CHAPTER - I

Introduction to quinoline and benzo[b]thiophene derivatives
Introduction

Drugs are known to develop immunity in the organization gradually. Hence, efficacy of the present drugs may decrease in the course of time. This needs the replacement of existing drugs periodically by newer drugs. They can also be made potent by structural alterations through chemical reactions. In addition to this these drugs are also associated with some unwanted side effects. Attempts to improve the potency of the drugs and also to eliminate the unwanted side effects are being made continuously throughout the world.

The efficacy of heterocycles of various biological and pharmacological activities is as old as recorded history. Number of heterocycles form an important pharmacophore in several medicines and natural products, possessing biological properties also they have found to possesses heterocyclic moieties, such as thiophene, furan, pyridine, quinoline etc. In particular, literature is well documented with the biological and pharmacological efficacy of quinoline and benzo[b]thiophene derivatives. In view of these facts, the work of synthesis of heterocyclic analogs of quinoline and benzo[b]thiophene molecules, and investigation of their biological and pharmacological activity was undertaken.

This chapter starts with general introduction to the field of quinoline and benzo[b]thiophene derivatives. The introduction includes brief explanation for selecting quinoline and benzo[b]thiophene derivatives as research program. The chapter ends with the scope of the present work taken for pursuing Ph.D. degree.

Quinoline derivatives

Quinoline was discovered in coal tar distillate by Runge\textsuperscript{1} in 1834 and named “Leukol”. The base was also obtained by Gerhardt\textsuperscript{2} in 1842 by alkaline distillation of quinine, cinchonine, or strychnine, and was named by him “Chinolein” or “Chinolin”. Not
until 1882 was the identity of leukol and Chinolin firmly established, when Hoogewerff
and Van Drop showed that the samples from coal tar and from alkaloid distillation had the
same boiling point, formed the same hydrate (3H₂O), platinichloride, bichromate, and
argentonitrate. Both specimens were also converted by oxidation into quinolinic acid,
which was decarboxylated to nicotinic acid. Körner was cited as the first to propose the
structural formula for quinoline (in Die Chemie von Pyridins and Seiner Derivate by A.
Calm) but Dewar in 1871 suggested that quinoline bore the same relationship to pyridine
that naphthalene bore to benzene. The structure (1) was confirmed by the synthesis in
which allylaniline was passed over glowing lead oxide, or from o-nitrocinnamaldehyde as
shown in reaction.

Quinoline, also known as 1-azanaphthalene, 1-benzazine, or benzo[b]pyridine, is a
heterocyclic aromatic organic compound. It has the formula C₉H₇N and is a colourless
hygroscopic liquid with a strong odour. Aged samples, if exposed to light, become yellow
and later brown. Quinoline is only slightly soluble in cold water but dissolves readily in hot
water and most organic solvents.

Quinoline is mainly used as a building block to other specialty chemicals. Its
principal use is as a precursor to 8-hydroxyquinoline, which is a versatile chelating agent
and precursor to pesticides. Its 2- and 4-methyl derivatives are precursors to cyanine dyes.
Oxidation of quinoline affords quinolinic acid (pyridine-2,3-dicarboxylic acid), a
precursor to the herbicide sold under the name "Assert".
Properties

Molecular formula: $C_9H_7N$
Molar mass: 129.16 g/mol
Density: 1.093 g/ml
Melting point: $-15 ^\circ C$
Boiling point: 238 $^\circ C$

Methods of synthesis

There are several methods of synthesis for quinoline derivatives of which some are as follows:

01. The Combes quinoline synthesis

Combes quinoline synthesis is a chemical reaction involving the condensation of unsubstituted anilines with $\beta$-diketones to form substituted quinolines after an acid-catalyzed ring closure of an intermediate Schiff base.

02. The Conrad-Limpach synthesis

The Conrad-Limpach synthesis is the chemical reaction of anilines with $\beta$-ketoesters to form 4-hydroxyquinolines via a Schiff base.
03. The Doebner-Miller synthesis

The Doebner-Miller reaction is the organic reaction of an aniline with α,β-unsaturated carbonyl compounds to form quinolines.

\[
\begin{align*}
\text{R} & \quad \text{H} \\
\text{NH}_2 & \quad -\text{H}_2\text{O}
\end{align*}
\]

04. The Friedländer synthesis

The Friedländer synthesis is the chemical reaction of 2-aminobenzaldehydes with ketones to form quinoline derivatives. It is named after German chemist Paul Friedländer.

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{NH}_2 & \quad -2\text{H}_2\text{O}
\end{align*}
\]

05. The Skraup synthesis

The Skraup synthesis is a chemical reaction used to synthesize quinolines. It is named after the Czech chemist Zdenko Hans Skraup. In the archetypal Skraup, aniline is heated with sulfuric acid, glycerol, and an oxidizing agent to yield quinoline.

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{NH}_2 & \quad \text{H}_2\text{SO}_4, \text{PhNO}_2
\end{align*}
\]

06. The Knorr quinoline synthesis

The Knorr quinoline synthesis is an intramolecular organic reaction converting a β-ketoanilide to a 2-hydroxyquinoline using sulfuric acid. This reaction was first described by Ludwig Knorr in 1886.

\[
\begin{align*}
\text{R} & \quad \text{H}_2\text{SO}_4
\end{align*}
\]
07. The Camps quinoline synthesis

The Camps quinoline synthesis (also known as the Camps cyclization) is a chemical reaction whereby an o-acylaminoacetophenone is transformed into two different hydroxyquinolines (products A and B) using hydroxide ion.

\[
\begin{align*}
\text{O} & \quad \text{R} \\
\text{NH} & \quad \text{R} \\
\text{R} & \quad \text{OH} \\
\text{R} & \quad \text{OH}
\end{align*}
\]

It is common knowledge that quinolines and their derivatives are very useful compounds because a large number of natural products and drugs contain this heterocyclic unit. They have attracted strong interest due to their useful biological and pharmacological properties, such as antitumor, antiviral, antitubercular, antidiabetic and antibacterial activities.

The quinoline nucleus features prominently in compounds which exhibit medicinal properties. Notable amongst these are synthetic antimalarials such as chloroquine and primaquine, fungicides such as halacrinate, antibacterial 4-quinolones such as ciprofloxacin and norfloxacin, the HIV-1 protease inhibitor saquinavir, and styrylquinolines as potential HIV-1 integrase inhibitors. Not surprisingly, an array of synthetic methods have been developed to access quinoline derivatives, including the classic Skraup, Doebner-von Miller, Conrad-Limpachand Knorr syntheses.

The quinolines condensed with furan in a linear and angular fashion is present in the alkaloids isolated from Rutaceae, Dictamine, skimmianine, confusameline, evolitrine, haplopine, kokusaginine and γ-fagarine are the most important among them. These alkaloids exhibits considerable amount of biological activity via, the Dictamine, is found to strongly contract smooth muscle and to stop the isolated frog heart in diastole. Skimmianine is known to relax intestinal muscle. The X-ray crystal structure of the known
alkaloid flindersiamine isolated for the first time from *Raulinoa echinata*, has been reported\(^{25}\). This alkaloid and its congeners *kokusaginine, Skimmianine* and *maculine* exhibits antifungal activity against *Leucoagaricus gongylophorus*. Quinolines derivatives form an important class of N-heterocycles in that they display alternative application as pharmacological (e.g. antimalarial drugs) as well as being general synthetic building blocks due to their chemical and biological relevance\(^{26,27}\).

Furoquinoline alkaloids are well known in nature, some of these compounds of the types (2-7) have been found to possess many interesting pharmacological activities\(^{28-32}\).

