CHAPTER 3
Synthetic Routes of Thiazole and Thiophene Derivatives and Their Therapeutic Importance

Introduction:

The ideal goal of drug-discovery is to create a chemical substance that acts specifically and optimally at appropriate specific targets to perturb in *in vivo* biochemistry, in order to eliminate the biochemical challenges that have taken place due to diseased condition. [1] From the medicinal chemistry point of view the gamut of options available to design the chemical substance are a) Macromolecular structure based drug discovery and b) chemical leads used as models or templates by the designed chemical synthesis approach.

In both these approaches, the crux of the factors involved; i) The binding’s epitope (the pharmacophore) in the candidate and ii) an ideal molecular scaffolding tethered to it which helps in conferring optimal physiochemical properties to the designed drug candidate.

Literature is replete with instances where five member heterocyclic rings have turned out to be optimal molecular scaffolding thiazole and thiophene moieties, due to \( \pi \) excessive and \( \pi \) deficient features in the former and \( \pi \) excessive features in the latter have been widely incorporated in drug like candidates as useful templates. An amino feature attached to both there scaffolding have been adopted extensively in the design of new chemical entities.[2]

It is of interest to note that thiophene is a bioisoster of benzene. Thiazole can be considered as bioisosteres of oxazole, imidazole, and pyridine.

In literature there are reports giving various synthetic routes and therapeutic importance of thiazole and thiophene derivatives. Here we discuss in brief about the synthetic routes and their therapeutic importance.

3.1 Synthetic Routes of Thiazole Derivatives

Literature survey of synthesis of 5-substituted thiazole derivatives has revealed the synthetic methods with wide possibility of molecular diversity.

The first thiazole derivative 2,4-dihydroxythiazole was prepared in 1895. However, the history of thiazole series begins in 1879 with the work of Hoffmann, who synthesized a number of benzothiazole derivatives.[3] Compounds containing simple thiazole nucleus were first reported by Hantzsch et al.[4] in a series of papers beginning in 1887. After this
pioneering work, knowledge of the thiazole ring system developed steadily and many different routes of its synthesis were disclosed.

Reaction of chloroacetaldehyde with thioformamide yields thiazole while thioformamide and bromoethylamine condenses to give 2-thiazoline.[5]

\[
\begin{align*}
\text{H}_2\text{S} & + \text{CHO} \rightarrow \text{NH}_2
\\
\text{H}_2\text{S} & + \text{NH}_2\text{CH}_2\text{Br} \rightarrow \text{NH}_2
\\
\end{align*}
\]

1,4-dicarbonyl compounds containing nitrogen atom between two carbonyl groups make a synthon for thiazole formation according to Gabriel synthesis of 1910. He showed the cyclization of α-acylaminoacetophenone in the presence of \( \text{P}_2\text{S}_5 \) at 170°C. He made the acylaminoacetophenone from acyl chloride and aminoacetophenone in quantitative yield.[6]

![Diagram of Gabriel synthesis](image)

Tosylmethyl isocyanide (TOSMIC) has also been used for the synthesis of thiazoles. It reacts with carbon disulfide to form tetrabutylammonium salt of 2-mercapto-1,3-thiazole which on reaction with alkyl halide produces 4-tosyl-5-alkylthio thiazoles as shown in the following scheme.[7]
2-aminothiazoles can be synthesized cleanly and in high yields from an α-bromoketone and a thiourea via the Hantzsch thiazole synthesis.[8] A modification of Hantzsch synthesis was reported by Moriarty et al. in 1992. They avoided the use of general α-halocarbonyl compounds, instead, they made the tosyloxylated ketone by a reaction of ketone with (Hydroxy[tosyloxy]iodo) benzene which reacted with thioamide to produce thiazole derivative. They also utilized the same method for 1,3-dicarbonyl compounds to synthesize 5-acyl thiazoles.[9]

5-substituted ketone derivatives were synthesized by the reaction of thioacetamide with 3-bromo-2,4-pentanedione.[10] Formamide reacts with POCl₃ in chloroform and then treated with thioamide to produce N-thiocarbamyl formamidines which reacts with α-halocarbonyl compounds to yield 5-acyl thiazole derivatives.[11] 1-aminothioenolether reacts with thionyl chloride and intramolecularly cyclizes to 5-acyl thiazole derivatives.[12]
In 1986, Rajasekharan et al. reported the synthesis of 2,4-diamino-5-thiazolyl carbonyl compounds using 1-amidino-3-arylthioureas and reacting it with α-halocarbonyl compounds such as phenacyl bromide. The use of thiourea as the sulfur component with 2-chloroacetamides as the second unit gives rise to 2,4-diaminothiazoles.

