Abstract

The thesis entitled "***Synthesis and evaluation of hybrid heterocycles as novel antitubercular agents and total synthesis of Enigmol"*** has been divided into four Chapters.

Chapter I : Design, synthesis and evaluation of novel dihydroquinoline derivatives as inhibitors of *Mycobacterium tuberculosis*.

Chapter II : Synthesis and antitubercular evaluation of novel dibenzo[*b,d*] thiophene-1,2,3-triazoles appended with cyclic and acyclic amines.

Chapter III : This chapter is subdivided into two sections.

Section A : Synthesis and antitubercular evaluation of novel dibenzo[*b,d*] thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamides.

Section B : Synthesis and evaluation of substituted thiazole/benzothiazole coupled (*E*)-dibenzo[*b,d*]thiophene-2-yl acrylamides as potent inhibitors of *Mycobacterium tuberculosis*.

Chapter IV : Total synthesis of Enigmol

Chapter I : Design, Synthesis and evaluation of novel dihydroquinolino derivatives as inhibitors of *Mycobacterium Tuberculosis*.

INTRODUCTION:

Tuberculosis:

Tuberculosis (TB) is an ancient, contagious disease caused by pathogen called *Mycobacterium tuberculosis*. The TB bacteria usually affect the lungs. The resurgence of tuberculosis (TB) is one of the most serious public health concerns worldwide. The causative pathogen *Mycobacterium tuberculosis* (*Mtb*) is observed more frequently in immune-compromised individuals suffering from human immune deficiency virus (HIV). According to World Health Organization (WHO) global tuberculosis report 2015, TB killed 890,000 men, 480,000 women and 140,000 children in 2014 alone, and the disease ranked alongside HIV as a leading killer worldwide. The current situation necessitates examination of various old drug families for developing new antimycobacterial entities with novel mechanism of action to achieve effective TB control even against the resistant forms of TB. It has been also noticed that more than 50 years elapsed, there is no single drug developed for the treatment of TB. The worsening situation has prompted WHO to declare tuberculosis as a global public health crisis.

In recent time drug-resistant tuberculosis was emerged as a major clinical and public health challenge in the forms of multidrug-resistant tuberculosis (MDR-TB) and extensively drug resistant TB (XDR-TB). Multidrug-resistant (MDR) tuberculosis is defined as disease caused by strains of *Mycobacterium tuberculosis* that are resistant to treatment with isoniazid and rifampicin. Extensively drug-resistant (XDR) tuberculosis refers to disease caused by multidrug-resistant strains that are also resistant to treatment with any fluoroquinolone and any of the injectable drugs used in treatment with second-line anti-tuberculosis drugs.

The standard short course for the treatment of TB utilizes standard first line drugs (Figure 1) such as Isoniazid (along with pyridoxal phosphate to obviate peripheral neuropathy caused by Isoniazid), Rifampicin, Pyrazinamide and Ethambutol for two months, then Isoniazid and Rifampicin alone for a further four months. The reason for the long term treatment is that, it is very difficult to entirely eliminate the causative pathogen, *Mycobacterium tuberculosis* (*Mtb*), from the patient.

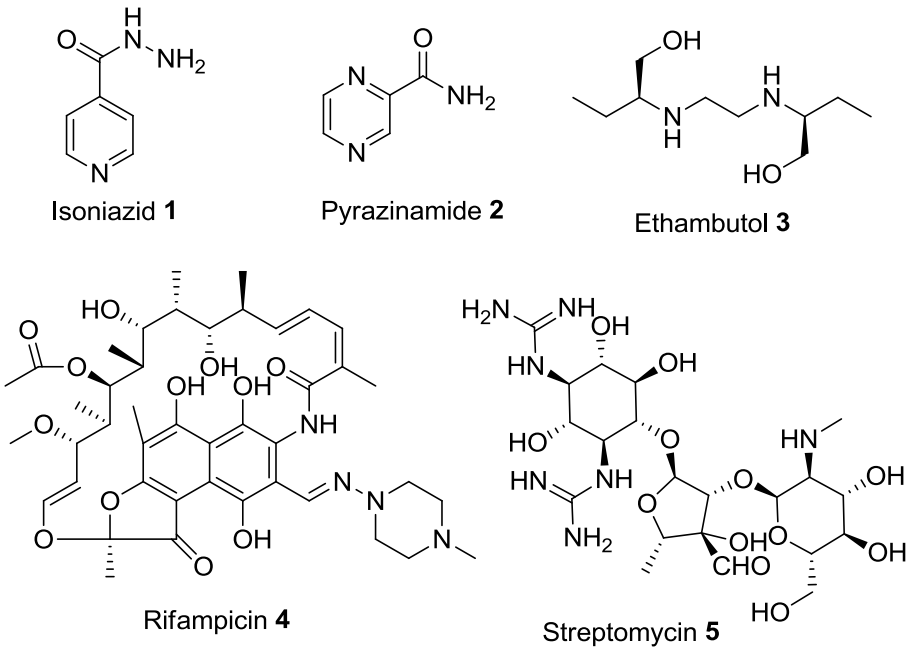


Figure 1

Quinolines:

Quinoline and their derivatives are an important class of aza-heterocycles found in many natural products and active pharmaceuticals. Several quinoline containing compounds exhibit a wide spectrum of pharmacological activities, such as antimalarial, antiplasmodial, cytotoxic, antibacterial, antiproliferative, antituberculosis and anticancer activity. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties.

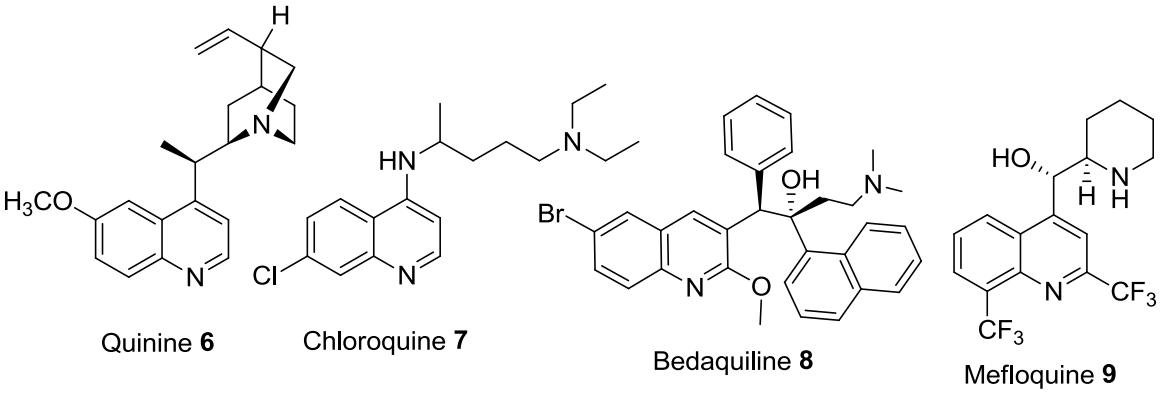


Figure 2

In recent years quinoline derivatives fused and/or substituted with heterocyclic rings were demonstrated to have significant biological activities. In perticular antimicrobial and antituberculosis activity was found in heterocycles **10** & **11** where in oxazole and isoxazole ring in the quinoline core. Pyrazole containing pharmacoactive agents play important role in medicinal chemistry. The prevalence of pyrazole cores in biologically

active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead.

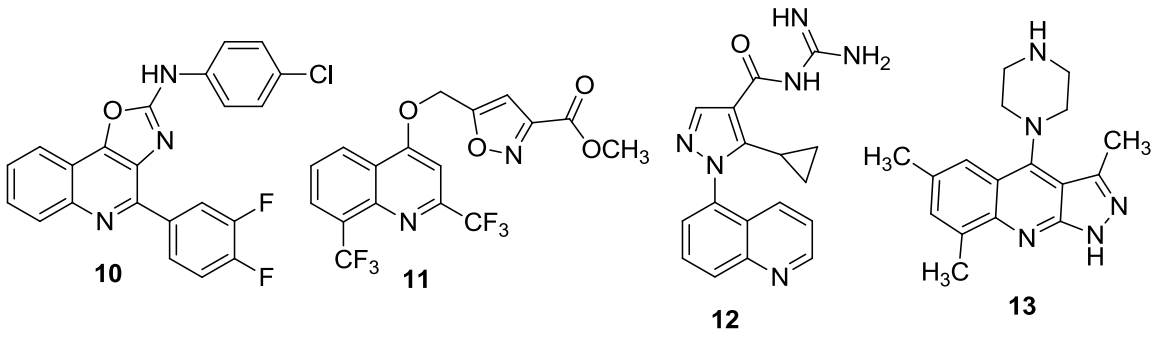
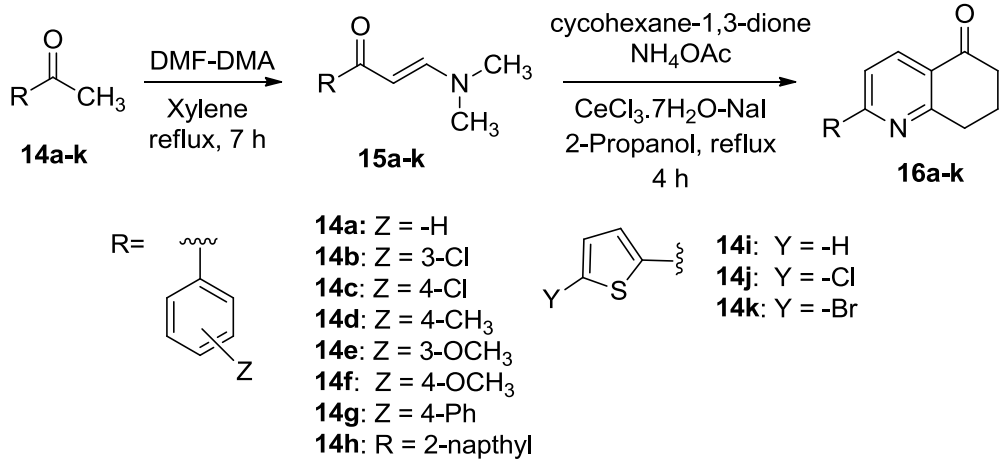


Figure 3

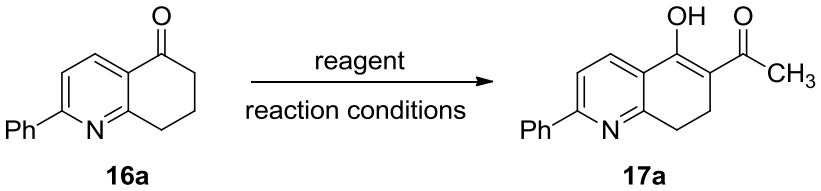
PRESENT WORK:

As a part of our ongoing investigations in the discovery of new antitubercular compounds and the importance of quinoline derivatives in medicinal chemistry, we envisioned to synthesize new fused heterocyclic dihydroquinolines. To begin with, dihydro-6*H*-quinolin-5-one **14a-k** derivatives, required were prepared from acetophenones.



