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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of benzo[*b*][1,4]oxazin-3(4*H*)-ones via smiles rearrangement for antimicrobial activity

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Abstract The benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives, **1a**–**p**, carrying F, Br, and Cl on the benzene ring, or benzyl, cyclohexyl, *n*-hexyl, and tetrafuryl methylene groups attached to nitrogen atom were synthesized via Smiles rearrangement and assayed in vitro for their antimicrobial activity against Gram-positive, Gram-negative bacteria, and fungi. The antimicrobial activity of the benzo[*b*][1,4]oxazin-3(4*H*)-ones showed, on the whole, potency toward all the tested Gram-positive and Gram-negative microorganism (MIC ranging from 16 to 64 μg/ml), whereas weak effectiveness was exhibited against fungi. Data obtained suggest that fluorine atom in the compounds, **1c**, **1f**, **1i** plays an important role in enhancing the antimicrobial properties of this class of compounds. These observations provide some predictions to design further antimicrobial active compounds prior to their synthesis according to molecular modeling studies.

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Keywords Antimicrobial activity · Benzo[*b*][1,4]oxazin-3(4*H*)-one · Smiles rearrangement · Synthesis

Introduction

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistance against man-made antibiotics in human pathogens (Tenover and McDonald, 2005; Roberts, 2004; Muroi *et al.* 2004). A potential approach to overcome the resistance problem is to design innovative agents with a different mode of action so that no cross resistance with the present therapeuticals can occur.

1,4-Oxazinones derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity, including antiulcer (Katsura *et al.* 1991), antihypertensive (Kajino *et al.* 1991), antifungal (Fringuelli *et al.* 2002; Macchiarulo *et al.* 2002), anticancer (Nair *et al.* 1983), anti-inflammatory (Wahidulla and Bhattacharjee, 2001; Lanni *et al.* 2007), antithromobotic (Buckman *et al.* 1998), antipsychotics (Smid *et al.* 2005), and other activities (Anderluh *et al.* 2005; Caliendo *et al.* 2002). They are also widely used as photochromic compounds (Christie *et al.* 1995; Sun *et al.* 1997) and some possess herbicidal activity (Huang *et al.* 2005).

As part of our ongoing studies in developing new methodology and novel compounds (Ma *et al.* 2004; Cho *et al.* 2003; Cho *et al.* 2004; Shin and Park 2007; Zuo *et al.* 2008) for diverse activities, we herein report the synthesis of a new class of structurally novel benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives. The structural variations were

selected by introducing, at different positions of F, Cl, and Br to benzene moiety, different alkyl or aryl substituents at *N*-position.

The benzo[*b*][1,4]oxazin-3(*4H*)-ones (16 samples) were synthesized by three-step reaction via Smiles rearrangement, different from all the existing methods, and this protocol allows the generation of large combinatorial chemical libraries of benzo[*b*][1,4]oxazin-3(4*H*)-ones. All the compounds were tested in vitro antimicrobial properties against Gram-positive, Gram-negative bacteria, and fungi and exhibited moderate to excellent activity.

