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Graphical Abstract

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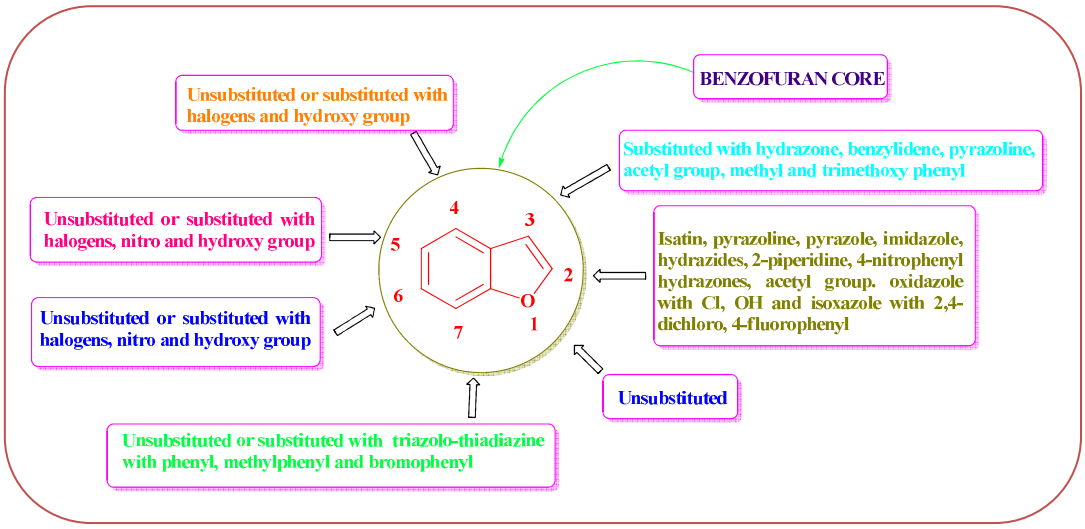
The present article systematically gives a comprehensive review in current development of benzofuran-based compounds as antimicrobial agents and the perspectives that they hold for future research.



Benzofuran: An emerging scaffold for antimicrobial agents

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Abstract

Resistance to antibiotics is a major global problem and there is an urgent need to develop new therapeutic agents. Although, many such class of active compounds have been established as efficient derivatives in diverse fields of antimicrobial therapy, they have not yet found wide applications against few deadly microbes. In the recent years, the compounds developed have solved some of the problems as improved bioavailability is one of the targets achieved with most of the more recent compounds allowing for once-daily dosing. Benzofuran and its derivatives are found to be suitable structures, existing widely in natural products and unnatural compounds with wide range of biological and pharmacological potentials; thus, much attention has been paid for chemist and biologist for discovery of new drugs in the fields of drug inventions and developments. Some of its derivatives like psoralen, 8-methoxypsoralen and angelicin have been used for the treatment of skin diseases such as cancer or psoriasis. The unique structural features of benzofuran and its wide array of biological activities made it privileged structure in drug discovery, especially as efficient antimicrobial candidates. Recently, this scaffold has emerged as a pharmacophore of choice for designing antimicrobial agents active on different clinically approved targets. To pave the way for future research, there is a need to collect the latest

information in this promising area. In the present review, we collated the published reports on this versatile core to provide a deeper insight so that its full therapeutic potential can be utilized for the treatment of microbial diseases. This work systematically provides a comprehensive report on current developments in benzofuran-based compounds as antimicrobial agents, and is also helpful for the researchers to work on the substitution pattern around the nucleus with an aim to help medicinal chemists to develop structure activity relationships (SAR) on this derivative as antimicrobial drugs.

Key words: Benzofuran, Synthesis, Biological activity, Antibacterial, Antifungal

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1. Introduction

The contagious microbial diseases are increasing with course of time round the world due to the emergence of new multidrug resistant bacteria because of the development of mutagenicity.[1] They are a major cause of morbidity and mortality especially, in immune suppressed and the patients were acquired by hospitals.[2] This challenge is the conscious usage of the currently marketed antibiotics and also development of novel efficient antibiotic agents is more crucial than ever.[3,4] In view of this, it is imperative to discover new chemotherapeutic agents to prevent the emergence of resistance and ideally shorten the duration of therapy. In this perspective, one of the best ways to design new antimicrobial agents is, to synthesis/generate bioactive heterocyclic moieties in a single molecular scaffold.

Heterocyclic ring systems are the powerful backbones for many biological properties. Among the heterocyclic compounds, benzofuran is an important class of compounds occupied its place in numerous bioactive natural products and was first time synthesized by Perkin in 1870.[5] After that, the research and developments of benzofuran-based biologically active compounds has been quite a rapidly developing and increasingly active field due to their wide potential applications as medicinal drugs (pharmaceuticals), agrochemicals, molecular electronic and functional polymers man-made materials, artificial acceptors, supramolecular ligands, and so on.[6] Especially, the applications of benzofuran derivatives in medicinal chemistry have achieved great progress. Many benzofuran-anchored drugs play an important role in the treatment of various types of diseases, and new benzofuran derivatives with medicinal value are being actively explored worldwide.[7] The accepted name for ring system **1** in chemical abstracts is benzo*(b)*furan. In order to shorten, *(b)* is conveniently dropped and it is commonly known by the generic name benzofuran. The name, coumarone used in the earlier literature for this nucleus is

now rejected. The positions of benzofuran ring are numbered starting from heteroatom as shown in figure 1.

Insert Figure 1

Benzofuran derivatives exhibit significant activity against several viruses including antifungal[8,9], antiprotozoal[8] antitubercular[10], antiinflammatory[11], anticonvulsant[12], anticancer[13], antiHIV[14], analgesic[15], antiparasitic[16], antihyperlipidemic[17], antioxidant[18], antidiabetic[19], antihypertensive[20], antiplasmodial[21], Alzheimer's[22], vasodilating and hypotensive[23], arrhythmic activities[24] and so on. Moreover, some of the benzofuran derivatives have been demonstrated to be potent topoisomerase I inhibitors[25], sigma receptors[26], Pim-1 inhibitors[27], farnesyl transferase inhibitors[28], Histamine H_3 Receptor[29] and carbonic anhydrase inhibitors.[30] On the other hand, this heterocyclic compound found in various branches of chemical research namely, in polymer and[31, 32], dyes industries[33, 34] and in silver photography.[35, 36] Benzofuran derivatives are important heterocycles frequently found in both, bioactive compounds and organic materials. To list a few benzofuran derivatives that are actively used in pharmacological field are illustrated in Figure 2. The members of the furocoumarin class of natural products including psoralen **2**, 8-methoxypsoralen **3** and angelicin **4** can cross-link with DNA upon light irradiation. As a result they have been used for the treatment of skin diseases such as cancer or psoriasis.[37-40] The natural product coumestrol **5** is found especially, in soya beans and has estrogenic activity.[41] Synthetic bioactive compounds containing benzofurans are also important as exemplified by amiodarone **6**, which is an antiarrythmic drug.[42,43] Recently, benzofurans have also emerged as an important structural elements for organic materials such as the organic transistor **7**.[44] *(-)*-1-

(Benzofuran-2-yl)-2-propylaminopentane {*(-)*-BPAP} **8** is another benzofuran-based drug used as a catecholaminergic and serotonergic activity enhancer. This stimulates the impulse propagation mediated transmitter release of the neurotransmitters dopamine, norepinephrine and serotonin in the brain.[45] 5-(2-Aminopropyl)-2, 3-dihydrobenzofuran (5-APDB) **9** and 6-(2-aminopropyl)-2,3-dihydrobenzofuran (5-APDB) **10** are putative entactogen drugs of the phenethylamine and amphetamine classes.[46] 5-(2-Aminopropyl)benzofuran (5-APB) **11** and 6-(2-aminopropyl) benzofuran(6-APB) **12** are triple monoamine reuptake inhibitor[47,48] and also an agonist of the 5-HT_2C receptor.[48] This agonists for 5-HT_{2B} makes it likely that 5-APB would be cardiotoxic with long term use, as seen in other 5-HT_{2B} agonists such as fenfluramine and MDMA. 6-APB is an entactogenic compound of the phenethylamine and amphetamine classes.[49]

Insert Figure 2

Therefore, the vast range of biological effects associated with this scaffold has resulted in the benzofuran ring system being considered as a privileged structure. This has been strongly promoting much effort to focus on benzofuran-based medicinal agents, and the expanding research and developments have become rapidly developing and increasingly active domains of research, and are almost extended to the whole range of medicinal field. It is still a challenge for the pharmaceutical chemist to develop more effective and less toxic agents to treat infectious diseases. A large amount of effort has been invested in the past decade to develop benzofuran-based compounds as microbial agents that are active on different clinically approved therapeutic targets showing excellent therapeutic potency.

A spectrum of pharmacological activities exhibited by benzofuran and its derivatives has been reviewed by some researchers[50], but, in this review we focused on the applications of benzofuran scaffolds (as organic molecules, inorganic complexes and natural occurrence

together) as antimicrobial agents in details. By looking into the importance of this therapeutic area we decided to collect the literature on antimicrobial potency of benzofurans, the indispensable anchor in medicinal chemistry. In this review, we have attempted to shed light and compile published reports on benzofuran derivatives along with some opinions on different approaches to help the medicinal chemists in designing future generation potent yet safer antimicrobial agents. The purpose of this review is to update the most recent reports on the development of microbial agents as potential drug candidates for the treatment of infectious diseases.

2. Chemistry of Benzofuran

Benzofurans are a class of very important heterocyclic compounds existing widely in natural products and unnatural compounds with biological and pharmacological potentials. It is therefore little surprising that an enormous amount of research has been carried out to develop efficient synthetic methods for their assemblies. The most pertinent and often employed strategies involve the one-pot etherification and dehydrative cyclization of *o*-hydroxyacetophenones **13** under basic conditions.[51] The dehydrative cyclization of *o*-hydroxybenzyl ketones **16** or *R*-(phenoxy)alkyl ketones **17** (Figure 3)[52] and the cyclization of aryl acetylenes using transition-metal catalysis.[53] Although, numerous synthetic approaches have been developed to prepare this family of compounds in the past decades, general protocols for the synthesis of these compounds are still of high interest.[50]

Insert Figure 3

3. Structural requirements of Benzofuran derivatives for antimicrobial activity

A close proximity exists between the chemistry of furan and benzofuran. The increased stabilization of benzofuran compared with furan is due to annexation of benzene ring. Like furan,

oxygen contributes 2π electrons to form a 10 π electron system in the case of benzofuran. This compound belongs to a group, which is commonly known as "electron rich" of "π excessive" heteroaromatics. As anticipated of such compounds, benzofuran ring is highly reactive towards electrophilic substitution however; the overall reactivity of furan ring in benzofuran is decreased by the annelated benzene ring. Resonance considerations of such condensed systems indicate that electrophilic substitution should occur at C-3. It is true with the analogous heterocycle, indole, and to some extent with thionaphthene. But, benzofuran undergoes electrophilic substitution almost exclusively at C-2 position, in contrast to the general prediction. This unusual difference in orientation between benzofuran and thionaphthene is realized to be associated with the electronegativity of oxygen and sulphur. Since oxygen is more electronegative than sulphur the unshared electrons around oxygen are held more tightly than those of sulphur. Thus, the strongly electronegative character of oxygen cuts down the extent to which an unshared pair interacts with the two double bonds to form the aromatic system, so that benzofuran behaves to a considerable extent like an olefin. Due to this distortion of electrons, benzofuran would lead to the greater importance of ionic structure **18** and consequently the electrophilic substitution at C-2 position is favored. But, in thianaphthene, the electronegativity of sulphur is secondary to the stabilizing influence of benzene resonance and the ionic structure **19** with a negative charge at C-2 position is of greater importance (Figure 4).[54]

Insert Figure 4

From collected literature, it is found that the benzofuran nucleus substituted at all position with varied substituents has produced potent antimicrobial activity however, the 1-position contains core oxygen and therefore it is unsubstituted. The 2-position of benzofuran may be unsubstituted or substituents with isatin, pyrazoline, pyrazole, imidazole, oxidazole with -Cl, -

OH, hydrazides, 2-piperidine, 4-nitrophenyl hydrazones, acetyl group and 2,4-dichloro-isoxazole, 4-fluorophenyl-isoxazole enhances the antimicrobial activity. Similarly, the 3-position substituted with hydrazone, benzylidene, pyrazoline, acetyl group and methyl group depicted a good activity. The 4-position of the benzofuran may be substituted or unsubstituited but, the substituent on 4-position containging halogens and hydroxyl groups exhibit good antimicrobial activity. The 5- or 6-position of the nucleus may be unsubstituted or substituents with halogens, nitro and hydroxyl groups have also displayed potent antibacterial activity. To exhibit antibacterial activity it is essential that the benzofuran containing halogens, nitro and hydroxyl groups at position 4,5,6 is a must. Benzofuran with triazolo-thiadiazine with phenyl, methylphenyl and bromophenyl at 7-position displayed good antimicrobial activity (Figure 5).

Insert Figure 5

4. Benzofuran derivatives as antimicrobial agents

Nowadays a number of common and uncommon bacteria previously susceptible to common antimicrobials are reported to have developed resistance to diverse antibiotics. Initially, these bacteria caused significant nosocomial infections and were the cause of major morbidity and mortality in patients. More recently, they have spread to community, causing severe illnesses in previously healthy and otherwise non-vulnerable patients.[55-58] Owing to this increased microbial resistance, new classes of antimicrobial agents with their mode of action are today's need to fight against the multidrug-resistant infections.

Mohamed *et. al.,* reported the synthesis of a series of benzofuran-based pyrazoline-thiazoles **21(a-d)** and fluorinated pyrazole-thiazole **(22-26)** derivatives and tested for their potential antimicrobial activities against four Gram-positive bacteria (*Staphylococcus aureus* (*S. aureus (SA)), Bacillus subtilis (B. subtilis (BS)), Bacillus megaterium (B. megaterium (BM)),*

Sarcinalutea), and Gram-negative bacteria (*Klebsiella pneumoniae (K. pneumonia (KP)), Pseudomonas aeruginosa (P. aeruginosa (PA)), Escherichia coli (E. coli (EC))*. Among these compounds **21c** displayed excellent antimicrobial activity and highest potency against all tested organisms with respect to reference drugs (ciprofloxacin and ketoconazole). Compounds **21d** and **22b** inhibited the growth of *S. aureus* with the inhibition zone (IZ) of 23 and 20 mm, respectively, while compound **22a** evidenced promising antifungal activities against *K. pneumoniae*, *P. aeruginosa*, and *E. coli* with the IZ of about 24 mm. Also, compound **21c** showed the highest activity against *S. aureus*, *S. cerevisiae*, and *C. albicans* with IZ of about 23 mm. SAR study reveals that, the presence of -chloro substituent on pyrazoline and pyrazole moieties (**21c** and **22a)**, increases the antimicrobial activities (Figure 6).[59]

Insert Figure 6

In the literature we found that, the antimicrobial activity of benzofuran derivatives appears to be dependent on substitution at the heterocyclic furan ring than that of aromatic moiety.[60] Telvekar and co-workers investigated a series of benzofuran-3-carbohydrazide derivatives and screened for their potential antifungal activity against *candida albicans* (*C. albicans)*. The combination of unsubstituted benzylidene and chloro di-substituted benzofuran ring evinced greater activity compared to the activity of other members. Whereas, in the case of benzofuran derivative substituted with two electron withdrawing groups **27** the activity was increased around fourfold. The electron withdrawing group on the benzofuran ring and electron donating group on *para* position of aromatic side chain showed good activity **28** (Figure 7).[61]

Insert Figure 7

Structural modification of the clinically approved benzofuran-based antimicrobial drugs is an effective strategy to increase biological activities and broaden the active spectrum of current drugs. Therefore, there are some reports on amidrazone derivatives that were found to possess remarkable biological activities[62,63] and additionally these compounds have been reported as precursors of some effective antifungal azoles.[64] Abdel-Aziz and co-workers presented the synthesis of benzofuran-amidrazones **29(a-e)**, **30(a**,**b)** and **31(a-c)**, and screened for their antifungal/antibacterial activities. These derivatives showed significant antifungal potency, which is more than their antibacterial potency. Compound **30b** exhibited the highest potency against all tested fungal organisms with respect to reference drug, griseofulvin. *C. albicans* (MIC = 75 µg/mL) was the most sensitive fungus with potency of griseofulvin (MIC = 75 µg/mL) followed by *Aspergillus fumigatus* (*A. fumigates), Geotrichum candidum (G. candidum)* and *Syncephalastrum racemosum (S. racemosum)*. Also, same compound exhibited activity (MIC = 75 µg/mL) against *S. aureus*, which is a little lesser than the standard drug amoxicillin (MIC = 50 µg/mL). SAR study reveals that, the piperidine moiety and 4-nitrophenylhydazone functions found essential for the potential antimicrobial activity. Piperidines, which are frequently found in the side chains of therapeutic agents, are not usually associated with pharmacophores; they simply serve as surrogates for open-chain tertiary amines (Figure 8).[65]

