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Perspectives on Antimicrobial Potential of Benzothiophene Derivatives

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ABSTRACT

Emergence of new infectious diseases such as tuberculosis, bacterial and fungal diseases have stimulated public interest and inspired commitments by medicinal chemists to control these diseases. Increasing microbial resistance has become a very serious clinical problem for many classes of antibiotics. Therefore, it is an urgent requirement to design and synthesize novel antimicrobial agents to solve the problem of microbial resistance towards conventional antimicrobial agents. Among the various types of heterocyclic compounds, benzothiophene plays an important role in the medicinal chemistry because it possesses promising antibacterial, antifungal and antitubercular activities. This articles aims to review antimicrobial activities of novel benzothiophene derivatives during recent years which reveal their biological potential as anti-infective agents.

Keywords: Benzothiophene, antibacterial, antifungal, antitubercular activity.

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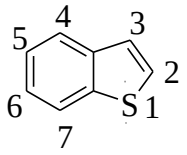
INTRODUCTION

Understanding structure activity relationships (SARs) at the level of inherent physical organic properties such as lipophilic, electronic and steric parameters coupled with consideration of molecular conformation has soon become the hallmark of medicinal chemistry research [1-3]. These fundamental SARs could be useful during the design of new drugs. The design of drug molecules arguably offers some of the greatest hopes for success in present and future era [4, 5]. 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 [6]. The investigational approaches towards SAR focusing the search of optimized candidates have become immensely important. Benzothiophene **(1)** belongs to a class of heterocyclic compounds containing a benzene ring fused with five membered aromatic ring made up of one sulphur as heteroatom with the formula C_8H_4S. The rings are numbered in a way which gives the sulphur heteroatom lowest possible number. Electrophillic aromatic substitutions in benzothiophene takes place at five membered ring because it is more reactive towards electrophillic aromatic substitution than the benzene ring. Benzothiophene undergoes electrophillic aromatic substitution at C-2 and C-3 equally [7]. Its aromaticity makes it relatively stable. Although as a heterocycle, it has reactive sites which allow for functionalization. Novel benzothiophene analogs are priviledge structures which are used in many biological active compounds.



(1)

Antimicrobial Activities

Benzo[b]thiophene molecules are found to be important scaffolds in synthetic medicinal chemistry. They are of current interest due to their wide spectrum of pharmacological activities like antimicrobial, antiviral and anticancer activities etc. The literature survey of the recent studies done on benzothiophene derivatives indicates that they have antimicrobial activities like anti-bacterial, antifungal and anti-tubercular activities which have been summarized as given below:

Ishloor *et al.* proposed the synthesis of some new benzo[b]thiophene derivatives **(2a-2c)**. Some of the selected compounds were screened for their antibacterial and antifungal studies. Antibacterial activity studies of newly synthesized compounds were carried out against four different pathogenic organisms, two each of Gram-negative and Gram-positive bacteria including *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa.* The antibacterial study revealed that compounds **2b** and **2c** having 5-nitro-2-thienyl substitution exhibited maximum inhibition against *S. aureus* at the concentration of 6 µg/mL. Similarly compound **2a** and **2c** had shown maximum inhibition against fungus *C. albicans* at the concentration of 3 µg/ml. Antimicrobial studies were assessed by Minimum Inhibitory

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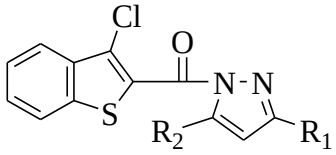
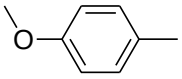
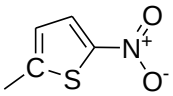
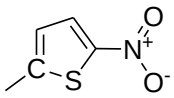
Concentration (MIC) by serial dilution method. Furacin was taken as the standard drug for antibacterial studies, while Fluconazol was used as standard for the antifungal studies. Some compounds showed significant antimicrobial activity [8].



(2a-2c)

	R_1	**R_2**
2a	 p-anisyl	C_6H_5
2b	 5-nitro-2-thienyl	4-Cl.C_6H_5
2c	 5-nitro-2-thienyl	C_6H_5

The antifungal activity of several di(hetero)arylamine derivatives of the benzo[b]thiophene system was evaluated against clinically relevant *Candida, Aspergillus,* and *dermatophyte* species by Pinto *et al*. The most active compound showed a broad spectrum of activity (against all tested fungal strains including fluconazole-resistant fungi) with particularly low MICs for dermatophytes. With this study, it was possible to establish some structure-activity relationships (SARs). The hydroxy groups proved to be essential for the activity in the aryl derivatives. Furthermore, the spectrum of activity in the pyridine derivatives was broadened by the absence of the ester group on position 2 of the benzo[b]thiophene system. A novel series of compounds **(3a-3g)** were screened for antifungal activity against clinical isolates and reference stains of *candida* species *(C. albicans, C. glabrata, C. Krusei* and *C. tropicalis), Aspergillus* species *(A. fumigatus, A. niger* and *A. flavus),* and dermatophytes *(microsporium canis, microsporium gypseum, thichophyton mentagrophytes, thichophyton rubrum,* and *epidermophyton floccosum)* and compared to standard drugs like Amphotericin B and Flocunazole. There was no activity detected against any of the tested stain for compound **3a, 3c** and **3d** at concentration up to 200 µg/mL. Dermatophytes were found to be sensitive to compound **3b** and **3f** whereas these compounds exhibited no antifungal activity against *Aspergillus* and *Candida* species. Compounds **3e** and **3g** exhibited a larger spectrum of activity

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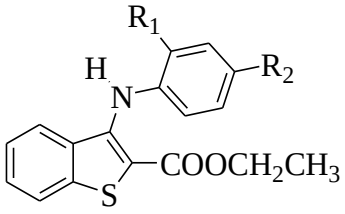
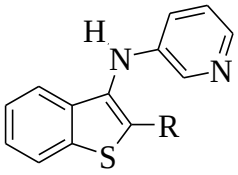
than compound **3b** and **3f**, particularly compound **3g**, additionally showed moderate activity against both *Candida* and *Aspergillus* species. The presence of free OH group in **3b** instead of an OMe group in **3a** was responsible for the antidermatophyte activity. The presence of two OH groups in **3e** broadened the spectrum of activity to include yeasts, but with higher MIC values 25-50 µg/mL than those for dermatophytes having MIC values of 6.25-12.5 µg/mL. It was found that on comparing the compound **3f** and **3g** that the absence of the ester group in the latter widened the spectrum of the activity. Nevertheless the MIC value for dermatophytes remains lower (3.13-12.5 µg/mL) than those for *Candida* having the MIC values in range of 50-100 µg/mL and *Aspergillus* with MIC value in range of 25-50 µg/mL. Compound **3e** added a moderate activity against the tested yeast to its reffered high activity against dermatophytes whereas compound **3g** achieved the broadest spectrum of the activity, including all tested pathogenic yeast and moulds. It was thus active against fungi with decreased susceptibility to standard drug fluconazole, such as *C. Krusei, C. glabrata* and *Aspergillus spp.* The activity of these compounds was not affected by the Fluconazole susceptibility profile of the tested stains [9].