Materials and methods

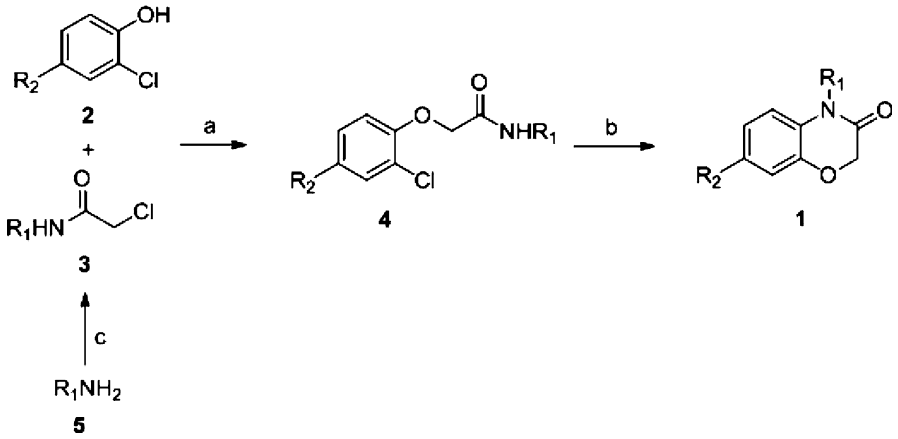
Synthesis

We herein used three-step reaction procedure under conventional condition (Scheme 1), different from the one-pot protocol reported earlier by us (Zuo *et al.* 2008). Therefore, the intermediates were separated and characterized, and the proposed Smiles rearrangement mechanism was verified by the evidence presented in this study. The synthetic procedures were carried out by refluxing substituted 2-chlorophenol (**2**) with equal equivalent of the acetamide, **3** and 1.2 equivalent of potassium carbonate, in anhydrous acetonitrile to afford acetamide, **4**. The synthesis of acetamide, **3** was easily achieved by reacting of amine, **5**, chloroacetyl chloride and K_2CO_3, in a molar ratio of 1: 1.2: 1.5 in anhydrous acetonitrile. Cyclization of substituted acetamide, **4** by treating it with cesium carbonate in anhydrous DMF gave substituted benzo[*b*][1,4]oxazin-3(4*H*)-ones in good yield.

The structure of compound **4** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and GC-MS. The broad peak in ^{1}H NMR of substituted benzo[*b*][1,4]oxazin-3(4*H*)-one, **4** disappeared in ^{1}H NMR proton spectrum of **1**, which indicated the cyclization of **4**. The evidence was further confirmed by the disappearance of N–H stretching in IR spectrum of product **1**. The spectral data of **1a—p** were in accordance with the reported data by one-pot protocol (Zuo *et al.* 2008). Furthermore, the single-crystal structure analysis of compound **1 m** showed the right approach of Smiles rearrangement (Fig. 1).

General procedure for the synthesis of *N*-substituted-2-chloroacetamide (**4**)

The solution of substituted 2-chlorophenol (**2**) (1.0 mmol), *N*-substituted-2-chloroacetamide, **3** (1.0 mmol), K_2CO_3 (1.2 mmol) and CH_3CN (20 ml) was refluxed. After completion of the reaction (monitored by TLC), the solution was cooled; the solvent was evaporated under reduced pressure. The residue was poured into water and pH adjusted to 6–7 and



Scheme 1 Reagents and condition: (*a*) K_2CO_3, anhydrous MeCN, reflux; (*b*) Cs_2CO_3, anhydrous DMF, reflux; and (*c*) $ClCOCH_2Cl$, K_2CO_3, anhydrous MeCN; 0°C, r.t.

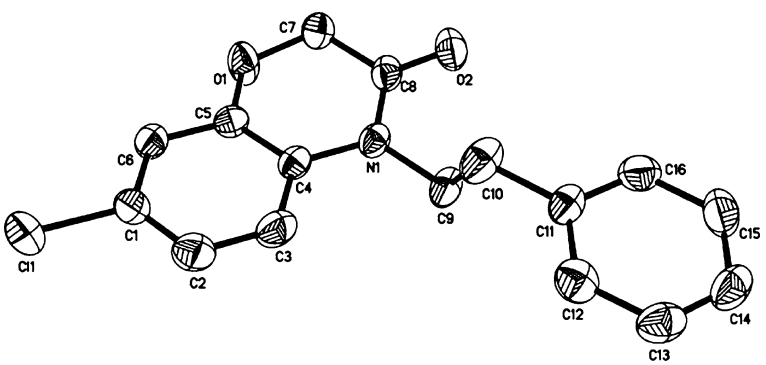


Fig. 1 The single-crystal structure of **1 m**

extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Removal of solvent afforded the corresponding *N*-substituted-2-chloroacetamide, **4**.