![Chemical structures](attachment:chemical_structures.png)

Quinolines and their derivatives occur in numerous natural products\(^{33a}\). Many quinolines display interesting physiological activities and have found attractive applications as pharmaceuticals and agrochemicals as well as being general synthetic building blocks\(^{33b}\). Many synthetic methods have been developed for the preparation of quinolines\(^{34}\). But, due to their great importance, the development of novel synthetic methods remains an active research area\(^{35}\).

The presence of heterocyclic structures in many natural and synthetic products endowed with biological activities makes account for the large amount of searches devoted in the past years to the synthesis of novel polycyclic systems, containing one or more hetero atoms. Various tricyclic pyrrole annulated rings, including pyrroloquinoxalines and
pyrroloquinolines, have been used as lead chemical structures for developing chemotherapeutic agents and drugs acting on Central Nervous System.

Quinoline (8) is a heterocyclic base which has attracted the attention of organic chemists for more than 150 years. Quinoline ring system is present both in the natural products and synthetic compounds of biological interest. Among the natural products containing quinoline system, the most important ones are the antimalarial alkaloids cinchonine (9a) and quinine (9b) present in the cinchona bark. Among the synthetic compounds of therapeutic properties, the most important ones are antimalarial drugs plasmoquine (10), pentaquine (11) and chloroquine (12).

The synthesis of quinolines and their derivatives has been of considerable interest to organic and medicinal chemists for many years as large number of natural products and drugs contain this heterocyclic nucleus. The synthesis of the quinoline ring has been the subject of continued interest as several derivatives of this heterocyclic unit have been found to possess useful biological activities such as bactericidal, antimalarial, antiinflammatory etc. Quinoline derivatives are very important in medicinal chemistry because of their wide occurrence in natural products and drugs. It is well known that replacement of hydrogen with fluorine frequently confers bioactivity to organic molecules.

Literature survey shows that, there is evidence that antitumour activity is due to intercalation between the base pairs of DNA and interferences with normal functioning of
enzyme topoisomerase-II which is involved in the breaking and releasing of DNA strands\textsuperscript{44}. The antitumour drugs that intercalate DNA are of growing interest in the field of anticancer derivatives. Generally, they are characterized by planar chromophore, often constituted by three or four condensed rings, which can intercalate into base pairs. The results of these various binding studies have been useful in designing new and promising anticancer agent for clinical use\textsuperscript{45}. The DNA binding studies of pyrimidothienoquinolines have been recently reported in literature\textsuperscript{46,47}.

**Tricyclic Condensed Quinolines**

Quinoline ring fused with five or six membered heterocyclic ring containing one or two heteroatoms in linear fashion is also found in natural products as well as in the synthetic compounds of biological interest. Quinoline condensed with furan in a linear fashion is present in the alkaloids isolated from Rutaceae. Dictamine (13), skimmianine (14) and v-fagarine (15) are the most important among them\textsuperscript{48-50}. Though plants containing furoquinoline alkaloids have been used medicinally, the alkaloids themselves have found no significant place in medicine. However, dictamnine (16) is found to strongly contract smooth muscle and to stop the isolated frog heart in diastole\textsuperscript{51}. Skimmianine (17) is known to relax intestinal muscle.

![Structural formulae of quinolines](image)

Interest in nitrogen analogues of the nucleus of dictamnine, i.e., pyrralo[2,3-\textit{b}]quinoline (16) system, started during the investigations of constituents of harmala alkaloids. In connection with the constitution of harmine and harmaline, Perkin and
Robinson attempted a synthesis of 1H-pyrrolo[2,3-b]quinoline (16), naming it as norisoharman and its methyl derivative (17) as isoharman. Tanaka et al., reported the synthesis of all aromatic 1H-pyrrolo[2,3-b]quinoline system both by dehydrohalogenation and by oxidation of reduced 1H-pyrrolo[2,3-b]quinolines, while Shanmugam et al., have reported stating from 2-chloro-3-vinylquinolines or 2-chloro-3(2-chloroethyl)quinolines. A number of reduced pyrrolo[2,3-b]quinolines are known to exhibit anti-inflammatory, analgesic, anticonvulsant, antibacterial, antipyretic, antihypertensive and interferon inducing activity.

Synthesis of thienoquinolines (18) and tetrahydrotienoquinolines (19) have also been reported in the literature and are found to display antibacterial and antimicrobial activity.

Japanese workers have reported that thienoquinolones (20) exhibit antitumour activity in mice inoculated with P388 cells in addition to antibacterial activity. Quinolines condensed with pyrazole and imidazole systems are also known in the literature. Alfred Brack reported the synthesis of pyrazoloquinolines (21) starting from azomethines of 5-chloropyrazole-4-carboxaldehydes. In 1973 Siminoff et al., reported the interferon inducing activity of a different structural type, viz., pyrazolo[3,4-b]quinoline (22) [BL-20803]. Encouraged by this, Censhaw et al., in a later paper reported the synthesis and interferon inducing activity for 137 relatives of 1,3-dimethyl-4[3-dimethylaminopropylamine]-4(1H)-pyrazolo[3,4-b] quinoline (23). In general all the compounds tested, are found to be active and some members of the series are among the most potent low molecular weight interferon inducers. Pyrazoloquinolines are also
reported to exhibit hypocholesterolemic, hypolemic activity\textsuperscript{62}, antifungal activity\textsuperscript{63}, antibacterial activity\textsuperscript{64} and antiviral activity\textsuperscript{65}.

![Chemical structures](image)

With a view to exploring imidazo[4,5-\(b\)]quinolin-2-one system (24), Meanwell and Collaborators\textsuperscript{66-71} have synthesized a series of 1,3-dihydro-(2\(H\))-imidazo[4,5-\(b\)] quinolin-2-one derivatives and evaluated as inhibitors of human blood platelet CAMP phosphodiesterase (PDE), as well as ADP and collagen induced platelet aggregation, in vitro. The parent heterocycle (25) displayed potent activity that was enhanced by the introduction of substituents like alkyl, alkoxy or halogen, at 6, 7, and 8 positions, while methylation at \(N_1\) and \(N_3\) was unfavourable. Particularly interesting was, substitution at position -7 by groups like piperazinamide (26) and alkoxy alkanoic piperazinamide derivative (27).

Structural modification in these compounds by variation of the side chain terminus, side chain length, and side chain connecting atoms resulted in the identification of compound (27) by Bristol-Myers laboratory under the name BMY 43351, as a new drug for inhibitors of blood platelet CAMP phosphodiesterase\textsuperscript{72}. 
The pyrimido[4,5-b]quinoline ring system is of interest because of its structural similarity to the pyrimido[4,5-b]quinoxaline system of naturally occurring flavins. Synthesis of several pyrimido[4,5-b]quinolines (28, 29) have been reported in the literature, with a view to develop new chemotherapeutic agents.\(^{73-75}\)

Recently, Althuis\(^76\) et al., have synthesized and tested a number of pyrimido[4,5-b]quinolines for their antiallergic property. Among the compounds tested, (30) was found to possess high oral activity. Pyrimido[5,4-b]quinolines (31), which are regarded as 10-deazaflavins have been synthesized and are found to be inhibitors of riboflavin synthesis.\(^{77-79}\)

U.S. Patent\(^80\) describes the preparation of polyfluorinated mono and dioxo tricyclic quinolines (32). These compounds are reported to display antifungal activity against *Trichophyton rubrum* and *Epidermophyton floccosum* at 1.6 and 0.39 mg/ml. Tilakraj and Ambekar\(^81,82\) have reported the synthesis of 2H-pyrano[2,3-b]quinolin-2-ones (33), which may be considered as benzazacoumarins.
Biological testing of these compounds reveal that relatively these compounds are more promising as antifungal than as antibacterial agents.

