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Research Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF AMIDE DERIVATIVES OF THIAZOLES AND ANTICANCER AGENTS

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ABSTRACT

In this study, a series of amide derivatives (11a-j) containing thiazole moiety were designed and synthesized. All these synthesized compounds were confirmed by 1HNMR, 13CNMR and mass spectral data. Further, these were evaluated for anticancer activity against three human cancer cell lines including MCF-7 (breast), A-549 (lung), and A375 (melanoma). Among them, compounds 11b, 11d, 11e, 11f and 11g were exhibited more potent activity than positive control.

Keywords: Inthomycin C, Oxaprozin, Pemoline and anticancer activity.

INTRODUCTION

The 1,3-oxazoles an important class of five member heterocyclic scaffolds in medicinal chemistry and commonly found in many natural products[1]. These have been the focus of great interest due to their significant biological properties such as (6, oxazole) anti-HIV agents[2], anti-tuberculotic agents[3], antifungal agents[4], insecticidal[5], herbicidal[6], anti-cancer[7], inhibitors of receptor tyrosine kinases (RTK)[8], and A_{2A} adenosine receptor antagonists[9]. Some of the oxazole nucleus contains compounds like Inthomycin C (**1**) (antineoplastic)[10], Oxaprozin (**2**) (anti-inflammatory)[11], Pemoline (**3**) (nervous system stimulant)[12]. (Figure 1)

In addition, 1,3-thiazole are sulfur and nitrogen contain heterocyclic molecules have recently attracted great attention due to their prominent biological activity[13-16]. These compounds are showed a broad-spectrum of biological activities including insecticidal[17], antifungal[18,19], herbicidal[20], regulating plant growth[21], antiviral[22], anti-inflammatory[23], sedative, anaesthetic[24], analgesic[25], antitubercular[26] and antioxidants.

In view of the above-mentioned findings and continuous of efforts, we have synthesized a novel series of thiazole derivatives containing amide skeleton. All these synthesized (**11a-j**) compounds were confirmed by ^{1}HNMR, ^{13}CNMR and mass spectral data. Further, these were evaluated for anticancer activity.

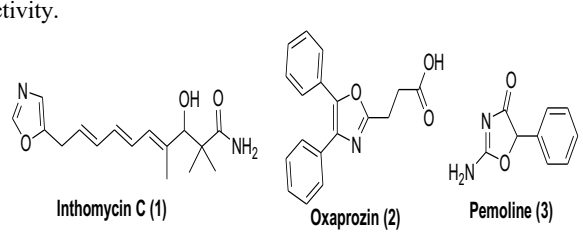


Figure 1

MATERIALS AND METHODS

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), 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 visualization on TLC was achieved by UV light or iodine indicator. ^{1}H and ^{13}C NMR spectra were recorded on Bruker, Bruker UXNMR/XWIN-NMR (400 MHz, 300 MHz) instrument. Chemical shifts (d) are reported in ppm downfield from internal TMS standard. 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 with an electrothermal melting point apparatus and are uncorrected.

Methyl 4-(6-acetylbenzo[d]oxazol-2-yl)benzoate (5)

The compound 1-(3-amino-4-hydroxyphenyl)ethanone (**3**) (20 g, 132.2 mmol) and methyl 4-formylbenzoate (**4**) (18.1 ml, 132.2 mmol) were refluxed in 50 mL ethanol for 3 hours. After the reaction mixture was cooled, ethanol was removed in vacuo. The resulting Schiff base was dissolved in 12 mL of acetic acid and lead tetraacetate (58 g, 132.2 mmol) was added and stirred at room temperature for 1 hour. Reaction was then diluted with 100 mL H_2O and extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **5**, 31.8 g in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (s, 3H), 3.86 (s, 3H), 7.20 (d, 1H, J = 8.12 Hz), 7.49 (s, 1H), 7.65 (d, 2H, J = 8.23 Hz), 7.89-7.95 (m, 3H); MS (ESI): 296 $[M+H]^+$.

