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A Review on Synthesis and Medicinal Importance of Thiophene

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----------**ABSTRACT**----------
Thiophene nucleus is one of the most important potential entities in the largely growing chemical world of heterocyclic compounds exhibiting remarkable pharmacological activities. The knowledge of various synthetic pathways and diverse physicochemical parameters of such compounds draw the especial attention of medicinal chemists to produce combinatorial library and carry out exhaustive efforts in the search of lead molecules. The similar compounds synthesized through different routes bear variable magnitudes of biological activities. The present review highlights a broad view on various synthetic methods and medicinal importance of compounds having thiazole nucleus.

Keywords *- Heterocycles, Thiophene: Biological Activity, Medicinal Importance, Synthesis.*

I. INTRODUCTION

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease. The process of establishing a new drug is exceeding complex and involves talent of people from variety of disciplines [1].

The design of drug molecules arguably offers some of the greatest hopes for success in present and future era. Heterocyclic compounds are widely distributed in nature and are essential for life. There are vast numbers of pharmacologically active heterocyclic compounds many of which are in regular clinical use [2].

Thiophene (Fig.1) belongs to a class of heterocyclic compounds containing a five membered ring made up of one sulphur as heteroatom with the formula C_4H_4S. Thiophene and its derivatives exist in petroleum or coal. Thiophene is taken from the word *theion*, the Greek word for sulfur, and another Greek word *phaino* which means shinning. Thiophene structure can be found in certain natural products and is also incorporated in several pharmacologically active compounds.

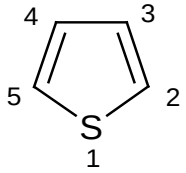


Figure 1. Structure of Thiophene

The simple thiophenes are stable liquids which closely resemble the corresponding benzene compounds in boiling point and even in smell [3]. Thiophene was discovered as a contaminant in benzene [4]. It was observed that isatin (1H-indole-2, 3- Dione) forms a blue dye if it is mixed with sulfuric acid and crude benzene. Victor Meyer was able to isolate the substance responsible for this reaction. The compound was found to be a heterocyclic compound- Thiophene.

II. VARIOUS SYNTHETIC ROUTES FOR THIOPHENE NUCLEUS FORMATION

A method of preparing thiophene involves reaction of an organic compound containing a chain of at least four carbon atoms linked by single or double bonds with a source of sulphur. The nature and type of the synthesized substituted thiophene compounds depends on the starting material. Thus a st arting material containing solely four carbon atoms in a straight chain produces unsubstituted thiophene while those containing more than four carbon atoms lead to synthesis of substituted thiophene.

Various synthetic approaches to the construction of thiophene and substituted thiophene have been efficiently developed. Thiophene ring can be constructed from non-heterocyclic precursors by two reaction pathways [5]:

a. Construction of thiophene ring from appropriately substituted open chain precursors: This method involves the introduction of sulphur into a starting material containing the complete carbon skeleton.
b. The functionalization at the positions α and β to the sulphur atom of the preconstructed thiophene nucleus: This method employ either the reaction of a m ercaptoacetate with a 1 , 3-dicarbonyl compound or the reaction of a thiodiacetate with a 1,2-dicarbonyl compound.

III. GENERAL SYNTHETIC ROUTES FOR THIOPHENE NUCLEUS FORMATION

The general synthetic procedure includes the following:

- From thiazoles: When thiazoles are heated strongly with an alkyne, generates 2, 5- unsubstituted thiophenes. Though the conditions are vigorous, excellent yield can be obtained. (Fig. 2)

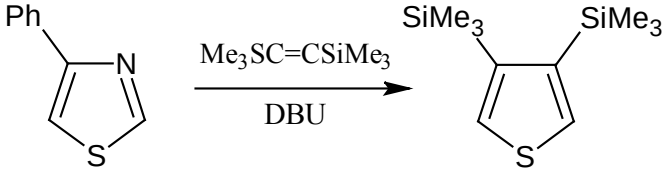


Figure 2

- By carbon disulfide: 2-alkylthiophenes [6] can be synthesized by the addition of a carbanion to carbon disulfide with a subsequent S-alkylation. (Fig. 3)

