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Thiophene: Versatile Medicine

D. N. Ware[1] and S. Pillai[2*]

[1]*Institute of Science, Chemistry Division, Under Faculty of Science, Nirma University, Ahmedabad-382481, INDIA*
[2]*Institute of Technology, Chemical Engineering Department, Nirma University, Ahmedabad-382481, INDIA*

[*] *Correspondence: E-mail: shibu.pillai@nirmauni.ac.in*

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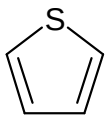
ABSTRACT: In the growing world of heterocyclic chemistry, thiophene is one of the most important potential entities. Thiophene containing molecules have significant biological potential. The innumerable physicochemical properties and different synthetic pathways of thiophene containing compounds have drawn the special attention of chemists and scientists to carry out comprehensive efforts in search of new thiophene based molecules. The present review includes the properties, synthesis, and a wide spectrum of biological activities of thiophene based scaffolds, and summary of thiophene containing active pharmaceutical ingredients (APIs) available in the market.

Keywords: Thiophene; biological activity; medicinal importance and API.

INTRODUCTION: Heterocyclic chemistry is the wide subject in the field of organic chemistry. A heterocyclic ring containing one or more heteroatoms, a ring may be saturated or unsaturated have remarkable value in the medicinal chemistry. The drug discovery and development of new molecule for the treatment of various diseases attracts most of the chemist. The discovery of new drug is a complex task and it requires scholar people from various disciplines. Heterocyclic compounds are extensively available on the earth and are important for human life. A huge number of pharmacologically active heterocycles are in regular clinical use [1-2]. Among these heterocyclic compounds, thiophene containing molecules have shown remarkable pharmacological activities such as anticancer, antimicrobial, analgesic, anti-inflammatory, antioxidant, antiallergic, antihypertensive, etc. These diverse pharmacological activities of thiophene have attracted most of the chemists and scientists to discover new thiophene containing bioactive molecules. Apart from the pharmacological activities, thiophene containing compounds have shown their applications in different fields like paint, photodiodes, agriculture and other applications in bio-diagnostics, optoelectronic devices and electroluminescent polymers [3-6].
Victor Meyer discovered thiophene (Fig. 1) in 1882, as an impurity in benzene [7]. It was detected that mixture of crude benzene and sulphuric acid reacts with isatin to form blue dye (indophenin) [8]. Thiophene is a five member heterocyclic compound having molecular formula C_4H_4S. Thiophene name is derived from a Greek word i.e. theion means sulphur and phaino means shinning.



Thiophene

Figure 1: Structure of thiophene.

AROMATICITY AND PHYSICO-CHEMICAL PROPERTIES OF THIOPHENE:

Aromaticity: In thiophene, four carbon atom and sulphur atom are in sp^2 hybridized state. The p-orbital of each carbon atom contributes one electron and forms π-bond with adjacent carbon. The three σ-bonds of the sp^2 hybridised sulphur lie in the plan of the molecule. The third p-orbital, which is orthogonal to the plane of the atoms, contributes its lone pair of electrons. This p-orbital of sulphur atom with an electron pair interacts with other four p-orbital of carbons resulting in to a cyclic π electron system involving five p-orbitals and six π-electrons in three bonding molecular orbitals π_1, π_2 and π_3. Therefore, thiophene has three pairs of delocalised π-electrons. Two of the pairs are shown as π-bonds in the Fig. (2) and one pair is shown as nonbonding electrons on the sulphur atom. Hence, these five sp^2 hybridised atoms form

planar six electron delocalised π-cloud, which is responsible for the aromatic character of thiophene ring.

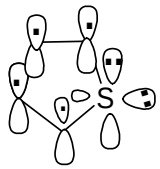


Figure2: π electron delocalization.

Hence, thiophene is aromatic and has the highest resonance energy as compared to other five member heterocyclic compounds like furan and pyrrole. The order of aromaticity is Thiophene > Pyrrole > Furan.

Physico-Chemical Properties: Thiophene is aromatic in nature and it shows some similar chemical properties like benzene. Although, thiophene is aromatic but the degree of aromaticity is less as compared to benzene. Thiophene is colourless liquid with mildly pleasant odour. It is soluble in alcohol (methanol, ethanol) and ether but insoluble in water. Thiophene is toxic and flammable organic compound having melting point -38°C and boiling point is 84°C.

Thiophene undergoes different electrophilic substitution reactions such as nitration, sulfonation, halogenation, Friedel-Crafts acylation etc. In addition to this, it also shows Reimer-Tiemann reaction and diazonium salts formation reaction. The resonance stabilization energy of thiophene is 22-28 kcal/mol [9]. Thiophene is a thio-analogue to nitrogen-bearing pyrrole, the sulphur atom in thiophene, however, carries a lone pair (i.e. an unshared electrons pair) in an sp^2 hybridized orbital, albeit in pyrrole the analogous nitrogen is bond to a hydrogen atom.

Electrophilic substitution reaction: The electron density in thiophene ring is higher than in benzene; therefore, thiophene undergoes electrophilic substitution reactions more readily than benzene. It undergoes electrophilic substitution reactions like halogenation, nitration and sulfonation etc. The substitution takes place most preferably at C-2 position due to greater resonance stabilization of positive charge as compared to C-3 position (Fig 3).

