Med Chem Res (2011) 20:626–636
DOI 10.1007/s00044-010-9367-5

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# CsF–Celite catalyzed facile *N*-alkylation of 2(3*H*)-benzoxazolones and antimicrobial properties of 2-substituted benzoxazole and 3-substituted-2(3*H*)-benzoxazolone derivatives

**M. S. R. Murty · Kesur R. Ram · Rayudu Venkateswara Rao · J. S. Yadav · U. S. N. Murty · K. Pranay Kumar**

Received: 11 February 2010 / Accepted: 5 May 2010 / Published online: 29 May 2010


**Abstract** The synthesis and antimicrobial activity studies of a new series of cyclic amine containing benzoxazoles and benzoxazolone-2(3*H*)-ones derivatives were described. The alkylation of benzoxazolone was carried out using cesium fluoride–Celite. The newly synthesized compounds with the influence of the induction of the cyclic amine moiety in the benzoxazole scaffold have been evaluated with respect to the antibacterial and antifungal activity. The 2-cyclic amine-1,3-benzoxazoles (**5a–l**), 5-chloro-3-alkyl substituted-1,3-benzoxazol-2(3*H*)-ones (**8a–f**), and 3-[3-(cyclic amine)propyl]-1,3-benzoxazol-2(3*H*)-ones (**9a–f**) were synthesized. These derivatives were tested for antibacterial and antifungal activity. Among the compounds tested, **8c** and **9f** showed moderate to good antibacterial and antifungal activity. Compound **8a** showed good antifungal activity.

**Keywords** Benzoxazole · Benzoxazolone · Cyclic amine · Cesium fluoride–Celite · Antibacterial and antifungal

Dedicated to Dr. J. Madhusudhana Rao, Director Grade Scientist & Head, Organic Chemistry Division-I, I.I.C.T., Hyderabad, India on his 60th Birth Day.

M. S. R. Murty (✉) · K. R. Ram · R. V. Rao · J. S. Yadav
Discovery Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500607, India
e-mail: msrmurty@ymail.com

U. S. N. Murty · K. Pranay Kumar
Biology Division, Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500607, India

## Introduction

An essential component of the search for new leads in a drug designing program is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds. These are known pharmacophores of a number of biologically active and medicinally useful molecules (Silverman, 1992; Thompson and Ellman, 1996; Robert, 2000). The rapidly increasing occurrence of multiple drug-resistant microbial strains is a serious problem. As the emergence of anti resistant bacteria is inevitable, there is an urgency for the discovery of novel active agents, which is of the highest priority (Norrby, 2001; Tomasz, 1994). Previous reports reveal that benzoxazole derivatives are biologically significant compounds and are known to exhibit various biological activities such as anticancer (Kumar *et al*., 2002; Easmon *et al*., 2001; Jauhari *et al*., 2008; Rida *et al*., 2005), antimicrobial (Kumar *et al*., 2002; Temiz-Arpacı *et al*., 2005), anti-HIV (Rida *et al*., 2005; Temiz-Arpacı *et al*., 2005), and dopamine D4 agonists (Wang *et al*., 2005). The substitution at second position in benzoxazole skeleton is influential for the biological activity of the molecule. Thus, the 2-substituted bis(benzoxazole), UK-1 (**A**) is a natural product (Fig. 1) (Ueki *et al*., 1993) and it showed a wide spectrum of potent anticancer activity against leukemia and lymphoma. The cytotoxicity of the synthetic analogs (Kerwin and Mckee, 2008) of UK-1 was studied toward selective cancer cell lines. Routiennocin (**B**) (Fig. 1) is a spiroketal antibiotic, isolated from a strain of *Streptomyces chartreusis* possessing a benzoxazole ring in its molecular structure, was found to be very active especially against some Gram-positive bacteria by acting as a good ionophore

(Prudhomme *et al*., 1986; Martin *et al*., 1992). Chlorzoxazone (**C**) is a muscle relaxant, benoxaprofen (**D**) and flunoxaprofen (**E**) are anti-inflammatory drugs and these molecules contain benzoxazole pharmacophore. The chemical structures of the drugs are depicted in Fig. 1.

The 2(3*H*)-benzoxazolone heterocycles are considered as "privileged scaffolds" in the design of pharmacological probes. The 2(*3H*)-benzoxazolone heterocycles and its bioisosteric surrogates such as 2(*3H*)-benzothiazolinone, benzoxazinone, etc., have received considerable attention from the medicinal chemists owing to their capacity to mimic a phenol or a catechol moiety in a metabolically stable template (Poupaert *et al*., 2005). The benzoxazolone heterocycle has high flexibility in chemical modifications, allowing changes to the characteristics of side-chains on a rigid platform (Chiarotto *et al*., 2009). Due to that, this template has very broad therapeutic applications. The 2(*3H*)-benzoxazolone heterocycles exhibits various biological activities like anti-HIV (Deng *et al*., 2006), anticancer (Ivanova *et al*., 2007), analgesic (Unlu *et al*., 2003), anti-inflammatory (Koksal *et al*., 2005), antinociceptive (Onkol *et al*., 2001), antimicrobial (Koksal *et al*., 2002), anticonvulsant (Ucar *et al*., 1998), antimalarial (Courtois *et al*., 2004), PPAR$\gamma$ agonist (Blanc-Delmas *et al*., 2006). The functionalization of the nitrogen atom at the third position of benzoxazole is of interest since the electronic characteristics of this atom can be decisive for the biological activity. Several nitrogen heterocycles containing piperazine moiety have been described as potent chemotherapeutic agents. This cyclic amine moiety is also found in drug candidates displaying antiallergic (John *et al*., 1995), antibacterial (Michel *et al*., 1992), antianxiety, antiemetic, antimigraine (Christine *et al*., 1996), and anti-inflammatory (Dogruer *et al*., 1998; Gulcan *et al*., 2003) activities. As a consequence, the development of general economical methods for the synthesis of benzoxazole derivatives containing piperidine moiety in a single molecule frame work has been the subject of considerable synthetic effort.

## Discussion

### Chemistry

In our on going research program of drug designing for new leads, various 2-cyclic amine substituted-1,3-benzoxazoles (**5a–l**), 5-chloro-3-alkyl substituted-1,3-benzoxazol-2(3*H*)-ones (**8a–f**), and 3-[3-(cyclic amine)propyl]-1,3-benzoxazol-2(3*H*)-ones (**9a–f**) were synthesized and were evaluated for antibacterial and antifungal activities. The 2-chlorobenzoxazole (**3**) was commercially available chemical and also otherwise we prepared starting from 2-amino phenol (**1**) (Yamada *et al*., 1998). The 2-aminophenol was treated with carbon disulfide under basic conditions to obtain 2-mercapto-1,3-benzoxazole (**2**), which was further reacted with phosphorus pentachloride ($PCl_5$) to obtain 2-chlorobenzoxazole (**3**). The 2-chlorobenzoxazole was treated with various cyclic amines (**4**) in acetonitrile at 0°C to obtain the compounds **5a–l** (Scheme 1). The products and the corresponding yields are listed in Table 1. When 1 equivalent of 2-methylpiperazine was reacted with 2-chlorobenzoxazole, only mono alkylated product **5i** formed, i.e., alkylation occurred at the less hindered nitrogen. Similarly, when 1 equivalent homopiperazine reacted with 2-chlorobenzoxazole, only mono alkylated product **5j** formed.

Compounds **8a–f** and **9a–f** were synthesized starting from commercially available 5-chlorobenzoxazolone (**6**) as shown in Scheme 2 and the results were mentioned in Table 2.

