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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and preliminary evaluation of 2-substituted-1,3-benzoxazole and 3-[(3-substituted)propyl]-1,3-benzoxazol-2(3*H*)-one derivatives as potent anticancer agents

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Abstract The synthesis and cytotoxic activity studies of a new series of cyclic amine containing benzoxazole and benzoxazolone derivatives are described. The 2-cyclic amine-1,3-benzoxazoles **5a–k**, 5-chloro-3-(3-chloropropyl)-1,3-benzoxazol-2(3*H*)-one **8** and 3-[3-(cyclic amino)-propyl]-1,3-benzoxazol-2(3*H*)-ones **9a–f** were synthesized. The newly synthesized compounds with the influence of the presence of cyclic amine moiety in the benzoxazole scaffold have been evaluated with respect to their cytotoxic effect toward four human cancer cell lines. The new compounds were evaluated to see whether substitution at the second and third position of the benzoxazole motif influence their cytotoxic effect toward cancer cells.

Keywords Benzoxazole · Cyclic amine · Alkylation · Zinc · Anticancer · Cell lines

Introduction

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. The 2-substituted bis(benzoxazole), UK-1 (**A**) is a natural product (Fig. 1), and it showed that a wide spectrum of potent anticancer activity against leukemia and lymphoma (Ueki *et al.*, 1993). The synthetic analogs of UK-1, i.e., 2-(2′-hydroxyphenyl)benzoxazole derivatives exhibited cytotoxicity toward selective cancer cells (Kerwin and Mckee, 2008). Chlorzoxazone (**B**) a muscle relaxant, benoxaprofen (**C**), and flunoxaprofen (**D**) are anti-inflammatory drugs and these molecules contain benzoxazole pharmacophore. The chemical structures of the drugs are depicted in Fig. 1.

The benzoxazolone heterocycles are considered as "privileged scaffolds" in the design of pharmacological probes. The benzoxazolone heterocycles and its bioisosteric surrogates, such as 2(*3H*)-benzothiazolinone and benzoxazinone have received considerable attention from the medicinal chemists due to their capacity to mimic a phenol or a catechol moiety in a metabolically stable template (Poupaert *et al.*, 2005). The benzoxazolone heterocycles have high flexibility for chemical modifications, allowing changes to the characteristics of side-chains on a rigid platform (Chiarotto *et al.*, 2009). Due to its ability, the therapeutic applications of the benzoxazolone template have very broad applications. Thus, the 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),

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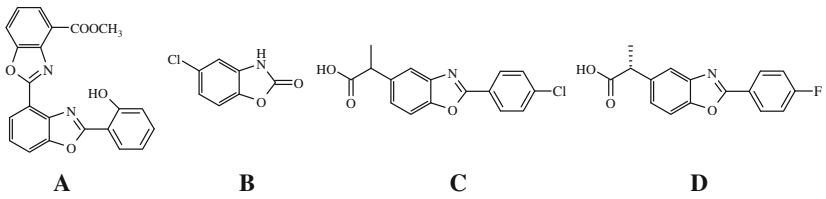


Fig. 1 Structures of benzoxazole drugs and bio molecules

antimicrobial (Koksal *et al.*, 2002), anticonvulsant (Ucar *et al.*, 1998), antimalarial (Courtois *et al.*, 2004), PPARγ agonist (Blanc-Delmas *et al.*, 2006), etc. The functionalization of the nitrogen atom at the third position of the benzoxazolone moiety 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.

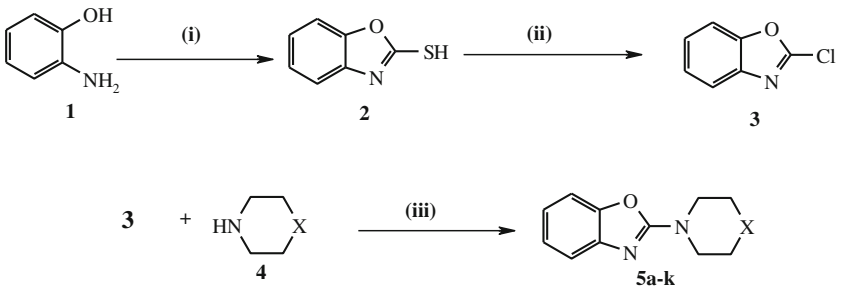
Many of the major classes of drugs in current use owe their overall therapeutic effectiveness, but lack of selectivity for tumor cells over normal cells can lead to severe side effects (Atkins and Gershell, 2002). Design and synthesis of novel small molecules which can specifically block some targets in tumor cells are in perspective direction in modern medicinal chemistry. Therefore, there is an urgent need to establish a process to assess anticancer drug action, i.e., safety, efficacy, and mechanism of action. Many synthetic heterocyclic small molecules with cytotoxic activity have been reported and several of them under gone for the clinical trials (Lesyk *et al.*, 2007).

