ANTIMICROBIAL POTENTIAL OF THIOPHENE DERIVATIVES OF SYNTHETIC ORIGIN: A REVIEW

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Thiophene, a five membered heterocycle is considered as biologically important dynamic scaffold that holds wide range of biological activities. The fruitful application of Cephoxitin as antimicrobial, Thenaldine as anti inflammatory, Ralitrexed as anticancer and Erdosteine as antioxidant proved the potential of thiophene moiety. Diverse biological response profile has pulled in consideration of many researchers to investigate this heterocycle to its multiple potential against several activities. This review is complementary to previous reviews and focuses to review the work reported on antimicrobial activities of thiophene derivatives.

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Introduction

As the world's population increases, the health problems expand accordingly and therefore the development of new therapeutics is essentially vital.[1] A steady increase in complexity of the structure and introduction of different molecular functions has been a highlighted feature of pharmaceutical research and development.[2] Even today only limited repertoires of synthetic transformations are utilized for the construction of simple structures of drug molecules.

As far as antimicrobial activity is concerned, antibiotics were considered as miracle drugs when first became available about 60 years ago, proving to be the major asset in the fight against infectious bacteria.[3] Resistance to antibiotics threatens the effectiveness of successful treatment of infection.

Design of new drug molecules arguably offers some of the greatest hopes for success in present and future era. Five membered aromatic rings are the building blocks of many drugs. Amongst the five membered aromatic rings, thiophene has proven to be an alternative isostere, resulting in improved effectiveness of drug molecules. For structures like phenyl, thiophene can serve as biostere which can result in improved pharmacokinetic and pharmacodynamic properties of the drug.[4]

Thiophene comprises of a five membered ring with a sulfur as heteroatom having a molecular formula C_4H_4S. The thiophene ring has been incorporated into a broad range of known biologically active compounds. It is incorporated as a substituent group or as a substitute of another ring that inspired researchers to synthesize several compounds containing this moiety. Well defined antimicrobial agents bearing thiophene moiety (Figure 1) are cefoxitin **(1a)**, cephalothin **(1b)**, cephaloridine **(1c)** and temocillin **(1d)**.[5]

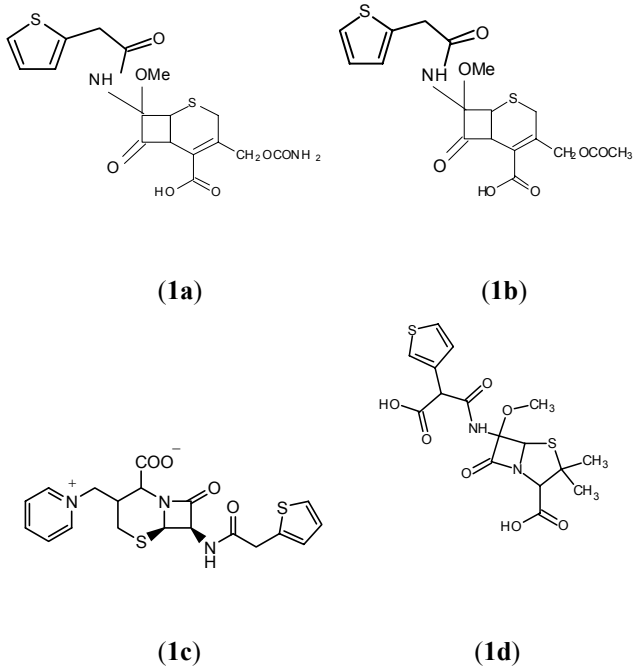


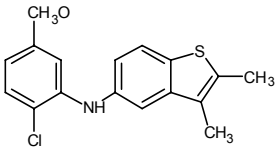
Figure 1. Some antimicrobial agents bearing thiophene moiety.

There are several reports in the literature describing the thiophene derivatives for their antimicrobial activities. The aim of present review is to give emphasis on antimicrobial properties associated with substituted thiophenes and structurally related thiophenes.

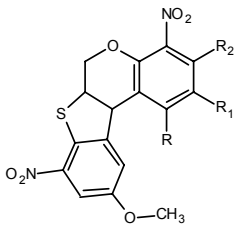
Antimicrobial activity of thiophenes

ortho-Chlorodiarylamines were synthesized from 2,3,7-trimethylbenzo[*b*]thiophene series by Queiroz *et al*.[6] Cyclisation of these coupling products gave thienocarbazoles and dechlorinated diary amines, which were then evaluated and compared for antimicrobial activity using Ampicillin and Cycloheximide as standard. Compound **(2)** with methoxy group as a substituent was found active against *E. coli*. The thienocarboline showed lower Minimum Inhibitory Concentration (MICs) for *B. cereus* and *C. albicans* than the corresponding thiocarbazole but for *B. subtilis* both showed the same MIC.[6]

Derivatives of 10-methoxy-4,8-dinitro-6*H*-benzothieno [2,3-c] chromen-6-one were reported by Havaldar *et al*. All the synthesized compounds were evaluated for antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli* and *S. typhosa*. The tested compounds (**3**) exhibited much higher inhibitory effect on the growth of bacteria.[7]



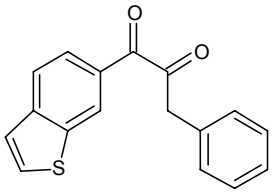
(**2**)



R= H, CH_3, OCH_3, Cl; R_1= H, NO_2, CH_3, OCH_3, Cl;
R_2= H, CH_3, Cl

(**3**)

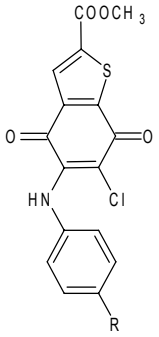
Maurya *et al.* synthesized 4-hydroxy-1-methylindole and benzo[*b*]thiophene-4-ol based unnatural flavanoids as a new class of antimicrobial agents. The majority of the compounds exhibited good antifungal activity against *Trichophyton mentagrophytes*.[8] It was found that substitution of heterocyclic oxygen by sulfur had produced a marked increase in antifungal activity. Compound (**4**) exhibited comparable MIC to the known Karanjin.