Insert Figure 8

3-Methanone-6-substituted-benzofuran derivatives were synthesized by Liu and co-workers, evaluated for their *in vitro* antibacterial activities against *E. coli*, *S. aureus*, *Methicillin-resistant staphylococcus aureus* (*MRSA)*, *B. subtilis*, and *P. aeruginosa*. Some of the compounds **32(a-c)** and **33** with MIC_{80} = 0.78-12.5 µg/mL displayed excellent antibacterial activities compared to the positive controls (cefotaxime and sodium penicillin). Compound **34** and **35**

displayed the strain-specific *to S. aureus* with MIC_{80} = 3.12-12.5 µg/mL. SAR studies reveals that the hydroxyl group at C-6 position of benzofuran is essential for antibacterial activities, and the functional groups at C-3 position play an important role in the antibacterial selectivity of these compounds (Figure 9).[66]

Insert Figure 9

Further, benzofuran skeleton bearing aryl substituents at C-3 position through methanone linker as an antibacterial agent has also been investigated. Compound **36a** with a hydroxyl group at C-4 position, showcased moderate antibacterial activities against *S. aureus* (MIC_{80} = 0.39 mg/mL) and *MRSA* (MIC_{80} = 0.78 mg/mL), with compared to the positive control drugs. On other hand, compounds with methylation of hydroxyl group had reduced the solubility and decrease their antimicrobial abilities, and compounds with halogen substituents showed no antimicrobial activity, where as in the case of compound **36b** had favorable activity against *B. subtilis* (MIC_{80} = 0.78 mg/mL).[67] Chandrashekar *et al.,* demonstrated the synthesis and antimicrobial applications of 5-phenyl-1-benzofuran-2-yl derivatives and the biphenyl methanones **37** and **38(a-c)**. These derivatives exhibited antimicrobial activities with MIC values ranging between 0.001-0.5 µg/mL. The carbinol and tertiary alcohols corresponding to methanone evinced no antimicrobial activity (Figure 10).[68]

Insert Figure 10

Rao and co-workers reported a series of 2,4,6-trimethoxy benzofuran derivatives as antibacterial agents. The synthesized compounds benzofuran carbohydrazide, **39**, displayed excellent activities with IZ of 27 mm and 26 mm against *E. coli* and *S. aureus*, respectively at 25 μg/mL, when compared with standard drug, norfloxacin (IZ = 25 mm) for the same strains. Also benzofuran carboxylic acid **40**, showed remarkable activity against *P. aeruginosa* (IZ = 21 mm) and *S. pyogenes* (IZ = 23 mm) and their SAR study has not been known.[69] Soliman and co-workers described the synthesis of naturally occurring visnagin derivatives and tested for their antimicrobial activity against different bacterial and fungal strains. Surprisingly, these compounds showed better antimycotic activities than the reference drug, fluconazole. Especially, compounds **41** (0.64 μM) and **42** (0.532 μM) demonstrated promising antifungal activity. The tested compounds give higher hindrance activity against *A. flavus* than against *C. albicans*.[70] A series of benzyl-benzofurylcarboxamido benzoxazole derivatives are reported by Yildiz *et al*., and their antimicrobial activity was determined against some Gram-positive and Gram-negative bacteria and fungi. Among the tested derivatives **43(a-d)** evinced higher activity against *P. aeruginosa* than ampicillin (MIC > 500 μg/mL), rifampicin (MIC > 500 μg/mL) and ofloxacin (MIC = 62.5 μg/mL) and had the same potency with gentamycin (MIC = 31.25 μg/mL). Compound **43c** displayed promising activity with a MIC value 15.6 μg/mL against drug-resistant *P. aeruginosa* found more potent than all standard drugs. Compound **43b** carrying benzyl group at the second position of the benzoxazole ring showed remarkable antifungal activity. In addition, attaching a hydrogen or bromine on position "R" played a role for getting a good inhibitory potency. However, substituting position R_1 with the bromine atom, while the main structure was 2-phenylbenzoxazole decreased the inhibitory effect (Figure 11).[71]

Insert Figure 11

Rangaswamy and co-workers reported the synthesis of a new class of functionalized benzofuranyl methoxy phenyl pyrazole scaffolds. The synthesized compounds were evaluated for antibacterial and antifungal activities by the well plate method in Mueller-Hinton agar method. The -chloro, -fluoro, -bromo, and -nitro functionalized derivatives demonstrated better activity while the others showed less activity against all the tested bacterial strains. Compounds **44a** (*p*-fluro substituted) and **44b** (*p*-chlorosubstituted) on the 1-substituted phenyl ring showed significant activity against *P. aeruginosa* and *E. coli* at the concentrations of 1 and 0.5 µg/mL, which is almost 15 times better than the standard drug, streptomycin (12 mm and 17 mm at 0.5 µg/mL). Compounds **44c** (*p*-bromo substituted) and **44d** (*m*-chloro substituted) evidenced similar activity as that of standard, against *E. coli*. Like antibacterial activities, the presence of halogen substituents on the phenyl ring reflected in better antifungal activity compared to other analogues.[72]

Further, a series of benzofuran-based pyrazole derivatives as antibacterial/antifungal agents are reported. Introduction of substituted anilines into pyrazole ring enhanced the antibacterial activity. Compounds **45a** and **45b** possessing *p*-chloro and *p*-fluoro substituents on the 1-substituted phenyl ring showed excellent activity against *P. aeruginosa* and *E. coli* at concentrations of 1 and 0.5 µg/mL. The activity is considerably affected by halogen substituents present at the *para* position of phenyl ring. Whereas in the case of compound **45b** possessing fluoro substituent on phenyl ring at *para*-position accounted for the enhanced antifungal activity against *C. albicans* than the standard drug, fluconazole.[73] Kirilmis and co-workers designed mesitylene substituted benzofuran derivatives for antimicrobial activity against *S. aureus, E. coli*

and *C. albicans*. Among the synthesized compounds, *(E)*-1-(1-benzofuran-2-yl)-2-mesitylethanone-*O*-benzoyloxime **(46)** was found most effective derivative against *S. aureus* and *E. coli* at MIC values of 4 and 32 µg/mL, respectively (Figure 12).[74]

Insert Figure 12

Koca *et al.,* developed a series of benzofuran-ketoxime derivatives as effective antimicrobial agents and among reported, compounds **(51a)** exhibited promising activity (MIC = 0.039 µg/mL) against *S. aureus*. The compounds **47**, **48**, **49b**, **49c**, **50** and **51b** revealed almost the same antimicrobial effect against *C. albicans* (0.625 µg/mL). Compound **(49a)** displayed good antimicrobial effect against *C. albicans* (2.5 µg/mL).[75] Synthesis and antimicrobial efficacies of a series of benzodifuran amide derivatives are reported by Soni *et al*. Compounds indicated higher MIC values (600 µg/mL) against Gram-negative bacteria *P. aeruginosa*, and fungus *C. albicans*. SAR study reveals that the presence of electron withdrawing group at *para* position of amine is responsible for their moderate activity against Gram-positive bacteria *B. subtilis* **52(a-c)**, while the presence of electron releasing group at *para* position of amine showed moderate activity against *S. aureus* (Figure 13).[76]

Insert Figure 13

Triheterocycles with coumarin, benzofuran and furan rings are reported by Khan and co-workers. The synthesized compounds were screened against two bacterial and two fungal species by the standard cup plate method. Introduction of monochloro and dichloro substituents on

benzofuran ring enhanced the antimicrobial potency against *Pseudomonas chinchori*, *A. fumigatus*, and *P. wortmanni*. Among the reported compounds, **53(a-e)** derivatives exhibited considerable inhibition of the microbial growth of all the species at 50 μg/mL concentration. SAR studies showed that chlorination to the benzofuran ring enhances both, the antibacterial and antifungal potencies, of the triheterocycles.[77] In a same array, angularly fused polycyclic heterocycles with coumarin, benzofuran and pyridine **54(a-f)** rings as antimicrobial agents are reported. All the synthesized compounds inhibited microbial activity against *P. chinchori* at MIC of 25 μg/mL and for antifungal screening, the growth inhibition found at 25 μg/mL concentration against *A. fumigatus*, whereas alongside *P. wortmanni*, these derivatives found active at a concentration of 100 μg/mL.[78]

Abdel-Wahab *et. al.,* reported the synthesis of a series of benzofuranyl nitro arylbutanones and benzofuranyl dihydro aryl thiazolyl pyrazoles derivatives and their antimicrobial activity at 100 μg concentration. The 1-(thiazol-2-yl)pyrazoline **55** revealed excellent antimicrobial activity against Gram-negative bacteria (with a IZ of 25 mm), good activity against Gram-positive bacteria (with a IZ of 17 mm). It is concluded that, benzofuran, pyrazoline, and thiazole moieties are essential for the potential antimicrobial activity.[79] Further, they reported a series of benzofuranylpyrazole derivatives as antimicrobial agents. Compounds (**56-59)** presented promising antifungal activities against *C. albicans*, which is more than the reference compound, fucanazole. Also, compounds **58** and **59** exhibited noticeable antibacterial activities against *B. subitilis* which are better than that of the control, amoxicillin. SAR studies reveal that the benzofuran moieties are essential for antimicrobial activity and increase in the activity is found with the increase in the number of nitrogen atoms. The phthalimide moieties in compounds are also found essential for the potential antimicrobial activities.[80] On the other hand, benzofuran-

thiazole and phenyl pyrazole conjugated compounds as antimicrobial agents are reported. Benzofuran derivatives (**60-65)**, resulted in highest IZ with 30-40 mm against *C. albicans*, which is concluded that the benzofuran, pyrazole, and thiazole moieties are essential for the antimicrobial activity (Figure 14).[81]

Insert Figure 14

Ugale and co-workers developed benzofurano-isatin derivatives as antimicrobial agents. Compound **66a** with a nitro group at C-7 of isatin exhibited significant antibacterial activity against *E. coli* and *P. vulgaris* with the same MIC value of 31.25 µg/mL. Also, the presence of fluoro group at the C-7 position in the case of compound **66b** displayed good activities against *B. subtilis, E. coli* and *P. vulgaris* with an MIC value of 31.25 µg/mL. This derivative found active with compared to standard drugs, ampicillin and norfloxacin. SAR study reveals that the introduction of an electron withdrawing substituent on the isatin nucleus at C-5 and C-7 positions enhances the antibacterial potencial.[82] Shanker Rao and co-workers reported the synthesis of imidazole/thiazole-benzofuran conjugated compounds and their antibacterial and antifungal activities. Compounds **67a** and **68a** indicated an excellent effect on *S. aureus, P. aeruginosa* and *Enterococcus feltis (E. feltis)* bacterial strains. Compounds **67c** and **68a** evinced effective antimicrobial activity against *S. aureus* and *E. coli*. Antifungal activity was carried against two human pathogen fungal species, *A. niger* and *T. virdae.* Compounds **67(a,b)** and **68b** showed significant activities against both the tested organisms.[83] In continuation of this work on benzofuran, they also reported the synthesis of thiazolidinone nucleus bridged with quinoline and benzofuran. Compounds **69a** and **70** showcased highest activities against *Klbesilla pneumona,*

whereas, the compounds **69d** and **70** exhibited highest activities against *E. coli*. Amongst the antifungal activity results, compound **70** demonstrated highest activities against *A. niger* and compounds **69a**, **69d** and **70** showed highest activity against *C. albicans.* Compound **69c** exhibited very good activity against *P. chrysozenous, while* compound **69b** and **70** displayed highest activity against *T. vridar*.[84] The imidazole substituted benzofuran conjugated compounds are reported for along with their antimicrobial potentials. Compounds **71(b**, **c)** displayed effective IZ against *B. subtilis*, while compounds **71a**, **71(c,d)** presented similar level of activity against *F. moniliformae*. Compound **71b** showed comparatively higher activity against *T. viridae* and *F. moniliformae*. From SAR, the activity increased by the presence of halo (-I, -Br and -Cl) groups as substituents at R and R_2-position on the benzene ring and the compounds bearing methyl groups at R_1 or R_2 position in combination with -I and -Br at R position enhanced the activity (Figure 15).[85]

Insert Figure 15

Hadj-Esfandiari and co-workers reported the synthesis of 5-nitroimidazolebenzofuranone and 4-nitroimidazolebenzofuranone derivatives and their antibacterial activity against Gram-positive and Gram-negative bacteria. All 5-nitroimidazole analogues showed a remarkable inhibition evincing their potential antimicrobial activity. Benzofuran with 4-nitroimidazole core or phenyl group, exhibited antibacterial activity with a MIC of 100 µg/mL. Benzofuranone **72**, was slightly superior in inhibiting the growth of *K. pneumona* with MIC of 0.39 µg/mL, which is 2- to 8-fold higher than the 5-nitrobenzimidazole derivatives against Gram-positive bacteria. The antibacterial activity was enhanced by negative

charge of -NO_2 group on C-5 position of imidazole and partial charge on carbonyl oxygen in benzofuran is necessary for the activity.[86] Manna and co-workers reported the synthesis of quinoxalino/benzofuran-pyrazole derivatives under microwave conditions and their antibacterial activity evaluated against seven different multidrug resistant organisms in various concentrations and results were compared with standard fluoroquinolone drugs. Among the reported compounds, **73(a-e)** found better activities against *E. coli, P. aeruginosa, S. typhi* and *S. aureus.* SAR study reveals, the *ortho* substitution in phenyl ring with -OH, -NO_2 and *para* substitution on phenyl ring by -OCH_3 at 5-position of pyrazole ring evidenced the best antibacterial activity against Gram-negative bacteria.[87] Aminopyridine-benzofuran derivatives **74(a-e)** prepared under microwave assisted synthetic protocols and were tested for their antimicrobial activity against *P. aeruginosa* and *S. aureus* and none of the compounds exhibit good antimicrobial activity.[88] Basavaraja *et al.,* reported a series of oxadiazole and pyrazole derivatives incorporating benzofuran core as microbial agents. The compounds bearing chloro substitution, **75a**, and hydroxyl group, **75b**, exhibited potent antimicrobial activity.[89] Abdel-Aziz and co-workers synthesized 2-substituted-3-methylbenzofuran derivatives and screened for their antimicrobial activity. The highest antifungal and antibacterial activities were demonstrated by ethoxymethylene derivative **76** and ethylene **77**, respectively. The presence of pyrazole moiety beside benzofuran ring **(**in the cases of **78** and **79)** impart high antifungal and antibacterial activities. The significant antimicrobial activity of **77** and **80** may be due to the presence of benzofuran moieties in addition to hydrazide function in both the derivatives.[90] Further, they reported the stereoselective synthesis of benzofuran-based piperidinylarylamidrazines and tested them for *in vitro* antimicrobial activity. Compound **81** showed low MIC (25 μg/mL) against *A. fumigatus* and revealed MIC of 75 μg/mL against *C. albicans* compared with standard drug,

griseofulvin which showed 50 and 75 µg/mL against *A. fumigates* and *C. albicans*, respectively. From SAR study, it is concluded that both, the piperidine moiety and 4-nitrophenylhydazine function were essential for the antimicrobial activity (Figure 16).[91]

