ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 5, pp. 1003–1008. © Pleiades Publishing, Ltd., 2019.

Synthesis and Anticancer Evaluation of Amide Derivatives of 1,3,4-Oxadiazole Linked with Benzoxazole

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Received October 10, 2018; revised March 3, 2019; accepted May 28, 2019

Abstract—A novel series of amide 1,3,4–oxadiazole linked benzoxazole derivatives **12a**–**12j** are synthesized and their anticancer activity is screened against four human cancer cell lines including A549 (Lung cancer), MCF7 (Breast cancer), A375 (Melanoma cancer), HT-29 (Colon cancer) using Combretastatin-A4 as a control drug. Among the synthesized compounds, **12c** and **12g** demonstrate potent anticancer activity against HT-29 cancer cell line with IC_{50} values of 0.018 and 0.093 μM, respectively, which is higher than the standard drug.

Keywords: benzoxazole, AJI9561, zibotentan, amide, 1,3,4-oxadiazole and anticancer activity

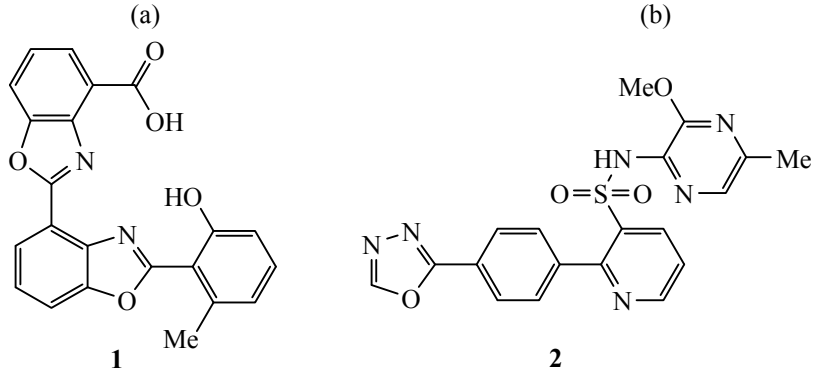
DOI: 10.1134/S1070363219050219

INTRODUCTION

A big number of recent publications is devoted to synthesis of heterocyclic compounds as important components in construction of anticancer agents (drugs) against a panel of different human cancer cell lines, to mention a few [1–15]. Benzoxazole derivatives are highly recognized by medicinal chemists as biologically active compounds, that demonstrate antitumor [17-20], DNA-topoisomerase [21], antitubercular [22], antimicrobial [23], antiviral [24], antibacterial, antifungal [25, 26], antihistaminic [27], antiallergic [28], herbicidal [29], and antiparasitic [30] activities. Compound AJI9561 (Fig. 1a) is a bis-benzoxazole isolated from *Streptomyces* sp. AJ956 [31] which exhibited promising growth inhibitory activity against murine cancer cell line P388.

1,3,4-Oxadiazole derivatives are considered to be active bioisosteres of amides and esters due to formation of hydrogen bonds with receptors [32] characterized by various types of biological properties. For example, Zibotentan (Fig. 1b) is one of the most important anticancer drugs available on the market [33].