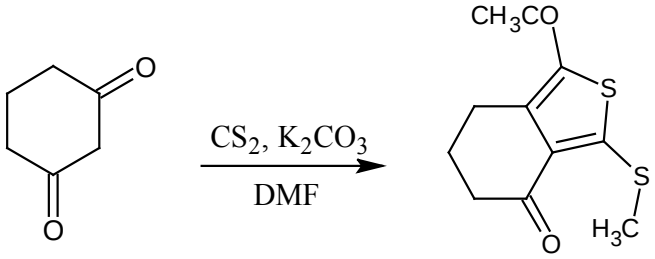


Figure 3

- From thio-nitroacetamides: The S-alkylation of thio-nitroacetamides with 2-bromoketones produces 2-amino-3-nitrothiophenes [7]. (Fig. 4)

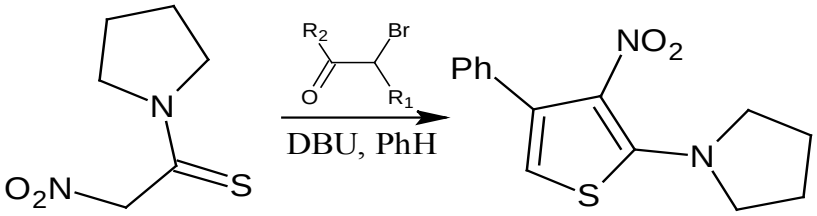


Figure 4

- From thiocarbony1 compounds: 2-Keto-thiols added to alkenyl phosphonium ions followed by ring closure via Witting reaction gives 2, 5-dihydrothiophenes which can be dehydrogenated [8]. (Fig. 5)

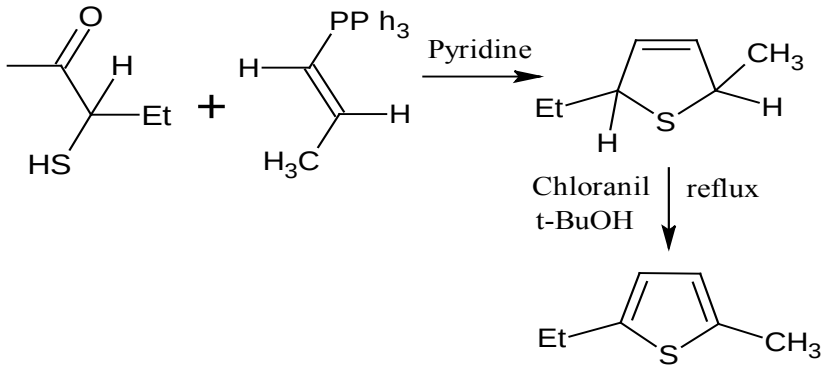


Figure 5

IV. MAJOR SYNTHETIC ROUTES FOR THIOPHENE NUCLEUS FORMATION

The major synthetic procedures for the synthesis of thiophene moiety includes following:

- Paal- Knorr Thiophene Synthesis: This reaction is also known as Paal Thiophene Synthesis. In this, 1, 4-Dicarbony1 compounds are reacted with a source of sulfur to give thiophene. (Fig. 6)

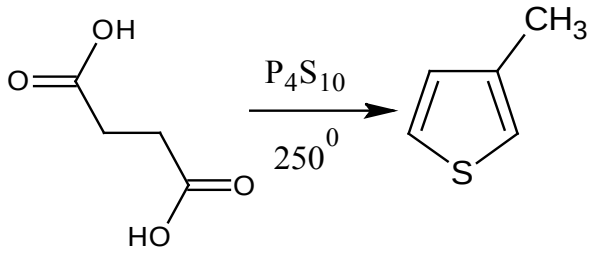


Figure 6

Source of sulfur used are traditionally phosphorus sulfides, latterly Lawesson's reagent(LR) or bis(trimethylsilyl) sulfide [9]. (Fig. 7)