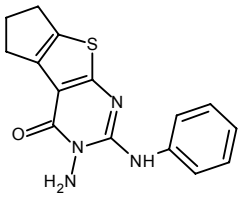
(**4**)

Ryu *et al.* reported synthesis of 5-arylamino-4,7-dioxobenzo[*b*]thiophene derivatives and tested for *in vitro* antifungal activity against *Candida* and *Aspergillus* species. Among the synthesized derivatives, 5-(4-substitutedphenylamino)-6-chloro-2-(methoxycarbonyl)-4,7-dioxobenzo[*b*]thiophenes (**5**) exhibited more potent antifungal activity. The 6-chloro moiety had contributed to their antifungal activity significantly.[9]

A series of 2-substituted-amino-3-aminocyclopenteno or cyclohexeno[*b*]thieno[2,3-*d*]-3,4-dihydropyridin-4-ones was synthesized by Sherbeny *et al.* The synthesized derivatives were screened for antimicrobial, antiviral and anticancer activity. Some of the compounds showed promising activity. Compound **(6)** presented remarkable broad spectrum potency against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis* and *Candida albicans*.[10]

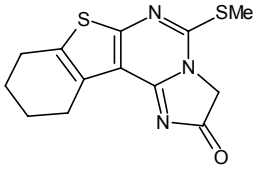


(**5**)



(**6**)

Bhuiyan *et al.* synthesized various derivatives by treatment of hydrazinothieno[2,3-*d*]pyrimidine with acetyl acetone, benzaldehyde and acetic anhydride. These derivatives were screened for antibacterial and antifungal activity using disc diffusion method and poisoned food techniques. Some of these derivatives showed marked antimicrobial activity. The structure activity relationship study (SAR) depicted that fused pyrimidine containing imidazo **(7)** and pyrazolo **(8)** rings showed higher antimicrobial and antifungal activity.[11]



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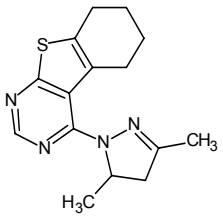
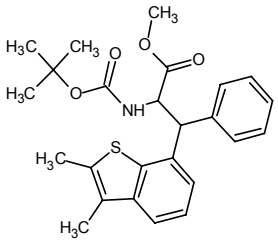


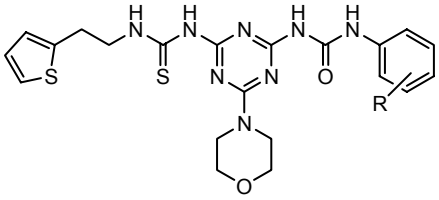
(**8**)

Ferreira *et al.* reported synthesis of pure steriosomers of benzo[*b*]thienyl dehydrophenylalanines by Suzuki cross-coupling reaction and evaluation of their antimicrobial activity. It was concluded that the Z-isomer (**9**) was selective and very much active at very low MIC against Gram-positive bacteria: *B. cereus* and *B. subtilis*. Compounds were also active against *Candida albicans* presenting similar MICs.[12]

A new series of aliphatic thiourea derivatives containing S-triazine moiety was synthesized by Chikhalia *et al.* and tested *in vitro* antibacterial activity against different microorganisms using Tetracycline and Chloramphenicol as standard drugs. Some of the synthesized derivatives were tested for antifungal activity using Miconazole as standard drug. Incorporation of ureido linkage showed moderate to good activity. Structural variation such as methyl and halogen group at the *ortho*, *meta* or *para* positions (**10**) to ureido linkage resulted in enhanced antibacterial activity against all the tested microorganisms.[13]



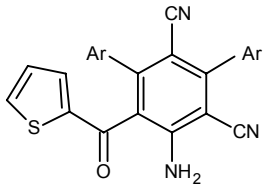
(**9**)



R= H, 4-Cl, 3-Cl, 2-CH_3, 3-NO_2

(**10**)

Darwish *et al.* synthesized thiophene and aniline derivatives (**11**) by the reaction of 2-picolinium N-ylide with arylidene derivatives of cyanothioacetamide and malanonitrile. All compounds displayed moderate activity against bacterial species *E.coli* and *S.albus*. Ampicillin and tetracycline were used as references to evaluate the potency of tested compounds.[14]

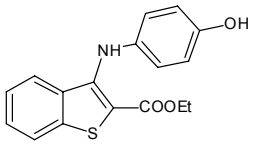


Ar = pheny, 2-theinyl or 2-furyl

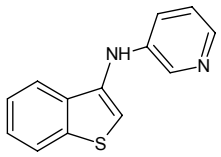
(**11**)

Antifungal activity of diarylamine derivatives of benzo(*b*)thiophene was determined against *Candida*, *Aspergillus* and dermatophyte species employing broth macrodilution test methods by Pinto *et al*. Most active compounds exhibited a broad spectrum activity against all tested fungal strains with particularly low MIC for dermatophyte. It was observed that hydroxyl group is essential for activity in aryl derivatives (**12**). The spectrum of activity in pyridine derivatives was broadened by the absence of ester group on position-2 of benzo[*b*]thiophene system (**13**).[15]