4-(6-Acetylbenzo[d]oxazol-2-yl)benzaldehyde (6)

Diisobutylaluminum hydride solution (36 mL of 1.0 M solution in hexane) was added drop wise to a vigorously stirred solution

of the compound **5** (30 g, 101.7 mmol) in anhydrous dichloromethane (50 mL) under dry nitrogen at –78 ºC (dry ice-acetone). After the mixture was stirred for an additional 45 minutes, excess of reagent was decomposed by careful addition of methanol (20 mL) followed by 5% HCl (2 mL). The resulting mixture was allowed to warm to room temperature and the solvent was evaporated under vacuum**.** The aqueous layer was extracted with ethyl acetate (4x20 mL), the organic combined layers were dried over Na_2SO_4 and the solvent was evaporated under vacuum to afford the crude aldehyde **6** (25.2 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.20 (d, 1H, J = 8.12 Hz), 7.50 (s, 1H), 7.68 (d, 2H, J = 8.24 Hz), 7.88 (d, 2H, J = 8.24 Hz), 7.94 (d, 1H, J = 8.12 Hz), 10.13 (s, 1H); MS (ESI): 266 $[M+H]^+$.

1-(2-(4-(Oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)ethanone (7)

To a mixture of compound **6** (23 g, 86.7 mmol) and tosylmethyl isocyanide (16.9 g, 86.7 mmol) in 75 ml of methanol was added K_2CO_3 (11.9 g, 86.7 mmol). The solution was stirred for 2 hours and the solvent was removed under reduced pressure. The residue was poured into icewater and extracted with ether. The ether layer was washed with 2% HCl and water and the obtained solid was filtered and dried over Na_2SO_4. **7** as 24.8 g, with 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.19-7.25 (m, 3H), 7.50 (s, 1H), 7.76 (s, 1H), 7.94 (d, 1H, J = 8.12 Hz), 8.19 (d, 2H, J = 8.25 Hz), 8.56 (s, 1H); MS (ESI): 305 $[M+H]^+$.

4-(2-(4-(Oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-amine (9)

To a mixture of ketone (**7**) (23 g, 75.6 mmol), thiourea (5.7 g, 75.6 mmol), and triethylamine (10.6 ml, 75.6 mmol) in acetonitrile (50 mL) was added carbon tetrabromide (7.3 ml, 75.6 mmol) in a round bottom flask at room temperature and the reaction mixture was stirred for 6 hours. After completion of the reaction (monitored by TLC), water (5 mL) was added and the mixture was extracted with ethyl acetate (3×5 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product. The resulting product was purified by silica gel column chromatography using a gradient mixture of hexane/ethyl acetate (1:1) as eluent to afford an analytically pure sample of **9** as 22.5 g, with 83% yield**.** ^{1}H NMR (400 MHz, DMSO-d6): δ 6.13 (brs, 2H), 6.56 (s, 1H), 7.20-7.28 (m, 3H), 7.47 (d, 1H, J = 8.09 Hz), 7.58 (d, 1H, J = 8.09 Hz), 7.75 (s, 1H), 8.19 (d, 2H, J = 8.17 Hz), 8.55 (s, 1H); MS (ESI): 361 $[M+H]^+$.

N-(4-(2-(4-(Oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11a)

The compound 4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-amine (**9**) (200 mg, 5.5 mmol) was dissolved in 10 mL of dried dichloromethane, followed by addition of benzoyl chloride (**10a**) (0.6 ml, 5.5 mmol), and Et_3N (2.3 mL, 16.5 mmol). The reaction mixture was stirred at room temperature for 12 hours, till the completion of the reaction as monitored by TLC. The reaction mixture was washed with water and extracted with dichloromethane, dried over anhydrous Na_2SO_4 and the crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to obtain pure compound **11a** in 210 mg, 82% yield. Mp: 198–200 ºC, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (s, 1H), 7.21 (d, 2H, J = 8.10 Hz), 7.45-7.57 (m, 4H), 7.58 (d, 1H, J = 8.09 Hz), 7.61 (s, 1H), 7.76-7.81 (m, 3H), 8.18 (d, 2H, J = 8.10 Hz), 8.21 (s, 1H), 9.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.6, 121.5, 123.4, 125.2, 127.2, 127.5, 128.4, 128.8, 129.2, 129.6, 132.3, 134.6, 137.4, 143.5, 145.6, 150.5, 151.5, 156.3, 157.4, 158.7, 160.3, 169.4; MS (ESI): 465 $[M+H]^+$.