Scheme 1

Synthesis of Hydroxy acetyl dihydroquinolines:



Scheme 2

With the desired quinolinone building block **16a** in hand, various reaction conditions were screened to effect the desired hydroxy acetyl quinolines (Table 1). Initial efforts using BF_3-etherate in acetic anhydride and with acetyl chloride, silver perchlorate in nitro

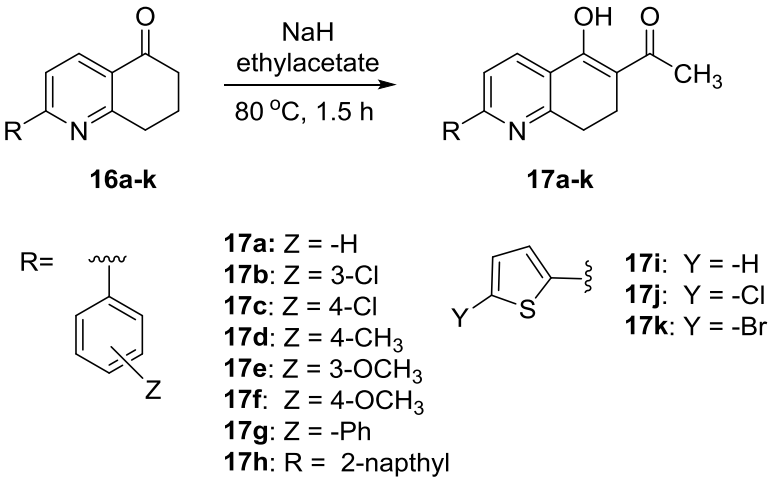
methane unsuccessful for the acylation of quinolinone **16a**. Acylation of **16a** was successful using NaH in ethyl acetate gave the product **17a** in 15% yield. Finally, acylation preceded smoothly using sodium hydride in ethyl acetate at 80 °C to give the desired product **17a** in 80% yield.

Table 1: Optimization of reaction conditions for the acylation of quinolinone **16a**

S.No	Reagent	Solvent	Temperature	Time	Yield (%)
1	BF_3-etherate	AC_2O	0 ^oC to RT	24 h	--
2	Acetyl chloride, $AgClO_4$	CH_3NO_2	0 ^oC to RT	24 h	--
3	NaH	EtOAc	RT	24 h	15
4	NaH	EtOAc	80 ^oC	1.5 h	85

[a]All the reactions were performed with **16a** (1.0 mmol) & solvent (5 mL)

Reaction of various dihydro-6*H*-quinolin-5-ones (**16a-k**) with sodium hydride and ethyl acetate at 80 ^oC for 1.5 h resulted hydroxyl acetyl dihydroquinolines (**17a-k**) in good yield (Scheme 3). The crude isomeric mixture of **17a-k** was separated over silica gel column chromatography. All the products thus obtained were fully characterized by their NMR and mass spectral data.



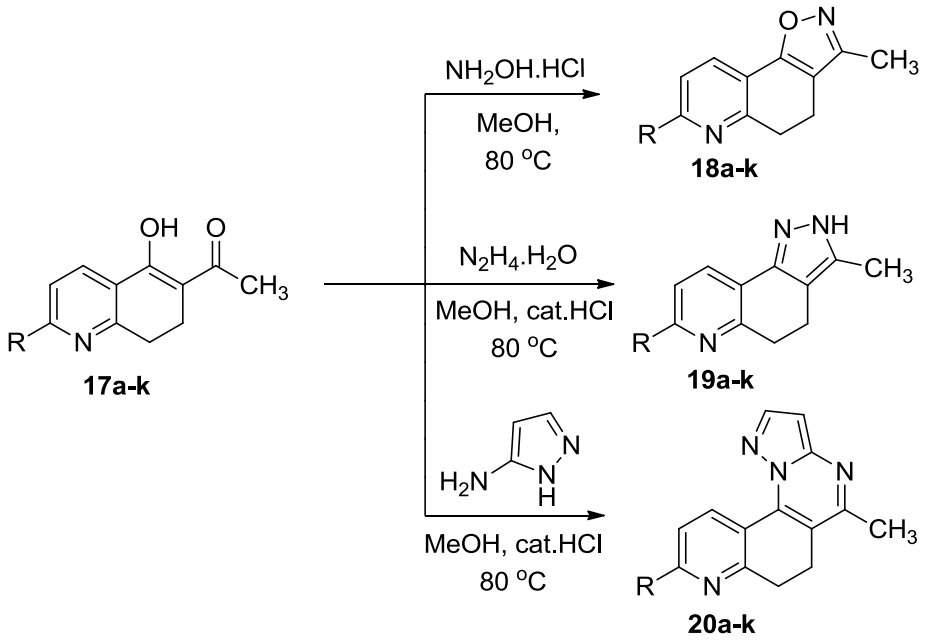
Scheme 3

The ^{1}H-NMR spectrum of **17e** revealed aromatic protons at δ 8.21 (1H) as doublet (J = 8.0 Hz), at δ 7.69 (1H) as doublet (J = 8.0 Hz), δ 7.65-7.58 (1H) as multiplet, δ 7.39 (1H) as triplet (J = 7.9 Hz), δ 7.02-6.97 (1H). The methoxy (-OCH_3) protons appeared at δ 3.90 (3H) as singlet, the methylene (-CH_2) protons appeared at δ 3.15 (2H) as triplet (J = 7.6 Hz) and at δ 2.77 (2H) as triplet (J = 7.6 Hz) and the characteristic methyl

protons (-CH_3) appeared at δ 2.27 (3H) as singlet. In HR-MS (ESI) spectrum the peak observed at *m/z* 296.12753 for $C_{18}H_{18}NO_3$ $[M+H]^+$ confirmed the structure **17e** as 1-(5-hydroxy-2-(3-methoxyphenyl)-7,8-dihydroquinolin-6-yl)ethanone.

Synthesis of dihydroquinoline derivatives from hydroxy acetyl dihydroquinolines 17a-k:

With the required Hydroxy acetyl dihyroquinolines **17a-k** in hand, we have performed a reactions involving with hydroxylamine, hydrazine hydrate and 3-aminopyrazole in methanol at 80 ^oC for 12 h gave dihydroisoxazoloquinolines **18a-k**, dihydropyrazolo quinolines **19a-k** and dihydropyrazolopyridoquinazolines **20a-k** respectively in good yields (Scheme 4).



Scheme 4

The compound **18g** was characterized from the ^{1}H-NMR spectrum by the appearance of aromatic protons at δ 8.11 (2H) as doublet (*J* = 9.0 Hz), δ 7.94 (1H) as doublet (*J* = 8.3 Hz), δ 7.77-7.62 (5H) as multiplet, δ 7.48 (2H) as triplet (*J* = 8.3 Hz), δ 7.43-7.33 (1H) as multiplet. The methylene (-CH_2) protons appeared at δ 3.33 (2H) as triplet (*J* = 8.3 Hz) and at δ 2.83 (2H) as triplet (*J* = 8.3 Hz), methyl protons (-CH_3) appeared at δ 2.33 (3H) as singlet. In HR-MS (ESI) spectrum the peak observed at *m/z* 313.13322 for $C_{23}H_{19}N_2O$ $[M+H]^+$ confirmed the structure **18g** as 7-([1,1'-biphenyl]-4-yl)-3-methyl-4,5-dihydro isoxazolo[5,4-*f*]quinoline. All the derivatives were fully characterized by their ^{1}H, ^{13}C NMR, IR and Mass spectral analysis.

The structure of the compound **18g** and its regioselectivity was unambiguously confirmed by its single crystal X-ray analysis (Figure 4).

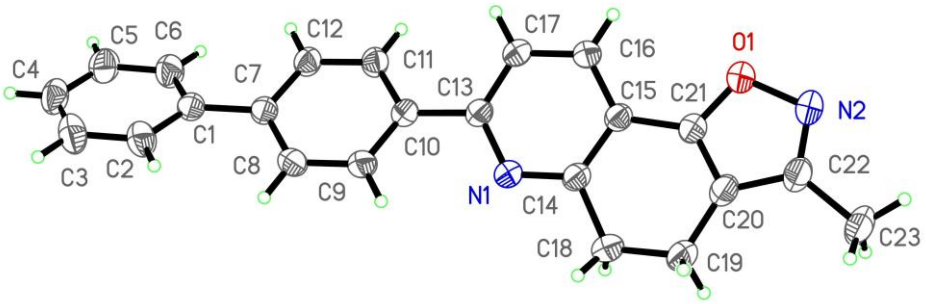


Figure 4: ORTEP diagram of compound **18g**

The compound **19g** was characterized from the ^{1}H-NMR spectrum by the appearance of aromatic protons at δ 8.21 (1H) as doublet (*J* = 8.3 Hz), δ 8.08-7.86 (2H) as multiplet, δ 7.84-7.71 (4H) as multiplet, δ 7.50 (2H) as triplet (*J* = 7.1 Hz), δ 7.44-7.36 (1H) as multiplet. The methylene (-CH_2) protons appeared at δ 3.12 (2H) as triplet (*J* = 7.5 Hz) and at δ 2.78 (2H) as triplet (*J* = 7.5 Hz) and methyl protons (-CH_3) appeared at δ 2.22 (3H) as singlet. In HR-MS (ESI) spectrum the peak observed at *m/z* 338.16579 for $C_{23}H_{20}N_3$ $[M+H]^+$ confirmed the structure **19g** as 7-(biphenyl-4-yl)-3-methyl-4,5-dihydro-2*H*-pyrazolo[3,4-*f*]quinoline. All the derivatives were fully characterized by their ^{1}H, ^{13}C NMR, IR and Mass spectral analysis.

The structure of the compound **19g** and its regioselectivity was unambiguously confirmed by its single crystal X-ray analysis (Figure 5).