5-thiazolyl carboxylate derivatives were obtained from the reaction of secondary α-halocarbonyl compounds with thioacetamides. In another method, isothiourea derivative was reacted with methyl thioglycolate to yield 5-thiazolyl carboxylate derivatives. Recently, Dridi, K. et al. reported that N-thiocarbamoylimidates reacted with methyl thioglycolate in sodium methoxide solution in methanol to afford 4-amino-5-thiazolyl carboxylate derivative. It was hypothesized that the reaction consists of two steps: formation of the N-thiocarbamoylthioimidate intermediate which cyclized after liberation of hydrogen sulfide as a neutral molecule.
Monosubstituted thiourea derivatives were reacted with α-halocarbonyl compounds to yield 4-thiazolines.\[18-20\] 4-Thiazoline-2-thione was prepared from phenacylmercaptan derivatives in the presence of sulphuric acid.\[21\]

Starting from 1970, from the first report of the novel synthesis of thiazole ring, a series of papers were published by Rajappa, S. et al.\[22\] In the first paper, they reacted isothiocyanate with acetamidine yielding an adduct which was further reacted with phenacyl bromide to afford 5-acyl thiazole.\[23\] The first step in the cyclization is the S-alkylation followed by attack of active methylene group on amidine carbon eliminating an amino group. In the next paper, they reacted the similar adduct with bromonitromethane to yield thiazole substituted by nitro group at 5\(^{th}\) position of the thiazole ring.\[24\] In the third publication they evaluated the role of arylamino as a leaving group.\[25\] In the fourth paper, tetramethylguanidine was used instead of acetamidine.\[26\] They found that with this also the reaction proceeded well. In all the above reactions, phenacyl bromide or chloroacetone or bromonitromethane was used as α-halocarbonyl/nitro compound. They also reacted heterocyclic derivatives instead of α-halocarbonyl compounds such as 2-chloromethyl pyridine, 2-chloromethyl quinoline etc.\[27\] They also studied the reaction of monosubstituted thiourea derivatives with α-halocarbonyl compound to give thiazolines.
From all these reported synthesis of different 5-substituted thiazole derivatives, the most efficient method which can give rise to a wide variety of substituents at 2nd, 4th and 5th position of the thiazole ring and can provide the necessary structural features needed for the target molecules is of Rajappa, S. et al.[24] This method was adopted for synthesis of target molecules which is mentioned in above figure.

3.2 Synthetic Routes of Thiophene Derivatives

There are several methods available for the synthesis of the thiophenes. One of the oldest methods reported for the synthesis of thiophenes was by Gewald.

**Gewald reaction:**

Ketones and aldehydes [28] with free methylene group at α position condense with nitrile [29] and elemental sulfur in presence of a secondary amine (diethyl amine, piperidine, morpholine) to yield 2- amino-3- substituted thiophene (11). The condensation of carbonyl compounds, S and malononitrile derivatives in presence of secondary amine catalyst, which involves the formation of alkylidene nitrile, thiolation and finally intramolecular cyclisation to substituted thiophene system proceeds smoothly and uniformly around 45°C. This one pot modified Wilgerodt-Kindler (13) type reaction has become known as Gewald reaction[30].
Chapter 3 Synthetic Routes of Thiazole and Thiophene

Willgerodt-Kindler reaction:

1-Phenyl butanones when reacted with 2 molecules of morpholine and 2 gram atom of sulfur at 130°C yield an intermediate thiomorpholide, which when subjected to similar treatment [31] affords thiophene.

The synthesis of thiophenes has been reviewed excessively [32, 33]. The synthesis of 2,5 disubstituted thiophenes has been described by Smutny, where he utilized amino dithio acrylates and α-halo carbonyl compounds as synthetic equivalents in the presence of a base. A polar aprotic solvent like acetone was utilized [34].

Tetra substituted thiophenes were synthesized by Gompper using dithiolates and α-halogen derivatives in the presence of a base [35].