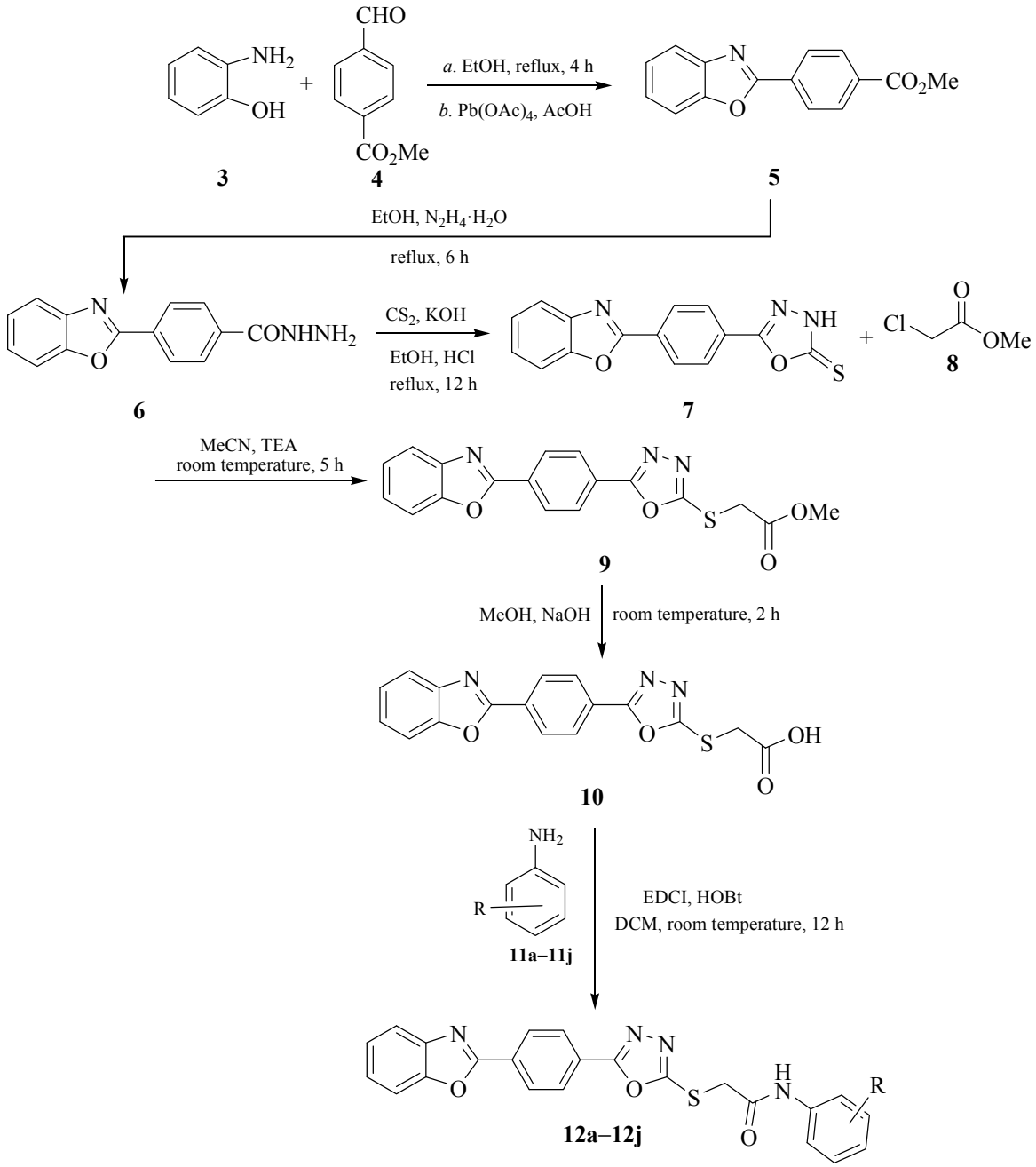
In view of the above information and in continuation of our earlier efforts, we have synthesized a novel series of amide derivatives of benzoxazole. Their structures were supported by ^{1}H and ^{13}C NMR, and



1 **2**

Fig. 1. Structures of (a) AJI9561 **1** and (b) Zibotentan **2**.

Scheme 1. Synthesis of amide derivatives of 1,3,4-oxadiazole linked with benzoxazole.



R = H (**11a**, **12a**), 3,4,5-trimethoxy (**11b**, **12b**), 4-methoxy (**11c**, **12c**), 4-chloro (**11d**, **12d**), 4-bromo (**11e**, **12e**), 4-fluoro (**11f**, **12f**), 4-nitro (**11g**, **12g**), 4-methyl (**11h**, **12h**), 4-cyano (**11i**, **12i**), 3,5-dimethoxy (**11j**, **12j**).

mass spectral data. The synthesized compounds were tested for their anticancer activity against four human cancer cell lines.

