Cl solution (50 ml) and the organic layer was washed, separated with water, brine and dried over Na$_2$SO$_4$. The desired compound was isolated via column chromatography on silica gel eluted with ethyl acetate/hexane (20:80). The product was collected as yellowish white solid (yield: 42%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84-7.11(m, 10H), 6.89(s, 1H), 5.98(s, 1H), 4.73(s, 1H).

HRMS: C$_{18}$H$_{16}$O$_2$Se; 344.031, observed 367.021 (M+Na)$^+$

2,5-bis(phenyl(1H-pyrrol-2-yl)methyl)selenophene (12)

Compound **11** (0.7 g, 0.002 mol) was taken in a two-necked, round-bottomed flask (100 ml) under inert atmosphere and was dissolved in excess pyrrole (5.6 ml, 0.0816 mol). Borontrifluoride-etherate (0.3 ml) was added to it and the resulting mixture was allowed to stir for 1 hr. Then the reaction was quenched by the addition of dichloromethane (100 ml) followed by 40% NaOH (30 ml). The Organic layer was separated, washed with water and brine then dried over sodium sulphate. The dark yellowish residual was purified via chromatography on silica gel eluted with ethyl acetate/hexane (5:95) and the desired product was collected as yellow sticky solid. ^{1}H NMR (400 MHz, DMSO) δ 10.70(s, 1H), 7.79-7.17(m, 10H), 6.71-6.68(t, 2H), 6.62(s, 1H), 5.97-5.76(m, 1H), 5.20-5.17(t, 1H), 4.52-4.50(d, 1H)

HRMS: $C_{26}H_{22}N_2Se$; 442.094, observed 443.102 $(M+H)^+$

1.5 Characterization spectral data

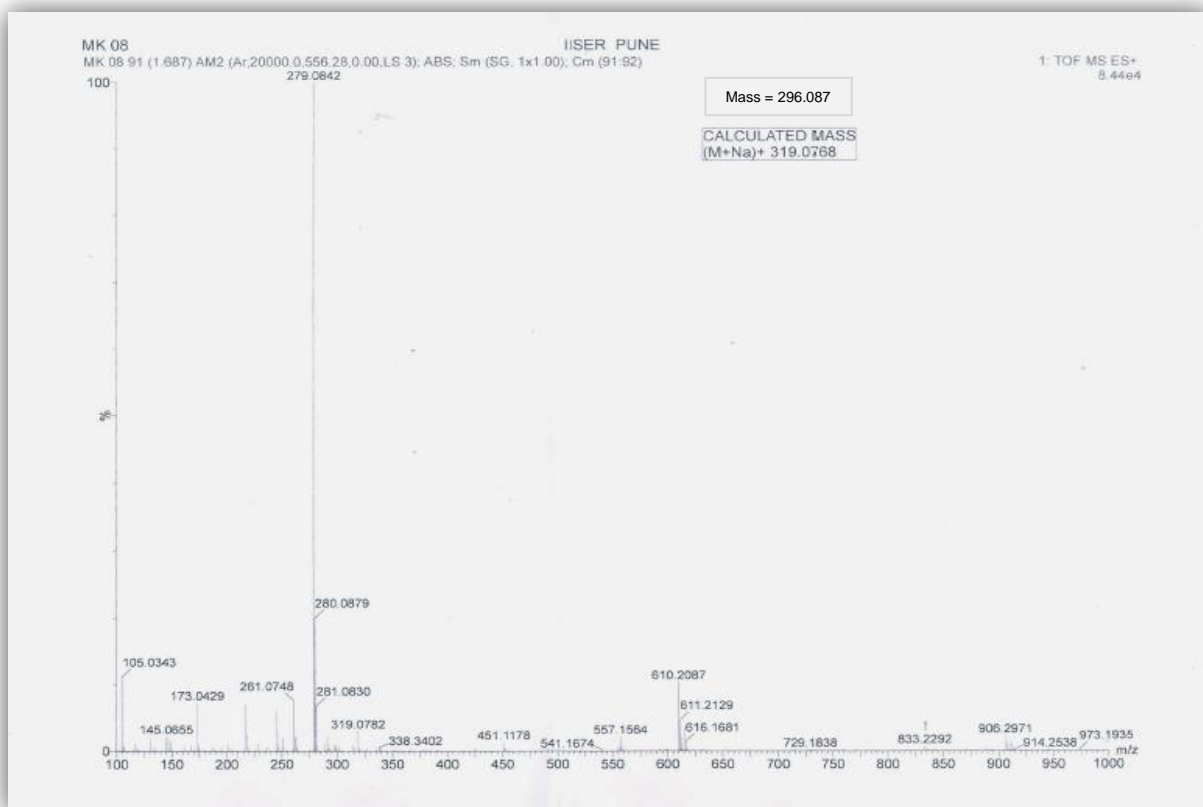**Figure 1.9 ^{1}H NMR and Mass spectra of Thiophene Diol (3)**
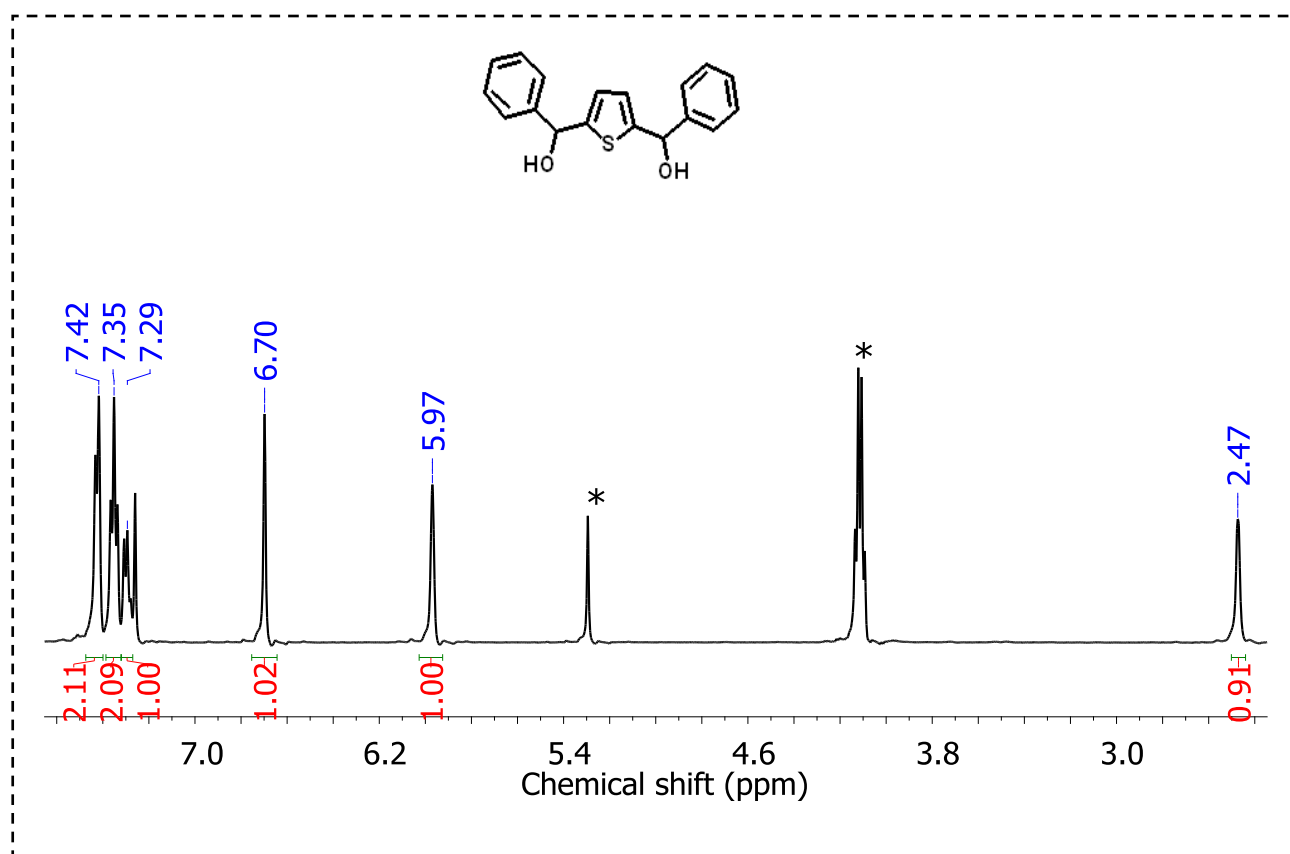
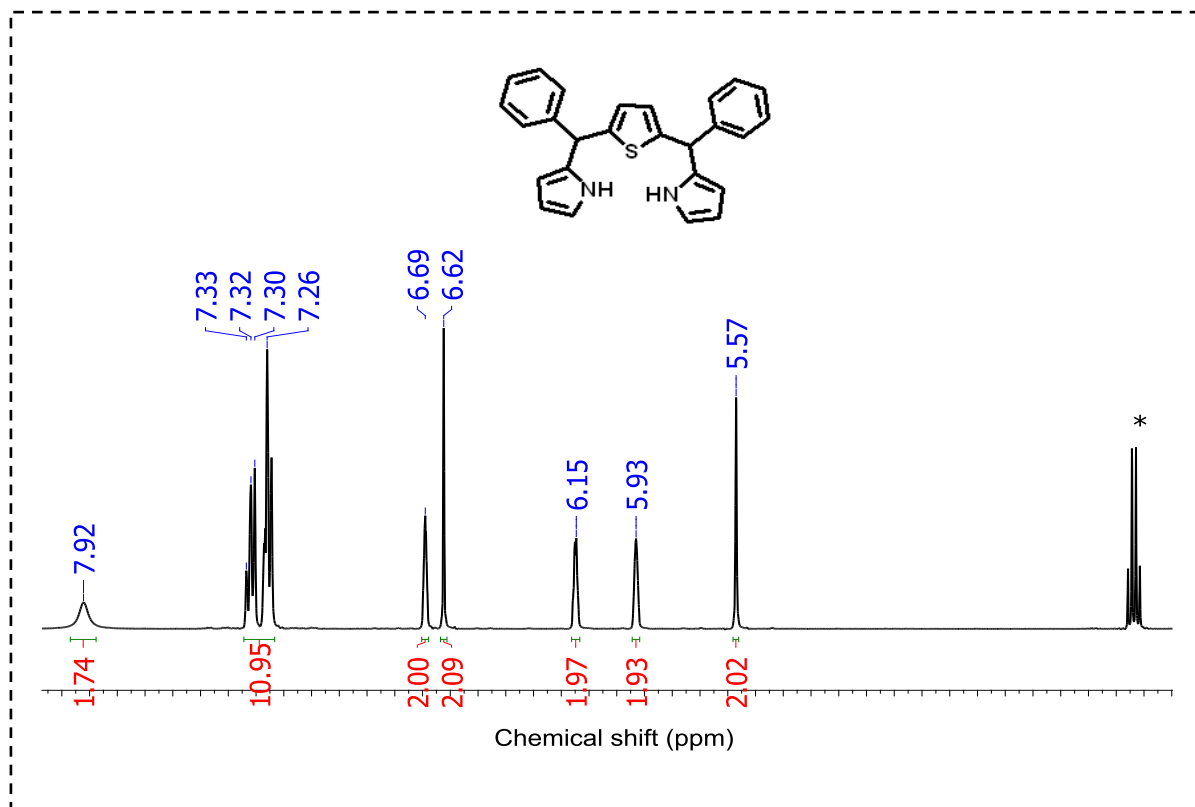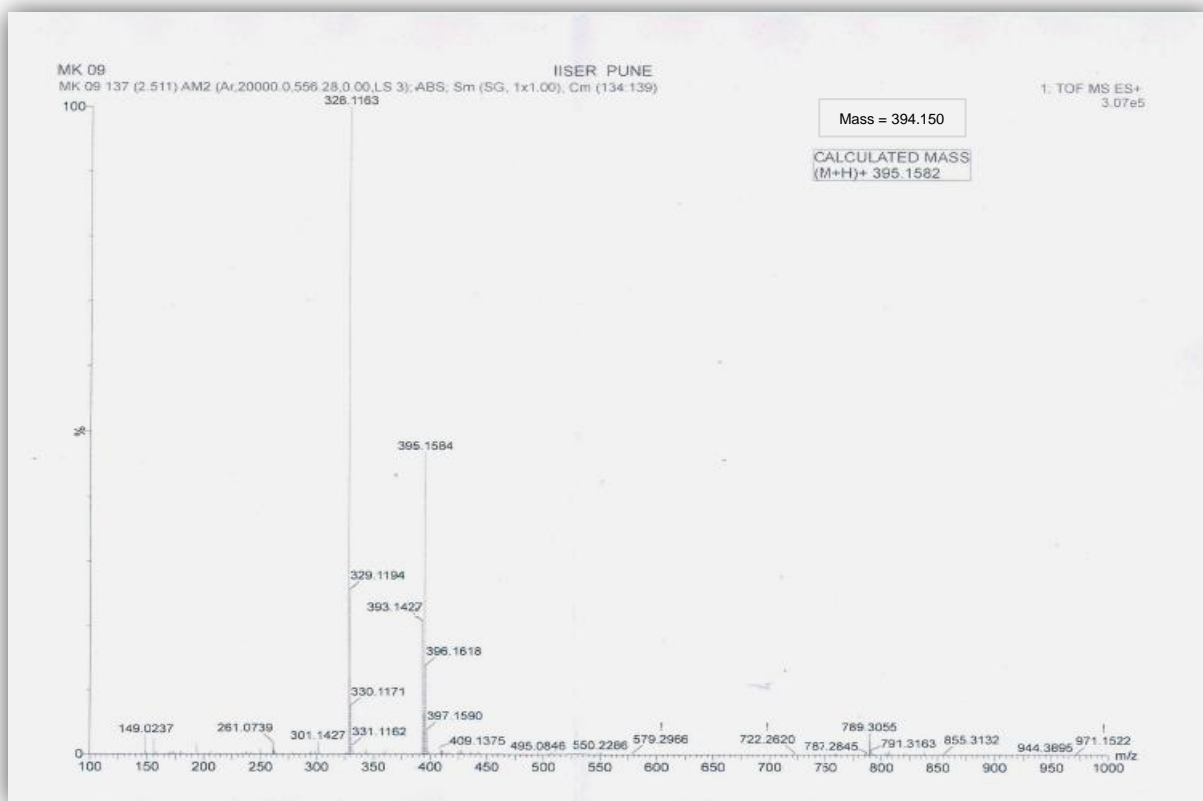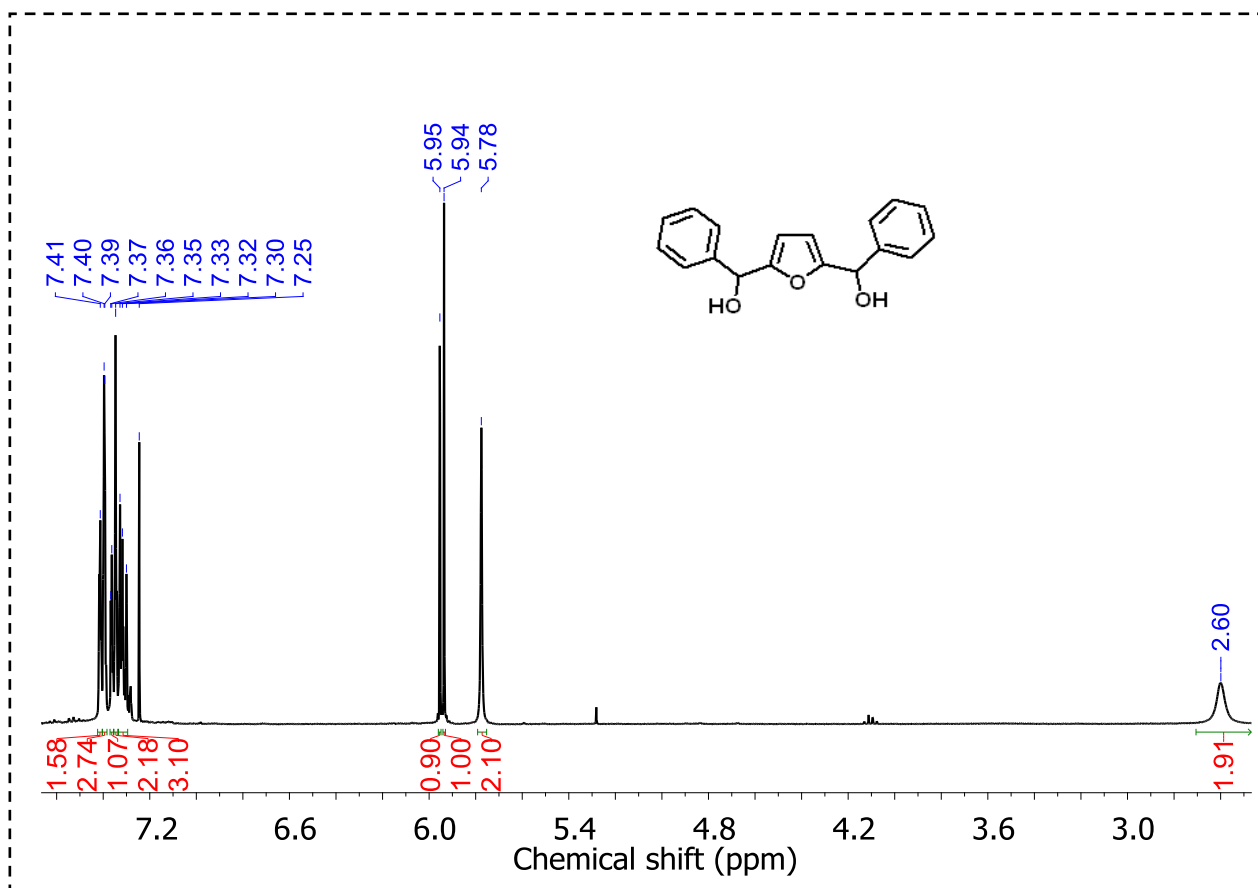**Figure 1.10 ^{1}H NMR and Mass spectra of Thiophene Tripyrrine (4)**