The alkylation of benzoxazolone under basic conditions, which makes use of base like $K_2CO_3$, is known in literature (Soyer *et al*., 2005). The method involves tedious work up, gives poor to moderate yield with less purity of the product. Hence, herein we report a practical and convenient

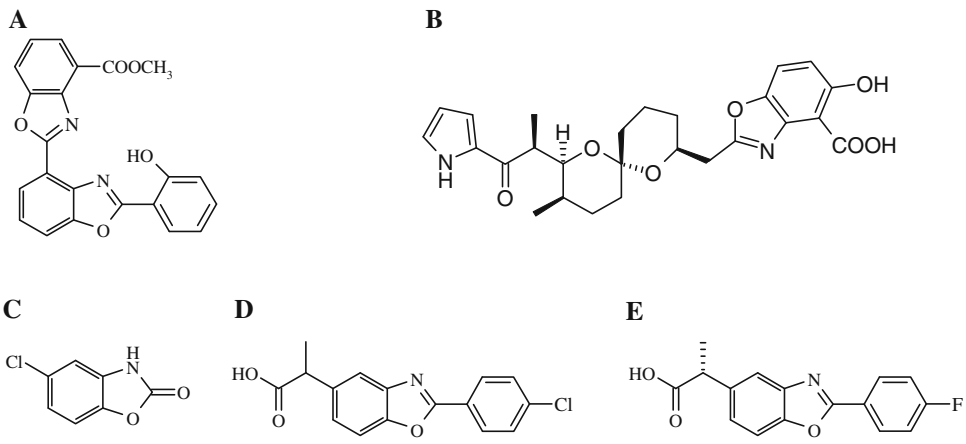
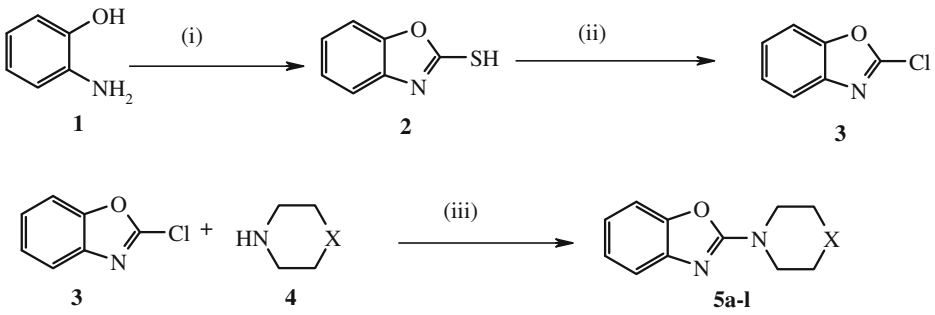



**Fig. 1** Structures of benzoxazole drugs and biomolecules

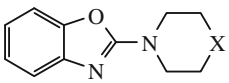
**Scheme 1** Synthesis of 2-cyclic amine benzoxazoles (**5a–l**)



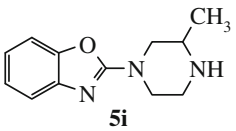
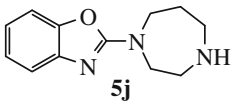

Reagents:(i) $CS_2$, KOH, Ethanol(reflux); (ii) $PCl_5$, dry Toluene; (iii) Acetonitrile, 0°C-rt

X = N-methyl, N-ethyl, N-benzyl, N-phenyl, N-pyridyl, N-pyrimidyl, N-(3-chlorophenyl), N-(2-hydroxyethyl), $CH_2$ , O.
entry 9: 2-(3-methylpiperazin-1-yl)-1,3-benzoxazole.
entry 10: 2-(1,4-Diazepan-1-yl)-1,3-benzoxazole.

**Table 1** Newly synthesized piperazinyl benzoxazoles (**5a–l**) derivatives




**5**

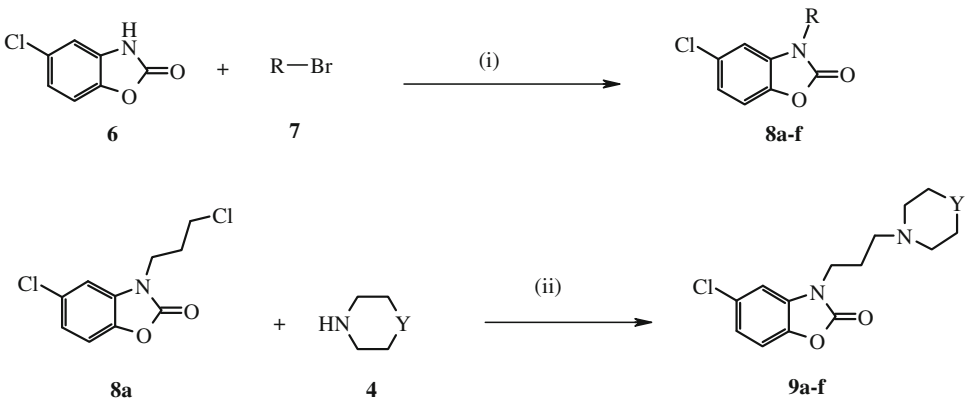
| Entry | X | Product[a] | Yield (%)[b] | Entry | X | Product[a] | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | *N*-methyl | **5a** | 70 | 7 | *N*-3-chlorophenyl | **5g** | 82 |
| 2 | *N*-ethyl | **5b** | 65 | 8 | *N*-2-hydroxyethyl | **5h** | 70 |
| 3 | *N*-benzyl | **5c** | 75 | 9 | – |  **5i** | 69 |
| 4 | *N*-phenyl | **5d** | 80 | 10 | – |  **5j** | 74 |
| 5 | *N*-2-pyridyl | **5e** | 78 | 11 | $CH_2$ | **5k** | 78 |
| 6 | *N*-2-pyrimidyl | **5f** | 85 | 12 | O | **5l** | 68 |

[a] All the products were characterized by $^1$H NMR, $^{13}$C NMR, Mass and IR spectroscopy

[b] Isolated and optimized yields

method for the alkylation of benzoxazolone using cesium fluoride–Celite (CsF–Celite). The synthetic utility of CsF–Celite to synthesize ethers and esters was earlier reported (Shah *et al*., 2002; Polshettiwar and Kaushik, 2005). The alkylation of benzoxazolone catalyzed by CsF–Celite was carried out under mild reaction conditions with high yields and simple work up. Thus, we explored the utility of CsF–Celite system as an efficient, inexpensive, economical, non-corrosive, and eco-friendly reagent for the alkylation process. The preparation of the CsF–Celite was carried out in the same manner as described earlier (Hayat *et al*., 2001). A comparative yields of alkylations using $K_2CO_3$ (Method A) and CsF–Celite (Method B) was mentioned in Table 2. *N*-alkylation of 5-chlorobenzoxazolone was confirmed by the presence of carbonyl stretching at 1774 $cm^{-1}$ in the IR spectrum of 5-chloro-3-(3-chloropropyl)-1,3-

**Scheme 2** Synthesis of 3-substituted benzoxazolones (**8a–f** and **9a–f**)

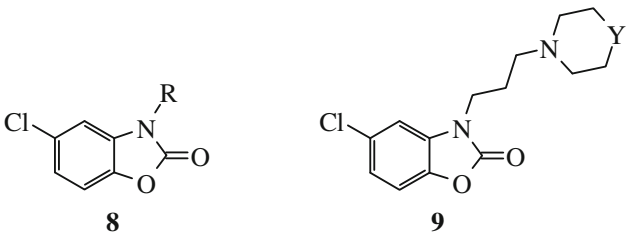



Reagents: (i) Method A: $K_2CO_3$, Acetonitrile, rt; Method B: CsF-Celite, THF, rt;
(ii) Method A: $K_2CO_3$, DMF, 100 $^0$C; Method B: CsF-Celite, THF, Reflux

R=3-chloropropyl, allyl, propagyl, benzyl, 3-butenyl, 3-methyl-2-butenyl

Y=N-benzyl, N-phenyl, N-Pyridyl, N-Pyrimidyl, N-3-chlorophenyl, O

**Table 2** Newly synthesized benzoxazole-2(3*H*)-ones (**8a–f**, **9a–f**) derivatives




| Entry | R | Product[a] | Yield (%)[b] | | Entry | Y | Product[a] | Yield (%)[b] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Method A | Method B | | | | Method A | Method B |
| 1 | 3-Chloropropyl | **8a** | 65 | 86 | 7 | *N*-benzyl | **9a** | 67 | 89 |
| 2 | Allyl | **8b** | 77 | 90 | 8 | *N*-phenyl | **9b** | 72 | 88 |
| 3 | Propagyl | **8c** | 80 | 92 | 9 | *N*-2-pyridyl | **9c** | 77 | 92 |
| 4 | Benzyl | **8d** | 80 | 94 | 10 | *N*-2-pyrimidyl | **9d** | 73 | 90 |
| 5 | 3-Butenyl | **8e** | 70 | 88 | 11 | *N*-3-chlorophenyl | **9e** | 78 | 91 |
| 6 | 3-Methyl-2-butenyl | **8f** | 78 | 92 | 12 | O | **9f** | 75 | 88 |