Results and discussion

Since the benzoxazole skeleton which is responsible for selective cytotoxicity of UK-1 (Kumar *et al.*, 2002), the synthesis and cytotoxic studies of the C-2 and N-3 substituted benzoxazole derivatives was under taken employing simple and straightforward chemical transformations. The 2-cyclic amine-1,3-benzoxazoles **5a–k**, 5-chloro-3-(3-chloropropyl)-1,3-benzoxazol-2(3*H*)-one **8** and 5-chloro-3-[3-(cyclic amine)propyl]-1,3-benzoxazol-2(3*H*)-one **9a–f** were synthesized. The newly synthesized compounds were tested for their cytotoxicity toward human cancer cells.

Chemistry

The facile and practical synthesis of compounds **5**, **8**, and **9** was achieved using commercially available chemicals with simple chemistry. As a part of our on going research work on the synthesis of bio molecules, we have developed environmentally benign, economical and reusable catalysts for alkylation (Murty *et al.*, 2003) and sulfonylation (Murty *et al.*, 2006) of amines using zinc dust as the reaction medium. In this study, we adapted the same methodology for alkylation reactions and the details are illustrated as follows. The 2-chlorobenzoxazole **3** was commercially available chemical and otherwise prepared from 2-aminophenol **1**. The 2-aminophenol was treated with carbon disulfide (CS_2) under basic conditions to obtain 2-mercapto-1,3-benzoxazole **2** which was then reacted with phosphorus pentachloride (PCl_5) to obtain **3** (Yamada *et al.*, 1998). The 2-chlorobenzoxazole (**3**) was treated with various cyclic amines **4** in acetonitrile at 0°C to afford the 2-cyclic amine substituted benzoxazoles **5a–k** as shown in Scheme 1. No improvement in the yield as well as the reaction time was observed, when the reaction was carried



X = N-Me, N-Et, N-phenyl,N-pyridyl,N-pyrimidyl,N-benzyl, N-(3-chlorophenyl), CH_2 , O.
entry 10: 2-(3-methylpiperazin-1-yl)-1,3-benzoxazole
entry 11: 2-(1,4-Diazepan-1-yl)-1,3-benzoxazole

Scheme 1 Reagents and conditions: (i) CS_2, KOH, EtOH, Reflux; (ii) PCl_5, Dry Toluene; (iii) Acetonitrile, 0°C–room temperature

out in the presence of zinc dust, and hence the usage of zinc dust in this reaction is insignificant. The products and the corresponding yields were listed in Table 1. The condensation of 2-methylpiperazine with 2-chlorobenzoxazole yielded only mono-substituted product **5j**, i.e., the substitution occurred at the less-hindered nitrogen. Similarly, when one equivalent of homopiperazine was reacted with 2-chlorobenzoxazole, only mono substituted product **5k** was formed.

5-Chloro-3-(3-chloropropyl)-1,3-benzoxazol-2(3*H*)-one **8** and 5-chloro-3-[3-(cyclic amine)propyl]-1,3-benzoxazol-2(3*H*)-one **9a–f** were synthesized starting from commercially available 5-chlorobenzoxazolone **6** as shown in the Scheme 2.