Insert Figure 16

Rida and co-workers studied a series of benzofuran derivatives containing heterocyclic ring substituents linked to the benzofuran nucleus at C-2 position by a two- to four-atom spacer as potential antimicrobial agents. Compounds were evaluated for their *in vitro* activity against *S. aureus*, Gram-positive bacteria, *E. coli*, Gram-negative bacteria, and *C. albicans*, a fungus and ampicillin and clotrimazole were used as reference drugs. Compound **82** exhibited less activity against *S. aureus* with MIC of 500 µg/mL. SAR study reveals that the presence of a spacer between the heterocyclic substituent and the benzofuran nucleus may be essential for the biological activity.[92] Bis-benzofuran-thiadiazine derivatives were reported as antibacterial and antifungal agents. Compounds containing the phenyl **83a**, methoxyphenyl **83b** and bromophenyl **83c** substituents at C-3 position of triazolo-thiadiazine ring demonstrated promising activity against bacterial and fungal strains. Compound **83b** is highly active against all the tested organisms employed and the IZ found greater than the standard drug neomycin. [93] 2-Substituted and diacetyl benzofurans are reported by Khan *et al.,* using palladium-catalyzed reactions. The compounds demonstrated mild to significant growth inhibition against Gram-positive and Gram-negative bacteria. The isomeric mixture of diacetylbenzofurans emerged as the most potent microbial agent. Especially, 2,3-diacetylbenzofuran **84** as most potent compound. From this data it is concluded that the catalytic site for benzofurans in the target biomolecule are those with at least one hydrophobic pocket and two *H*-bond donors- a polar hydroxylated and imino nitrogen

containing amino acid residues. Also, substitution at the C_{4-7} positions of benzofuran ring and the replacement of 3-acetyl group by other acyl/lower alkyl functionalities are to be envisaged for functional characterization of target biomolecule (Figure 17).[94]

Insert Figure 17

A series of fluorine-substituted benzofuran chalcones, benzofuran-pyrazoles and benzofuran-isoxazoles were synthesized and screened for their antibacterial and antifungal activity, and the results were compared with standards ampicillin and greseofulvin, respectively. Compound **85a** displayed good activity with MIC of 62.5 μg/mL against *S. typhi* and *S. pyogenes*, whereas compounds **85b, 86(a,b)** showed similar antibacterial activity with reference drug, ampicllin. For antifungal activity, compounds **85c**, **86c**, **87a** and **87b** evinced better activity than reference drug, greseofulvin against *C. albicans*.[95] Further, a series of fluorine containing benzofuran-pyrimidine conjugates as antimicrobial agents are reported. Compounds **88 (a-c)** showed excellent antibacterial activities against *S. pyogenes,* which is similar with the activity of reference drug, ampicillin. For antifungal activity compounds **88(b,c)** showed almost similar activity against *C. albicans.*[96] Benzofuran-salicylic acid derivatives as antimicrobial agents were described by Hassan and co-workers. Azo derivatives **89(a-c)** exhibited good antibacterial activity against both Gram-positive and Gram-negative bacteria and compound **90** demonstrated a promising antifungal activity. SAR study reveals that, the substitution of salicylic acid with amino group either at position C-5, C-4, or C-3 was improved the antimicrobial activity.[97] Kenchappa *et. al.,* demonstrated the synthesis and antimicrobial activity of benzofuran barbitone/thiobarbitone derivatives. Compounds **91(a,b)** having two bromo substituents on C-5 of benzofuran and C-4 of phenyl ring, respectively were found to exhibit

excellent antibacterial activity against all the tested bacterial strains with MIC value ranging between 29.76-31.96 μmol/L. Same compounds also exhibited equipotent activity against all fungal strains with MIC value in the range 12.50-66.49 μmol/L. SAR studies reveal that the substitution at the *ortho* position of benzofuran ring and *para* position of aryl ring are responsible for the increased antimicrobial activity. Compounds containing two bromo substituents are accountable for increased antimicrobial activity than those bearing a single halogen/other substituent group.[98] Same group further developed β-amino carbonyl derivatives of benzofuran as antimicrobial agents. From these studies it is concluded that the electron-withdrawing groups substituted on aromatic ring, particularly at the *para* position, **92(a-c)**, exhibited potential antimicrobial activity.[99] Srinivas and co-workers investigated the synthesis of benzofuran-isoxazole and tested for antibacterial and antifungal activity by using serial tube dilution technique, and results were compared with ampicillin and fluconazole as reference standard. Among tested derivatives, compounds **93a** and **93b** possessed maximum activity, which may be due to electron withdrawing substituents such as 2,4-dichlorophenyl and 4-fluorophenyl appended at C-5 position of isoxazole core. Also, the presence of 2-chlorophenyl, 2,4-dichlorophenyl, 4-nitrophenyl **93(a,b)** at C-5 position of isoxazole structure exhibited good antifungal activity. This reveals the importance of the electronic effects of the substituents present on the aromatic ring in enhancing the antibacterial/antifungal activity.[100] Kumar *et al*., invented a series of tricyclic compounds containing benzofuran, benzothiazole and lactum derivatives as antimicrobial agents against *B. subtilus, E. coli* and *C. albicans*. Compounds **94(a-c)** exhibited moderate activities with IZ ranging from 11-17 mm (Figure 18).[101]

Insert Figure 18

5. Benzofuran-based metal complexes as antimicrobial agents

Metal ions play an important role in biochemical processes. Many biochemical reactions depend on the presence of metal ions, which are the part of coordination complexes. There has been an increasing attention in the biological applications of benzofuran-based metal complexes including late transition metals such as cobalt(II), nickel(II), copper(II) and zinc(II) in the last decade. Many of these complexes were evinced considerable antibacterial and anticancer properties in *invitro* and/or *invivo* assays. The choice of a suitable substitution on benzofuran-based ligand system is found crucial in the design of novel target specific bioactive metal complexes. In this section, the important benzofuran-based ligands and their metal complexes reported for potential biological applications are discussed.

Halli and co-workers reported the synthesis of a benzofuran-2-carbohydrazide **95** and its Co(II), Cu(II), Ni(II), Cd(II), Hg(II), Zn(II), UO_2(II) complexes and Th(IV) complexes of phenylisocyanate (BCPT)/*p*-chlorophenylisothiocyanate (BCCIPT). All the complexes and ligands were screened for their potential antimicrobial activity. The Zn(II), Cd(II), Hg(II), Ni(II), and UO_2(II) complexes displayed a significant growth inhibition activity against *Pseudomonas* and *Wild bacillus* bacteria compared with the free ligand BCCIPT and metal ions.[102] Further, a series of mixed ligand complexes of the type [MLL'Cl_2] of Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) derived from benzofuran-2-carbohydrazide and 3,4,5-trimethoxybenzaldehyde, and *ortho*-phenylenediamine/2,6-diaminopyridine **(96, 97)** were reported. All the complexes and ligands were screened for potential antimicrobial activity against bacterial strains. The Zn(II), Cd(II) and Hg(II) complexes evinced potential antimicrobial activity against both, the bacteria and fungi, having higher activity than ligands against the same microorganisms.[103] Furthermore, the complexes of Co(II), Ni(II), Zn(II), Cd(II) and Hg(II) from benzofuran-2-carbohydrazide with 2-acetylthiophene/acetophenone as

microbial agents were reported. The Schiff bases were inactive against all the bacteria tested, while Hg(II) complexes **(98, 99)** showed significantly enhanced activity against both the bacterial, *E. coli* and *S. aureus* and fungal *A. niger* and *A. flavus* strains. All other complexes showed less growth inhibition activity against all bacteria tested.[104-106] Goel *et al.,* synthesized Cu(II) and Fe(III) complexes derived from 2-acetylbenzofuran and semicarbazone/thiosemicarbazone ligands and screened for their antibacterial activities. The metal complexes **(100, 101)** displayed effective antibacterial properties against all the pathogenic bacteria, especially complexes of thiosemicarbazone demonstrated remarkable antibacterial activity. The metal complexes found higher antibacterial activities compared with their respective Schiff base ligands (Figure 19).[107]

Insert Figure 19

6. Benzofuran-based natural products as antimicrobial agents

Natural products play an important role in both drug discovery and chemical biology. In fact, many approved therapeutics as well as drug candidates are derived from natural sources. Benzofuran natural products isolated from the Styracaceae family such as *Styrax japonicum*, *S. formosanus*, *S. obassia*, *S. macranthus* and *S. officinalis* showed variety of biological activities including insecticidal, fungicidal, antimicrobial, antiproliferative, cytotoxic and antioxidant properties.[108-109] Over the years, several newer/modified approaches were adopted for the isolation of benzofuran and the compounds and screened for antibacterial/antifungal activities. All the related compounds their tabulated in Table 1 (Figure 20).

Insert Figure 20

Table 1. List of novel benzofuran derivatives as antimicrobial agents isolated from natural source

S.No.	Species	Family	Compound	Reference(s)
1	*Cotula coronopifolia*	Asteraceae	6-Methoxy-1-benzofuran-4-ol **(102)**	110
2	*Heliotropium filifolium*	Boraginaceae	Methyl-3'-hydroxy-2',2',6'-trimethyl-3*H*-spiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylate **(103)**	111
			3'-Hydroxy-2',2',6'-trimethyl-3*H*-spiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylic acid **(104)**	
			Methyl-3'-acetyloxy-2', 2', 6'-trimethyl-3*H*-spiro[1-benzofuran-2, 1'-cyclohexane]-5-carboxylate **(105)**	
			Methyl-3'-isopentanoyloxy-2',2',6'-trimethyl-3*H*-spiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylate **(106)**	
			Methyl-3'-benzoyloxy-2',2',6'-trimethyl-3*H*-spiro[1-benzofuran-2,1'-cyclohexane]-5-carboxylate **(107)**	
3	*Phomopsis sp.*	**----**	3-(Hydroxymethyl)-6,7-dihydrobenzofuran-4(5*H*)-one	112

			(108)	
4	*Eupatorium aschenbornianum*	Asteraceae	5-Acetyl-3β-angeloyloxy-2β-(1-hydroxyisopropyl)-2,3-dihydrobenzofurane **(109)**	113
			5-Acetyl-3β-angeloyloxy-2β-(1-hydroxyisopropyl)-6-methoxy-2,3-dihydrobenzofurane **(110)**	
5	*Glycyrrhiza*	Xibei licorice	4-(6-Hydroxy-4-methoxy-5-(3-methylbut-2-enyl)benzofuran-2-yl)benzene-1,3-diol or Licocoumarone **(111)**	114
			2-(2,4-Dimethoxyphenyl)-4,6-dimethoxy-5-(3-methylbut-2-enyl)benzofuran **(112)**	
6	*Ligularia veitchiana*	Compositae	1,3-Dimethoxy-4,6-dimethylnaphthofuran **(113)**	115
7	*Cladonia rangiferina*	Cladoniaceae	Ddymic acid **(114)** Condidymic acid **(115)**	116
8	*Achyrocline satureioides*	Asteraceae	1′,1″-[6,7,9-Trihydroxy-8-(2-hydroxy-3-methylbut-3-en-1-yl)-3,3-dimethyl-3*H*-benzofuro[2,3-f]chromene-5,10-diyl]bis(2-*(S)*-methylbutan-1-one) **(116)**	117
			1′,1″-[6,7,9-Trihydroxy-8-(2-hydroxy-3-methylbut-dihydroxy)-	

			3,3-dimethyl-3*H*-benzofuro[2,3-f]chromene-5,10-diyl]bis(2-(S)-methylbutan-1-one) **(117)**	
9	*Dalea spinosa (Psorothamnus spinosus)*	Fabaceae	Spinosan A **(118)** Spinosan A Acetate **(119)** *(+)*-Medicarpin **(120)**	118
10	*Helianthella quinquenervis*	Asteraceae	Euparin **(121)**	119
11	*Stemona aphylla*	Stemonaceae	Stemofuran E **(122)** Stemofuran J **(123)** Stemofuran M **(124)** Stemofuran P **(125)** Stemofuran R **(126)**	120
12	*Gnetum gnemon L*	Gnetacea	Stilbenoid **(127)** Gnetin C **(128)**	121
13	*Allium cepa*	Alliaceae	2-(3,4-Dihydroxyphenyl)-4,6-dihydroxy-2-methoxybenzofuran-3-one **(129)**	122
14	*Caesalpinia pulcherrima*	Leguminosae	Isovouacapenol D or [(4aα,5*β*,11b*β*)-1,2,3,4,4a,5,6,11b-octahydro-	123

			4,4,7,11b-tetramethyl phenanthro[3,2-*b*]furan- 4a,5-diol-5-benzoate] **(130)**	
15	*Murraya koenigii*	Rutaceae	3ε-(1 ε-Hydroxyethyl)-7-hydroxy-1-isobenzofuranone **(131)**	124
16	*Calea platylepis*	Asteraceae/ Heliantheae	Euparin (**132**), Caleprunin A (**133**), Caleprunin B (**134**), Euparone **(135)**	125

7. Conclusions and future aspects

The incidences of bacterial and fungal infections have been increased significantly in the past 25 years. The evolution of resistance in bacterial strains against currently available antibacterial agents is an increasing concern in recent years. In order to overcome the threat of wide spread multidrug resistance in Gram positive and Gram negative bacterial strains as well as fungi, there is ongoing demand for new antimicrobial agents. The discovery of novel drugs in many fields, i.e. antibacterial, has been stalled for many years. There is an urgent need for new pharmaceuticals that have a broader spectrum of activity or act through novel mechanisms of action, i.e. to overcome the increasing incidence of microbial resistance observed for currently used drugs. Numerous outstanding achievements revealed that benzofuran-based compounds are extensively potential antimicrobial agents. To further optimize the complete potential of benzofuran compounds, the SAR-based study will likely continue to play an

important role. It is very likely that optimized benzofuran compounds with excellent potency and little side effects will continue to be created. Some of these benzofuran compounds will undoubtedly be used as antimicrobial therapeutic agents in the near future. The present review, covering literature from last fifteen years, is expected to provide a low height flying bird's eye view of the benzofuran derived compounds to a drug designer and medicinal chemist for a comprehensive and target oriented information for development of clinically viable molecules. Further, future research in this field will bring innovative pharmaceutical developments with a considerable spectrum of use.

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Abbreviations

A. fumigates (AF)	*aspergillus fumigatus*
A. niger (AN)	*aspergillus niger*
APB	aminopropyl benzofuran
APDB	aminopropyl-2, 3-dihydrobenzofuran
B. megaterium (BM)	*bacillus megaterium*
BPAP	benzofuran-2-yl-2-propylaminopentane
B. subtilis (BS)	*bacillus subtilis*
C. albicans (CA)	*candida albicans*
C. glabrata (CG)	*candida glabrata*
DNA	deoxyribonucleic acid
E. coli (EC)	*escherichia coli*
E. feltis (EF)	*escherichia feltis*
F. moniliformae (FM)	*fusarium moniliforme*
G. candidum (GC)	*geotrichum candidum*
HIV	human immunodeficiency virus
IZ	inhibition zone
K. pneumonia (KP)	*klebsiella pneumoniae*
MIC	minimum inhibitory concentration
µg	micro gram
mL	milli litre
ML	*Micrococcus luteus*
mm	milli metre

MRSA	*methicillin-resistant staphylococcus aureus*
P. aeruginosa (PA)	*pseudomonas aeruginosa*
P. chinchori (PC)	*pseudomonas chinchori*
P. vulgaris (PV)	*proteus vulgaris*
P. wortmanni (PW)	*pseudomonas wortmanni*
S. aureus (SA)	*staphylococcus aureus*
SAR	structure activity relationship
S. cerevisiae (SC)	*saccharomyces cerevisiae*
S. pyogenes (SP)	*streptococcus pyogenes*
S. racemosum (SR)	*syncephalastrum racemosum*
S. typhi (ST)	*salmonella typhimurium*
S. mentagrophytes (TM)	*trichophyton mentagrophytes*
T. virdae (TV)	*trichoderma viride*

References

1. Y. He, B. Wu, J. Yang, D. Robinson, L. Risen, R. Ranken, L. Blyn, S. Sheng and E. E. Swayze, *Bioorg. Med. Chem. Lett.,* 2003, **13**, 3253-3256.

2. B.P. Mathew and M. Nath, *ChemMedChem.,* 2009, **4**, 310-323.

3. I. Berber, C. Cokmus and E. Atalan, *Microbiol.,* 2003, **72**, 42-47.

4. W. S. Sung, H. J. Jung, K. Park, H.S. Kim, L.S. Lee and D.G. Lee, *Life Sci.,* 2007, **80**, 586-591.

5. W. H. Perkin, F.R.S, XXIX. *J. Chem. Soc.,* 1870, **23**, 368-371.

6. B.A. Keay, J.M. Hopkins and P.W. Dibble, In: A. R. Katritzky, C.A. Ramsden, E.F.V. Scriven, R.J.K. Taylor, Comprehensive heterocyclic chemistry III, Elsevier, Oxford, 2008.