IISER PUNE

1: TOF MS ES+
3.07e5

Mass = 394.150

CALCULATED MASS
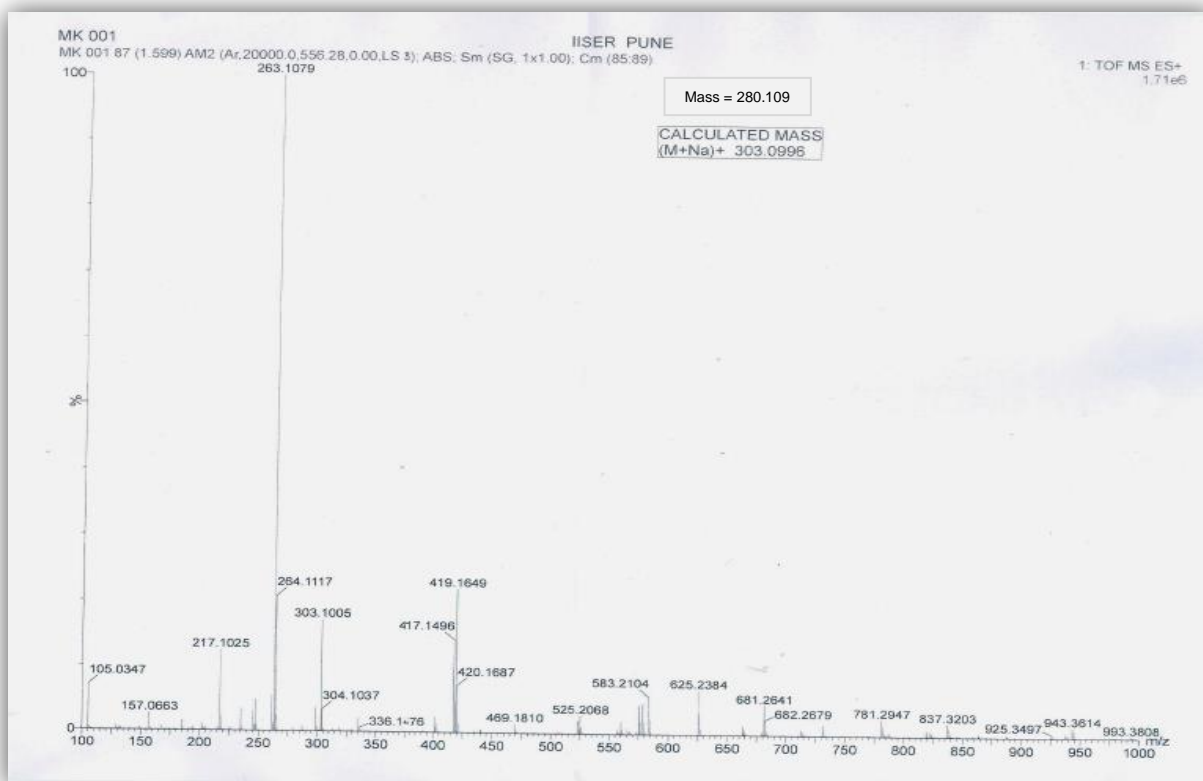(M+H)+ 395.1582

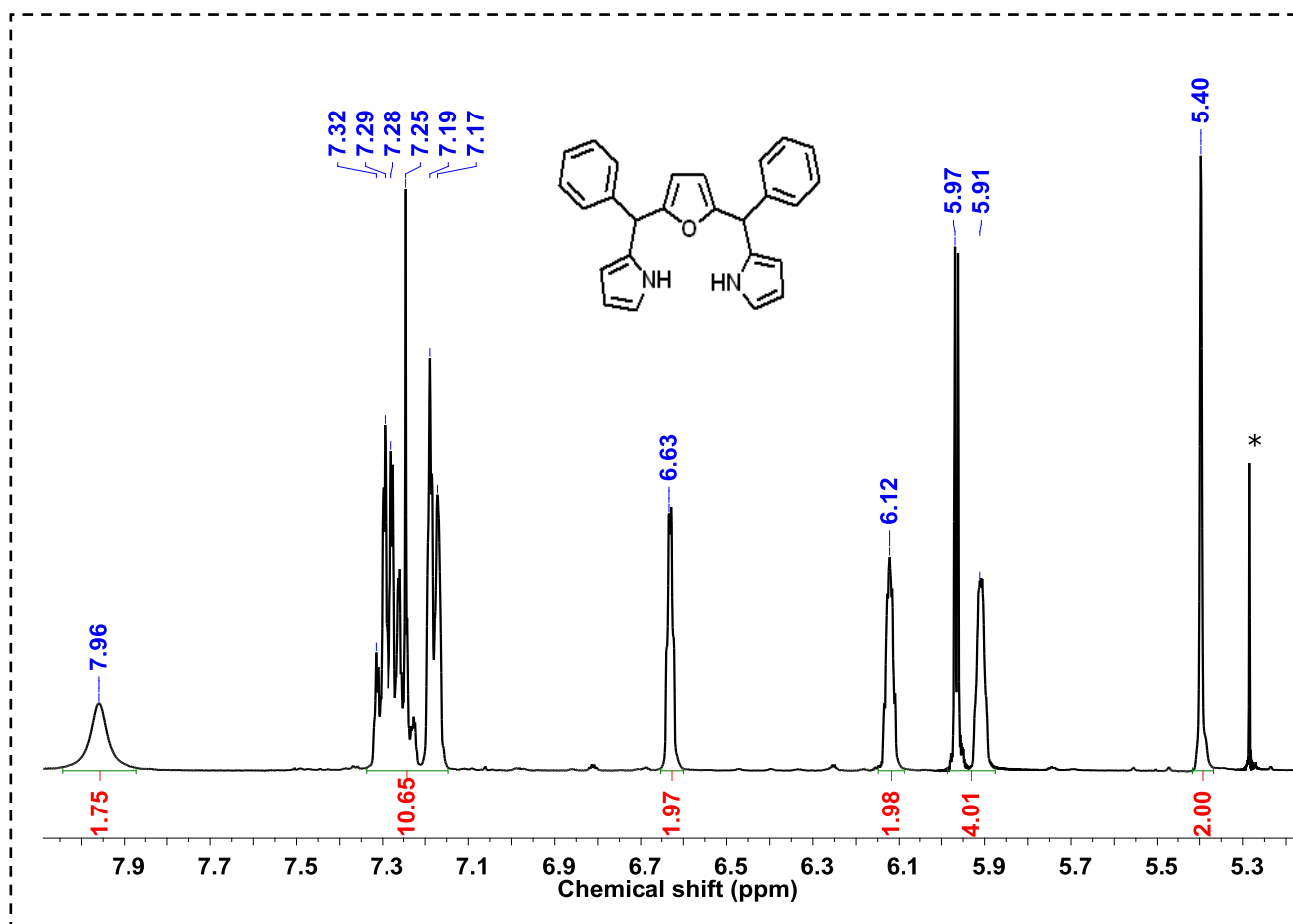**Figure 1.11 ^{1}H NMR and Mass spectra of Furan Diol (7)**