RESULTS AND DISCUSSION

Synthetic approach to the series of ten amide derivatives of benzoxazoles (Scheme 1) started with condensation of compound **3** with methyl 4-formylbenzoate **4** upon refluxing in ethanol medium. The following addition of $Pb(OAc)_4$ and acetic acid led to compound **5** at room temperature. Refluxing of the intermediate **5** with hydrazine hydrate in ethanol afforded acid hydrazide **6**. The subsequent cyclization of compound **6** with CS_2 in alkali medium led to compound **7**, which was reacted with methyl chloroacetate

8 in presence of TEA with formation of compound **9**. The ester **9** was hydrolyzed with aq NaOH in methanol at room temperature to give the corresponding acid intermediate **10**, coupling of which with substituted aromatic amines **11a**–**11j** in presence of EDCI, HOBt in CH_2Cl_2 at room temperature afforded the corresponding target compounds **12a**–**12j**.

Biological evaluation. *In vitro cytotoxicity.* The newly synthesized compounds **12a**–**12j** were tested for their anticancer activity against four human cancer cell lines including A549 (Lung cancer), MCF7 (Breast cancer), A375 (Melanoma cancer), HT-29 (Colon cancer) by MTT assay (see the table). The CA4 was used as a positive control. All the compounds exhibited significant anticancer activity with IC_{50} values ranging from 0.01 to 10.40 μM, while for the positive control IC_{50} was in the range of 0.11–0.93 μM. The compounds **12c**, **12g**, and **12b** demonstrated most potent anticancer activity against HT-29 cancer cell line with IC_{50} values of 0.018, 0.093, and 0.22 μM, respectively, while the compounds **12f**, **12g**, **12b**, and **12i** were determined to be the most potent anticancer agents against MCF-7 cell line. The compounds **12b** and **12i** showed good anticancer activity against A549 cell line. So, the most active products can be considered as drug lead compounds.

Anticancer activity of compounds **12a**–**12j**

Compound	IC_{50}[a], μM			
	A549	MCF-7	A375	HT-29
12a	2.78	3.670	2.33	4.780
12b	0.13	0.100	–	0.220
12c	1.56	0.330	1.77	0.018
12d	2.77	3.600	–	–
12e	4.90	5.100	7.56	2.110
12f	0.77	0.018	1.39	–
12g	0.67	0.076	1.55	0.093
12h	10.40	8.290	–	9.340
12i	0.24	0.130	1.90	0.900
12j	1.09	0.980	2.10	8.900
Combretastatin-A4	0.11	0.180	0.21	0.930

[a] (–) Not active.

EXPERIMENTAL

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA) and Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA), and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualized under UV light or by iodine indicator. ^{1}H and ^{13}C NMR spectra were measured on a Gemini Varian-VXR-unity (300 and 400 MHz) spectrometer using TMS as a standard and DMSO-d_6 as a solvent. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined on an electrothermal melting point apparatus, and are uncorrected.

Methyl 4-(1,3-benzoxazol-2-yl)benzoate (5). A mixture of 2-aminophenol (3) (19 g, 174 mmol) with methyl 4-formylbenzoate **4** (28 g, 174 mmol) was refluxed in 70 mL of ethanol for 3 h. Then it was cooled down, and ethanol was removed in vacuum. The resulting Schiff base was dissolved in 100 mL of acetic acid, mixed with lead tetraacetate (77 g, 174 mmol) and stirred at room temperature for 1 h. The reaction mixture was then diluted with 30 mL of H_2O, extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the crude product was purified by column chromatography with ethyl acetate–hexane (3 : 7) to afford pure compound **5**, yield 77%. ^{1}H NMR spectrum, δ, ppm: 3.87 s (3H), 7.10 d (1H, J = 8.04 Hz), 7.33–7.37 m (3H), 7.56 br.s (1H), 7.69 br.s (2H), 7.83 d (2H, J = 8.10 Hz), 8.07 d (2H, J = 8.10 Hz). MS (ESI): 254 $[M + H]^+$.

4-(1,3-Benzoxazol-2-yl)-1-benzenecarbohydrazide (6). A mixture of methyl 4-(1,3-benzoxazol-2-yl)-benzoate **5** (25 g, 98.8 mmol) with hydrazine hydrate (92 mL, 296 mmol) in ethanol was refluxed for 3 h. The crude product was obtained after distilling off the excess ethanol, cooling down, filtering, and washing with small quantity of cold water. Thus obtained product **6** (yield 74%) was introduced in the next step without further purification. ^{1}H NMR spectrum, δ, ppm: 7.09 d (1H, J = 8.05 Hz), 7.32–7.38 m (3H), 7.56 br.s (1H), 7.69 br.s (2H), 7.84 d (2H, J = 8.13 Hz), 8.08 d (2H, J = 8.13 Hz). MS (ESI): 254 $[M + H]^+$.