7. a) S. Shimazu, K. Takahata, H. Katsuki, H. Tsunekawa, A. Tanigawa, F. Yoneda, J. Knoll and A. Akaike, *Eur. J. Pharmacol.,* 2001, **421**, 181-189.

b) S. Shimazu, H. Tsunekawa, F. Yoneda, H. Katsuki, A. Akaike and A. Janowsky, *Eur. J. Pharmacol.,* 2003, **482**, 9-16.

c) J. Knoll, F. Yoneda, B. Knoll, H. Ohde and I. Miklya, *Brit. J. Pharmaco.,* 1999, **128**, 1723-1732.

8. C. Ryu, A. Song, J. Y. Lee, J. Hong, J. H. Yoon and A. Kim, *Bioorg. Med. Chem. Lett.* 2010, **20**, 6777-6780.

9. a) B. F. Abdel-Wahab, H. A. Abdel-Aziz and E. M. Ahmed*, Eur. J. Med. Chem.,* 2009, **44**, 2632-2635.

b) F. Pan and T. C. Wang, *J. Chin. Chem. Soc*., 1961, **8**, 220-225.

c) F. Pan and T.C. Wang, *J. Chin. Chem. Soc.* 1961, **8**, 374-379.

10. a) K. Manna and Y. K. Agrawal, *Eur. J. Med. Chem.,* 2010, **45**, 3831-3839.

b) M. Brandvang, V. Bakken and L. L. Gundersen, *Bioorg. Med. Chem. Lett.*, 2009, **17**, 6512-6516. c) S. M. Bakunova, S. A. Bakunov, T. Wenzler, T. Barszcz, K. A. Werbovetz, J. E. Reto Brun Hall and R. R. Tidwell, *J. Med. Chem.,* 2007, **50**, 5807-5823.

11. F.A. Ragab, N.M. Eid, G.S. Hassan and Y.M. Nissan, *Chem. Pharm. Bull.,* 2012, **60**, 110-120.

12. K.M. Dawood, H. Abdel-Gawad, E.A. Rageb, M. Ellithey and H. A. Mohamed, *Bioorg. Med. Chem.,* 2006, **14**, 3672-3680.

13. M. O. Abdelhafez, K. M. Amin, H. I. Ali, M. M. Abdallad and E. Y. Ahmed, *RSC Adv.,* 2014, **4**, 11569-11579.

14. S.M. Rida, S.A. El-Hawash, H.T. Fahmy, A.A. Hazza and M.M. El-Meligy, *Arch. Pharm. Res.,* 2006, **29**, 16-25.

15. S. Rádl, P. Hezký, P. Konvička and I. Krejčí, *Chem. Comm.,* 2000, **65**, 1093-1108.

16. S.P. Gibson and C. Laurate, Benzofuran antiparasitic agents**,** WO/2008/102232, 2008.

17. K. V. Sashidhara, R. K. Modukuri, R. Sonkar, K. B. Rao and G. Bhatia, *Eur. J. Med. Chem.,* 2013, **68**, 38-46.

18. S. S. Rindhe, M. A. Rode and B. K. Karale, *Indian J. Pharm. Sci.*, 2010, **72**, 231-235.

19. K.A. Reddy, B.B. Lohray, V. Bhushan, A.C. Bajji, K.V. Reddy, P.R. Reddy, T.H. Krishna, I.N Rao, H.K. Jajoo, N.V. Rao, R. T. Chakrabarti, D. Kumar and R. Rajagopalan*, J. Med. Chem.,* 1999, **42**, 1927-1940.

20. B.C. Ross, D. Middlemiss, D. I. C. Scopes, T. I. M. Jack, K. S. Cardwell, M. D. Dowle, J. G. Montana, M. Pass and D. B. Judd, EP0514197 A1, 1992.

21. S. Ravikumar, G. Ramanathan and M. Gnanadesigan, *Asian Pac. J. Trop. Med.* 2012, **5**, 358-361.

22. M. Ono, M.P. Kung, C. Hou and H. F. Kung, *Nucl. Med. Biol.,* 2002, **29**, 633-642.

23. M. B. Isman, P. Proksch and L. Witte, *Arch. Insect. Biochem. Physiol.*, 1987 **6**, 109-120.

24. M. B. Isman, In insecticides of plant origin; J. T. Arnason, B. J. R. Philoge'ne, P. Morand, ACS Symposium Series 387, Washington, DC, 1989, 44-58.

25. K. Suzuki, T. Okawara, T. Higashijima, K. Yokomizo, T. Mizushima and M. Otsuka. *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2065-2068.

26. K.S. C. Marriott, A. Z. Morrison, M. Moore, O. Olubajo and L. E. Stewart*, Bioorg. Med. Chem. Lett.,* 2012, **20**, 6856-6861.

27. Y. Xiang, B. Hirth, G. Asmussen, H-P. Biemann, K. A. Bishop, A. Good, M. Fitzgerald, T. Gladysheva, A. Jain, K. Jancsics, J. Liu, M. Metz, A. Papoulis, R. Skerlj, J. D. Stepp and R. R. Wei*, Bioorg. Med. Chem. Lett.,* 2011, **21**, 3050-3056.

28. K. Asoh, M. Kohchi, I. Hyoudoh, T. Ohtsuka, M. Masubuchi, K. Kawasaki, H.Ebiike, Y. Shiratori, T. A. Fukami, O. Kondoh, T. Tsukaguchi, N. Ishii, Y. Aoki, N. Shimma and M. Sakaitani, *Bioorg. Med. Chem. Lett.,* 2009, **19**, 1753-1757.

29. M. Sun, C. Zhao, G. A. Gfesser, C. Thiffault, T. R. Miller, K. Marsh, J. Wetter, M. Curtis, R. Faghih, T. A. Esbenshade, A. A. Hancock and M. Cowart, *J. Med. Chem.*, 2005, **48**, 6482-6490.

30. S. L. Graham, J. M. Hoffman, P. Gautheron, S. R. Michelson, T. H. Scholz, H. Schwam, K. L. Shepard, A. M. Smith and R. L. Smith, *J. Med. Chem.*, 1990, **33**, 749-754.

31. B. Pourabas and A. Banihashemi, *Polym. Int.,* 2002, **51**, 1086-1099.

32. J. Xu, G. Nie, S. Zhang, X. Han, S. Pu, L. Shen and Q. Xiao*, Eur. Polym. J.,* 2005, **41**, 1654-1661.

33. C.H. Chen, N.Y. Fairport, L. J. Fox and Md. Balmnore: Novel benzofuran dyes, US 4900831 A, 1990.

34. C. H. Chen and J. L. Fox: Novel benzofuran dyes, US 4948893 A, 1990.

35. R. Sato, K. Kato, T. Sasaki, H. Sugit, Silver halide photosensitive materials for color photography, EP 0148536 A2, 1985.

36. H. Odenwalder, H. Langen, J. Hagemann, K. Henseler, Color photographic silver halide, material US 5981160 A, 1999.

37. P.S Song and K. J. Jr. Tapley, *Photochem. Photobiol.*, 1979, **29**, 1177-1197.

38. F. P. Gasparro, R. Dallamico, D. Goldminz, E. Simmons and D. Weingold, *Yale J. Biol. Med.,* 1989, **62**, 579-593.

39. S. Caffieri, *Photochem. Photobiol. Sci.,* 2002, **1**, 149-157.

40. L. Santana, E. Uriarte, F. Roleira, N. Milhazes and F. Borges, *Curr. Med. Chem.,* 2004, **11**, 3239-3261.

41. E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson and F. Deeds, *Science,* 1957, **126**, 969-970.

42. J. W. Mason*, N. Engl. J. Med.,* 1987, **316**, 455-566.

43. F. Bogazzi, L. Tomisti, L. Bartalena, F. Aghini-Lombardi and E. Martino, *J. Endocrinol. Invest.*, 2012, **35**, 340-348.

44. C. Mitsui, J. Soeda, K. Miwa, H. Tsuji, J. Takeya and E. Nakamura, *J. Am. Chem. Soc.,* 2012, **134**, 5448-5451.

45. F. Yoneda, J. Knoll, H. Ode, M. Sakae, M. Katurada, T. Moto, T. Ando, S. Shimazu, K. Takahata, M. Fujimoto, Ethylamine derivatives, US Patent 6214859, 2001.

46. A.P. Monte, D. Marona-Lewicka, N.V. Cozzi and D.E. Nichols, *J. Med. Chem.,* 1993, **36**, 3700-3706.

47. P. Dawson, J. Opacka-Juffry, J.D. Moffatt, Y. Daniju, N. Dutta, J. Ramsey and C. Davidson. *Prog. Neuro-psychoph. Bio. Psy.,* 2014, **48**, 57-63.

48. L. Iversen, S. Gibbons, R. Treble, V. Setola, X. P. Huang and B.L. Roth, *Eur. J. Pharmaco.* 2012, **700**, 147-151.

49. K. Briner, J. P. Burkhart, T. P. Burkholder, M. J. Fisher, W. H. Gritton, D.T. Kohlman, S. X. Liang, S. C. Miller, J. T. Mullaney, Y.C. Xu and Y. Xu, US patent 7045545, 2006.

50. a) R. Naik, D. S. Harmalkar, X. Xu, K. Jang and K. Lee, *Eur. J. Med. Chem.*, 2015, **90**, 379-393.

b) A. Radadiya and A. Shah, *Eur. J. Med. Chem.,* 2015, **97**, 356-376.

c) R. J. Nevagi, S. N. Dighe and S. N. Dighe, *Eur. J. Med. Chem.*, In press; 2015, doi: http://dx.doi.org/10.1016/j.ejmech.2014.10.085.

d) K. M. Dawood, *Expert Opin. Ther. Pat.,* 2013, **23**, 1133-1156.

e) M. G. Kadieva and É. T. Oganesyan, *Chem. of Heterocycl. Comp.*, 1997, **33**, 1245-1258.

f) H. Khanam and Shamsuzzaman, *Eur. J. Med. Chem.* 2015, **5**, 483-504.

51. (a) N. G. Karaburun, K. Benkli, Y. Tunali, Ü. Uçucu and Ş. Demirayak, *Eur. Med. Chem.*, 2006, **41**, 651-656.

(b) D. Bogdal and M. Warzala, *Tetrahedron,* 2000, **56**, 8769-8773.

(c) A.R. Katrizky, Y. Ji, Y. Fang and I. Prakash, *J. Org. Chem.,* 2001, **66**, 5613-5615.

(d) K. Ando, Y. Kawamura, Y. Akai, J. Kunitomo, T. Yokomizo, M. Yamashita, S. Ohta, T. Ohishi and Y. Ohishi, *Org. Biomol. Chem.,* 2008, **6**, 296-307.

52. (a) W. Boehme, *Org. Synth.,* 1953, **33**,43-46.

(b) R. Adams, L. Whitaker, Quinone Imides. XXXIX. Adducts of quinone monoimides and conversion of active methylene adducts to benzofurans, J. Am. Chem. Soc. 1956, **78**, 658-663.

53. (a) A. Arcadi, S. Cacchi, M. D. Rosario, G. Fabrizi and F. Marinelli, *J. Org. Chem.*, 1996, **61**, 9280-9288.

(b) C. Amatore, E. Blart, J. P. Genet, A. Jutand, S. Lemaire-Audoire and M. Savignac, *J. Org. Chem.* 1995, **60**, 6829-6839.

(c) A. Sogawa, M. Tsukayama, H. Nozaki and M. Nakayama, *Heterocycles,* 1996, **43**, 101-111.

(d) S. Cacchi, G. Fabrizi and L. Moro, *Tetrahedron Lett*., 1998, **39**, 5101-5104.

(e) A. Furstner, and P.W. Davies, *J. Am. Chem. Soc.,* 2005, **127**, 15024-15025.

(f) J. Oppenheimer, W. Johnson, M. Tracey, R. Hsung, P. Y. Yao, R. Liu and K. Zhao, *Org. Lett.,* 2007, **9**, 2361-2364.

(g) V. Patel, G. Pattenden and J. Russell, *Tetrahedron Lett.*, 1986, **27**, 2303-2306.

54. A. Weissberger, and E.C. Taylor, *Chemistry of heterocyclic compounds*, 1974, **29**, John Wiley & Sons, New York.

55. P. Frohberg, C. Kupfer, P. Stenger, U. Baumeister and P. Nuhn, *Arch. Pharm.,* 1995, **328**, 505-516.

56. J. Debord, P. N. Diaye, J.C. Bollinger, K. Fikri, B. Penicaut, J.M. Robert, P.S. Robert and G. Le-Baut, *J. Enzyme Inhib.* Med. Chem., 1997, **12**, 13-26.

57. E.S.H. El Ashry, N.A. Rashed and H.S. Shobier, *Pharmazie,* 2000, **55**, 403-415.

58. J.M. Robert, O. Rideau, S.R. Piessard, M. Duflos, G. LeBaut, N. Grimaud, M. Juge and J.Y. Petit, *Arzneim.-Forsch./Drug Res.,* 1997, **47**, 635-642.

59. H. A. Mohamed, E. Abdel-Latif, B. F. Abdel-Wahab and G.E. A. Awad, *Inter. J. Med. Chem.,* In press ; 2013, http://dx.doi.org/10.1155/2013/986536.

60. E.P. Davies, J.D. Pittam, K.B. Mallion and N.P. Taylor, Process for preparing an antifungal azole with hydrazino and amidrazone intermediates, US patent 5861516, 1999, 19.

61. V. N. Telvekar, A. Belubbi, V. K. Bairwa and K. Satardekar, *Bioorg. Med. Chem. Lett.,* 2012, **22**, 2343-2346.

62. M.G. Mamolo, V. Falagiani, L. Vio and E. Banfi, *Farmaco,* 1999, **54**, 761-767.

63. D. Ranft, G. Lehwark-Yvetot, K.J. Schaper and A. Buge, *Arch. Pharm.,* 1997, **330**, 169-172.

64. D. Ranft, T. Seyfarth, K. Schaper, G. Lehwark-Yvetot, C. Bruhn and A. Buge, *Arch. Pharm.,* 1999, **332**, 427-430.

65. H.A. Abdel-Aziz and A.A.I. Mekawey*, Eur. J. Med. Chem.,* 2009, **44**, 4985-4997.

66. J. Liu, F. Jiang , X. Jiang, W. Zhang, J. Liu, W. Liu and L. Fu, *Eur. J. Med. Chem.,* 2012, **54**, 879-886.

67. X. Jiang, W. Liu, W. Zhang, F. Jiang, Z. Gao, H. Zhuang and L. Fu, *Eur. J. Med. Chem.,* 2011, **46**, 3526-3530.

68. A. Chandrashekar, E. Bheemappa, Y. D. Bodke, V. K. Bhovi, R. Ningegowda, M. C. Shivakumar, S.K. Peethambar and S. Telkar, *Med. Chem. Res.,* 2013, **22**, 78-87.

69. V. K. Reddy, J. V. Rao, L. B. Reddy, B. Ram and B. Balram, *Der Pharma Chemica,* 2013, **5**, 237-242.

70. S.S. EI-Nakkady, H.F. Roaiah, W.S. El-Serwy, A.M. Soliman, S.I. Abd-EI-Moez and A.A. Abdel-Rahman, *Acta Pol. Pharma.,* 2012, **69**, 645-655.

71. S. Alper-Hayta, M. Arisoy, Ö. Temiz-Arpaci, I. Yildiz, E. Aki, S. Özkan and F. Kaynak, *Eur. J. Med. Chem.,* 2008, **43**, 2568-2578.

72. J. Rangaswamy, H. Vijay Kumar, S. T. Harini and N. Naik, *Arab. J. Chem.*, in press; 2013, doi:10.1016/j.arabjc.2013.10.012.

73. J. Rangaswamy, H. Vijay Kumar, S. T. Harini and N. Naik*, Bioorg. Med. Chem. Lett.*, 2012, **22**, 4773-4777.

74. C. Kirilmis, M. Ahmedzade, S. Servi, M. Koca , A. Kizirgil and C. Kazaz, *Eur. J. Med. Chem.,* 2008, **43**, 300-308.

75. M. Koca, S. Servi, C. Kirilmis, M. Ahmedzade, C. Kazaz, B. Özbek and G. Ötük, *Eur. J. Med. Chem.,* 2005, **40**, 1351-1358.

76. J. N. Soni and S. S. Soman, *Eur. J. Med. Chem.*, 2014, **75**, 77-81.

77. I. A. Khan, M. V. Kulkarni and C.M. Sun, *Eur. J. Med. Chem.,* 2005, **40**, 1168-1172.

78. I. A. Khan, M. V. Kulkarni, M. Gopal, M. S. Shahabuddin and C. M. Sun, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 3584-3587.