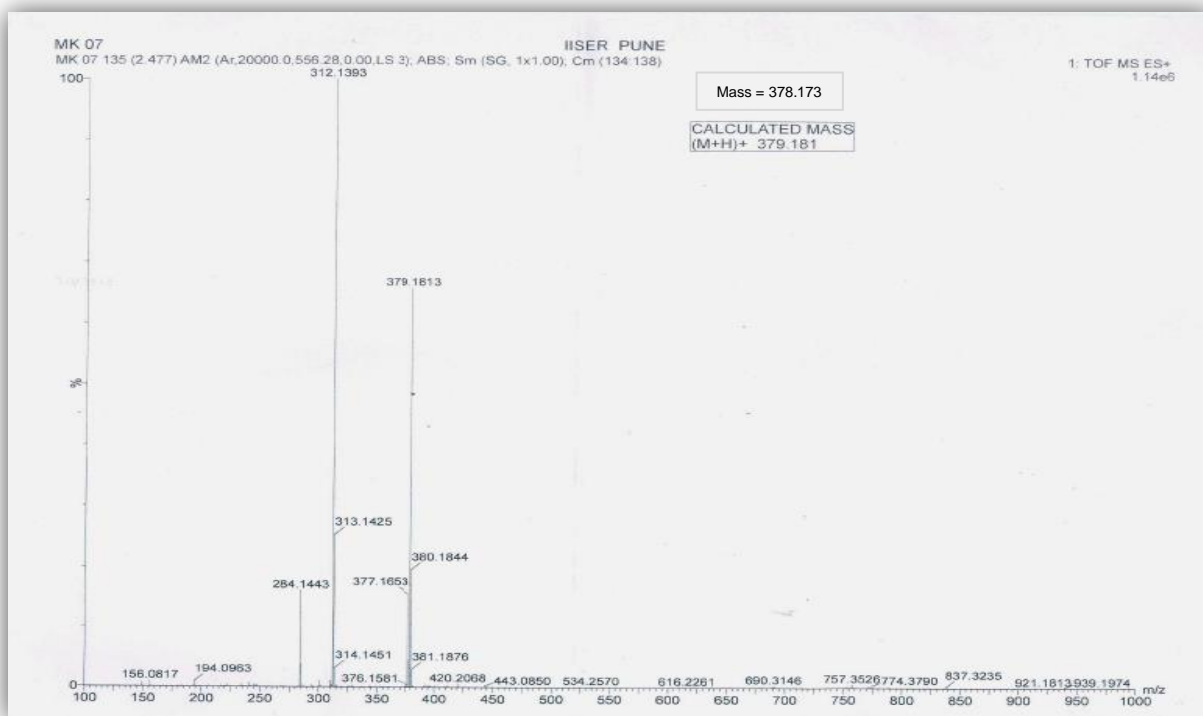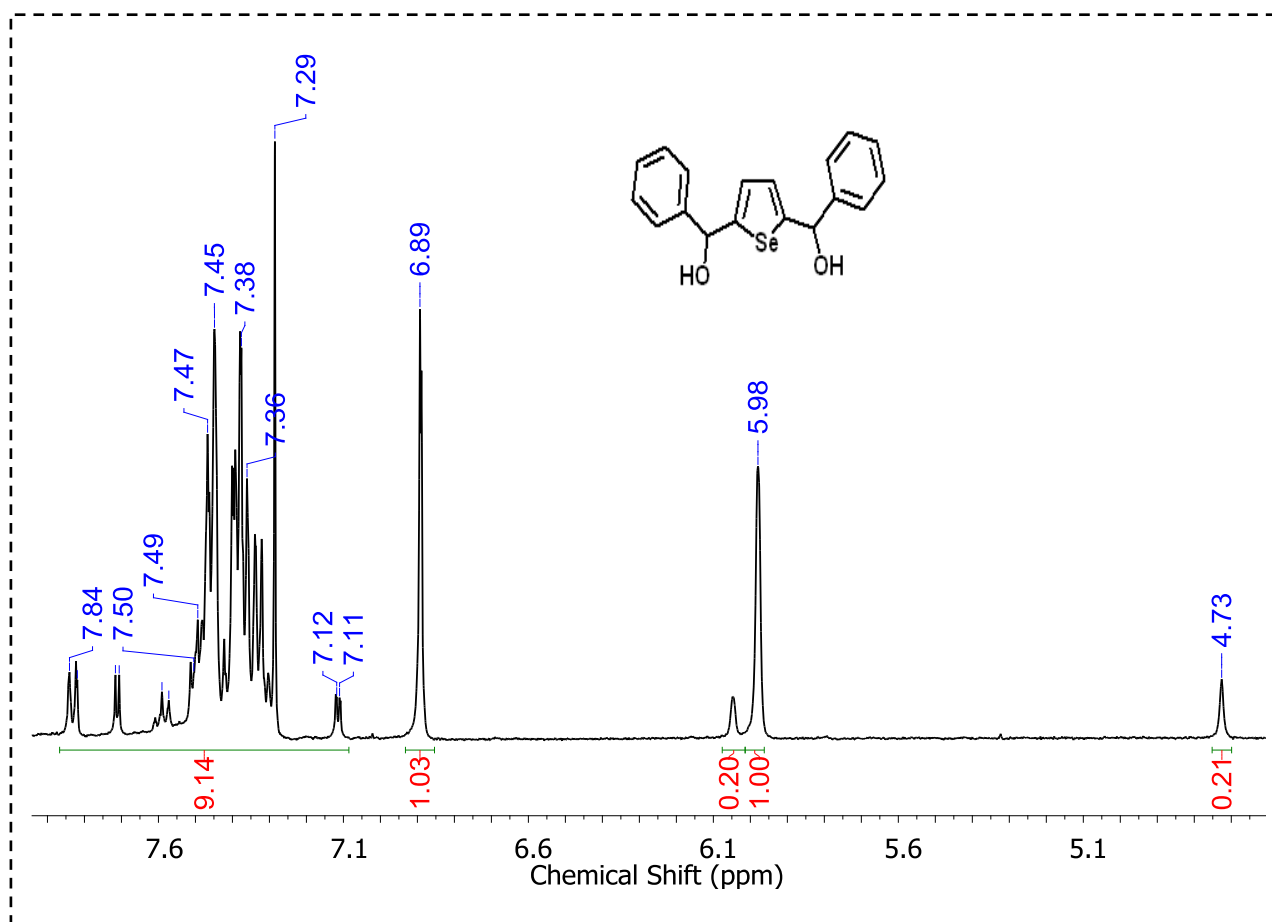
Figure 1.12 ^{1}H NMR and Mass spectra of Furan Tripyrrine (8)
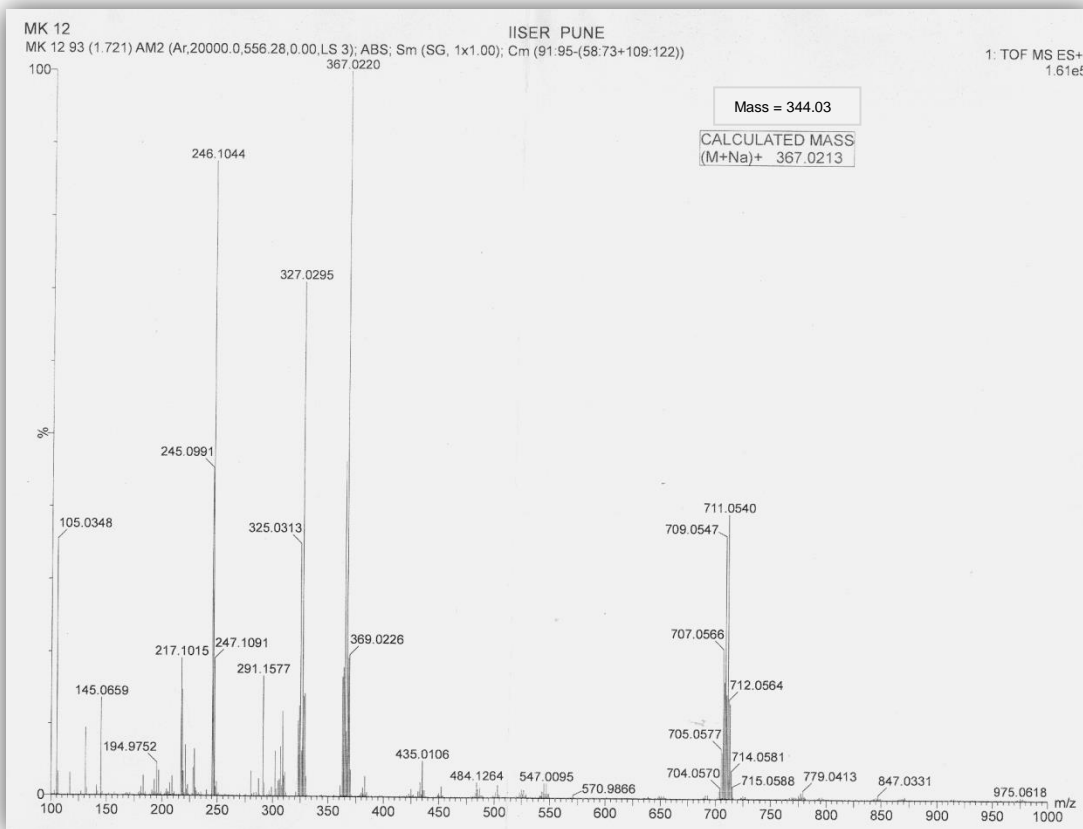
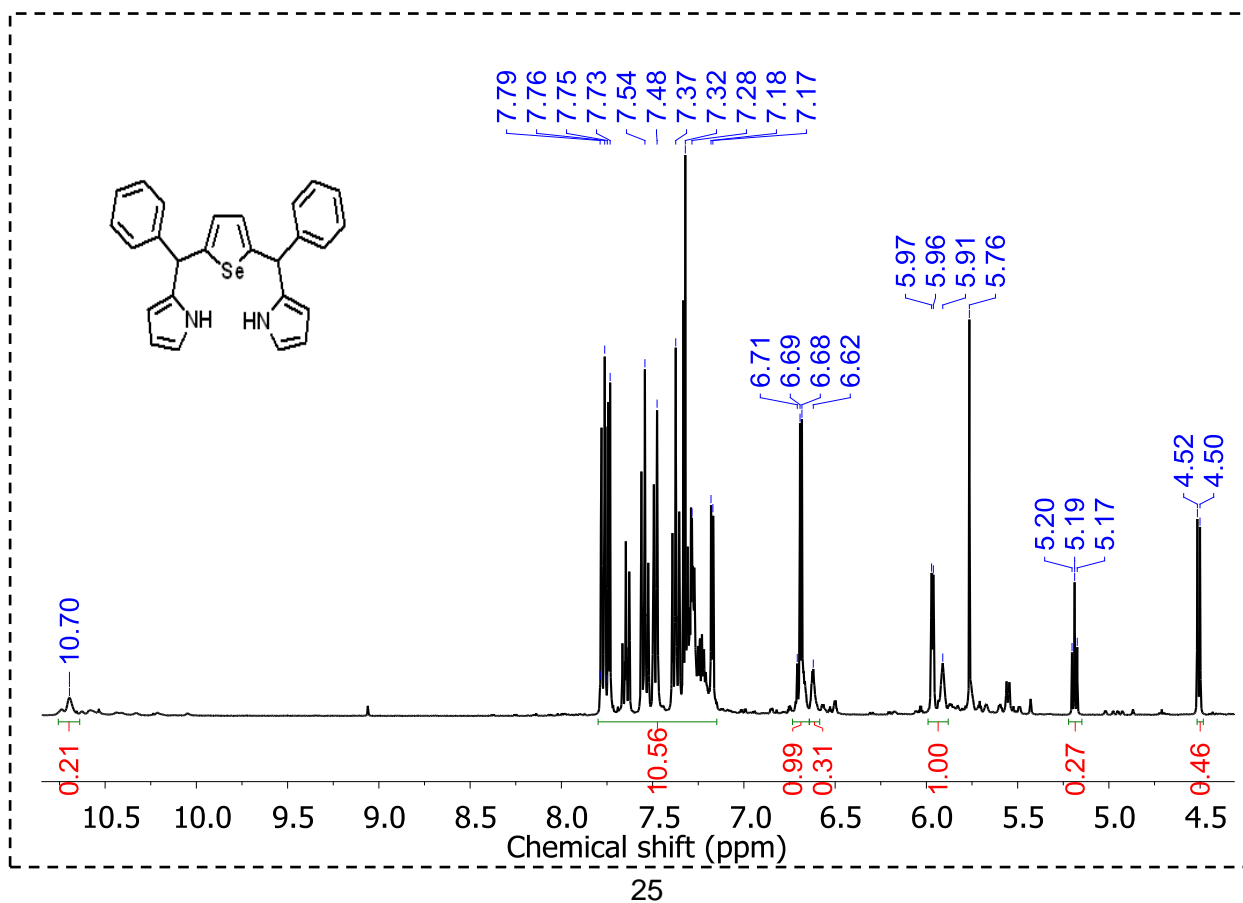**Figure 1.13 ^{1}H NMR and Mass spectra of Selenophene Diol (11)**

