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Design and Synthesis of Different Aryl Substituted 1,3,4-Oxadiazole-imidazo[1,5-*a*]pyridine Derivatives as Anticancer Agents

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Abstract—A new series of 1,3,4-oxadiazole incorporated imidazo[1,5-*a*]pyridine derivatives was prepared. Anticancer activity of all the obtained compounds was investigated by employing MTT assay. Among them, six compounds showed most prominent anticancer activity than etoposide.

Keywords: Alpidem, imidazo[1,5-*a*]pyridine, 1,3,4-oxadiazole, Zibotentan, anticancer activity

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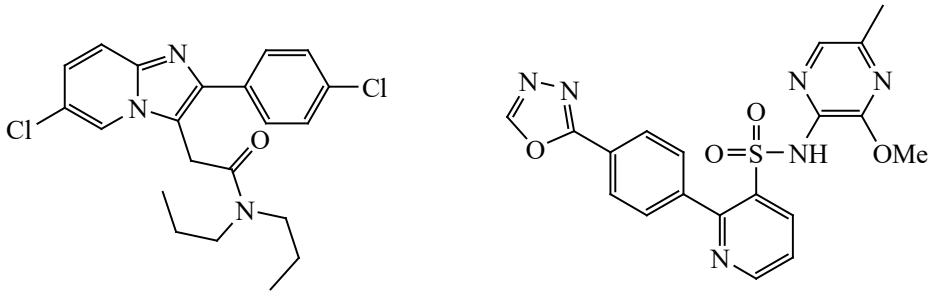
INTRODUCTION

Cancer is a one of the leading illnesses and causes of death for humans all over the World and which can be caused by abnormal cell division of normal cells [1, 2]. This is induced by genetic and epigenetic deviations, which can be divided into two types such as external (radiations, infections and tobacco) [3–5] and internal factors (hormones, mutations) [6–8]. Cancer treatments include surgery, radiation therapy, and chemotherapy, in which chemotherapy is the finest treatment for cure of various cancers [9]. Nitrogen-containing heterocycles are the best source for discovery and development of new types of chemotherapeutic agents. Among them, hetero-aromatic, imidazo[1,5-*a*]pyridines are the distinguished nitrogenous-bridgehead fused building blocks and highly attracted compounds due to their numerous biological application in the field of medicinal and synthetic chemistry [10–13]. They exhibit different kinds of biological properties including antiviral [14], aromatase [15], thromboxane synthetase inhibitors [16], positive inotropic agents [17], antibacterial [18], (VEGF)-receptor KDR [19], and apoptosis [20]. Alpidem (**1**, Scheme 1) [21] is the US FDA accepted chemotherapeutic drug bearing imidazole-pyridine skeleton as a part of the chemical structure, it is used for treatment of non-sedative agent.