79. B. F. Abdel-Wahab, H. A. Abdel-Aziz and E.M. Ahmed, *Eur. J. Med. Chem.,* 2009, **44**, 2632-2635.

80. B. F. Abdel-Waha, H. A. Abdel-Aziz and E. M. Ahmed, *Arch. Pharm. Chem. Life Sci.,* 2008, **341**, 734-739.

81. B. F. Abdel-Wahab, H. A. Abdel-Aziz and E. M. Ahmed, *Monatsh. Chem.,* 2009, **140**, 601-605.

82. V. Ugale, H. Patel, B. Patel and S. Bari, *Arab. J. Chem.,* In Press; 2012, doi:10.1016/j.arabjc.2012.09.011.

83. S. Shankerrao, Y. D. Bodke and S. Santoshkumar, *Arab. J. Chem.*, 2012, doi:10.1016/j.arabjc.2012.10.018.

84. V. K. Bhovia, Y. D. Bodke, S. Biradar, B. E. Kumaraswamy and S. Umesh, *Phosphorus, Sulfur, and Silicon*, 2010, **185**, 110-116.

85. B. S. Dawane1, S. G. Konda, N. T. Khandare, S. S. Chobe, B. M. Shaikh, R. G. Bodade and V. D. Joshi, *Org. Commun,.* 2010, **3**, 22-29.

86. N. Hadj-Esfandiari, L. Navidpour, H. Shadnia, M. Amini, N. Samadi, M. A. Faramarzi and A. Shafiee, *Bioorg. Med. Chem. Lett.,* 2007, **17**, 6354-6363.

87. K. Manna and Y. K. Agrawal, *Bioorg. Med. Chem. Lett.* 2009, **19**, 2688-2692.

88. D.B. Arun Kumar, G.K. Prakash, M.N. Kumaraswamy, B.P. Nandeshwarappa, B.S. Shrigara and K.M. Mahadevan, *Ind. J. Chem. B.,* 2006, **45B**, 1699-1703.

89. H. Hanumanagoud and K. M. Basavaraj, DerPharmaChemica., 2013, **5**, 87-98.

90. H. A. Abdel-Aziz, A.A.I. Mekawey and K. M. Dawood, *Eur. J. Med. Chem.,* 2009, **44**, 3637-3644.

91. H. A. Abdel-Aziz and A.A.I. Mekawey, *Eur. J. Med. Chem.*, 2009, **44**, 4985-4997.

92. S. M. Rida, S. A. M. EI-Hawash, H. T. Y. Fahmy, A. A. Hazza and M. M. M. EI-Meligy, *Arch. Pharm. Res.,* 2006, **29**, 826-833.

93. C. S. Reddy, D. Chandrasekhar Rao, V. Yakub and A. Nagaraj, *Acta. Chim. Slov.,* 2011, **58**, 582-589.

94. M. W. Khan, M. J. Alam, M. A. Rashid and R. Chowdhury, *Bioorg. Med. Chem.,* 2005, **13**, 4796-4805.

95. T. S. Chundawat, N. Sharma and S. Bhagat, *Med. Chem. Res.,* 2014, **23**, 1350-1359.

96. T. S. Chundawat, N. Sharma and S. Bhagat, *Med. Chem.,* 2014, **10**, 409-417.

97. G. S. Hassan and G. A. Soliman, *Eur. J. Med. Chem.,* 2010, **45**, 4104-4112.

98. R. Kenchappa, Y. D. Bodke, B. Asha, S. Telkar and M. A. Sindhe, *Med. Chem. Res.,* 2014, **23**, 3065-3081.

99. R. Kenchappa, Y. D. Bodke, S. K. Peethambar, S. Telkar and V. K. Bhovi, *Med. Chem. Res.,* 2013, **22**, 4787-4797.

100. M. Srinivas, D. Swapna, K. Haritha and K. Rao, *Pharmanest.* 2013, **4**, 1219 -1228.

101. D. R. Harish Kumar and M. D. Karvelar, *E- J. Chem.,* 2010, **7**, 636-640.

102. M.B. Halli and Z.S. Qureshi*, Ind. J. Chem.,* 2004, **43A**, 2347-2351.

103. M.B. Halli, V. B. Patil, M. Kinni and R.B. Sumathi, *J. Coord. Chem.,* 2011, **64**, 651-662.

104. M. B. Halli and R. S. Malipatil, *Der Pharma Chemica.,* 2011, **3**, 146-157.

105. M. B. Halli, V. B. Patil and S. R. Bevinamaradha, *Turk. J. Chem.,* 2011, **35**, 393-404.

106. M. B. Halli, R.S. Malipatil and R. B. Sumathi, *Int. J. Pharm. Bio. Sci.* 2012, **3**, 547-557.

107. S. Goel, S. Chandra and S. D. Dwivedi, *J. Saudi Chem. Soc.*, In press; 2013, http://dx.doi.org/10.1016/j.jscs.2013.07.005

108. a) M. Takanashi, Y. Takizawa and T. Mitsuhashi, *Chem. Lett.* 1974, **8**, 869-871.

b) Y. Luo, Z. He and H. Li, *Fitoterapia*, 2007, **78**, 211-214.

109. D. H. Choi, J. W. Hwang, H. S. Lee, D. M. Yang and J. G. Jun, *Bull. Korean Chem. Soc.*, 2008, **29**, 1594-1596.

110. K. Liouane, K. B. H. Salah, H. B. Abdel-kader, M. A. Mahjoub, M. Aouni, K. Said and Z. Mighri, *Afr. J. Microbiol. Res.,* 2012, **6**, 4662-4666.

111. A. Urzúa, J. Echeverría, M. C. Rezende and M. Wilkens, *Molecules,* 2008, **13**, 2385-2393.

112. X. Du, C. Lu, Y. Li, Z. Zheng, W. Su and Y. Shen, *J. Antibiot.,* 2008, **61**, 250-253.

113. M. Y. Rios, A. B. Aguilar-guadarrama and V. Navarro*, Planta Med.,* 2003, **69**, 967-970.

114. S. Demizu, K. Kajiyama, K. Takahashi, Y. Hiraga, S. Yamamoto, Y. Tamura, K. Okada and T. Kinoshita, *Chem. Pharm. Bull.,* 1988, **36**, 3474-3479.

115. Q. Liu, L. Shen, T-T. Wang, J. Chen, W. Y. Qi and K. Gao, *Food Chem.,* 2010, **122**, 55-59.

116. K. Yoshikawa, N. Kokudo, M. Tanaka, T. Nakano, H. Shibata, N. Aragaki, T. Higuchi and T. Hashimoto, *Chem. Pharm. Bull.,* 2008, **56**, 89-92.

117. C. Casero, F. Machín, S. Méndez-Álvarez, M. Demo, Á. G. Ravelo, N. Pérez-Hernández, P. Joseph-Nathan and A. Estévez-Braun*, J. Nat. Prod.,* 2015, **78**, 93-102.

118. G. Belofsky, R. Carreno, K. Lewis, A. Ball, G. Casadei and G. P. Tegos, *J. Nat. Prod.,* 2006, **69**, 261-264.

119. P. Castaneda, L. Gomez and R. Mata, *J. Nat.* and *Prod.,* 1996, **59**, 323-326.

120. T. Sastraruji, S. Chaiyong, A. Jatisatienr, S. G. Pyne, A. T. Ung and W. Lie, *J. Nat. Prod.*, 2011, **74**, 60-64.

121. E. Kato, Y. Tokunaga and F. Sakan, *J. Agric. Food Chem.* 2009, **57**, 2544-2549.

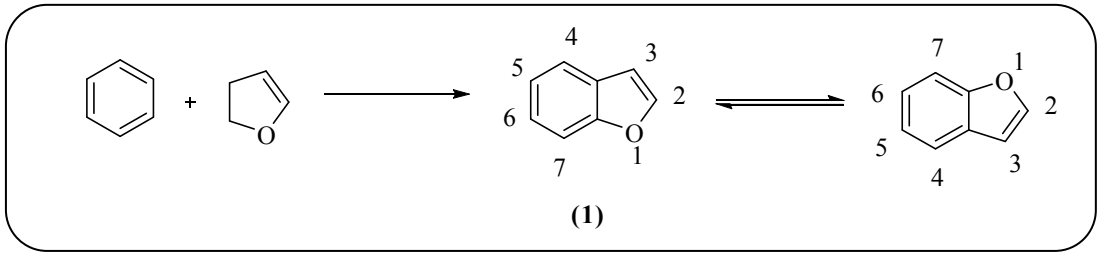
122. F. A. Ramos, Y. Takaishi, M. Shirotori, Y. Kawaguchi, K. Tsuchiya, H. Shibata, T. Higuti, T. Tadokoro and M. Takeuchi, *J. Agric. Food Chem.,* 2006, **54**, 3551-3557.

123. C. Y. Ragasa, J. G. Hofilena and J. A. Rideout, *J. Nat. Prod.,* 2002, **65**, 1107-1110.

124. M. M. Rahman and A. I. Gray, *Phytochemistry,* 2005, **66**, 1601-1606.

125. A. M. Do Nascimento, M. J. Salvador, R. C. Candidoc, I. Y. Ito and D.C.R. de Oliveira, *Fitoterapia,* 2004, **75**, 514-519.

Figure and captions



(1)

Figure 1. Structure/numbering system in benzofuran

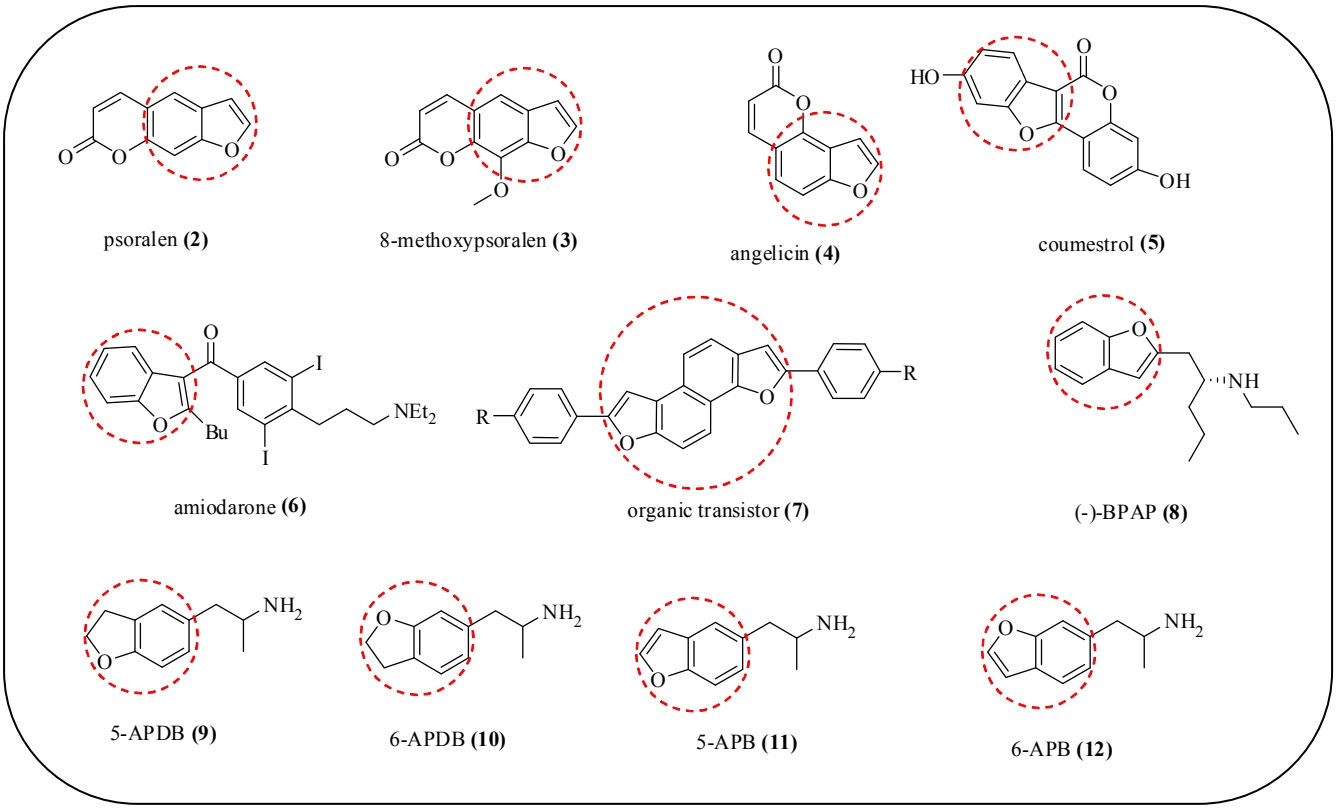


Figure 2. Benzofuran core, a multifunctional nucleus

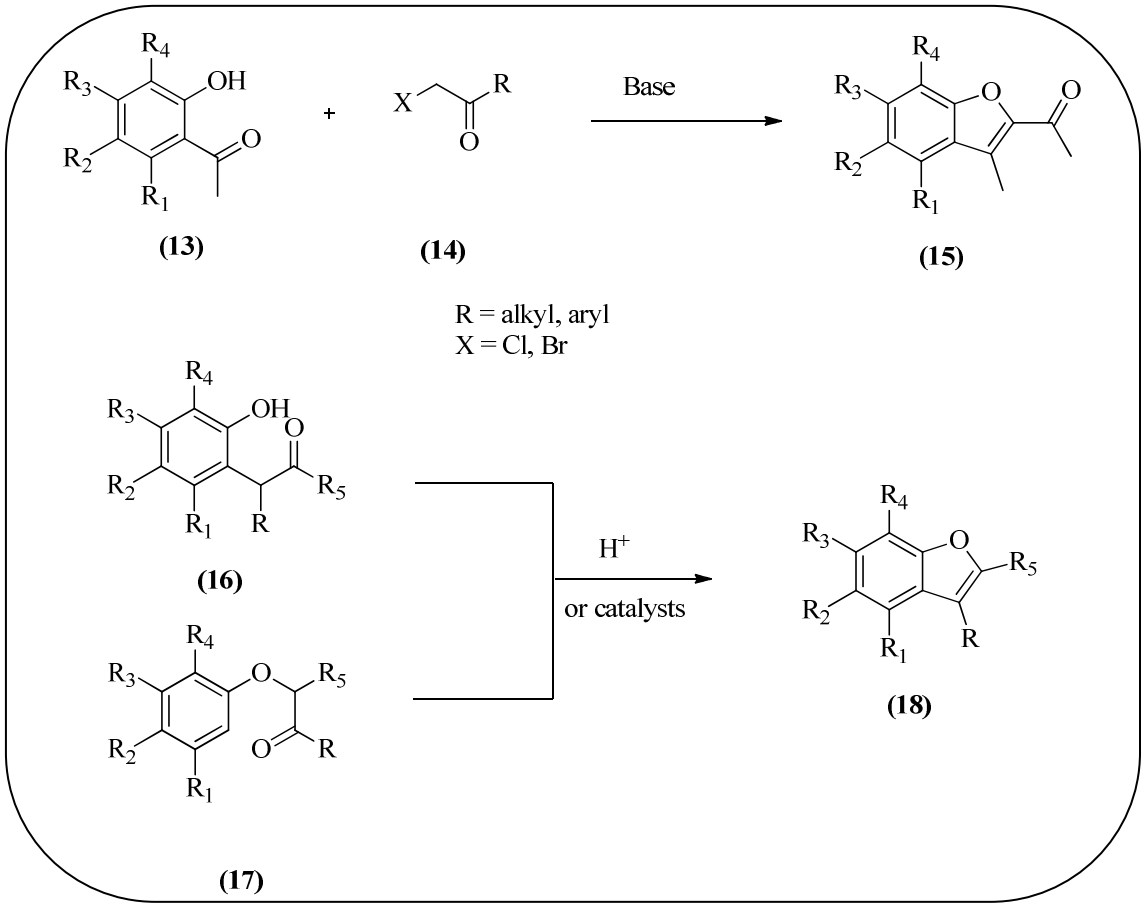


Figure 3. General scheme for the synthesis of benzofuran derivatives.