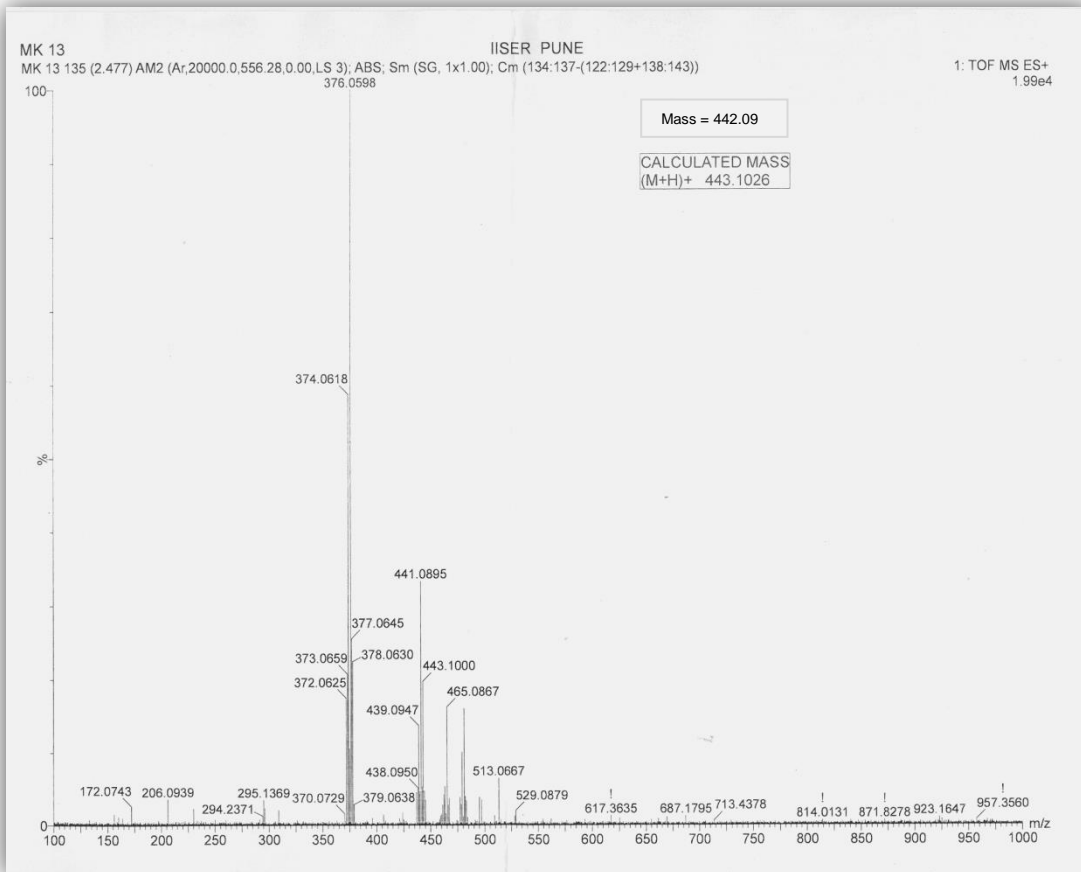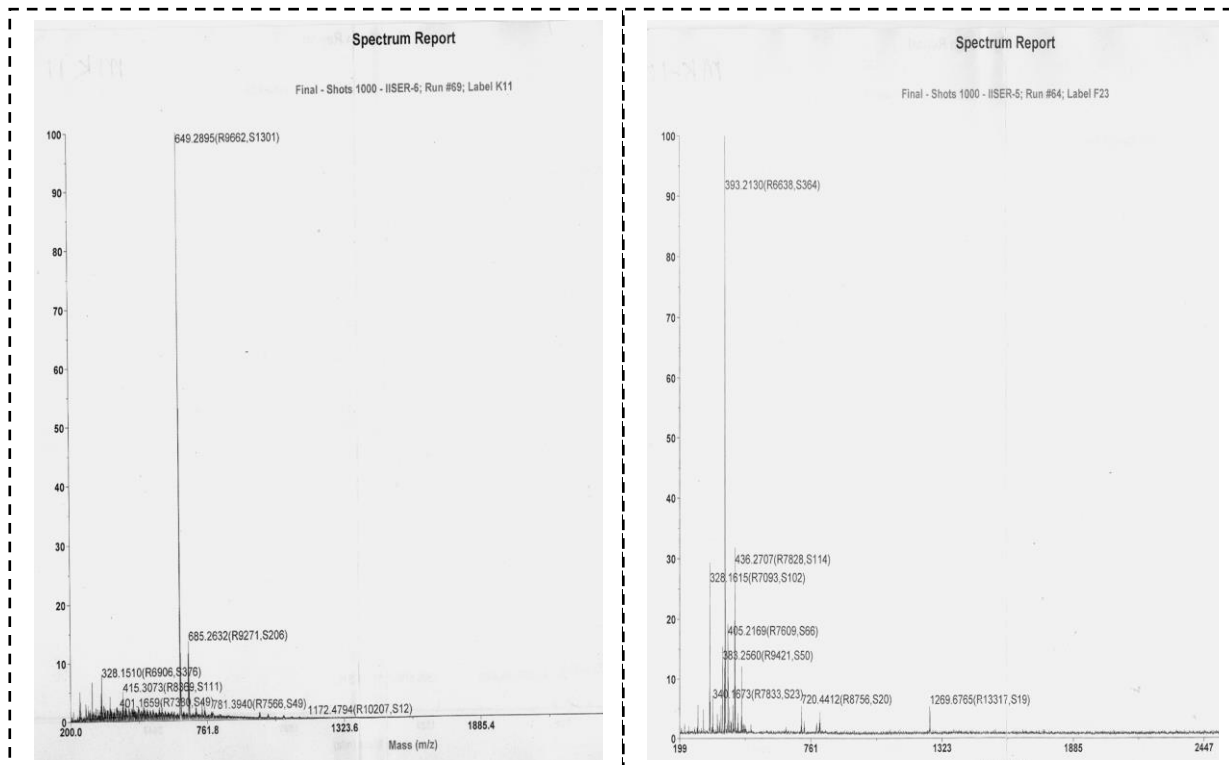**Figure 1.14 ^{1}H NMR and Mass spectra of Selenophene Tripyrrine (12)**

Figure 1.15 Mass spectras of Rubyrin

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1.6 References:

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Chapter 2: Synthesis and Characterization of conjugated Furan Macrocycles

2.1 Introduction

Porphyrin is the leading naturally occurring conjugated macrocycle mainly because of its metal complexing ability in diverse biological functions of organisms as well as in plants [1]. These functions are the reason, which led many groups to synthesize similar compounds with distinct electronic features. Modified Isophlorins are such macrocycles which have same conjugated aromatic rings, similar structural motifs and its properties are very much dependent on the modified hetero-atoms such as O, S etc present at the core of the macrocycle [2][3]. These macrocycles attract interest because of their electronic properties and structural features similar to that of porphyrin and annulenes.
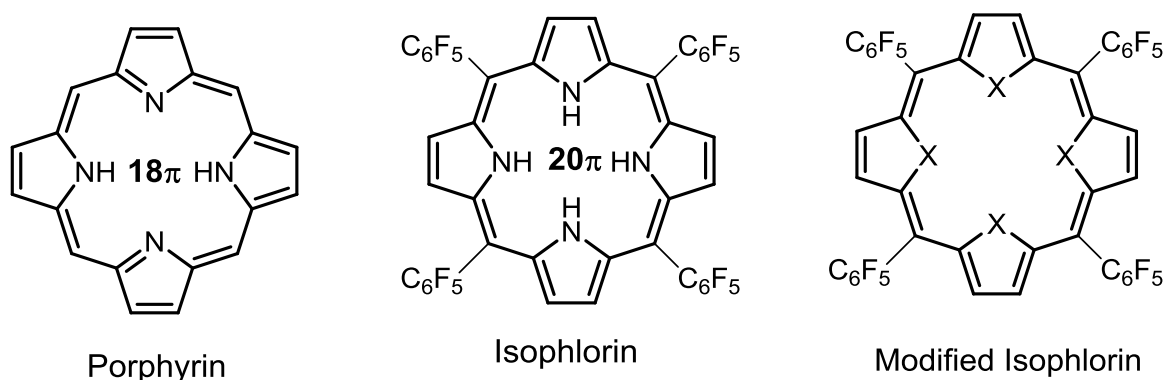
Figure 2.1 Chemical structures of Porphyrin, Isophlorin and Modified Isophlorin

They can be aromatic and anti-aromatic depending upon the number of π electrons along the planar conjugated system. This property is governed by an empirical Huckel's formula of $(4n+2)\pi$ and $4n\pi$ [4]. One such striking example of aromatic and anti-aromatic macrocycles are 18π porphyrin and 20π Isophlorin described in figure 2.1. This formula simply suggests the inter-conversion between two forms of macrocycle due to a two-electron redox process. The Porphyrin/Isophlorin redox couple explains a lot about the unstable nature of Isophlorin when compared to porphyrin, hence shows it can always transform into the aromatic 18π system when presented under ambient conditions [5].