4-Chloro-N-(4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11b)

This compound **11b** was prepared following the method described for the preparation of the compound **11a**, employing **9** (200 mg, 5.5 mmol) with 4-chlorobenzoyl chloride (**10b**) (0.7 ml, 5.5 mmol), Et_3N (2.3 mL, 16.5 mmol) and the crude product was purified by column chromatography with ethyl acetate/hexane (3:6) to afford pure compound **11b**, 218 mg in 79% yield. Mp: 231–233 ºC, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (s, 1H), 7.21 (d, 2H, J = 8.10 Hz), 7.40 (d, 2H, J = 8.26 Hz), 7.45 (d, 1H, J = 8.07 Hz), 7.57 (d, 1H, J = 8.07 Hz), 7.61 (s, 1H), 7.74 (s, 1H), 7.82 (d, 2H, J = 8.26 Hz), 8.18 (d, 2H, J = 8.10 Hz), 8.21 (s, 1H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.4, 121.6, 123.6, 125.7, 126.5, 127.4, 128.3, 128.7, 129.6, 133.4, 134.6, 136.5, 142.2, 143.5, 145.6, 150.2, 151.4, 156.7, 157.3, 158.6, 160.5, 169.7; MS (ESI): 499 $[M+H]^+$.

4-Bromo-N-(4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11c)

This compound **11c** was prepared following the method described for the preparation of the compound **11a**, employing **9** (200 mg, 5.5 mmol) with 4-bromobenzoyl chloride (**10c**) (120 mg, 5.5 mmol), Et_3N (2.3 mL, 16.5 mmol) and the crude product was purified by column chromatography with ethyl acetate/hexane (3:6) to afford pure compound **11c**, 232 mg in 77% yield. Mp: 235–237 ºC, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (s, 1H), 7.21 (d, 2H, J = 8.11 Hz), 7.41 (d, 1H, J = 8.08 Hz), 7.55 (d, 1H, J = 8.08 Hz), 7.61 (s, 1H), 7.76 (d, 2H, J = 8.29 Hz), 7.78 (s, 1H), 7.82 (d, 2H, J = 8.29 Hz), 8.19 (d, 2H, J = 8.11 Hz), 8.21 (s, 1H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.7, 121.4, 123.7, 125.7, 125.8, 126.6, 127.4, 128.4, 128.8, 129.5, 132.5, 134.6, 137.6, 143.5, 145.6, 150.6, 151.4, 156.7, 157.8, 159.5, 160.7, 169.8; MS (ESI): 544 $[M+H]^+$.

4-Nitro-N-(4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11d)

This compound **11d** was prepared following the method described for the preparation of the compound **11a**, employing **9** (200 mg, 5.5 mmol) with 4-nitrobenzoyl chloride (**10d**) (102 mg, 5.5 mmol), Et_3N (2.3 mL, 16.5 mmol) and the crude product was purified by column chromatography with ethyl acetate/hexane (4:6) to afford pure compound **11d**, 221 mg in 78% yield. Mp: 232–234 ºC, ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (s, 1H), 7.21 (d, 2H, J = 8.12 Hz), 7.43 (d, 2H, J = 8.09 Hz), 7.55 (d, 1H, J = 8.09 Hz), 7.60 (s, 1H), 7.78 (s, 1H), 7.86 (d, 2H, J = 8.30 Hz), 7.88 (d, 2H, J = 8.30 Hz), 8.19 (d, 2H, J = 8.11 Hz), 8.21 (s, 1H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.8, 121.7, 123.8, 125.6, 125.9, 127.5, 127.9, 128.3, 128.7, 130.5, 134.5, 137.5, 143.6, 145.8, 150.6, 151.4, 152.5, 156.6, 157.7, 159.5, 160.7, 169.8; MS (ESI): 510 $[M+H]^+$.