(3a-3e)

3a; R_1=H, R_2=OMe
3b; R_1=H, R_2=OH
3c; R_1=H, R_2=F
3d; R_1=R_2=OMe
3e; R_1=R_2=OH



(3f-3g)

3f; R=$COOCH_2CH_3$
3g; R=H

Androsov *et al* synthesized 3-aminobenzo[b]thiophene derivatives **(4)**. It was found that some derivatives exhibited high antifungal activity against clinically relevant *Candida, Aspergillus* and *dermatophyte* species with low minimum inhibitory concentrations. The most active compound which showed a broad spectrum of activity against all tested fungal stains, including fluconazole-resistant yeasts and *Aspergillus fumigatus,* especially important organisms from the clinical point of view. *In-vitro* antimicrobial activity was also evaluated selectivly against *Bacillus cereus* and compared with standard drug [10].

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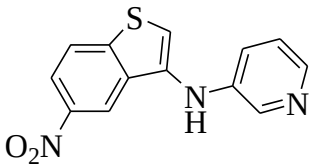
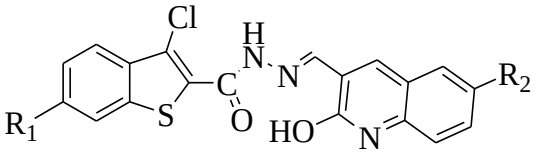
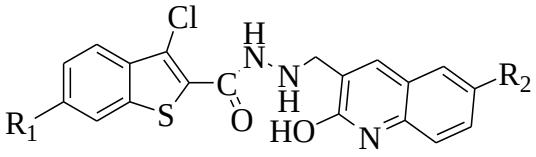


(4)

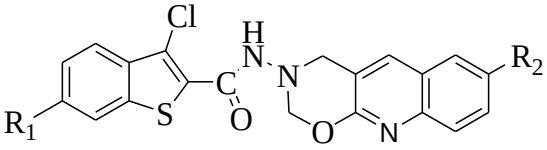
β-chloro-N'-((6-substituted-2-hydroxyquinoline-3-yl)methyl)-6-substituted benzo[b] thiophene-2-carbohydrazides derivatives were synthesized by Guruparsad *et al*. All these compounds were screened for their antibacterial activity against Gram-positive bacteria *S. aureus* and *B. subtilus,* Gram-negative bacteria *E. coli* and *K. pneumonia* using the Gentamycin as positive control and antifungal activity against *A. niger* and *C. albicans* using the Fluconazole as standard drug. The compounds **5a, 6b, 6d, 7b, 7c** and **7d** showed good antibacterial activity, compounds **5c, 5d, 6c,** and **7a** exhibited moderate activity against *S. aureus* when compared with standard drug Gentamycin. Compounds **5a, 5c, 6b, 6d, 7a, 7b** and **7d** showed good activity, compounds **5d, 6a** and **7c** exhibited moderate activity when compared to Gentamycin against *B. subtilus*. Compounds **5a, 5c, 6a, 6b, 6d** and **7d** showed good activity, compounds **6c, 7a,** and **7b** showed moderate activity against *E.coli* when compared to Gentamycin. Compounds **5a, 5c, 6d, 7a, 7b** and **7d** showed good activity, compounds **5b, 5d** and **6b** exhibited moderate activity when compared to Gentamycin against *K. pneumonia*. A good antifungal activity was shown by compounds **5a, 6c** and **7d**. Compounds **5c, 5d, 6a, 6b, 6d** and **7c** exhibited moderate activity when compared to Fluconazole against *A. niger*. Compounds **5a, 6a** and **6c** showed good activity, compounds **5b, 5c, 5d, 6b, 7a** and **7d** showed moderate activity when compared to Fluconazole against *C. albicans*. While rest of the compounds showed less activity against the entire microorganism tested when compared to that of standard drug at the same concentration as that of tested compounds [11].



(5a-5d)



(6a-6d)

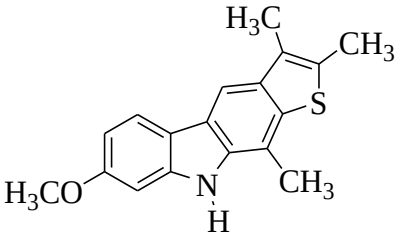


(7a-7d)

	R_1	R_2
a	H	H
b	OCH_3	H
c	OCH_3	CH_3
d	H	CH_3

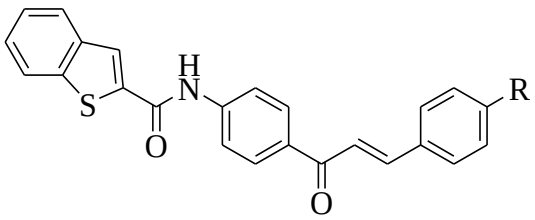
A series of ortho-chlorodiarylamines having 2,3,7-trimethylbenzo[b]thiophene nucleus **(8)** were prepared by Queiroz *et al.* in high yields (70-85%). Studies of antimicrobial activity of the compounds obtained against representative species of bacteria *Escherichia coli, Pseudomonas aeruginosa, Bacillus cereus* and *Bacillus subtilis* and fungi *Candida albicans,* were

performed. Some compounds showed significant activity when compared with standard drug [12].