5-[4-(1,3-Benzoxazol-2-yl)phenyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione (7). A mixture of compound **6** (17 g, 67 mmol) with potassium hydroxide (3.7 g, 67 mmol), carbon disulfide (4.6 mL, 67 mmol) and absolute ethanol (50 mL) was refluxed upon stirring for 12 h. The solvent was evaporated

under vacuum. The residue was dissolved in water and acidified with hydrochloric acid (10%). The formed precipitate was filtered off, washed with water, dried, and recrystallized from absolute ethanol to give compound **7**. Yield 72%, mp 230–232°C. ^{1}H NMR spectrum, δ, ppm: 7.09 d (1H, J = 8.05 Hz), 7.32 –7.38 m (3H), 7.84 d (2H, J = 8.13 Hz), 8.02 s (1H), 8.08 d (2H, J = 8.13 Hz). MS (ESI): 296 $[M + H]^+$.

Methyl 2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetate (9). To a stirred mixture of the appropriate oxadiazole **7** (13 g, 44 mmol) with methyl chloroacetate **8** (4.1 mL, 44 mmol) in CH_3CN (30 mL), triethylamine (18 mL, 132 mmol) was added. The mixture was stirred at room temperature for 5 h and the immediately formed precipitate was filtered off, washed with methanol, and recrystallized from absolute ethanol, yield 92%. ^{1}H NMR spectrum, δ, ppm: 3.84 s (3H), 4.09 s (2H), 7.09 d (1H, J = 8.02 Hz), 7.35–7.41 m (3H), 7.85 d (2H, J = 8.09 Hz), 8.09 d (2H, J = 8.09 Hz). MS (ESI): 368 $[M + H]^+$.

2-{5-[4-(1,3-Benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetic acid (10). A solution of 50% NaOH (20 mL) was added to a solution of **9** (13 g, 35.4 mmol) in methanol (50 mL), and the mixture was stirred at room temperature for 2 h. Upon evaporation of most of ethanol the aqueous phase was acidified with 6 N HCl to pH 7 and extracted with ethyl acetate (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford pure compound **10**, yield 82%. ^{1}H NMR spectrum, δ, ppm: 4.09 s (2H), 7.10 d (1H, J = 8.01 Hz), 7.34–7.40 m (3H), 7.85 d (2H, J = 8.10 Hz), 8.09 d (2H, J = 8.10 Hz), 11.55 br.s (1H). MS (ESI): 354 $[M + H]^+$.

***N*^{1}-Phenyl-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (12a).** To the solution of compound **10** (500 mg, 1.41 mmol) in 10 mL of dry CH_2Cl_2, aniline **11a** (0.13 mL, 1.41 mmol), EDCI (270 mg, 1.41 mmol) and HOBt (19 mg, 0.141 mmol) were added. The reaction mixture was stirred at room temperature for 6 h, washed with saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography with ethyl acetate–hexane (1 : 1) to afford the pure compound **12a**. Yield 87%, mp 230–232°C. ^{1}H NMR spectrum, δ, ppm: 4.10 s (2H), 7.09 d (1H, J = 8.02 Hz), 7.32–7.53 m (6H), 7.65 d (2H, J = 8.20 Hz), 7.86 d (2H, J = 8.12 Hz), 8.10 d (2H, J = 8.12 Hz), 9.20 d (1H). ^{13}C NMR spectrum, δ, ppm: 40.5, 111.6, 119.6, 121.4, 124.8, 125.3, 125.8, 126.3, 127.6, 128.7, 134.3, 134.8, 139.6, 143.3, 150.8, 156.7, 159.4, 161.3, 164.8. MS (ESI): 429 $[M + H]^+$.

The compounds **12b**–**12j** were synthesized according to the method presented above for compound **12a** using the corresponding substituted anilines.