3,4,5-Trimethoxy-N-(4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11e)

This compound **11e** was prepared following the method described for the preparation of the compound **11a**, employing **9** (200 mg, 5.5 mmol) with 3,4,5-trimethoxybenzoyl chloride (**10e**) (126 mg, 5.5 mmol), Et_3N (2.3 mL, 16.5 mmol) and the crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound **11e**, 262 mg in 85% yield. Mp: 228–230 ºC, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.92 (s, 6H), 6.48 (s, 1H), 7.21 (d, 2H, J = 8.10 Hz), 7.24 (s, 2H), 7.41 (d, 1H, J = 8.08 Hz), 7.54 (d, 1H, J = 8.08 Hz), 7.61 (s, 1H), 7.78 (s, 1H), 8.19 (d, 2H, J = 8.10 Hz), 8.21 (s, 1H), 9.13 (s, 1H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 57.6, 62.8, 105.6, 107.6, 121.4, 123.5, 125.6, 127.4, 127.8, 128.4, 128.8, 132.4, 134.7, 143.5, 144.7, 145.8, 150.5, 151.5, 156.7, 156.9, 157.8, 159.7, 160.8, 169.8; MS (ESI): 555 $[M+H]^+$.

4-Methoxy-N-(4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11f)

This compound **11f** was prepared following the method described for the preparation of the compound **11a**, employing **9** (200 mg, 5.5 mmol) with 4-methoxybenzoyl chloride (**10f**) (0.7 mg, 5.5 mmol), Et_3N (2.3 mL, 16.5 mmol) and the crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound **11f**, 237 mg in 86% yield. Mp: 222–224 ºC, ^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.48 (s, 1H), 7.21 (d, 2H, *J* = 8.10 Hz), 7.41 (d, 1H, *J* = 8.08 Hz), 7.54 (d, 1H, *J* = 8.08 Hz), 7.60 (s, 1H), 7.65 (d, 2H, *J* = 8.20 Hz), 7.75-7.82 (m, 3H), 8.19 (d, 2H, *J* = 8.10 Hz), 8.21 (s, 1H), 9.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.8, 105.8, 115.8, 121.6, 123.6, 125.7, 127.4, 127.6, 128.5, 128.7, 129.6, 130.7, 134.6, 143.6, 145.8, 150.6, 151.7, 156.7, 157.8, 159.5, 166.5, 169.8, 169.8; MS (ESI): 495 $[M+H]^+$.

4-Cyano-N-(4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11g)

This compound **11g** was prepared following the method described for the preparation of the compound **11a**, employing **9** (200 mg, 5.5 mmol) with 4-cyanobenzoyl chloride (**10g**) (91 mg, 5.5 mmol), Et_3N (2.3 mL, 16.5 mmol) and the crude product was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **11g**, 246 mg in 91% yield. Mp: 218–220 ºC, ^1H NMR (300 MHz, $CDCl_3$): δ 6.48 (s, 1H), 7.21 (d, 2H, *J* = 8.10 Hz), 7.41 (d, 1H, *J* = 8.08 Hz), 7.54 (d, 1H, *J* = 8.08 Hz), 7.61 (s, 1H), 7.78 (s, 1H), 7.82 (d, 2H, *J* = 8.24 Hz), 8.09 (d, 2H, *J* = 8.24 Hz), 8.19 (d, 2H, *J* = 8.10 Hz), 8.21 (s, 1H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.7, 115.7, 119.6, 121.5, 123.6, 125.7, 127.5, 127.7, 128.4, 128.7, 131.4, 133.5, 134.6, 140.6, 143.5, 145.6, 150.6, 151.7, 156.6, 157.8, 159.5, 160.7, 169.8; MS (ESI): 490 $[M+H]^+$.