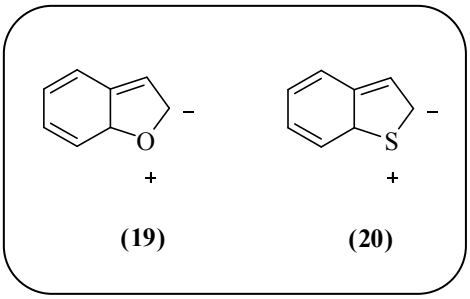


Figure 4. Orientation between benzofuran and thionaphthene

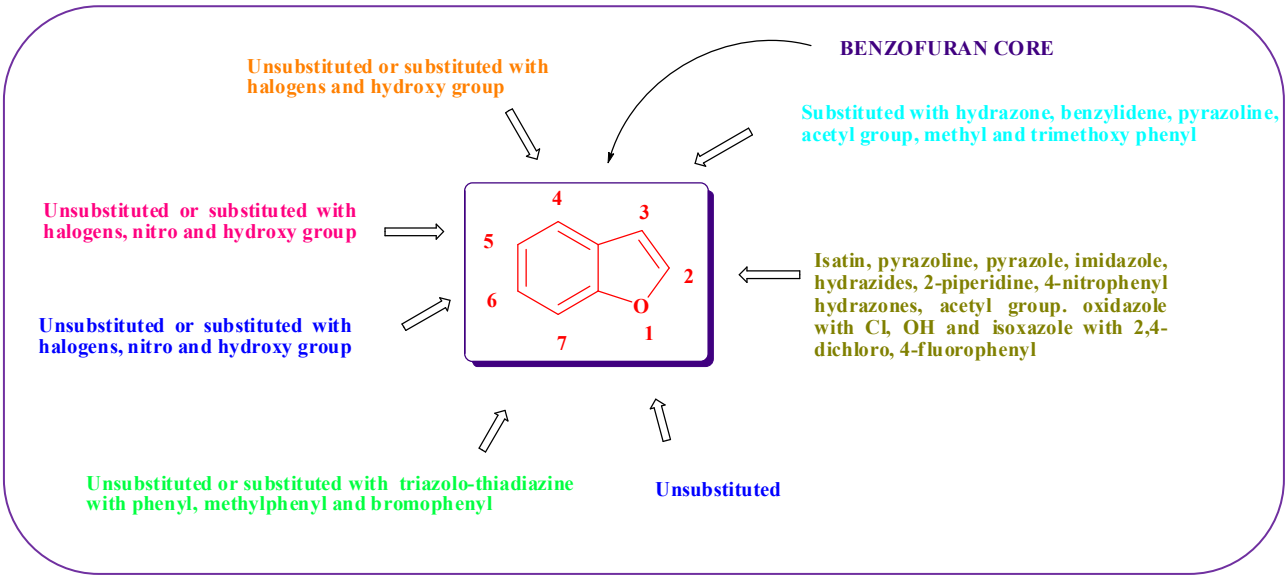


Figure 5. Benzofuran scaffold as antimicrobial agents

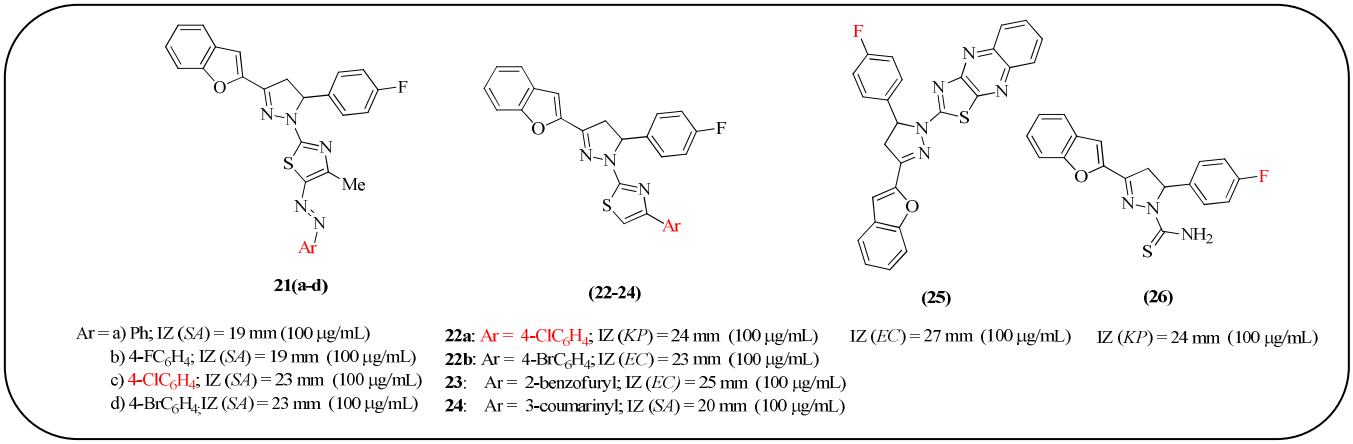


Figure 6. Structures of fluorinated 2-(3-(benzofuran-2-yl) pyrazol-1-yl)thiazoles

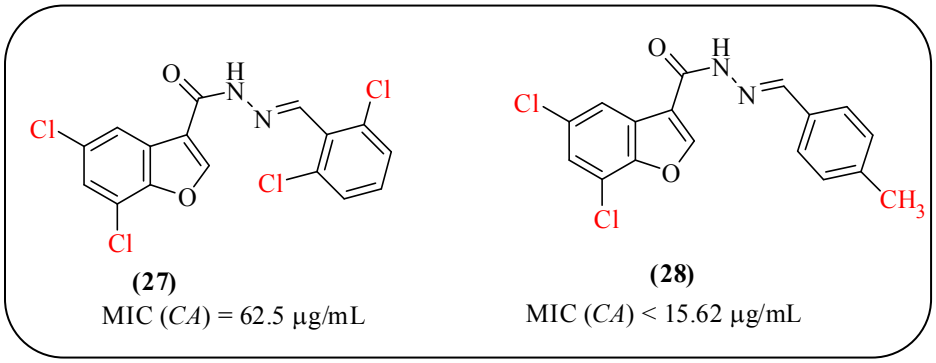


Figure 7. Structures of substituted benzofuran-3-carbohydrazones

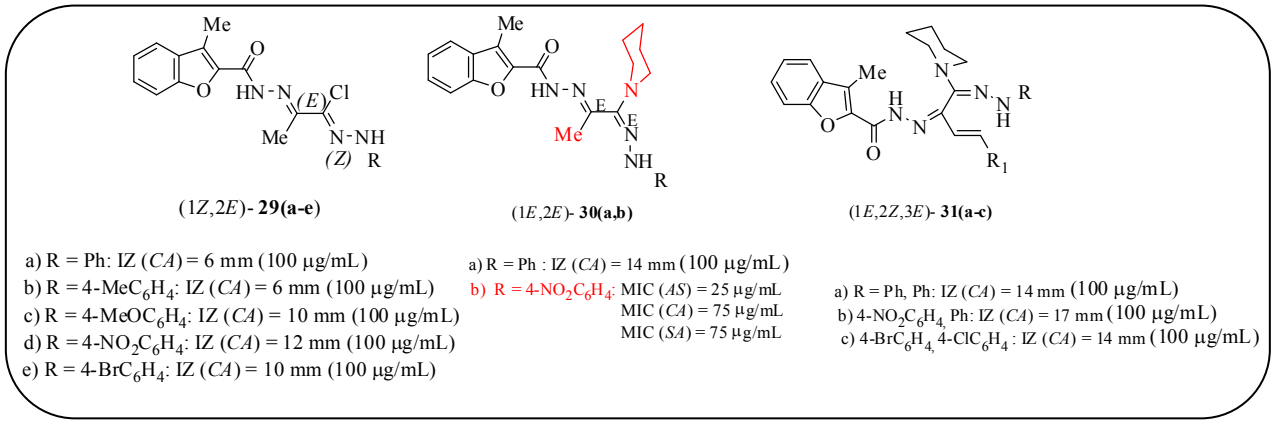
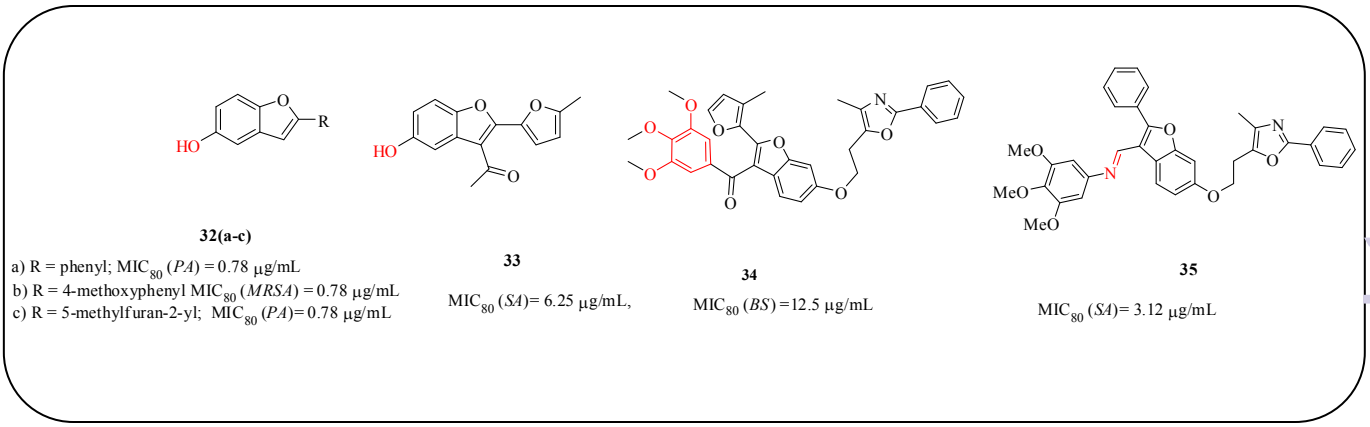


Figure 8. Structures of benzofuran-arylamidrazone derivatives



32(a-c)

a) R = phenyl; MIC_{80} (*PA*) = 0.78 µg/mL
b) R = 4-methoxyphenyl MIC_{80} (*MRSA*) = 0.78 µg/mL
c) R = 5-methylfuran-2-yl; MIC_{80} (*PA*) = 0.78 µg/mL

33

MIC_{80} (*SA*) = 6.25 µg/mL,

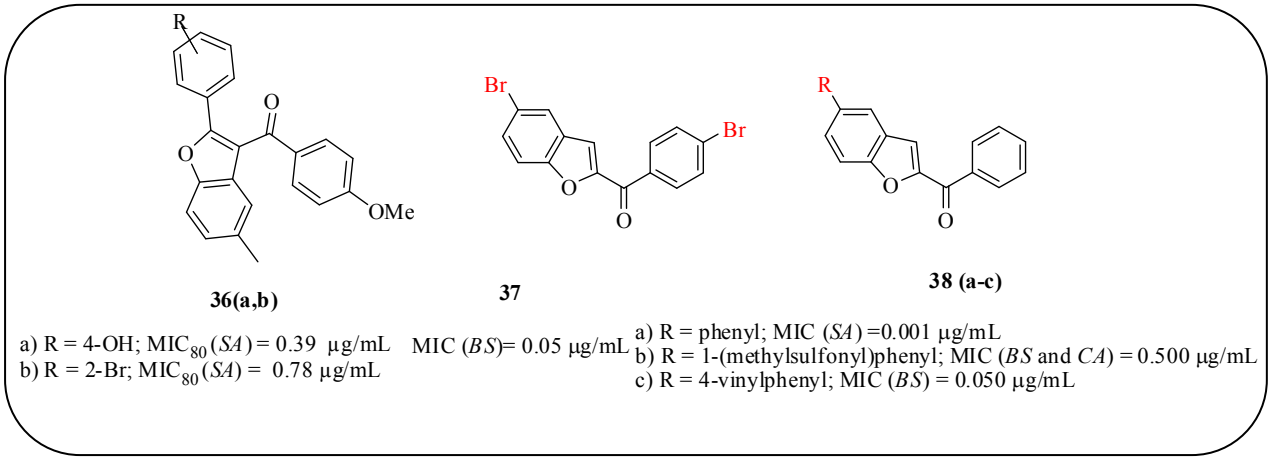
34

MIC_{80} (*BS*) = 12.5 µg/mL

35

MIC_{80} (*SA*) = 3.12 µg/mL

Figure 9. Structures of 3-methanone-benzofuran derivatives



36(a,b)

a) R = 4-OH; MIC_{80} (*SA*) = 0.39 µg/mL
b) R = 2-Br; MIC_{80} (*SA*) = 0.78 µg/mL

37

MIC (*BS*)= 0.05 µg/mL

38 (a-c)

a) R = phenyl; MIC (*SA*) =0.001 µg/mL
b) R = 1-(methylsulfonyl)phenyl; MIC (*BS* and *CA*) = 0.500 µg/mL
c) R = 4-vinylphenyl; MIC (*BS*) = 0.050 µg/mL

Figure 10. Structures of phenyl benzofuran derivatives

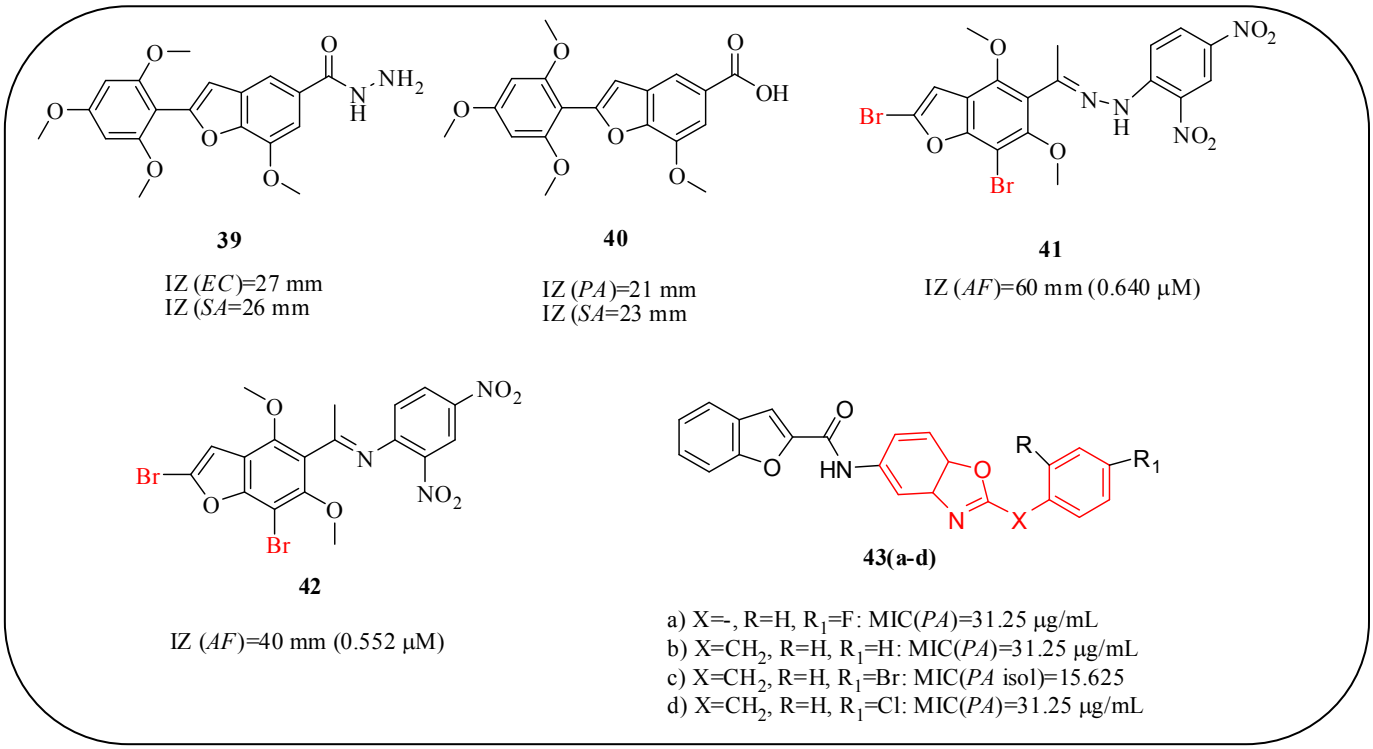


Figure 11. Structures of compounds **(39-43)**

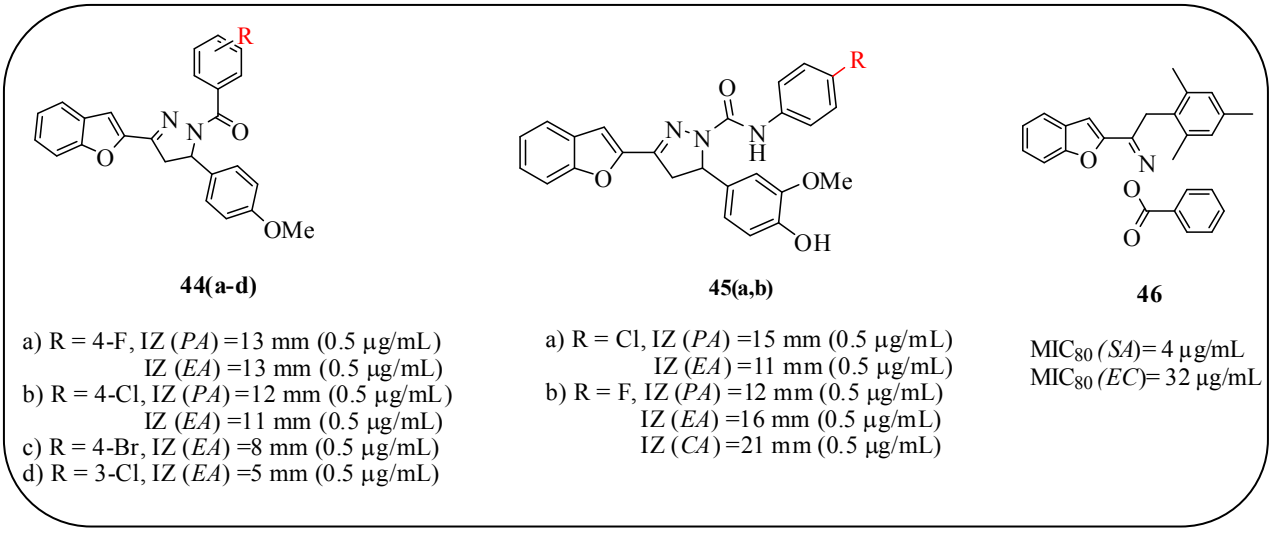


Figure 12. Structures of phenyl benzofuran-pyrazole and mesitylene-benzofuran derivatives