Gouda *et al.* synthesized thiocarbamoyl and thioamide derivatives which were utilized as key intermediates for the synthesis of new derivatives of thiazole and thiophene. All the synthesized derivatives were examined for antibacterial activity using ampicillin and chloramphenicol as a standard. Incorporation of phthalazine moiety to thiophene (**14**) resulted in substantial activity against *E.coli* and *B. theringiensis.*[16]



(**12**)



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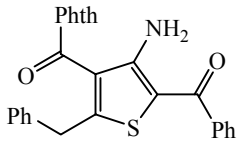
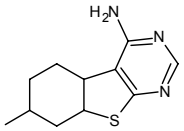
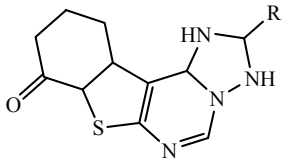


(**14**)



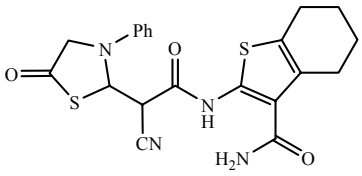
(**15**)

Khazi *et al.*, by employing Gewald reaction, synthesized tricyclic thienopyrimidines and triazole fused tetracyclicthienopyrimidines and screened them for antimicrobial activity. It was found that tricyclic aminothienopyrimidines (**15**) and tetracyclic triazole fused thienopyrimidine (**16**) exhibited promising antibacterial activity against *B. subtilis*. Some compounds also displayed better antifungal activity against *C. albicans* comparable to the standard fluconazole.[17]



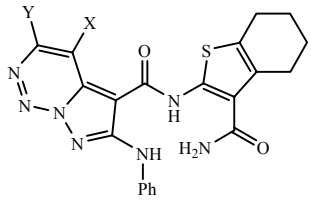
(**16**)

Gouda *et al.* synthesized thiazole and pyrazole derivatives using 4,5,6,7-tetrahydrobenzothiophene moiety as a base. The synthesized derivatives were evaluated for antimicrobial activity *in vitro*. As an indicator for the activity of the compounds, zone of inhibition was measured and Ampicillin was taken as reference. Most of the synthesized compounds evinced good to moderate antibacterial and antifungal activity. Incorporation of benzothiophene nucleus to thiazole (**17**) or pyrazole (**18**) moieties resulted in remarkable activity against *B. theringiensis*, *K. pneumoniae*, *B. fabe* and *F. oxysporum*.[18]



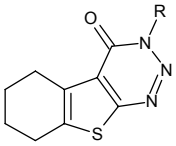
(**17**)

Antimicrobial activity of series of substituted amino-4,5-tetramethylenethieno[2,3-d][1,2,3]-triazine-4(3*H*)-ones was reported by Saravanan *et al*. Compounds with lipophilic groups like chlorophenyl and fluorophenyl groups (**19**) exhibited appreciable antimicrobial activities while substituting with electron donating groups like methyl, ethyl were found less active against all the microbes used.[19]



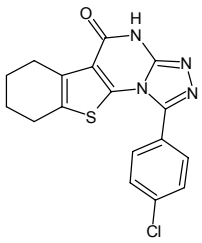
X = NH_2, CH_3; Y = CN, $COCH_3$

(**18**)



R= 4-ClC_6H_4, 4-FC_6H_4

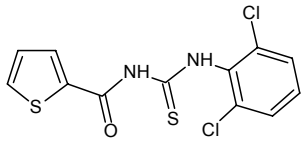
(**19**)



(**20**)

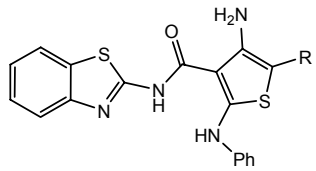
Taisan *et al.* synthesized a series of new thienopyrimidin-4-one(thione) derivatives and evaluated their antimicrobial activity against *S. aureus*, *K. monas*, *P. aeruginosa* and *E. coli* employing Vancomycin and Cefatzine as standard. Compound (**20**) showed promising antimicrobial activity.[20]

Badiceanu *et al.* prepared new thioureides of 2-thiophene carboxylic acid and evaluated them for antibacterial and antifungal activity. *In vitro* antimicrobial activity assay showed that these derivatives presented significant antimicrobial activity with MIC ranging from 7.8µg/ml to 500µg/ml. The majority of the tested compounds showed a broad spectrum of antimicrobial activity at low concentration on Gram-positive, Gram-negative bacteria and fungal strains. Because of the contribution of electron withdrawing group, most effective compound was (**21**) with low MIC value on majority of testing microbial strains.[3]



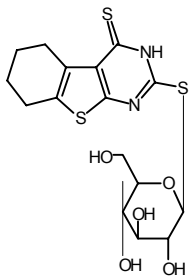
(**21**)

A series of thiazole, pyrazole, thiophene derivatives having benzothiazole moiety in common were reported by Bondock *et al.* by using N-(benzo-thiazol-2-yl)-2-cyanoacetamide as reactant. Synthesized compounds were screened for antimicrobial activity against *S. aureus* and *S. pyogenes* (Gram-positive bacteria), *P. phaseolicola* and *P. fluorescens* (Gram-negative bacteria), *F. oxysporum* and *A. fumigates* (fungal strains). It was noticed that compounds belonging to thiophene and pyrazole series exhibited better antibacterial potential than thiazole series. Incorporation of thiophene nucleus to benzothiazole at position-3 via carboxamide linker produced high antimicrobial activity. Also thiophenes with electron withdrawing groups like -COOEt **(22)** or -COPh (**23**) recorded higher activity.[21]

