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Design, Synthesis, and Anticancer Activity of 1,2,3-Triazole Linked 1,2-Isoxazole-imidazo[4,5-*b*]pyridine Derivatives

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Abstract—A series of novel 1,2-isoxazole-pyridobenzimidazole is synthesized. Structures of the products are supported by ^{1}H and ^{13}C NMR, and mass spectra. All compounds have been tested for their anticancer activity towards four human cancer cell lines including MCF-7 (breast cancer), A549 (lung cancer), Colon-205 (colon cancer), and A2780 (ovarian cancer). Etoposide was used as a standard drug. The determined IC_{50} values range from 0.01±0.003 to 23.7±3.72 μM. Among all compounds, six products exhibit the most significant activities.

Keywords: CCT 129202, carboxyamido triazole, imidazo[4,5-*b*]pyridine, 1,2,3-triazol and anticancer activity

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INTRODUCTION

Pyridine ring fused imidazole moiety are useful intermediates in drug design and development [1]. These are considered as structural analogues of purine [2] and exhibit potent biological activities such as anticancer [3], antimitotic [4], antioxidant [5], anti-inflammatory [6], antiviral [7], and more. Biological activity of triazole derivatives is well documented elsewhere. In conjunction with the major objective of the current study we have to mention anticancer activity of benzotriazole derivatives [8].

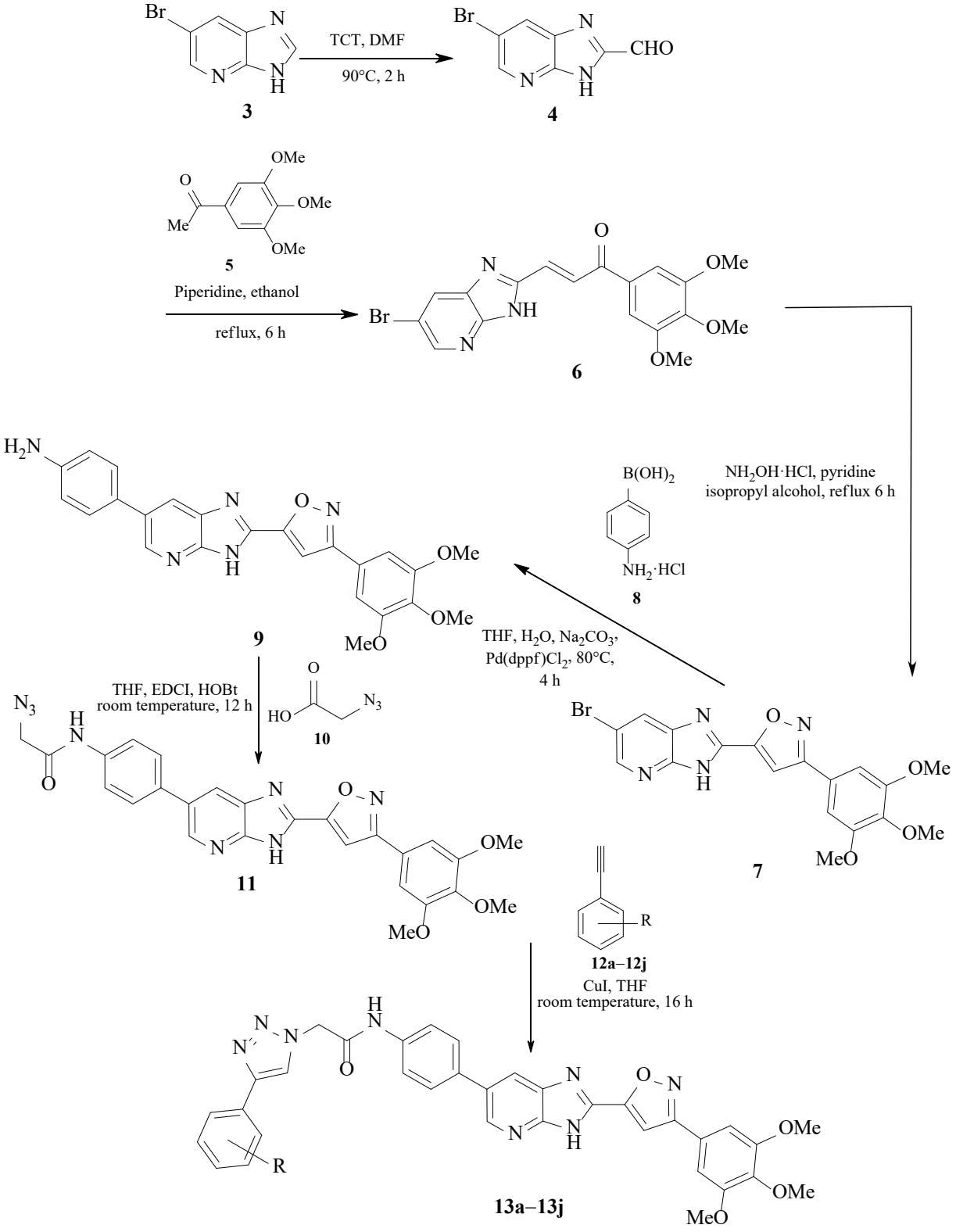
Based on the literature information on both pharmacophores involved (imidazo[4,5-*b*]pyridine and 1,2,3-triazole) we have designed and synthesized a series of 1,2,3-triazole linked 1,2-isoxazole-imidazo[4,5-*b*]-pyridines and characterized their structures by ^{1}H and ^{13}C NMR and mass spectra. All compounds were screened for their anticancer activity against human cancer cell lines.

