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Synthesis and antimicrobial activity of novel benzoxazine sulfonamide derivatives

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ABSTRACT

A new series of benzoxazine-6-sulfonamide derivatives were synthesized in excellent yields and the resulting compounds were evaluated for their antimicrobial activities. All the synthesized compounds were assessed for their antibacterial and antifungal activities. Among them **1a**, **1b**, **1c**, **1e**, **1h**, **2c**, **2d**, **2e**, **2g**, **2h**, **2i**, **2j**, **2k** and **2l** showed low inhibitory concentration (MIC of 31.25 and 62.5 μg/mL) against Gram-positive bacteria, Gram-negative bacteria and fungi, which are comparable to the inhibitory effect of standard drugs.

The present treatments of bacterial and fungal infections are a bit unsatisfactory, owing to rapidly developing drug resistance and side effects. This effect has a negative impact on the usage of most antimicrobial agents.[1–4] 2,3-Dihydro-1,4-benzoxazines have shown their significance as a part of biologically active and medicinally important compounds. It is evident by the several biological activities, such as anti-inflammatory,[5] antiulcer,[6] antibacterial,[7] shown by 1,4-benzoxazin-3(4*H*)-one derivatives. Ofloxacin, (Fig. 1) one of the antimicrobial agents, possess 1,4-benzoxazine ring system in its structure.

Sulfonamides forms the basis for a large multiplicity of drugs and are known for antibacterial,[8] antiviral,[9] diuretic,[10] antimalarial,[11] anticonvulsant,[12] hypoglycemic,[13] anti-carbonic anhydrase[14,15] and antithyroid[16] activities. A marketable sulfonamide derivative, KCN1 was shown to display both in vitro and in vivo antitumor activity.[17,18] Recently Walsh et al. evaluated benzoxazine-6-sulfonamides (e) as activators of the tumor cell specific M2 isoform of pyruvate kinase.[19] Newly, certain benzoxazine and sulfonamides (Fig. 1), have been reported to exhibit interesting antibacterial(b&d)[7,19] and anticancer activity.[19]

The piperazine-based heterocyclic nuclei are a varied class of chemical compounds, some of which demonstrate significant pharmacological properties. A small adjustment in the additional design in the piperazine core causes obvious distinction in their biological events. A few related arylsulfamides with a spacer to phenyl-piperazine were testified as active structure for 5-HT_7 antagonist.[20]

Considering the importance of benzoxazine-6-sulfonamide, and in continuation of our research program to discover and develop novel biologically active compounds,[21–24] we have planned to synthesize a new series of compounds having benzoxazine-6-sulfonamide moiety and screened them for their antimicrobial activities. The antibacterial and antifungal activities of all the newly synthesized compounds were evaluated in vitro against one Gram-positive bacterium, three Gram-negative bacteria and one fungus.

The synthetic pathways for the preparation of the target compounds are shown in Schemes 1–4. The intermediate3-oxo-3, 4-dihydro-2*H*-benzo[*b*][1,4]oxazine-6-sulfonyl chloride **5a–b** was attained by the two-step synthetic route (Scheme 1).

Treatment of substituted *o*-amino phenol **3a–b** with chloroacetyl chloride in presence of benzyl triethyl ammonium chloride (TEBA), afforded 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one **4a–b**, which was further subjected to chlorosulfonylation to give compounds **5a–b** (Scheme 1). The synthesis of the intermediates **10a–g** was achieved as per the Scheme 2. Reaction of phthalimide (**6**) with 1,3-dibromo propane (**7**) in presence of potassium carbonate, in DMF furnished 2-(3-bromopropyl)isoindoline-1,3-dione (**8**). Treatment of **8** with various piperazines and thiomorpholine in presence of potassium

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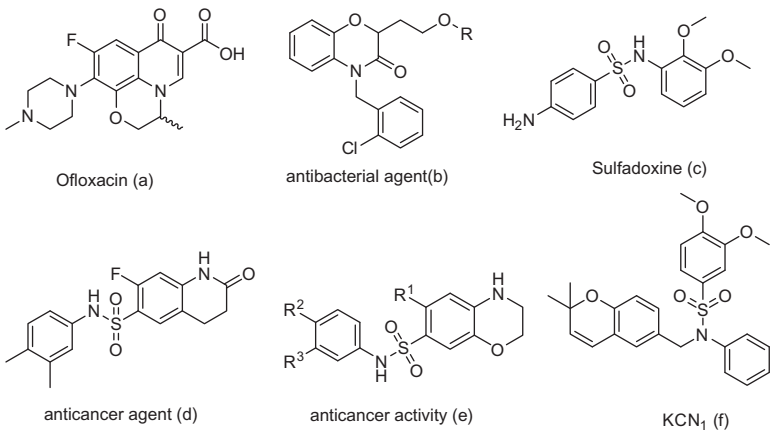
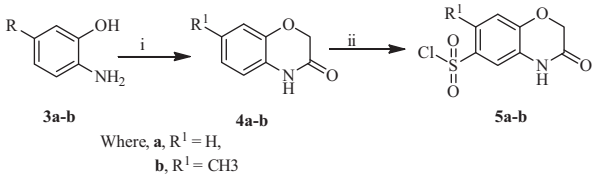


Figure 1. Structure of 1,4-benzoxazine ring system and sulfonamide derivatives with antibacterial, anticancer activity.