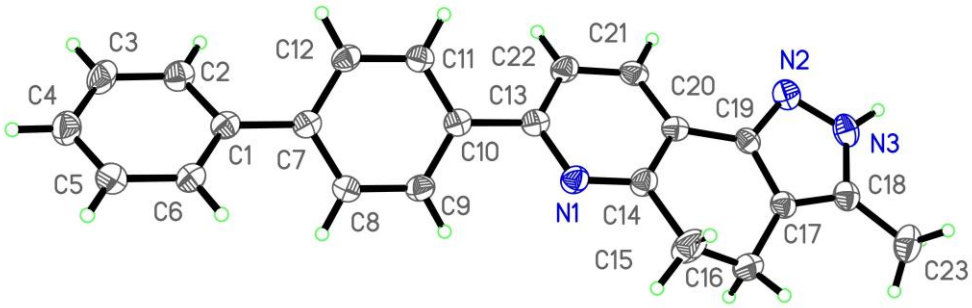


Figure 5: ORTEP diagram of compound **19g**

The compound **20k** was characterized from the ^{1}H-NMR spectrum by the appearance of aromatic protons at δ 9.68 (1H) as doublet (*J* = 8.5 Hz), δ 8.12 (1H) as doublet (*J* = 2.2 Hz), δ 7.71-7.66 (2H), 7.45 (1H) as doublet of doublet (*J* = 5.0, 0.9 Hz) , δ 7.14 (1H) as doublet of doublet (*J* = 5.0, 3.6 Hz), δ 6.64 (1H) as doublet (*J* = 2.2 Hz). The methylene (-CH_2) protons appeared at δ 3.25-3.20 (2H) and at δ 3.07-3.02 (2H), methyl protons (-CH_3) appeared at δ 2.65 (3H) as singlet. In HR-MS (ESI) spectrum the peak observed at *m/z* 319.10123 for $C_{18}H_{15}N_4S$ $[M+H]^+$ confirmed the structure **20i** as 5-methyl-9-

(thiophen-2-yl)-6,7-dihydropyrazolo [1,5-*a*]pyrido[2,3-*h*]quinazoline. All the derivatives were fully characterized by their ^{1}H, ^{13}C NMR, IR and Mass spectral analysis.

The structure of the compound **20i** and its regioselectivity was unambiguously confirmed by its single crystal X-ray analysis (Figure 6).

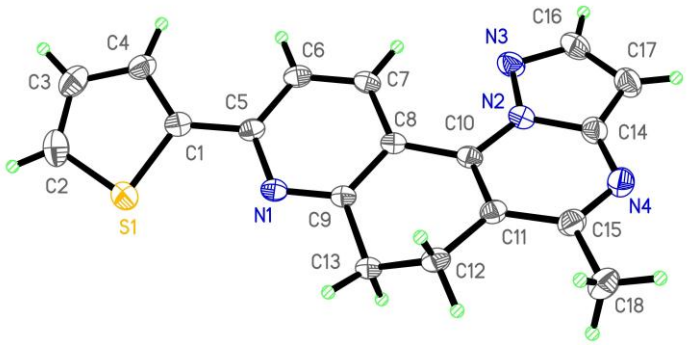


Figure 6: ORTEP diagram of compound **20i**.

Pharmacology:

The antitubercular activity of all the synthesized compounds **18a-k, 19a-k & 20a-k** screened have showed *in vitro* activity against *Mycobacterium tuberculosis* H37Rv with MIC values ranging from 0.40-25 µg/mL. Among them, one compound **20h** with MIC 0.40 µg/mL, three compounds **18e, 18i** and **19i** with MIC 1.56 µg/mL and five compounds **18d, 19b, 19j, 20b** and **20k** with MIC 3.13 µg/mL. The *in vitro* cytotoxicity evaluation of all compounds revealed that compounds **18e, 18i, 19i** and **20h** exhibited 26.5%, 42.1%, 19.5% and 21.5% inhibition at 50 µg/mL.

CONCLUSION:

In conclusion we have synthesized a new class of dihydroisoxazoloquinolines **18a-k**, dihydropyrazoloquinolines **19a-k** and dihydropyrazolopyridoquinazolines **20a-k**. Screening all these new analogues against *Mtb* resulted one compound **20h** (MIC 0.40 µg/mL) as most potent antitubercular agent with low cytotoxicity.

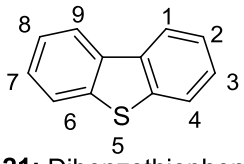
Chapter II : Synthesis and antitubercular evaluation of novel dibenzo [*b,d*]thiophene-1,2,3-triazoles appended with cyclic and acyclic amines.

INTRODUCTION:

DIBENZOTHIOPHENE:

Dibenzothiophene **21** is a tricyclic organosulfur compound consisting of two benzene rings fused to a central thiophene ring. It is occurring widely in heavier fractions of petroleum. The chemistry of dibenzothiophene was first reported by Stenhouse in 1870.

Graebe contributed a lot in understanding the regioselectivity and other properties of dibenzothiophene.



21: Dibenzothiophene

Synthetic bioactive analogues of dibenzothiophene:

Cano et al., synthesized DNA-dependent Protein Kinase (DNA-PK) Inhibitors of dibenzo thiophene containing Quinolin-4-one and Pyridopyrimidin-4-one surrogates for the chromen-4-one. Curtin et al., described chemosensitisation of cancer cells, dual inhibitor of DNA-PK and PI-3K by KU-0060648 (Figure 7**)**.

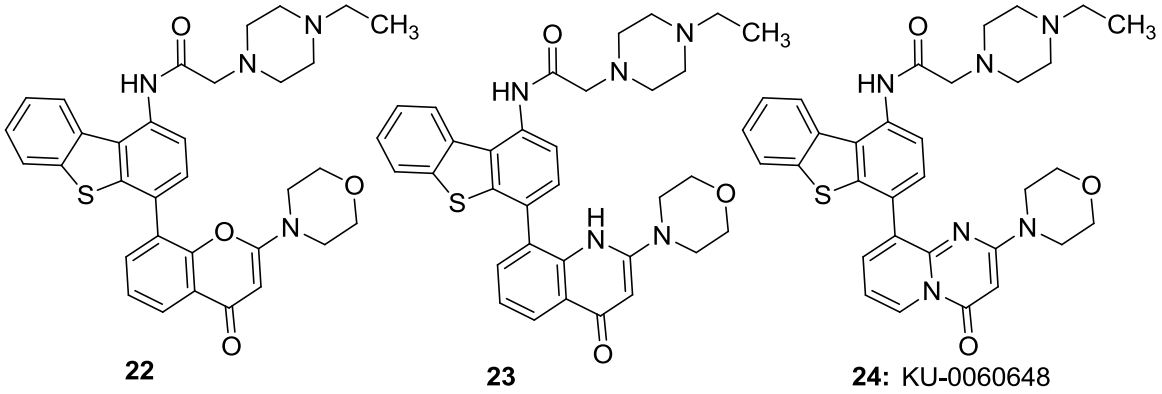


Figure 7

Triazoles:

The basic heterocyclic rings present in the various medicinal agents are mainly 1,2,3-triazole and 1,2,4-triazole. A large volume of research has been carried out on triazole and their derivatives exhibiting wide range of biological activities, such as anticancer, antitubercular, antifungal, anticonvulsant, antibacterial and HIV protease inhibitors.

There are very few 1,2,3-triazole containing molecules on the market or are in the last stage of clinical trials. Potential pharmaceuticals based on 1,2,3-triazoles include the anticancer compound Carboxyamidotriazole (CAI), the nucleoside derivative non-nucloside reverse transcriptase inhibitor *tert*-Butyldimethylsilylspiroaminooxathiole dioxide (TSAO), β-lactum antibiotic Tazobactum (Figure 8).

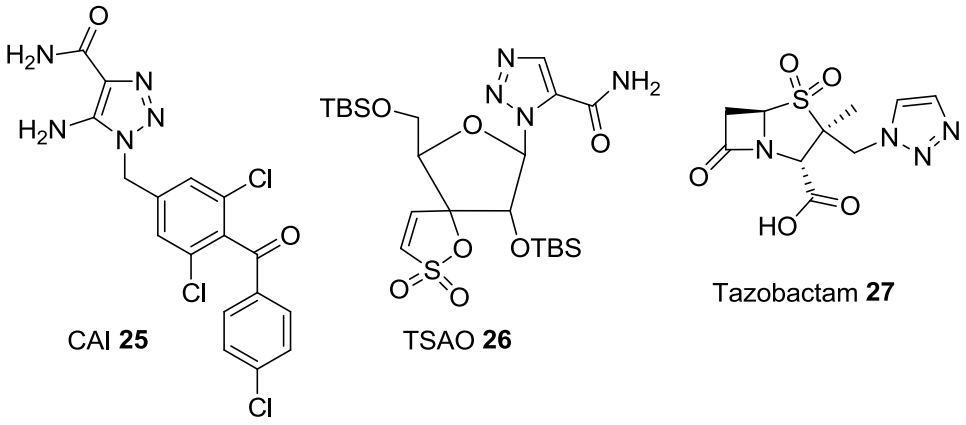


Figure 8

PRESENT WORK:

Earlier work from our group on development of novel bioactives resulted dibenzo[*b,d*]furan, dibenzo[*b,d*]thiophene and N-methyl carbazole tethered substituted 1,2,3-triazoles with potent antimycobacterial activity. Structure-activity relationships (SAR) revealed that dibenzo[*b,d*] thiophene tethered 1,2,3-triazoles exhibited *M. tuberculosis* inhibition at lower concentrations compared to the corresponding dibenzo[*b,d*]furan and N-methyl carbazole derivatives.