5-Chlorobenzoxazolone **6**, K_2CO_3, and 1-bromo-3-chloropropane **7** were reacted in acetonitrile at ambient temperature to obtain the N-alkylated product **8** (Soyer *et al.*, 2005) as shown in the Scheme 2. The *N*-alkylation product **8** was confirmed by the two observations: (1) The 5-chorobenzoxazolone carbonyl stretching (υ C=O, 1771 cm^{-1}) was retained in the IR spectrum of **8** (υ C=O, 1774 cm^{-1}). (2) The ^{13}C chemical shift value for the carbonyl carbon ($\delta = 152.6$ ppm) of the 5-chorobenzoxazolone **6** was retained in the ^{13}C spectrum of **8** ($\delta = 154.2$ ppm). The alkylation of **6** with **7** in the presence of zinc dust yielded the product with less purity in low yield. Hence, the reaction was carried out under conventional method using a base. Compounds **9a–f** were synthesized by means of the following two methods as shown in the Scheme 2: (i) Compound **8** was reacted with various cyclic amines **4** using K_2CO_3 in dry DMF at 100°C to obtain different **9a–f** (Saxena *et al.*, 2007). (ii) A simple and convenient new synthesis of **9a–f** was carried out using zinc dust under neutral conditions. Thus, the synthesis of **9a–f** was illustrated by the use of environmentally benign protocol that involves the utilization of the recyclable metal, zinc dust as the reaction medium that enables economical, efficient, and high yield products. The products and the corresponding yields of the two methods were presented in the Table 1. It was also investigated for the possibility of zinc dust in

Table 1 Newly synthesized benzoxazoles **5a–k** and benzoxazole-2(3*H*)-ones **8**, **9a–f** derivatives

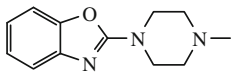
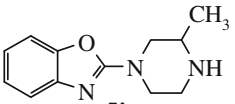
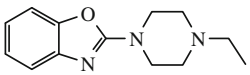
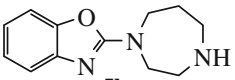
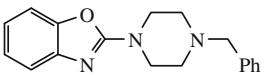
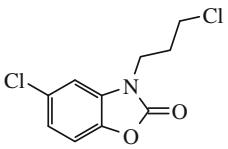
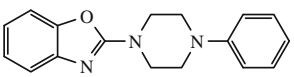
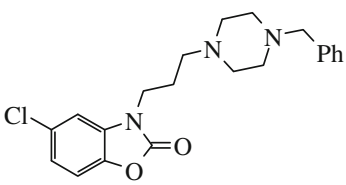
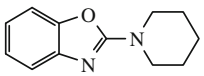
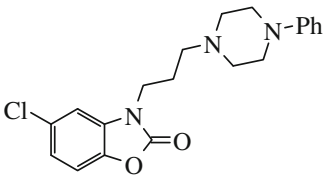
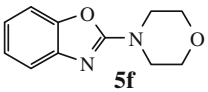
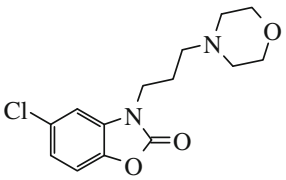
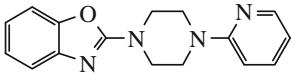
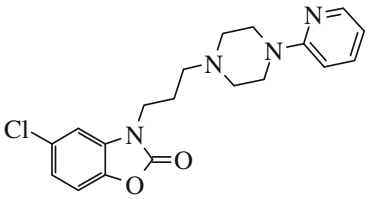
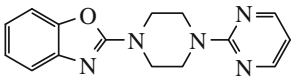
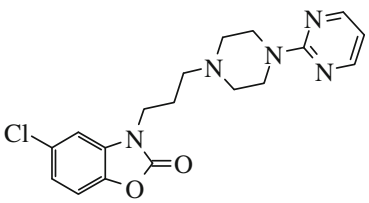
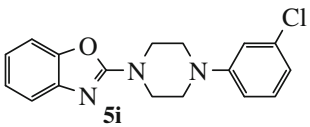
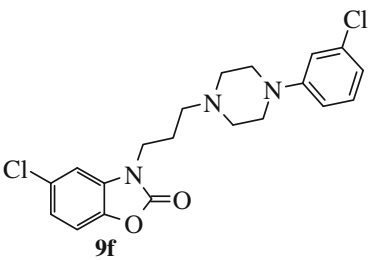
Entry	Products[a]	Yield(%)[b]	Entry	Products[a]	Yield(%)[b]	
					Method A	Method B
1	 **5a**	70	10	 **5j**	69	
2	 **5b**	65	11	 **5k**	74	
3	 **5c**	75	12	 **8**	65	–
4	 **5d**	80	13	 **9a**	67	82