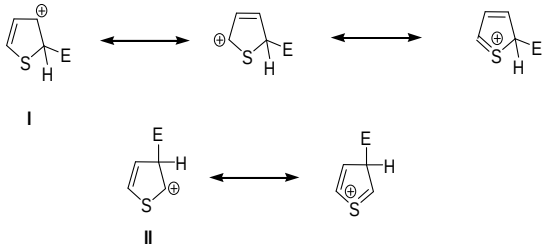
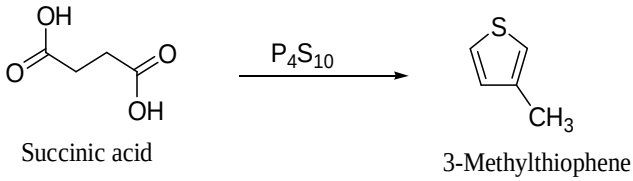


Figure3: Resonance stabilization.

SYNTHESIS OF THIOPHENE: The substituted thiophenes are mainly prepared by the reaction between dicarbonyl compounds with source of sulphur from phosphorous sulphide. The major synthetic routes are Paal thiophene synthesis, Gewald aminothiophene synthesis, Fiesselmann thiophene synthesis and Hinsberg synthesis. In addition, substituted thiophene can be prepared from thiocarbonyl compound, thio-nitroacetamide, thiazoles. The details of major synthetic routes are outlined below.

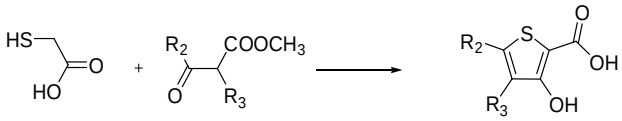
Paal Thiophene Synthesis: Paal thiophene synthesis is condensation reaction, in which 1,4-Dicarbonyl reacts with sulphur to obtain thiophene [Scheme 1]. In this reaction, mainly the sulphur source is from phosphorous sulphides, Lawessons reagents [10] or bis (trimethylsilyl) sulphide [11].



Succinic acid — 3-Methylthiophene

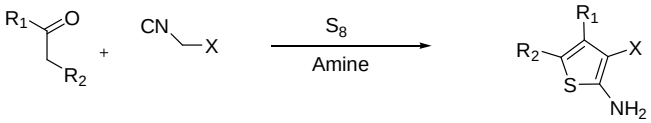
Scheme: 1

Fiesselmann Thiophene Synthesis: Fiesselmann thiophene synthesis is a condensation reaction between α, β-acetylenic ester, and thioglycolic acid which upon basification gives 3-hydroxyl-2-thiophene carboxylic acid [12]. It is 1,4-conjugated base catalysed addition reaction, in which ketone is formed by intermolecular reaction through Dieckmann condensation. Ketone on tautomerization eliminates methyl-thioglycolate to give 3- hydroxyl-2-thiophene carboxylic acid [13].



Scheme: 2

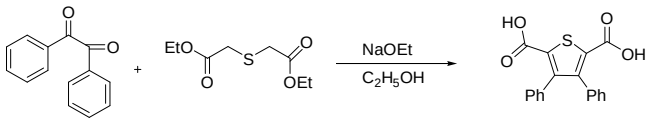
Gewald Aminothiophene Synthesis: Gewald synthesis is used for amino thiophene preparation. In this reaction, an olefin is formed by the base-catalyzed condensation of a ketone with a β-ketonitrile followed by cyclisation of olefin with elemental sulphur to give amniothiophene [14].



Scheme: 3

Hinsberg Synthesis: The Aldol condensation between diethylthiodiacetate and 1,2-dicarbony1 gives

ester-acid intermediate which after hydrolysis gives thiophene containing diacid [15].

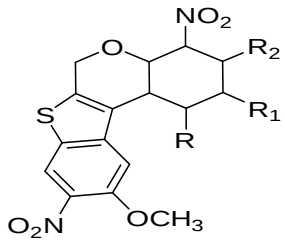


Scheme: 4

BIOLOGICAL ACTIVITY: In the era of medicinal chemistry, thiophene containing molecules are well versed for their therapeutic and chemotherapeutic applications. The fused heterocyclic compounds have more biological activity than monocyclic compound (i.e. thienopyrimines and purines). Thiophene is widely used as building block in many chemical, pharmaceutical, paint and agrochemical fields. Thiophene possesses various biological activities such as, antimicrobial, analgesic, anti-inflammatory, anticancer, antioxidant, antiallergic, antihypertensive etc [16].

Antimicrobial and Antibacterial Activity: The microorganism causes various types of diseases such as typhoid, pneumonia, malaria, cough and few serious diseases like AIDS, tuberculosis, influenza etc. From literature search, it was observed that many scientists have synthesized series of compounds having antimicrobial activities. The synthesis and study of antimicrobial and antibacterial activities of some representative compounds are mentioned below. These compounds revealed their significant efficacy on different bacteria like *S. typhi*, *E. coli*, *S. aureus*, *B. cereus*, *V. cholerae* as compared to reference drugs like Ampicillin, Gentamycin, Nystatin and Amoxicillin. Also, many drugs having thiophene nucleus like Cefoxitin, Cephalothin, Cephaloridine and Temocillin showing significant antimicrobial activities are available in the market. They are tabulated in Table 1.