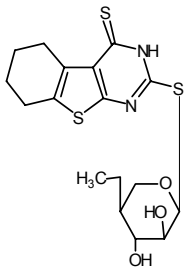


(**22**): R = CO_2Et; (**23**): R = COPh

Hafez *et al.* synthesized thieno[2,3-*d*]pyrimidine-2,4-dithione derivatives by using 3-(2-amino-thiophene)-carbonitrile derivative precursor as a synthon. The compounds were designed in such a way so that the heterocyclic substituents are straight away linked to thienopyrimidine nucleus at C-2. Triazolo[4,3-*a*]benzothieno[2,3-*d*]pyrimidines were also derived from 2-thioxothienopyrimidine as isosteres. All the compounds were screened for antiviral and antibacterial activity. Some of the compounds showed complete inhibition at 128 mg mL^{-1} or less while the rest of the compounds showed incomplete inhibition using ampicillin as the standard drug. Introduction of diphenyl-triazolo group at C-2-C-3 ring resulted in ineffectiveness towards *E. coli* but found to be effective against *S. aureus* and *P. putida*. Any other substitution at position C-2-N-3 of pyrimidine ring and C-4-C-5 of the thiophene ring system resulted in a decrease in efficacy of resulting compounds. Substitution of acylated arabino-furanosyl group at C-2 in pyrimidine ring on thieno[2,3-*d*]pyrimidine ensued in potent compounds when compared to other compounds. Deacylated S-glycoside group incorporation in thienopyrimidine resulted in compounds (**24**) and (**25**) which were active against *P. putida*.[22]



(**24**)

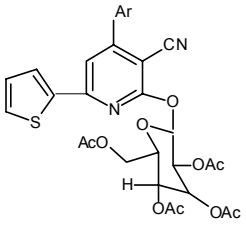


(**25**)

El-Sayed *et al.* reported the synthesis of glycoxyloxy derivatives by glycosylation of pyridine-2-(1*H*)-one. The initial material was obtained by the reaction of 2-acetyl thiophene with 4-chlorobenzaldehyde and ethylcyanoacetate or by reaction of α, β-unsaturated compounds with ethylcyanoacetate in the presence of ammonium acetate. The derivatives were screened for antibacterial activity. The compounds (**26**), (**27**) and (**28**) exhibited higher activity than Ampicillin while other derivative showed moderate activity.[23]

Srivastava *et al.* synthesized a series of tetrahydrobenzothiophene as potential antibacterial and mycolytic agents. The antibacterial activity was screened against *Staphylococcus aureus*, *Bacillus subtilis*,

Escherichia coli and *Klebsiella pneumoniae* using Ampicillin as a reference. Miconazole nitrate was used as standard for evaluation of antifungal activity against *Aspergillus niger* and *Candida albicans*. The derivatives showed moderate to significant activity. It was concluded that electron donating and withdrawing groups on aldehydic phenyl ring influenced the activity. Aldehydic phenyl group containing electron withdrawing group like 2-Cl and 2-NO_2 (**29**) showed promising activity.[24]



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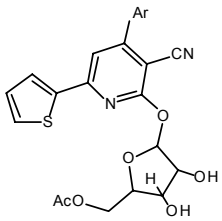

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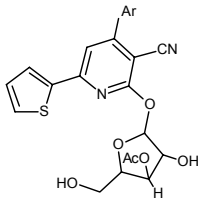

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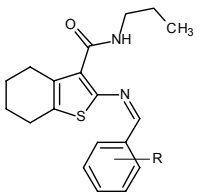
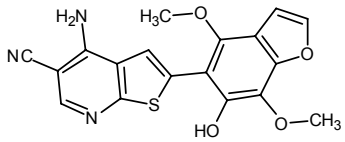
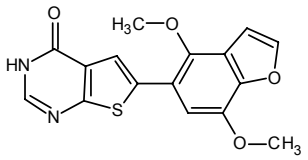


(**29**)

New thienopyridine and thienopyrimidine derivatives were synthesized by Ahmed *et al.*[25] from 2-aminothiophen-3-carbonitriles. The carbonitrile derivatives were synthesized via Gewald reaction using visnaginone and khellinone as initial reactant. Antibacterial screening was done against *P. aeruginosa*, *E. coli*, *S. aureus* and *B. subtilis* while for antifungal screening *A. fumigates*, *P. italicum*, *S. racemosum* and *C. albicans* were used. The antimicrobial activity of the synthesized derivatives was measured in comparison to chloramphenicol and terbiatin as standard drugs. Most of the compounds were active and showed moderate activity. From the synthesized series, the most active compounds were compounds (**30**) and (**31**).[25]

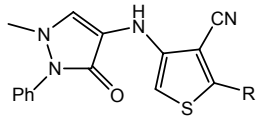


(**30**)



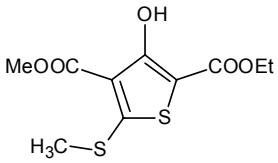
(**31**)

Synthesis and antimicrobial screening of new derivatives of acetamide, oxaloacetyl, acetohydrazide, thiophene and thiophenacrylamide was reported by Aly *et al.* For antifungal activity, four fungal strains: *A. fumigates*, *G. candimum*, *C. albicans* and *S. racemosum* were used. Clotrimazole and Itraconazole were taken as reference. For antibacterial activity, four bacterial strains: *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli* were used. As a standard drug, Penecillin G and Streptomycin were used as reference to evaluate the potency of tested compounds. All the synthesized compounds exhibited moderate to good activity. From the study, it was observed that synthesized compounds substituted with $–OC_2H_5$, $-COCH_2$, $-CH_3$, -Cl group showed potent activity. Compounds **(32)** and **(33)** were found to have strong antifungal activity.[26]



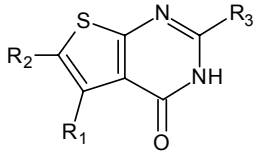
(**32**) R = -N = CH-OC_2H_5; (**33**) R = -NHCOCH_2Cl