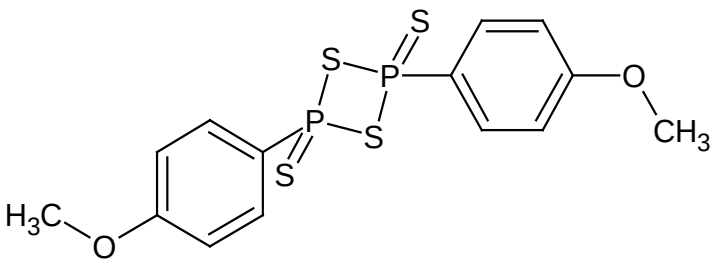


Figure 7

- Fiesselmann Thiophene Synthesis: Condensation reaction of thioglycolic acid with α, β- acetylenic esters, which upon treatment with base result in the formation of 3- hydroxyl- 2-thiophenecarboxylic acid [10]. (Fig. 8)

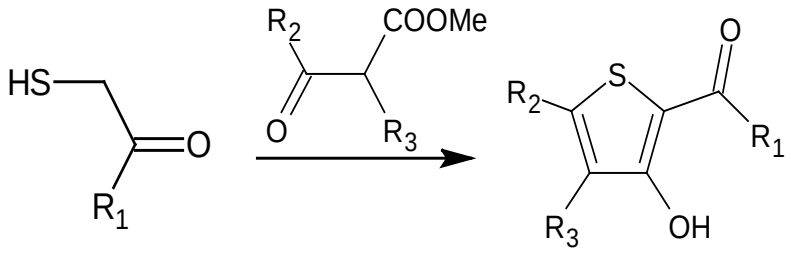


Figure 8

- Gewald Aminothiophene Synthesis: This method was reported by Gewald in 1966 [11]. Gewald synthesis is the usual route to 2-aminothiophenes. It consists of the base-catalyzed condensation of a ketone having a CH_2 group with a β-ketonitrile to form an olefin, followed by cyclisation with elemental sulfur. (Fig. 9)

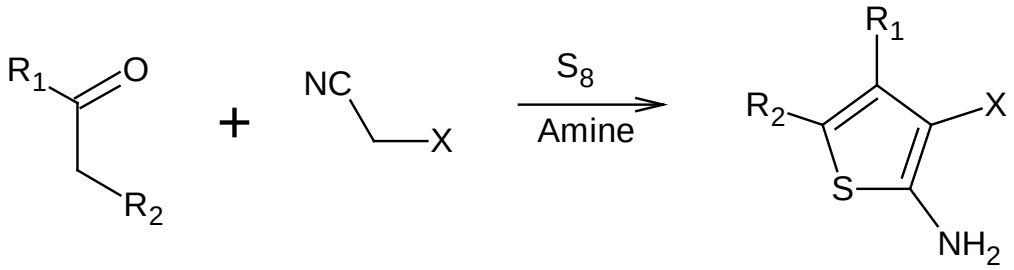


Figure 9

- The Hinsberg Synthesis: Two consecutive aldol condensations between a 1, 2-dicarbony1 compound and diethy1 thiodiacetates gives thiophene. The immediate product is an ester-acid produced [12] by a Stobbe-type mechanism but the reactions are often worked up via hydrolysis to afford an isolated diacid. (Fig. 10)