Spectral data of the selected product *N*-cyclohexyl-2-(2,3-dichlorophenoxy) acetamide (**4n**): White solid, mp 163-164°C; IR (KBr) *v*/cm-1: 3280, 3083, 2978, 2931, 2858, 1655, 1579, 1557, 1459, 1445, 1386, 1300, 1268, 1250, 1118, 1101, 971, 954, 883, 860, 768, 702, 637; ^{1}H NMR (400 MHz, CDCl3) δ 1.23–1.31 (m, 3H), 1.37–1.47 (m, 2H), 1.60–1.64 (m, 1H), 1.70–1.76 (m, 2H), 1.92–1.96 (m, 2H), 3.85–3.94 (m, 1H), 4.51 (s, 2H), 6.75 (br, 1H), 6.81 (dd, $J = 6.8$, 2.0 Hz, 1H), 7.15–7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 25.5, 32.9, 47.8, 68.3, 111.7, 122.0, 123.7, 127.8, 134.1, 154.1, 166.1; MS (EI) m/z: 267 (M + , 100%), 220 (17), 184 (40), 175 (15), 140 (15), 83 (26), 55 (17).

General procedure for the synthesis of benzo[*b*][1,4] oxazin-3(4*H*)-ones (**1**)

The reaction mixture of appropriate *N*-substituted-2-chloroacetamide, **4** (1.0 mmol) and Cs_2CO_3 (1.2 mmol) was refluxed in dry DMF (10 ml). After the completion of the reaction (monitored by TLC), the DMF was removed under vacuum. Water (20 ml) was added to the residue. The aqueous solution was extracted by ethyl acetate (4 × 30 ml), and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum to obtain the crude product which was purified by column chromatography (silica gel) to afford the desired pure compound.

Spectral data of the selected product 8-chloro-4-cyclohexyl-2*H*-benzo[*b*] [1,4] oxazin-3(4*H*)-one (**1n**): Light pink solid, mp 74–76°C; IR (KBr) *v*/cm^{-1}: 3002, 2924, 2854, 1679, 1594, 1467, 1451, 1444, 1409, 1361, 1336, 1282, 1258, 1149, 1086, 1041, 984, 859, 768, 732, 704, 642; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.43 (m, 3H), 1.71 (t, 1H), 1.79–1.91 (m, 4H), 2.30–2.40 (m, 2H), 4.10–4.18 (m, 1H), 4.56 (s, 2H), 6.95 (t, $J = 8.0$ Hz, 1H), 7.06–7.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 26.4, 29.4, 57.5, 68.9, 114.8, 122.6, 122.7, 124.7, 131.3, 142.8, 165.7; MS (EI) m/z: 265 (M^+, 23%), 183 (100), 154 (45), 55 (14), 44 (10).

Antimicrobial susceptibility test

Test compounds

Test compounds **1a**–**p** were synthesized according to the above procedure

Strains

Gram-positive bacteria were *Staphylococcus aureus* ATCC 25923; and *Bacillus subtilis* ATCC 6633, and Gram-negative bacteria were *Escherichia coli* ATCC 25922; *Proteus vulgaris* (ATCC 6896); and *Pseudomonas aeruginosa* ATCC 27853. Fungi were *Candida albicans* ATCC 76615; and *Aspergillus flavus* ATCC 10124.

MIC tests

The microorganisms originated from the American Type Culture Collection (ATCC). The antimicrobial activity was assayed in vitro by the twofold broth dilution technique (Ericcsson and Sherris, 1971; Stalons and Thornsberry *et al.* 1975) against Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6633), Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Proteus vulgaris* ATCC 6896, and *Pseudomonas aeruginosa* ATCC 27853), and fungi (*Candida albicans ATCC* 76615 and *Aspergillus aflavus* ATCC 10124). The minimal inhibitory concentrations (MIC, μg/ml) were defined as the lowest concentrations of compound that completely inhibited the growth of each strain.