4-Fluoro-N-(4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11h)

This compound **11h** was prepared following the method described for the preparation of the compound **11a**, employing **9** (200 mg, 5.5 mmol) with 4-fluorobenzoyl chloride (**10h**) (0.6 ml, 5.5 mmol), Et_3N (2.3 mL, 16.5 mmol) and the crude product was purified by column chromatography with ethyl acetate/hexane (4:6) to afford pure compound **11h**, 211 mg in 79% yield. Mp: 205–207 ºC, ^1H NMR (300 MHz, $CDCl_3$): δ 6.48 (s, 1H), 7.21 (d, 2H, *J* = 8.10 Hz), 7.41 (d, 1H, *J* = 8.08 Hz), 7.47 (d, 2H, *J* = 8.23 Hz), 7.54 (d, 1H, *J* = 8.08 Hz), 7.61 (s, 1H), 7.77-7.82 (m, 3H), 8.19 (d, 2H, *J* = 8.10 Hz), 8.21 (s, 1H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.7, 116.7, 121.4, 123.6, 125.6, 127.5, 127.8, 128.4, 128.7, 130.5, 133.4, 134.6, 143.6, 145.7, 150.6, 151.5, 156.5, 157.6, 158.5, 159.6, 160.6, 168.7; MS (ESI): 483 $[M+H]^+$.

4-(Trifluoromethyl)-N-(4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11i)

This compound **11i** was prepared following the method described for the preparation of the compound **11a**, employing **9** (200 mg, 5.5 mmol) with 4-trifluoromethyl benzoyl chloride (**10i**) (0.8 ml, 5.5 mmol), Et_3N (2.3 mL, 16.5 mmol) and the crude product was purified by column chromatography with ethyl acetate/hexane (4:6) to afford pure compound **11i**, 261 mg in 88% yield. Mp: 210–212 ºC, ^1H NMR (300 MHz, $CDCl_3$): δ 6.48 (s, 1H), 7.21 (d, 2H, *J* = 8.10 Hz), 7.41 (d, 1H, *J* = 8.08 Hz), 7.47 (d, 2H, *J* = 8.23 Hz), 7.61 (s, 1H), 7.76 (s, 1H), 7.80 (d, 2H, *J* = 8.17 Hz), 8.09 (d, 2H, *J* = 8.17 Hz), 8.20 (d, 2H, *J* = 8.10 Hz), 8.21 (s, 1H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.6, 114.6, 121.4, 123.6, 125.7, 127.5, 127.9, 128.6, 128.9, 131.5, 134.6, 136.6, 140.6, 143.5, 145.7, 150.6, 151.7, 156.7, 157.7, 159.7, 160.6, 169.7; MS (ESI): 533 $[M+H]^+$.

4-(Dimethylamino)-N-(4-(2-(4-(oxazol-5-yl)phenyl)benzo[d]oxazol-6-yl)thiazol-2-yl)benzamide (11j)