In 2007 [2], Reddy and Anand reported core modified isophlorin having pentafluro-phenyl groups at the meso position from commercially available precursors. It also showed that geometry depends on the hetero-atoms present at the core of the macrocycle. Similarly in 2009 [3], they prepared expanded aromatic isophlorins with very simple precursors and showed that the macrocycles adopt ring inverted structures depending on nature of hetero-atoms present at the core. It also showed a hexathioisophlorin to be the first thiophene macrocycle which displayed annulenoid-type delocalization of π electrons. Further reports from our group in 2013 showed different characteristics of expanded Isophlorins, such as intermolecular interactions in the 32π isophlorins which suggested these macrocycles can also act as anti-aromatic supramolecules [6]. These expanded isophlorins can undergo reversible redox reaction to attain anti-aromatic state from the aromatic one [7]. These range of results forced us to focus on in this yet very much unexplored area and do our next set of reactions on synthesis of macrocycles given as figure 2.2.
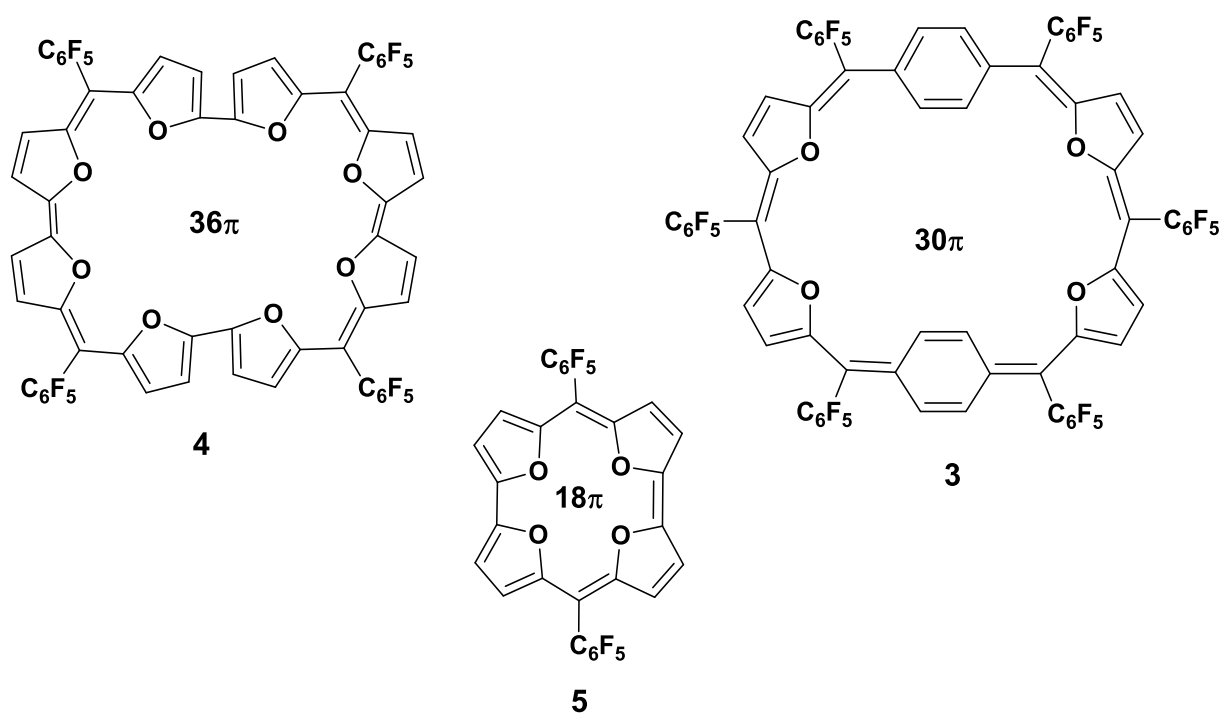

Figure 2.2 Chemical structures of proposed furan macrocycles

2.2 Synthesis, Results & Discussion

Thiophene has been useful building block in the synthesis of pi-conjugated macrocycles [8]. In this chapter the attempts to synthesize furan based macrocycles will be described. The macrocycles synthesized are from very simple and easy to make precursors. The macrocycle **3** is a blend of difuran **1** and benzene derivative **2** subunits. Difuran **1** was prepared by reacting **2 equivalents** of furan with **1 equivalent** of pentafluoro-benzaldehyde in acidic conditions under inert atmosphere in the absence of any solvent. The resultant difuran **1** was collected and purified. The product was isolated in good yield and confirmed through proton NMR spectra.
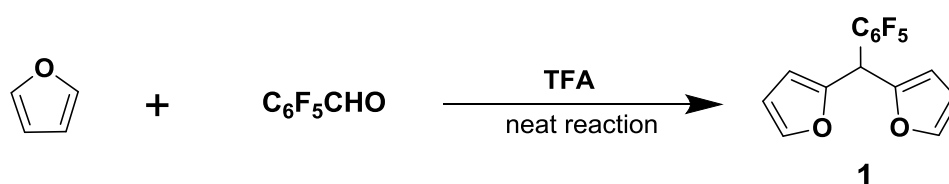

Figure 2.3 Synthetic scheme of difuran **1**

The synthesis of phenyl derivative **2** involved a two-step reaction. The first step involves preparation of pentafluoropenyl Grignard **2a** followed by the addition of freshly prepared Grignard **2a** to terephthalaldehyde at $0^{o}c$ and later slowly increased to room temperature. The expected diol was isolated in good yield and confirmed through proton NMR and Mass spectra.
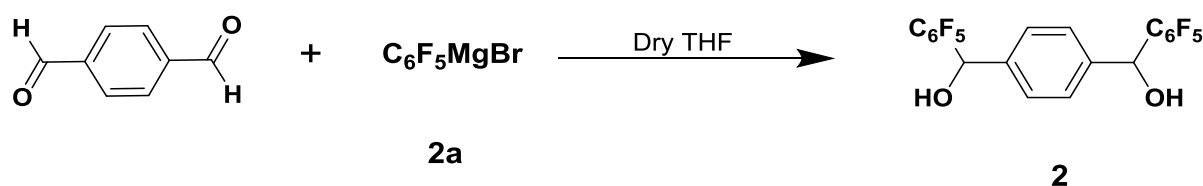
Figure 2.4 Synthetic scheme of phenyl diol derivative **2**

The final step towards synthesis of proposed macrocycle **3** involves the reaction of difuran **1** and phenyl diol derivative **2** in equimolar concentrations. $BF_3.OEt_2$ was added as a catalyst and followed by oxidation with $FeCl_3$. The reaction mixture was then washed with water and passed through short alumina column. And silica gel column chromatographic purification of this mixture resulted in a pink band with yield of 10%. The reaction and scheme is described in below.

Proposed mechanism
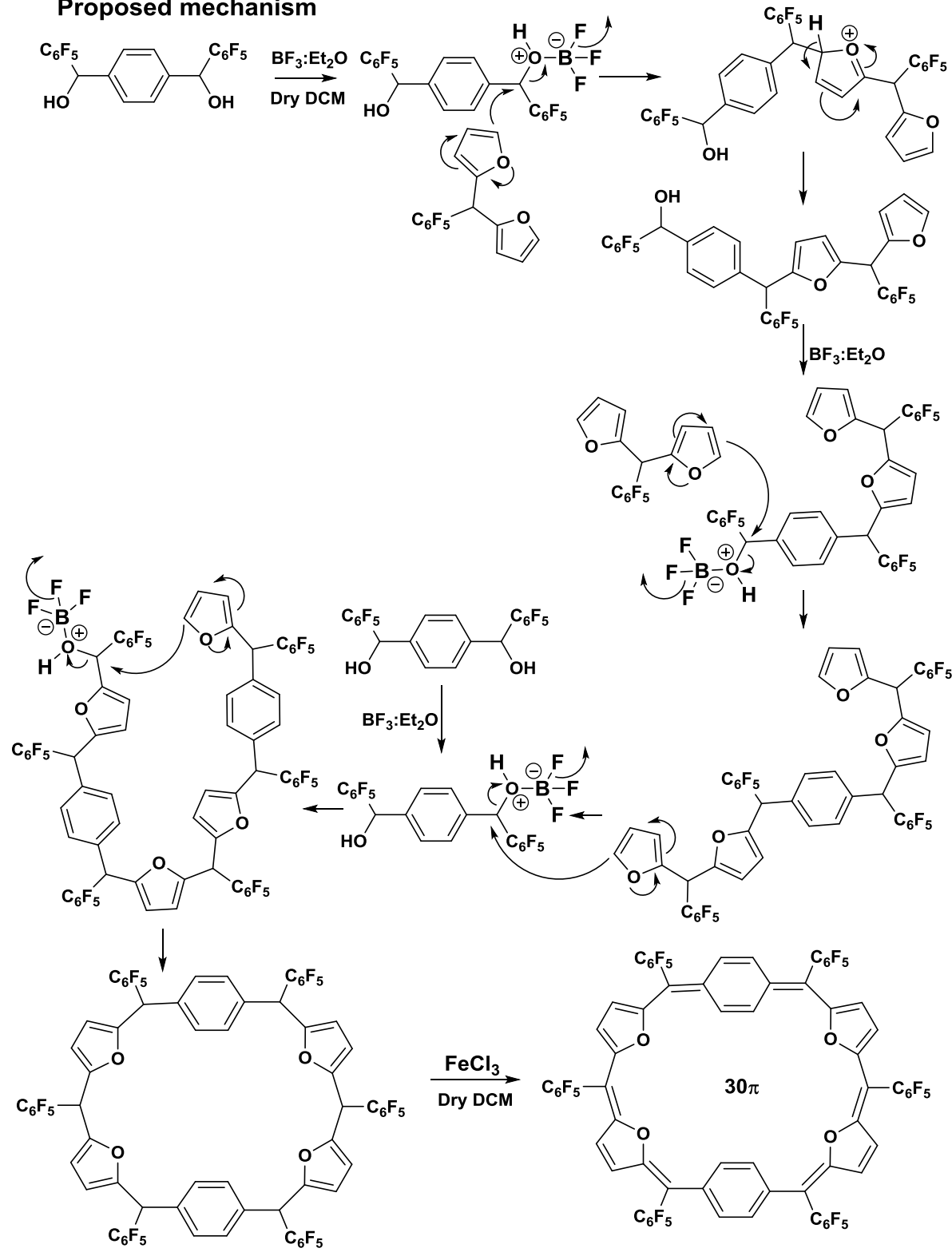
Figure 2.5 Synthetic scheme of macrocycle **3**

Though the expected m/z value for macrocycle **3** was 1490.06 but value found from the mass spectra after purification was 1526.49. So it was inferred that the purified compound can be a chlori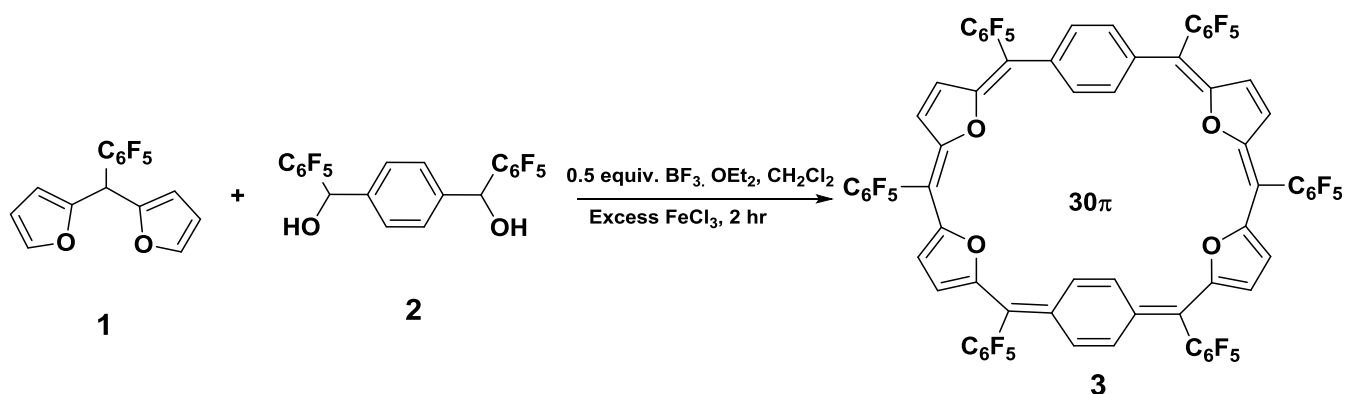nated macrocycle. To obtain the macrocycle without the chlorine, the reaction was repeated with DDQ instead of $FeCl_3$ for oxidation. But the results were not successful as the macrocycle was not identified through in mass spectral analysis.