Tetracyclic Condensed Quinolines

Quinoline condensed with indole ring system in linear fashion, i.e., indolo[3,2-b]quinoline system, is present in the alkaloids cryptolepine (34) and norcryptolepine (35) isolated from the West African medicinal plant “Cyptolepis sanguinolenta Sch.” Cryptolepine (34) is known to produce lowering of the body temperature and has marked vasodilator property.

Mastoshi et al., have reported the synthesis and antitumour activity of several anilinoindolo[3,2-b]quinolines (36-39) and found majority of them to possess potent antileukemic property. Particularly, compounds (37) and (38) showed remarkable activity against P388 in mice. Optimal dose = 25 mg/kg, the median survival time of treated group / control group is greater than 333%.
German Patent\(^89\) describes synthesis of the indolo[2,3-b]quinolines of the type (40) and their usefulness as CNS active pharmaceuticals and antibiotics. Very recently Kaczmarek and Collaborators\(^90-92\) have reported the synthesis of number of indolo[2,3-b]quinolines (41) and tested them for their bacteriostatic, cytostatic, antifungal and anticancer activities.

Among the compounds tested, (42) showed significant antitumour activity against P388 and L1210 leukemias, melanoma B16 in mice. It improved the survival rate by 150% of control at 20 mg/kg administered in mice implanted with leukemia cells. Goerlitzer\(^93\) et al. have synthesized indoloquinolines, benzofuranoquinolines and benzothienoquinolines with N,N-dimethylamin opropylmercapto substituent (43) and tested them for their blood platelet aggregation inhibiting activity in platelet enriched human plasma \textit{in vitro}. Among the compounds tested, (43) \((X = NCH_3)\) was found to be the most active one. Its inhibitory action was comparable to that of aspirin in collagen induced platelet aggregation. Mastoshi\(^94\), in his recent patent describes the synthesis of several compounds (44) by replacing the mercapto side chain by substituted aniline and reported them to exhibit the neoplasm inhibition.
Tilakraj and Ambekar\textsuperscript{95,96} have reported synthesis of a new tetracyclic heterocyclic system, pyrimido[4',5':4,5]thieno[2,3-b]quinolin-4(3H)-ones and 4-aminopyimidoo[4',5':4,5]thieno[2,3-b]quinolines and tested them for their blood platelet disaggregation activity in human blood platelet aggregation induced by ADP and collagen. Among the compounds tested, compound (45) exhibited highest inhibition at the dose level 7.2 μM.

Mastoshi\textsuperscript{97} et al., have reported the synthesis of several fused tetracyclic condensed quinolines and their DNA intercalative properties, KB cytotoxicity, antitumour activity (P388 leukemia) and ability to induce topoisomerase-II dependent DNA cleavage. The benzofuro- (49) and benzothieno- (50) quinoline derivatives exhibited potent antitumour activities in vitro and in vivo, comparable to those of m-AMSA. They also intercalate DNA induced topoisomerase-II dependent DNA cleavage.
Pentacyclic Condensed Quinolines

Camptothecin (48) an alkaloid with a condensed quinoline ring system, exhibiting potent antileukemic and antitumour activity in animals, has been isolated from the stem wood of Chinese tree "Camptotheca acuminata Decstne Nyssacea". Against leukemia L1210 in mice, camptothecin gives life prolongation as high as 100% on a daily dose of 0.25-1.0 mg/kg against Walker 256 (intramuscular) tumour (rats); concentration as low as 1.25 mg/kg gives significant inhibition of growth. It also shows moderate toxicity against KB cell culture ED₅₀=0.07 mg/ml.

In 1991, Sawada and co-workers prepared a series of A-ring modified 7,10-disubstituted camptothecins. The cytotoxicity of A-ring modified camptothecin was evaluated against KB cells in vitro and leukemia L1210 in mice. Significant cytotoxicity was observed in the derivatives having electron withdrawing chloro and bromo substituents at the 9 position and electron donating hydroxyl and amino group at the 10 position. All the 7,10-disubstituted camptothecins tested exhibited antitumour activity with higher activity being observed in suspension administration. Among these, 7-ethyl-10-hydroxycamptothecin (49) was identified as a potential derivative for further modification.

Meth-Cohn et al., have reported an elegant method of synthesizing 3-formyl-2-chloroquinolines (50) in one step, starting from acetanilides (51).
Quinolines\textsuperscript{102-104} are an important class of heterocyclic compounds. Several compounds of this class have been screened for biological activities such as bactericidal\textsuperscript{105}, antitumor\textsuperscript{105}, anti-inflammatory\textsuperscript{107}, antimalarial\textsuperscript{108} etc. Among quinolines, 2-chloroquinolin-3-carbaldehydes occupy a prominent position, as the latter are key intermediates for further annelation of a wide variety of ring and for various functional group interconversions\textsuperscript{109,110}.

Quinolines and their derivatives are important constituents of several pharmacologically active synthetic compounds,\textsuperscript{111-113} including biological activities such as DNA binding capability\textsuperscript{114}, antitumor\textsuperscript{115,116}, and DNA-intercalating carrier\textsuperscript{117}. The development of general methods for the synthesis and biological evaluation of new agents retaining the 'core' quinoline moiety is the subject of considerable synthetic effort. Certain small heterocyclic molecules act as highly functional scaffolds and are known as pharmacophores of a number of biologically active and medicinally useful molecules\textsuperscript{118}. The Vilsmeier–Haack reagent is an efficient, economical and mild reagent for the formylation of reactive aromatic and heteroaromatic substrates\textsuperscript{119,120}.

The use of Vilsmeier–Haack reactions has led to novel and convenient routes for the synthesis of various heterocyclic compounds and its importance in various synthetic methodologies\textsuperscript{121-125} including microwave chemistry\textsuperscript{126-130} is remarkable and inspiring. The classical Vilsmeier–Haack reaction involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to yield the corresponding iminium species. Aghera\textsuperscript{131} et al., have reported the synthesis of novel quinoline derivatives \textit{via} the Vilsmeier–Haack reagent with the prospect of incorporating diverse bioactive heterocyclic
nuclei, intact, for evaluating antibacterial and antifungal significance and also as a reagent for effecting functional group interconversion.

DQ-113, which is 5-amino-7-[(3S,4R)-4-(1-aminocycloprop-1-yl)-3-fluoropyrrolidin-1-yl]-6-fluoro-1-[(1R,2S)-2-fluorocycloprop-1-yl]-1,4-dihydro-8-ethyl-4-oxoquinoline-3-carboxylic acid (52), is a new potent antibacterial agent for infections caused by Gram-positive pathogens including multi-drug resistant strains, and is currently undergoing preclinical evaluation by Daiichi.

One of the structural features of DQ-113 is its possession of the cis-oriented (3S,4R)-4-(1-aminocycloprop-1-yl)-3-fluoropyrrolidine moiety as the C-7 substituent, which has been shown to be indispensable for its effective biological properties.
Benzo[b]thiophene derivatives

Benzo[b]thiophene (53) is an aromatic organic compound with a molecular formula C₉H₆S and an odor similar to naphthalene (mothballs). It occurs naturally as a constituent of petroleum-related deposits such as lignite tar. Benzo[b]thiophene has no household use. It is used primarily in industry and research. Being a heterocyclic compound, benzo[b]thiophene finds use in research as a starting material for the synthesis of larger, usually bioactive structures. It is found within the chemical structures of pharmaceutical drugs such as raloxifene, zileuton, and sertaconazole. It is also used in the manufacturing of dyes such as thioindigo.

Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites which allow for functionalization.