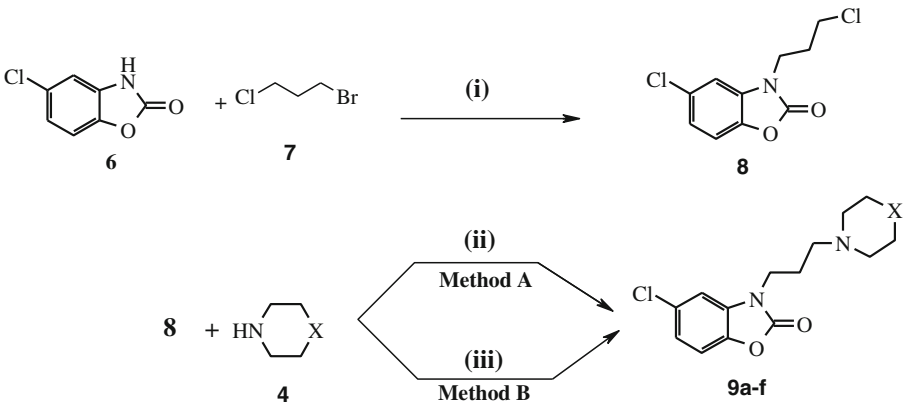
Table 1 continued

Entry	Products[a]	Yield(%)[b]	Entry	Products[a]	Yield(%)[b]	
					Method A	Method B
5	 **5e**	78	14	 **9b**	72	81
6	 **5f**	68	15	 **9c**	75	87
7	 **5g**	78	16	 **9d**	77	89
8	 **5h**	85	17	 **9e**	73	84
9	 **5i**	82	18	 **9f**	78	89

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

[b] Isolated and optimized yield

Scheme 2 Reagents and conditions : (i) K_2CO_3, CH_3CN, rt; (ii) K_2CO_3, KI, DMF, 100°C; (iii) Zn, THF, Reflux



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

Table 2 Recycle studies of zinc dust for compounds **9a** and **9d**

Number of uses		1	2	3	4	5
9a	Yield (%)	82	82	80	76	74
9d	Yield (%)	89	87	84	80	77

catalytical or less than stoichiometric quantities. However, high yields of the products with high purity were obtained with one equivalent of zinc dust. Reusability of zinc dust was also studied for **9a** and **d** and the results are illustrated in Table 2. The zinc dust was reactivated and used in subsequent runs. It has shown nearly same activity after each use. It was found that the new method is more economic, safe, and efficient. The typical experimental procedures for compounds **5a** (Yoshida *et al.*, 2007), **8** (Soyer *et al.*, 2005), and **9a** (Method A (Saxena *et al.*, 2007) and Method B) were described in the experimental part. All the synthesized compounds were characterized by IR, mass, NMR, and elemental analysis.

Antiproliferative activity

The synthesized compounds **5a–k**, **8**, and **9a–f** were subjected to cytotoxicity study using cancer cells of various origins as several reports indicate that benzoxazole derivatives show potent anti-cancer activity (Kumar *et al.*, 2002; Easmon *et al.*, 2001; Jauhari *et al.*, 2008; Rida *et al.*, 2005). The cytotoxicity studies of the compounds were determined against four human cancer cell lines using MTT assay as described earlier (Smitha *et al.*, 2005), and the results were presented in the Fig. 2. Among the compounds ($n = 16$) evaluated for their cytotoxic potential, about 9–10 entries showed dose-dependent inhibition of cancer cell proliferation (IC_{50} values are of <100 μM) and the IC_{50} values for the compounds are given in Table 3. It is evident from the results that these compounds are comparatively more effective on human breast cancer (MCF-7) and lung cancer cells (A549) than cervical cancer (HeLa) and colon cancer (SW-480) cells except the compound **5c** (entry 3) which showed maximum activity toward cervical cancer cells (IC_{50}-17.31 μM) followed by lung cancer cells (IC_{50}-32.35 μM), and is the most potent among the compounds screened. It was very interesting to note that the compound **5d** (entry 4) showed almost equal % of inhibition to the growth of lung, breast, and colon cancer cells (IC_{50}-51–54 μM), while almost double the amount was necessary to induce the same cytotoxic effect in cervical (IC_{50}-102.02 μM) cancer cells. Similarly, the compound **5b** (entry 2) induced almost equal cytotoxicity in breast (IC_{50}-54.55 μM) as well as lung (IC_{50}- 52.51 μM) cancer cells, while it did not show any effect in cervical or colon cancer cells. The compounds **5g** (entry 7) and **9f** (entry 18) were cytotoxic only to breast cancer cells (IC_{50}-52–57 μM) whereas the compound **5e** (entry 5) induced cytotoxicity only in lung cancer cells (IC_{50}-52.51 μM), while they could not induce cytotoxicity in any of the other cells studied.