[a] All the products were characterized by $^1$H NMR, $^{13}$C NMR, Mass and IR spectroscopy

[b] Isolated and optimized yield

benzoxazol-2(3*H*)-one (**8a**). The $^{13}$C chemical shift value for the carbonyl carbon ($\delta = 152.6$ ppm) of the 5-chorobenzoxazolone was retained in the $^{13}$C spectra of **8a** ($\delta = 154.2$ ppm). The compounds **9a–f** were synthesized by conventional conditions (Method A), i.e., by reacting **8a** with various cyclic amines **4** and $K_2CO_3$ (Saxena *et al*., 2007). A facile synthesis of the compounds **9a–f** was carried out by reacting **8a** with various cyclic amines **4** in the presence of catalytic amount of CsF–Celite (Method B) to obtain products in high yields with excellent purity (Scheme 2). The comparative yields of the two methods A and B are mentioned in Table 2. The synthesized compounds **5a–l**, **8a–f**, and **9a–f** were tested for antibacterial and antifungal activity.

## Biology

### Antibacterial activity

All the 24 synthesized compounds were evaluated for antibacterial activity and the results were summarized in

**Table 3** Antibacterial activity of **5a–l**, **8a–f**, and **9a–f**

| MIC(μg/ml) | | | | | | |
|---|---|---|---|---|---|---|
| Compound | Gram-positive | | | Gram-negative | | |
| | *B. subtilis* | *S. aureus* | *S. epidermidis* | *E. coli* | *P. aeroginosa* | *K. pneumoniae* |
| **5a** | 150 | 150 | 75 | 150 | 150 | 150 |
| **5b** | 150 | 150 | 75 | 150 | 150 | 75 |
| **5c** | 150 | 150 | 75 | 150 | 75 | 150 |
| **5d** | 150 | 150 | 150 | 75 | 75 | 150 |
| **5e** | 150 | 150 | 150 | 150 | 75 | 150 |
| **5f** | 150 | 150 | 150 | 150 | 75 | 75 |
| **5g** | 150 | 75 | 150 | 150 | 150 | 150 |
| **5h** | 150 | 75 | 150 | 150 | 75 | 75 |
| **5i** | 150 | 150 | 150 | 75 | 150 | 150 |
| **5j** | 150 | 150 | 150 | 75 | 75 | 75 |
| **5k** | 150 | 150 | 150 | 150 | 150 | 150 |
| **5l** | 150 | 75 | 150 | 150 | 150 | 37.5 |
| **8a** | 150 | 150 | 150 | 150 | 150 | 150 |
| **8b** | 150 | 150 | 150 | 150 | 75 | 37.5 |
| **8c** | 75 | 75 | 75 | 37.5 | 37.5 | 75 |
| **8d** | 150 | 75 | 75 | 150 | 150 | 75 |
| **8e** | 150 | 150 | 150 | 150 | 150 | 37.5 |
| **8f** | 150 | 150 | 75 | 150 | 75 | 150 |
| **9a** | 150 | 150 | 75 | 150 | 75 | 150 |
| **9b** | 150 | 150 | 150 | 150 | 150 | 150 |
| **9c** | 150 | 150 | 150 | 150 | 75 | 150 |
| **9d** | 150 | 150 | 150 | 150 | 150 | 150 |
| **9e** | 150 | 150 | 150 | 150 | 150 | 150 |
| **9f** | 75 | 75 | 75 | 37.5 | 37.5 | 75 |
| Penicillin | 1.562 | 1.562 | 3.125 | 12.5 | 12.5 | 6.25 |
| Streptomycin | 6.25 | 6.25 | 3.125 | 6.25 | 1.562 | 3.125 |

Table 3. In the **5** series of benzoxazole derivatives **5h**, **5j**, and **5l** showed moderate antibacterial activity against some bacteria, while other compounds were inactive. Among these three compounds, **5h** contains *N*-(2-hydroxyethyl) group while **5j** and **5l** contains NH and O at the fourth position of cyclic amine.

Among the **8** and **9** series of benzoxazolone derivatives, **8c** with *N*-propagyl group and **9f** with *N*-(3-morpholinyl)propyl group exhibited moderate activity against both Gram-positive and Gram-negative bacteria.

## Antifungal activity

All the 24 synthesized compounds were evaluated for antifungal activity and the results are summarized in Table 4. Among the antifungal activity of the **5** series compounds, **5k** with piperidine as cyclic amine showed moderate activity. In the **8** series compounds, **8a** with *N*-3-chloropropyl group and **8c** with *N*-propagyl group showed good antifungal activity, while **8f** with *N*-3-methyl-2-butenyl group showed moderate activity. In the **9** series compounds, only **9f** with *N*-(3-morpholinyl)propyl group showed moderate activity. None of the compound has shown higher antimicrobial activity than drugs used as a standard. These results indicate that larger groups at fourth position of cyclic amine and third position of benzoxazolone have no significant contribution to the antimicrobial activity of these compounds. The benzoxazolone derivatives were comparatively more active than benzoxazole derivatives toward antimicrobial activity. This may be attributed to the more functionality sites in the benzoxazolone skeleton to interact with the biological system in comparison with benzoxazole motif.

## Conclusions

Various 2-substituted benzoxazoles and 3-substituted-2(3*H*)-benzoxazolone derivatives were synthesized. The utility of CsF–Celite as a solid base for alkylation of

**Table 4** Antifungal activity of **5a–l**, **8a–f**, and **9a–f**

| Compound | *C. albicans* | | *S. cerevisiae* | | *R. oryzae* | | *A. niger* | |
|---|---|---|---|---|---|---|---|---|
| | 100 μg | 150 μg | 100 μg | 150 μg | 100 μg | 150 μg | 100 μg | 150 μg |
| **5a** | –[a] | – | – | – | – | – | – | – |
| **5b** | 8 | 10 | 7 | 9 | – | – | 9 | 12 |
| **5c** | – | 9 | 12 | 10 | – | 9 | – | 9 |
| **5d** | – | 9 | – | – | – | – | – | – |
| **5e** | 8 | 10 | – | – | – | – | – | – |
| **5f** | – | – | – | – | 8 | 10 | – | – |
| **5g** | – | – | – | – | – | – | – | – |
| **5h** | – | – | – | – | – | – | – | – |
| **5i** | – | – | – | – | – | – | – | – |
| **5j** | – | – | – | – | 8 | 10 | – | – |
| **5k** | 9 | 12 | 9 | 12 | 8 | 11 | 8 | 10 |
| **5l** | 7 | 9 | – | – | – | – | – | – |
| **8a** | 14 | 19 | 12 | 15 | 11 | 15 | 13 | 17 |
| **8b** | – | 8 | – | – | – | – | 8 | 10 |
| **8c** | 8 | 11 | 14 | 18 | 15 | 19 | 15 | 18 |
| **8d** | – | – | – | – | – | – | – | – |
| **8e** | – | – | – | – | 9 | 13 | – | – |
| **8f** | 7 | 10 | 8 | 10 | – | 9 | 8 | 11 |
| **9a** | – | 9 | – | – | – | – | 7 | 9 |
| **9b** | – | – | – | – | – | – | – | – |
| **9c** | – | – | – | – | – | – | – | – |
| **9d** | – | – | – | – | – | – | – | – |
| **9e** | – | – | – | – | – | – | – | – |
| **9f** | 8 | 10 | 8 | 10 | 10 | 13 | 8 | 10 |
| Amphotericin-B (50 μg) | 23.5 | | 22 | | 24 | | 25 | |

[a] Not active

Concentration used: 100 μg/150 μg

Negative control: DMSO (no activity)

Positive control: amphotericin-B (50 μg)

benzoxazolone was explored. The method offers advantages like easy work-up and excellent yields. The catalyst is non-corrosive, easy to handle, and can be easily prepared. Totally, 24 compounds were synthesized and evaluated for antibacterial and antifungal activity. Two compounds **8a** and **8c** showed good antifungal activity. The results indicate that larger groups at fourth position of cyclic amine and third position of benzoxazolone have no significant contribution to the antimicrobial activity of these compounds. The benzoxazolone derivatives are comparatively more active than benzoxazole derivatives. Further work to synthesize more active compounds is under progress.