A series of highly functionalized thiophene and thieno[3,2-*c*]pyran-4-one derivatives was designed by Ram *et al*. These derivatives were screened for antileishmanial and antifungal activities. SAR study revealed that position and nature of substituents at positions 3 and 4 of the thiophene ring are crucial for the activity. Compounds with a carboxymethoxy group at C-4 and hydroxyl group at C-3 **(34)** exhibited significant antifungal activity against all the fungal strain used. Increase in size of ester function from carboxymethoxy to carboxyethoxy resulted in a loss of efficacy. Change of substituent from carboxymethoxy to cyano group resulted in retention of activity. Some of the compounds also showed antileishmanial activity which may be due to the presence of the ester group.[27]



(**34**)

Newly synthesized 2-(pyridin-2-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-ones derivatives **(35)** were screened for antimicrobial activities against six bacterial strains and two fungal species by Bari *et al*. The presence of long chain aliphatic substituents at C-2 of thiophene ring and presence of the aromatic substituent at position-1 increases the antifungal and antibacterial activity.[28]

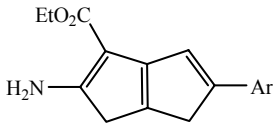


R_1 = H, Me, 4-ClC_6H_4
R_2 = Me, Et, $(CH_2)_4$
R_3 = 2-C_5H_4N, 3-C_5H_4N, 4-C_5H_4N

(**35**)

Balamurugun *et al.* synthesized a series of novel 2-amino-5-arylthieno[2,3-*b*]thiophene under thermal as well as microwave irradiation conditions employing Gewald dehydrogenation reaction. The synthesized compounds were screened for *in vitro* for antitubercular activity against *M. tuberculosis* (MTB) and multidrug resistant *M. tuberculosis*

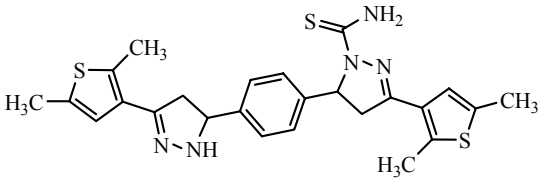
(MDR-TB). Compound (**36**) was found to be most active compound with MIC of 1.1µM against MTB and MDR-TB. Compounds with –CN group were found to be less active than –COOEt group. It was also reported that lipophilicity is an important factor for antitubercular activity.[29]



Ar= 1-naphthyl, C_6H_5

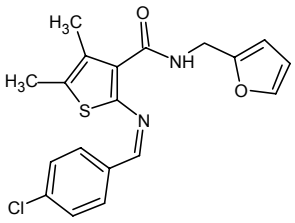
(**36**)

Khan *et al.* prepared pyrazoline, pyrazole and pyrimidine derivatives from chalcones previously obtained from the reaction of terephthaldehyde with 3-acetyl-2,5-dimethyl thiophene and evaluated antibacterial activity *in vitro* by disc diffusion assay against *S. aureus*, *S. pyogenes*, *S. typhimurium* and *E. coli*. Results showed that pyrazoline derivative (**37**) bearing thiophene moiety were better at inhibiting growth of both types of bacteria compared to Chloramphenicol.[30]



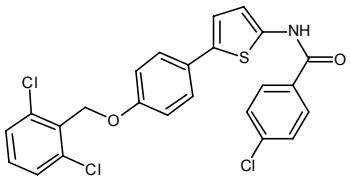
(**37**)

Various Schiff bases were synthesized by Iqbal *et al.* by reaction of substituted aromatic aldehydes with 2-amino-3-(N-furfurylamido)-4,5-dimethyl thiophene. The Schiff bases were screened for antibacterial and antifungal activity using Ampicillin and Miconazole nitrate as standard. Most of the compounds showed mild to moderate antimicrobial activity and some of them were found to be equipotent to the standard drug used. It was concluded that compounds having electron withdrawing group (**38**) on aldehydic phenyl ring showed better antibacterial and antifungal activity as compared to compounds having electron donating groups.[31]

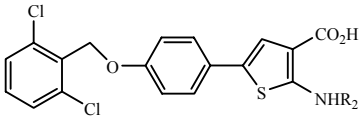


(**38**)

Lu *et al.* developed a series of acylated and alkylated amino-5-(4-(benzyloxy)phenyl)thiophene-3-carboxylic acid derivatives and evaluated them for anti-tubercular activity. Some of these derivatives inhibited *Mycobacterium tuberculosis* growth with MIC value between 1.9 and 7.7 µM and low toxicity against VERO cells. Compounds were found to show moderate activity against multidrug resistant tuberculosis and drug- resistant tuberculosis clinical strains. SAR studies of these derivatives idicated that 2,6-dichlorobenzyloxy group (**39**) is supposed to play a significant role in the activity. Amide derivatives were found to display superior anti-tubercular activity than amine derivatives. The data also suggested that compounds with C-3, C-4 alkyls showed best anti-tubercular activity (**40**). A further increase in the carbon chain resulted in decrease in potency.[32]



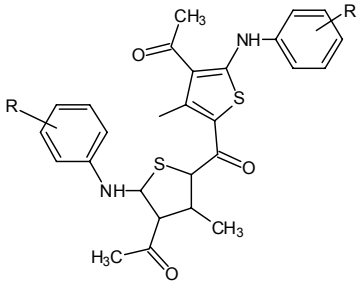
(**39**)



R_2 = n-butyl, carboxymethyl

(**40**)