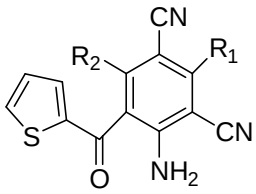
Havaldar *et al*. [17] developed novel 10-methoxy-4,8-dinitro-6H-benzothieno[2,3-c]chromen-6-one, an antibacterial agent. Their antimicrobial activity against *S. aureus*, *B. subtilis* and *E. Coli* were evaluated and compared to standard drug Ampicillin.



R= H, CH_3, Cl; R_1= H, NO_2, CH_3, Cl; R_2= H, CH_3

[Figure 4]

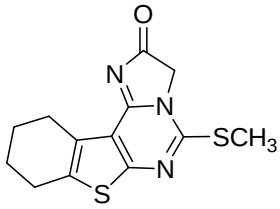
Darwish *et al.* [18] prepared thiophene fused aniline derivatives. Their antimicrobial activity against *E. coli* and *S. albus* were evaluated and compared to standard drugs Ampicillin, Tetracycline.



R_1, R_2 =phenyl, 2-furyl

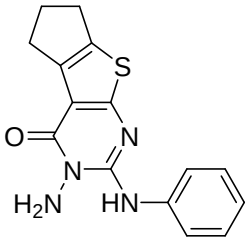
[Figure 5]

Kavitha P.N. *et al.* [19] synthesized the 3-(*substituted)*-amino-2-mercapto-5,6,7,8-tetrahydrobenzo (*b*)thieno[2,3-*d*] pyrimidin-4(3*H*)-one analogues. Their antimicrobial activity against *K. pneumonia*, *B. subtilus* and *A. niger* were evaluated and compared to standard drug Ampicillin.



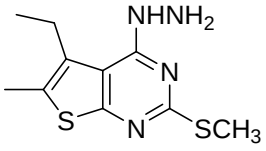
[Figure 6]

Sherbeny *et al.* [20] developed 2-(*substituted)*-amino-3-aminocyclohexeno[*b*] thieno[2,3-*d*]-3,4-dihydropyridin-4-ones. Their antimicrobial activity against *S. aureus*, *B. subtilis* and *C. Albicans* were evaluated.



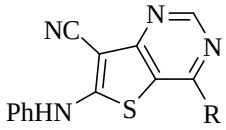
[Figure 7]

Bhuiyan Md. Mosharef Hossain *et al*. [21] prepared 4-hydrazino-2-mehylthio-5-ethyl-6-methylthieno[2,3-*d*] pyrimidine. Their antimicrobial activity against *B. cereus*, *A. alternate*, *V. chol-erae*, were evaluated and compared to standard drugs Ampicillin, Nystatin.



[Figure 8]

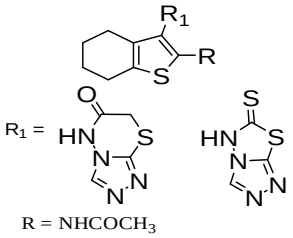
El-Saghier Ahmed M. M. *et al.* [22] developed 4-(*substituted*)-7-cyano-6-phenylaminothieno[3,2-*d*]pyrimidine analogues. Their antimicrobial activity against *B. subtilis* and *St. aureus* were evaluated and compared to standard drug Amoxicillin



R = 4-BrS$_6$H$_4$, CH$_3$

[Figure 9]

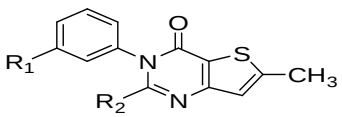
N-[3-(*substituted*)-7*H*- [1,2,4] triazolo [3,4-*b*] [1,3,4] thiadiazine / thiadiazol-4,5,6,7- tetrahydro-benzo[*b*]thiophene was prepared by Shiradkar M. *et al*. [23]. Their antimicrobial activity against *E. coli, S. aureus, A. nigar* were evaluated and compared to standard drug Gentamycin.



R = NHCOCH$_3$

[Figure 10]

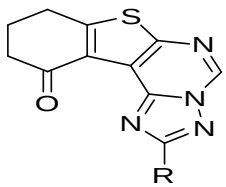
Chander Mohan *et al*. [24] synthesized 6-methyl-2-phenyl-3-(*substituted*)-3H-thieno[3,2-*d*]pyrimidin-4-one derivatives. Their antimicrobial activity against *B. subtilis, E. coli, P. aeruginosa* were evaluated and compared to standard drug Ciprofloxacin.



R$_1$ = o-CH$_3$, p-CH$_3$, p-Cl
R$_2$ = Ph, SCH$_3$, Ph

[Figure 11]

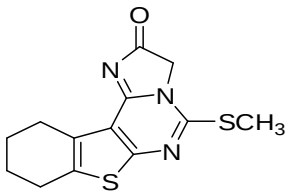
(*substituted*) 8,9,10,11-tetrahydro[1]benzothieno[3,2-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine-8-one analogues were synthesized by S. Shetty Nitin Kumar *et al.* [25]. Their antimicrobial activity against *B. Subtilis* was evaluated and compared to standard drug Ampicillin.