## Experimental

Melting points were determined on a Buchi capillary melting point apparatus. The $^{1}$H NMR (200 and 300 MHz) and $^{13}$C NMR (75 MHz) spectra was recorded on Varian Gemini and Bruker Avance spectrometers using TMS as an internal standard. The mass spectra were recorded on a VG Auto Spec mass spectrometer. Elemental analyses were performed on Elemental VARIO EL elemental analyzer. IR spectra were recorded on Perkin-Elmer Infrared-683.

### Typical procedure for preparation of 2-(4-methylpiperazin-1-yl)-1,3-benzoxazole (**5a**) as a typical procedure

The 2-chlorobenzoxazole (**3**) (2.6 mmol, 400 mg) was added to a solution of 1-methyl piperazine (2.6 mmol, 260 mg) in dry acetonitrile (30 ml) at 0°C. The mixture was stirred at 0°C–rt for 30 min, quenched in ice water (30 ml), extracted with ethyl acetate (3 × 20 ml), and dried over $Na_2SO_4$. After concentration, the residue was purified by flash chromatography to obtain the pure product and was crystallized from methanol.

White solid. m.p. 37–38°C; IR (KBr) *v* 3057, 2933, 2854, 2796, 1639, 1578, 1456, 1363. $^{1}$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.22 (t, 2H, $J = 7.3$ Hz); 7.09 (t, 1H, $J = 7.3$ Hz); 6.95 (t, 1H, $J = 7.3$ Hz); 3.67 (t, 4H, $J = 5.1$ Hz); 2.48 (t, 4H, $J = 5.1$ Hz); 2.30 (s, 3H). EI-MS (*m/z*): 217 ($M^+$). Anal. calcd for $C_{12}H_{15}N_3O$ (217): C, 66.34; H, 6.96; N, 19.34. Found: C, 66.36; H, 6.94; N, 19.37.

2-(4-Ethylpiperazin-1-yl)-1,3-benzoxazole (**5b**)

White solid. m.p. 78–80°C; IR (KBr) *v* 2970, 2931, 2813, 1638, 1578, 1525, 1459, 1399. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.30 (d, 1H, $J = 7.7$ Hz); 7.20 (d, 1H, $J = 7.7$ Hz); 7.11 (t, 1H, $J = 7.7$ Hz); 6.96 (t, 1H, $J = 7.7$ Hz); 3.70 (t, 4H, $J = 4.9$ Hz); 2.54 (t, 4H, $J = 4.9$ Hz); 2.45 (q, 2H, $J = 7.2$ Hz); 1.11 (t, 3H, $J = 7.2$ Hz). EI-MS (*m/z*): 231 ($M^+$). Anal. calcd for $C_{13}H_{17}N_3O$ (231): C, 67.51; H, 7.41; N, 18.17. Found: C, 67.54; H, 7.39; N, 18.15.

2-(4-Benzylpiperazin-1-yl)-1,3-benzoxazole (**5c**)

White solid. m.p. 230–231°C; IR (KBr) *v* 3028, 2917, 2860, 2821, 1640, 1578, 1494, 1455,1 395. NMR (300 MHz, $CDCl_3$) $\delta$: 7.34–7.25 (m, 6H); 7.19 (d, 1H, $J = 7.$ 8 Hz); 7.11 (t, 1H, $J = 7.$ 8 Hz); 6.96 (t, 1H, $J = 7.8$ Hz); 3.70 (t, 4H, $J = 4.7$ Hz); 3.54 (s, 2H); 2.56 (t, 4H, $J = 4.7$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 162.1, 148.7, 143.0, 136.9, 129.2, 128.4, 127.4, 123.9, 120.6, 116.2, 108.7, 62.9, 52.1, 45.4. EI-MS (*m/z*): 293($M^+$). Anal. calcd for $C_{18}H_{19}N_3O$ (293): C, 73.70; H, 6.53; N, 14.32. Found: C, 73.74; H, 6.52; N, 14.33.

2-(4-Phenylpiperazin-1-yl)-1,3-benzoxazole (**5d**)

White solid. m.p. 147–148°C; IR (KBr) *v* 2980, 2914, 2822, 1629, 1575, 1497, 1455. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.33 (d, 1H, $J = 7.6$ Hz); 7.26 (d, 1H, $J = 7.6$ Hz); 7.23 (d, 2H, $J = 6.8$ Hz); 7.14 (t, 1H, $J = 6.8$ Hz); 6.99 (t, 1H, $J = 7.6$ Hz); 6.92 (d, 2H, $J = 6.8$ Hz); 6.88 (t, 1H, $J = 7.6$ Hz); 3.85 (t, 4H, $J = 5.3$ Hz); 3.29 (t, 4H, $J = 5.3$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 161.8, 150.8, 148.6, 142.6, 129.2, 124.1, 120.9, 120.8, 116.9, 116.3, 108.8, 49.2, 45.5. EI-MS (*m/z*): 279 ($M^+$). Anal. calcd for $C_{17}H_{17}N_3O$ (279): C, 73.10; H, 6.13; N, 15.04. Found: C, 73.08; H, 6.12; N, 15.05.

2-[4-(Pyridin-2-yl)piperazin-1-yl]-1,3-benzoxazole (**5e**)

White solid. m.p. 186–188°C; IR (KBr) *v* 2993, 2917, 2846, 1635, 1576, 1480, 1459, 1435. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 8.19–8.15 (m, 1H); 7.51–7.44 (m, 1H); 7.33 (d, 1H, $J = 7.7$ Hz); 7.23 (d, 1H, $J = 7.7$ Hz); 7.13 (dt, 1H, $J = 6.6$, 1.1 Hz); 6.99 (dt, 1H, $J = 6.6$, 1.3 Hz); 6.68–6.61 (m, 2H); 3.88–3.77 (m, 4H); 3.74–3.67 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 161.9, 158.2, 148.7, 146.8, 142.8, 138.4, 124.0, 120.9, 116.4, 113.8, 108.8, 107.8, 45.2, 44.9. EI-MS (*m/z*): 280 ($M^+$). Anal. calcd for $C_{16}H_{16}N_4O$ (280): C, 68.55; H, 5.75; N, 19.99. Found: C, 68.59; H, 5.78; N, 19.96.

2-[4-(Pyrimidin-2-yl)piperazin-1-yl]-1,3-benzoxa (**5f**)

White solid. m.p. 183–185°C; IR (KBr) *v* 2911, 2860, 1651, 1581, 1542, 1490, 1451, 1393. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 8.30 (d, 2H, $J = 5.0$ Hz); 7.33 (d, 1H, $J = 7.6$ Hz); 7.23 (d, 1H, $J = 7.6$ Hz); 7.13 (t, 1H, $J = 7.6$ Hz); 6.99 (t, 1H, $J = 7.6$ Hz); 6.51 (t, 1H, $J = 5.0$ Hz); 4.04–3.94 (m, 4H); 3.81–3.72 (m, 4H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 166.6, 161.4, 157.8, 148.6, 144.4, 124.3, 121.1, 116.3, 110.6, 108.9, 45.5, 43.2. EI-MS (*m/z*): 281 ($M^+$). Anal. calcd for $C_{15}H_{15}N_5O$ (281): C, 64.04; H, 5.37; N, 24.89. Found: C, 64.08; H, 5.41; N, 24.94.