***N*^{1}-(3,4,5-Trimethoxyphenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}-acetamide (12b).** Yield 86%, mp 245–247°C. ^{1}H NMR spectrum, δ, ppm: 3.87 s (6H), 3.90 s (3H), 4.10 s (2H), 6.99 s (2H), 7.10 d (1H, J = 8.03 Hz), 7.40–7.49 m (3H), 7.85 d (2H, J = 8.11 Hz), 8.10 d (2H, J = 8.11 Hz), 9.21 s (1H). ^{13}C NMR spectrum, δ, ppm: 40.4, 57.6, 61.8, 101.6, 111.7, 119.4, 124.7, 125.6, 126.4, 127.4, 134.2, 134.7, 137.6, 138.5, 143.7, 150.5, 152.3, 156.4, 159.6, 161.8, 164.8. MS (ESI): 519 $[M + H]^+$.

***N*^{1}-(4-Methoxyphenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (12c).** Yield 80%, mp 237–239°C. ^{1}H NMR spectrum, δ, ppm: 3.90 s (3H), 4.10 s (2H), 6.92 d (2H, J = 8.10 Hz), 7.09 d (1H, J = 8.03 Hz), 7.41–7.50 m (3H), 7.68 d (2H, J = 8.10 Hz), 7.86 d (2H, J = 8.13 Hz), 8.11 d (2H, J = 8.13 Hz), 9.21 s (1H). ^{13}C NMR spectrum, δ, ppm: 40.7, 56.7, 111.8, 117.4, 119.5, 122.4, 124.6, 125.7, 126.4, 127.8, 134.2, 134.7, 135.2, 143.6, 150.5, 154.6, 156.5, 159.7, 161.5, 164.8. MS (ESI): 459 $[M + H]^+$.

***N*^{1}-(4-Chlorophenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (12d).** Yield 90%, mp 249–251°C. ^{1}H NMR spectrum, δ, ppm: 4.11 s (2H), 7.10 d (1H, J = 8.04 Hz), 7.28 d (2H, J = 8.16 Hz), 7.42–7.51 m (3H), 7.65 d (2H, J = 8.16 Hz), 7.88 d (2H, J = 8.18 Hz), 8.12 d (2H, J = 8.18 Hz), 9.21 s (1H). ^{13}C NMR spectrum, δ, ppm: 40.6, 111.8, 119.7, 122.4, 124.6, 125.7, 126.3, 127.5, 127.9, 129.7, 134.5, 134.7, 139.8, 143.4, 150.5, 156.8, 159.8, 161.7, 164.8. MS (ESI): 463 $[M + H]^+$.

***N*^{1}-(4-Bromophenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (12e).** Yield 85%, mp 254–256°C. ^{1}H NMR spectrum, δ, ppm: 4.11 s (2H), 6.98 d (1H, J = 8.05 Hz), 7.29 d (2H, J = 8.17 Hz), 7.41–7.50 m (3H), 7.54 d (2H, J = 8.17 Hz), 7.89 d (2H, J = 8.19 Hz), 8.13 d (2H, J = 8.19 Hz), 9.21 s (1H). ^{13}C NMR spectrum, δ, ppm: 40.6, 111.7, 112.8, 119.5, 121.5, 124.3, 125.7, 126.5, 127.5, 131.2, 134.5, 134.7, 139.5, 143.5, 150.7, 156.7, 159.7, 161.8, 164.8. MS (ESI): 508 $[M + H]^+$.

***N*^{1}-(4-Fluorophenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (12f).** Yield 88%, mp 240–242°C. ^{1}H NMR spectrum, δ, ppm: 4.10 s (2H), 6.97 d (1H, *J* = 8.03 Hz), 7.14 d (2H, *J* = 8.14 Hz), 7.42–7.54 m (5H), 7.87 d (2H, *J* = 8.17 Hz), 8.11 d (2H, *J* = 8.17 Hz), 9.21 s (1H). ^{13}C NMR spectrum, δ, ppm: 40.5, 111.5, 115.6, 119.6, 123.5, 124.7, 125.8, 126.5, 127.8, 134.3, 134.8, 137.6, 138.7, 143.5, 150.7, 156.8, 160.7, 161.9, 164.9. MS (ESI): 447 $[M + H]^+$.