R =H, CH$_3$, C$_2$H$_5$

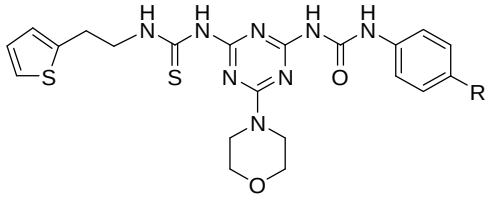
[Figure12]

Bhuiyan Md. Mosharef Hossain *et al*. [26] synthesized thieno[3,2-*e*]imidazo[1,2-*c*]pyrimidin-2(3*H*)one derivative. Their antimicrobial activity against *B. cereus, S. typhi, A. alternata* were evaluated and compared to standard drug Ampicillin.



[Figure13]

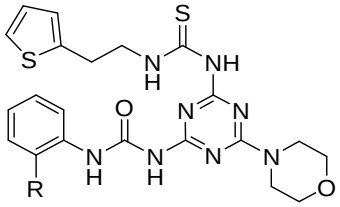
Chikhalia *et al.* [27] prepared s-triazine containing novel series of aliphatic thiourea derivatives. Their antimicrobial activity against *S. aureus* and *B. subtilis* were evaluated and compared to standard drugs Tetracycline, Chloramphenicol.



R= H, 4-Cl, 3-Cl, 2-CH$_3$, 3-NO$_2$

[Figure 14]

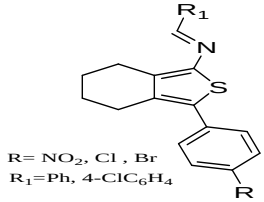
2-thiophene-2-ethylthioureido-4-morpholino-6-(aryl)ureido-s-triazine derivatives were synthesized by Akshay et al. [28]. Their antimicrobial activity against *S. Typhi* and *C. albicans* were evaluated and compared to standard drug Tetracycline.



R = 3-Cl, 2-NO$_2$, 4-Cl, 4-NO$_2$

[Figure 15]

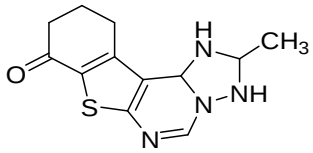
Murugan *et al.* [29] reported the synthesis and biological activity of some new 2,3-disubstituted-4,5,6,7-tetrahydrobenzo(*b*)thiophenes. They have shown major anti-microbial activity.



R= NO$_2$, Cl , Br
R$_1$=Ph, 4-ClC$_6$H$_4$

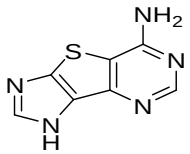
[Figure 16]

Khazi *et al.* [30] synthesized triazole joined thieno-pyrimidines derivatives. Their antimicrobial activity against *B. subtilis* was evaluated and compared to standard drug Chloramphenicol.



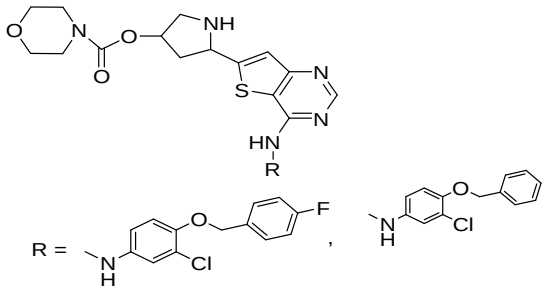
[Figure 17]

Anticancer activity: Seley L. Katherine *et al.* [31] synthesized 6-Aminoimidazo[4,5':4,5]thieno[3,2-*d*]pyrimidine derivatives. These derivatives were more potent anticancer agent than other thieno compounds.



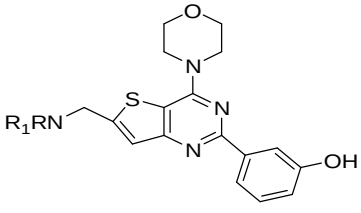
[Figure 18]

Waterson *et al.* [32] synthesized alkynyl thieno-pyrimidine are excellent EGFR/ErbB-2 kinase inhibitors. Their anticancer activity against *T. Brucei* was evaluated.



[Figure 19]

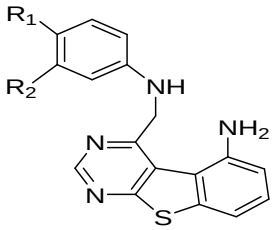
Folkes Adrian J. *et al.* [33] synthesized (*Substituted*) 4-morpholin-4-yl-thieno[3,2-*d*]pyrimidine analogues an anticancer agent. These compounds have shown potent inhibition of cancer cell proliferation as well as in vivo absorption and tumor exposure.



R,R_1 = N-methyl piperazine, CH_3NCH_2

[Figure 20]

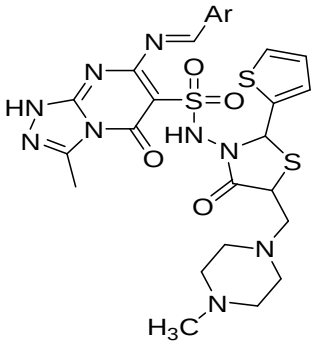
Stephane pedeboscq *et al.* [34] synthesized 4-(2-Methylanilino) and 4-(2-Methoxyanilino) benzo[b]thieno[2,3-*d*] pyrimidine; which showed a similar cytotoxicity to the standard anti-EGFR geftinib suggesting a blockade of the EGFR pathway by binding to the tyrosine kinase receptor.