2-[4-(3-Chlorophenyl)piperazin-1-yl]-1,3-benzoxazole (**5g**)

White solid. m.p. 134–136°C; IR (KBr) *v* 3015, 2913, 1769, 1739, 1625, 1593, 1478, 1397. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.33 (d, 1H, $J = 6.8$ Hz); 7.23 (d, 1H, $J = 7.6$ Hz); 7.17 (d, 1H, $J = 7.6$ Hz); 7.13 (t, 1H, $J = 7.6$ Hz); 7.00 (t, 1H, $J = 7.6$ Hz); 6.90 (t, 1H, $J = 2.3$ Hz); 6.85 (d, 1H, $J = 7.6$ Hz); 6.79 (d, 1H, $J = 7.6$ Hz); 3.84 (t, 4H, $J = 5.3$ Hz); 3.31 (t, 4H, $J = 5.3$ Hz,). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 161.9, 151.9, 150.9, 142.8, 135.0, 130.1, 124.1, 120.9, 120.3, 116.6, 116.4, 114.7, 108.8, 48.6, 45.3. EI-MS (*m/z*): 313 ($M^+$). Anal. calcd for $C_{17}H_{16}ClN_3O$ (313): C, 65.07; H, 5.14; N, 13.39. Found: C, 65.09; H, 5.14; N, 13.36.

2-[4-(1,3-Benzoxazol-2-yl)piperazine-1-yl]ethanol (**5h**)

Brown solid. m.p. 35–36°C; IR (KBr) *v* 3423, 2936, 2855, 1631, 1578, 1483, 1458. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.42 (d, 1H, $J = 7.6$ Hz); 7.30 (d, 1H, $J = 7.6$ Hz); 7.19 (t, 1H, $J = 7.6$ Hz); 7.11 (t, 1H, $J = 7.6$ Hz); 4.64 (t, 2H, $J = 6.0$ Hz); 2.82 (t, 2H, $J = 6.0$ Hz); 2.52 (t, 4H, $J = 5.2$ Hz); 1.60 (t, 4H, $J = 5.2$ Hz); 1.49–1.38 (m, 1H). EI-MS (*m/z*): 247($M^+$).

2-(3-Methylpiperazin-1-yl)-1,3-benzoxazole (**5i**)

Brown solid. m.p. 51–52°C; IR (KBr) *v* 3321, 3057, 2958, 2921, 2856, 1638, 1578, 1458, 1400. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.30 (d, 1H, $J = 7.6$ Hz); 7.19 (d, 1H, $J = 7.6$ Hz); 7.11 (t, 1H, $J = 7.6$ Hz); 6.95 (t, 1H, $J = 7.6$ Hz); 4.11 (d, 2H, $J = 11.3$ Hz); 3.07 (t, 2H, $J = 9.0$ Hz); 2.91 (t, 2H, $J = 9.0$ Hz); 2.71 (t, 1H, $J = 8.3$ Hz); 1.80 (s, 1H); 1.11 (d, 3H, $J = 8.3$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 162.2, 148.8, 143.1, 124.5, 120.8, 116.4, 108.9, 53.2, 50.5, 46.2, 45.7, 19.8. EI-MS (*m/z*): 217 ($M^+$). Anal. calcd for $C_{12}H_{15}N_3O$ (217): C, 66.34; H, 6.96; N, 19.34. Found: C, 66.36; H, 6.99; N, 19.29.

2-(1,4-Diazepan-1-yl)-1,3-benzoxazole (**5j**)

Brown solid. m.p. 195–198°C; IR (KBr) *v* 3399, 3050, 2934, 1639, 1578, 1459, 1402. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.31 (d, 1H, $J = 7.6$ Hz); 7.23 (d, 1H, $J = 7.6$ Hz); 7.13 (t, 1H, $J = 7.$ 6 Hz); 6.98 (t, 1H, $J = 7.6$ Hz); 3.96 (s, 2H); 3.76 (t, 4H, $J = 6.0$ Hz); 3.07 (t, 1H, $J = 5.2$ Hz); 2.91 (t, 1H, $J = 5.2$ Hz); 2.27(q, 1H, $J = 6.0$ Hz); 1.97 (q, 1H, $J = 6.0$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 161.6, 148.9, 143.1, 124.0, 120.6, 116.2, 108.7, 49.5, 49.1, 48.4, 47.4, 26.7. EI-MS (*m/z*): 217 ($M^+$). Anal. calcd for $C_{12}H_{15}N_3O$ (217): C, 66.34; H, 6.96; N, 19.34. Found: C, 66.31; H, 6.97; N, 19.32.

2-(Piperidin-1-yl)-1,3-benzoxazole (**5k**)

Brown solid. m.p. 71–72°C; IR (KBr) *v* 3057, 2936, 2854, 1638, 1577, 1525, 1455, 1394. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.33 (d, 1H, $J = 7.9$ Hz); 7.23 (d, 1H, $J = 7.9$ Hz); 7.14 (t, 1H, $J = 7.9$ Hz); 6.99 (t, 1H, $J = 7.9$ Hz); 3.70 (s, 4H); 1.74 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 161.9, 148.4, 142.2, 124.1, 120.7, 115.8, 108.7, 46.8, 25.2, 23.9. EI-MS (*m/z*): 202 ($M^+$). Anal. calcd for $C_{12}H_{14}N_2O$ (202): C, 71.26; H, 6.98; N, 13.85. Found: C, 71.29; H, 7.00; N, 13.82.

2-(Morpholin-4-yl)-1,3-benzoxazole (**5l**)

Brown solid. m.p. 205–206°C; IR (KBr) *v* 3057, 2966, 2920, 2863, 1637, 1578, 1525, 1454, 1398. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.32 (d, 1H, $J = 7.9$ Hz); 7.21 (d, 1H, $J = 7.9$ Hz); 7.13 (t, 1H, $J = 7.9$ Hz); 6.98 (t, 1H, $J = 7.9$ Hz); 3.77 (t, 4H, $J = 4.5$ Hz); 3.64 (t, 4H, $J = 4.5$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 161.2, 148.2, 141.1, 124.3, 121.3, 116.0, 108.9, 66.0, 45.8. EI-MS (*m/z*): 204 ($M^+$). Anal. calcd for $C_{11}H_{12}N_2O_2$ (204): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.65; H, 5.94; N, 13.69.

Typical procedure for the preparation of the 5-chloro-3-(3-chloropropyl)-1,3-benzoxazol-2(3*H*)-one (**8a**)

*Method A (Soyer et al., 2005)*

A mixture of 5-chlorobenzoxazolone (**6**) (3.0 mmol) and $K_2CO_3$ (4.5 mmol) in dry acetonitrile (15 ml) was stirred for 10 min under $N_2$ atmosphere. 3-Chloro-1-bromopropane (3.2 mmol) was added through syringe to the above mixture and stirred for 8 h. After the reaction completed (TLC), cold water was added to the reaction mixture and stirred for 30 min. The separated solid was filtered, washed with cold water, and crystallized from ethanol to give the pure product.

*Method B*

A mixture of 5-chlorobenzoxazolone (**6**) (3.0 mmol) and CsF–Celite (4.5 mmol) in dry THF (15 ml) was stirred for 10 min under $N_2$ atmosphere. 3-Chloro-1-bromopropane (3.2 mmol) was added through syringe to the above mixture and stirred for 4 h. After the reaction was completed (TLC), the reaction mixture was filtered through Celite and solid was washed with ethylacetate (2 × 10 ml). The combined filtrate was dried ($Na_2SO_4$) and evaporated to give the pure product.

White solid. m.p. 82–84°C; IR (KBr) *v* 3063, 2933, 1774, 1611, 1485, 1369, 1247, 1061, 829, 721. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.17–7.03 (m, 3H); 3.99 (t, 2H, $J = 7.0$ Hz); 3.62 (t, 2H, $J = 5.5$ Hz); 2.28 (quintet, 2H, $J = 7.0$ Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 154.2, 141.1, 132.1, 129.5, 122.4, 109.9, 108.6, 41.6, 39.7, 30.3. EI-MS (*m/z*): 246 ($M^+$). Anal. calcd for $C_{10}H_9Cl_2NO_2$ (246): C, 48.81; H, 3.69; N, 5.69. Found: C, 48.84; H, 3.71; N, 5.65.