So the next set of reactions for synthesizing macrocycle **4** involved addition of **1 equivalent** of difuran **1** in dry DCM. In this reaction **0.5 equivalent** of $BF_3.OEt_2$ was added as a catalyst followed by **3 equivalents** of $FeCl_3$ for oxidation. The reaction mixture was then washed with water and passed through short alumina column. An orange color band was purified through silica gel column chromatography in 7% yield.
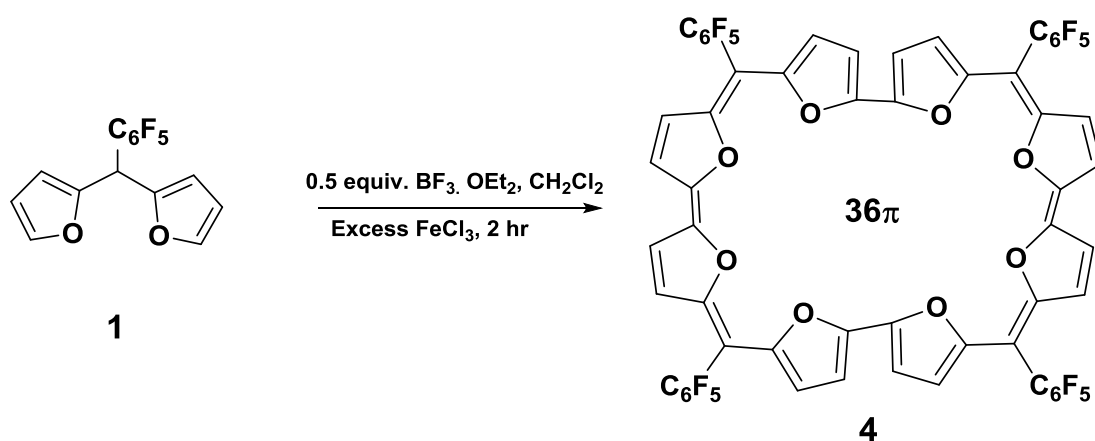

Figure 2.6 Synthetic scheme of macrocycle **4**

The expected m/z value for this macrocycle **4** is 1244.05 and the value we observed from MALDI-TOF spectra was 1244.06 along with other peaks at 839.18, 635.02 and

32

242.25. The product was purified based on color observed in the column chromatography and the orange color band exhibited the m/z peak at 1244.

In the next reaction **1 equivalent** of difuran **1** in dry DCM was oxidized by **3 equivalents** of FeCl$_3$ for oxidation. The reaction mixture was then washed with water and passed through short alumina column. And silica gel column chromatographic purification of this mixture resulted in a yellow band.
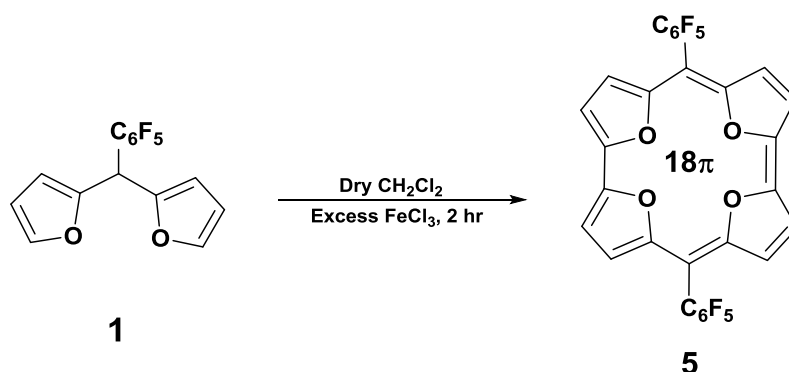

Figure 2.7 Synthetic scheme of macrocycle **5**

The product obtained was confirmed through ^{1}H NMR, ^{1}H-^{1}H COSY NMR and mass spectra taken by MALDI-TOF showed the highest peak at 626.13. Although the expected mass peak was at 622.03 but peak observed after isolation was the highest peak observed in the spectra with no other peaks around inferring that the isolated macrocycle is stable at un-oxidized state.

The NMR spectra was taken in 2-Dimension to show the correlation between the different protons present in the macrocycle hence confirming the structure of the macrocycle.

2.3 Summary

In this chapter of our study, we have synthesized, purified, characterized and identified different macrocycles and their simple & easy to make precursors.

Easy and efficient synthetic routes were provided and applied to produce these macrocycles along with their precursors. The mass characterizations were done

several times to confirm the formation of the product such as the reaction mixture, the quenched product and purified products have the same m/z values. The proton NMR and ^{1}H-^{1}HCOSY were done to confirm the structure of the purified macrocycle. However, these macrocycles do not undergo easy oxidation to yield pi-conjugated macrocycles. Further studies in this area will explore new dimensions in furan macrocyclic chemistry.

2.4 Experimental Methods and Techniques

2.4.1 Chemicals used for Synthesis:

Normal solvent used for synthesis were purified and dried according to known procedures. Furan and pentafluro-benzaldehyde were distilled before use. Terephthalaldehyde, Magnesium, Bromo-pentafluorobenzene, $BF_3.(OEt)_2$ were used from Aldrich chemicals, USA. Pentafluoro-Benzaldehyde was used from Alfa Aesar. Furan and TFA were used from Spectrochem chemicals, India. Anhydrous sodium sulphate and ammonium chloride were obtained from Rankem Fine chemicals, India.

2.4.2 Spectral characterization techniques

Electronic spectra were recorded on a Perkin Elmer-Lambda 20 UV-Vis spectrophotometer. The data analyses were done using the UV-winlab software package. ^{1}H-NMR spectra were obtained either from 500 MHz Bruker Advance DPX spectrometer or 400 MHz Jeol machine in $CDCl_3$ using tetramethylsilane (TMS) as integral standard. ESI HRMS data were recorded on Waters Synapt G2 spectrometer. MALDI-TOF was carried out on Voyager-De-STR (Applied Biosystems).

2.4.3 Synthesis of Chemical Compounds

2,2'-((perfluorophenyl)methylene)difuran (1)

In a two neck (250 ml) round bottomed flask, the freshly distilled furan (6.813 ml, 0.1 mol) is added with distilled pentaflurobenzaldehyde (0.601 ml, 0.005 mol). Since this is a neat reaction hence no solvent involved to assist the mixing of reactants. The mixture is stirred under inert conditions for 10 mins. Then follows addition of Trifluoroacetic acid (0.383 ml, 0.005 mol) and the reaction mixture are allowed to stir

for 30 mins at room temperature. The reaction is quenched with dichloromethane (100 ml) and then washed with 0.1 N NaOH solution (30 ml). The mixture is concentrated in reduced pressure followed by (DCM + H_2O) work up. The resultant viscous liquid is purified through silica gel column chromatography using Hexane as solvent resulting in yellow oily liquid (yield 37%).^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37(d, 2H), 6.37-6.36(dd, 2H), 6.22(d, 2H), 5.87(s, 1H).

1,4-phenylenebis((perfluorophenyl)methanol) (2)

The synthesis of this phenyl diol derivative is a two step process. **Step 1** involves preparation of Grignard **2a** where in a two neck (50 ml) round bottomed flask, dry THF (14 ml) is taken under inert atmosphere and then magnesium (0.401 gm, 0.016 mol) is added with a pinch of iodine to observe the color change. The reaction was stirred for 10 mins followed by addition of C_6F_5Br (1.907 ml, 0.015 mol). And then reaction mixture was stirred for 2 hours at RT. **Step 2** involves addition of this freshly prepared Grignard **2a** where in a two neck (100 ml) RB flask under inert conditions, terephthalaldehyde (0.82gm, 0.006 mol)is taken in dry THF (30 ml) and the Grignard is added to it at 0^oC. The reaction mixture is allowed to warm at RT and stirred for 3 hours. The product is confirmed using T.L.C and the mixture is quenched with saturated ammonium chloride with 30 mins stirring. Work up is done with ethyl acetate and a small width column is packed. At first, hexane (500 ml) is run through the silica gel column followed by 5% ethyl acetate/hexane solvent to remove the impurity; then the resultant product is observed with increasing the polarity of the solvent to 7% ethyl acetate/hexane as white solid (yield 42 %). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40(s, 2H), 6.25- 6.23(d, 1H), 2.69- 2.67(d, 1H)

HRMS: $C_{20}H_8F_{10}O_2$; 470.036, observed 471.044 $(M+H)^+$

Synthesis of macrocycle 3

Compound **1** (157.103 mg, 0.5 mmol) and compound **2** (235 mg, 0.5 mmol) are vacuum dried and added to a two neck (250 ml) RB flask under inert atmosphere. Dry DCM (100 ml) is added to it carefully and allowed to stir to mix proportionally. $BF_3.OEt_2$ (0.03 ml, 0.25 mmol) is added to it under dark, and the resulting solution is

stirred for 1 hour. After that excess $FeCl_3$ (0.24 gm, 1.5 mmol) / DDQ (0.34 gm, 1.5 mmol) is added and reaction mixture is opened to air and stirred for 2 more hrs. Then the reaction mixture is washed with water and passed through a short alumina column. This mixture is separated via silica gel column chromatography by using DCM/hexane as eluant. Light pink color fraction of macrocycle **3** is obtained and is repeatedly purified through silica gel column chromatography by using 5% Dichloromethane in hexane as eluant. MALDI-TOF: $C_{70}H_{16}F_{30}O_4$; 1490.06 (100%), observed 1526.499 (M+Cl) (100 %)

Synthesis of macrocycle 4 and 5

Compound **1** (157.103 mg, 0.5 mmol) is vacuum dried and taken into a two neck (250 ml) RB flask under inert atmosphere for both reactions. Dry DCM (100 ml) is added to it carefully and the compound is allowed to mix through stirring. **In case of macrocycle 4**, $BF_3.OEt_2$ (0.03 ml, 0.25 mmol) is added to it under dark, and the resulting solution is stirred for 1 hour and nothing is added **in case of macrocycle 5**. After that excess $FeCl_3$ (0.24 gm, 1.5 mmol) is added to both of them and the reaction mixtures are opened to air and stirred for 2 more hrs. Then the reaction mixtures are washed with water and passed through a short alumina column. These mixtures are separated through silica gel column chromatography by using DCM/hexane as eluant.