R_1= CH_3,OCH_3
R_2= H

[Figure 21]

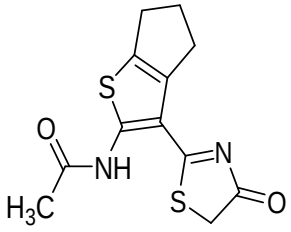
Hafez H. N. *et al.* [35] synthesized (*Aryl substituted)* 3-methyltriazolo[4,3-*a*]pyrimidine-6-sulfono-2-thieno[(4-methyl piperazine)] analogues. These compounds have inhibited the growth of cancer cell lines and shown a good selectivity on leukemia penal.



Ar = 4-$CH_3OC_6H_4$, 2-$CH_3C_6H_4$, C_6H_4

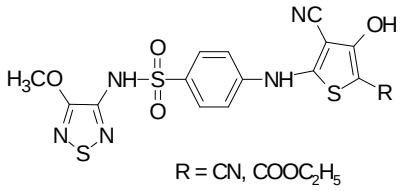
[Figure 22]

Eman M. Samir *et al.* [36] synthesized 4,5,6,7-tetrahydrobenzo[*b*]thiophene derivative as an anticancer agent. These derivatives have shown good anticancer activity against human cell line MCF-7, NCI-H460 and SF-268.



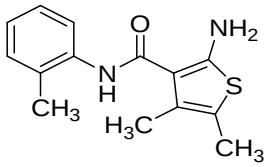
[Figure 23]

M. S. A. El-Gaby *et al.* [37] prepared 4-(3,5-Dicyano-4-hydroxythiophen-2-ylamino)-N-(4-methoxy-1,2,5-thiadiazol-3-*yl*)benzenesulfonamide derivatives. A sulfonamide linkage gives good anticancer activity against reference drug Doxorubicin.



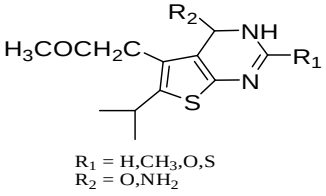
[Figure 24]

Anti-inflammatory and Analgesic activity: Mohan *et al.* [38] synthesized 2-substituted amino-3-(N-o-tolylcarboxamido)-4,5-dimethyl thiophenes. These compounds have shown good analgesic and anti-inflammatory activities.



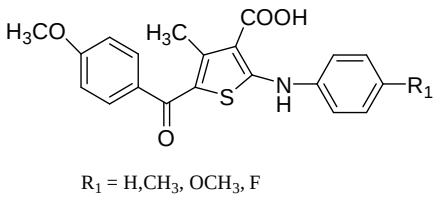
[Figure 25]

(*Substituted*) 6-isopropyl-3*H*-thieno[2,3-*d*] pyrimidine derivatives were synthesized by Abdal Rehman. B. A. El-Gazzar *et al.* [39]. These compounds have shown good anti-inflammatory and analgesic activities, when compare to standard drug Acetylsalicylic acid.



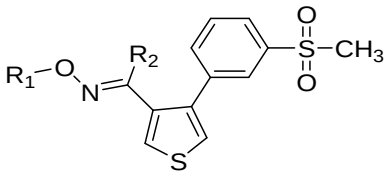
[Figure 26]

Molvi Khurshid I. *et al.* [40] synthesized 2-(substituted)-5-(4-methoxy benzoyl)-4-methylthiophene-3-carboxylic acids. These compounds have shown moderate anti-inflammatory and analgesic activities when compared with standard drug Ibuprofen.



[Figure 27]

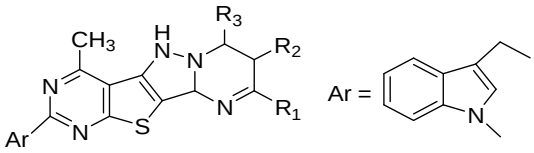
Balsamo Aldo *et al.* [41] reported synthesis of (*substituted*) (2-aryl-1-thiophene-1-alkylidene)-(arylmethyloxy)amine analogues. These compounds have shown good anti-inflammatory and COX-2 inhibitors when compared with standard drug Indomethacin.



R_1	R_2
$phCH_2$	H
$phCH_2$	CH_3

[Figure 28]

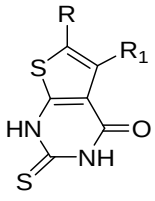
(*substituted*)-Pyrimido pyrazolothieno[2,3-*d*]pyrimidine derivatives were synthesized by Amr Abd El- Galil E. *et al.* [42]. These derivatives have shown good anti-inflammatory and analgesic activities when compared to standard drugs Prednisolone and Veldecoxib.



R_1	R_2	R_3
ph	H	NH_2
H	H	ph
ph	CN	NH_2

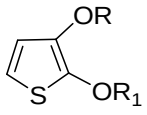
[Figure 29]

Cannito *et al.* [43] synthesized 3-substituted thieno-pyrimidin-4-one-2-thiones derivatives. These derivatives were screened for analgesic and anti-inflammatory activities.