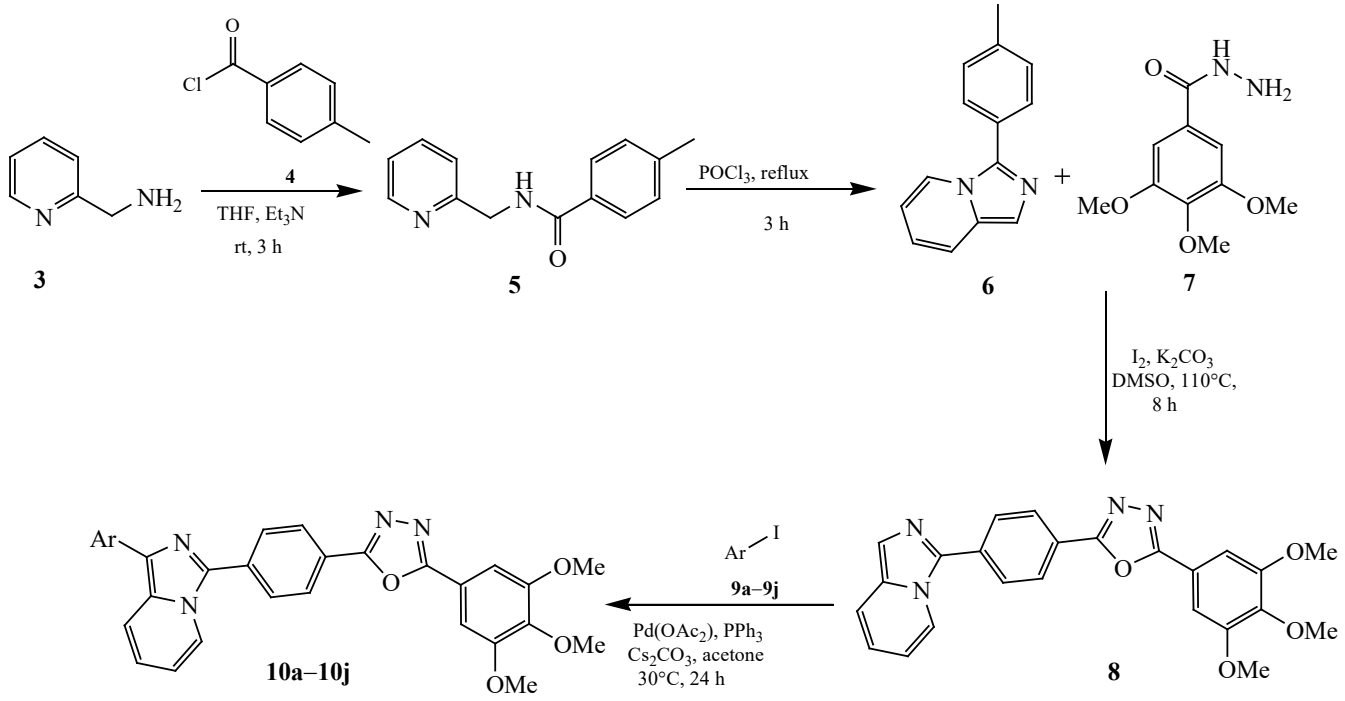
In addition, the *N*,*O*-five-membered ring system, namely 1,3,4-oxadiazoles, are the most privileged heterocyclic compounds, which can able to formation of hydrogen bonding with suitable target site [22, 23]. These derivatives displayed a different types of pharmacological properties like tubulin inhibitors [24], anticancer [25], antioxidant [26], HDACs [27], antibacterial [28], anti-inflammatory [29], insecticidal [30], antifungal [31], analgesics [32], antidepressant [33], antitubercular [34], antiviral [35], antidiabetic [36], antithrombotic

Scheme 1.



1 **2**

Scheme 2.



3 **5** **6** **7** **8** **10a–10j**

R = 3,4,5-trimethoxyphenyl (**a**), 4-methoxyphenyl (**b**), 4-cyanophenyl (**c**), 4-nitrophenyl (**d**), 4-methylphenyl (**e**), pyridin-4-yl (**f**), thien-2-yl (**g**), pyrazol-4-yl (**h**), isoxazol-4-yl (**i**), 3-methylpyrazol-4-yl (**j**).

[37], and tyrosinase [38]. The US Food and Drug Administrations (FDA) approved chemotherapeutic agent as Zibotentan (**2**, Scheme 1), which was utilized for treatment of various cancers [39].

Based on the biological findings of imidazole[1,5-*a*]-pyridines and 1,3,4-oxadiazole moieties, we have design and prepared a new series of structurally modified different aryl substituted 1,3,4-oxadiazole-imidazo[1,5-*a*]-pyridine derivatives and examined their preliminary anticancer activity against human cancer cell lines (MCF-7, A549, Colon-205 and A2780).

RESULTS AND DISCUSSION

The synthetic route for the preparation of 1,3,4-oxadiazole incorporated imidazo[1,5-*a*]pyridine derivatives **10a**–**10j** is outlined in Scheme 2. Intermediate **3** was coupled with 4-methyl benzoyl chloride **4** in the presence of triethyl amine in anhydrous THF.