Orange color fraction of macrocycle **4** and yellow color fraction of macrocycle **5** are obtained and repeatedly purified through silica gel column chromatography by using 5% Dichloromethane in hexane as eluant. MALDI-TOF for **4**: $C_{60}H_{16}F_{20}O_8$; 1244.05 (100%), observed 1244.06 (~80 %)

MALDI-TOF for **5**: $C_{30}H_8F_{10}O_4$; 622.03 (100%), observed 626.13 (100 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.16(m, 6H), 6.74-6.45(m, 8H), 6.21-6.20(d, 3H), 5.86(s, 2H), 5.29(s, 2H), 5.01(s, 1H).

2.5 Characterization spectral data

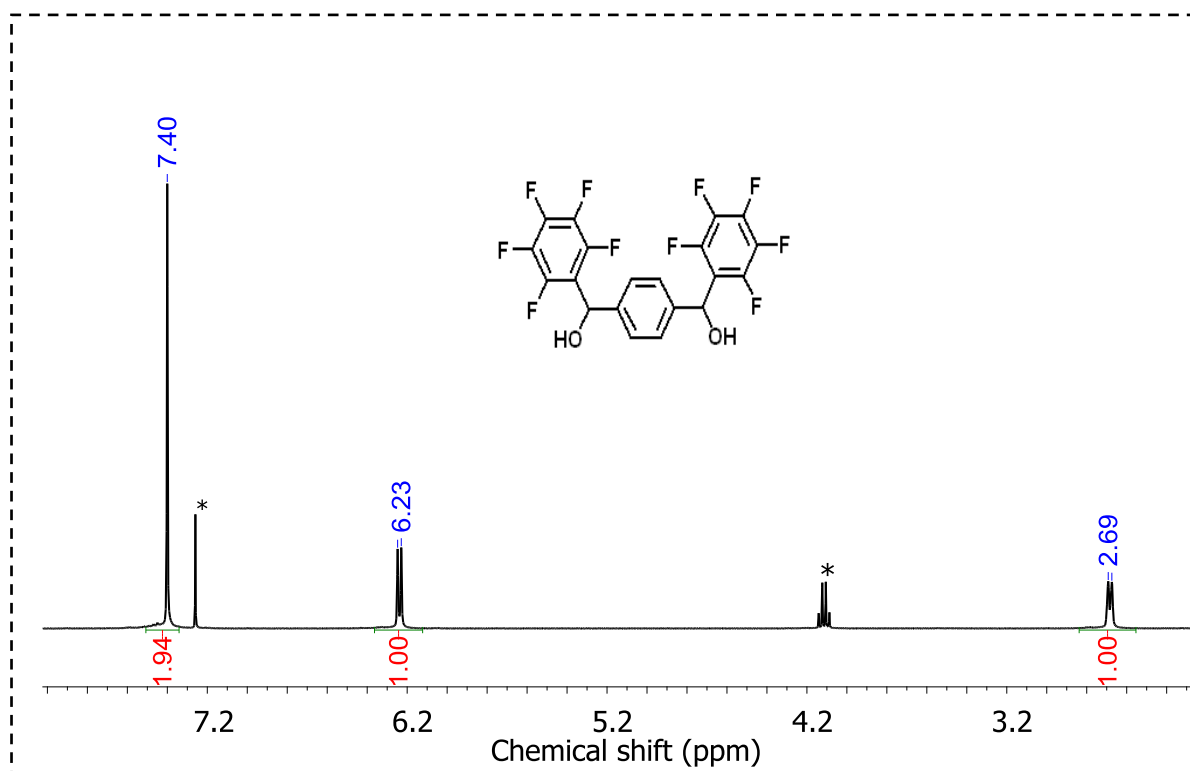**Figure 2.8 ^{1}H NMR of difuran (1) and phenyl diol derivative (2)**
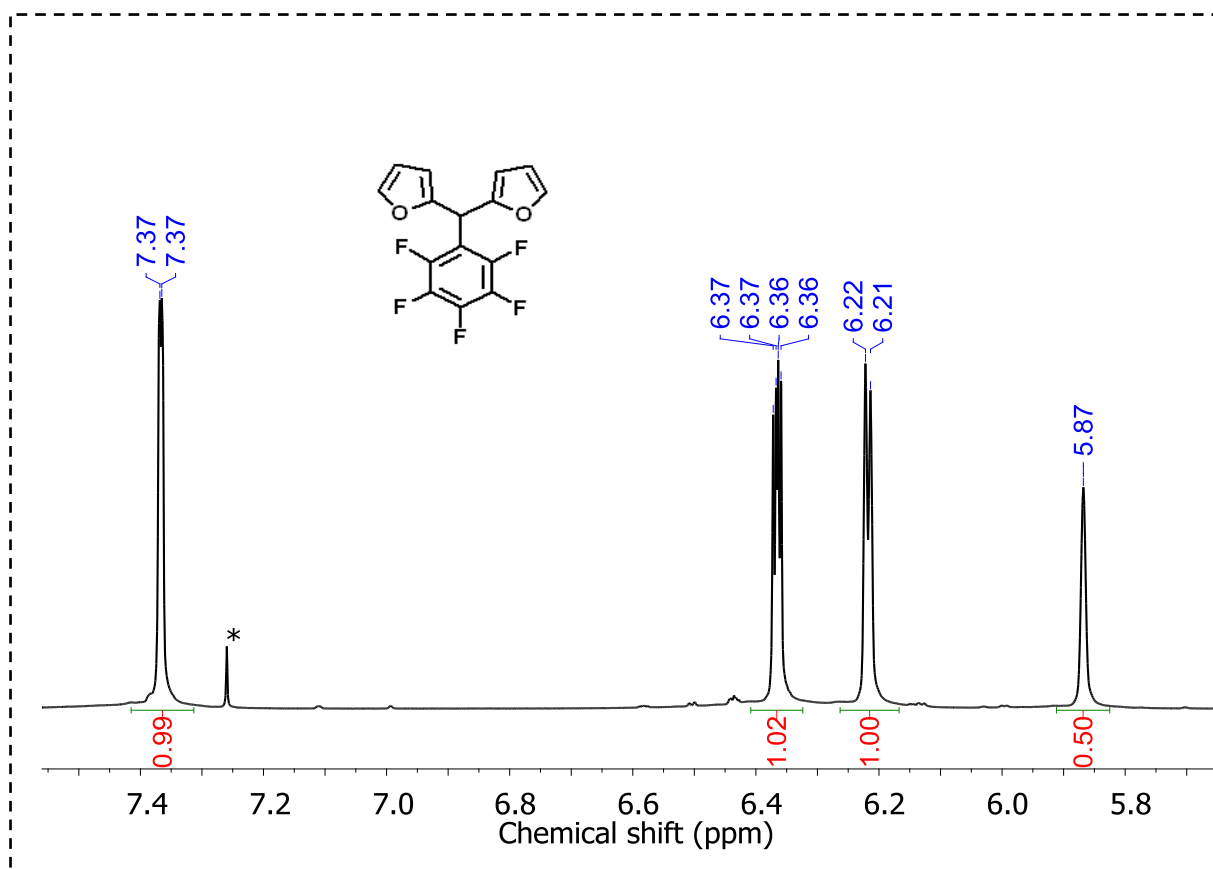
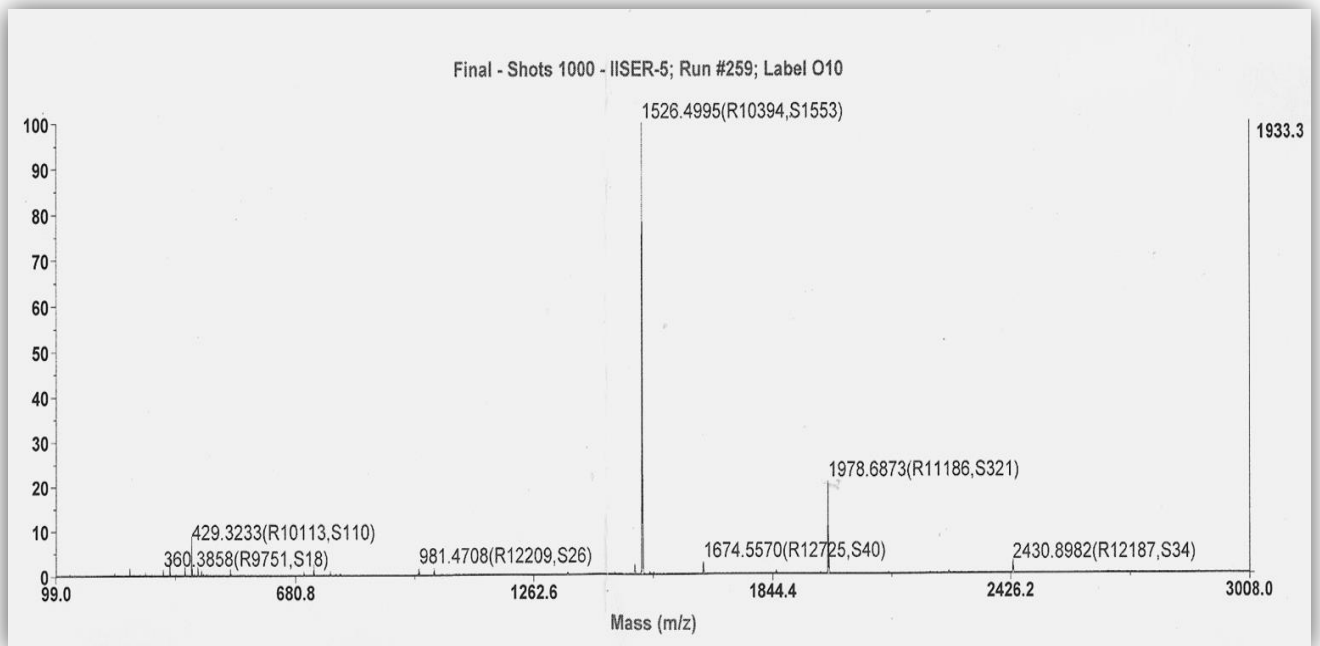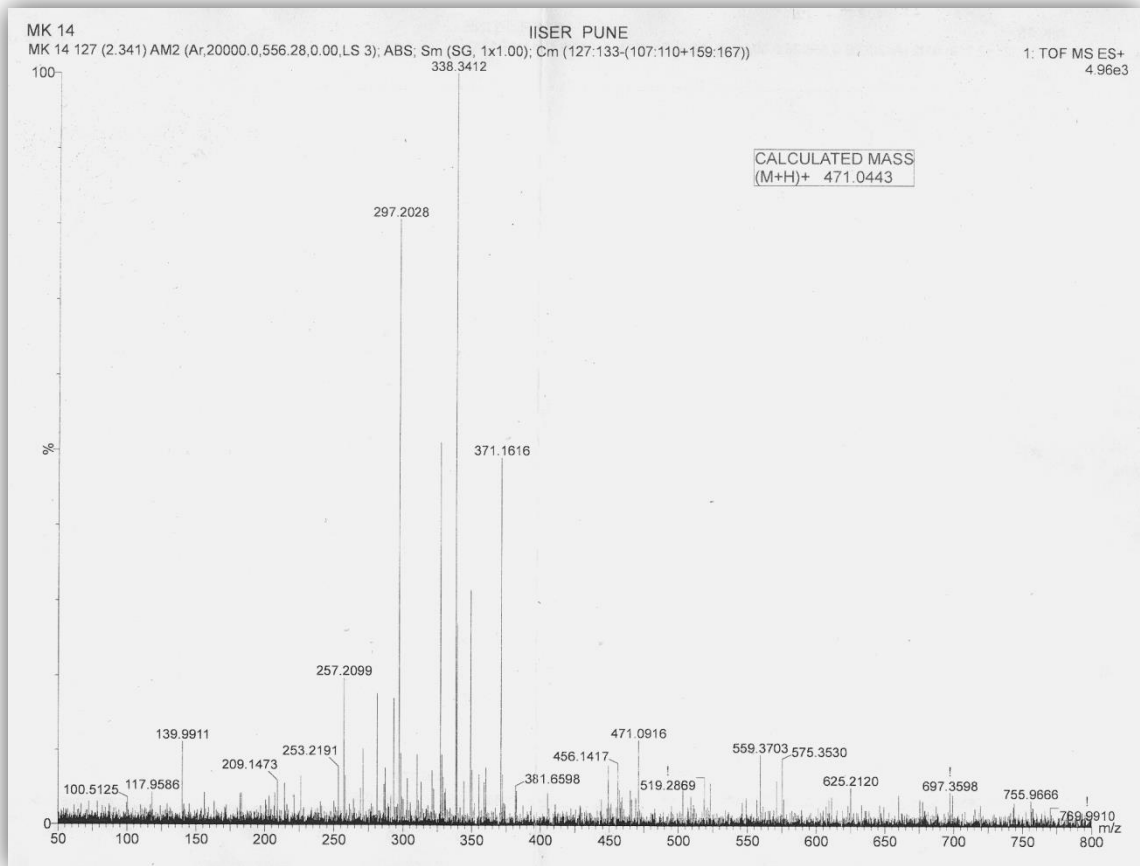**Figure 2.9 Mass spectra of phenyl diol derivative (2) and macrocycle (3)**