Hence, our preliminary studies indicate that even though both **5** and **9** series of the compounds showed that good to moderate activity toward various cancer cells, the **5** series compounds are comparatively more effective than **9** series. The specificity of some of the compounds toward certain types of cancers also looks interesting. However, further studies are necessary to evaluate the signal transduction pathways induced by these compounds.

Experimental

General procedures

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

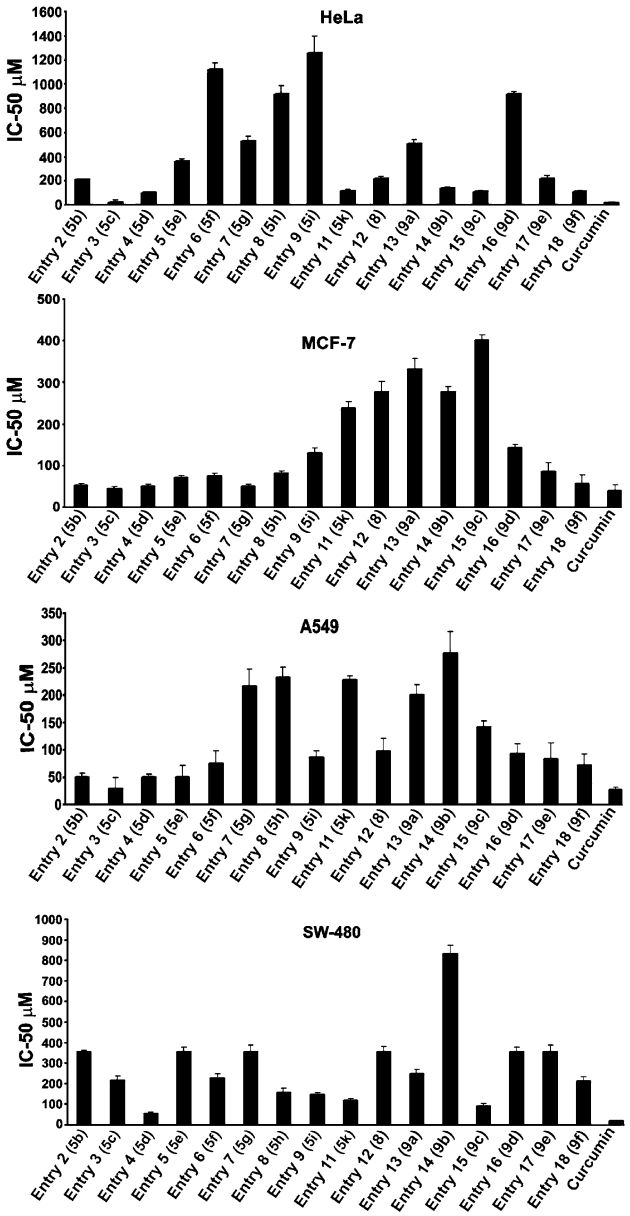


Fig. 2 The IC_{50} values of the compounds **5a–k**, **8**, and **9a–f**

performed on Elemental VARIO EL elemental analyzer. IR spectra were recorded on Perkin-Elmer Infrared-683.