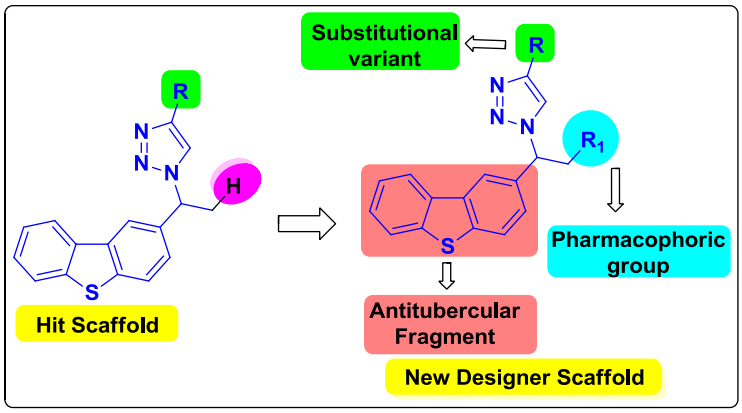
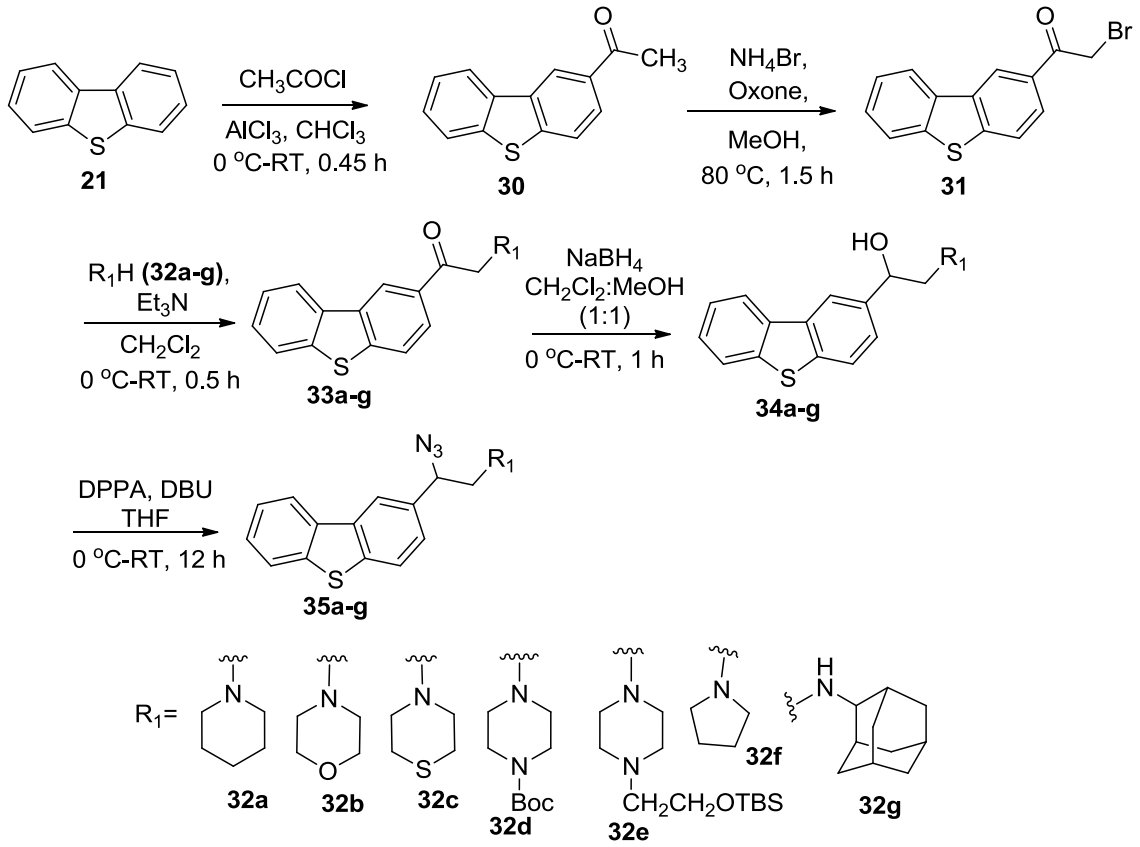


Figure 9

These observations led us to focus on development of dibenzo[*b,d*]thiophene derived newer scaffolds to screen their antitubercular activity. In clinical antitubercular agents pharmacophoric morpholine, thiomorpholine, piperidine or piperazine units play vital role in the inhibition of *M. tuberculosis*. Continuing our efforts on the development of newer and potent antitubercular agents, we envisaged that, maneuvering dibenzo[*b,d*]thiophene-1,2,3-triazoles appended with morpholine, thiomorpholine, piperidine, piperazine, pyrrolidine and 2-adamantane amine in single molecular frame could deliver new scaffolds for screening against *Mycobacterium tuberculosis* (*Mtb*). The method adopted

for synthesis of 1,2,3-triazole conjugates was based on Huisgen 1,3-dipolar cycloaddition reaction (click reaction) of alkynes and azides.

A more holistic approach for design strategy would be through, i) correlation of the structural features of widely used drugs; ii) identification of common pharmacophoric unit(s) and iii) incorporate them to generate newer scaffolds with envisaged activity profile. With the fact that piperidine, piperazine, morpholine, thiomorpholine, pyrrolidine and 2-adamantane amine are prominent in TB drugs, a design strategy is formulated to inculcate these units into the dibenzo[*b,d*]thiophene-1,2,3-triazole architecture (Figure 9).

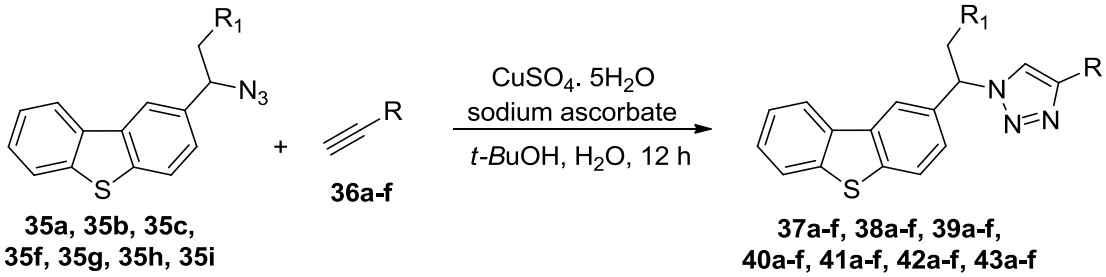


Scheme 5

Compound **30** was prepared by acylation of dibenzo[*b,d*]thiophene **21**, was alpha brominated with NH_4Br and oxone gave **31**, coupled to various cyclic and acyclic amines **32a-g** gave **33a-g**, reduced to alcohol derivatives **34a-g** using $NaBH_4$. The azide building blocks **35a-g** were accomplished in excellent yields (85-92%) from alcohols **34a-g** with DPPA, DBU in THF at 0 °C to RT for 12 h. Boc deprotection of **35d** with methanolic HCl gave **35h** and TBS deprotection of **35e** with TBAF gave **35i**.

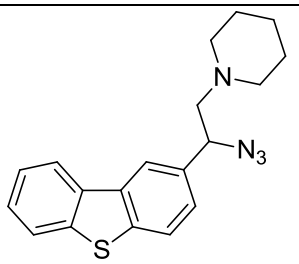
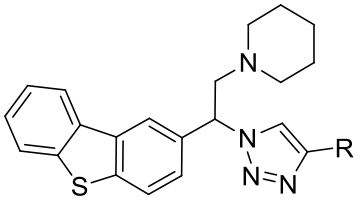
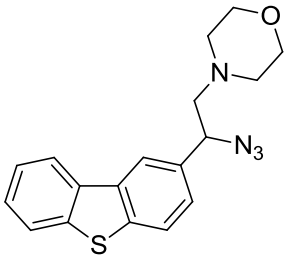
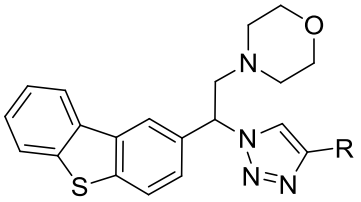
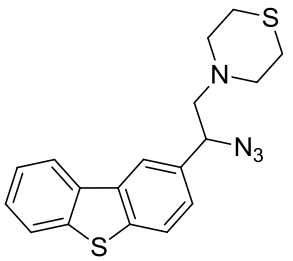
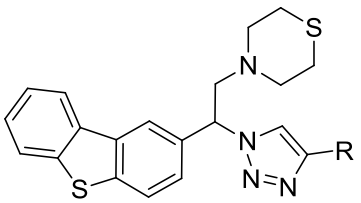
With the required azides in hand, the 1,3-dipolar cycloaddition reactions of azides **25a-c** & **35f-i** with various alkynes **36a-f** were studied. Thus, the reaction of **35c** with **36b**

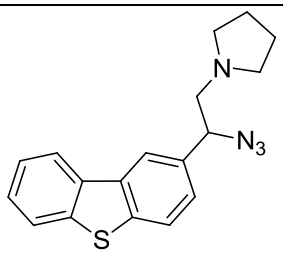
using copper sulfate and sodium ascorbate at room temperature in aqueous *tert*-butanol for 12 h gave 4-(2-(dibenzo[*b*,*d*]thiophen-2-yl)-2-(4-*p*-tolyl-1*H*-1,2,3-triazol-1-yl)ethyl) thiomorpholine (**39b**) in 84% yield (Scheme 6).



Scheme 6

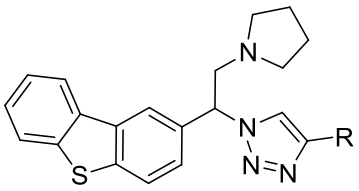
Table: Synthesis of 1,2,3-triazole derivatives using click chemistry

S.No	Azide	Acetylene	Triazole
1.	 **35a**	 **36a-f**	 **37a-f**
2.	 **35b**	 **36a-f**	 **38a-f**
3.	 **35c**	 **36a-f**	 **39a-f**

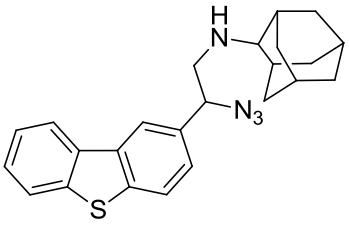
4. 

35f

36a-f

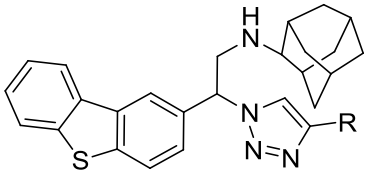


40a-f

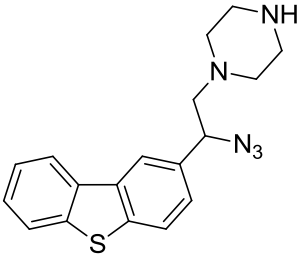
5. 

35g

36a-f

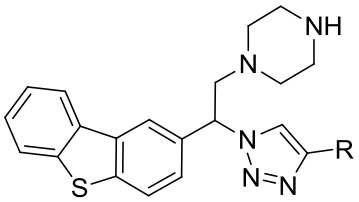


41a-f

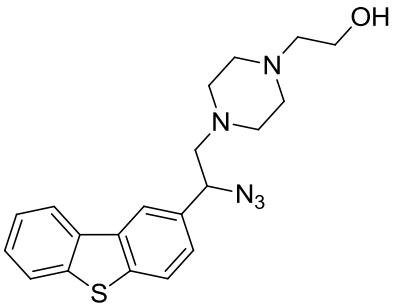
6. 