Sable *et al.* synthesized ethyl 2-(4-acetyl-3-methyl-5-(phenylamino)thiophen-2-yl)-2-oxoacetate derivatives, ethyl 3-(4- acetyl-3-methyl-5-(phenylamino)thiophen-2-yl)-3-oxopropanoate derivatives and di((4-acetyl-3- methyl-5-phenylamino)thiophen-2-yl)ketone derivatives under mild conditions from acetyl acetone, phenyl isothiocyanates and 2-chloromethyl derivatives. All the synthesized compounds exhibited good to moderate activity. Compounds having R= H/Cl (**41**) were found to be more potent against Gram-positive bacteria with moderate potential against fungal strains. With R= CH_3/OCH_3, compounds were more active against *B. subtilis*, *P. aeruginosa* and *E. coli* .[33]

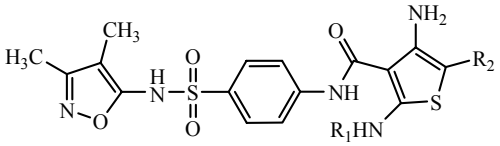


R = H, 4-OCH3, 4-Cl

(**41**)

A new series of thiophene, acrylamide, pyrazole and pyridine derivatives tagged with sulfisoxazole moieties were synthesized by Nasr *et al. In vitro* antimicrobial activity screening was done against Gram- positive bacteria *S. pneumoniae*, *B. subtilis* and *S. Epidermidis*, Gram- negative bacteria *E. coli*, *P. vulgaris* and *K. pneumoniae* and fungal strain *A. fumigates*, *S. racemosum* and *G. candimum* using agar diffusion method and Ampicillin, Gentamycin, Sulfisoxazole and Amphotericin B as reference drugs. Most of the newly synthesized compounds (**42**) were found to be more potent than sulfisoxazole. The synthesized compounds had higher lipophilic character than sulfisoxazole, and therefore had more intracellular concentration due to their

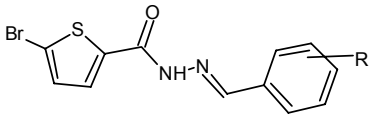
improved cellular penetration. Molecular docking simulations represented that the synthesized compounds can be accommodated in p-aminobenzoic acid pocket of dihydropteroate synthase thereby acting in a similar way as that of sulfa drugs. Therefore, thiophene derivatives bearing larger N-alkyl substituent exhibited better antimicrobial activity.[34]



R_1 = -CH_3, -C_2H_5, -CH_2-CH=CH_2, -C_6H_5; R_2 = -$COCH_3$, -CN

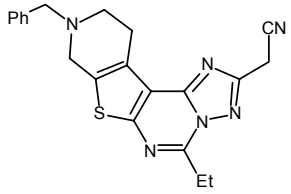
(**42**)

Naliapara *et al.* prepared a convenient method for the synthesis of Schiff bases of 5-bromothiophene-2-carbohydrazide having good to moderate yield. All the compounds were evaluated for antimicrobial activity by well- diffusion method against bacterial strains (*E. coli*, *P. aeruginosa*, *S.aureus* and *S. pyogenus*) and fungal strains (*C. albicans*, *A. niger* and *A. clavatus*). Compounds like (**43**), having electron withdrawing groups, exhibited good antibacterial and antifungal activity.[35]



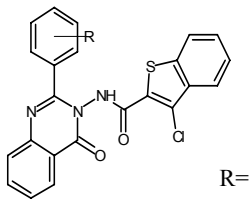
R= 4-F, 4-Cl, 4-Br, 3-Cl, 4-CN (**43**)

Jabli *et al.* designed a new series of 2-cyano-methylthieno-triazolopyrimidines using substituted aminothiophene-3-carbonitrile and cyanoacetic acid hydrazide as starting material. All the compounds were screened for antibacterial activity using Tetracycline as reference. The strains used were *S. typhimurium*, *P.aeruginosa*, *E. coli* and *S. aureus*. All the synthesized compounds showed moderate antibacterial activity. Among these, compound **(44)** exhibited highest antibacterial activity. It may be attributed because of the presence of dihydronaphtho and benzyl moiety.[36]



(**44**)

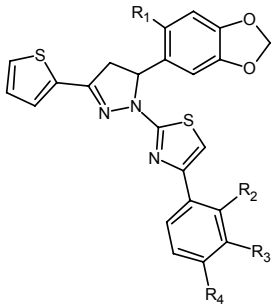
Analogs of 3-chloro-N-(4-oxo-2arylquinazolin-3(4H)-yl)-1-benzothiophene-2-carboxamide were prepared from 3-amino-2-arylquinazolin-4(3*H*)-one by Rao *et al.* These compounds were evaluated for *in vitro* antibacterial activity against Gram-positive bacteria and Gram-negative bacteria using Ciprofloxacin as standard. Compound with 3-methyl substitution on phenyl ring (**45**) at position-2 of quinazoline moiety showed significant activity against *S. aureus* while compound with -Cl, -CH_3 and -NO_2 group substitution showed moderate activity against both Gram-positive microorganisms. Most of the compounds showed moderate activity against Gram-negative bacteria.[37]



R= -Cl, -CH_3, -NO_2

(**45**)

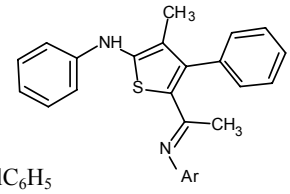
Series of thiophene and benzodioxole appended thiazolyl-pyrazoline derivatives (**46**) were synthesized and screened for antimicrobial activity by Antony *et al*. Some of the compounds presented good antimicrobial activity against bacterial and fungal strain used. Docking study revealed that all synthesized derivatives showed good binding energy toward target receptor DNA topoisomerase IV, ranging from -10.42 to -11.66 kcal mol^{-1}. Substitution of -Br at R_1 position and –CN group at R_3 position resulted in a marked increase in antimicrobial activity.[38]