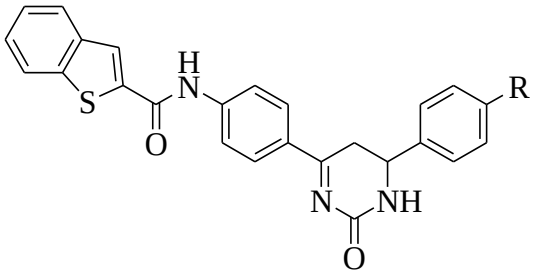


(8)

A series of various benzothiophene derivatives having oxapyrimidines, isoxazolines, pyrazoles, pyrazolines and thiopyrimidines nuclei were synthesized by Naganagowda *et al*. The structures of all the synthesized compounds were confirmed by spectral data and screened for antibacterial activity against two Gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis* and Gram-negative bacteria, *Pseudomonas aeruginosa* and *Escherichia coli.* The tested compounds **9b, 12e, 14b, 13a, 13b** showed moderate activity against *Escherichia coli, Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus* respectively as compared to the standard antibacterial drugs Streptomycin and Ampicilline against all microorganisms. The antifungal activity of the synthesized compounds was tested against four different fungi i.e. *Candida albicans, Crysosporium pannical, Aspergillus niger* and *Rhizopus oryzae* by a filter paper disc technique. The concentration of test compounds was 1000 µg/mL. Zone of inhibition was produced after 48 hrs of treatment by each compound and was measured in mm. It was found that tested compounds **10b**, **12a** had maximum zone of inhibition against *Rhizopus oryzae* whereas **11a, 14a** against *Aspergillus niger,* **13a** against *Candida albicans* and compound **11a** against *Crysosporium pannical* as compared to the standard antifungal agent Griseofulvin [13].



(9a-9h)



(10a-10h)

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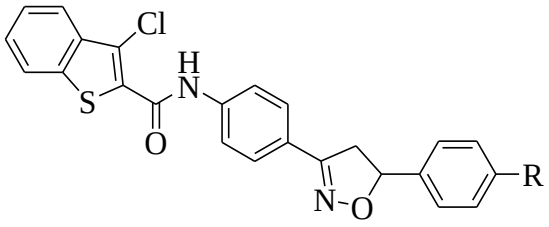
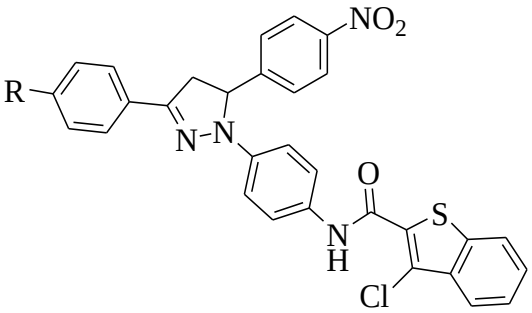
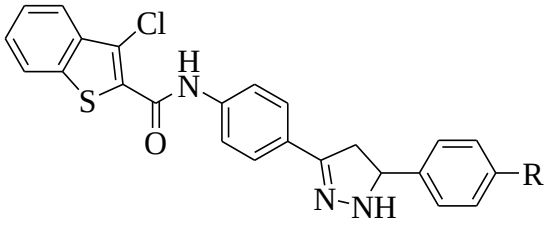


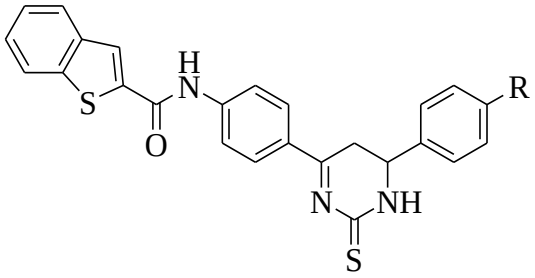
(11a-11h)



(12a-12h)



(13a-13h)



(14a-14h)

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R	H	OCH_3	Cl	NO_2	H	OCH_3	Cl	NO_2

A series of new-arylated benzo[*b*]thiophenes was described by Dit Chabert *et al*. In a first screening assay, the compounds were used at a concentration of 100 mg/L against a susceptible strain of *S. aureus* (ATCC 25923). Ampicillin (MIC=8 mg/L) at conc. of 16 mg/L was used as a positive control. Two resistant bacteria harbouring efflux mechanisms were used in this case: (i) *S. aureus* SA-1199B (resistant to Fluoroquinolones through overexpression of the NorA efflux pump and having the mutation in A subunit of gyrase), which was designated as *S. aureus* NorA, and its susceptible parental strain *S. aureus* SA-1199,40 (ii) S. aureus MsrA (resistant to 14- and 15-membered macrolides, harbouring the multicopies plasmid pUL 5054) standard drug Ciprofloxacin had a MIC value of 0.37 mg/L against susceptible *S. aureus* at conc. of 16 mg/L against *S. aureus* NorA. The gyrA mutation alone conferred a MIC of 2 mg/L. Erythromycin had MIC value of 0.5 mg/L against the susceptible *S. aureus,* and of 128 mg/L against *S. aureus* MsrA. Compounds **(15a-15e)** displayed antibacterial activity against both susceptible and resistant strains. As the MICs against the susceptible *S. aureus* were only moderate, these compounds were not studied further. The diarylated thiophene exhibited a specific but poor activity on *S. aureus* MsrA stain and was also not studied further. Only compounds which specifically restored the activity of standard drug Ciprofloxacin against *S. aureus* NorA were retained. As a comparison, compound **15d** (highly active) was compared to less active compounds such as **15a, 15b, 15c** and **15e** [14].

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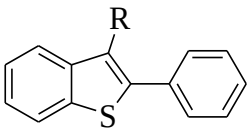
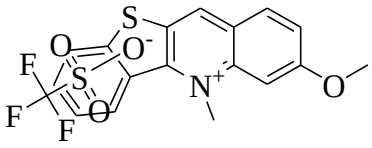


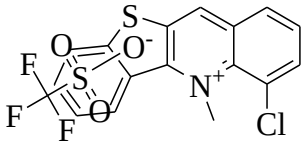
(15a-15e)

	R
15a;	H
15b;	CHO
15c;	CN
15d;	OCH_3
15e;	OCH_2CF_3

Substitution around 5-methyl benzothieno[3,2-*b*]quinolinium ring system was explored by Boateng *et al.* in order to identify positions of substitution that improved its antifungal profile. The 3-methoxy derivative **16a** was active against *C. albicans*, *C. neoformans* and *A. fumigatus* and the 4-chloro analogue **16b** showed moderate increase in anti-cryptococcal and anti-aspergillus activities. The effectiveness of **16a** and **16b** were validated in murine models of candidiasis and cryptococcosis, respectively. The efficacy of **16b** in reducing brain cryptococcal infection and its observation in the brain of mice injected with this quaternary compound confirmed the capacity of these compounds to cross the blood–brain barrier of mice. Overall, several of the chloro and methoxy substituted compounds showed significant improvements in activity against *A. fumigatus*, the fungal pathogen prevalent in patients receiving organ transplant. Opening the benzothiophene ring to form 1-(5-cyclohexylpentyl)-3-(phenylthio)quinolinium compound resulted in the identification of several novel compounds with over 50-fold increase in potency while retaining low cytotoxicities. Thus, these compounds may constitute a new scaffold for development of antifungal drugs against opportunistic infections [15].