![Molecular structure of Benzo[b]thiophene](image)

- **Molecular formula**: C₉H₆S
- **Molar mass**: 134.20 g/mol
- **Appearance**: white solid
- **Melting point**: 32 °C
- **Boiling point**: 221 °C

Benzo[b]thiophene is frequently referred to simply as the sulphur analogue of indole.
Methods of synthesis

01. From 2-aryltio-aldehydes, -ketones or acids

Cyclization of 2-aryltio-aldehydes, -ketones or acids via intramolecular electrophilic attack on the aromatic ring, with the loss of water, creates the heterocyclic ring; this route is the commonest method for benzo[b]thiophenes.

\[
\text{aryl} - \text{aldehyde} + \text{H}_2\text{O} \rightarrow \text{heterocycle}
\]

In order to produce hetero-ring unsubstituted benzo[b]thiophenes\(^{140}\) an arylthioacetaldehyde acetal is generally employed prepared, in turn, from bromoacetaldehyde acetal and the thiophenol.

\[
\text{aryl} + \text{PPA} \rightarrow \text{heterocycle}
\]

Comparable acid catalyzed ring closures of 2-aryltio-\(^{141}\) -ketones and 2-aryltioacetyl\(^{142}\) chlorides lead to 3-substituted heterocycles. Attempted formation of 3-aryl benzo[b]thiophenes by this route is always accompanied by partial or complete isomerisation to the 2-aryl-heterocycle\(^{143}\).

\[
\text{aryl} + \text{AlCl}_3 \rightarrow \text{heterocycle}
\]

02. Preparation from 2-(orthothioxyaryl)-acetaldehydes, -ketones or -acids.

Cyclising dehydration of 2-(ortho-thioxyaryl)-acetaldehydes, -ketones or -acids give the heterocycles.
The employment of aryl 2-chloroprop-2-enyl-sulfides (or ethers) as thio-Claisen rearrangement substrates neatly eliminates the necessity for an oxidative step thus providing a route to 2-methyl-benzo[b]thiophenes\textsuperscript{144}.

![Chemical structure of 2-methyl-benzo[b]thiophenes](image)

\textbf{03. From ortho-acylarylthioacetic acids or esters or ketones}

Cyclising condensation of ortho-acylarylthioacetic acid (esters) or (ketones) gives the bicyclic heterocycles.

![Chemical structure of bicyclic heterocycles](image)

The intramolecular aldol/Perkin type condensation of ortho-formylaryl thioacetic acid ester produces benzo[b]thiophene-2-ester\textsuperscript{145}.

![Chemical structure of benzo[b]thiophene-2-ester](image)

\textbf{04. Synthesis which involve making the benzene ring}

6,7-Dihydrobenzo[b]thiophenes react as diens with alkynes, subsequent retro-Diels-Alder elimination of ethene giving a benzo[b]thiophene, as illustrated\textsuperscript{146}.

![Chemical structure of retro-Diels-Alder elimination](image)
Among the most commonly found sulfur heterocycles are thiophenes. These may have alkyl side chains or may be condensed with one or more benzene ring(s) to form benzo[b]thiophenes, dibenzo[b]thiophenes, naphthothiophenes or benzonaphthothiophenes. Indeed, sulfur is the third most abundant element in crude oils\textsuperscript{147}, and the condensed thiophenes are the most common form in which sulfur is present. Alkyl dibenzo[b]thiophenes have been shown to be quite persistent in petroleum contaminated environments\textsuperscript{148-150} and they concentrate in the tissues of aquatic species\textsuperscript{151,152}. Nonetheless, C-1 and C-2 dibenzo[b]thiophenes are susceptible to biodegradation\textsuperscript{153-157}. Bressler\textsuperscript{158} et al., have reviewed the literature on the ring cleavage of sulfur heterocycles. The types, sources and structures of various sulfur heterocycles have been examined and have found the ring cleavage.

Compounds containing thiophene moiety (63, 64) also have been isolated from plants\textsuperscript{159}, and bitumens, crude oils and in pyrolysates of kerogens and asphaltenes\textsuperscript{160}. 

![Alpha-terthienyl 63](image)

\begin{itemize}
  \item 2-Hexadecyl-5-methylthiophene
  \item 2-Methyl-5-tridecylthiophene
  \item 2-Butyl-5-tridecylthiophene
  \item 2-Methyl-5[3,7,11,15-tetramethylhexadecyl]thiophene 64
\end{itemize}
The molecules possessing benzo[b]thiophene moiety have been found to possess interesting pharmacological properties as observed with the literature. Zileuton (65) for example is a potent and selective inhibitor of 5-lipoxygenase\(^{161}\), while many 2-substituted benzo[b]thiophenes are selective estrogen receptor modulator and one such compound is raloxifene (66), is used to treat osteoporosis\(^{162}\). Some inhibit serine proteases, such as thrombin\(^{163,164}\) and factor Xa\(^{165}\) and so have potential as anticoagulants or inhibit the cysteine protease cathepsin K., providing the potential alternative route for the treatment of osteoporosis\(^{166}\).

The estrogen receptor is a ligand activated transcription factor, which plays a critical role in female reproductive function and influences skeletal, cardiovascular and CNS health. There are two known subtypes, ERα and ERβ which are expressionally and functionally unique. Selective estrogen receptor modulators (SERM’s) are compounds that may mimic the effects of estrogen in some tissues, while antagonizing the effects of estrogen in others\(^{167}\). While the precise reason for this tissue selectivity is not fully understood, it is clear that the conformation of the receptor and its ability to interact with cofactors is critically important. Moreover subtle changes of ring and structure can have a dramatic impact on receptor conformation.

Of significant importance for ligand’s ability to act as a SERM is, the nature of the basic side chain and its orientation relative to the ligand backbone. It is known that in the X-ray crystal structure of raloxifene bound to ERα, the basic side chain of the ligand occupies an orthogonal position relative to the benzo[b]thiophene core\(^{168}\). In an effort to
constrain the side chain into its presumed active conformation Owen et al., have reported the synthesis of benzo[b]thiophene and naphthalene derived SERMs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) possessing anti-inflammatory, analgesic, and antipyretic activities have been widely used in the treatment of acute and subchronic inflammatory conditions. In early 1970s it was reported that NSAIDs prevent the production of prostaglandins (PGs) by inhibiting the enzyme cyclooxygenase (COX), which catalyzes the conversion of arachidonic acid (eicosa-5,8,11,14-tetraenoic acid) to prostaglandins. For many years it was believed that COX was a single enzyme (COX-1) constitutively expressed in most tissues. In contrast to COX-1, COX-2 is an inducible isoenzyme, which is essentially undetectable under normal physiological conditions; however, its expression is markedly elevated during inflammation. It was shown that compounds inhibiting selectively COX-2 do not cause ulcers in stomach or intestines. The observation supports the hypothesis that the constitutive COX-1 isoenzyme protects the gastrointestinal tract whereas the individual COX-2 isoform mediates inflammatory PG production.

Leukotrienes (LTs) represent another class of arachidonic acid metabolites, synthesized by leucocytes in response to a variety of inflammatory and immunological stimuli. 5-Lipoxigenase (5-LO) starts the metabolism of arachidonic acid through LTA₄ to LTB₄, a potent chemotactic agent for leucocytes that was thought to be a key component in a variety of inflammation diseases, and peptidoleukotrienes LTC₄, LTD₄ and LTE₄, which are implicated in allergic hyperactivity disorders such as asthma. Elevated levels of these LTs, associated with several inflammatory and allergic disorders, have been found in various pathological tissues. Thus, compounds restricting LT synthesis by inhibition of 5-LO will have therapeutic utility in such pathological conditions. Recently it has been
shown\(^{175,176}\) that some hydroxomic acids, example, Zileuton possessing the 1-benzo[b]thiophene moiety, can be strong 5-LO inhibitors.