Rajappa described a two-step synthetic process for the synthesis of tetra-substituted thiophenes [36].
3.3 Bio-isosteres: Concept for Drug Design

Bioisosterism is a strategy of used for the rational design of new drugs, based on chemical lead [37]. The chemical lead should possess well-known mechanism of action, if possible at the level of topographic interaction with the receptor, including knowledge of all of its pharmacophoric groups. Furthermore, the pathways of metabolic inactivation [38], as well as the main determining structural factors of the physicochemical properties which regulate the bioavailability, and its side effects, whether directly or not, should be known so as to allow for a broad prediction of the definition of the bioisosteric relation to be used.

The success of this strategy in developing new substances, which are therapeutically attractive, has achieved significant growth in distinct therapeutic classes, being amply used by the pharmaceutical industry to discover new analogs of therapeutic innovations commercially attractive, and also as a tool useful in the molecular modification.

There may be numerous reasons for the use of bioisosterism to design new drugs, including the necessity to improve pharmacological activity, gain selectivity for a determined receptor or enzymatic isoform subtype with simultaneous reduction of certain adverse effects, or even optimize the pharmacokinetics the LC might present. In this part of the chapter, we will discuss bioisosterism as a strategy of molecular modification, showing its importance in building a new series of congeners compounds designed as candidate of new drugs, giving examples of successful cases in distinct therapeutic classes.

3.3.1 Background

The bioisosteric rationale for the modification of lead compounds is traced back to the observation by Langmuir in 1919 regarding the similarities of various physicochemical properties of atoms, groups, radicals, and molecules. Langmuir compared the physical properties of various molecules such as N₂ and CO, NO₂ and CO₂, and N₃⁻ and NCO⁻ and found them to be similar. On the basis of these similarities he identified 21 groups of
isosteres. Some of these groups are listed in Table 1. He further deduced from the octet theory that the number and arrangement of electrons in these molecules are the same. Thus, isosteres were initially defined as those compounds or groups of atoms that have the same number and arrangement of electrons. He further defined other relationships in a similar manner. Argon was viewed as an isostere of K+ ion and methane as an isostere of NH4 + ion. He deduced, therefore, that K+ ions and NH4 + ions must be similar because argon and methane are very similar in physical properties. The biological similarity of molecules such as CO2 and N2O was later coincidentally acknowledged as both compounds were capable of acting as reversible anesthetics to the slime mold Physarum polycephalum. [39]

<table>
<thead>
<tr>
<th>Table 1. Groups of Isosteres as Identified by Langmuir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>groups</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
</tbody>
</table>

A further extension to this concept of isosteres came about in 1925 with Grimm's Hydride Displacement Law. This law states: “Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places respectively, to their right.” Each vertical column as illustrated in Table 2, according to Grimm, would represent a group of isosteres. [40]
Table 2. Grimm’s Hydride Displacement Law

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>N</th>
<th>O</th>
<th>F</th>
<th>Ne</th>
<th>Na</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH</td>
<td>NH</td>
<td>OH</td>
<td>FH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CH₂</td>
<td>NH₂</td>
<td>CH₃</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CH₄</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Erlenmeyer further broadened Grimm’s classification and redefined isosteres as atoms, ions, and molecules in which the peripheral layers of electrons can be considered identical (Table 3). [41]

Table 3. Isosteres Based on the Number of Peripheral Electrons

<table>
<thead>
<tr>
<th>no. of peripheral electrons</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>N⁺</td>
<td>P</td>
<td>S</td>
<td>Cl</td>
<td>CIH</td>
<td></td>
</tr>
<tr>
<td>P⁺</td>
<td>As</td>
<td>Se</td>
<td>Br</td>
<td>BrH</td>
<td></td>
</tr>
<tr>
<td>S⁺</td>
<td>Sb</td>
<td>Te</td>
<td>I</td>
<td>IH</td>
<td></td>
</tr>
<tr>
<td>As⁺</td>
<td>PH</td>
<td>SH</td>
<td>PH₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sb⁺</td>
<td>PH₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Over the years, innumerable bioisosteric relations have been identified in compounds both natural and synthetic. In nature, people have identified many examples of isosterism as a form of broadening chemodiversity (Scheme 1), striking among which are the classic bioisosteric relation existing between the essential amino acids serine (1) and cysteine (2), tyrosine (3) and histidine (4) among the pyrimidine and purine bases cytosine (5) and uracil (6), adenine (7) and guanine (8); among the xanthines caffeine (9) and theophylline (10); and among the salicylic (11) and anthranilic (12) acids, which originated two important classes of non-steroid anti-inflammatory drugs, e.g. acetylsalicylic acid and mefenamic acids, respectively. Furthermore, examples of the application of non-classic bioisosterism are also found in nature - such as the bioisosteric relationship existing between γ-aminobutyric acid (GABA) (13) and muscimol (14), between the neurotransmitters glutamate (15) and AMPA (16).
3.3.2 CLASSIFICATION OF BIOISOSTERISM: CLASSIC AND NON-CLASSIC