5-Chloro-3-(prop-2-en-1-yl)-1,3-benzoxazol-2(3*H*)-one (**8b**)

White solid. m.p. 64–66°C; IR (KBr) *v* 3070, 2932, 1768, 1607, 1487, 1374, 1341, 1245, 1006, 801, 704. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.15–7.02 (m, 2H); 6.91 (d, 1H, $J = 1.7$ Hz); 6.00-5.79 (m, 1H); 5.39–5.27 (m, 2H); 4.42 (d, 2H, $J = 6.1$ Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 154.1, 141.0, 131.9, 130.0, 129.3, 122.3, 119.2, 110.7, 109.4, 44.7. EI-MS (*m/z*): 210 ($M^+$). Anal. calcd for $C_{10}H_8ClNO_2$ (210): C, 57.30; H, 3.85; N, 6.68. Found: C, 57.33; H, 3.83; N, 6.72.

5-Chloro-3-(prop-2-yn-1-yl)-1,3-benzoxazol-2(3*H*)-one (**8c**)

White solid. m.p. 91–93°C; IR (KBr) *v* 3087, 2925, 2125, 1779, 1605, 1485, 1377, 1350, 1200, 1023, 813, 747. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.18-6.99 (m, 3H); 4.57 (d, 2H, $J = 2.6$ Hz); 2.48 (t, 1H, $J = 2.6$ Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 153.4, 140.9, 130.8, 129.5, 122.8, 110.8, 109.7, 74.9, 74.4, 31.9. EI-MS (*m/z*): 208 ($M^+$). Anal. calcd for $C_{10}H_6ClNO_2$ (208): C, 57.85; H, 2.91; N, 6.75. Found: C, 57.84; H, 2.95; N, 6.73.

3-Benzyl-5-chloro-1,3-benzoxazol-2(3*H*)-one (**8d**)

White solid. m.p. 172–174°C; IR (KBr) *v* 3064, 2937, 1769, 1610, 1484, 1341, 1251, 1012, 811, 700. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.40–7.26 (m, 5H); 7.13–7.00 (m, 2H); 6.78 (d, 1H, $J = 1.5$ Hz); 4.95 (s, 2H). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 154.5, 140.9, 134.1, 131.8, 129.3,

129.1, 128.5, 127.6, 122.4, 110.8, 109.3, 46.2. EI-MS (*m/z*): 260 ($M^+$). Anal. calcd for $C_{14}H_{10}ClNO_2$ (260): C, 64.75; H, 3.88; N, 5.39. Found: C, 64.77; H, 3.85; N, 5.43.

3-(But-3-en-1-yl)-5-chloro-1,3-benzoxazol-2(3*H*)-one (**8e**)

White solid. m.p. 53–54°C; IR (KBr) *v* 3059, 2953, 1763, 1612, 1487, 1343, 1246, 1060, 796, 682. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.13–7.02 (m, 2H); 6.93 (d, 1H, $J = 2.3$ Hz); 5.88–5.71 (m, 1H); 5.16–5.06 (m, 2H); 3.85 (t, 2H, $J = 7.6$ Hz); 2.53 (quartet, 2H, $J = 7.6$). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 154.4, 141.1, 133.2, 132.1, 129.3, 122.3, 118.6, 110.8, 108.9, 41.8, 32.0. EI-MS (*m/z*): 224 ($M^+$). Anal. calcd for $C_{11}H_{10}ClNO_2$ (224): C, 59.07; H, 4.51; N, 6.26. Found: C, 59.03; H, 4.52; N, 6.29.

5-Chloro-3-(3-methylbut-2-en-1-yl)-1,3-benzoxazol-2(3*H*)-one (**8f**)

White solid. m.p. 74–75°C; IR (KBr) *v* 3065, 2925, 1772, 1612, 1484, 1343, 1248, 1007, 834, 748. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.13–6.98 (m, 2H); 6.85 (s, 1H); 5.26 (t, 1H, $J = 6.8$ Hz); 4.37 (d, 2H, $J = 6.8$ Hz); 1.85 (s, 3H); 1.77 (s, 3H). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 154.2, 141.0, 138.9, 131.9, 129.1, 122.2, 116.5, 110.6, 109.1, 40.3, 25.7, 18.0. EI-MS (*m/z*): 239 (M + 1). Anal. calcd for $C_{12}H_{12}ClNO_2$ (238): C, 60.64; H, 5.09; N, 5.89. Found: C, 60.62; H, 5.12; N, 5.93.

Typical procedure for the preparation of the 5-chloro-3-[3-(4-benzylpiperazin-1-yl)propyl]-1,3-benzoxazol-2(3*H*)-one (**9a**)

*Method A (Saxena et al., 2007)*

A mixture of *N*-benzylpiperazine (2 mmol) and $K_2CO_3$ (3 mmol) in dry *N*,*N*-dimethyl formamide (10 ml) was stirred for 10 min under $N_2$ atmosphere. 5-Chloro-3-(3-chloropropyl)-2,3-dihydro-1,3-benzoxazol-2-one (**8a**) (2 mmol) in dry *N*,*N*-dimethyl formamide (5 ml) was added through syringe to the above mixture and stirred for 5 h at 100°C. After the reaction completed (TLC), cold water was added to the reaction mixture and was stirred for 30 min. The separated solid was filtered, washed with cold water, and crystallized from ethanol to give the pure product.

*Method B*

CsF–Celite (3 mmol) was added to a solution of *N*-benzylpiperazine (2 mmol) and 5-chloro-3-(3-chloropropyl)-2,3-dihydro-1,3-benzoxazol-2-one (**8a**) (2 mmol) in dry THF (15 ml) and stirred under reflux for 4 h. After completion of the reaction (TLC), the mixture was filtered through Celite and the solid was washed with ethylacetate (2 × 10 ml). The combined filtrate was dried ($Na_2SO_4$) and evaporated to give the pure product.

Brown solid. m.p. 103–105°C; IR (KBr) *v* 2939, 2811, 1782, 1612, 1488, 1370, 1248, 1010, 804, 744. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.31–7.16 (m, 5H); 7.13 (d, 1H, $J = 2.3$ Hz); 7.09–6.98 (m, 2H); 3.86 (t, 2H, $J = 6.8$ Hz); 3.49 (s, 2H); 2.55–2.29 (m, 10H); 1.91 (quintet, 2H, $J = 6.8$ Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 154.4, 141.0, 137.9, 132.7, 129.2, 129.1, 128.2, 126.9, 121.9, 110.6, 109.2, 63.0, 54.5, 53.0, 40.3, 24.5. EI-MS (*m/z*): 386 ($M^+$). Anal. calcd for $C_{21}H_{24}ClN_3O_2$ (386): C, 65.36; H, 6.27; N, 10.89. Found: C, 65.34; H, 6.28; N, 10.91.

5-Chloro-3-[3-(4-phenylpiperazin-1-yl)propyl]-1,3-benzoxazol-2(3*H*)-one (**9b**)

Brown solid. m.p. 128–129°C; IR (KBr) *v* 3056, 3010, 2940, 2827, 1783, 1598, 1489, 1355, 1241, 1058, 834, 751. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$: 7.30–6.98 (m, 5H); 6.92–6.75 (m, 3H); 3.91 (t, 2H, $J = 6.3$ Hz); 3.14 (t, 4H, $J = 5.5$ Hz); 2.52 (t, 4H, $J = 5.5$ Hz); 2.42 (t, 2H, $J = 6.3$ Hz); 1.97 (quintet, 2H, $J = 6.3$ Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 154.3, 151.1, 141.0, 132.6, 129.1, 129.0, 122.0, 119.7, 116.7, 110.7, 109.1, 54.6, 52.0, 49.0, 40.3, 24.4. EI-MS (*m/z*): 372 ($M^+$). Anal. calcd for $C_{20}H_{22}ClN_3O_2$ (372): C, 64.60; H, 5.96; N, 11.33. Found: C, 64.63; H, 5.92; N, 11.34.