Classical NSAIDs, such as ibuprofen, have been found to active primarily via inhibition of COX pathways. Piroxicam (67), an eno-carboxamide type of NSAID, is also a potent COX inhibitor. Tenidap\(^{177}\) [5-chloro-2-oxo-3-(2-thenoyl)indoline-1-carboxamide] containing a similar fragment, is distinguished by the inhibition of both COX and 5-LO. In continuation of research on new anti-inflammatory agents with dual mechanism of 5-LO and COX inhibition, Svoboda\(^{178}\) et al., have reported synthesis of 3-substituted 1-benzo[b]thiophene-2-carboxanilides (68-71).

\[
\begin{align*}
\text{67} & \\
\text{68, } X = H & \quad \text{69, } X = Cl & \quad \text{70, } X = OCH}_3 & \quad \text{71, } X = OH
\end{align*}
\]

The central concept in the treatment of glaucoma is that reduction of intraocular pressure (IOP) will preserve visual function. While a variety of pharmacological and surgical methods have evolved for lowering IOP in glaucoma patients, none of these is entirely satisfactory\(^{179}\). It is well established that effective reduction of IOP can be achieved by the systemic administration of carbonic anhydrase inhibitors (CAIs), which act by reducing the rate of aqueous humor secretion. Unfortunately, systematic therapy with CAIs leads to significant side effects, which have limited their utility in treating glaucoma. These side effects are a direct result of inhibition of carbonic anhydrase in extraocular tissues. An attractive approach to achieving an adequate ocular hypotensive response, while minimizing side effects, is the development of a topically active CAI. Although this has been a goal for over 30 years, only recently has any measure of success been recorded\(^{180}\). Benzothiazolesulfonamide (72) is a topically active ocular hypotensive agent
in rabbits\textsuperscript{34f}. However, clinical development of (72) was precluded by two observations. First, benzothiazolesulfonamides undergo rapid metabolism involving nucleophillic displacement of the sulphonamide group by reduced glutathione (GSH)\textsuperscript{181}. For compound (72), the half-life of this process under simulated physiological conditions (leading to 73) is less than 1 hour. Of greater consequence was the observation, during a 3-month ocular safety study in rabbits, that a significant number of animals developed an allergic reaction to (72). Subsequent evaluation of (72) in a guinea pig model for dermal-sensitization potential\textsuperscript{182} revealed that (72) was a potent allergen. A number of other benzothiazolesulfonamides were found to share this property\textsuperscript{183}. Thus; the electrophilic nature of benzothiazolesulfonamides is manifested by both rapid metabolism and a presumed arylation reaction of biological macromolecules leading to an immune response.

Samuel\textsuperscript{184} et al., have described the syntheses and properties of derivatives of benzo[\textit{b}]thiophene-2-sulfonamide (74). The decision to pursue these studies was based primarily on the premise that the electrophilic nature of (72) (and related benzothiazoles) is due to the presence of the imino group in the ring system. Deaza analogues of (72), such as (74), therefore might prove less reactive toward nucleophillic substitution. It also was hoped that removal of the nitrogen atom in the ring would lead to improved topical bioavailability. It has been postulated that translocation through the cornea is the major route of access of topically applied drugs to the anterior segment of the eye\textsuperscript{185}.

![Chemical structures](image)

Thiophene compounds are useful as antianxiety drugs, hypnotics and antiepileptic drugs. There is continuous interest in benzo[\textit{b}]thiophene derivatives because of their many varied uses. Besides the manifold uses of this class of compounds, it has been reported that
benzo[b]thiophene derivatives carrying sidechains have shown anticancer activities. Uses of benzo[b]thiophene derivatives as excitatory amino acid antagonists, in the treatment of myocardial eschemia, hypertension, fungal infection, or as oral contraceptives and as hypoglycemic agents are also known. More recently there have been reports on the anti-inflammatory, antiexudative, analgesic and antipsychotic activities of benzo[b]thiophene derivatives as well as their inhibitory action on protein tyrosin phosphatase and 5-lypoxygenase.

Makino et al., have reported the new anti-autoimmune agents that selectively suppress activation of autoreactive T cells, one such agent, 5-methyl-3-(1-methylethoxy)benzo[b]thiophene-2-carboxamide (CI-959-A), was found to be effective. This compound, which is known to suppress tumor necrosis factor alpha (TNF-α)-induced CD54 expression, inhibited the primary proliferative response of the T cell to antigen (Ag)-presenting cells (APCs) including allogenic dendritic cells (DCs), autologous Epstein-Barr virus-infected B cells, and human T lymphotropic virus type I (HTLV-I)-infected T cells. Autoreactive T cells from patients with HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) spontaneously proliferate in vitro, and their activation is reported to be associated with CD54 expression. The spontaneous proliferation of T cells from patients with HAM/TSP was entirely blocked by CI-959-A. However, in this study, the T-cell proliferation in 15 patients with HAM/TSP was found to depend more extensively on major histocompatibility complex (MHC) class II and CD86 than on CD54 Ags. Since most important APCs for the development of HAM/TSP are DCs and HTLV-I-infected T cells, the effect of CI-959-A on DC generation and on the expression of surface molecules on activated T cells is examined. CI-959-A suppressed recombinant granulocyte-macrophage colony stimulating factor (GM-CSF) and recombinant interleukin-4-dependent differentiation of DCs from monocytes and inhibited the expression of CD54
and, more extensively, MHC class II and CD86 Ags. CI-959-A showed little toxicity toward lymphoma or HTLV-I-infected T-cell lines or toward monocytes and cultured DCs. These results suggest that CI-959-A might be a potent anti-HAM/TSP agent.

Sato et al. have reported that LY353381·HCl (75) is a benzo[b]thiophene analog that is structurally related to raloxifene with potent selective estrogen receptor modulator activity in the ovariectomized rat model of postmenopausal osteoporosis. The effects of LY353381·HCl on bones, body weight, and uterine weight were evaluated in 7-month-old rats with osteopenia that was induced by ovariectomizing animals for 1 month before initiation of treatment with several agents individually, in combination, or in sequence. LY353381·HCl was administered daily by itself for 90 days, in combination with the amino-terminal fragment of PTH-(1-34) (PTH) for 90 days, or sequentially after PTH when PTH was discontinued after 45 days of treatment. Additionally, comparisons were made of animals treated with PTH alone, 17α-ethynyl estradiol alone, equine estrogens (Premarin) alone, raloxifene alone, or combinations of PTH and equine estrogens or raloxifene. Ovariectomy induced increases in the rate of bone turnover and body weight while decreasing bone mineral density, bone mineral content, bone strength, trabecular bone volume, trabecular thickness, trabecular number, and uterine weight. LY353381·HCl at 0.01–1 mg/kg had marginal effects on body weight and no effect on uterine weight compared with those in ovariectomized controls, in contrast to 17α-ethynyl estradiol or equine estrogens. LY353381·HCl prevented further bone loss due to ovariectomy in tibia, femora, and lumbar vertebra, like 17α-ethynyl estradiol but unlike equine estrogens. LY353381·HCl prevented the resorption of trabecular bone spicules, like 17α-ethynyl estradiol, but inhibited bone formation activity to a lesser extent than 17α-ethynyl estradiol. In this model, 17α-ethynyl estradiol appeared to be more efficacious after 3 months of treatment than equine estrogens in the proximal tibia metaphysis, suggesting
efficacy differences between metabolites of 17β-estradiol in bone. PTH at 10 mg/kg had no effect on body weight or uterine weight, but significantly increased bone mass to beyond those in sham-operated controls, baseline controls, and groups receiving other individual treatments at both axial and appendicular sites. The combination of LY353381HCl and PTH increased bone mass at a faster rate and to a greater extent than PTH alone or the combinations of equine estrogens/PTH and raloxifene/PTH at trabecular bone sites. The LY353381 HCl/PTH combination improved bone mass and quality beyond any agent alone in regions enriched for cancellous bone, but was not significantly better than PTH alone on cortical bone. Additionally, when PTH was discontinued at 45 days, LY353381HCl prevented the rapid loss of bone observed in controls. Therefore, LY353381HCl appears to be useful by itself, in combination, or in sequence with PTH to replace lost bone in postmenopausal women.