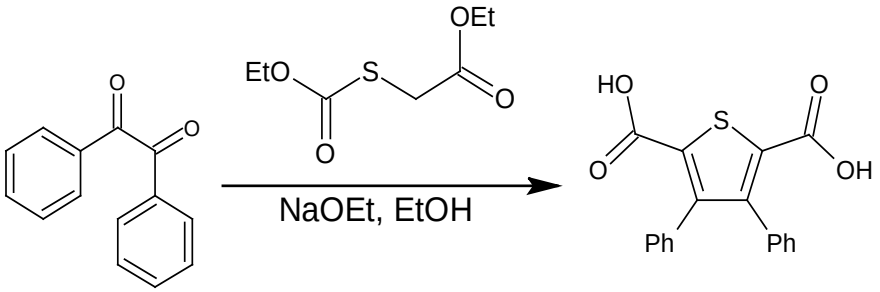


Figure 10

V. MEDICINAL IMPORTANCE OF THIOPHENE

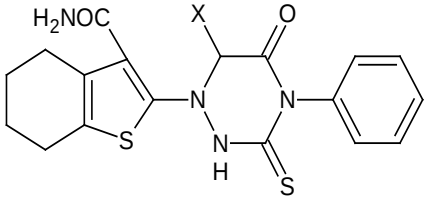
In medicinal chemistry, thiophene derivatives have been very well known for their therapeutic applications. Although thiophene have been known from long ago to be biologically active, their varied biological features are still of great scientific interest.

Thiophene can be fused with various heterocyclic systems giving rise to various new heterocyclic system with enhanced biological activity. Thienopyrimidines occupy a special position among these compounds.

Antimicrobial Activity

Different approaches were made to check the role of thiophene moiety as antimicrobial agent from the discovery of molecule to the present scenario.

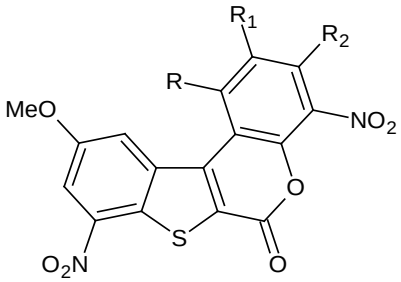
- Mohareb Rafat *et al* [13] synthesized various thiophenylhydrozoneacetates (tetrahydrobenzo (b) thiophene- 3- carboxamide) and reported their antimicrobial activity. (Fig. 11)



X = CN, $COCH_3$

Figure 11

- Havaldar *et al* [14] synthesized 10 methoxy- 4,8-dinitro-6H benzothieno [2,3-c] chromen-6-one and screened them for antibacterial activity. (Fig. 12)



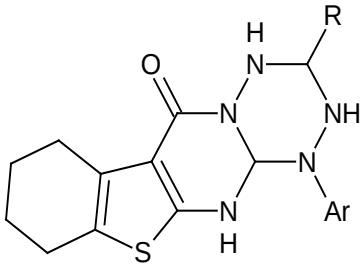
R = H, CH_3, OCH_3, Cl

R_1 = H, NO_2, CH_3, OCH_3, Cl

R_2 = H, CH_3, Cl

Figure 12

- Abdullah *et al* [15] synthesized 1,4,7,8,9,10-hexa hydro-6H-[1]- benzathieno[2',3':4,5]pyrimido[1, 2- b][1, 2, 4, 5] tetrazin- 6- ones and evaluated their antibacterial activity. (Fig. 13)



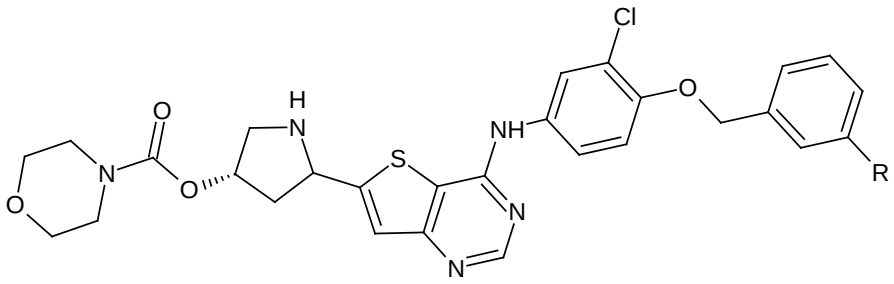
R= H, CH_3

Figure 13

In other words it can be stated that thiophene moiety serves as a royal warrior against almost all types of microbes.