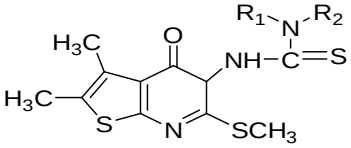
[Figure 30]

Daris *et al.* [44] synthesized and studied the preliminary pharmacological activities of thiophene analogues of the antipyretic and analgesic agent an athenzamide.



[Figure 31]

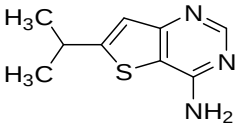
Alagarsamy V. *et al*. [45] synthesized 2-Methylthio-3-(*substituted*)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(*3H*)-ones. These compounds have shown good analgesic activity when compared with standard drug diclofenac.



R_1,R_2= $(CH_3CH_2)_2N$, pyroolindinyl

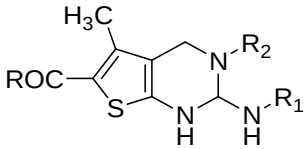
[Figure 32]

El-Gazzar *et al.* [46] reported thieno[2,3-*d*]pyrimidine derivatives and screened them for anti-inflammatory and analgesic activities.



[Figure 33]

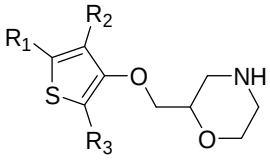
Rathod *et al.* [47] synthesized substituted thieno[2,3-*d*]pyrimidine-4(3*H*)-one derivatives and screened them for analgesic activity.



R= CH_3, NHPh
R_1, R_2= Ph, o-Anisyl

[Figure 34]

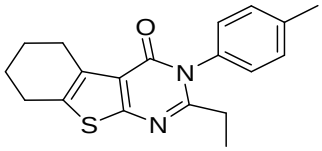
CNS Activity: Corral *et al.* [48] reported synthesis and preliminary pharmacological activities of thiophene analogues of Viloxazine as potential antidepressant drugs.



R_1= R_3= H
R_2= Ph

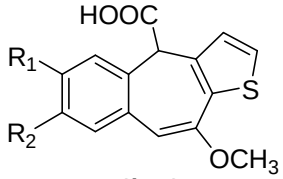
[Figure 35]

Manjunath *et al.* [49] reported synthesis of substituted aryl thienopyrimidin-4-ones derivatives and these derivatives were evaluated for CNS depressant activity. This compound shows good results with standard CNS drug.



[Figure 36]

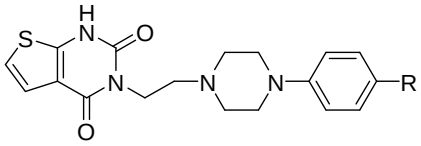
Bollinger *et al.* [50] synthesized *novel benzo(*4,5*)cyclohepto(*1,2-*b)thiophen-4-ylidene* acetic acids. These compounds have shown non- ulcerogenic and anti-inflammatory activities.



R_1=R_2=H,Cl,F, CH_3

[Figure 37]

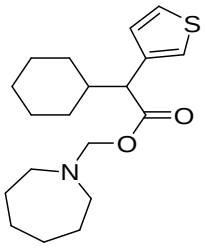
Antihypertensive Activity: Russell *et al.* [51] developed thienopyrimidine-diones derivatives and evaluated them for antihypertensive activity.



R = 2-OCH_3, 3-OCH_3, H

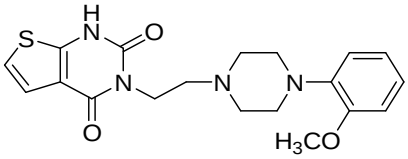
[Figure 38]

Benton *et al.* [52] developed some of Citedil analogues of the following type as a calcium channel blockers.



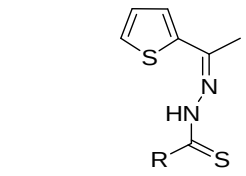
[Figure 39]

Mery. B. Press *et al.* [53] synthesized novel derivatives thienopyrimidine-diones derivatives. This compound has shown good results when compared with standard drug minoxidil.



[Figure 40]

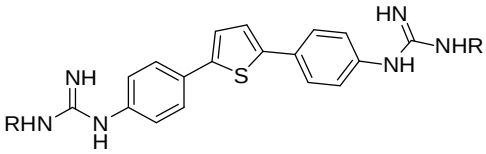
Miscellaneous Activity: Sangita Sharma *et al*. [54] synthesized thiophene-2-carboxaldehyde-(*substituted-*)thiosemi-carbazones. These compounds have shown antiamoebic activity against *E. histolytica*.



R =$NHCH_2CH_2CH_3$, $NHCH_2CH_2CH_2CH_3$

[Figure 41]

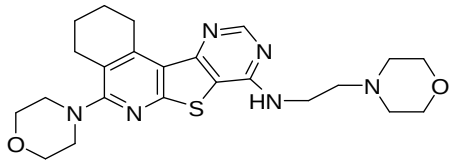
Gonzalez Jose L. *et al*. [55] synthesized (*Substituted*) bis-2,5-[4-guanidino phenyl]thiophenes. These compounds have shown antiparasitic activity against *T. brucei rhodesiense, P. falciparum, L. donovani and T. cruzi* parasites.