Tamoxifen (76) is the archetypal selective estrogen receptor modulator (SERM). Despite the demonstrated, increased risk of endometrial cancer, tamoxifen has been the therapy of choice in the endocrine treatment of all stages of hormone-dependent breast cancer and in the primary and secondary chemoprevention of breast cancer. Although the introduction of aromatase inhibitors may change this clinical paradigm, SERMs are likely to be in clinical use for many years. The increased use of SERMs is anticipated on the basis of favorable clinical trial results for the benzo[b]thiophene SERMs, raloxifene (22) and arzoxifene, and because SERMs are hoped to provide an alternative to current hormone replacement therapy (HRT) that has been causally linked to breast cancer.
Raloxifene is in current clinical use in post-menopausal osteoporosis and is expected to find use in other postmenopausal indications associated with HRT\textsuperscript{194,195}. The STAR trial (study of tamoxifen and raloxifene) reported that raloxifene was as effective as tamoxifen in breast cancer chemoprevention in postmenopausal women at high risk and was less likely to cause the potentially dangerous side effects associated with tamoxifen, such as uterine cancer and blood clots. The RUTH trial (raloxifene use for the heart) did not show a significantly increased risk of coronary artery disease, although there is still debate on the potential beneficial or negative effects of raloxifene on other cardiovascular events\textsuperscript{196,197}. Arzoxifene (36), designed to improve upon the therapeutic properties of raloxifene, is in late stage clinical trials with the promise of substantial therapeutic benefits and is likely to find use in cancer chemoprevention\textsuperscript{198,199}. The carcinogenic effects of tamoxifen have been attributed variously to regulation of gene transcription (i.e., hormonal carcinogenesis) and to genotoxicity due to oxidative metabolites (i.e., chemical carcinogenesis). Chemical carcinogenesis can contribute to cancer initiation through damage to DNA and other biomolecules following drug bioactivation to redox-active and electrophilic quinoid metabolites (\textit{o-quinones, quinone methides, and di-quinone methides})\textsuperscript{200,201}. Human estrogens and equine estrogens contained in current HRT agents are also proposed to elicit hormonal and chemical carcinogenesis pathways, the latter via \textit{o-quinone metabolites}\textsuperscript{202,203}. Interestingly, many SERMs in clinical use and clinical development are also highly susceptible to oxidative metabolism to electrophilic and redoxactive quinoids simply because they are based on polyaromatic phenol scaffolds\textsuperscript{204}. The SERMs, raloxifene, desmethylarzoxifene (DMA) (80), acolbifene (82), toremifene (77), and droloxifene (78) are all oxidatively metabolized to quinoids, which have been shown to form adducts with biomolecules, including glutathione (GSH), proteins, and nucleosides\textsuperscript{205-210}. Whereas generation of reactive oxygen species (ROS) and covalent modification of
biomolecules by redox-active quinoids may contribute to initiation and promotion of carcinogenesis, induction of oxidative stress and oxidation or covalent modification of sensor proteins may trigger cellular stress responses that are cytoprotective\(^{211,212}\). This balance between the carcinogenic and the chemopreventive capacity of a drug is determined by the reactivity toward oxidative bioactivation and the chemistry of the reactive metabolite formed and, therefore, can be controlled by structural modification.

The contribution of oxidative bioactivation to therapeutic activity versus toxicity is of particular relevance to SERMs, which are designed for chronic use in healthy women who are peri- or postmenopausal or who have known risk factors. The continued development of SERMs based on polyaromatic phenolic scaffolds requires increased understanding of the influence of oxidative bioactivation. Intensive research is currently directed at discovery of the ideal SERM an agent that is antiestrogenic in breast and endometrial tissue, but proestrogenic in the vasculature and brain, which would be of use in cancer chemoprevention and an attractive alternative to HRT. However, there has been little attention to structural modifications designed to control oxidative bioactivation and thereby enhance therapeutic activity and attenuate toxicity\(^{213}\).
This approach requires a family of SERMs in which structure is used to modulate both redox reactivity and activity at the estrogen receptor. To that end, a family of benzothiophene SERMs related to arzoxifene has been synthesized, requiring development of a new synthetic methodology for arzoxifene itself.

Arzoxifene (79) is a structural analogue of raloxifene (66) in which the carbonyl hinge has been replaced by an ether linkage and the 4'-hydroxy group is methylated. Arzoxifene is in late stage clinical trials as a next generation SERM with promise of substantial therapeutic benefits\(^{214}\) that are suggested to result from (a) increased antiestrogenic potency and (b) improved bioavailability relative to raloxifene\(^ {215}\). DMA (80) is an active metabolite of arzoxifene, which has been observed with highly variable steady-state plasma concentrations\(^ {197}\). In vitro metabolic studies showed that both DMA and raloxifene undergo bioactivation to electrophilic diquinone methides (60, 80, 81, 83),
resulting in potentially cytotoxic actions: depletion of cellular GSH, irreversible inhibition of P450 3A4, and liver protein modification. The desired chemopreventive actions of SERMs will be compromised by the formation of covalent adducts between electrophilic quinoid metabolites and cellular proteins or DNA if these adducts cause genotoxicity or organ toxicity. In an effort to obtain safer benzothiophene SERMs that retain efficacy and have attenuated reactivity toward bioactivation, the arzoxifene analogue, 4'-fluoro-4'-desmethoxyarzoxifene, has been developed (F-DMA, 81). F-DMA showed similar antiestrogenic activity to both DMA and raloxifene, and 4'-fluorination was shown to successfully block the formation of an electrophilic diquinone methide and to suppress phase II metabolism. These properties are predictive of improved bioavailability compared to DMA and raloxifene.

Qin et al have reported that regulation of estrogenic and antiestrogenic effects of selective estrogen receptor modulators (SERMs) is thought to underlie their clinical use. Most SERMs are polyaromatic phenols susceptible to oxidative metabolism to quinoids, which are proposed to be genotoxic. Conversely, the redox reactivity of SERMs may contribute to antioxidant and chemopreventive mechanisms, providing a new approach to improve the therapeutic properties of SERMs.
An improved synthetic strategy was developed to generate a family of benzothiophene SERMs. Using computational modeling methods and measurements of antioxidant activity and estrogen receptor (ER) ligand binding, this SERM family was shown to provide both a range of ERR/ERα selectivity from 1.2- to 67-fold and a range of redox activity. Antioxidant activity was successfully modulated by varying a substituent remote from the OH group; the source of the antioxidant capacity. An efficient synthetic procedure was reported by Quin et al., yielding benzothiophene SERMs wherein redox activity and ER affinity are modulated.

Raloxifene (66) is the best known member of the benzothiophene family that has previously been referred to as keoxifene, LY139481, or LY156758. Raloxifene had, at one point, been considered a candidate for the treatment of breast cancer but was never developed for this indication. However, recently raloxifene has been shown to be efficacious in preventing bone loss in postmenopausal women. Specifically, a double-blind study with 601 postmenopausal women showed a 2.4% increase in DXA BMD or the spine and hip compared to placebo controls after 2 years of treatment with 60 mg of
raloxifene. Despite the modest effects on spinal BMD, raloxifene was recently shown to reduce fracture incidence by 50% after 2 years of treatment with the 60 mg dose.