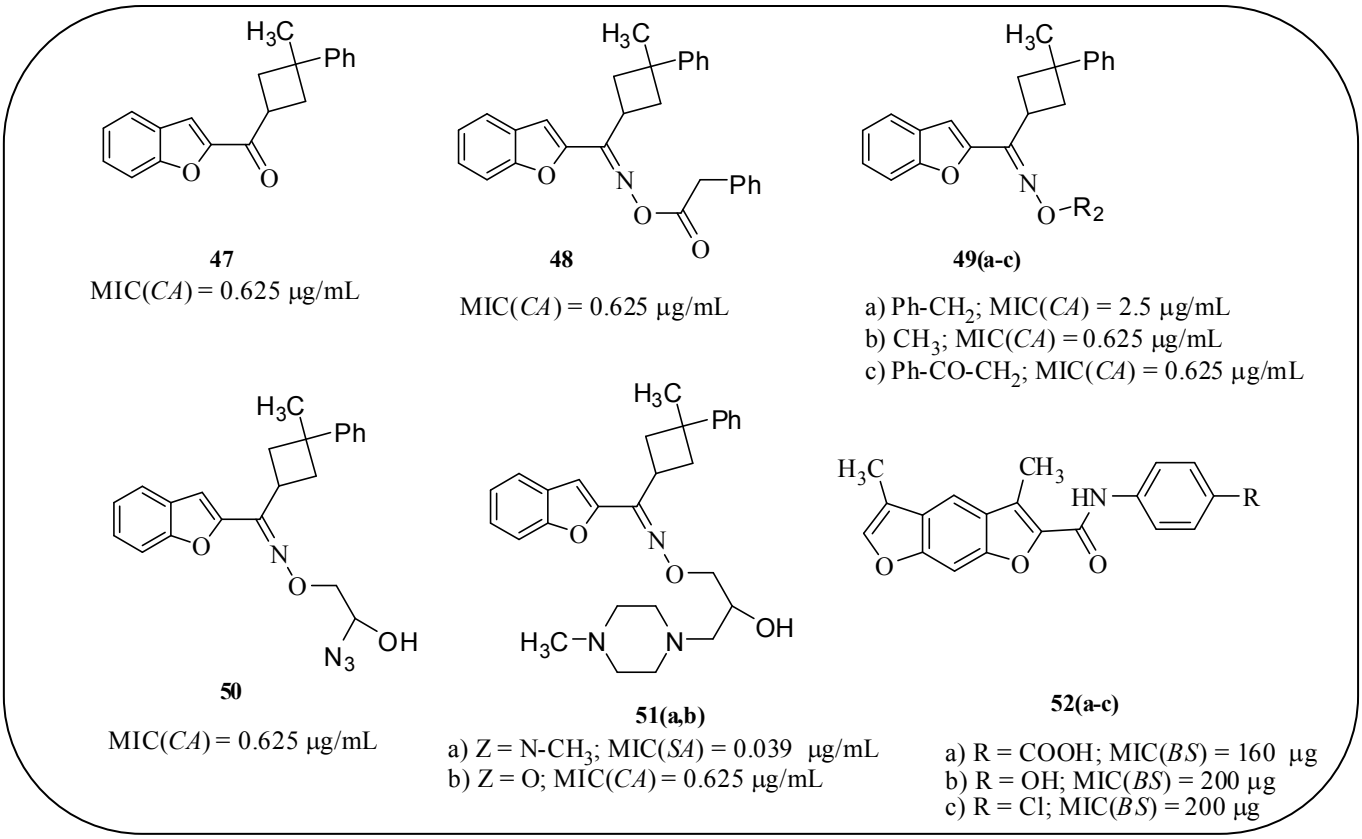
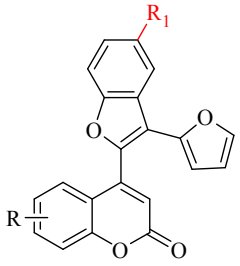
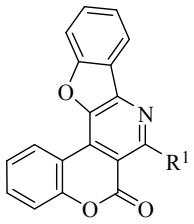


Figure 13. Structures of benzofuran-cyclobutylketoxime and benzodifuran amide derivatives



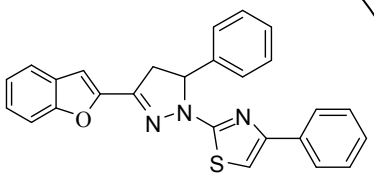
53(a-e)

a) R = 6-CH_3, R_1 = Cl: % Inh(*AF*)= 96.4 (100 µg/mL)
b) R = 7-CH_3, R_1 = Cl: % Inh(*PC*)= 91.6 (100 µg/mL)
c) R = 6-OCH_3, R_1 = Cl: % Inh(*PC*)=95.8 (100 µg/mL)
d) R = 6-CH_3, R_1 = 5,7-Cl: % Inh(*MA*)=100(100 µg/mL)
e) R = 7-CH_3, R_1 = Cl: % Inh(*AF*)=100 (100 µg/mL)



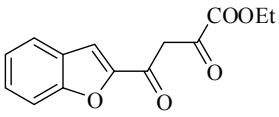
54(a-g)

a) R = 7-CH_3, R_1 = H: MIC(*PA, AS*)=25 µg/mL
b) R = 7-CH_3, R_1 = CH_3; MIC(*PA, AS*)=25 µg/mL
c) R = 7-CH_3, R_1 = C_2H_5; MIC(*PA, AS*)=25 µg/mL
d) R = 7-Cl, R_1 = H; MIC(*PA, AS*)=25 µg/mL
e) R = 7-Cl, R_1 = CH_3; MIC(*PA, AS*)=25 µg/mL)
f) R = 7-OCH_3, R_1 = C_2H_5; MIC(*PA, AS*)=25 µg/mL)
g) R = 6-CH_3, R_1 = H; MIC(*PA, AS*)=25 µg/mL



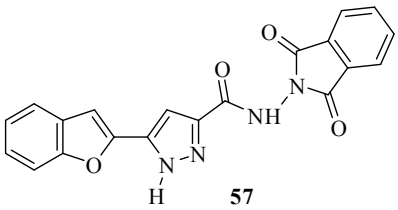
55

IZ(*SA*) = 17 mm
IZ(*EA*) = 25 mm



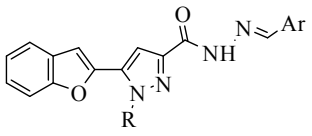
56

IZ*(CA)* =30 mm
IZ *(EA)*=40 mm



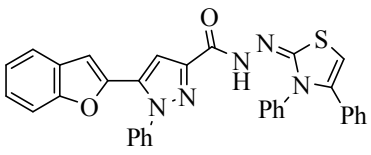
57

IZ *(CA)* = 30 mm



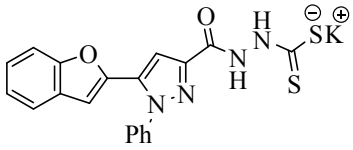
(58,59)

58; R=H, Ar=2,4-Cl_2-C_6H_4; IZ *(CA)* =30 mm
59; R=Ph, Ar=4-NO_2-C_6H_4; IZ*(EC)*=30 mm
IZ *(CA)* 40 mm



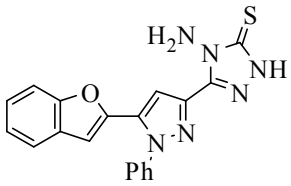
60

IZ *(EC)* = 40 mm



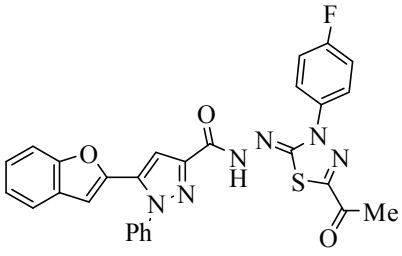
61

IZ*(CA)*= 30 mm



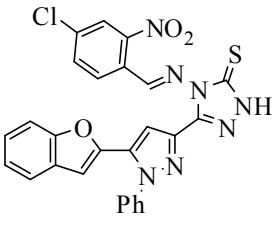
62

IZ *(CA)* =30 mm



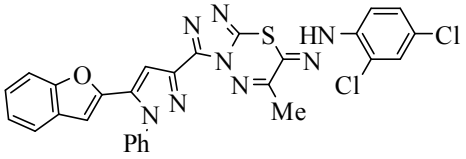
63

IZ *(CA)*= 30 mm



64

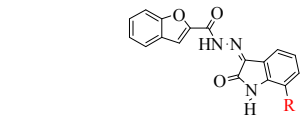
IZ*(CA)* = 40 mm



65

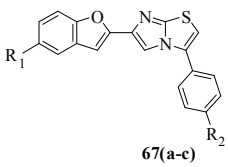
IZ*(CA)*=30 mm

Figure 14. Structures of compounds **(53-65)**



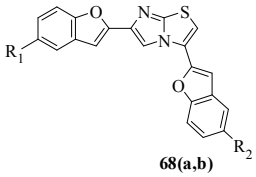
66(a,b)

a) R = NO_2: MIC(*EC, PV*) = 31.25 µg/mL
b) R = NO_2: MIC(*BS, EC, PV*) = 31.25 µg/mL



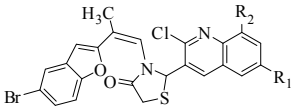
67(a-c)

a) R_1 = Br, R_2= H: IZ (*SA*) = 27 mm (100 µg/mL)
b) R_1 = H, R_2= CH_3: IZ (*SA*) = 24 mm (100 µg/mL)
c) R_1 = H, R_2= CH_3: IZ (*SA*) = 17 mm (100 µg/mL)



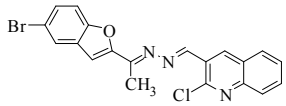
68(a,b)

a) R_1 = H, R_2= Br: IZ (*SA*) = 24 mm (100 µg/mL)
b) R_1 = Br, R_2= Br: IZ (*AN*) = 26 mm (100 µg/mL)



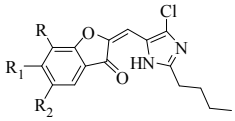
69(a-c)

a) R_1 =R_2= H: IZ (*KP*) = 18.3 mm (0.001mol/mL)
b) R_1 =CH_3,R_2= H: IZ (*AN*) = 24.8 mm (0.001mol/mL)
c) R_1 =H, R_2= CH_3: IZ (*PC*) = 19 mm (0.001mol/mL)
d) R_1 =OCH_3,R_2= H: IZ (*EC*) = 15 mm (0.001mol/mL)



70

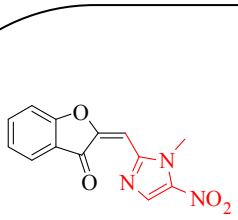
IZ (*KA*)=22.34 mm (0.001mol/mL)
IZ(*EC*) =14.57 mm (0.001mol/mL)
IZ(*TV*)=21.42 mm (0.001mol/mL)



71

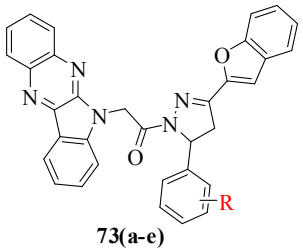
a) R=I, R_1 =H, R_2= Cl: IZ (*FM*) = 10 mm (25 µg/mL)
b) R=Br, R_1 =H, R_2= Cl: IZ (*BS*) = 19 mm (25 µg/mL)
(*TV*) = 19 mm (25 µg/mL)
(*FM*) = 15 mm (25 µg/mL)
c) R=I, R_1 =CH_3, R_2= Cl: IZ (*BS*) = 18 mm (25 µg/mL)
d) R=I, R_1 =H, R_2= I: IZ (*EC*) = 10 mm (25 µg/mL)

Figure 15. Structures of compounds **(56-71)**



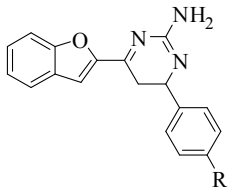
72

MIC *(KP)*=0.39 µg/mL



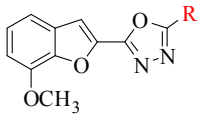
73(a-e)

a) R = 2-OH: MIC(*EC*) = 1 µg/mL
b) R = 3-NO_2: MIC(*ST*) = 8 µg/mL
c) R = 4-NO_2: MIC(*SA*) = 9.5 µg/mL
d) R = 4-OCH_3: MIC(*EC*) = 5 µg/mL
c) R = H: MIC(*ST*) = 2 µg/mL



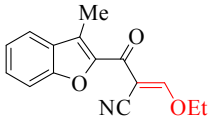
74(a-e)

a) R = H: IZ(*SA*) =14 mm (0.001 mol/mL)
b) R = NO_2: IZ(*SA*) =11 mm (0.001 mol/mL)
c) a) R = Cl: IZ(*PA*) =18 mm (0.001 mol/mL)
d) R = CH_3: IZ(*PA*) =17 mm (0.001 mol/mL)
e) R = OCH_3: IZ(*SA*) =16 mm (0.001 mol/mL)



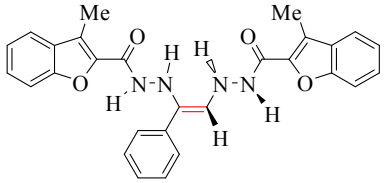
75(a,b)

a) R = Cl: IZ (*SF*) =19 mm (50 µg/mL)
(*AF*) =28 mm (50 µg/mL)
b) R = OH: MIC(*ST*) = (*SF*) =18 mm (50 µg/mL)
(*AF*) =30 mm (50 µg/mL)



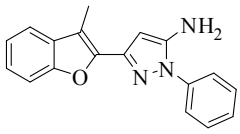
76

MIC(*CA, AN*) =250 µg/mL



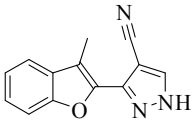
77

MIC(*SA, AF*) =500 µg/mL



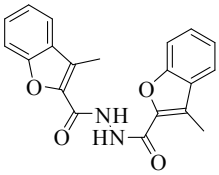
78

MIC(*CA, AN*) =250 µg/mL



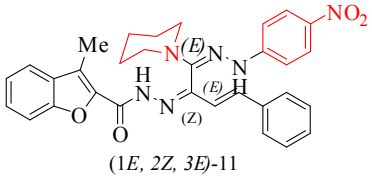
79

MIC(*CA, FA*) =50 µg/mL



80

MIC(*CA, FA*) =50 µg/mL

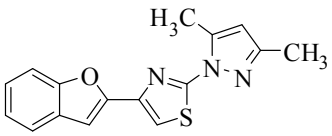


(1*E*, 2*Z*, 3*E*)-11

81

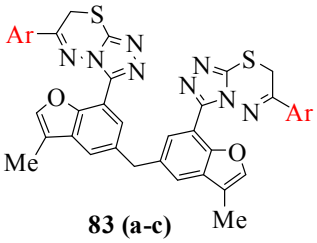
MIC (*AF*) =25 µg/mL
MIC (*CA*) =75 µg/mL