***N*^{1}-(4-Nitrophenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)-phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (12g).** Yield 89%, mp 259–261°C. ^{1}H NMR spectrum, δ, ppm: 4.12 s (2H), 6.97 d (1H, *J* = 8.06 Hz), 7.42–7.54 m (3H), 7.88 d (2H, *J* = 8.20 Hz), 8.12 d (2H, *J* = 8.17 Hz), 8.17–8.23 m (4H), 9.21 s (1H). ^{13}C NMR spectrum, δ, ppm: 40.7, 111.8, 119.5, 120.6, 123.5, 124.6, 125.7, 126.4, 127.5, 134.2, 134.7, 143.6, 144.3, 150.7, 156.8, 160.5, 161.8, 164.9. MS (ESI): 474 $[M + H]^+$.

***N*^{1}-(4-Methylphenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (12h).** Yield 87%, mp 239–241°C. ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H), 4.10 s (2H), 6.96 d (1H, *J* = 8.03 Hz), 7.09 d (2H, *J* = 8.14 Hz), 7.41–7.51 m (5H), 7.85 d (2H, *J* = 8.18 Hz), 8.10 d (2H, *J* = 8.18 Hz), 9.21 s (1H). ^{13}C NMR spectrum, δ, ppm: 22.4, 40.6, 111.7, 119.6, 121.5, 124.3, 125.6, 126.4, 127.4, 127.8, 134.2, 134.8, 135.3, 139.6, 143.5, 150.6, 156.7, 159.6, 161.8, 164.9. MS (ESI): 443 $[M + H]^+$.

***N*^{1}-(4-Cyanophenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (12i).** Yield 90%, mp 260–262°C. ^{1}H NMR spectrum, δ, ppm: 4.12 s (2H), 6.98 d (1H, *J* = 8.05 Hz), 7.42–7.49 m (3H), 7.64 d (2H, *J* = 8.20 Hz), 7.78 d (2H, *J* = 8.20 Hz), 7.87 d (2H, *J* = 8.19 Hz), 8.12 d (2H, *J* = 8.19 Hz), 9.21 s (1H). ^{13}C NMR spectrum, δ, ppm: 40.5, 106.7, 111.8, 119.5, 120.5, 121.5, 124.6, 125.7, 126.4, 127.5, 133.5, 134.5, 134.8, 142.3, 143.8, 150.6, 156.9, 160.5, 162.4, 165.2. MS (ESI): 454 $[M + H]^+$.

***N*^{1}-(3,5-Dimethoxyphenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (12j).** Yield 81%, mp 244–246°C. ^{1}H NMR spectrum, δ, ppm: 3.86 s (6H), 3.90 s (3H), 4.10 s (2H), 6.28 s (1H), 6.78 s (2H), 7.42–7.49 m (3H), 7.85 d (2H, *J* = 8.16 Hz), 8.10 d (2H, *J* = 8.16 Hz), 9.21 s (1H). ^{13}C NMR spectrum, δ, ppm: 40.3, 56.8, 98.5, 101.5, 111.8, 119.6, 124.5, 125.7, 126.4, 127.8, 134.3, 134.8, 141.3, 143.5, 150.7, 156.7, 159.8, 161.6, 164.9. MS (ESI): 489 $[M + H]^+$.

MTT assay. Cytotoxic activity of the compounds was tested using MTT assay. 1×10^4 Cells/well were seeded in 200 mL DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 h at 37°C in a CO_2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, 10 mL (5 mg/mL) of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] were added to each well and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formazan crystals were dissolved in 100 mL of DMSO and absorbance at wavelength of 540 nm was recorded.

CONCLUSIONS

A series of amides of benzoxazole derivatives **12a**–**12j** is synthesized. Their structures are confirmed by ^{1}H and ^{13}C NMR, and mass spectra. The synthesized compounds are tested for their anticancer activity against four human cancer cell lines, A549 (Lung cancer), MCF7 (Breast cancer), A375 (Melanoma cancer), and HT-29 (Colon cancer). The compounds **12b**, **12c**, **12f**, **12g**, **12i**, and **12j** demonstrated activity more potent than the control CA4.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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