Anticancer Activity

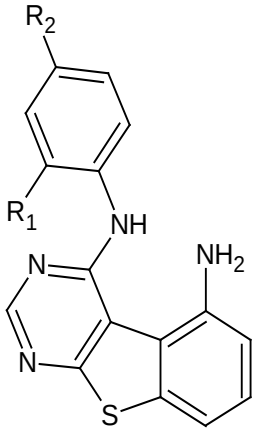
- Waterson *et al* [16] designed and evaluated aniline headgroups for alkynyl thienopyrimidine dual EGFR/ErbB-2 kinase inhibitors. (Fig. 14)



R= H, F

Figure 14

- Pedeboscq *et al* [17] developed 4-(2-Methylanilino) benzo [b] thieno [2, 3-d]pyrimidine and 4-(2-Methoxyanilino) benzo[b]thieno[2,3-d]pyrimidine which exhibited a similar cytotoxicity to the standard anti-EGFR Geftinib. (Fig. 15)

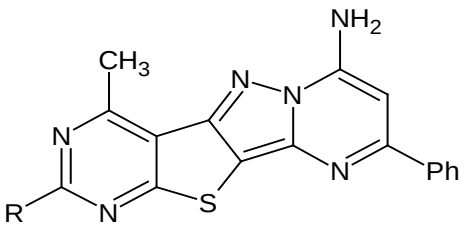


R_1= CH_3, OCH_3
R_2=H

Figure 15

Antiinflammatory Activity

- Fayed *et al* [18] synthesized some new thieno[2,3-d]pyrimidine and pyrimidopyrazolothienopyrimidine derivatives and evaluated them for anti-inflammatory and analgesic activity. (Fig. 16)



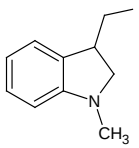
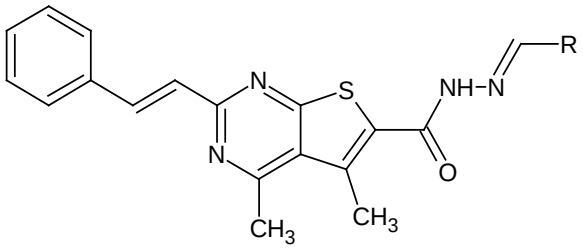
R= 

Figure 16

- Pyrimidines and thienopyrimidines derivatives were synthesized by Ouf *et al* [19] and evaluated them for anti-inflammatory activity. (Fig. 17)

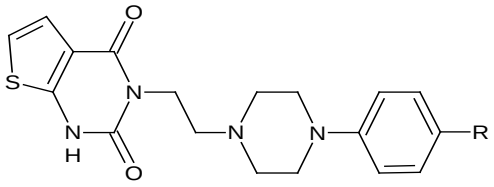


R= C_6H_5, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4- $NO_2C_6H_4$

Figure 17

Antihypertensive Activity

- Russell *et al* [20] developed thienopyrimidine-diones derivatives and then evaluated them for antihypertensive activity. (Fig. 18)



R= 2-OCH_3, 3-OCH_3, H

Figure 18

- Benton *et al* [21] developed some of Citedil analogues of the following type as blockers of calcium channel blockers. (Fig. 19)

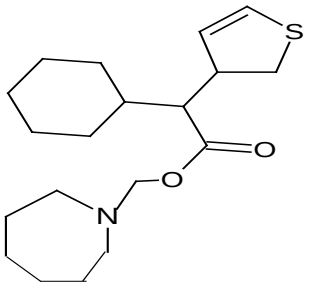
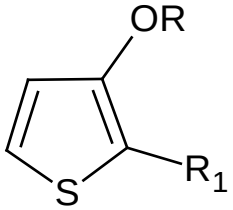


Figure 19

Analgesic Activity

- Daris *et al* [22] synthesized and studied the preliminary pharmacological study of thiophene analogs of the antipyretic and analgesic agent Athenzamide. (Fig. 20)