Table 1. Anticancer activity of compounds **10a**–**10j** towards human cancer cell lines[a]

Compound	IC_{50}, μM			
	MCF-7	A549	Colo-205	A2780
10a	0.19±0.038	1.66±0.28	1.98±0.77	0.55±0.014
10b	3.57±2.88	3.99±2.11	5.26±3.28	Not determined
10c	Not determined	10.6±3.77	5.77±2.15	8.53±4.38
10d	14.76±6.98	Not determined	8.37±3.79	Not determined
10e	Not determined	Not determined	9.21±	Not determined
10f	1.37±0.33	1.28±0.82	1.63±0.66	1.07±0.045
10g	2.18±1.60	Not determined	2.55±1.56	2.19±1.25
10h	0.012±0.005	0.43±0.017	0.038±0.002	0.77±0.018
10i	1.88±0.72	1.35±0.82	0.66±0.013	0.89±0.056
10j	0.83±0.017	0.33±0.038	0.10±0.018	0.23±0.063
Etoposide	2.19 ± 1.87	3.34 ± 0.152	0.17 ± 0.034	1.38 ± 0.56

[a] MCF-7—human breast cancer cell line, A549—human lung cancer cell line, Colo-205—human colon cancer cell line, A2780—human ovarian cancer cell line.

The reaction proceeded at room temperature for 3 h to afford pure compound **5**. The latter underwent cyclization in $POCl_3$ at reflux for 3 h to form 3-*p*-tolyl-imidazo[1,5-*a*]pyridine **6**. This compound reacted with 3,4,5-trimethoxyphenyl acid hydrazide **7** in the presence of iodine and K_2CO_3 in DMSO at 110°C for 8 h to furnish 3-{4-[5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}imidazo[1,5-*a*]pyridine **8**. Further Suzuki-coupling with various types of aryl boronic acids **9a**–**9j** in presence of $Pd(OAc)_2$, triphenyl phosphine and Cs_2CO_3 in dry acetone at 30°C for 24 h resulted in the formation of final compounds **10a**–**10j.**

Structure of newly prepared compounds was analysed by ^1H NMR, ^{13}C NMR and mass spectral data

The anticancer activity profile of newly prepared compounds **10a**–**10j** against breast cancer (MCF-7), lung cancer (A549), colon cancer (Colon-205) and ovarian cancer (A2780) cell lines was examined by employing MTT assay, and compared with reference drug candidate as etoposide. These obtained results are summarized in Table 1. Among all the synthesized compounds, six derivatives **10a**, **10f**, **10g**, **10h**, **10i** and **10j** demonstrated more potent anticancer activity than etoposide. Further, these compounds were studied for SARs profile, the results indicated that the compound **10a** with 3,4,5-trimethoxyphenyl ring shows good inhibitory anticancer activity (MCF-7 0.19±0.038 μM; A549 1.66±0.28 μM; Colo-205 1.98±0.77 μM and A2780 0.55±0.014 μM) to compare with reference drug. Compounds **10b** (R = 4-methoxyphenyl) and **10c** (R = 4-methylphenyl) show very lower activity than **10a**. In addition, compounds **10c** and **10d** bearing strong electron-withdrawing substituents display moderate activity. Interestingly, heteroaromatic compound **10h** with pyrazole skeleton exhibit excellent activity among all the tested cancer cell lines (MCF-7 0.012±0.005 μM; A549 0.43±0.017μM; Colo-205 0.038±0.002μM and A2780 0.77±0.018μM). Similarly, compound **10j** having 3-methylpyrazole motif demonstrates slightly decreased activity (MCF-7 0.83±0.017μM; A549 0.33±0.038μM; Colo-205 0.10±0.018μM and A2780 0.23±0.063μM) than imidazo[1,5-*a*]pyridine **10h**. When replacing pyrazole skeleton with isoxazole ring, compound **10i** shows better activity (MCF-7 1.88±0.72 μM; A549 1.35±0.82 μM; Colo-205 0.66±0.013 μM and A2780= 0.89±0.056μM), whereas compound **10g** bearing thienyl unit exhibit lowest activity (MCF-7 2.18±1.60 μM; Colo-205 2.55±1.56 μM and A2780 2.19±1.25 μM) compared to compounds **10f**, **10h**, and **10j**. Moreover, compound **10f** with pyridine substituent displays slightly improved activity (MCF-7 1.37±0.33 μM; A549 1.28±0.82 μM; Colo-205 1.63±0.66μM and A2780= 1.07±0.045 μM).

EXPERIMENTAL

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, USA), Lancaster (Alfa Aesar, 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 a 300 MHz spectrometer. Chemical shifts are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC spectrometer equipped with ESI mode positive ion trap detector. Melting points were determined with an electro thermal melting point apparatus, and were uncorrected.