Bioisosteres have been classified as either classical or nonclassical. Grimm's Hydride Displacement Law and Erlenmeyer's definition of isosteres outline a series of replacements which have been referred to as classical bioisosteres. Classical bioisosteres have been traditionally divided into several distinct categories: (A) monovalent atoms or groups; (B) divalent atoms or groups; (C) trivalent atoms or groups; (D) tetrasubstituted atoms; and (E) ring equivalents. (see table 1)

Nonclassical isosteres do not obey the steric and electronic definition of classical isosteres. A second notable characteristic of nonclassical bioisosteres is that they do not have the same number of atoms as the substituent or moiety for which they are used as a replacement. Nonclassical bioisosteres can be further divided into groups: (A) rings vs noncyclic structures; and (B) exchangeable groups. (see table 2)
3.3.3 BIOISOSTERISM AS A STRATEGY OF MOLECULAR MODIFICATION

Among the most recent numerous examples used in the strategy of bioisosterism for designing new pharmaceutically attractive substances [42], there is a significant predominance on non-classic bioisosterism, distributed in distinct therapeutic categories, be they selective receptor antagonist or agonist drugs, enzymatic inhibitors or anti-metabolites. The use of classic bioisosterism for the structural design of new drugs, while less numerous, has also been carried out successfully [43].
The correct use of bioisosterism demands physical, chemical, electronic and conformational parameters involved in the planned bioisosteric substitution, carefully analyzed so as to predict, although theoretically, any eventual alterations in terms of the pharmacodynamic and pharmacokinetic properties which the new bioisosteric substance presents. Thus being, any bioisosteric replacement should be rigorously preceded by careful analysis of the following parameters:

a) size, volume and electronic distribution of the atoms or the considerations on the degree of hybridization, polarizability, bonding angles and inductive and mesomeric effects when fitting;

b) degree of lipidic and aqueous solubility, so as to allow prediction of alteration of the physicochemical properties such as logP and pKa;

c) chemical reactivity of the functional groups or bioisosteric structural subunits, mainly to predict significant alterations in the processes of biotransformation, including for the eventual alteration of the toxicity profile relative to the main metabolites;

d) conformational factors, including the differential capacity formation of inter- or intramolecular hydrogen bonds.

3.3.4 BIOISOSTERISM AND ALTERATIONS OF PHYSICOCHEMICAL PROPERTIES

Some bioisosteric groups dramatically alter the physicochemical properties of substances and, therefore, their activities. This can be easily understood by comparing classic isosteres resulting from bioisosteric replacement between hydroxyl (−OH) and amine (−NH₂), an example of classic bioisosterism of monovalent groups according to Grimm’s Rule. In this case, considering the bioisosteric replacement of aromatic amine present in aniline by hydroxyl, we have phenol resulting in a significant change in the acid-base properties of isosteres, with dramatic modification of the pKa of the compounds, which is responsible for the distinct pharmacokinetic profiles among the isosteres in question. Thus, in this example, we may predict that the use of bioisosterism, even the classic type, can promote severe alterations of molecular properties, as much in terms of lipidic-aqueous solubility as well as chemical reactivity, among others, which, broadly speaking, is not observed in the same homologue carbonic series.
Chapter 3 Synthetic Routes of Thiazole and Thiophene

Here we have discussed the basics and the importance of the bioisosteric replacement. Here in this thesis several bioisosterism will be exemplified.