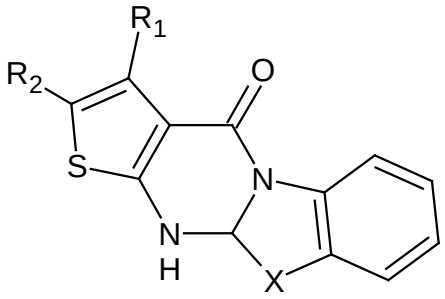


R= H, CH_3, Et

R_1= CO_2CH_3, COCl, $CONH_2$

Figure 20

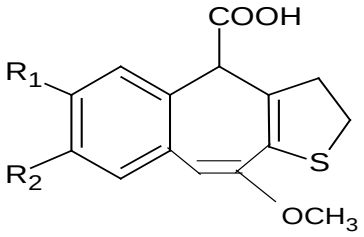
- Russo *et al* [23] synthesized new thienopyrimidobenzothiazole and thieno pyrimidobenzoxazoles and then screened them for analgesic and anti-inflammatory activity. (Fig. 21)



X= O, S
R_1= CH_3, H
R_2= CH_3, H, C_6H_5

Figure 21

- Bollinger *et al* [24] prepared benzo(4,5)cyclohepto(1,2-b)thiophen-4-ylidene acetic acids as novel non- ulcerogenic anti-inflammatory agents. (Fig. 22)



R_1= R_2= H, Cl, F, CH_3

Figure 22

- El-Gazzar *et al* [25] synthesized thieno[2,3-d]pyrimidine derivatives and screened them for anti-inflammatory, analgesic and ulcerogenic activity. (Fig. 23)

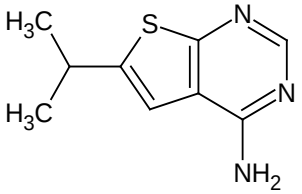


Figure 23

CNS Activity

- Oganisyan *et al* [26] designed a series of new pyrano (thiopyrano) [4'3':4,5] thieno[2,3-d]pyrimidines and screened them for their anticonvulsant activity. (Fig. 24)

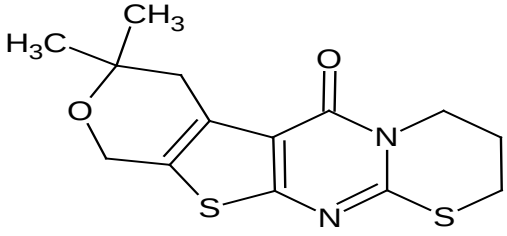
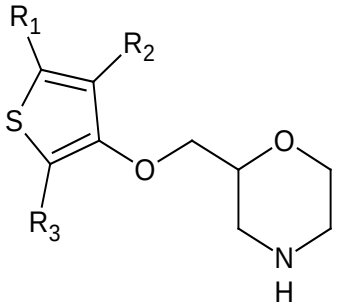


Figure 24

- Corral *et al* [27] reported the synthesis and preliminary pharmacological evaluation of thiophene analogues of Viloxazine as potential antidepressant drugs. (Fig. 25)



R_1= R_3= H
R_2= Ph

Figure 25

Miscellaneous Activity

- Edie *et al* [28] synthesized thienopyrimidines as pesticides. (Fig. 26)

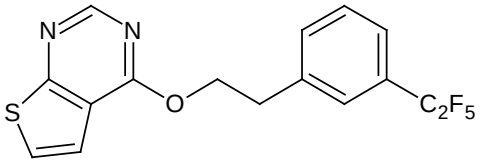


Figure 26

- Briggs *et al* [29] during X-Ray crystallographic studies found that their newly synthesized diaminobenzo (b) thiophenes derivatives revealed a new binding site at the human α-thrombin. (Fig. 27 and Fig. 28)

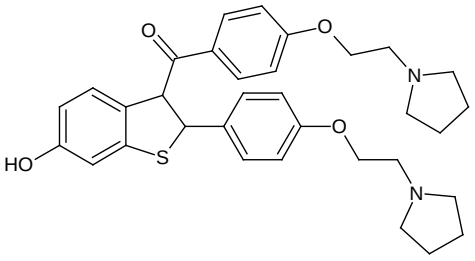


Figure 27

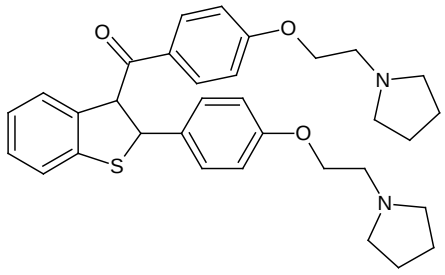
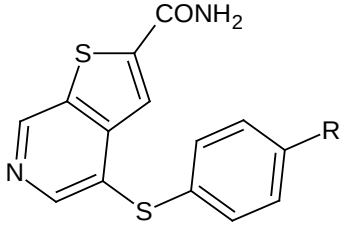