Ampicillin, streptomycin, ceftazidime, and clotrimazole were used as reference antibacterial and antifungal substances. Test compounds were dissolved in distilled dimethylsulfoxide and then were plated in 96-well microplates. Each tested compound (1024 μg/ml in DMSO) was transferred to each microplate well, to be diluted in 100 μl of broth and 100 μl of inocula (Broth Agar Medium for all Gram-positive and Gram-negative bacteria and Sabouraud Liquid Medium for fungi) to obtain final concentrations at 512, 256, 128, 64, 32, 16, 8, 4, 2, 1 μg/ml. Dimethylsulfoxide never exceeded 1% v/v. The amount of inocula was 5.00×10^5 bacteria/ml and 1.00×10^4 fungi/ml. After incubation at 37°C for 24 h (bacteria) and at 30°C for 48 h (fungi), the last tube remaining clear with no growth of microorganism was recorded to represent MIC. The MICs were read after incubation at 37°C for 24 h (bacteria) and at 30°C for 48 h (fungi). Growth controls consisting of media and media with 1% v/v dimethylsulfoxide were employed.

The minimal bactericidal concentrations (MBC, μg/ml) were measured by subculturing 100 μl of each sample remaining clear in tubes containing 1 ml of fresh medium. The tubes were then incubated at 37°C for 24 h. All the experiments were performed in duplicate and repeated three times.

Table 1 Antimicrobial activity of **1a**–**p** expressed as MIC (μg/ml)

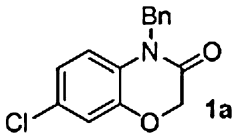
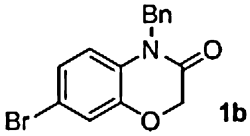
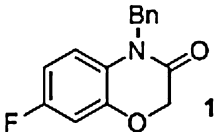
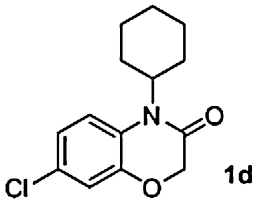
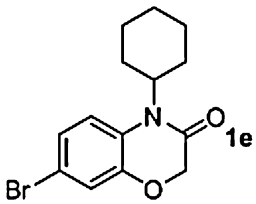
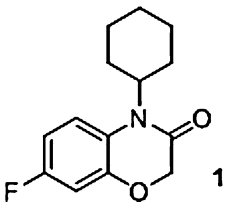
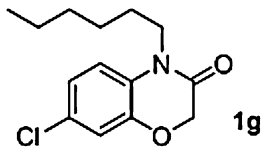
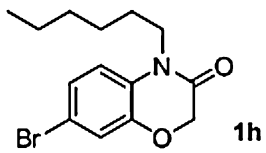
Entry	Product	Microorganisms[a]						
		Gram-positive		Gram-negative			Fungi[a]	
		SA	BS	EC	PV	PA	CA	AF
1	 **1a**	64	32	64	64	16	128	128
2	 **1b**	32	32	32	32	16	128	128
3	 **1c**	64	32	16	32	16	256	128
4	 **1d**	64	64	32	64	32	256	128
5	 **1e**	32	32	16	32	16	256	–[c]
6	 **1f**	16	32	16	16	16	256	64
7	 **1g**	32	32	32	16	32	512	–
8	 **1h**	32	32	32	16	32	128	–