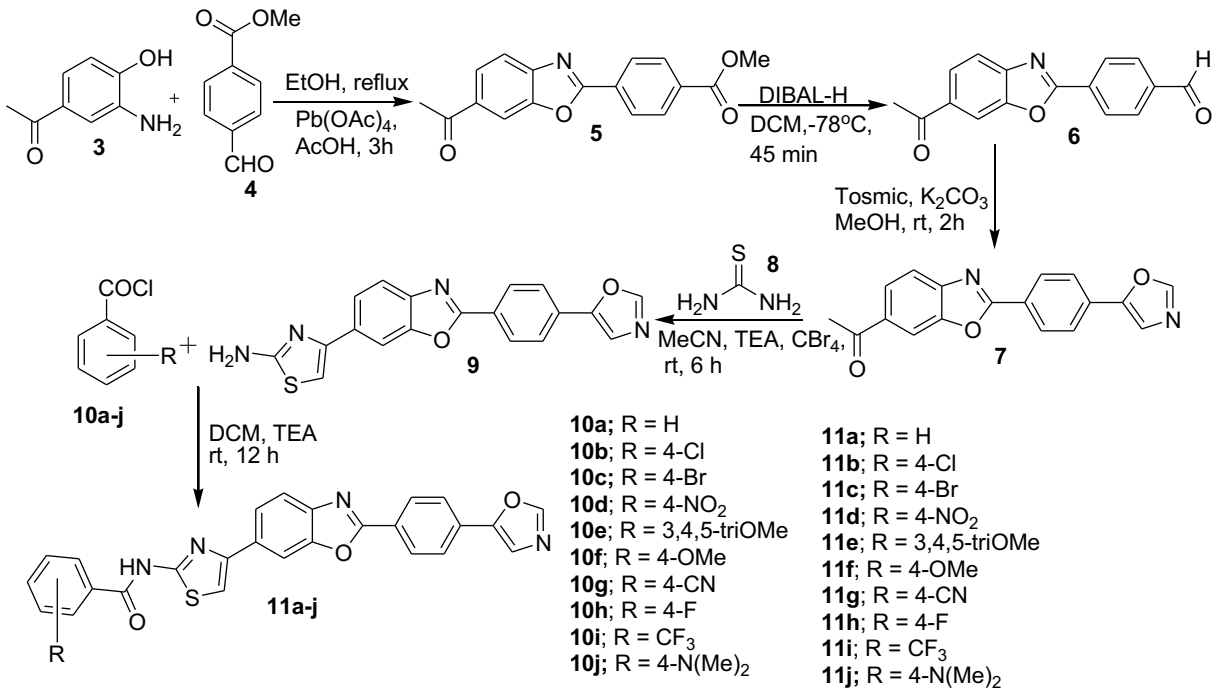
This compound **11j** was prepared following the method described for the preparation of the compound **11a**, employing **9** (200 mg, 5.5 mmol) with 4-N,N-dimethylbenzoyl chloride (**10j**) (100 mg, 5.5 mmol), Et_3N (2.3 mL, 16.5 mmol) and the crude product was purified by column chromatography with ethyl acetate/hexane (4:6) to afford pure compound **11j**, 215 mg in 77% yield. Mp: 207–209 ºC, ^1H NMR (300 MHz, $CDCl_3$): δ 2.93 (s, 6H), 6.48 (s, 1H), 6.67 (d, 2H, *J* = 8.16 Hz), 7.20 (d, 2H, *J* = 8.10 Hz), 7.41 (d, 1H, *J* = 8.08 Hz), 7.55 (d, 1H, J = 8.08 Hz), 7.61 (s, 1H), 7.76 (s, 1H), 7.80 (d, 2H, *J* = 8.16 Hz), 8.19 (d, 2H, *J* = 8.10 Hz), 8.21 (s, 1H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.5, 105.7, 114.6, 121.4, 123.6, 125.6, 125.7, 127.4, 127.8, 128.5, 128.9, 130.6, 134.6, 143.5, 145.8, 150.3, 151.8, 156.4, 156.9, 157.5, 159.6, 160.6, 169.8; MS (ESI): 508 $[M+H]^+$.

MTT Assay

The cytotoxic activity of the compounds was determined using MTT assay. 1 × 104 cells/well were seeded in 200 ml DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 hours at 37 ºC 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 hours of incubation, 10 ml MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (5 mg/ml) was added to each well and the plates were further incubated for 4 hours. Then the supernatant from each well was carefully removed, formazon crystals were dissolved in 100 ml of DMSO and absorbance at 540 nm wavelength was recorded.

RESULTS AND DISCUSSION

The synthetic route for newly synthesized compounds **11a-j** was described in Scheme 1. The mixture of 1-(3-amino-4-hydroxyphenyl)ethanone (**3**) and methyl 4-formylbenzoate (**4**) were refluxed in ethanol for 3 hours. After reflux $Pb(OAc)_4$ and acetic acid were added to this reaction and stirred at room temperature for 1 hour to afford pure compound **5**. Then intermediate **5** was reduction with DIBAL-H in dry CH_2Cl_2 at -78 ºC for 45 minutes to afford pure aldehyde intermediate (**6**) in good yield. Intermediate 6 was cyclized with Tosmic reagent in methanol solvent and K_2CO_3 at room temperature for 2 hours to afford pure compound **7**. Compound **7** was cyclized with thiourea in acetonitrile solvent and CBr_4. The reaction stirred at room temperature for 6 hours to afford pure target compound **9**. Finally this 2-aminothiazole intermediate **9** was coupled with substituted aromatic acid chlorides (**10a-j**) in presence of triethyl amine in CH_2Cl_2 and was stirred at room temperature for 12 hours to afford final compounds (**11a-j**).