Figure 28

- Bhatia *et al* [30] synthesized thieno[2,3-c] pyridine amides and reported to have the ability to penetrate cells and selectively inhibit the surface expression of the cell adhesion molecules ICAM-1 in human endothelial cells. (Fig. 29)



R= CH_3, Br

Figure 29

- Ivan *et al* [31] synthesized 2-alkoxy and 5-substituted thiophenes as local anesthetics. (Fig. 30 and Fig. 31)

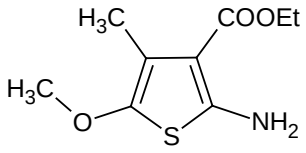


Figure 30a

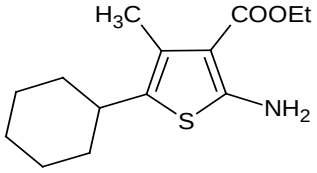


Figure 30b

Thiophene as an Antimicrobial Agent: Cefoxitin (Fig. 31) [32], Cephalothin (Fig. 32) [33], Cephaloridine (Fig. 33) [34], Temocillin (Fig. 34) [35].

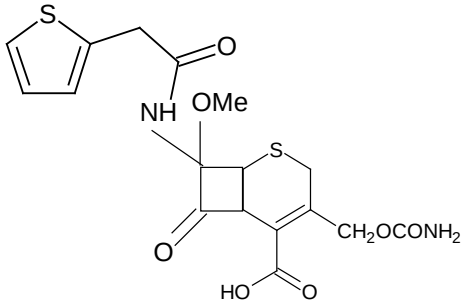


Figure 31

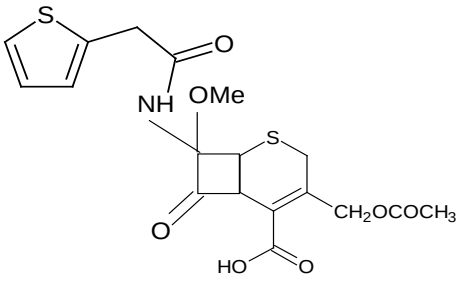


Figure 32

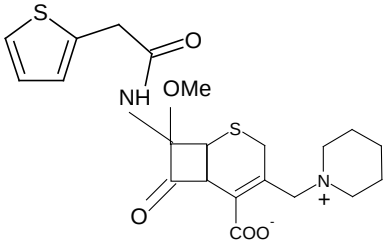


Figure. 33

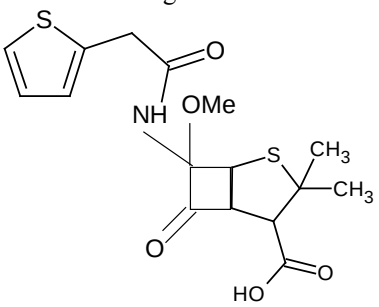


Figure 34

Thiophene as an Anticancer Agent: Raltitrexed (Fig. 35) [36].

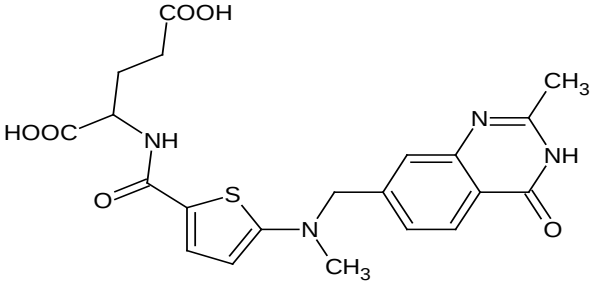
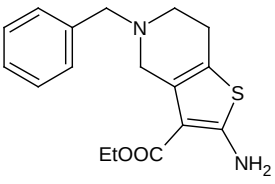


Figure 35

Thiophene as an Antiinflammatory Agent: Tinoridine (Fig. 36) [37], Tiaprofenic acid (Fig. 37) [38], Tenoxicam (Fig. 38) [39], Suproprofen (Fig. 39) [40].