Chemistry

Typical procedure for the preparation of 2-(4-methylpiperazin-1-yl)-1,3-benzoxazole (Yoshida et al., 2007) ***(5a)***

The 2-chlorobenzoxazole (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–room temperature 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.: 36–38°C (reported m.p.: 37–38°C; Yoshida *et al.*, 2007); IR (KBr) *v* 3057 (=C–H), 2933, 2854 (–C–H), 1639, 1578 (–C=C), 1456 (–C–H ben), 1363 (–C–N), 1285, 1002 (–C–O), 746 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 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). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0, 148.7, 142.8, 124.0, 120.8, 116.3, 108.7, 54.0, 45.9, 45.2. 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* 3052 (=C–H), 2970 (–C–H), 1638, 1578, 1525 (–C=C), 1459 (–C–H ben), 1399 (–C–N), 1243 (–C–O), 746 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 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). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0, 148.6, 142.9, 123.9, 120.6, 116.1, 108.6, 52.2, 51.9, 45.4, 11.7. 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 (=C–H), 2917, 2860 (–C–H), 1640, 1578, 1494 (–C=C), 1455 (–C–H ben), 1395 (–C–N), 1245 (–C–O), 739 (=C–H ben) cm^{-1}. NMR (300 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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 (reported m.p.: 150–151°C; Yamada *et al.*, 1998); IR (KBr) *v* 3045 (=C–H), 2980, 2914 (–C–H), 1629, 1575, 1497(–C=C), 1455 (–C–H ben), 1237 (–C–O), 735 (=C–H ben) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 161.8, 150.8, 148.6, 142.6, 129.2, 124.1, 120.9, 120.8, 116.9, 116.3,

Table 3 IC_{50} values on different cell lines for the compounds **5a–k**, **8**, and **9a–f**

Compound	IC_{50} values (μM)			
	HeLa	MCF-7	A549	SW-480
Entry-2 (**5b**)	212.93 ± 19.18	54.55 ± 3.65	52.51 ± 6.66	NA
Entry-3 (**5c**)	17.31 ± 6.09	46.21 ± 4.83	32.35 ± 17.6	214.68 ± 21.65
Entry-4 (**5d**)	102.02 ± 14.97	52.21 ± 5.99	51.59 ± 5.94	54.11 ± 8.31
Entry-5 (**5e**)	NA	72.54 ± 5.99	52.51 ± 20.07	NA
Entry-6 (**5f**)	NA	77.36 ± 6.0	77.60 ± 20.98	226.67 ± 16.67
Entry-7 (**5g**)	NA	52.21 ± 4.82	216.82 ± 32.12	NA
Entry-8 (**5h**)	NA	84.52 ± 3.66	233.61 ± 18.53	159.40 ± 14.63
Entry-9 (**5i**)	NA	132.49 ± 12.0	89.37 ± 9.21	145.07 ± 9.02
Entry-11 (**5k**)	109.51 ± 19.18	241.44 ± 14.48	229.41 ± 5.94	116.41 ± 11.99
Entry-12 (**8**)	216.67 ± 23.41	279.91 ± 23.83	98.58 ± 24.37	NA
Entry-13 (**9a**)	NA	NA	201.77 ± 17.61	248.32 ± 16.67
Entry-14 (**9b**)	136.18 ± 15.44	281.07 ± 10.82	278.14 ± 38.49	NA
Entry-15 (**9c**)	109.51 ± 11.69	NA	143.01 ± 10.95	90.08 ± 14.34
Entry-16 (**9d**)	NA	144.48 ± 8.34	94.38 ± 17.61	NA
Entry-17 (**9e**)	216.67 ± 23.4	87.01 ± 12.50	85.99 ± 27.74	NA
Entry-18 (**9f**)	109.51 ± 11.7	57.37 ± 19.16	74.32 ± 18.43	212.34 ± 19.01
Curcumin	17.31 ± 3.7	21.39 ± 4.99	24.59 ± 5.12	18.13 ± 4.99

NA not active

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-(Piperidin-1-yl)-1,3-benzoxazole ***(5e)*** Brown solid. m.p.: 71–72°C; IR (KBr) *v* 3057 (=C–H), 2936, 2854 (–C–H), 1638, 1577, 1525 (–C=C), 1455 (–C–H ben), 1394 (–C–N), 1221 (–C–O), 744 (=C–H ben) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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 ***(5f)*** Brown solid. m.p.: 205–206°C; IR (KBr) *v* 3057 (=C–H), 2966, 2863 (–C–H), 1637, 1578, 1525 (–C=C), 1454 (–C–H ben), 1398 (–C–N), 1242, 1105 (–C–O), 745 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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.