35h

36a-f

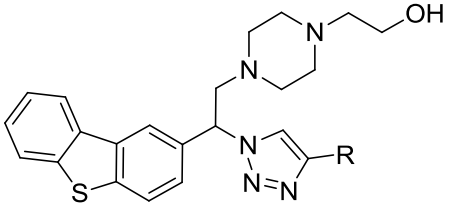


42a-f

7. 

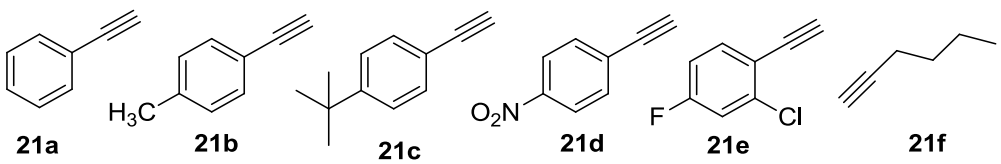
35i

36a-f



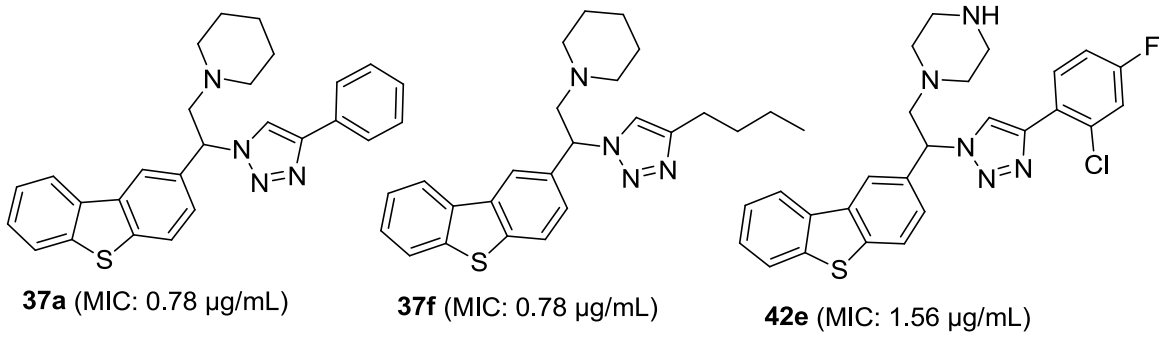
43a-f

Acetylenes:



21a **21b** **21c** **21d** **21e** **21f**

The triazole derivative **39c** was characterized from ^{1}H NMR spectrum by the appearance of aromatic protons at δ 8.18-8.10 (2H) as multiplet, at δ 7.89-7.82 (2H) as multiplet, at δ 7.78 (1H) as singlet, at δ 7.76-7.68 (2H) as multiplet, at δ 7.52-7.41 (3H) as multiplet, at δ 7.22 (2H) as doublet (*J* = 7.9 Hz). The benzylic proton (Ar-CH) appeared at δ 5.90 (1H) as doublet of doublet (*J* = 8.6, 5.4 Hz), methylene protons (-CH_2) at δ 3.65 (1H) as doublet of doublet (*J* = 13.7, 8.6 Hz) and δ 3.24 (1H) as doublet of doublet (*J* = 13.7, 5.4 Hz), thiomorpholine protons at δ 2.96-2.75 (4H) as multiplet (N-attached) and δ 2.57 (4H) as triplet (*J* = 4.9 Hz) (S-attached), methyl protons (-CH_3) at δ 2.37 (3H) as singlet. In HR-MS (ESI) spectrum the peak observed at *m/z* 471.16585 for $C_{27}H_{27}N_4S_2$ $(M+H)^+$ confirmed the structure **39c** as 4-(2-(dibenzo[*b,d*]thiophen-2-yl)-2-(4-*p*-tolyl-1*H*-1,2,3-triazol-1-yl)ethyl)thiomorpholine.



37a (MIC: 0.78 µg/mL) **37f** (MIC: 0.78 µg/mL) **42e** (MIC: 1.56 µg/mL)

Pharmacology:

A total of '42' newly synthesized dibenzo[*b,d*]thiophene-1,2,3-triazole analogues were screened for antimycobacterial activity and have showed *in vitro* activity against *Mtb* with MICs ranging from 0.78-50.0 µg/mL. Among them, two compounds **37a** & **37f** inhibited *Mtb* with MIC 0.78 µg/mL. The *in vitro* cytotoxicity evaluation of all compounds **37a-f, 38a-f, 39a-f, 40a-f, 41a-f 42a-f & 43a-f** revealed that compounds **37a** and **37f** exhibited 25.4% and 20.6% inhibition at 50µg/mL.

CONCLUSION:

In conclusion, we synthesized a series of new dibenzo[*b,d*]thiophene clubbed-1,2,3-triazole appended with cyclic and acyclic amines. Screening all the compounds for *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H_{37}Rv resulted, almost all the derivatives were more potent than standard drugs. Among all the compounds screened, **37a** and **37f** possess the maximum *Mtb* inhibitory activity with MIC 0.78 µg/mL and has low toxicity profile.

Chapter III & *Section A* : **Synthesis and antitubercular evaluation of novel dibenzo [*b,d*]thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamides.**

INTRODUCTION:

Imidazopyridine, the imidazole moiety fused with the pyridine ring, is an important biologically active nitrogen containing heterocycle. Among the various imidazopyridine derivatives, the imidazo[1,2-*a*]pyridine moiety is the most important in the area of natural products and pharmaceuticals.

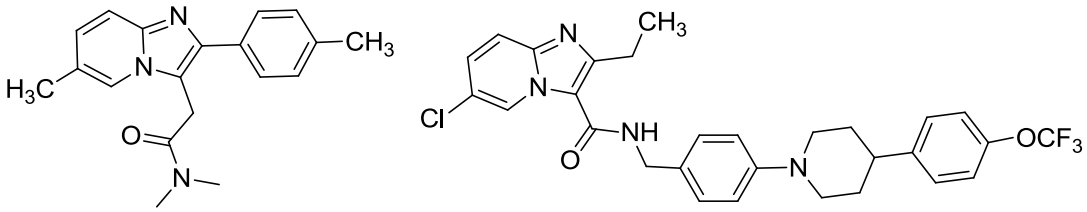


Figure 10

As a result of our interest in the synthesis of imidazopyridine-containing compounds and their antimicrobial activity, we initiated a program directed towards the synthesis of the new imidazopyridine amide derivatives. Imidazopyridine amides (IPA) are a new class of therapeutic agents against MDR and XDR tuberculosis. Recently, Qurient therapeutics discovered **45**: Q-203 (Figure 10), a highly innovative drug for MDR and XDR tuberculosis and the first drug in its class with an original mechanism of action.

PRESENT WORK:

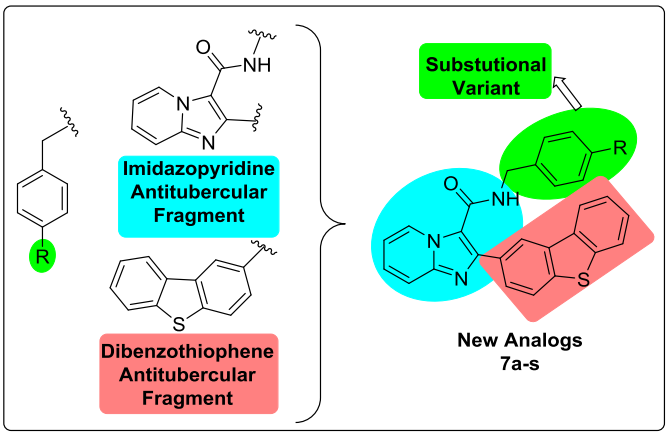
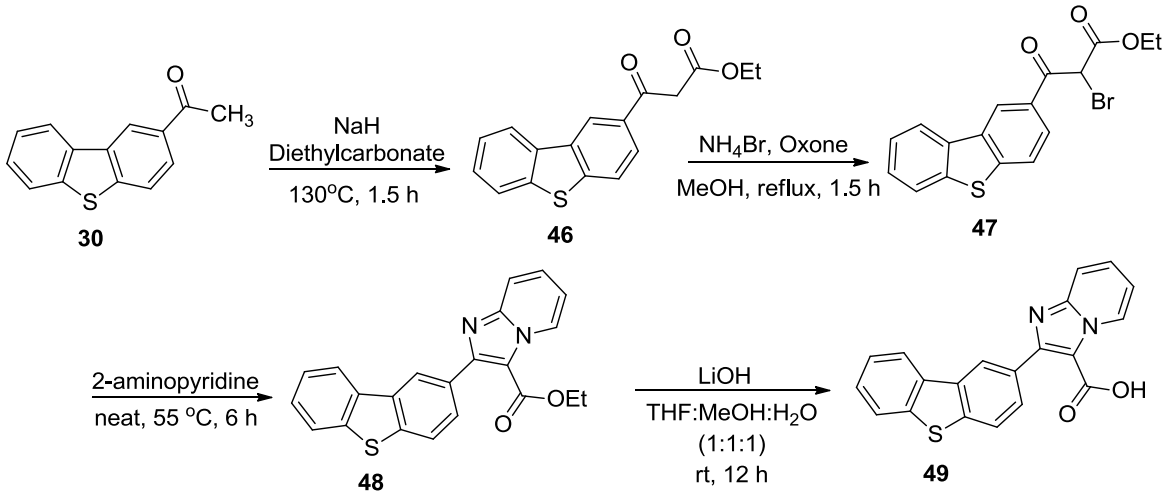


Figure 11

Inspired by the applications of dibenzo[*b,d*]thiophene derivatives in the field of medicinal chemistry, especially in treatment of tuberculosis. Since imidazopyridine constitutes an important class of heterocyclic compound possessing diverse pharmacological activities, we decided to develop a novel dibenzothiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamide derived conjugates as antimycobacterial agents.

The designed scaffold was broadly divided into three segments (Figure 11). First segment is imidazo[1,2-*a*]pyridine, an active pharmacophore from clinical antitubercular TB drug Q-203. Bioactive dibenzo[*b,d*]thiophene is the second segment tethered to imidazo[1,2-*a*]pyridine core for desired pharmacological behavior. Anti-TB activity profile of the proposed scaffold was tuned with the choice of appended substituted benzyl amines in the third segment.