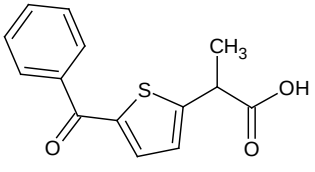


Figure 36

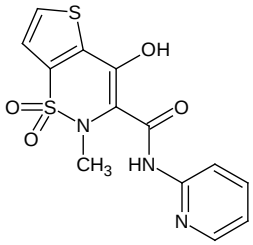


Figure 38

Figure 37

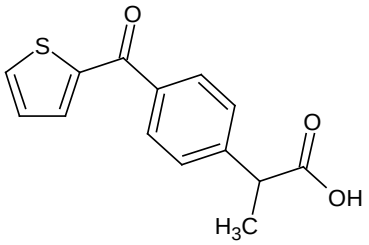


Figure 39

Thiophene as an Antihypertensive Agent: Tiamenidine (Fig. 40) [41], Ticrynafen (Fig. 41) [42].

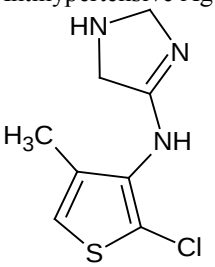


Figure 40

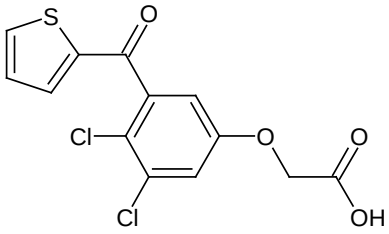


Figure 41

Thiophene as a CNS Agent: Clotiazepam (Fig. 42), Phethenylate sodium (Fig. 43).

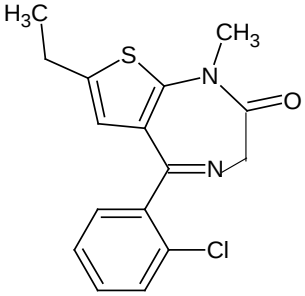


Figure 42

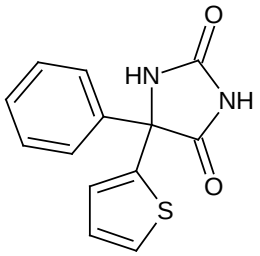


Figure 43

Thiophene as platelet aggregation inhibitor: Ticlopidine (Fig. 44) [43], Ticlomarol (Fig. 45) [44].

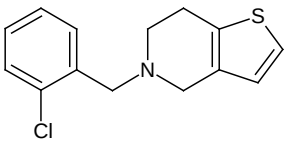


Figure 44

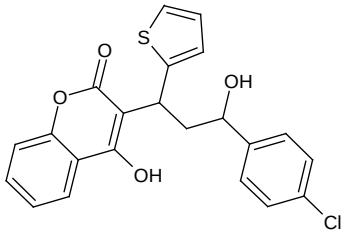


Figure 45

VI. CONCLUSION

The analytical and other informational data, available in literature so far, have rendered thiophene significantly important class of heterocyclic compounds and their applications in ever challenging chemotherapy of various ailments/ infections since last two decades immensely hiked interests of medicinal chemist and biochemist. It has been seen that the thiophene analogues incorporated with different nuclei have shown variety of pharmacological profiles. Fused hetero-

aromatic systems are often of greater interest than monocyclic compounds as far as the biological activity is concerned. Thiophene can be fused with various heterocyclic systems resulting in various new heterocyclic systems with enhanced biological activity.

This particular review article, established the fact that thiophene derivatives could be a rich source of potential entities in search of new generation of biologically active compounds and be worthwhile to explore the possibility in this area by fusing differently substituted moieties which may result in better pharmacological activities. Thus the quest to explore many more modifications on thiophene moiety needs to be continued.

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