2-[4-(Pyridin-2-yl)piperazin-1-yl]-1,3-benzoxazole ***(5g)*** White solid. m.p.: 186–188°C; IR (KBr) *v* 3053 (=C–H), 2993, 2917 (–C–H), 1635, 1576, 1480 (–C=C), 1459 (–C–H ben), 1435 (–C–N), 1242 (–C–O), 744 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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-benzoxazole ***(5h)*** White solid. m.p.: 183–185°C; IR (KBr) *v* 2911, 2860 (–C–H), 1651, 1581, 1490 (–C=C), 1451 (–C–H ben), 1393 (–C–N), 1251 (–C–O), 733 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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 ***(5i)*** White solid. m.p.: 134–136°C; IR (KBr) *v* 3015

(=C–H), 2913 (–C–H), 1625, 1593, 1478 (–C=C), 1397 (–C–N), 1253 (–C–O), 695 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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-(3-Methylpiperazin-1-yl)-1,3-benzoxazole ***(5j)*** Brown solid. m.p.: 51–52°C; IR (KBr) *v* 3321 (–N–H), 3057 (=C–H), 2958, 2856 (–C–H), 1638, 1578 (–C=C), 1458 (–C–H ben), 1400 (–C–N), 1246 (–C–O), 805, 744 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 161.5, 148.5, 142.8, 123.6, 120.3, 116.0, 108.3, 51.7, 50.0, 44.9, 44.5, 18.5. 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 ***(5k)*** Brown solid. m.p.: 195–198°C; IR (KBr) *v* 3399 (–N–H), 3050 (=C–H), 2934 (–C–H), 1639, 1578 (–C=C), 1459 (–C–H ben), 1402 (–C–N), 1244 (–C–O), 744 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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.

Typical procedure for the preparation of the 5-chloro-3-(3-chloropropyl)-1,3-benzoxazol-2(3H)-one ***(8)*** *(Soyer et al., 2005)*

A mixture of 5-chlorobenzoxazolone (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 (thin layer chromatography, 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.

White solid. m.p.: 82–84°C; IR (KBr) *v* 3063 (=C–H), 2933 (–C–H), 1774 (–C=O), 1611, 1485 (–C=C), 1369 (–C–N), 1247, 1061 (–C–O), 829, 721 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.17–7.03 (m, 3H); 3.99 (t, 2H, $J = 7.0$ Hz); 3.62 (t, 2H, $J = 5.5$ Hz); 2.28 (q, 2H, $J = 7.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 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.

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

Method A (Saxena et al., 2007) A mixture of *N*-benzylpiperizine (2.0 mmol) and K_2CO_3 (3.0 mmol) in dry DMF (5 ml) was stirred for 10 min under N_2 atmosphere. 5-Chloro-3-(3-chloropropyl)-2,3-dihydro-1,3-benzoxazol-2-one (**8**) (2.0 mmol) in dry DMF (2 ml)and catalytic KI (0.1 mmol) were added to the above mixture, and was heated at 100°C for 4 h. After the reaction completed (TLC), the reaction mixture was cooled and then poured into cold water. The separated solid was filtered, washed with cold water, and crystallized from ethanol to give the pure product.

Method B A mixture of *N*-benzylpiperizine (2.0 mmol) and activated zinc dust (2.0 mmol) in dry tetrahydro furan (THF) (5 ml) was stirred for 5 min under N_2 atmosphere. 5-Chloro-3-(3-chloropropyl)-2,3-dihydro-1,3-benzoxazol-2-one (**8**) (2.0 mmol) in dry THF (3 ml) and catalytic amount of tetrabutyl ammonium iodide (TBAI) (0.2 mmol) were added to the above mixture, and was refluxed for 3 h. After the reaction was completed (TLC), ethyl acetate was added to the reaction mixture, the zinc dust was filtered off, washed with ethyl acetate. The combined organic layer was washed with water, brine, and dried over Na_2SO_4. The organic layer was concentrated and the residue was purified by flash chromatography, and the product was crystallized from ethanol to obtain the pure product.