(16a)



(16b)

Some new 3-acetyl-5-(3-chloro-1-benzo[b]thiophen-2-yl)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles **17a** and 2-(3-chloro-1-benzo[b]thiophen-2-yl)-5-substituted phenyl-1,3,4-oxadiazoles **17b** were synthesized and evaluated for antimicrobial activity by Chawla *et al*. All the compounds were screened for their antibacterial activities against *Staphylococcus aureus, Bacillus subtilis*. *Escherichia coli* and *Pseudomonas aeruginosa* and for antifungal activity against *Candida albicans* and *Asperigillus niger*. Some compounds exhibited significant antibacterial and moderate antifungal activities. A few compounds were found to be most potent with activities, even better than standard drug ciprofloxacin against *S. aureus* and *B. subtilis* [16].

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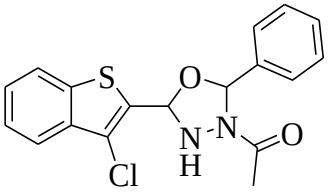
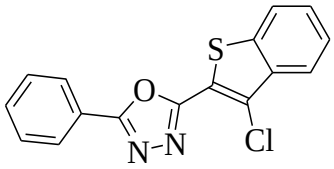
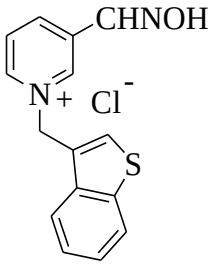


(17a)

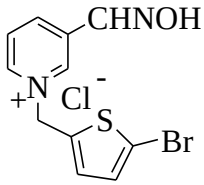


(17b)

Bharate *et al* reported *in-vitro* antimicrobial activities of a series of quaternary pyridinium oximes of benzothiophene nucleus against a number of lower pathogenicity BSL-1 and 2 agents. Compounds **18a** and **18b** that showed moderate antibacterial activity against *Staphylococus aureus* and methicillin-resistant *S. aureus* with IC_{50} values ranging from 12.2-17.7 µg/mL. Susceptibility testing for antifungal activity was carried out using organisms including *Candida albicans, C. glabrata, C. krusei, Aspergillus fumigates, Cryptococcus neoformans* and antibacterial activity on *Staphylococcus aureus,* methicillin-resistant *S. aureus* (MRS), *Pseudomonas aerugenosa, Escherichia coli.* Ciprofloxacin (0.07 and 0.08 µg/mL for *S. Aureus* and MRS) and Amphotericin B (IC_{50} = 0.76 µg/mL for *Cryptococcus neoformans)* were used as standard drugs respectively [17].

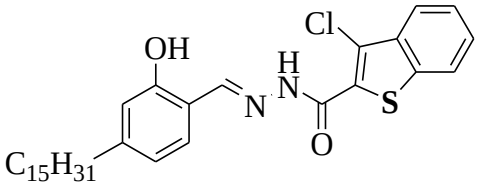


(18a)



(18b)

A novel series of 3-chloro-*N'*-(2-hydroxy-4-pentadecylbenzylidene)- benzo[*b*]thiophene-2-carbohydrazides **(19)** was synthesized by Naganagowda *et al.* and screened for their antimicrobial activities. Some compounds showed appreciable activity when compared with standard drug [18].



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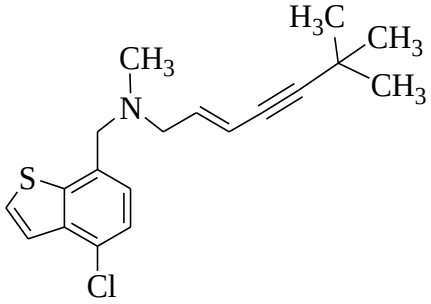
Terbinafine and its analogues, which are a major class of non-azole antifungal agents, are known to act by inhibition of squalene epoxidase enzyme in fungal cells. Gokhale *et al.* had performed a quantitative structure activity relationship (QSAR) study on a series of 92 molecules using different types of physicochemical descriptors. Inhibitors were divided into five classes depending upon chemical structure. QSAR models were generated for correlation between antifungal activities against *Candida albicans* using genetic function approximation (GFA) technique. Equations were evaluated using internal as well as external test set predictions. Models generated for all these classes showed that steric properties and conformational rigidity of side chains played an important role for the activity. The present QSAR analysis agreed with the results of the previously reported CoMFA study. Terbinafine analogue the benzothiophene **(20)** class was characterized by the presence of sulfur atom in the ring. The presence of benzothiophene ring instead of naphthalene ring was responsible for better activity against *C. albicans* when compared with standard drug [19].



(20)

Various 1,3-oxazol-5-ones **(21a)**, imidazol-4-ones (**21b)**, 1,2,4-triazin-6-ones **(21c)** containing benzothiophene nucleus were synthesized by Naganagowda *et al.* and screened for antibacterial activity against two Gram-positive bacteria, *Staphylococcus aureus* (ATCC 25923), and *Bacillus subtilis* (ATCC 6633) and Gram-negative bacteria, *Pseudomonas aeruginosa* (ATCC 10145) and *Escherichia coli* (ATCC 35218). Each test compound (50 mg) was dissolved in dimethyl formamide (50 mL, 1000 µg/mL) to obtain a sample solution. Chloramphenicol and Streptomycin were used as reference drugs. The tested compounds showed slightly to moderate antibacterial activity compared to standard drugs against each microorganism. The antifungal activity of the synthesized compounds was tested against *Candida albicans, Crysosporium pannical,* and *Aspergillus niger* by a filter paper disc technique. The concentration of test compounds was 1000 µg/mL. Griseofulvin was used as the standard antifungal agent. Tested compounds showed slight to moderate antifungal activity when compared with standard drug [20].