Pharmacologically, raloxifene is distinguished from triphenylethylenes, tamoxifen, droloxifene, idoxifene, and toremifene primarily on the basis of its uterine effects, where a qualitative difference has been observed\textsuperscript{219,220}. In direct comparison with tamoxifen, droloxifene, and idoxifene, raloxifene functioned essentially as a complete antagonist of estrogen action in the immature female rat uterus, while the triphenylethylenes functioned as partial agonists, inhibiting the effects of estrogen on uterine weight gain only to the level of their own intrinsic agonist activity\textsuperscript{221}. Similarly, in ovariectomized rats, the first generation triphenylethylenes were found to induce a larger maximal stimulation of uterine weight, larger uterine epithelial cell height, and uterine eosinophilia while raloxifene did not. Raloxifene does stimulate a modest increase in uterine wet weight of rats; however, this increase was not coincident with increases in other measures of uterine hypertrophy and may be attributed to water retention, although this point has been disputed\textsuperscript{222}. Transvaginal ultrasonography of postmenopausal women showed no stimulatory effect of raloxifene on endometrial thickness at any time during the 2 years of treatment. Recent studies have suggested that distinct and specific structural features of raloxifene may be responsible for its improved tissue selectivity\textsuperscript{223,224}. The strategy of incorporating the stilbene moiety of a triphenylethylene into a bicyclic ring system (i.e., naphthalene or benzothiophene) has, with varied success, been used to confer configurational stability upon the olefin, thus reducing metabolic conversion to potentially uterotrophic double-bond isomers\textsuperscript{225}. Nevertheless, the well-established uterine stimulatory effects of nafoxidine, a nonisomerizable analogue of tamoxifen, demonstrates that this is an incomplete solution. The carbonyl hinge, which is imposed between the benzothiophene moiety of raloxifene and its aminoethoxyphenyl side chain, has also been hypothesized to
contribute to its profile of tissue selectivity. Comparison of the low energy conformations of raloxifene and tamoxifen demonstrates that this subtle structural modification produces a major change in the orientation of the side chain, from coplanar with the stilbene nucleus in tamoxifen to roughly orthogonal in raloxifene. This orthogonal side chain orientation, which is consistent with the crystal structure of raloxifene bound to the estrogen receptor\textsuperscript{226}, has been postulated to be a critical determinant of raloxifene’s enhanced tissue specificity. Indeed, biological evaluation of a raloxifene analogue in which the carbonyl hinge has been excised demonstrated a profile of activity very similar to that of tamoxifen. Likewise, several other estrogen receptor modulators which demonstrate tissue specific estrogen agonist activity without significant uterine stimulation have been shown to have similar side chain orientations\textsuperscript{227,228}. LY353381·HCl (75) is a new benzothiophene analogue with efficacy similar to that of raloxifene but with improved potency in rat models. This compound has beneficial effects on bone and serum cholesterol while functioning as an estrogen antagonist in the uterus\textsuperscript{229}. LY353381·HCl is currently in clinical trials with breast cancer patients\textsuperscript{230}. Additional studies are necessary to ascertain if LY353381·HCl has significant advantages over raloxifene or other more recent SERMs as therapy for postmenopausal women.

The effect of naturally occurring estrogens, such as 17\textbeta-estradiol, on numerous tissues has been recognized for a long time. The declining levels of estrogens during and after menopause have been connected to a large number of post-menopausal pathologies, not only osteoporosis\textsuperscript{231} but also cardiovascular diseases, depression and schizophrenia,
and Alzheimer's disease. Hormone replacement therapy can restore estrogen levels; therefore, it reduces the risks associated with these pathologies, but it has also been linked to an increased risk of hormone dependent cancers along with numerous side effects. Therefore, researchers have focused on the development of treatment alternatives to better satisfy this medical need. Several synthetic molecules have been described as selective estrogen receptor modulators (SERMs). These molecules antagonize the effects of estrogen on reproductive tissues while mimicking the effects of estrogen on bone and the cardiovascular system. The combination of these effects is thought to provide a uniquely advantageous therapeutic profile for the post-menopausal female population.

A few years ago, particular interest was given to the synthesis of SERM analogues, such as Raloxifene (66) and Arzoxifene (79). In fact, Raloxifene (66), a 2-arylbenzo[b]thiophene, is already commercially available for the prevention of osteoporosis. A structure-activity relationship study showed that the replacement of the carbonyl group with an oxygen resulted in a 10-fold increase in antiestrogen potency both in vivo and in vitro. In addition, the methoxy analogue, Arzoxifene, has improved bioavailability compared with that of Raloxifene. Arzoxifene (79) is currently under investigation as a breast cancer therapy in advanced disease. Substituted 2-arylbenzo[b]thiophenes are usually synthesized by multistep intramolecular cyclization of thiophenol derivatives, according to the procedures of Kost, De, and Flynn.
Nevertheless, these methods often require many steps as well as acidic and/or basic conditions which are not compatible with sensitive functional groups. Surprisingly, little interest has been given to direct access to substituted 2-arylbenzo[b]thiophenes from benzo[b]thiophene. David et al., have described a new and rapid route to Arzoxifene analogues with heteroatoms at the 3-positions. This synthetic approach was based on the nucleophilic aromatic substitution (SNAr) of 3-bromobenzo[b]thiophene followed by a one-step Heck-type coupling of the corresponding 3-substituted benzo[b]-thiophenes with aryl halides.

Benzo[b]thiophene, second in importance to thiophene among sulfur heterocycles and discovered soon after the latter's discovery, has attracted scant attention at that time, apart from some interest shown towards thioindigo dyes. The scenario has, however, changed with the advent of bioisosterism when organic chemists started showing interest in benzo[b]thiophene since it is a bioisoster of indole. Indeed, the main area of activity in the chemistry of benzo[b]thiophene, in the sixties and seventies of the last century, centred around the synthesis of its derivatives that are analogues of bioactive indole derivatives including indole alkaloids. The synthesis of several sulfur analogues of bioactive furanochromones and furanocoumarins are also reported in the literature. These analogues, consisting of a benzo[b]thiophene core, are usually obtained from the latter through suitable annulation reactions. This line of work continues till date and its literature up to 1980 has been reviewed. Mukherjee et al., have reported the chemistry and uses of hydroxybenzo[b]thiophenes. The interest which this class of compounds has received, among the benzo[b]thiophene derivatives, is principally due to their usefulness in the (a) synthesis of sulfur analogues of several important bioactive indole derivatives, viz. serotonin, and (b) annulation of oxygenated rings onto the benzo[b]thiophene core.
Benzo[\textit{b}]thiophenes are emerging as an important class of pharmacophores for medicinal chemistry, as exemplified by the successful launch of raloxifene (66), a representative of a class of compounds known as selective estrogen receptor modulators (SERMs) that exhibit estrogen agonist-like actions on bone tissues and serum lipids while displaying potent estrogen antagonist properties in the breast and uterus. Recently, 3-oxygenated benzo[\textit{b}]thiophene (DMA) (37) has been reported to display a substantial (10-fold) increase in estrogen antagonist potency relative to raloxifene\textsuperscript{248-252}. To further expand the structure activity relationship (SAR) studies for this class of molecules, compound 6-Methoxy-3-4-[2-(1-piperidinyl)ethoxy]phenoxy-2-(4-bromophenyl)benzo[\textit{b}]thiophene (84) was identified as a pivotal intermediate to explore the chemical space around the 2-position of this particular platform. However, there is paucity for the existence, let alone method of preparation for this type of compound in the chemical literature. Zhang\textsuperscript{253} et al., have reported the preparation of 2-bromo-3-aryloxybenzo[\textit{b}]thiophenes as versatile intermediates for SAR. The nucleophilic displacement of a bromide in the 3-position of a benzo[\textit{b}]thiophene sulfoxide has been reported.