R_1= H, Br; R_2= H, Cl; R_3= H, CN; R_4= H, F

(**46**)

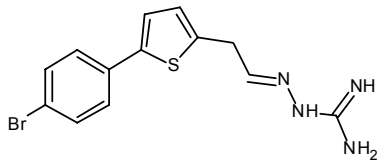
Mabkhot *et al.* synthesized derivatives of thiophene using 5-acyl-4-phenyl-2-(phenyl-amino)thiophene-3-carboxylate as precursor. These derivatives were screened for antibacterial activity against Gram-positive bacteria (*B. subtilis and S. pneumoniae*) and Gram-negative bacteria (*E. coli and P. aeruginosa*) using disc diffusion method with Ampicillin and Gentamycin as standard drugs. For antifungal activity, four fungal strains (*A. fumigates*, *S. racemosum*, *G. cardimum*, *C. albicans*) were used and Amphotericin B was taken as standard drug. All the compounds exhibited moderate to good antimicrobial activity. SAR studies suggested that introduction of appropriate substituent at position-5 of thiophene ring (**47**) enhanced antibacterial activity.[39]



Ar = -C_6H_5, 4-ClC_6H_5

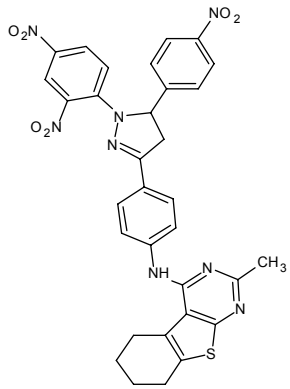
(**47**)

Ajdacic *et al.* designed a series of new thiophene- based guanylhydrazones and evaluated antifungal activity against broad ambit of medically valued fungal strains including yeast, moulds and dermatophytes in comparison to drug Voriconazole. All guanylhydrazones showed significant activity against *Candida* spp., *A. fumigates*, *F. oxysporum*, *M. canis* and *T. mentagrophytes*. Some of the compounds exhibited excellent activity against voriconazole resistant *Candida albicans* with very low MIC value < 2 μg mL^{-1}. Compound (**48**) having –Br group on phenyl ring was found to be most effective with MIC ranging from 0.25-6.25 μg mL^{-1}. It was concluded that thiophene based guanynyl hydrazone showed higher inhibitory activity than corresponding furan.[40]



(**48**)

Various chalcones were used as building block for the synthesis of various thieno[2,3-d]pyrimidine derivatives by Elissa *et al.* These derivatives were screened for antimicrobial activity against Gram-positive, Gram-negative and fungal strains. MIC was determined by the paper disc diffusion method. It was observed that substitution with a methyl group at position-2 of tetrahydrothienopyrimidine derivative of enone series decreased the activity against Gram-positive bacteria and removed the activity against *C. albicans*. A terminal amino group of the hydrazine group when unsubstituted, together with the presence of methyl group position-2 showed broad spectrum activity. The presence of phenyl group at N^1 and dinitrophenyl group of dihydropyrazol ring (**49**) yielded derivative with broad spectrum activity.[41]



(**49**)

Conclusion

Considerable attention has been given to compounds which possess thiophene rings in order to search for drugs with a higher degree of potency and fewer toxic side effects. The analytical and other informational data, available in literature so far, have lightened thiophene as a significantly important class of heterocyclic compounds and their applications in the ever challenging chemotherapy of various ailments/ infections since last two decades. A large number of thiophene derivatives have been discovered and reflected significant antimicrobial activity with appreciably wider spectrum.

Thiophene can be fused with various heterocyclic systems, resulting in various new heterocyclic systems with enhanced biological activity. Thienopyrimidine and benzothiophene occupy a special position among these compounds. Most of the positions were explored to improve the antimicrobial profile of thiophene analogs. Derivatives with C-2 and C-4 substituted positions and comportment of electron-withdrawing group on the aromatic ring on C-2 position of thiophene presents varied degrees of inhibition against Gram-positive bacteria, Gram-negative bacteria and fungal strains, showing inhibition as good as to the standard drugs used. The versatile synthetic applicability and biological activity of this heterocyclic moiety will help the medicinal chemists to plan, organize and implement new approaches towards discovery of novel drugs. Further combinatorial libraries of these compounds can be generated which can be screened optimal pharmacological activities by optimization techniques using 2D and 3D QSAR investigation.

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References

[1]Mishra, R., Jha, K. K., Kumar, S., Tomer, I., *Pharm. Chem.*, **2011**, *3*, 38.

[2]Baumann, M., Barendale, I. R., Ley, S. V., Nikbin, N., *Beilstein J. Org. Chem.*, **2011**, *7*, 442.

[3]Badiceanu, C. D., Missir, A. V., Chifiriuc, M. C., Dracea, O., Raut, J., Larion, C., Dity, L. M., Mihaescu, G., *Rom. Biotech. Lett.*, **2010**, *15*, 5545.

[4]Dalvie, D. K., Kalgutkar, A. S., Khojasteh-Bakht, S. C., Obach, R. S., O'Donnell, J. P., *Chem. Res. Toxicol.*, **2002,** *15*, 269.

[5]Jha, K. K., Tomer, I., Mishra, R., *J. Pharm. Res.*, **2010**, *5*, 560.

[6]Queiroz, M. R. P., Ferreira, I. C. F. R., Goetano, Y. D., Kirsch, G., Calhelha, R. C., Estevinho, L. M., *Bioorg. Med. Chem. Lett.*, **2006**, *14*, 6827.

[7]Havaldar, F. H., Bhise, S., Burudkar, S., *J. Serb. Chem. Soc.*, **2004**, *69*, 527.