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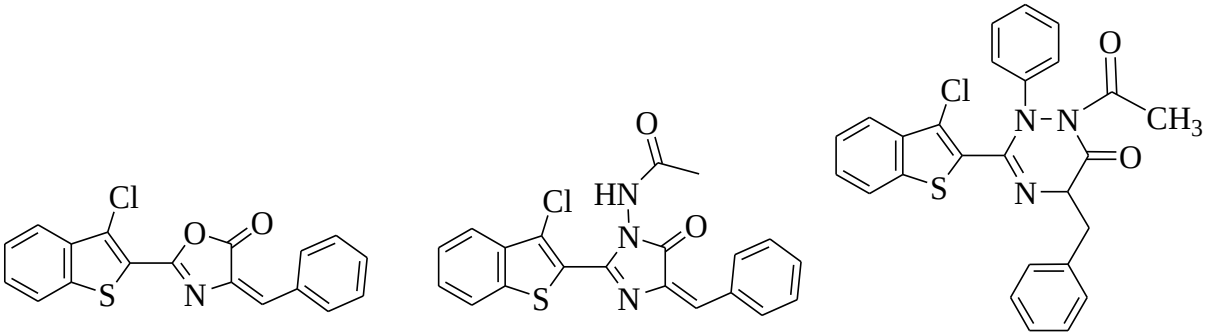
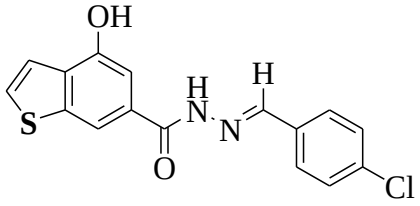


(21a) **(21b)** **(21c)**

A versatile method for the synthesis of novel Schiff bases of 4-hydroxy 6-carboxhydrazino benzothiophene derivatives **(22)** was described by Venugopala *et al*. The titled compounds were characterized on the bases of spectroscopic techniques and evaluated for their qualitative and quantitative antibacterial activity by agar cup method, respectively. From the biological activity it was possible to observe that some of the substituents on the phenyl ring of the benzothiophene analogs influenced biological activity. The antibacterial activity of the test samples were determined by agar cup plate method using four microorganisms such as *B. Subtilis, S. aureus, E. coli,* and *K. pneumoniae* and two standard drugs Ampicillin and Streptomycin at concentration of 100µg/mL. Some compounds showed appreciable antimicrobial activity [21].



(22)

A series of tetrahydrobenzothiophene derivatives **(23a-23i)** were synthesized by Mishra *et al*. These synthesized compounds were purified, characterized and evaluated for their antimicrobial activity. Most of the compounds exhibited moderate to significant activities. All the synthesized compounds were subjected to antimicrobial screening at a concentration of 100µg/ml involving three Gram-negative bacteria *(Eschericha Coli, Staphylococcus aureus* and *Klebsiella pneumoniae)*, three Gram-positive *(Seratia reticulata, Bacillus subtilis* and *Streptococcus pneumoniae)* and two fungal strains *(P. aeruginosa* and *C. albicans)* using Ampicillin as standard at the same concentration by Agar disc diffusion method in reference. The response of organisms to the synthesized compounds were measured in terms of zone of inhibition and compared with that obtained with standard. The results showed that the compound **23c** against *E. Coli. S. Reticulata*, compound **23e** against *S. Aureus.* Compound **23a** against *S. Subtilus*, compound **23f** against *S. Pneumonia*, compound **23e** against *K. Pneumonia* were found to be most active as an antibacterial agent. Similarly the Compound **23f** against *P.*

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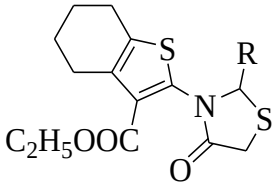
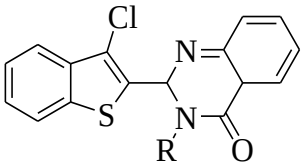
Aeruginosa, compound **23b** against *C. Albicans* were found to be most active as antifungal agent [22].



(23)

	R
23a;	4-Cl C_6H_4
23b;	C_6H_5
23c;	3-OH C_6H_4
23d;	CH_3
23e;	H
23f;	2-CH_3 C_6H_4
23g;	3-CH_3 C_6H_4
23h;	3-OCH_3 C_6H_4
23i;	C_2H_5

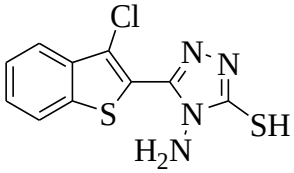
3-substituted phenyl-2-(3'-chlorobenzo (b) thiophene-2`-yl) quinazol-4-ones derivatives were produced by Trilapur *et al*. The *in-vitro* antibacterial activity of the new compounds were determined by cup-plate method using *E. coli, P. aeruginosa, S. epidermatitis* and *B. Subtilis* organism at the concentration of 100 µg/ ml. These compounds **24a, 24b** and **24c** exhibited activity nearly equal to that of standard drug Ampicillin against all the organisms. Few Compounds exhibited moderate activity against organisms. The *in-vitro* antifungal activity of the new compounds was determined by cup-plate method against *A. niger* and *C. albicans* by using Nyatatin as a standard drug [23].



(24a-24c)

	R
(a)	4-$C_6H_5(OCH_3)$
(b)	4-$C_6H_4(Cl)$
(c)	4-$C_6H_4(Br)$

A novel series of 3-chloro-2-Chlorocarbonylbenzo [*b*]thiophene **(25)** was synthesized by El Ashry *et al.* and screened for antimicrobial activity. Some compound showed significant activity as compared with the standard drug [24].



(25)

Naganagowda *et al.* synthesized heterocyclic compound containing benzothiophene nucleus **(26a-26e)** with thiazoles, triazoles and oxadiazoles. Some compounds showed better antimicrobial activity when compared with standard drug [25].