Figure 2.10 Mass spectra of macrocycle (4) and macrocycle (5)

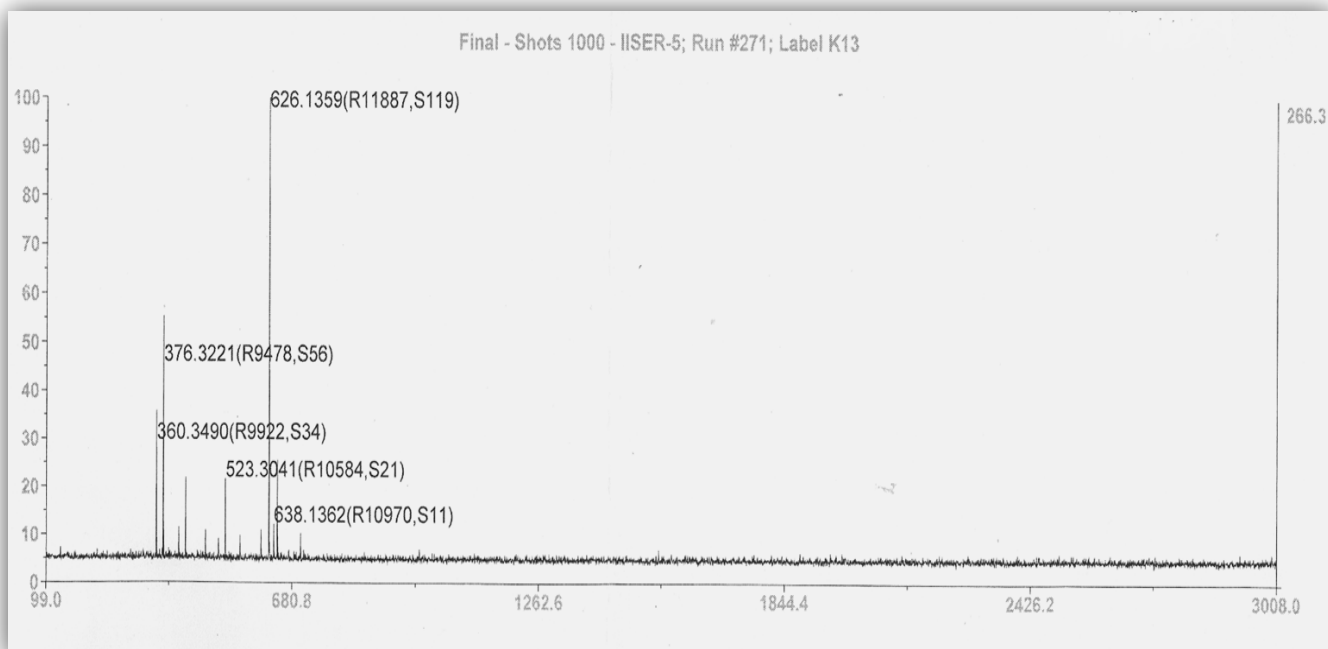Final - Shots 1000 - IISER-5; Run #254; Label F11

242.2506(R7718,S1096)
635.0245(R11637,S1042)
1244.0641(R14293,S1004)
1673.3
839.1827(R12510,S270)
933.0424(R13397,S237)
890.0587(R12939,S179)
332.3028(R9081,S230)
649.0416(R11868,S146)
368.4002(R9711,S78)
907.0661(R14046,S23)
1555.0969(R16166,S102)

Mass (m/z)

Final - Shots 1000 - IISER-5; Run #271; Label K13

626.1359(R11887,S119)
266.3
376.3221(R9478,S56)
360.3490(R9922,S34)
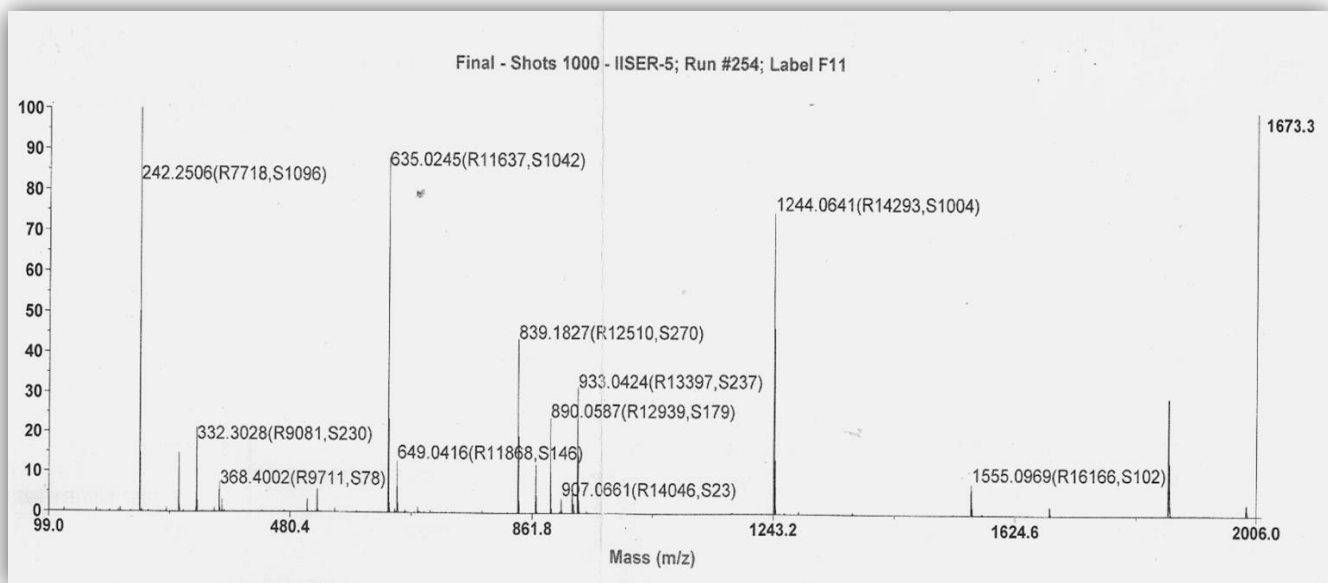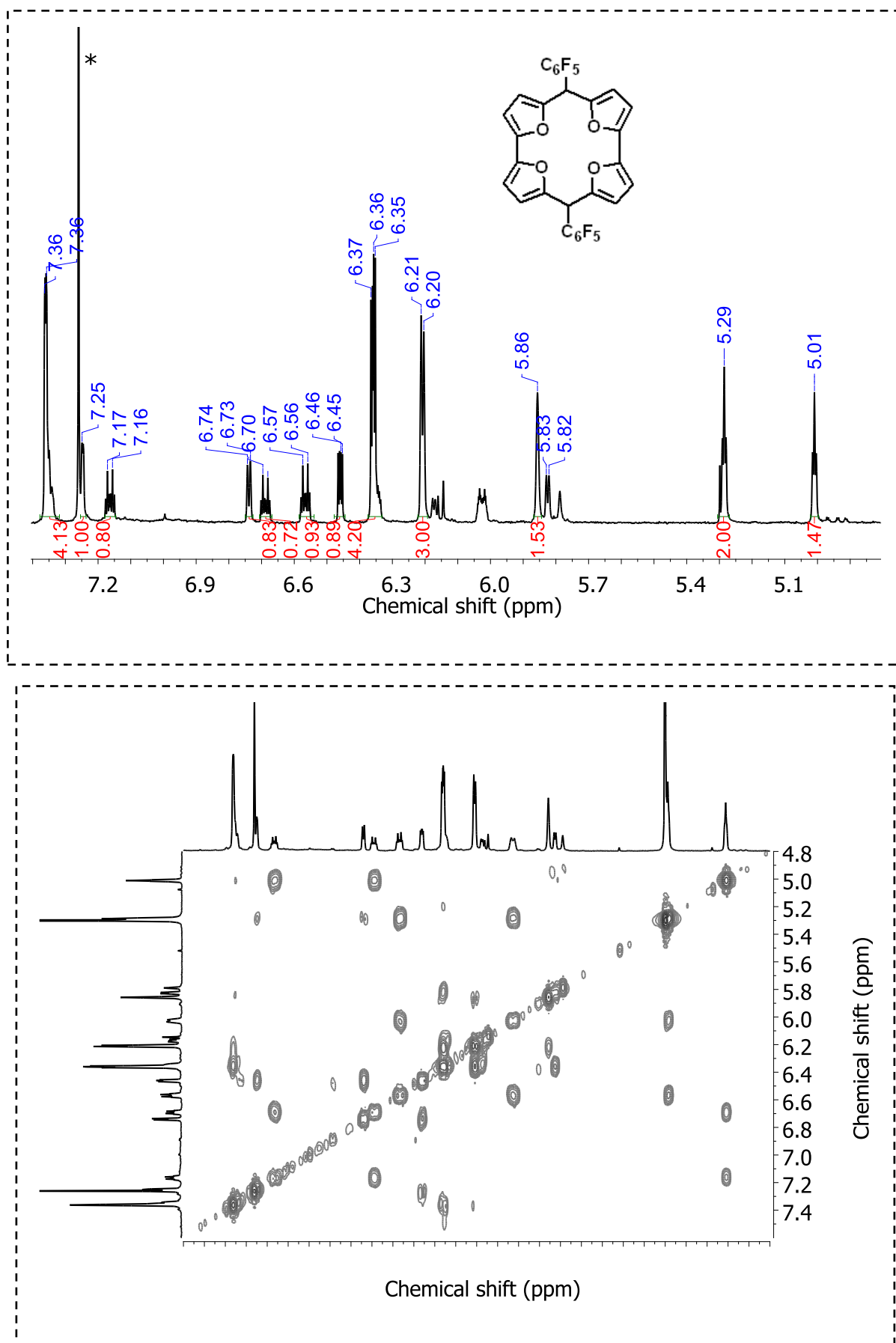523.3041(R10584,S21)
638.1362(R10970,S11)

Figure 2.11 ^{1}H NMR and ^{1}H-^{1}H COSY of Macrocycle (5)

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