Figure 16. Structures of compounds **(72-81)**



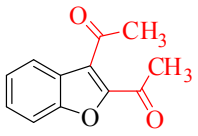
82

MIC(*SA*) =500 µg/mL



83 (a-c)

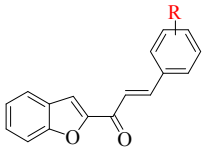
a) R = Phenyl: IZ (*EC*) =22 mm (100 µg/mL)
b) R = 4-methoxypheyl: IZ (*EC*) =27 mm (100 µg/mL)
IZ (*AN*) =24 mm (100 µg/mL)
c) R = 4-Bromophenyl: IZ (*KP*) =21 mm (100 µg/mL)
IZ (*SD*) =22 mm (100 µg/mL)



84

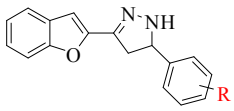
IZ (*AF*) =10 mm (30 µg/mL)

Figure 17. Structures of compounds **(82-84)**



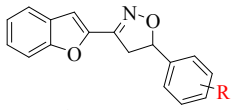
85 (a-c)

a) R = 2,6-F: MIC (*ST*) =62.5 μg/mL
b) R = 3,4-F: MIC (*SP*) =100 μg/mL
c) R = 2,4-F: MIC (*CA*) =250 μg/mL



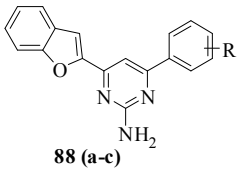
86 (a-c)

a) R = 4-F: MIC (*SP*) =100 μg/mL
b) R = 2-CF_3: MIC (*SP*) =100 μg/mL
c) R = 3,4-F: MIC (*CA*) =250 μg/mL



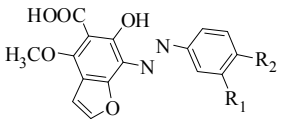
87 (a,b)

a) R = 3, 4-F: MIC (*CA*) =250 μg/mL
b) R =4-F: MIC (*CA*) = 250 μg/mL



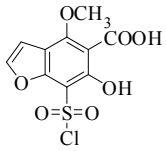
88 (a-c)

a) R = 4-F: MIC (*SP*) =250 μg/mL
b) R =2,4-F: MIC (*SP*) = 125 μg/mL
MIC (*CA*) = 500 μg/mL
c) R =3,4-F: MIC (*SP*) = 250 μg/mL
MIC (*CA*) = 500 μg/mL



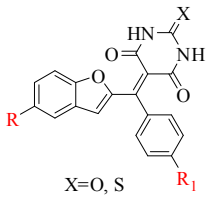
89 (a-c)

a) R_1 = R_2 = H: IZ (*CA*) =18 mm
b) R_1 = OH, R_2 = COOH: IZ (*CA*) =25 mm
c) R_1 =  , R_2 = H: IZ (*CA*) =22 mm



90

IZ (*CA*) =20 mm

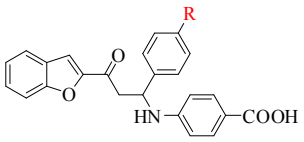


X=O, S

91 (a,b)

a) R = R_1= Br; X=O; MIC (*BS*) =31.96 μmol/mL
MIC (*EC*) =31.96 μmol/mL

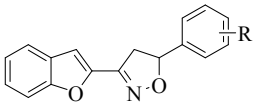
b) R = R_1= Br; X=S; MIC (*BS*) =31.64 μmol/mL
MIC (*EC*) =31.05 μmol/mL



MIC=0.040 - 0.500 mg/mL

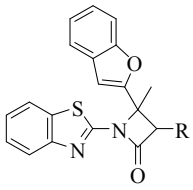
92 (a-c)

a) R =Cl; MIC (*EC*) = 0.12 mg/mL
b) R =F; MIC (*CA*) = 1 mg/mL
b) R =$N(CH_3)_2$; MIC (*PA*) = 0.040 mg/mL



93(a-d)

a) R = 2,4-Cl: MIC(*BS,EC, AN*) = 64 μg/mL
b) R = 4-Cl: MIC(*BS,PV*) = 64 μg/mL
c) 2-Cl: MIC(*BS,AN*) = 64 μg/mL
d) R = 4-NO_2: MIC(*AN*) = 64 μg/mL



94(a-c)

a) R = CH_3: IZ (*BS*) =15 mm (100 μg/mL)
IZ (*EC*) =15 mm (100 μg/mL)
b) R = C_2H_5: IZ (*BS*) =17 mm (100 μg/mL)
IZ (*EC*) =16 mm (100 μg/mL)
c) R = $BrCH_2$: IZ (*BS*) =16 mm (100 μg/mL)
IZ (*EC*) =15 mm (100 μg/mL)

Figure 18. Structures of compounds **(88-94)**

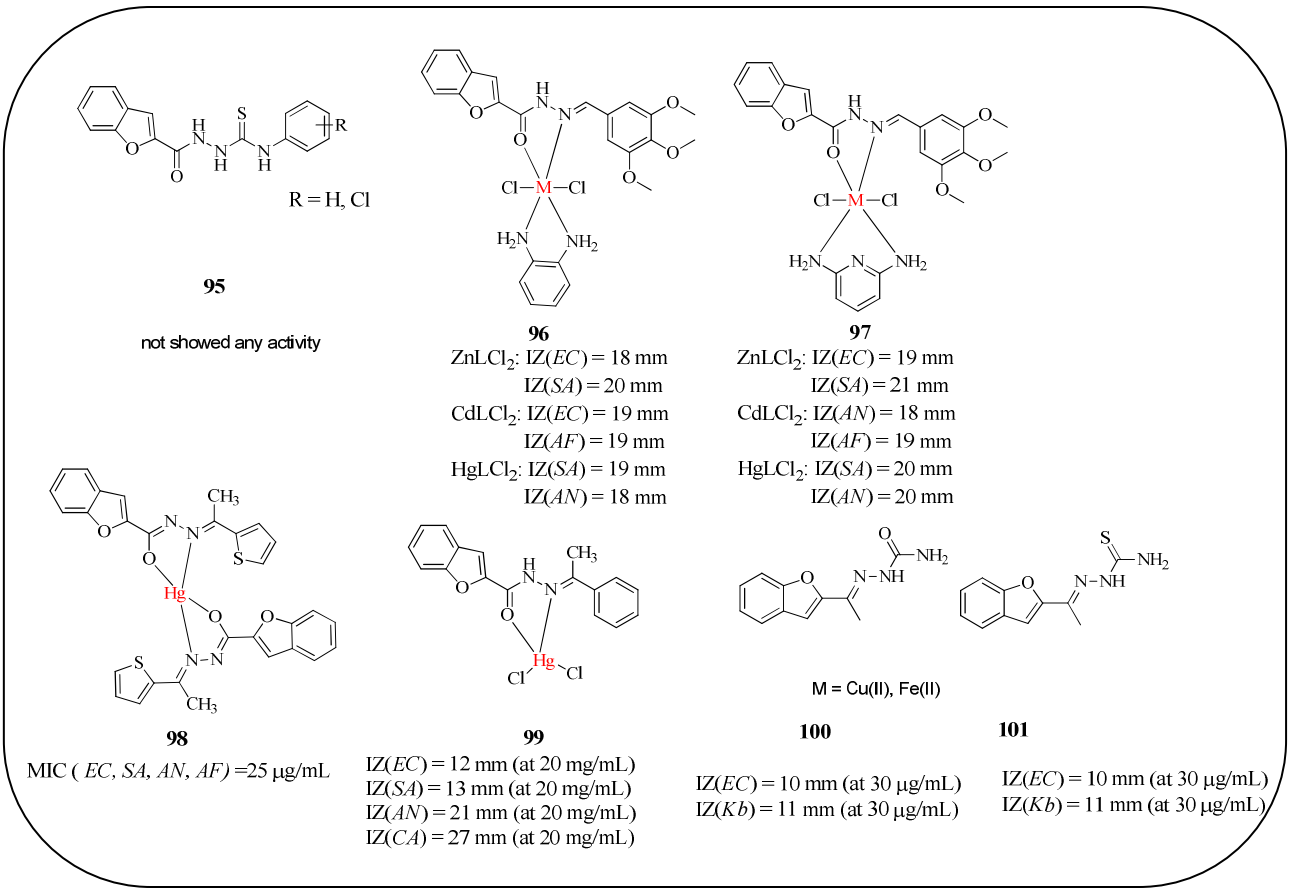
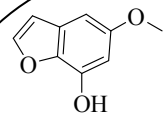
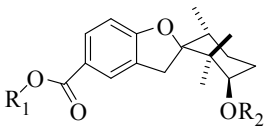


Figure 19. Structures of benzofuran-based metal complexes as antimicrobial agents

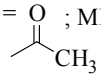


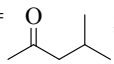
102

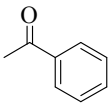
MIC (*SA*) = 31.25 μg/mL

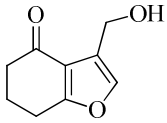


103-107

103: R_1= Me, R_2=H; MIC (*BS*) = 512 μg/mL
104: R_1 = H, R_2 = H; MIC (*BS*) = inactive
105: R_1 = Me, R_2 =  ; MIC (*ML*) = 256 μg/mL

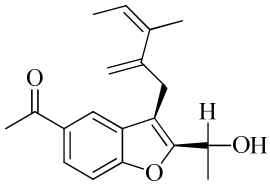
106: R_1= Me, R_2=  ; MIC (*SA*) = 16 μg/mL

107: R_1= Me, R_2=  ; MIC (*BS, ML, SA*) = 16 μg/mL



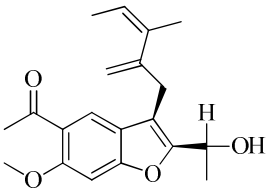
108

MIC (*CA, SC*) = 10 μg/mL
MIC (*EC*) = 5 μg/mL
MIC (*SA, SC*) = 1.25 μg/mL



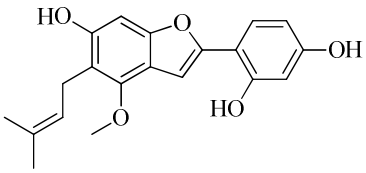
109

MIC (*TM*) = 200 μg/mL
MIC (*TR*) = 100 μg/mL



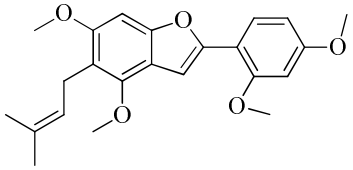
110

MIC (*TM*) = 50 μg/mL
MIC (*TR*) = 50 μg/mL



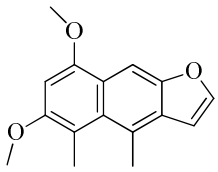
111

MIC (*SM*) = 12.5 μg/mL
MIC (*SA*) = 6.25 μg/mL



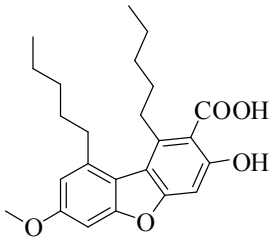
112

not showed any activity



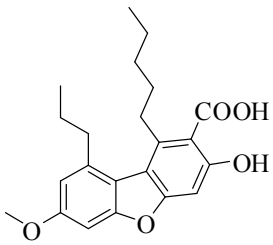
113

MIC (*SA*) = 62.5 μg/mL



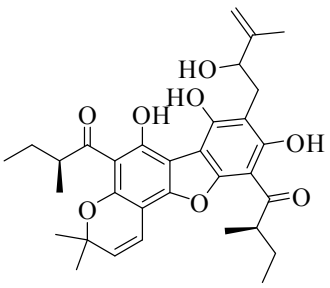
114

IZ (*SA*) = 28 mm (100 μg/mL)
IZ (*EF*) = 22 mm (100 μg/mL)



115

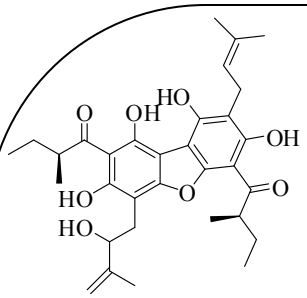
IZ (*SA*) = 17 mm (100 μg/mL)
IZ (*EF*) = 22 mm (100 μg/mL)



116

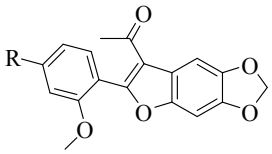
MIC (*SA*) = 32 μM
MIC (*EF*) = 64 μM

Figure 20. Structures of benzofuran-based natural products as antimicrobial agents (continued)



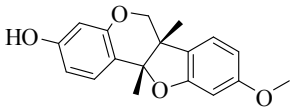
117

MIC (*SA*) < 1 μM
MIC (*EF*) =2 μM



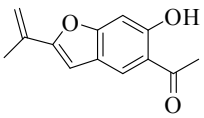
118,119

118: MIC (*SA*) = 45 μM
119: MIC (*SA*) = 6 μM



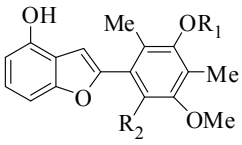
120

MIC (*SA*) = 89 μM



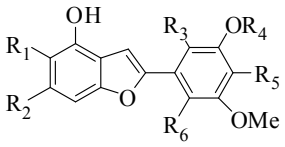
121

MIC (*TM*) = 29 μg/mL



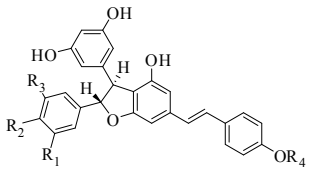
122,123

122:R_1=R_2=H: MIC (*MRSA*) = 15.6 μg/mL
MIC (*CA*) = 31.3 μg/mL
MIC (*CN*) = 7.8 μg/mL
122:R_1=Me,R_2=H: MIC (*MRSA*) = 15.6 μg/mL
MIC (*SP*) = 62.5 μg/mL
MIC (*CN*) = 7.8 μg/mL



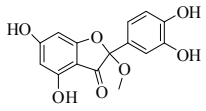
124-126

124:R_1=R_4=R_5=R_6=H,R_2=OMe, R_3=Me: MIC (*MRSA*) = 31.3 μg/mL
MIC (*CA*) = 31.3 μg/mL
MIC (*SP*) = 62.5 μg/mL
125:R_1=R_5=R_6=H,R_2=OMe, R_3=R_4=Me : MIC (*EC*) = 62.5 μg/mL
MIC (*SA*) = 31.3 μg/mL
MIC (*CA*) = 15.6 μg/mL
126:R_1=R_6=H,R_2=OMe, R_3=R_4=R_5=Me : MIC (*EC*) = 62.5 μg/mL
MIC (*MRSA*) = 15.6 μg/mL
MIC (*CA*) = 15.6 μg/mL



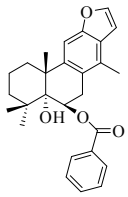
127,128

127: R_1=OCH_3, R_2=R_4=H, R_3=OH: MIC (*BS*) = 10 μg/mL
128: R_1=R_3=R_4=H, R_2=OH: MIC (*BS*) = 20 μg/mL



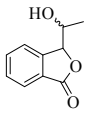
129

IZ (*HP, SS-1*) =12 mm (100 μg/mL)
IZ (*HP, 43504*) =15 mm (100 μg/mL)



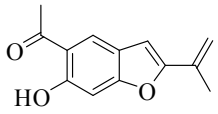
130

IZ(*SA, EC, BS, CA*) = 12mm (30 μg)



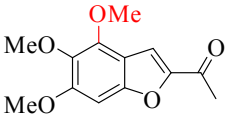
131

MIC (*SA, AN*) = 0.474 μmol
MIC (*BS, EC, PV*) = 0.237 μmol



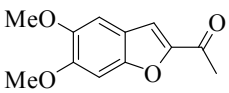
132

MIC (*CG*) = 250 μg/mL



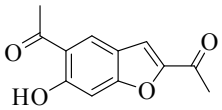
133

MIC (*TM*) = 500 μg/mL



134

MIC (*SA, TM*) =500 μg/mL



135

MIC (*SA, CA*) =500 μg/mL

Figure 20. Structures of benzofuran-based natural products as antimicrobial agents