5-Chloro-3-{3-[4-(pyridin-2-yl)piperazin-1-yl]propyl}-1,3-benzoxazol-2(3*H*)-one (**9c**)

White solid. m.p. 132–133°C; IR (KBr) *v* 2944, 2826, 1780, 1594, 1487, 1370, 1250, 1060, 774. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.12 (dd, 1H, $J = 3.8$, 1.5 Hz); 7.41 (dt, 1H, $J = 7.6$, 1.5 Hz); 7.14 (d, 1H, $J = 1.5$ Hz); 7.11–7.00 (m, 2H); 6.58 (dt, 2H, $J = 7.6$, 2.3); 3.91 (t, 2H, $J = 6.8$ Hz); 3.49 (t, 4H, $J = 5.3$ Hz); 2.46 (t, 4H, $J = 5.3$ Hz); 2.40 (t, 2H, $J = 6.0$ Hz); 1.96 (quintet, 2H, $J = 6.0$ Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 159.4, 154.5, 148.0, 140.7, 137.4, 132.8, 129.2, 122.0, 113.3, 110.5, 108.9, 107.0, 54.8, 53.0, 44.9, 40.2, 24.6. EI-MS (*m/z*): 373 ($M^+$). Anal. calcd for $C_{19}H_{21}ClN_4O_2$ (373): C, 61.21; H, 5.68; N, 15.03. Found: C, 61.23; H, 5.65; N, 15.01.

5-Chloro-3-{3-[4-(pyrimidin-2-yl)piperazin-1-yl]propyl}-1,3-benzoxazol-2(3*H*)-one (**9d**)

White solid. m.p. 125–126°C; IR (KBr) *v* 2927, 2853, 1781, 1585, 1488, 1362, 1252, 981, 801, 750. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 8.24 (d, 2H, $J = 4.9$ Hz); 7.14 (d,

1H, $J = 2.0$ Hz); 7.11–7.03 (m, 2H); 6.43 (t, 1H, $J = 4.9$ Hz); 3.93 (t, 2H, $J = 6.8$ Hz); 3.78 (t, 4H, $J = 4.9$ Hz); 2.45–2.38 (m, 6H); 1.98 (quintet, 2H, $J = 6.8$ Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 161.6, 157.4, 154.8, 150.8, 132.9, 129.4, 122.1, 110.7, 109.8, 109.1, 54.8, 53.0, 43.4, 40.3, 24.3. EI-MS (*m/z*): 374 ($M^+$). Anal. calcd for $C_{18}H_{20}ClN_5O_2$ (374): C, 57.83; H, 5.39; N, 18.73. Found: C, 57.80; H, 5.43; N, 18.76.

5-Chloro-3-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}-1,3-benzoxazol-2(3*H*)-one (**9e**)

Brown solid. m.p. 138–140°C; IR (KBr) *v* 2947, 2824, 1781, 1594, 1487, 1372, 1246, 985, 770. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.17–7.01 (m, 4H); 6.86–6.68 (m, 3H); 3.91 (t, 2H, $J = 6.2$ Hz); 3.14 (t, 4H, $J = 5.0$ Hz); 2.50 (t, 4H, $J = 4.9$ Hz); 2.42 (t, 2H, $J = 6.4$ Hz); 1.96 (quintet, 2H, $J = 6.2$ Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 152.2, 141.1, 135.0, 132.6, 130.0, 129.3, 122.1, 120.0, 119.3, 115.7, 113.8, 110.7, 109.0, 54.6, 52.9, 48.5, 40.3, 24.4. EI-MS (*m/z*): 406 ($M^+$). Anal. calcd for $C_{20}H_{21}Cl_2N_3O_2$ (406): C, 59.12; H, 5.21; N, 10.34. Found: C, 59.15; H, 5.22; N, 10.32.

5-Chloro-3-[3-(morpholin-4-yl)propyl]-1,3-benzoxazol-2(3*H*)-one (**9f**)

Brown solid. m.p. 97–99°C; IR (KBr) *v* 2953, 2855, 1782, 1613, 1488, 1370, 1251, 1117, 805, 750. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 7.13–7.01 (m, 3H); 3.89 (t, 2H, $J = 6.4$ Hz); 3.63 (t, 4H, $J = 4.5$ Hz); 2.40–2.29 (m, 6H); 1.93 (quintet, 2H, $J = 6.4$ Hz). $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$: 154.6, 153.1, 141.2, 129.4, 122.1, 110.8, 109.0, 66.9, 55.0, 53.4, 40.3, 24.0. EI-MS (*m/z*): 297 ($M^+$). Anal. calcd for $C_{14}H_{17}ClN_2O_3$ (297): C, 56.66; H, 5.77; N, 9.44. Found: C, 56.62; H, 5.78; N, 9.47.

## Antibacterial activity

### Determination of minimum inhibitory concentration

The minimum inhibitory concentrations (MIC) of the new compounds **5a–l**, **8a–f**, and **9a–f** were tested against three representative Gram-positive organisms viz. *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), *Staphylococcus epidermidis*, and Gram-negative organisms viz *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 741), and *klebsiella pneumoniae* (MTCC 618) by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards (NCCLS, 2000).

Standard antibacterial agents like Penicillin and Streptomycin were also screened under identical conditions for comparison. The minimum inhibitory concentration (MIC) values are presented in Table 3.

## Antifungal activity

In vitro antifungal activity of the **5a–l**, **8a–f**, and **9a–f** was studied against the fungal strains, *Candida albicans* (MTCC 227), *Saccharomyces cereviseae* (MTCC 36), *Rhizopus oryzae* (MTCC 262), *Aspergillus niger* (MTCC 282) by agar well diffusion method (Linday, 1962). Standard antifungal agent Amphotericin-B was also screened under identical conditions for comparison. The zone of inhibition values of the tested compounds was mentioned in Table 4.

The ready-made potato dextrose agar (PDA) medium (Hi-media, 39 g) was suspended in distilled water (1000 ml) and heated to boiling until it dissolved completely, the medium and Petri dishes were autoclaved at pressure of 15 lb/in.$^2$ for 20 min. Agar well bioassay was employed for testing antifungal activity. The medium was poured into sterile Petri dishes under aseptic conditions in a laminar air flow chamber. When the medium in the plates solidified, 0.5 ml of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in DMSO and different concentrations were made. After inoculation, wells were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each well, different concentrations of test solutions were added. Controls were maintained. The treated and the controls were kept at 27°C for 48 h. Inhibition zones were measured and the diameter was calculated in millimeter. Three to four replicates were maintained for each treatment.

**Acknowledgment** K.R.R., R.V.R., and K.P.K. thank Council of Scientific and Industrial Research (CSIR, New Delhi, India) for the award of fellowships.

## References

Blanc-Delmas E, Lebegue N, Wallez V, Leclerc V, Yous S, Carato P, Farce A, Bennejean C, Renard P, Caignard DH, Audinot-Bouchez V, Chomarat P, Boutin J, Hennuyer N, Louche K, Carmona MC, Staels B, Penicaud L, Casteilla L, Lonchampt M, Dacquet C, Chavatte P, Berthelot P, Lesieur D (2006) Novel 1, 3-dicarbonyl compounds having 2(3*H*)-benzazolonic heterocycles as PPARc agonists. Bioorg Med Chem 14:7377–7391

Chiarotto I, Feroci M, Orsini M, Sotgiu G, Inesi A (2009) Electrogenerated N-heterocyclic carbenes: N-functionalization of benzoxazolones. Tetrahedron 65:3704–3710

Christine HS, John RA, Andrew SG, Joseph SL, Giulio MV, Stuart CM (1996) Piperazine, piperidine and tetrahydropyridine derivative of indol-3-alkyl as 5-HT.sub.1D-.alpha. agonists. Merk Sharp and Dohme Ltd., US Patent 5807857, 1998. Chem Abst 124:232488

Courtois M, Mincheva Z, Andreu F, Rideau M, Viaud-Massuard MC (2004) Synthesis and biological evaluation with plant cells of new fosmidomycin analogues containing a benzoxazolone or oxazolopyridinone ring. J Enzyme Inhib Med Chem 19:559–565

Deng BL, Cullen MD, Zhou Z, Hartman TL, Buckheit RW Jr, Pannecouque C, Clercq ED, Fanwick PE, Cushman M (2006) Synthesis and anti-HIV activity of new alkenyldiarylmethane (ADAM) non-nucleoside reverse transcriptase inhibitors (NNRTIs) incorporating benzoxazolone and benzisoxazole rings. Bioorg Med Chem 14:2366–2374

Dogruer DS, Unlu S, Sahin MF, Yqilada E (1998) Anti-nociceptive and anti-inflammatory activity of some (2-benzoxazolone-3-yl and 2-benzothiazolone-3-yl) acetic acid derivatives. II Farmaco 53:80–84