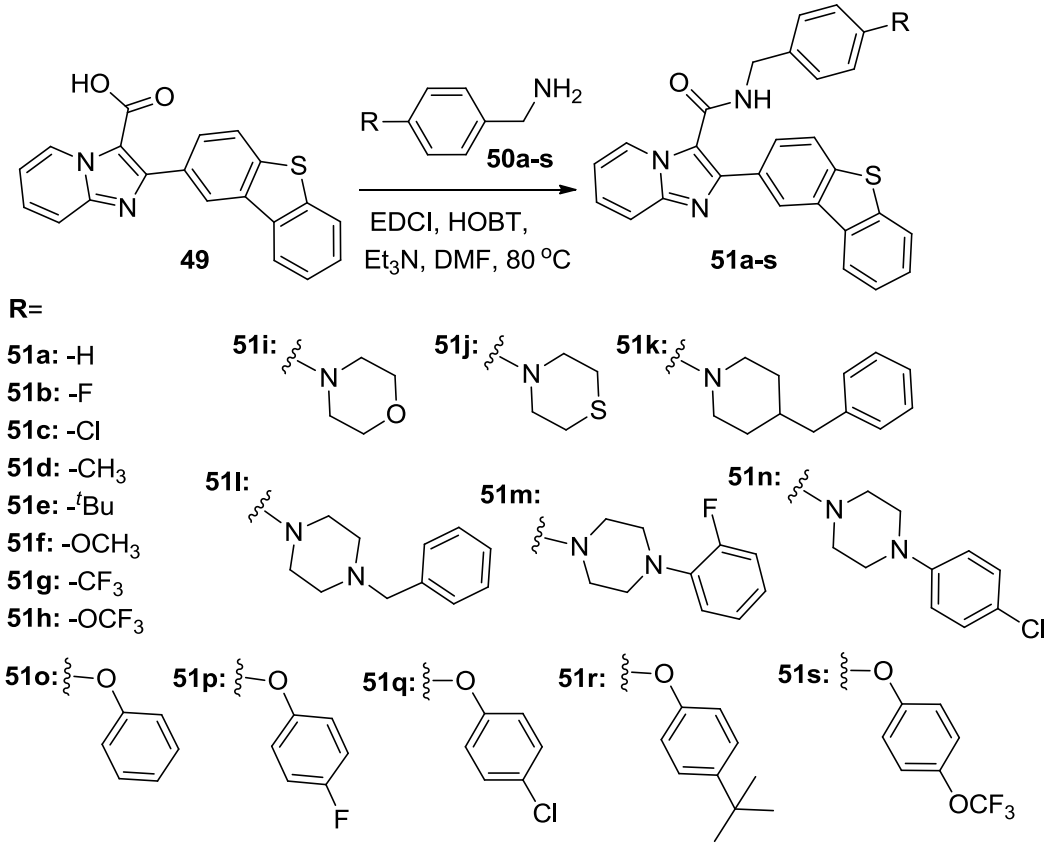


Scheme 7

The required building block, 2-dibenzo[*b,d*]thiophenyl imidazo[1,2-*a*]pyridine carboxylic acid **49** was synthesized from commercial dibenzo[*b,d*]thiophene. 1-(dibenzo[*b,d*]thiophen-2-yl)ethanone **30** prepared in chapter-II was used as starting material. Reaction of 1-(dibenzo[*b,d*]thiophen-2-yl)ethanone **30** with sodium hydride in diethyl carbonate at 130 ^{o}C for 1.5 h afforded ethyl 3-(dibenzo[*b,d*]thiophen-2-yl)-3-oxopropanoate **46**, which was α-brominated with ammonium bromide and Oxone in methanol at 80 ^{o}C for 1.5 h afforded ethyl 2-bromo-3-(dibenzo[*b,d*]thiophen-2-yl)-3-oxopropanoate **47**. Ethyl 2-bromo-3-(dibenzo[*b,d*]thiophen-2-yl)-3-oxo propanoate **47** was reacted with 2-amino pyridine at 55 ^{o}C for 6 h afforded ethyl 2-(dibenzo[*b,d*] thiophen-2-yl)imidazo[1,2-*a*]pyridine-3-carboxylate **48**. Ethyl 2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[1,2-*a*]pyridine-3-carboxylate **48** saponification with lithium hydroxide followed by acidic work up gave the desired 2-(dibenzo[*b,d*]thiophen-2-yl)imidazo[1,2-*a*] pyridine-3-carboxylic acid **49** in 70% overall yield as white solid (Scheme 7).

Further to build the desired amide analogues, 2-(dibenzo[*b,d*]thiophen-2-yl)imidazo [1,2-*a*]pyridine-3-carboxylic acid **49** was coupled with various benzyl amines **50a-s** using classical EDCI-HOBT protocol (Scheme 8). For example, compound **49** was reacted with benzyl amine **50d** using EDCI/HOBT in presence of triethylamine in DMF at 80 ^{o}C gave

2-(dibenzo[*b*,*d*]thiophen-2-yl)-*N*-(4-methylbenzyl)imidazo[1,2-*a*]pyridine-3-carboxamide **51d** in 71% yield. All the synthesized derivatives **51a-s** was fully characterized from their spectral data.



Scheme 8

The carboxamide derivative **51d** was characterized from ^{1}H-NMR spectrum by the appearance of aromatic proton at δ 9.52 (1H) as doublet (*J* = 6.9 Hz), δ 8.40 (1H) as doublet (*J* = 1.1 Hz), δ 8.09-8.02 (1H) as multiplet, δ 7.92-7.86 (1H) as multiplet, δ 7.79 (1H) as doublet (*J* = 8.3 Hz), δ 7.69-7.62 (2H) as multiplet, δ 7.55-7.43 (2H) as multiplet, δ 7.41-7.33 (1H) as multiplet, δ 7.01-6.82 (5H) as multiplet and amide proton (-NH) appeared at δ 6.21 (1H) as triplet (*J* = 4.9 Hz), benzylic protons (-CH_2) appeared at δ 4.41 (2H) as doublet (*J* = 5.4 Hz) and methyl protons (-CH_3) appeared at δ 2.21 (3H) as singlet. In HR-MS (ESI) spectrum the peak observed at *m/z* 448.14664 for $C_{28}H_{22}N_3OS$ $[M+H]^+$ confirmed the structure **51d** as 2-(dibenzo[*b*,*d*]thiophen-2-yl)-*N*-(4-methyl benzyl)imidazo[1,2-*a*]pyridine-3-carboxamide.

Antitubercular evaluation:

The *in vitro* antitubercular evaluation of all the synthesized **51a-s** against *Mycobacterium tuberculosis* H37Rv (*Mtb*) showed MIC values ranging from 0.78–50.0 µg/mL. Among them, one compound **51k** inhibited *Mtb* with an MIC of 0.78 µg/mL, two

compounds **51e & 51n** inhibited *Mtb* with MIC 1.56 µg/mL. The *in vitro* cytotoxicity evaluation of all compounds **51a-s** revealed that compounds **51k**, **51e** and **51n** exhibited 34.7%, 18.7% and 24.3% inhibition at 50µg/mL.

CONCLUSION:

In conclusion, we have synthesized a series of novel dibenzo[*b,d*]thiophene tethered imidazo[1,2-*a*]pyridine-3-carboxamides **51a-s**. Screening all these new derivatives **51a-s** against *M. tuberculosis* H37Rv (*Mtb*) resulted three compounds **51e**, **51k** and **51n** are active antitubercular agents with lower cytotoxicity profile and among these three, **51k** is the most active (MIC 0.78 µg/mL) and least cytotoxic compound.

Chapter III & *Section B* : **Synthesis and evaluation of substituted thiazole/benzothiazole coupled (*E*)-dibenzo[*b,d*]thiophene-2-yl acrylamides as potent inhibitors of *Mycobacterium tuberculosis***

INTRODUCTION:

Cinnamic acid is a component of plant-derived scents and flavourings. It belongs to the class of auxin, which is recognized as plant hormones regulating cell growth and differentiation. Cinnamic acid **52** and its derivatives have a century-old history as antituberculosis agents. For example, gradual improvement was observed when the TB-patients were treated with cinnamic acid and ethylcinnamate **53**. The hydroxyl cinnamic acids such as *p*-coumaric acid **54**, caffeic acid **55**, ferulic acid **56**, sinapic acid **57** are natural products arising from the deamination of the phenyl alanine.

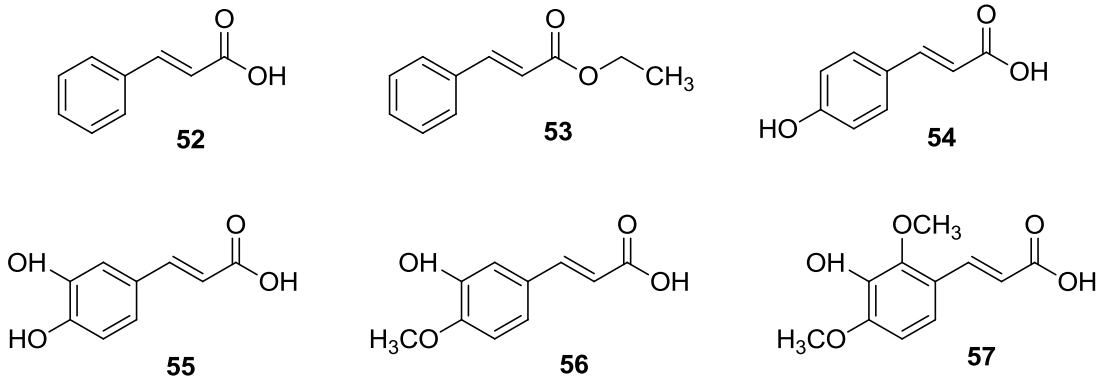


Figure 12

Thiazoles are one of the most intensively investigated classes of aromatic five-membered heterocycles. These are found in many potent biologically active molecules and show a various pharmacological application. Several natural and synthetic thiazole unit containing compounds displayed broad range of biological activities and found in

many potent biologically active molecules such as Sulfathiazole **58** as antibacterial drug, Riluzole **61** as anticonvulsant drug, Talipexole **62** as antiparkinsonian drug.