4-Methyl-(*N*-pyridin-2-yl)methylbenzamide (5). To a stirred solution of (pyridin-2-yl)metha namine **3** (15 g, 138.7 mmol) in anhydrous THF (200 mL) was added triethylamine (57.9 mL, 416.1 mmol) followed by 4-methylbenzoylchloride **4** (4.8 mL, 166.4 mmol) at 0°C. The reaction mixture was stirred at room temperature for 3 h. After the reaction completed, THF was removed under vacuum to afford crude product, which was further purified by column chromatography with ethyl acetate–hexane (2 : 3) to afford pure compound **5**. Yield 21.6 g (69%). ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H), 4.70 d (2H, *J* = 5.0 Hz), 6.83 t (1H, *J* = 8.3, 6.7 Hz), 7.20 d. d (1H, *J* = 6.7, 6.0 Hz), 7.32 d (2H, *J* = 8.3 Hz), 7.64 d (2H, *J* = 8.3 Hz), 8.33 s (1H), 8.36 d (1H, *J* = 4.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23.2, 49.5, 124.6, 125.3, 129.5, 130.4, 131, 139.6, 141.3, 151.1, 160.3, 167.8. Mass spectrum (ESI), *m*/*z*: 227 $[M + H]^+$.

3-*p*-Tolylimidazo[1,5-*a*]pyridine (6). A mixture of compound **5** (20 g, 88.4 mmol) and 100 mL of $POCl_3$ was stirred at reflux for 3 h. After the reaction completed, the mixture was poured into cold water and neutralized with $NaHCO_3$ solution. The water layer was extracted three times with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue thus obtained was purified by column chromatography using ethyl acetate–hexane (4 : 6) to give compound **6**. Yield 13.1 g (71%), white solid. ^{1}H NMR spectrum, δ, ppm: 8.06 d (1H, *J* = 7.3 Hz), 7.51 d (2H, *J* = 8.1 Hz), 7.32 s (1H), 7.29 d (1H, *J* = 9.0 Hz), 7.14 d (2H, *J* = 7.9 Hz), 6.49 d. d (1H, *J* = 6.4, 6.2 Hz), 6.33 d. d (1H, *J* = 7.3, 7.1 Hz), 2.27 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 23.7, 114.9, 124.4, 125.3, 128.2, 129.4, 130.1, 130.7, 131.5, 140.2, 141.7, 146.5. Mass spectrum (ESI), *m/z*: 209 $[M + H]^+$.

3-{4-[5-(3,4,5-Trimethoxyphenyl)[1,3,4]oxadiazol-2-yl]phenyl}imidazo[1,5-*a*]pyridine (8). A clean and dry 500 mL pressure tube was charged with compound **6** (11 g, 52.8 mmol), I_2 (33.4 g, 132.2 mmol) and DMSO (200 mL). The vial was sealed and the resulting mixture was stirred at 110°C for 6 h. After completion of the reaction, 3,4,5-trimethoxybenzohydrazide **7** (14.3 g, 63.3 mmol) and K_2CO_3 (43.7 g, 316.8 mmol) were added. The resulting mixture was stirred at 110°C for 6 h. After the reaction completed, the mixture was treated with 300 mL of water and extracted with MTBE (3 × 200 mL). The extract was washed with 10% $Na_2S_2O_3$ solution (w/w), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (ethyl acetate–hexane, 1 : 1). Yield 13.9 g (62%), white solid, mp 207–209°C. ^{1}H NMR spectrum, δ, ppm: 3.77 s (6H), 3.86 s (3H), 7.28 s (2H), 7.36 d. d (1H, *J* = 8.0, 1.3 Hz), 7.42–7.44 m (1H), 7.74 d (1H, *J* = 7.3 Hz), 7.81 d (2H, *J* = 7.9 Hz), 8.30 d (2H, *J* = 7.9 Hz), 8.43 s (1H), 8.55 t (1H, *J* = 8.3). ^{13}C NMR spectrum, δ_C, ppm: 58.4, 62.9, 113.6, 114.9, 124.4, 125.3, 126.7, 127.2, 128.2, 129.4, 130.8, 131.4, 132.2, 140.2, 141.3, 146.5, 154.8, 165.9, 167.5. Mass spectrum (ESI), *m/z*: 429 $[M + H]^+$.