Brown solid. m.p.: 103–105°C; IR (KBr) *v* 2939 (–C–H), 1782 (–C=O), 1612, 1488 (–C=C), 1370 (–C–N), 1248, 1010 (–C–O), 804, 744 (=C–H ben) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 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 (q, 2H, $J = 6.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 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(3H)-one ***(9b)*** Brown solid. m.p.: 128–129°C; IR (KBr) ν 3056(=C–H), 2940 (–C–H), 1783 (–C=O), 1598, 1489 (–C=C), 1355 (–C–N), 1241, 1058 (–C–O), 834, 751 (=C–H ben) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 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 (q, 2H, $J = 6.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 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-(morpholin-4-yl)propyl]-1,3-benzoxazol-2(3H)-one ***(9c)*** Brown solid. m.p.: 97–99°C; IR (KBr) ν 2953, 2855 (–C–H), 1782 (–C=O), 1613, 1488 (–C=C), 1370 (–C–N), 1251, 1117 (–C–O), 805, 750 (=C–H ben) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 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 (q, 2H, $J = 6.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 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.

5-Chloro-3-{3-[4-(pyridin-2-yl)piperazin-1-yl]propyl}-1,3-benzoxazol-2(3H)-one ***(9d)*** White solid. m.p.: 132–133°C; IR (KBr) ν 2944, 2826 (–C–H), 1780 (–C=O), 1594, 1487 (–C=C), 1370 (–C–N), 1250, 1060 (–C–O), 774 (=C–H ben) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 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 (q, 2H, $J = 6.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 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(3H)-one ***(9e)*** White solid. m.p.: 125–126°C; IR (KBr) ν 2927, 2853 (–C–H), 1781 (–C=O), 1585, 1488 (–C=C), 1362 (–C–N), 1252, 1061 (–C–O), 801, 750 (=C–H ben) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 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 (q, 2H, $J = 6.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 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(3H)-one ***(9f)*** Brown solid. m.p.: 138–140°C; IR (KBr) ν 2947, 2824 (–C–H), 1781 (–C=O), 1594, 1487 (–C=C), 1372 (–C–N), 1246, 1061 (–C–O), 770 (=C–H ben) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 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 (q, 2H, $J = 6.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 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.

Evaluation of cytotoxicity of the compounds toward cancer cells

Maintenance of the cells

The human cancer cells of various origin (HeLa: Cervix, MCF-7: Breast, A549: Lung, SW 480: Colon) were procured from National Centre for Cell sciences, Pune and maintained in DMEM containing 10% FBS with antibiotics and antimycotics at 37°C in a CO_2 incubator.

MTT assay

This assay helps to measure the toxicity induced by the compounds on the cells. Active mitochondrial dehydrogenases of living cells convert the water soluble yellow tetrazolium salt to an insoluble purple formazan. This can be solubilized by 20% SDS dissolved in 50% dimethyl formamide and the intensity of color developed is an indicator of percentage of viable cells present. The assay was conducted as described earlier (Smitha *et al.*, 2005).

Briefly, cells (5×10^3/well) were plated in 96-well plates and kept overnight at 37°C. Next day, the cells were incubated with and without various concentrations of the compounds (5, 10, 25, and 50 μM). Curcumin was used as the positive control. At the end of the incubation, medium was removed and fresh medium containing 20% MTT solution (5 mg/ml in PBS) was added to each well. After 2 h, 0.1 ml of the extraction buffer (20% SDS and 50% DMF) was added, and the optical density was measured at 570 nm using a 96-well multiscanner auto reader after 4 h and compared with that of the untreated control. The percentage of inhibition of cell viability was determined with reference to the untreated control. The data were subjected to linear regression analysis and the regression lines were

plotted for the best straight-line fit. The IC_{50} concentrations were calculated using the respective regression analysis.

Conclusions

In conclusion, various **5a–k**, **8**, and **9a–f** derivatives were synthesized using simple chemical transformations and commercially available chemicals. The N-alkylation of **6** with **7** was occurred under conventional basic conditions and the same reaction was not facile in the presence of zinc dust. The alkylation of **8** on cyclic amines **4** was achieved using zinc dust under neutral conditions. The zinc–THF combination provided an efficient and convenient method for the N-alkylation of cyclic amines **4**. This method offers advantages like good yields and cleaner products. The benefits of this method are the easy handling, commercially availability, inexpensiveness, and reusability of the reagent zinc dust. The antiproliferative activity studies of the newly synthesized compounds were examined and majority of the compounds from the two series were found to exhibit good to moderate activity. This study provides a good starting point to develop unsymmetrical benzoxazoles as novel anticancer agents. Further lead optimization is ongoing.

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