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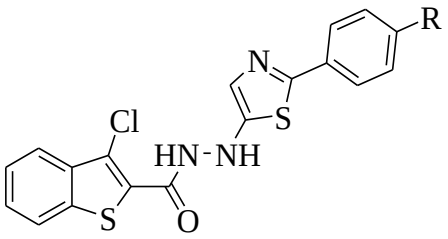
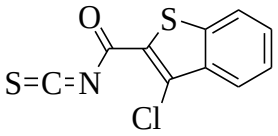


(26a-26e)

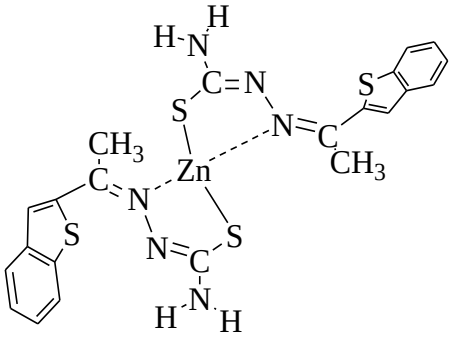
Compound	R
26a	H
26b	F
26c	NO_2
26d	Br
26e	Cl

Novel derivatives of 3-chlorobenzothiophene-2-carbonylisothiocyanate **(27)** were investigated by Naganagowda *et al.* The structures of the newly synthesized compounds were elucidated against *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *E. coli.* The antifungal activity of the synthesized compounds was tested against four different fungi, *C. albicans*, *C. pannical*, *A. niger*, and *R. Oryzae.* Some compounds showed appreciable antimicrobial activity as compared to the standard drugs [26].



(27)

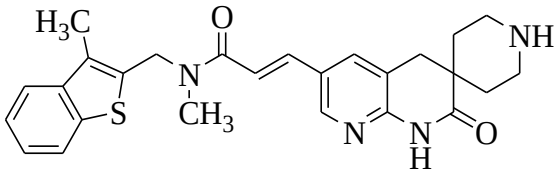
A novel series of zinc (II) complex of 2-acetylbenzothiophene 3-thiosemicarbazone $[Zn(BTTS)_2]$ **(28)** were prepared by Kayed *et al.* and evaluated for antimicrobial activities. The compound showed significant activity when compared with the standard drug [27].



(28)

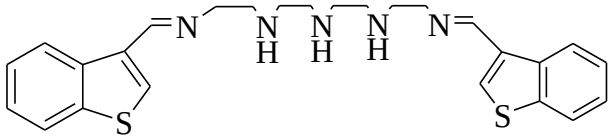
Some spiropiperidine naphthyridinone inhibitor derivatives having benzothiophene nucleus **(29)** of *Staphylococcus aureus* and *Escherichia coli* Fab_I were prepared by Sampson *et al*. Few Compounds were identified as having sub-nanomolar *E. coli* Fab_I activity and were among the most potent Fab_I inhibitors yet described. In some cases a noticeable increase in MIC against the MRSA strain was observed. The N-methyl derivatives appeared to improve potency and whole cell activity compared to the analogues which carried the free amine. It was possible that increased whole cell activity was related to the enhanced permeability of the methylated species. Excellent potency was observed with respect to *E. coli* Fab_I, with one

compound showing sub-nanomolar potency. In contrast with *S. aureus,* the free amine analogues appeared to exhibit improved MIC values relative to the N-methyl series. The MIC's of this series also offered a dramatic improvement in antimicrobial activity over the naphthyridinone compounds, as was evident in the high MIC values when compared with standard drug [28].



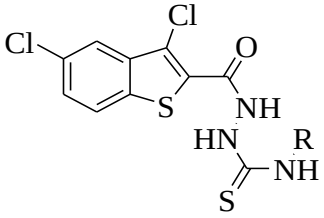
(29)

A novel series of benzo[*b*]thiophen-3-ylmethylidene derivatives **(30)** was synthesized by Nunez *et al.* and evaluated for antimicrobial activity and compared with standard drug. Some compounds showed good antibacterial activity [29].



(30)

2-(3', 5'-dichlorobenzo[b]thiophene-2'yl)-5-arylamino-1,3,4-thaidiazole derivatives **(31-32a-j)** were synthesised by Thaker *et al* and their pharmacological evaluation was performed for their antimicrobial and antitubercular activities. All the compounds were screened *in-vitro* for their antimicrobial activity against a variety of microbial stains such as *E. coli, P. vulgaris, B. Mega, S. Aureus* and fungi stain as *A. Niger*. The known antibiotics like benzyl penicillin, Amoxycillin., Ciprofloxacin, Erythromycin and Griseofulvin were used as standard drugs. It was shown that the compounds containing the functional groups (NO2, Cl, and CH_3) were more potent against these stains. Primary screening of the compounds for antitubercular activity was conducted at 6.25 µg/mL towards *Mycobacterium tuberculosis* H37Rv in BACTEC 12B medium using the BACTEC 460 radiometric system. Since compounds demonstrated at least >90% inhibition in the primary screen were compared with standard drug using Refampicin at 0.25 µg/mL concentrations and showed 98% inhibition. It was found that compound carrying Methyl and chloro groups were more potent against the *E. coli* stain [30].



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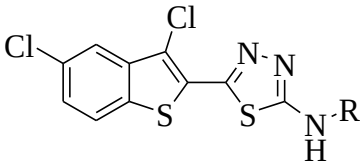

(32)

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Compound	R
31a	C_6H_5
31b	2-Cl-C_6H_4
31c	3-Cl-C_6H_5
31d	2-Cl-5-CH_3-C_6H_3
31e	2,3-$(CH_3)_2C_6H_3$
31f	4-OCH_3-C_6H_4
31g	2-CH_3-C_6H_4
31h	4-CH_3-C_6H_4
31i	2-NO_2-C_6H_4
31j	4-NO_2-C_6H_4

Compound	R
32a	C_6H_5
32b	2-Cl-C_6H_4
32c	3-Cl-C_6H_5
32d	2-Cl-5-CH_3-C_6H_3
32e	2,3-$(CH_3)_2C_6H_3$
32f	2-OCH_3-C_6H_4
32g	2-CH_3-C_6H_4
32h	4-CH_3-C_6H_4
32i	2-NO_2-C_6H_4
32j	4-NO_2-C_6H_4

Synthesis of several β-substituted dehydrophenylalanines derivatives of benzo[*b*]thiophene nucleus was carried out by Abreu *et al.* and screening of antibacterial activities with two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram positive bacteria (*Bacillus subtilis* and *Bacillus cereus)* and of antifungal activity with *Candida albicans* for compounds **(33-38)**. The compounds tested were not active against *Pseudomonas aeruginosa*, starting from DMSO solutions of 6000 μg**/**mL of each compound. Compounds **33** and **34** were also not active against *Escherichia coli,* but were the only ones active against *Candida albicans,* **33** (MIC = 6 μg**/**mL) being more active than **34** (MIC = 600 μg**/**mL) and than cyclohexamide (MIC = 12.5 μg**/**mL). Against Gram-positive bacteria **33** was more active against *B. cereus,* but **35** showed a lower MIC, even lower than ampicillin, against *B. subtilis.* Against *Escherichia coli*, indoles **37** and **38** were more active (MIC = 0.06 μg**/**mL) than thienoindole **36** (MIC = 0.6 μg**/**mL). All the cyclized products were active against Gram-positive bacteria, presenting lower MICs than their precursors **33**, **34** and ampicillin, indole **35** being the most active compounds in this series (MIC = 0.006 μg**/**mL) [31].