[8]Yadav, P. P., Gupta, P., Chaturvedi, A. K., Shukla, P. K., Maurya, R., *Bioorg. Med. Chem.*, **2005**, *13*, 1497.

[9]Ryu, C. K., Lee, S. K., Hen, J. Y., Jung, O. J., Lee, J. Y., Jeong, S. H., *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 2617.

[10]Sherbeny, M. A., El-Ashmawy, M. B., Subbagh, H. I., El-Emam, A. A., Badria, F. A., *Eur. J. Med. Chem.*, **1995**, *30*, 445.

[11]Bhuiyan, M. H., Rahman, K. M. M., Hussain K., Rahim, A., Hussain, I., Naser, A., *Acta. Pharm.*, **2006**, *56*, 441.

[12]Abreu, A. S., Ferreira, P. M. T., Monterio, L. S., Queiroz, M. J. R. P., Ferreira, I. L. F. R., Calhelha, R. C., Estevinha, L. M.., *Tetrahedron*, **2004**, *60*, 11821.

[13]Desai, A. D., Mahajan, D. H., Chikhalia, K. H., *Indian J. Chem.*, **2007**, *46B*, 1169.

[14]Darwish, E. S., *Molecules*, **2008**, *13*, 1066.

[15]Pinto, E., Queiroz, M. J. R. P., Vale-Silva, L. A., Oliveira, J. F., Begowin, A., Begowin, J. M., Kirsch, G., *Bioorg. Med. Chem.*, **2008**, *16*, 8172.

[16]Khalil, A. M., Berghot, M. A., Gouda, M. A., *Eur. J. Med. Chem.*, **2006**, *44*, 4434.

[17]Shetty, N. K. S., Lamani, R. S., Khazi, I. A. M., *J. Chem. Sci.*, **2009**, *121*, 301.

[18]Gouda, M. A., Berghot, M. A., Abd El-Ghani, G. E., Khalil, A. M., *Eur. J. Med. Chem.*, **2010**, *45*, 1338.

[19]Saravanan, J., Mohan, S., Roy, J. J., *Eur. J. Med. Chem.*, **2010**, *45*, 4365.

[20]Al-Taisan, K. M., Al-Hazimi, H. M. A., Al-Shihry, S. S., *Molecules*, **2010**, *15*, 3932.

[21]Bondock, S., Fadaly, W., Mefwally, M. A., *Eur. J. Med. Chem.*, **2010**, *45*, 3692.

[22]Hafez, H. N., Hussein, H. A. R., El-Gazzar, A. B. B. A., *Eur. J. Med. Chem.*, **2010**, *45*, 4026.

[23]El- Sayed, H. A., Moustafa, A. H., Haikal, A. E. Z., El-Halawa, R. A., El- Ashry, E. H., *Eur. J. Med. Chem.*, **2011**, *46*, 2948.

[24]Srivastava, S., Das, B., *Der Pharm. Chemica*, **2011**, *3*, 103.

[25]Ahmed, E. M., Marzouk, N. A., Hessein, S. A., Ali, A. M., *World J. Chem.*, **2011**, *6*, 25.

[26]Aly, H. M., Saleh, N. M., Elhady, H. A., *Eur. J. Med. Chem.*, **2011**, *46*, 4566.

[27]Ram, V. J., Goel, A., Shukla, P. K., Kapil, A., *Bioorg. Med. Chem. Lett.*, **1997**, *7*, 3101.

[28]Haswani, N. G., Bari, S. B., *Turk. J. Chem.*, **2011**, *35*, 915.

[29]Balamurugan, K., Perumal, S., Reddy, A. S. K., Yogeeswari, P., Sriram, D., *Tetrahedron Lett.*, **2009**, *50*, 6191.

[30]Asiri, A. M., Khan, S. A., *Molecules*, **2011**, *16*, 523.

[31]Iqbal, M. I. C., Satyendra, D., Apurba, T., Patel, M., Monica, K., Girish, K., Mohan, S., Saravanan, J., *Hygeia. J. D. Med.*, **2012**, *4*, 116.

[32]Lu, X., Wan, B., Franzblau, S. G., You, Q., *Eur. J. Med. Chem.*, **2011**, *46*, 3551.

[33]Sable, P. N., Ganguly, S., Chaudhari, P. D., *Chin. Chem. Lett.*, **2014**, *25*, 1099.

[34]Nasr, T., Bondock, S., Eid, S., *Eur. J. Med. Chem.*, **2014**, *84*, 491.

[35]Makwana, H., Naliapara, Y. T., *Inter. J. Chem. Phy. Astro.*, **2014**, *14*, 99.

[36]Jabli, D., Lahbib, K., Dridi, K., Efrit, M. L., *J. Pharm. Chem. Biol. Sci.*, **2015**, *3*, 178.

[37]Rao, G. K., Subramaniam, R., *Chem. Sci. J.*, **2015**, *6*, 1.

[38]Sulthana, S. S., Antony, S. A., Balachandran, C., *Bioorg. Med. Chem. Lett.*, **2015**, *25*, 2753.

[39]Mabkhot, Y. N., Alatibi, F., El-Sayed, N. N. E., Al- Showiman, S., Kheder, N. A., Wadood, A., Rauf, A., Bawazeer, S., Handa, T. B., *Molecules*, **2016**, *21*, 01.

[40]Ajdacic, V., Senerovic, L., Vranic, M., Pehnezovic, M., Arsnijevic, V. A. , Veselinovic, A., Veselinovic, J., Solaja, B. A., Runic, J. N., Opsenica, I. M., *Bioorg. Med. Chem.*, **2016**, *24*, 1277.

[41]Elissa, A. A. H. M., Moneer, A. A., *Arch. Res. Pharm.*, **2004**, *27*, 885.

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