Scheme 1. Reagents and conditions: (i) chloro acetyl chloride, TEBA, $NaHCO_3$, $CHCl_3$ 0–55 °C, 67%, (ii) $ClSO_3H$, 0 °C, 1 h, 66%.

carbonate in DMF, resulted in the intermediates **9a–g**, which were then treated with hydrazine hydrate in MeOH to give compounds **10a–g**. Coupling of compounds **5a–b** with 3-(4-phenylpiperazin-1-yl) propan-1-amine derivatives **10a–g** using diisopropylethylamine (DIPEA) in DMF furnished benzo-[*b*][1,4]oxazine-6-sulfonamide derivatives **1a–m** (Scheme 3). The additional series **2a–n** (Scheme 4) were synthesized from **5b**. Compound **5b** was treated with piperazines in the presence of DIPEA in DMF to give compounds **11a–b**. Reaction of **11a–b** with various phenacyl bromides in the presence of potassium carbonate in MeOH afforded **2a–n**.

Benzoxazine-6-sulfonamides **1a–n**, **2a–m** and **11a–b** were tested in vitro for antibacterial and antifungal activity. The results obtained showed that the majority of these compounds show activity against Gram-positive bacteria such as *Bacillus megaterium*, Gram-negative bacteria: *Xanthomonas campestris*, *Pseudomonas aeruginosa*, *Escherichia coli* by broth micro dilution method.[25] The anti-fungal activity was performed against *Candida albicans* (MTCC 183) in comparison with Fluconazole by employing Sabouraud's dextrose broth.[26]

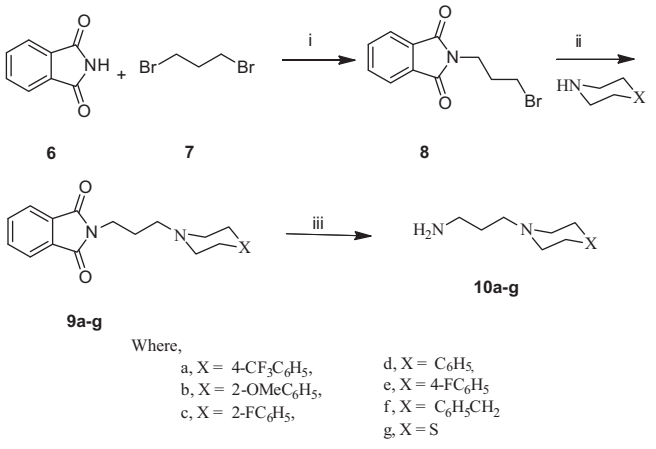
According to the obtained anti-bacterial data (Table 1), it is apparent that all the benzoxazine-6-sulfonamides showed promising activity. Compounds **1b**, **1c**, **2d**, **2g**, and **2l** showed low inhibitory concentration (MIC) of 31.25 (μg/mL) and **1a**, **1h**, **2e**, **2h**, **2i**, and **2k** MIC of 62.5 (μg/mL) and were found to be very active against *B. megaterium*. Among the tested compounds for antibacterial activity against Gram-negative bacteria, **1c**, **1h**, **2i**, and **2l** exhibited significant activity against *X. campestris*. In particular, compounds **1c**, **1e**, **2c**, **2d**, **2g** and **2l** showed excellent activity against *P. aeruginosa*. The compounds **2c**, **2d**, **2j**, and **2l** showed low inhibitory concentration (MIC of 62.5 μg/mL) against *E. coli*, as compared to Rifampicin (MIC of 64 μg/mL).The compounds with piperazine substituted sulfonamide moiety **11a** and **11b** exhibited moderate anti-bacterial activity. However attachment of the phenacyl group to them significantly enhanced the anti-bacterial activity. The existence of strong electron-donating and withdrawing substituent's, in compounds **1a**, **1b**, **1c**, **1e**, **1h**, **2c**, **2d**, **2e**, **2g**, **2h**, **2i**, **2j**, **2k**, and **2l** showed favorable antibacterial activity.

Most of the tested compounds were found to be remarkably active against *C. albicans*. Compounds **1b**, **2d**, **2g**, **2i**, **2j** and **2l** had comparable activity with the reference drug Fluconazole.

The structure–activity relationship (SAR) study reveals that the change in substitution on piperazine attached aromatic ring is important for inducing anti-microbial activity against particular Gram-positive bacteria, Gram-negative bacteria and fungi (Table 1). The compounds with fluoro substitution on aromatic ring had higher anti-microbial activity as compared to electron donating and strong electron withdrawing groups. For example, compounds **1a**, and **1h** with no substitution and **1b** and **1c** with fluoro substitution showed higher anti-microbial activity.

While the compounds with piperazine substituted sulfonamide moiety **11a** and **11b** exhibited moderate anti-microbial activity. However attachment of the phenacyl group to them significantly enhanced the anti-microbial activity. The presence of electron donating and withdrawing substituents ($-CH_3$, $-OCH_3$, $-NO_2$ and Ph) on the phenacyl group increases the activity, as indicated by the low inhibitory concentration (MIC) of 31.25 and 62.5 (μg/mL) displayed by them. Thus suggesting that substitution on phenacyl group is important for inducing anti-microbial activity.

In conclusion, we have synthesized two different series of novel benzoxazine-6-sulfonamides efficiently in excellent yields. All the synthesized compounds showed significant antimicrobial activity



Scheme 2. Reagents and conditions: (i) K_2CO_3, DMF, rt, 3 h, 85%; (ii) *N*-phenyl piperzine derivatives/thiomorpholine K_2CO_3, DMF, rt, 24 h, 95%; (iii) NH_2–NH_2·H_2O, methanol, rt, 12 h, 72%.