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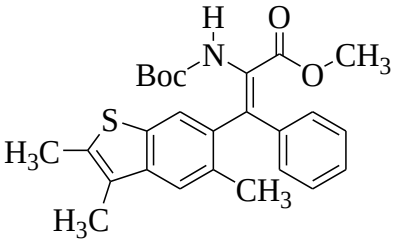

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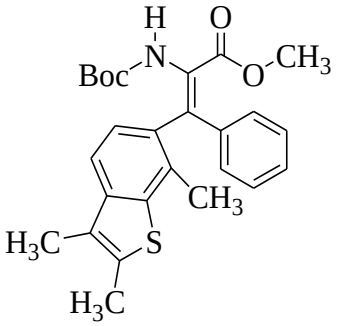

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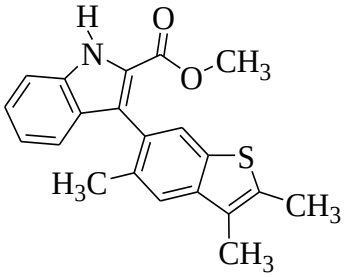

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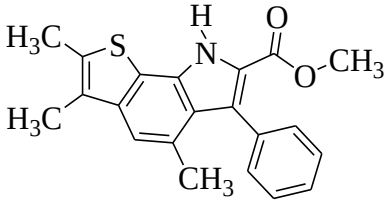

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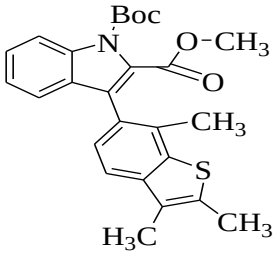

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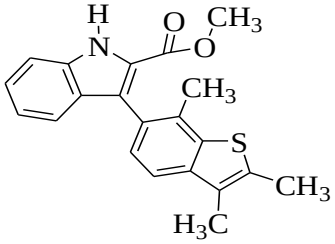

(38)

A novel series of benzothiophene compounds was synthesized by Narayana *et al*. The newly synthesized compounds **(39, 40)** were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Stapyhlococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATTC-27853) and *Klebsiella pneumonia* bacterial stain by disc diffution method by using Furacin as standard drug. One compound exhibited promising antimicrobial activity when compared with standard drug [32].

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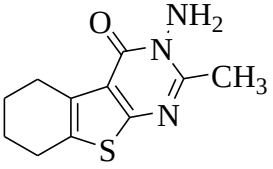

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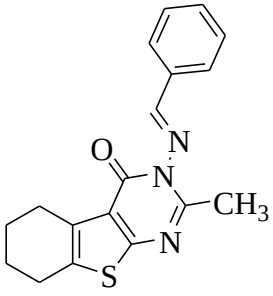
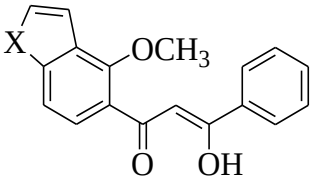


(40)

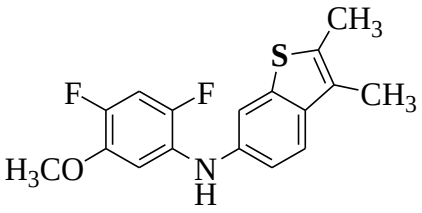
An efficient route for the synthesis of β-hydroxychalcones **(41)** containing benzofuran and benzothiophene rings was described by Yadav *et al*. As a part of ongoing interest in the study of furanoflavonoids and their heterocyclic analogues, they had previously reported synthesis of nitrogen and sulfur heterocyclic analogues and their antimicrobial activities. Some compounds showed god antimicrobial activity when compared with the standard drug [33].



X= O, S

(41)

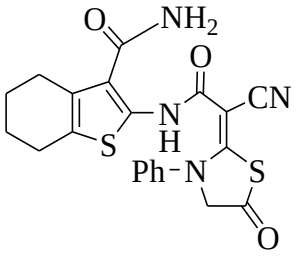
Gram-positive *(Bacillus cereus, B. subtilis)*, Gram-negative *(Pseudomonas aeruginosa, Escherichia coli)* bacteria, and *Candida albicans* as a representative of fungi were used for screening the *in-vitro* antimicrobial activity of diarylamines in the 2,3,5-trimethylbenzo[b]thiophene **(42)** series bearing different substituents were synthesized by Ferreira *et al*. The minimal inhibitory concentration (MIC) and structure-activity relationships (SARs) were evaluated. Some compounds showed god antimicrobial activity when compared with the standard drug [34].



(42)

Antimicrobial activity some of the new synthesized compounds **(43-50)** were screened *in-vitro* for their antimicrobial activity by Gouda *et al*. The diameter of inhibition of zone was measured as an indicator for the activity of the compounds using the Ampicillin as reference

drug. The result for anti bacterial activity revealed that compounds **43, 44, 45, 46, 48,** and **49** exhibited good activities against the reference chemotherapeutics while few compounds showed moderate antibacterial activity. Also compound **50b** exhibited moderate activities against *Klebsiella pneumonia* and negative against *theringiensis*, On the other hand, most of the prepared compounds exhibited moderate antifungal activity against the reference drug, where **44, 47, 48** and **49** exhibited good antifungal activities against *Fusarium oxysporum*. Also, compounds **50a, 50b** exhibited good antifungal activity against *F. oxysporum* and negative against *B. Fabe*. It was worth metioning that the incorporation of benzothiophene nucleus to thaizole or pyrazole moieties caused significance activity against *B. theringiensis, K. pneumonia, B. fabe* and *F. oxysporum* [35].