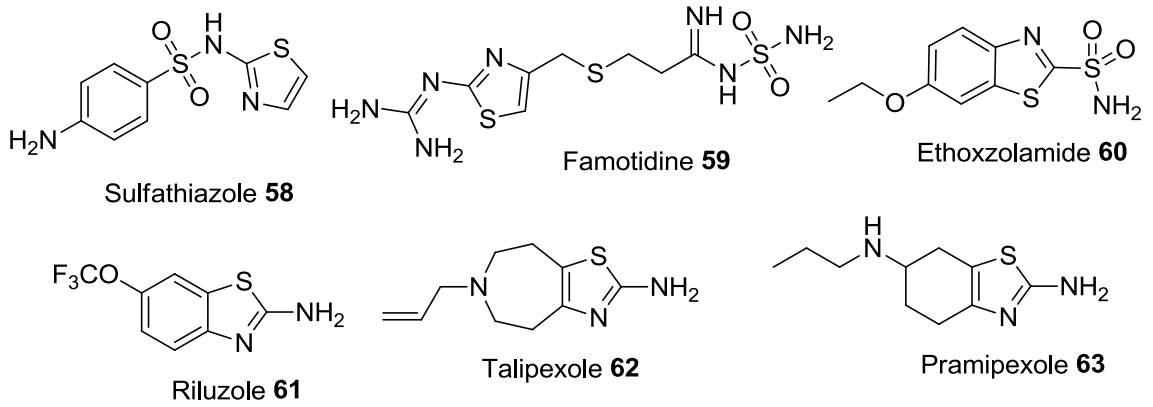
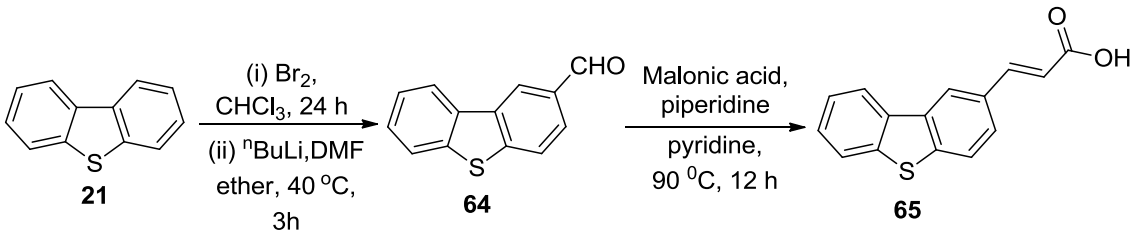


Figure 13

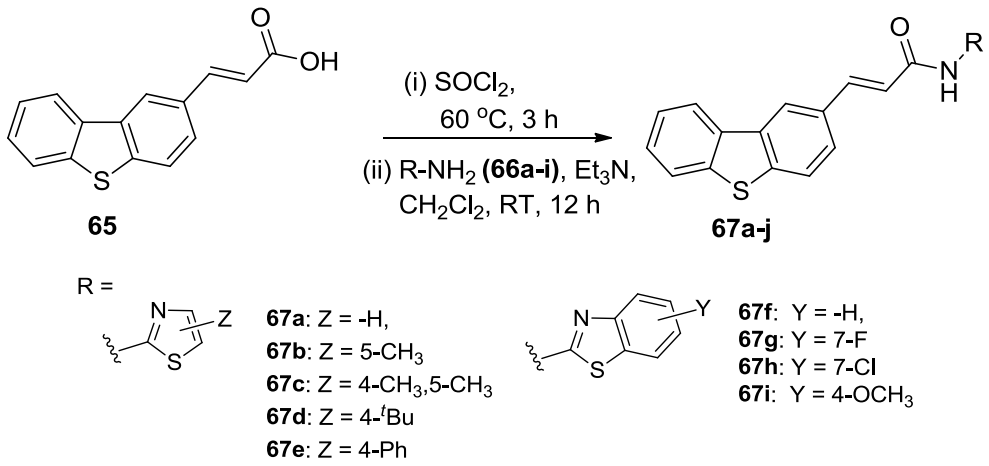
PRESENT WORK:

To begin with, dibenzo[*b,d*]thiophene-2-caraboxaldehyde **64**, required was prepared according to the literature procedure. (*E*)-3-(dibenzo[*b,d*]thiophen-2-yl)acrylicacid **65** required was prepared from dibenzo[*b,d*]thiophene-2-caraboxaldehyde **64**. Initially aldehyde **64** was reacted with malonic acid in presence of piperidine in pyridine solvent at 90 ^{o}C for 12 h gave (*E*)-3-(dibenzo[*b,d*]thiophen-2-yl)acrylicacid **65 (Scheme 9)**.



Scheme 9

The required cinnamide derivatives were synthesized by coupling of (*E*)-3-(dibenzo[*b,d*] thiophen-2-yl)acrylicacid **65** with different substituted 2-amino thiazoles and 2-amino benzothiazoles **66a-i**. Firstly, the (*E*)-3-(dibenzo[*b,d*]thiophen-2-yl)acrylic acid converted into (*E*)-3-(dibenzo[*b,d*]thiophen-2-yl)acryloyl chloride with thionyl chloride at 65 ^{o}C for 3 h, then coupling with **66a-i** in presence of triethylamine in dichloromethane for 12 h afforded cinnamides **67a-i** (**Scheme 10**).



Scheme 10

All the new compounds **67a-i** obtained were fully characterized by ^{1}H, ^{13}C NMR, IR and mass spectral data.

The compound **67d** was characterized from ^{1}H NMR spectrum by the appearance of amide proton at δ 12.26 (1H) as broad singlet, aromatic protons at δ 8.46 (1H) as singlet, δ 8.328-8.29 (1H) and δ 8.03-7.85 (3H) as multiplet, δ 7.75 (1H) as doublet (J = 8.2 Hz), δ 7.568-7.48 (2H) as multiplet. The characteristic trans olefin proton appeared at δ 7.06 (1H) as doublet (J = 15.6 Hz), thiazole proton at δ 6.63 (1H) as singlet and *tert* butyl protons at (-C(CH_3)$_3$) at δ 1.31 (9H) as singlet. In HR-MS (ESI) spectrum the peak observed at *m/z* 393 for $C_{22}H_{21}N_2OS_2$ $[M+H]^+$ confirmed the structure **67d** as *(E)*-*N*-(4-*tert*-butylthiazol-2-yl)-3-(dibenzo[*b*,*d*]thiophen-2-yl)acrylamide.

The structure of the compound **67d** was unambiguously confirmed by its single crystal X-ray analysis (Figure 14)

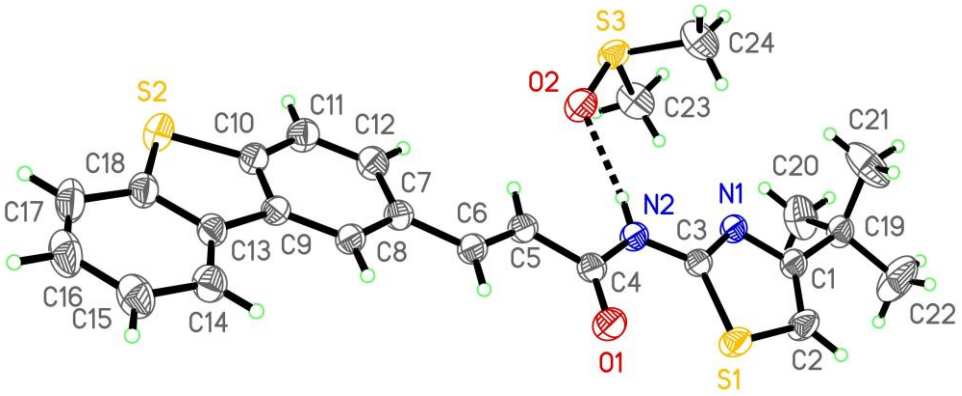


Figure 14: ORTEP diagram of compound **67d**

Pharmacology:

All the new compounds were screened showed *in vitro* activity against *Mtb* with MIC ranging from 3.13-25 µg/mL. Among them, one compound **67a** inhibited *Mtb* with MIC of 3.13 µg/mL, another compound **67h** inhibited *Mtb* with MIC 6.25 µg/mL. The *in vitro* cytotoxicity evaluation of all compounds **67a-i** revealed that compounds **67a** and **67h** exhibited 12.5% and 40.6% inhibition at 50 µg/mL.

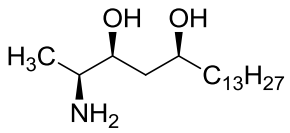
CONCLUSION:

In conclusion, we have synthesized a novel series of dibenzo[*b,d*]thiophene tethered cinnamides **67a-i**. Screening all these new derivatives against *Mtb* revealed that **67a** is active antitubercular agent.

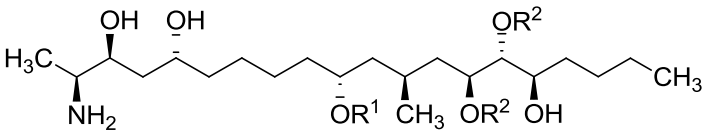
Chapter IV : Total synthesis of Enigmol

Introduction:

Sphingolipids are composed of a structurally related family of backbones termed sphingoid bases, which are sometimes referred to as "long-chain bases" or "sphingosines." Sphingolipids are a class of lipids derived from the aliphatic amino alcohol sphingosine. Sphingolipids are often found in neural tissues, and play an important role in both signal transmission and cell recognition.[2] This diverse family of biomolecules is structurally characterized by a long carbon chain 'sphingoid' base that is derivatized with amide linked fatty acids and various polar head groups.