1-(3,4,5-Trimethoxyphenyl)-3-{4-[5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}-imidazo[1,5-*a*]pyridine (10a). To a solution of compound **8** (500 mg, 1.16 mmol) and 3,4,5-trimethoxyphenyl iodide **9a** (687 mg, 2.33 mmol) in dry acetone (60 mL) were added $Pd(OAc)_2$ (13 mg, 0.058 mmol, 5 mol %), triphenylphosphine (60 mg, 0.232 mmol, 20 mol %) and Cs_2CO_3 (756 mg, 2.32 mmol). The reaction mixture was stirred at 30°C for 24 h. After completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under vacuum to afford crude product which was purified by column chromatography (hexane–ethyl acetate, 7 : 3). Yield 242.6 mg (35% yield), white solid, mp 328–330°C. ^{1}H NMR spectrum, δ, ppm: 3.77 s (6H), 3.80 s (3H), 3.87 s (3H), 3.94 s (6H), 7.12 s (2H), 7.27 s (2H), 7.36 d. d (1H, *J* = 8.0, 1.3 Hz), 7.42–7.45 m (1H), 7.68 d (1H, *J* = 7.2 Hz), 7.80 d (2H, *J* = 8.0 Hz), 8.31 d (2H, *J* = 8.0 Hz), 8.56 d. d (1H, *J* = 8.3, 1.01 Hz). ^{13}C NMR spectrum, δ_C, ppm: 58.4, 59.7, 62.1, 62.7, 113.6, 114.2, 115.9, 124.4, 125.3, 125.7, 127.2, 128.8, 129.4, 130.1, 133.8, 139.4, 139.8, 140.2, 141.3, 146.5, 154.8, 155.7, 165.6, 167.5. Mass spectrum (ESI), *m/z*: 595 $[M + H]^+$.

Compounds **10b**–**10j** were prepared similarly.

1-(4-Methoxyphenyl)-3-{4-[5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}imidazo-[1,5-*a*]pyridine (10b). Yield 279.5 mg (45%), white solid, mp 335–337°C. ^{1}H NMR spectrum, δ, ppm: 3.77 s (6H), 3.87 s (3H), 3.91 s (3H), 7.19 d (2H, *J* =

8.2 Hz), 7.29 s (2H), 7.36 d. d (1H, *J* = 8.0, 1.3 Hz), 7.43–7.45 m (1H), 7.62–7.69 m (3H), 7.82 d (2H, *J* = 8.1 Hz), 8.31 d (2H, *J* = 8.1 Hz), 8.57 d. d (1H, *J* = 8.3, 1.07 Hz). ^{13}C NMR spectrum, δ_C, ppm: 57.2, 58.4, 62.9, 113.6, 114.9, 116.3, 124.4, 125.3, 125.7, 127.2, 128.4, 129.8, 130.1, 131.4, 132.5, 139.9, 140.1, 141.2, 141.7, 146.5, 154.5, 162.6, 165.9, 167.5. Mass spectrum (ESI), *m/z*: 535 $[M + H]^+$.

4-(3-{4-[5-(3,4,5-Trimethoxyphenyl)1,3,4-oxadiazol-2-yl]phenyl}imidazo[1,5-*a*]pyridin-1-yl)-benzonitrile (10c). Yield 325.6 mg (53%), white solid, mp 370–372°C. ^{1}H NMR spectrum, δ, ppm: 3.77 s (6H), 3.87 s (3H), 7.29 s (2H), 7.36 d. d (1H, *J* = 8.0, 1.3 Hz), 7.44–7.47 m (1H), 7.67 d (1H, *J* = 7.3 Hz), 7.82–7.94 m (4H), 8.33–8.44 m (4H, *J* = 8.1 Hz), 8.60 d. d (1H, *J* = 8.4, 1.07 Hz). ^{13}C NMR spectrum, δ_C, ppm: 58.4, 62.9, 113.6, 114.9, 115.5, 120.2, 124.4, 125.3, 127.5, 128.7, 129.4, 130.8, 131.4, 132.3, 133.5, 134.2, 139.4, 140.7, 141.2, 142.3, 146.5, 154.5, 165.6, 167.6. Mass spectrum (ESI), *m/z*: 530 $[M + H]^+$.