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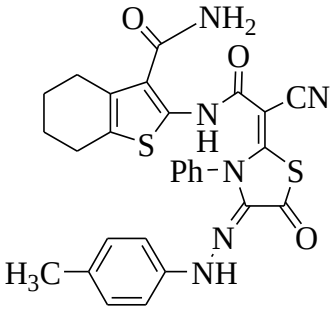

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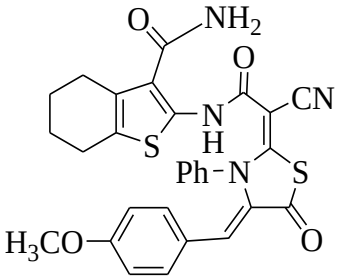

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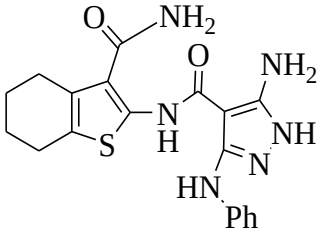

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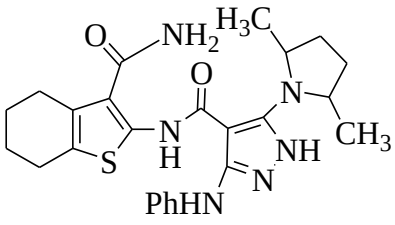

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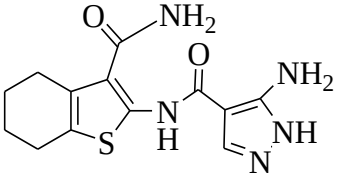

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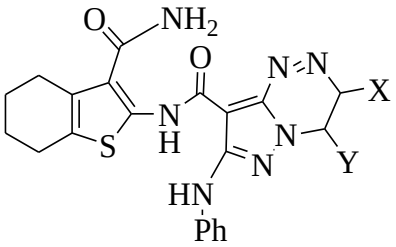
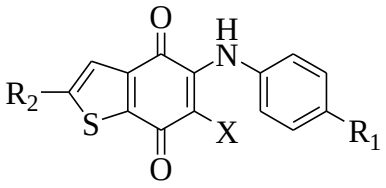


	X	Y
50a	NH_2	CN
50b	CH_3	$COCH_3$

(50a-b)

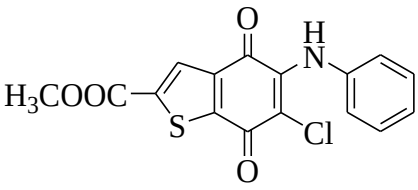
5-Arylamino-4,7-dioxobenzo[*b*]thiophenes **(51–58)** were synthesized and tested for *in-vitro* antifungal activity against *Candida* and *Aspergillus* species by Ryu *et al*. In term of SAR, the result suggested that 5-Arylamino-6-chloro-2-(methoxycarbonyl)-4,7-dioxobenzo[*b*]thiophenes (**53)** showed more potent antifungal activity against *Candida* species and *A.niger* than the other 4,7-dioxobenzo[*b*]thiophenes **51, 52** and **54** although many compounds of them exhibited good activity against *C. tropicalis* and *C. krusei*. The 6-chloro and 2-methoxy carbonyl moieties of compound **53** apears to contribute partially towards biological potency. In contrast 2-hydroxymethyl moiety did not improve their antifungal activity in comparison to compound **53** significantly. MIC values were determined by comparison with 5-fluorocytosine as a standard agent. Most of the 5-arylamino-2-hydroxymethyl-4,7-dioxobenzo[b]thiophenes **52** showed potent antifungal activity against *C. tropicalis, C.krusei* and *A.niger*. Most of compounds **(51-58)** were superior or comparable to those of 5-fluorocytosine against *C. tropicalis*. The activity of 4,7-dioxobenzo[b]thiophenes **55** and **56** was superior to those of 5-fluorocytosine against all tested fungi. The compounds **55** and **56** completely inhibited the growth of all fungal species tested at the MIC level of 12.5 µg/mL. In addition, the 4,7-dioxobenzo[b]thiophenes **55** and **56** without a 5-arylamino group exhibited poor antifungal activity. Thus 5-arylamino moiety of 4,7-dioxobenzo[b]thiophenes 3-6 partially improved the antifungal activity [36].



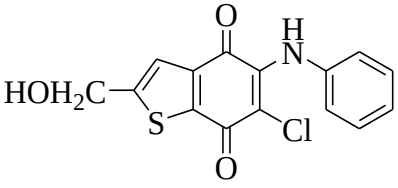
R_1= H, F, Cl

51) $\mathbf{R_2}$= CO_2Me; X=H
52) $\mathbf{R_2}$= CO_2OH; X=H
53) $\mathbf{R_2}$= CO_2Me; X=Cl
54) $\mathbf{R_2}$= CH_2OH; X=Cl

(51-54)



(55)



(56)

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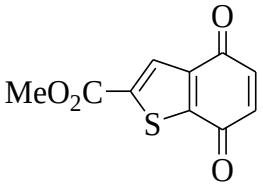
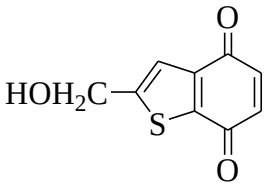
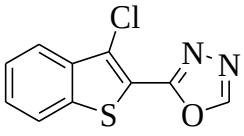


(57)

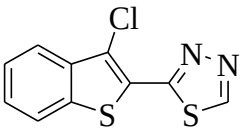


(58)

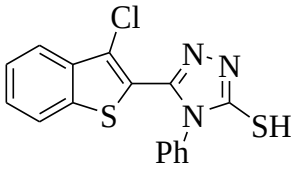
Sharba *et al.* reported synthesis of compounds derived from benzo[b]thiophene containing oxadiazole, thiadiazole and triazole moieties, with the purpose of investigating in the future their possible antibacterial and antifungal activities. Derivatives of 1,3,4–oxadiazole **(59)** and 1,3,4–thiadiazole **(60)** had been found to possessed a wide spectrum of pharmacological activities. Schiff bases had also been widely reported to be biologically versatile compounds having antifungal activity. Moreover derivatives of 1,2,4-triazole **(61)** were known to exhibit antimicrobial actviity. Some compounds showed better antimicrobial activity when compared with the standard drug [37].



(59)



(60)



(61)

CONCLUSION

Due to the presence of sulphur in the heterocyclic compounds skeleton like benzothiophene, it shows diverse pharmacological activities. On the basis of most recent literature review compiled in this manuscript, it is concluded that the various substituted benzothiophene derivatives show potent antimicrobial activities against various bacterial and fungal stains by different mode of actions. The valuable information given in this review article may help medicinal chemists for drug design of novel antimicrobial agents to deal with problem of increasing microbial resistance for effective treatment of various types of microbial diseases.

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