Scheme 1

BIOLOGICAL EVALUATION

In Vitro Cytotoxicity

These newly synthesized thiazole-amide (**11a-j**) derivatives were screened for their anticancer activity against three human cancer cell lines including MCF-7 (breast), A-549 (lung), and A375 (melanoma) by employing MTT assay. These results are summarized in Table 1 and doxorubicin used as a positive control. All these compounds were showed more potent activity with IC_{50} range from 0.11±0.027 to 16.4±7.23 µM with compared to positive control, doxorubicin (IC_{50} = 2.10±0.14 to 5.51±2.78 µM). Among them, compounds **11b, 11d, 11e, 11f** and **11g** were exhibited more potent activity than positive control. Structure-activity relationship (SAR) was evaluated for these compounds and results revealed that compound **11b** with 4-chloro substituted phenyl ring, and have displayed most promising anticancer activity in all tested cell lines with IC_{50} values (MCF-7 = 0.12±0.027 µM, A549 = 0.11±0.027 µM and A375 = 1.89±0.35 µM) respectively. Instead of 4-chloro group with 4-bromo group having compound **11c** have showed lower activity than **11b**. Replacement of 4-bromo group with 4-nitro group (**11d**) was showed increased activity in three cell lines (MCF-7 = 1.13±0.33 µM, A549 = 2.10±1.65 µM and A375 = 1.98±0.37 µM) compared to **11b.** Compound **11g** with 4-cyano substituent on phenyl ring, and have exhibited increased activity (MCF-7 = 0.26±0.028 µM, A549 = 1.26±0.28 µM and A375 = 2.56±1.96 µM). Interestingly, compounds **11e** and **11f** with electron donating groups such as 3,4,5-trimethoxy (MCF-7 = 0.93±0.038 µM, A549 = 1.67±0.30 µM and A375 = 3.90±2.18 µM), 4-methoxy (MCF-7 = 0.34±0.03 µM, A549 = 1.55±0.29 µM and A375 = 2.45±1.95 µM) on the phenyl ring and were showed improved anticancer activities.

Table 1: Cytotoxic activity (IC_{50} µM) of compounds 11a-j.[a]

Compound	MCF-7[c]	A-549[d]	A375[e]
11a	2.89±1.79	3.67±2.12	6.90±3.56
11b	0.12±0.027	0.11±0.027	1.89±0.35
11c	12.7±5.14	-	-
11d	1.13±0.33	2.10±1.65	1.98±0.37
11e	0.93±0.038	1.67±0.30	3.90±2.18
11f	0.34±0.03	1.55±0.29	2.45±1.95
11g	0.26±0.028	1.26±0.28	2.56±1.96
11h	-	7.34±4.78	8.10±5.39
11i	9.30±5.76	16.4±7.23	-
11j	5.89±4.23	-	-
Doxorubicin	3.12±0.17	2.10±0.14	5.51±2.78

"-" = Not active.

[a]Each data represents as mean ±S.D values. From three different experiments performed in triplicates.[b] [c]MCF-7: human breast cancer cell line. [d]A549: human lung cancer cell line. [e]A375: human melanoma cancer cell line.

CONCLUSION

In summary, we have synthesized a series of thiazole-amide (**11a-j**) derivatives, and were studied for their anticancer activity towards three human cancer cell lines (MCF-7 (breast), A-549 (lung), and A375 (melanoma). All these compounds were displayed more potent activity. Among them, compounds **11b, 11d, 11e, 11f** and **11g** exhibited more potent activity than positive control.

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