R = H, CH_3, Ph, p-Tolyl, c-Hexyl

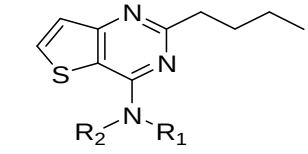
[Figure 42]

TaltavullJoan *et al*. [56] synthesized (*Substituted*) 1,2,3,4-tetrahydro pyrimido thieno[2,3-*c*]isoquinoline-8-amino(2-morpholin-4-yl ethyl) analogues as Phosphodiesterase IV inhibitors (PDE4) for the treatment of asthma and chronic obstructive pulmonary disease (COPD).



[Figure 43]

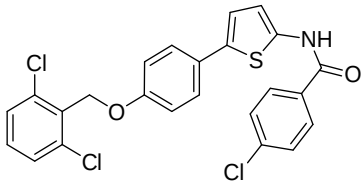
Crespo Maria I. *et al*. [57] synthesized 2-Butyl-4-(*substituted*)aminothieno[3,2-*d*]pyrimidine. Type 4 Phosphodiesterase inhibitors with respect to standard drug Rolipram.



R_1 = Cyclohexyl, Benzyl
R_2 = H, CH_3

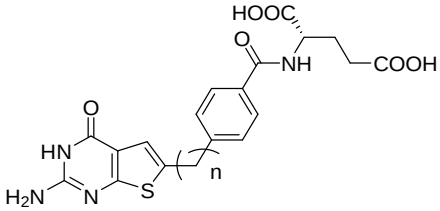
[Figure 44]

Lu *et al*. [58] synthesized series of 5-amino-(4-(benzyloxy) phenyl)thiophene-3-carboxylic acid derivatives. These derivatives are acylated and alkylated at 5-amino position and evaluated them for anti-tubercular activity**.** Novel derivatives have shown adequate activity against multidrug resistant tuberculosis clinical strains. Amide derivatives were found to display superior anti-tubercular activity than amine derivatives.



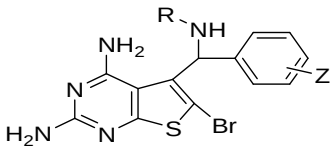
[Figure 45]

Deng Yijun *et al*. [59] synthesized 2-amino-4-oxo-6-*(substituted)* thieno [2,3-*d*] pyrimidines with a bridge length (from 2 to 8 carbon atoms) shown antitumor activity.



[Figure 46]

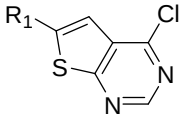
Roso-wsky Andre *et al*. [60] synthesized,4-Diamino-5-[(*substituted*) methyl]-6-bromothieno[2,3-*d*]pyrimidine analogues derivatives. Their dihydrofolate reductase (DHFR) inhibitors activity against *P. carinii, T. gondii* were evaluated and compared to standard drug Trimethoprim and pyrimethamine



R = H, Me, H
Z = $3,4,5\text{-}(OCH_3)_3$

[Figure 47]

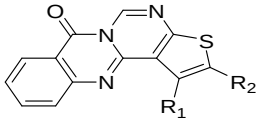
Sharma Chanchal *et al*.[61] synthesized 4-chloro-5,6-*(disubstituted)*thieno[2,3-d]pyrimidine analogues. These compounds have shown significant antipsychotic activity with reference drug Olanzapine.



R_1= CH_2, C_2H_5

[Figure 48]

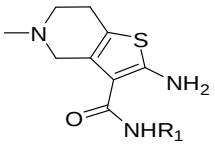
Laddha Sachin S. *et al.* [62] synthesized *(Substituted)*-1,2,9,11-tetrahydro-7H-thieno[2',3':4,5]pyrimido[6,1-*b*]- quinazolin-7-one. These compounds have shown potent anticonvulsant activity when compared with standard drugs Phenytoin and Phenobarbital.



R_1 =, R_2= $(CH_2)_4$, CH_3

[Figure 49]

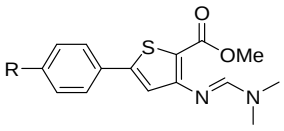
Aurelio Luigi *et al.* [63] synthesized 3-and 6-(*Substituted*) 2-amino-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine derivatives. These compounds have shown adenosine receptor allosteric modulators and antagonists activity.



R_1 = CONHBn, $CONHNH_2$, CONHNHPh

[Figure 50]

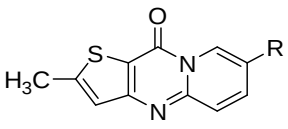
Tavares Francis X. et al. [64] synthesized (substituted) Methyl-3-(dimethylamino) methylidene amino-5-phenyl-2-thiophene carboxylate analogues. These derivatives have shown antagonists of Melanin-Concentrating Hormone (MCH) receptor 1, when oral dosing in rats. A representative analogue, when dosed orally once daily to mice, exhibited a very good dose responsive effect in reducing body weight. This work supports the advancement of small molecule MCHR1 antagonist into human clinical trials for the treatment of obesity.