Table 1 continued

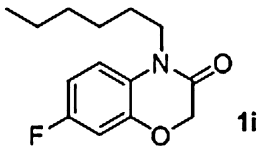
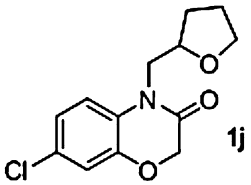
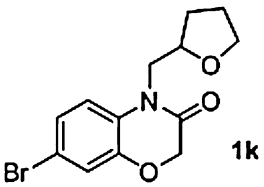
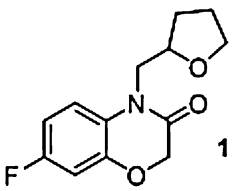
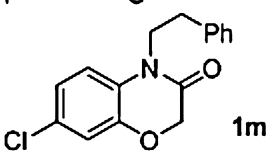
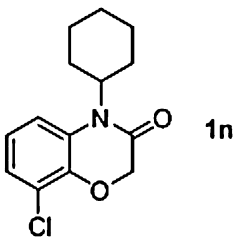
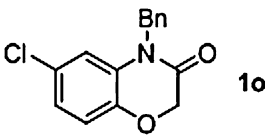
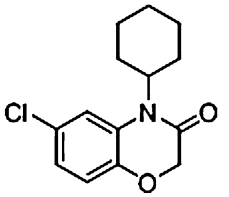
Entry	Product	Microorganisms[a]						
		Gram-positive		Gram-negative			Fungi[a]	
		SA	BS	EC	PV	PA	CA	AF
9	 1i	32	32	16	16	128	128	128
10	 1j	32	32	32	32	64	128	256
11	 1k	32	32	32	32	64	128	–
12	 1l	32	32	32	16	128	256	–
13	 1m	64	64	32	16	16	128	–
14	 1n	64	32	32	32	16	128	256
15	 1o	64	32	128	32	128	64	32
16	 1p	128	32	128	16	64	32	32

Table 1 continued

Entry	Product	Microorganisms[a]						
		Gram-positive		Gram-negative			Fungi[a]	
		SA	BS	EC	PV	PA	CA	AF
17	Ampicillin	2	1	16	16	128	–	–
18	Streptomycin	2	32	4	4	2	–	–
19	Ceftazidime	4	2	4	4	128	–	–
20	Clotrimazole	512	512	512	512	512	2	2

[a] Gram-positive bacteria: SA, *Staphylococcus aureus* ATCC 25923; BS, *Bacillus subtilis* ATCC 6633 and Gram-negative bacteria: EC, *Escherichia coli* ATCC 25922; PV, *Proteus vulgaris* (ATCC 6896); and PA, *Pseudomonas aeruginosa* ATCC 27853

[b] Fungi: CA *Candida albicans* ATCC 76615; and AF *Aspergillus flavus* ATCC 10124

[c] Not tested. Compounds resulted inactive against the fungi

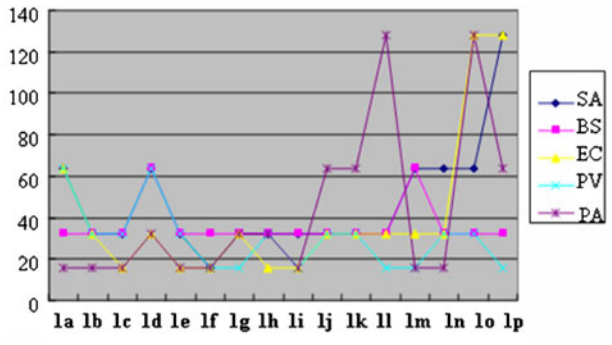


Fig. 2 MIC values (μg/mL) of benzo[*b*][1,4]oxazinones, **1a–p** against bacteria

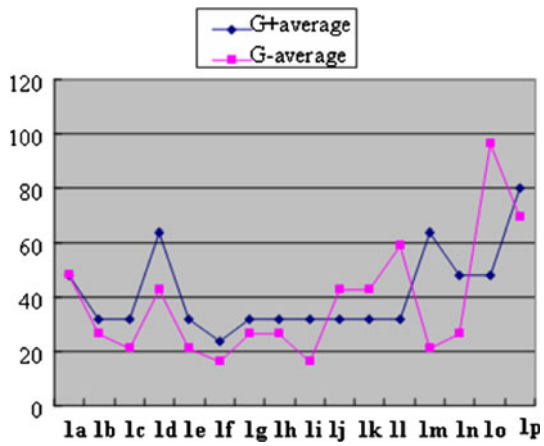


Fig. 3 Average MIC values (μg/ml) of [1,4]oxazinones, **1a–p** against bacteria

Results and discussion

The benzo[*b*][1,4]oxazin-3(4*H*)-ones, **1** were assayed in vitro for their antimicrobial activity against a panel of selected Gram-positive, Gram-negative bacteria, and fungi shown in Table 1, in comparison with those of the reference drugs ampicillin, streptomycin, ceftazidime, and clotrimazole, and the minimal inhibitory concentrations that inhibited the growth of the tested microorganisms (MIC) were detected.