3-{4-[5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}-1-(4-nitrophenyl)imidazo [1,5-*a*]pyridine (10d). Yield 342.8 mg (53%), white solid, mp 363–365°C. ^{1}H NMR spectrum, δ, ppm: 3.77 s (6H), 3.87 s (3H), 7.28 s (2H), 7.36 d. d (1H, *J* = 8.0, 1.3 Hz), 7.45–7.48 m (1H), 7.68 d (1H, *J* = 7.5 Hz), 7.85–7.98 m (4H), 8.35–8.47 m (4H, *J* = 8.1 Hz), 8.64 d. d (1H, *J* = 8.5, 1.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 58.4, 62.9, 113.6, 114.9, 122.5, 124.4, 125.7, 126.3, 127.2, 128.4, 129.8, 130.4, 131.6, 132.5, 139.9, 140.1, 140.8, 141.3, 146.5, 154.8, 165.6, 167.5, 168.7. Mass spectrum (ESI), *m/z*: 550 $[M + H]^+$.

3-{4-[5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}-1-*p*-tolylimidazo[1,5-*a*]pyridine (10e). Yield 291.7 mg (65%), white solid, mp 353–355°C. ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H), 3.78 s (6H), 3.88 s (3H), 7.28 s (2H), 7.32–7.40 m (3H), 7.44–7.55 m (3H), 7.63 d (1H, *J* = 7.3 Hz), 7.86 d (2H, *J* = 7.7 Hz), 8.31 d (2H, *J* = 7.7 Hz), 8.61 d. d (1H, *J* = 8.4, 1.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23.7, 58.4, 62.1, 113.6, 114.9, 124.4, 125.3, 126.7, 127.5, 128.4, 129.8, 130.4, 131.2, 132.4, 133.5, 139.9, 140.1, 141.2, 142.3, 146.5, 155.5, 165.6, 167.5. Mass spectrum (ESI), *m/z*: 519 $[M + H]^+$.

3-{4-[5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}-1-(pyridin-4-yl)imidazo[1,5-*a*]pyridine (10f). Yield 331.4 mg (56%), white solid, mp 368–370°C. ^{1}H NMR spectrum, δ, ppm: 3.78 s (6H), 3.88 s (3H), 7.29 s (2H), 7.38 d (1H, *J* = 8.0 Hz), 7.47–7.58 m (3H), 7.65 d (1H, *J* = 7.4 Hz), 7.86–7.95 m (4H), 8.31 d (2H, *J* = 7.7 Hz), 8.66 d. d (1H, *J* = 8.6, 1.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 58.4, 62.9, 113.6, 114.9, 119.3, 124.4, 125.3, 125.7, 127.2, 128.4, 129.4, 130.1, 132.8, 139.9, 140.1, 140.8, 141.3, 146.5, 152.4, 155.8, 165.6, 167.6. Mass spectrum (ESI), *m/z*: 506 $[M + H]^+$.

3-{4-[5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}-1-(thien-2-yl)imidazo[1,5-*a*]pyridine (10g). Yield 316.8 mg (53%), white solid, mp 338–340°C. ^{1}H NMR spectrum, δ, ppm: 3.78 s (6H), 3.88 s (3H), 7.30 s (2H), 7.36–7.43 m (2H), 7.47–7.59 m (3H), 7.66 d (1H, *J* = 7.5 Hz), 7.84 d (2H, *J* = 7.9 Hz), 8.33 d (2H, *J* = 7.9 Hz), 8.65 d. d (1H, *J* = 8.5, 1.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 58.4, 62.9, 113.6, 114.9, 124.4, 125.3, 126.7, 127.2, 127.7, 128.3, 129.4, 130.8, 131.1, 132.4, 135.4, 139.9, 140.2, 141.3, 146.5, 155.8, 165.6, 167.6. Mass spectrum (ESI), *m/z*: 511 $[M + H]^+$.