R = H, 4Cl, 2Cl, 4-CN, 4-OCH_3

[Figure 51]

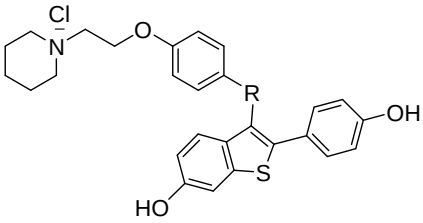
David T. Connor *et al.* [65] synthesized 7-(*substituted*)10-oxo-10H-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidine derivatives. These compounds have shown moderate antiallergic Activity.



R = COOH, $CONH_2$

[Figure 52]

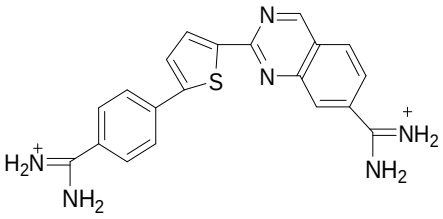
Palko-witz Alan D.*et al.* [66] prepared (*substituted*) [2-(4-Hydroxy phenyl)-6-hydroxybenzo[*b*]thieno-3-yl] [4-[2-(1-piperidinyl)ethoxy]phenyl]hydrochloride. These compounds have shown highly selective Estrogen Receptor Modulators (SERMs) with similar drugs Raloxifene and Tamoxifen.



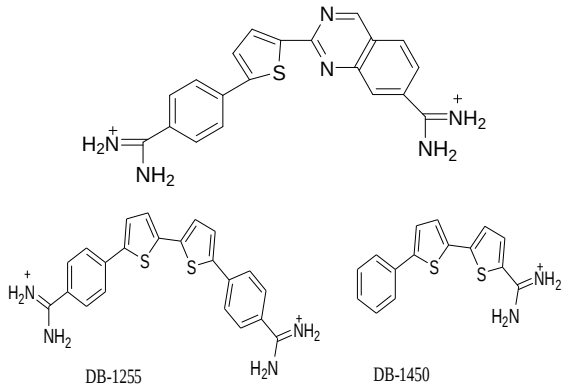
R = CO, CH_2, S, O, NH

[Figure 53]

W. David Wilson et al. [67, 68] designed a compound with best binding affinity and selectivity for a mixed A·T and G·C DNA sequences, many well-characterized A·T recognition units have been previously reported, such as benzimidazole/indole, phenylamidine with numerous types of linking groups, such as-O-, -NH-, furan were found in his initial research. Recently, his group have used an entirely new concept to design and prepare compounds that can recognize G·C bps binding site. By using the orienting interaction of a sulfur atom of thiophene sigma-hole with the unsubstituted nitrogen atom other ring.

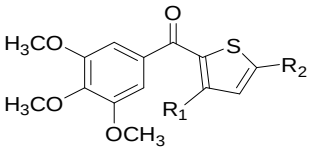


[Figure 54]



[Figure 55]

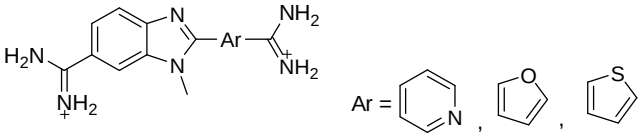
Harish rajak *et. al.* [69] synthesized a combretastatin A-4 based thiophene derivatives an antitumor agents.



$R_1 = NH_2$, $R_2 = C_6H_5$
$R_1 = H$, $R_2 = C_6H_5$
$R_1 = NH_2$, R_2 =2-thienyl
$R_1 = NH_2$, R_2 =2-thienyl

[Figure 56]

Antitrypanosomal activity: Abdelbasset A. Farahat *et. al*. [70] modified DAPI structure by replacing the phenyl group with substituted phenyl or heteroaryl rings. Amidines were synthesized and their DNA binding, fluorescence properties, in vitro and in vivo activities were evaluated. These compounds have shown to bind in the DNA minor groove with high affinity, and exhibit superior in vitro antitrypanosomal activity to that of DAPI.



[Figure 57]

ACTIVE PHARMACEUTICAL INGREDIENTS (APIs): Thiophene as a basic skeleton is widely used as building blocks in many chemical, pharmaceutical, paint and agrochemical fields. Thiophene possesses various biological activity such as, antimicrobial, analgesic, anti-inflammatory, anticancer, antioxidant, antiallergic, antihypertensive etc. A numerous thiophene containing Active Pharmaceuticals Ingredients (APIs) are available in the market as a medicine. The APIs with various biological activities and chemical structure are tabulated in table number 1.

CONCLUSION: The literature survey and the online information of thiophene available across the globe have attracted most of the chemists and scientists. The above discussion confirms thiophene and fused thiophene containing derivatives play an important role in the drug discovery and related research. Numerous researchers all over the world working on thiophene containing derivatives have made thiophene as a versatile medicine. The major outstanding achievements revealed that thiophene based synthesized compounds pass extensive potential applications as medicinal drug. This review includes the additional information and their references which will be fruitful for researchers and chemists in determining the best, most economical, and clinically important compounds of thiophene. In addition, we can conclude that many other thiophene and fused thiophene containing derivatives and APIs can be synthesized; which may show potent pharmacological and chemotherapeutical activities.

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