3.4 Therapeutic Importance of Thiazole and Thiophene Derivatives

3.4.1 Therapeutic Importance of Thiazole Derivatives:

One of the most important azoles is thiazole having nitrogen and sulfur as two heteroatoms with an aromatic character. [44] In nature, thiazole moiety, unlike oxazole present in experiment candidate Romazarit, has been found to be present in Vitamin-B_1.

Thiazole nucleus is reported to be important for various therapeutic activities, and there are briefly summarised below.

**Neurologic Disorders**

Jaen, J.C. et al. demonstrated the dopaminergic activity of 4-(1,2,5,6-tetrahydro-1-alkyl-3-pyridinyl)-2-thiazole derivative (22) and proposed it to be effective in parkinson's disease. Thiazole scaffold (23) has also been proved to be beneficial for the treatment of Schizophrenia.(34) Thiazoles condensed with itself giving rise to thiazolothiazole compounds (24, Ibazane) were found to be CNS depressant. [45]
Migraine and Pain

Replacement of the amide/ester linkage in the ICS-205-930 (25; Ki : 2.7 nM) series and ketone functionality in the Ondansetron (26; Ki : 16.2 nM) series with thiazole moiety (27; Ki : 0.42 nM) improved the 5-HT₃ receptor antagonistic activity. In this publication, authors established that thiazole is a carbonyl bioisostere.[46]

Anticancer

Thiazole-4-carboxamide moiety in 28 (TAD, Thiazole-4-carboxamide adenine dinucleotide) mimicks the nicotinamide ring in binding with cofactor site to inhibit dehydrogenases (GDH, ADH, LDH and MDH) exhibiting antitumor activity. Thiazolyl purine derivatives (29) were reported to be potent antitumor agents. Some of the phthalimidothiazole derivatives (30) showed considerable activity in the screen against Lewis lung carcinoma.[47]
Anti-inflammatory

Thiazole attached with quinoline by amide linkage as exemplified by RU43526 (31) produced anti-arthritis and analgesic compound showing the importance of thiazole moiety.[40] Bisaryl thiazoles (32) have been found to have platelet aggregation inhibitory activity as reported by Rynbrandt et al.[41] Thiazoles fused with another heterocycle, imidazole, named imidazothiazole (33) derivatives have shown anti-inflammatory activity.[42] A variety of novel 2,4-diaryl thiazole-5-acetic acids (34) were evaluated as anti-inflammatory agents as shown in carrageenan induced edema assay in the rat.[48]

It is worth mentioning that the replacement of isoxazole moiety as in Isoxicam and pyridine moiety as in Piroxicam by a thiazole moiety as in Meloxicam gave rise to significant COX-2 selectivity.[49]
The introduction of thiazole motif in the benzothiazine dioxide carboxamide (36) in place of aryl or alkyl group as in (35) resulted in the lower pKa value and very much improved potency as anti-inflammatory agents.[50]

When the thiazole ring (37) was replaced with cyclopentathiazole ring (38), anti-inflammatory activity of the compound completely vanished showing the importance of conformationally non-restricted thiazole in the potency.[51]
Steroidal [3,2-d] thiazoles (39) were found to be better anti-inflammatory compounds as compared to simple steroids.[52]

Selectivity of drugs towards 5-lipoxygenase enzyme in comparison to cyclooxygenase enzyme was achieved by a novel (methoxyalkyl) thiazole (40) [53] derivatives as 5-lipoxygenase inhibitors and in another study, Kerdesky et al. found that 4-hydroxythiazoles were potent and selective inhibitors of 5-lipoxygenase enzyme in-vitro [54].
Cardiovascular

Thiazolyl derivatives (42) having β-adrenergic blocking activity has been published by Baldwin et al. in 1980. They were useful as anti-hypertensive drugs.\(^{(50)}\) 2-Acetylamino thiazole derivatives (43) have shown hypotensive activity.\(^{(55)}\)

\[
\text{H}_2\text{C} \quad \text{CH}_3 \quad \text{OH} \quad \text{O} \quad \text{NC} \quad \text{N}
\]

Antifungives

Parasites were also not barred from the terror of thiazoles. 2-(5-Nitro-2-thienyl) thiazole derivatives (44) are reported to be antiprotozoal drugs.\(^{(56)}\)

\[
\text{O}_2\text{N} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{N}
\]