All the compounds displayed good inhibition of the growth of Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus, Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, and *Pseudomonas aeruginosa*. Most compounds exhibited MIC values in the range of 16–64 μg/ml, and the MIC values are represented in Table 1 and Fig. 1. All of the benzo[*b*][1,4]oxazin-3(4*H*)-ones exhibit activity lower than those of the reference drugs ampicillin, streptomycin, ceftazidime, and clotrimazole. The data of average MIC values against Gram-positive and Gram-negative bacteria reported in Figs. 2, 3 indicate that the antibacterial activity against Gram-positive bacteria is weaker than Gram-negative bacteria. It is noteworthy that, among the benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives the inhibitory effect appears to be dependent on the substitution at the benzene ring. The compounds containing fluorine atom possess stronger antimicrobial activity than the compounds holding either chlorine or bromine atom at the benzene ring (**1c**, **1f**, **1i**). It means the introduction of a fluorine atom enhancing the activity against Gram-positive and Gram-negative bacteria. Moreover, the position of the substituent exerts, in general, a certain effect on the activity against all the microorganisms. For instance, the introduction of a chlorine atom in the substances **1a–p** at 7,8-position at the benzene ring, respectively, shows higher antibacterial activity in respect of substances holding chlorine atom at 6-position of ring. On the other hand, with regard to the influence of substitutions on the nitrogen atom of the benzo[*b*] [1,4]oxazin-3(4*H*)-one ring, neither alkyl nor aryl substitution significantly affects the antibacterial activity, while the increase of methylene number attached to benzene group contributes to the activity (**1a** and **1 m**). It is also interesting to point out that benzyl, cyclohexyl, and n-hexyl moieties on *N*-atom attribute to slightly higher

activity compared to the moiety of tetrahydrofuryl methylene.

Among all the tested benzo[*b*][1,4]oxazinones, **1f** exerted the best antibacterial activity against Gram-positive and Gram-negative bacteria, while compound **1p** showed the highest antifungal activity against *Candida albicans* and *Aspergillus flavus.*

All the active compounds exhibit microbiostatic properties having MFC values higher than the corresponding MICs (data not shown).

These observations provide some predictions to design further antimicrobial active compounds prior to their synthesis following with molecular modeling studies.

Conclusions

New benzo[*b*][1,4]oxazin-3(4*H*)-one derivatives, **1a–p**, carrying F, Br and Cl on the benzene ring, or benzyl, cyclohexyl, *n*-hexyl and tetrahydrofuryl methylene groups attached to nitrogen atom were synthesized *via* Smiles rearrangement and assayed in vitro for their antimicrobial activity against Gram-positive, Gram-negative bacteria, and fungi. The method presents an efficient protocol for synthesizing benzo[*b*][1,4]oxazin-3(4*H*)-ones, and its antimicrobial activity showed, on the whole, very good potency toward a wide spectrum of Gram-positive and Gram-negative microorganism (MIC ranging from 16 to 64 μg/ml), whereas weak effectiveness was exhibited against fungi. Data obtained suggest that fluorine atom in the compounds, **1c**, **1f**, **1i** plays an important role in enhancing the antimicrobial properties of this class of compounds. The good properties of this new class of antibacterial substances deserve further investigation to clarify the mode of action at molecular level, responsible for deeper insight into structure–activity relationship and to optimize the effectiveness of this series of molecules.

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