3-{4-[5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}-1-(1*H*-pyrazol-4-yl)imidazo[1,5-*a*]-pyridine (10h). Yield 266.3 mg (46%), white solid, mp 344–346°C. ^{1}H NMR spectrum, δ, ppm: 3.78 s (6H), 3.88 s (3H), 7.30 s (2H), 7.33 d. d (1H, *J* = 8.1, 1.3 Hz), 7.42–7.44 m (1H), 7.64 d (1H, *J* = 7.6 Hz), 7.85–7.90 m (3H), 8.28–8.35 m (3H), 8.64 d. d (1H, *J* = 8.5, 1.2 Hz), 9.11 br. s (1H). ^{13}C NMR spectrum, δ_C, ppm: 58.4, 62.9, 113.6, 114.9, 124.3, 125.4, 126.7, 127.2, 128.4, 129.8, 130.4, 131.3, 136.6, 139.9, 140.2, 141.3, 141.7, 146.5, 155.5, 166.2, 167.7. Mass spectrum (ESI), *m/z*: 495 $[M + H]^+$.

1-(Isoxazol-4-yl)-3-{4-[5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}imidazo[1,5-*a*]pyridine (10i). Yield 270.5 mg (47%), white solid, mp 334–336°C. ^{1}H NMR spectrum, δ, ppm: 3.79 s (6H), 3.88 s (3H), 7.30 s (2H), 7.33 d. d (1H, *J* = 8.1, 1.3 Hz), 7.42–7.44 m (1H), 7.61–7.67 m (2H), 7.86–7.93 m (3H), 8.34 d (2H, *J* = 7.8 Hz), 8.67 d. d (1H, *J* = 8.5, 1.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 58.4, 62.9, 113.6, 114.9, 124.4, 125.3, 126.7, 127.2, 128.4, 129.8, 130.1, 130.8, 139.9, 140.2, 141.7, 146.5, 153.5, 154.6, 155.5, 165.6, 167.7. Mass spectrum (ESI), *m/z*: 496 $[M + H]^+$.

3-{4-[5-(3,4,5-Trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}-1-(3-methyl-1*H*-pyrazol-4-yl)-imidazo[1,5-*a*]pyridine (10j). Yield 210.6 mg (36%), white solid, mp 356–358°C. ^{1}H NMR spectrum, δ, ppm: 1.96 s (3H), 3.79 s (6H), 3.88 s (3H), 7.30 s (2H), 7.35 d. d (1H, *J* = 8.1, 1.3 Hz), 7.43–7.45 m (1H), 7.66–7.70 m (2H), 7.85 d (2H, *J* = 7.9 Hz), 8.34 d (2H, *J* = 7.8 Hz), 8.67 d. d (1H, *J* = 8.5, 1.2 Hz), 8.95 br. s (1H). ^{13}C NMR spectrum, δ_C, ppm: 15.1, 58.4, 62.9, 113.6,

114.9, 124.4, 125.3, 125.7, 127.2, 128.8, 129.8, 130.4, 131.3, 135.2, 139.9, 140.2, 141.3, 147.2, 148.5, 155.8, 165.9, 167.6. Mass spectrum (ESI), *m/z*: 509 $[M + H]^+$.

MTT assay. Each data represents as mean ±SD values from three different experiments performed in triplicates. Individual wells of a 96-well tissue culture microtiter plate were inoculated with 100 μL of complete medium containing 1×10^4 cells. The plates were incubated at 37°C in a humidified 5% CO_2 incubator for 18 h prior to the experiment. After medium removal, 100 μL of fresh medium containing the test compounds and etoposide at different concentrations such as 0.5, 1, and 2 μM were added to each well and incubated at 37°C for 24 h. Then the medium was discarded and replaced with 10 μL MTT dye. Plates were incubated at 37°C for 2 h. The resulting formazan crystals were solubilized in 100 μL extraction buffer. The optical density (OD) was read at 570 nm with micro plate reader (Multi-mode Varioskan Instrument-Themo Scientific). The percentage of DMSO in the medium never exceeded 0.25%.

CONCLUSIONS

In conclusion, we described a new library of 1,3,4-oxadiazole incorporated imidazo[1,5-*a*]pyridine derivatives. Anticancer activity of newly prepared compounds was investigated by employing MTT assay. These obtained results displayed significant anticancer activity compared with clinical drug etoposide.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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