68: Enigmol



69: R^1 = OH Fumonisin B_1
70: R^1 = H Fumonisin B_2

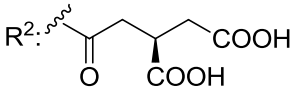


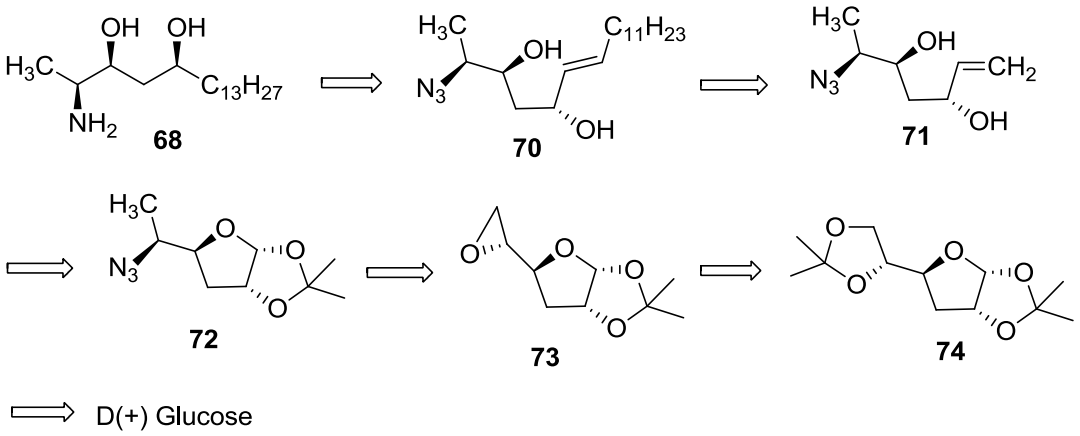
Figure 15

The 1,2-amino alcohol moiety is present in sphingolipids, and recently, the 1-deoxy-5-hydroxy sphingosine analogues have been identified as a potential new class of anticancer principles (Figure 15), Enigmol inhibits both sphingosine kinase and ceramide synthase *in vitro*, and it has demonstrated potent anticancer activity in cells derived from multiple types of cancer, including colon, breast, brain, and prostate. Due to potential applications we initiated the synthesis of Enigmol **68** from commercially available carbohydrate, D-glucose.

PRESENT WORK

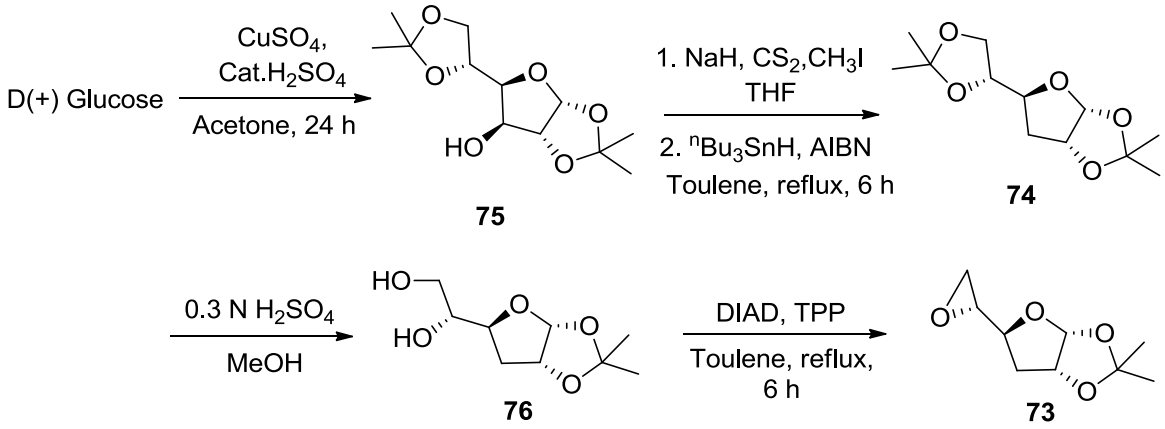
Synthesis of Enigmol 56:

We planned to synthesize Enigmol **68** from commercially available D-glucose. D-glucose was considered as the suitable precursor for the preparation of **68**. Retrosynthetic analysis for compound **68** is presented in Scheme 11.



Scheme 11

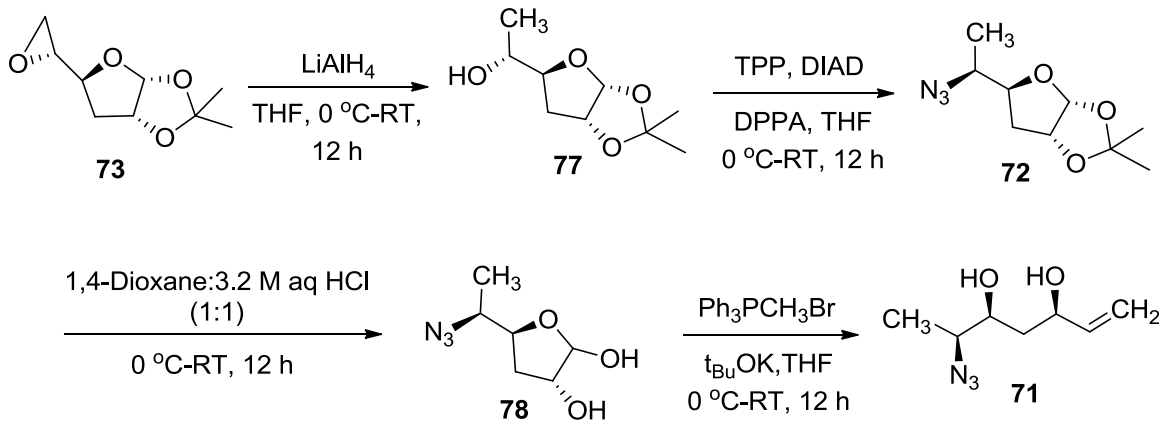
The key steps are (i) Formation of epoxide in C_1-C_2 (ii) Regioselective opening of epoxide (iii) Wittig olefination of lactol (iv) Grubbs reaction between synthesized alkene and 1-tridecene. Finally, reduction leads to the desired Enigmol **68**. Thus, retro synthetically enigmol could be derived from D-glucose.



Scheme 12

D-glucose was transformed to diacetonide **75** by reaction with anhydrous $CuSO_4$, cat. H_2SO_4 in acetone for 24 h in 85.6% yield. Formation of diacetonide **75** was evident from characteristic ^1H NMR spectrum by the appearance of methyl protons at δ 1.50 (3H), 1.44 (3H), 1.37 (3H) and 1.32 (3H) as singlets. D-glucose diacetonide was

converted into xanthate derivative followed by deoxygenation under the Barton–McCombie protocol using n-Bu_3SnH and a catalytic amount of AIBN in toluene under reflux conditions to provide the 3-deoxyglucose derivative **74** in 85.6% yield over two steps. Formation of deoxy glucose evident from ^{1}H NMR spectrum by the appearance of protons at δ 2.19 (1H) as doublet of doublet (J = 13.4, 4.1 Hz) and at δ 1.81-1.73 (1H) as multiplet. Selective deprotection of **74** with 0.3N H_2SO_4 in MeOH for 6 h leads to diol **76** as syrup in 94% yield (Scheme 11). Formation of diol **76** was evident from ^{1}H NMR spectrum by the disappearance of C-5, 6-acetonide protons at δ 1.43 (3H), 1.36 (3H) and appearance of hydroxyl absorptions at 3416 cm^{-1}. Epoxidation of **76** with triphenylphosphine and diisopropylazodicarboxylate (DIAD) in toluene afforded epoxide **73** in 84.7% yield. Formation of epoxide **73** was evident from IR spectrum by the disappearance hydroxyl absorptions at 3454 cm^{-1}.



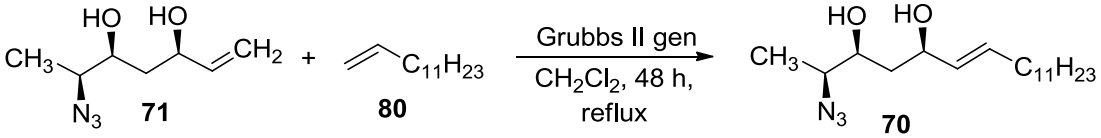
73 **77** **72** **78** **71**

Scheme 13

Regioselective opening of epoxide **73** with $LiAlH_4$ at 0 °C to RT for 12 h gave **77** in 96.3% yield. Formation of **77** was evident from ^{1}H spectrum by the appearance of methyl proton at δ 2.19 (3H) as doublet (J = 5.9 Hz) and appearance of hydroxyl absorptions at 3452 cm^{-1}. The hydroxy group in compound **77** was treated with triphenylphosphine, DIAD and diphenyl phosphoryl azide (DPPA) at 0 °C to RT for 12 h gave azido compound **72** as syrup in 71.2% yield. Formation of azide **72** was evident from IR spectrum by the appearance azide absorptions at 2171 cm^{-1}. Deprotection of 1,2-O-isopropylidene group of compound **72** with 1,4-dioxane and 3.2 M aq HCl (1:1) at 0 °C to RT for 12 h afforded the lactol **78** as a solid in 90.2% yield (m.p. 53-55 °C). Formation of lactol **78** was evident from the ^{1}H NMR spectrum by the disappearance of 1,2-acetonide protons at δ 1.51 (3H), δ 1.33 (3H) and appearance of hydroxyl absorptions at 3357 cm^{-1}.

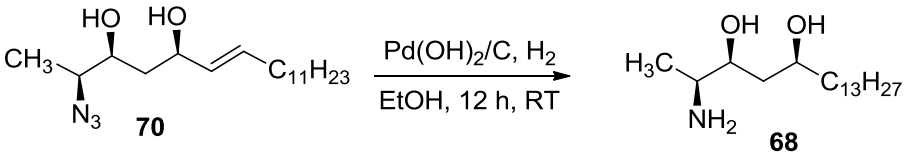
Scheme 14

The relative stereochemistry of the C-3 and C-5 1,3-diols was confirmed by using Rychnovsky's acetonide methodology with ^{13}C NMR analysis. Protection of the 1,3-syn diol **71** with 2,2-DMP and CSA (cat.) in CH_2Cl_2 at 0 ^oC to RT for 12 h gave acetonide **79** as colorless oil in 92% yield (Scheme 14). Analysis of the ^{13}C NMR chemical shifts at δ 19.6, 32.9 and 98.9 for **79**, confirmed the 1-3-syn relationship.



Scheme 15

Compound **70** was achieved from synthesized alkene **71** with 1-tridecene **80** using Grubbs-II generation catalyst in CH_2Cl_2 at reflux temperature for 48 h gave **70** as colorless oil in 42.1% yield. Formation of **70** was characterized from ^1H NMR spectrum by the appearance of olefinic protons at δ 5.73-5.65 (1H) as multiplet, 5.52-5.45 (1H) as multiplet and methylene protons at δ 1.40-1.24 (21 H) as multiplet.



Scheme 16

Reduction of **70** with Palladium hydroxide on carbon under hydrogen atmosphere in ethanol at RT for 12 h afforded Enigmol **68** as white solid (m.p. 68-70 ^oC) in 47.8% yield. Spectral and analytical data obtained for **68** was consistent with those reported in the literature. In conclusion, we have completed the total synthesis of the biologically active natural product Enigmol starting from D-glucose.

CONCLUSION:

In conclusion, an elegant approach to the synthesis of Enigmol **68** in 3.93% overall yield from D-glucose.