![Chemical structures](image)

Benzo[\textit{b}]thiophene derivatives possessing an acyl group as one of the substituents on the five-membered ring are of immense medicinal value because of their promising pharmacological properties. For example, Raloxifene, [2-(4-hydroxyphenyl)-6-hydroxybenzo[\textit{b}]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-ethanonehydrochloride (22), is representative of a class of compounds known as selective estrogen receptor modulators\textsuperscript{254} (SERMs) that possess estrogen agonist-like actions on bone tissues and serum lipids while displaying potent estrogen antagonist properties in the breast and uterus.
A most common example of SERM is tamoxifen which has been the therapy of choice in the endocrine treatment of all stages of hormone-dependent breast cancer and in the primary and secondary chemoprevention of breast cancer. Recently, raloxifene showed promising results in clinical trial and is expected to provide an alternative to current hormone replacement therapy (HRT) that has been causally linked to breast cancer. Another compound (85) was identified as a thrombin inhibitor that could be utilized in the chronic treatment of thrombotic disorders. Apart from medicinal interest, acyl derivatives of benzothiophene have synthetic value and a variety of diversity based benzothiophene derivatives have been prepared using these compounds. While a number of methods are known for the synthesis of acyl benzothiophenes, many of them however, are only suitable for the preparation of certain specific compounds, namely, acetyl, propanoyl and benzoyl derivatives. Some of these syntheses require complicated reaction conditions e.g. the use of an expensive transition metal catalyst along with toxic carbon monoxide gas or unstable diazo compounds, or pyrophoric BuLi, or a multistep synthesis of starting material. The simplest and straightforward method for the synthesis of acyl benzothiophenes appeared to be the Friedel Crafts acylation reaction. Pal et al., have reported the synthesis of acyl benzo[b]thiophenes via C-C bond forming reaction without the use of transition metal/Lewis acids.

Benzo[b]thiophene derivatives have been shown to have both anti-inflammatory and anti-HIV1 effects. Originally, these compounds were shown to block expression of
cellular adhesion molecules and to exhibit anti-inflammatory properties\textsuperscript{279}. Recently, benzothiophene derivatives were shown to block HIV-1 transcripción in response to tumor necrosis factor a stimulation of promyelocytes\textsuperscript{280}. Additionally, these compounds blocked constitutive HIV-1 transcription in chronically infected cells and induced a latency state in cytokine-activated cells. The benzo[b]thiophene derivatives did not block the activation of NF-kB in response to tumor necrosis factor a treatment and did not block Tat function. Gualberto\textsuperscript{293} et al., have studied the effects of PD 144795 (Parke-Davis Pharmaceuticals) (86) on HIV-1 LTR-directed transcription in Jurkat T cells. The expression of HIV-1 genes is controlled in part by the interaction of sequence-specific transcription factors with the LTR region of the provirus. NF-kB, Sp1, and other sequencespecific transcription factors have been shown to control transcription initiation directed by HIV LTR\textsuperscript{281,282}. We have recently identified an inducible form of p53 in Jurkat T cells that directly interacts with a specific DNA-binding site positioned immediately downstream to the most 59 Sp1-binding site in the HIV-1 LTR\textsuperscript{283,284}. We have also shown that this DNA element mediates the induction of the HIV-1 LTR transcriptional activity by tumor promoting mutant forms of p53. These results provide a mechanism to explain the dramatic increase in HIV-1 replication observed after the overexpression of mutant p53 in cells that completely lack expression of this protein\textsuperscript{285}. It is well known that the replication of the HIV-1 virus in lymphocytes correlates with the activation/proliferation status of the infected cell\textsuperscript{286,287}. Treatment of HIV-1-infected Jurkat cells with T cell receptor (TCR) or protein kinase C activators induces HIV-1 replication\textsuperscript{288,289}. Previous reports have indicated that ligands of the TCR activate LTR-dependent transcription through a CsA-sensitive mechanism\textsuperscript{290-292}. CsA, through its interaction with cyclophilin\textsuperscript{293}, acts as an strong inhibitor of the serine/threonine phosphatase CN\textsuperscript{294,295}. This enzyme is a heterotrimeric complex consisting of a 59-kDa catalytic subunit, calcineurin A subunit, a calcium-binding regulatory subunit.
of 19 kDa, calcineurin B subunit, and a 17-kDa calcium-binding protein, calmodulin. CN plays a critical role in the regulation of calcium-dependent signalling pathways that are necessary for T cell activation\textsuperscript{296,297}. This enzyme regulates the nuclear translocation of NF-ATp, a transcription factor implicated in the expression of several cytokines\textsuperscript{298}. Also, CN inhibitors are known to decrease HIV-1 viral replication and to inhibit HIV-1 LTR-mediated transcription\textsuperscript{299}. Inhibition of NF-kB binding to the LTR region of the HIV-1 provirus has been suggested as the mechanism by which CN inhibitors would repress the transcriptional activity mediated by this promoter\textsuperscript{300}. Intriguingly, the relatively large number of genes whose expression is modulated by CN inhibitors in T cells\textsuperscript{301,302} suggests that, in addition to NF-AT and NF-kB, other transcription factors could be affected by these drugs. Gualberto\textsuperscript{303} et al., have investigated the effect of CsA and PD 144795 on the transcriptional activity mediated by p53 and NF-kB. Using several approaches we demonstrate that calcineurin is implicated in the regulation of p53 transcriptional activity, that PD 144795 is an inhibitor of calcineurin, and that the DNA binding and transactivation of p53 to the HIV-1 LTR can be modulated by calcineurin inhibitors.

![Chemical structure of compound 86](image)

These results offer insight into the understanding of the molecular basis for the inflammatory and anti-HIV properties of benzo[b]thiophene derivatives.
Keeping in view of biological importance of quinoline and benzo[b]thiophene derivatives and inspired by the scope of research in this field, we have carried out the research work on the synthesis of quinoline and benzo[b]thiophene derivatives to explore their biological profile.

The starting materials 2-chloro-3-formyl-quinoline and 3-chloro-benzo[b]thiophene-2-carbonyl chloride were synthesised as shown in **Scheme-1**.

Employing sophisticated techniques such as IR, $^1$H NMR and UPLC-Mass spectroscopy, the structures of all the newly synthesized compounds were elucidated. The reaction mechanism was also predicted for reactions and in exploration of their biological investigation, we have searched for their antimicrobial and analgesic properties.
ORGANIZATION OF THE WORK

The thesis consists of seven chapters and each chapter contains proper classification of the work and discussion.

Chapter-I: Introduction: It starts with general introduction to the field of quinoline and benzo[b]thiophene derivatives. The introduction includes brief explanation for selecting quinoline and benzo[b]thiophene derivatives as research program.

Chapter-II: Microwave assisted facile synthesis of 3-chlorobenzo[b]thiophene-2-substituted-1,3,4-oxadiazolyls and comparison with conventional method of synthesis.

Chapter-III: Synthesis of pyrazole and thienopyrimidine substituted 2-chloroquinolines.


Chapter-VII: Biological Evaluation.
REFERENCES


140. B.D. Tilak, Tetrahedron, 1960, 9, 76.


Ferin, C.D. Wright, M.E. Lesch, K. Imre, G.C. Okonkwo, D.J. Schrier, M.C.


1994, 68, 4302.*

286. J.S. McDougal, A. Mawle, S.P. Cort, J.K. Nicholson, G.D. Cross, J.A. Scheppler-

287. T. Folks, J. Kelly, S. Benn, A. Kinter, J. Justement, J. Gold, R. Redfield, K.W. Sell,


289. S. Harada, Y. Koyanagi, H. Nakashima, N. Kobayashi and N. Yamamoto,
*Virology.*, 1986, 154, 249.


291. M. Siekevitz, S.F. Josephs, M. Dukovich, N. Peffer, F. Wong-Staal and


294. J. Liu, J. D. Jr. Farmer, W.S. Lane, J. Friedman, I. Weissman and


357, 692.