Thiazolines (45) were found to be active against heterakids, ascarids and capillarids type of worms, useful as anthelmintic. From 49 analogs, tetramisole (46) (2,3,5,6-tetrahydro-6-phenylimidazo-[2,1-b] thiazole hydrochloride) has been discovered as a novel broad spectrum anthelmintic.\(^{(57)}\)
Chapter 3 Synthetic Routes of Thiazole and Thiophene

Some 2-heteroylimino-5-nitro-4-thiazoline-3-acetamides (47) and 1-(carbamoylmethyl)-1-(5-nitro-2-thiazolyl) ureas (48) were reported by Islip et al. as antiparasitic agents. Various 2-acyl and 2-(alkoxycarbonylimino)-5-nitro-4-thiazoline-3-acetamides (49) were reported to have potent schistosomicidal activity. In another example, 1-alkyl-3-(3-alkyl-5-nitro-4-thiazolin-2-yl) ureas (50) was published as schistosomicides.

Thiazolyl imidazopyridines (51) were evaluated as anthelmintic and anti-fungal agents and found to be very potent lead candidates.

Anti-diabetic

New class of 4-(and 5-)thiazolyl pyridazinium salts (52) as oral hypoglycemic agents were reported.

Thiazolidinedione derivatives are reported to be very potent hypoglycemic and hypolipidemic agents. Recently, Sohda et al. reported that thiazolylalkoxylbenzylidene
thiazolidinedione (54) were more potent than Pioglitazone (53) which has recently been launched as an anti-diabetic drug in the market.[61]

![Chemical Structure](image)

**Antihistamine**

5-(2-aminoethy1)-thiazole derivatives elicited the histamine H$_2$ receptor agonistic activity. It was hypothesized that the acceptance of a proton by a thiazole nucleus from a receptor site stimulates the histamine H$_2$ receptor. Antamidine (55) is the most potent of this series.[62] Hargrave et al. reported that N-(4-substituted thiazoly1) oxamic acid derivatives (56) are potent antiallergy agents.[63]

![Chemical Structure](image)

**Anti HIV(Human Immunodeficiency Virus)**

N-(2-phenethyl)-N'-(2-thiazolyl) thiourea (LY 73497) (57) inhibits HIV-1 reverse transcriptase enzyme useful as anti AIDS molecule. [64]
All these reports have suggested the potential of thiazole moiety as a useful molecular scaffold in drug design.

3.4.2 Therapeutic Importance of Thiophene Derivatives:  
Thiophene derivatives have been used in different therapeutic areas. We have identified the thiophene molecular scaffolding as being useful for the design of new analogs for anti-inflammatory evaluation. Some of the compounds of interest are shown in (fig 24). [65]
The thiophene derivative tiaprofenic acid (fig 25) has been reported to have good efficacy as an anti-inflammatory drug. [66]

(Fig 25)

The initial reports of 2,3 diaryl thiophenes (fig 26) as a non-ulcerogenic anti-inflammatory agent has led to much activity in this area.[67]

(Fig 26)

Several laboratories have subsequently investigated 2, 3-diaryl thiophenes (fig 27) such as methyl sulphones and sulfonamides and found them to be selective COX-2 inhibitor. [68]

(Fig 27)

The thiophene analog had displayed a selective COX-2 inhibition (COX-1=0%, COX-2=69% inhibition at 0.01 microM, and it was found to be orally active (ED 30 = 1.4
mpk, P. O) in rat carrageenan induced foot paw edema (CFE). (67). The isomeric 3, 4-diaryl thiophene methyl sulphones and sulfonamides (fig 28) have also been reported as selective COX-2 inhibitors.[69, 70]

![Diagram of molecule](image)

(Fig 28)

The lack of cyclooxygenase selectivity observed with 3,4 bis-(4-methoxy phenyl) analog (COX-1 ID 50 = 0.3 micron, COX-2 ID 50 = 0.8 micron) suggests that the presence of a methyl sulphone or sulfonamide moiety is required for good selectivity. Replacement of one of the benzene rings in the scaffold of clozapine (which has the side effect of possible agranulocytosis) by thiophene has lead to olanzapine a drug which has superior efficacy and good safety profile and also a blockbuster drug as antipsychotic agent. These examples illustrate the utility of thiophene moiety as scaffolding in drug candidates.[71]

References:
20. Groth, B. CA-Vol.18 -1280, 1924.