Easmon J, Puerstinger G, Roth T, Fiebig HH, Jenny V, Jaeger W, Heinsch G, Hofmann J (2001) 2-Benzoxazolyl and 2-benzimidazolyl hydrazones derived from 2-acetylpyridine: a novel class of antitumor agents. Int J Cancer 94:89–96

Gulcan HO, Kupeli E, Unlu S, Yesilada E, Sahin MF (2003) 4-(5-Chloro-2(3*H*)-benzoxazolon-3-yl) butanoic acid derivatives: synthesis, antinociceptive and anti-inflammatory properties. Arch Pharm Pharm Med Chem 336:477–482

Hayat S, Atta-ur-Rahman, Choudhary MI, Khan KM, Schumann W, Bayer E (2001) *N*-Alkylation of anilines, carboxamides and several nitrogen heterocycles using CsF–Celite/alkyl halides/$CH_3CN$ combination. Tetrahedron 57:9951–9957

Ivanova Y, Momekov G, Petrov O, Karaivanova M, Kalcheva V (2007) Cytotoxic Mannich bases of 6-(3-aryl-2-propenoyl)-2(3*H*)-benzoxazolones. Eur J Med Chem 42:1382–1387

Jauhari PK, Bhavani A, Varalwar S, Singhal K, Raj P (2008) Synthesis of some novel 2-substituted benzoxazoles as anticancer, antifungal, and antimicrobial agents. Med Chem Res 17: 412–424

John JP, Jesse W, Michael JG, Vera S, Richard F (1995) Pyridine and pyridine N-oxide derivatives of diaryl methyl piperidines or piperazines, and compositions and methods of use thereof. Schering Corp., US Patent 5432175, 1995. Chem Abstr 123:228218

Kerwin SM, Mckee ML (2008) Synthesis, metal ion binding, and biological evaluation of new anticancer 2-(20-hydroxyphenyl) benzoxazole analogs of UK-1. Bioorg Med Chem 16:1775–1783

Koksal M, Gokhan N, Erdogan H, Ozalp M, Ekizoglu M (2002) Synthesis of 3-(4-substituted benzoylmethyl)-2-benzoxazolinones and screening antimicrobial activities. II Farmaco 57:535–538

Koksal M, Gokhan N, Kupeli E, Yesilada E, Erdogan H (2005) Synthesis, analgesic and antiinflammatory properties of certain 5-/6-acyl-3-(4-substituted-1-piperazinylmethyl)-2-benzoxazolinones derivatives. Arch Pharm Chem Life Sci 338:117–125

Kumar D, Jacob MR, Reynoldsa MB, Kerwina SM (2002) Synthesis and evaluation of anticancer benzoxazoles and benzimidazoles related to UK-1. Bioorg Med Chem 10:3997–4004

Linday ME (1962) Practical introduction to microbiology. E and F. N. Spon Ltd., London, p 177

Martin DD, Kotecha NR, Ley SV, Maqntegani S, Menendes JC, Organ HM, White AD (1992) Total synthesis of the ionophore antibiotic CP-61, 405 (routiennocin). Tetrahedron 48:7899–7938

Michel A, Michel B, Jean-Francois D, Philippe G, Guy P (1992) Benzo[1,8]naphthyridine derivatives, their preparation and compositions containing them. Laboratoire Roger Bellon, US Patent 5053509, 1991. Chem Abstr 116:6538

NCCLS (2000) Methods for dilution antimicrobial susceptibility tests for bacteria, which grows aerobically, 5th edn. Approved Standard M7-A5, NCCLS, Villanova, PA

Norrby R (2001) Linezolid—a review of the first oxazolidinone. Exp Opin Pharmacother 2:293–302

Onkol T, Ito S, Yildirim E, Erol K, Sahin MF (2001) Synthesis and antinociceptive activity of (2-benzazolon-3-yl)propionamide derivatives. Arch Pharm Pharm Med Chem 334:17–20

Polshettiwar V, Kaushik MP (2005) Microwave enhanced chemistry of CsF–Celite: an efficient catalyst for the synthesis of esters, ethers and their thio analogues. Catal Commun 6:191–194

Poupaert J, Carato P, Colacino E (2005) 2(3*H*)-Benzoxazolone and bioisosters as "privileged scaffold" in the design of pharmacological probes. Curr Med Chem 12:877–885

Prudhomme M, Guyot J, Jeminet G (1986) Semi-synthesis of A23187 (Calcimycin) analogs. IV. Cation carrier properties in mitochondria of analogs with modified benzoxazole rings. Antimicrobial activity. J Antibiot 39:934–937

Rida SM, Ashour FA, El-Hawash SA, ElSemary MM, Badr MH, Shalaby MA (2005) Synthesis of some novel benzoxazole derivatives as anticancer, anti-HIV-1 and antimicrobial agents. Eur J Med Chem 40:949–959

Robert GF (2000) Recent advances in the preparation of heterocycles on solid support: a review of the literature. J Comb Chem 2:195–214

Saxena AK, Rao J, Chakrabarty R, Saxena M, Srimal RC (2007) Synthesis and QSAR studies on hypotensive 1-[3-(4-substituted phenylthio) propyl]-4-(substituted phenyl) piperazines. Bioorg Med Chem Lett 17:1708–1712

Shah STA, Khan KM, Heinrich AM, Choudhary MI, Voelter W (2002) An efficient approach towards syntheses of ethers and esters using CsF–Celite as a solid base. Tetrahedron Lett 43: 8603–8606

Silverman RB (1992) Organic chemistry of drug design and drug action. Academic press, San Diego

Soyer Z, Bas M, Pabuccuoglu A, Pabuccuoglu V (2005) Synthesis of some 2(3*H*)-benzoxazolone derivatives and their in vitro effects on human leukocyte myeloperoxidase activity. Arch Pharm Chem Life Sci 338:405–410

Temiz-Arpacı O, Ozdemir A, Yalcin I, Yıldız I, Akı-Sener E, Altanlar N (2005) Synthesis and antimicrobial activity of some 5-[2-(morpholin-4-yl)acetamido] and/or 5-[2-(4-Substituted piperazin-1-yl)acetamido]-2-(*p*-substituted phenyl)benzoxazoles. Arch Pharm 338:105–111

Thompson LA, Ellman JA (1996) Synthesis and applications of small molecule libraries. Chem Rev 96:555–600

Tomasz A (1994) Multiple-antibiotic-resistant pathogenic bacteria—a report on the rockefeller university workshop. N Engl J Med 330:1247–1251

Ucar H, Van derpoorten K, Cacciaguerra S, Spampinato S, Stables JP, Depovere P, Isa M, Masereel B, Delarge J, Poupaert JH (1998) Synthesis and anticonvulsant activity of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone derivatives. J Med Chem 41:1138–1145

Ueki M, Miyadoh S, Abe K, Shibata K, Taniguchi M, Oi S (1993) UK-1, a novel cytotoxic metabolite from *Streptomyces* sp. 517–02. J Antibiot 46:1089–1094

Unlu S, Onkol T, Dundar Y, Okçelik B, Kupeli E, Yesilada E, Noyanalpan N, Sahin MF (2003) Synthesis and analgesic and anti-inflammatory activity of some new (6-acyl-2-benzoxazolinone and 6-acyl-2-benzothiazolinone derivatives with acetic acid and propanoic acid residues. Arch Pharm Pharm Med Chem 336: 353–361

Wang X, Bhatia PA, Daanen JF, Latsaw SP, Rohde J, Kolasa T, Hakeem AA, Matulenko MA, Nakane M, Uchic ME, Miller LN, Chang R, Moreland RB, Brioni JD, Stewart AO (2005) Synthesis and evaluation of 3-aryl piperidine analogs as potent and efficacious dopamine $D_4$ receptor agonists. Bioorg Med Chem 13:4667–4678

Yamada M, Sato Y, Kobayashi K, Konno F, Soneda T, Watanable T (1998) A new 5-$HT_3$ receptor ligand II: structure-activity analysis of 5-$HT_3$ receptor agonist action in the gut. Chem Pharm Bull 46:445–451