RESULTS AND DISCUSSION

Synthetic approach to 1,2,3-triazole linked to 1,2-isoxazole-pyridobenzimidazoles **13a**–**13j** is presented in Scheme 1. The intermediate 6-bromo-3*H*-imidazo[4,5-*b*]-pyridine-2-carbaldehyde (**4**) was synthesized by the Vilsmeier-Haack reaction of 6-bromo-3*H*-imidazo[4,5-*b*]-pyridine (**3**) in presence of anhydrous DMF in TCT at 90°C. Its following aldol condensation with 3,4,5-trimethoxyacetophenone (**5**) in presence of catalytic amount of piperidine afforded pure chalcone intermediate **6**, which was converted into the product of cyclization **7**. The Suzuki-coupling reaction of the intermediate **7** with 4-aminophenylboronic acid (**8**) in presence of a catalyst [Pd(dppf)Cl_2] and Na_2CO_3 in THF–H_2O gave benzenamine derivative **9**, which was coupled with 2-azidoacetic acid (**10**) in presence of EDCI, HOBt with formation of the azide derivative **11.** The following reaction of the azide intermediate **11** with different substituted aryl alkynes **12a-j** under catalysis by CuI led to the corresponding target compounds **13a**–**13j.**

***In vitro* cytotoxicity.** Anticancer activity of the newly synthesized 1,2,3-triazole linked 1,2-isoxazole-pyridobenzimidazole hybrids **13a**–**13j** against human tumour cell lines including MCF-7 (breast cancer), A549 (lung cancer), Colon-205 (colon cancer), and A2780 (ovarian cancer) was tested by the MTT assay and compared with the standard drug etoposide. The unsubstituted 1,2,3-triazole linked 1,2-isoxazole-pyridobenzimidazole (**13a**) demonstrated very weak potency on four cell lines. The accumulated data (Table 1) exposed good anticancer activity of compounds **13b, 13c, 13d, 13e, 13g,** and **13j.** The structure-activity relationship (SAR) study indicated that the compound **13b** containing the 3,4,5-trimethoxyphenyl substituent on triazole cycle demonstrated the highest

Scheme 1. Synthetic approach to 1,2,3-triazole linked 1,2-isoxazole- imidazo[4,5-*b*]pyridine derivatives **13a**–**13j**.



R = H (**12a**, **13a**), 3,4,5-trimethoxy (**12b**, **13b**), 3,5-dimethoxy (**12c**, **13c**), 4-methoxy (**12d**, **13d**), 4-chloro (**12e**, **13e**), 4-bromo (**12f**, **13f**), 4-nitro (**12g**, **13g**), 3,5-dinitro (**12h**, **13h**), 4-methyl (**12i**, **13i**), 3,5-dimethyl (**12j**, **13j**).

In vitro cytotoxicity data of the synthesized compounds **13a**–**13j** towards a panel of human cancer cell lines[a]

Compound	MCF-7[b]	A549[c]	Colo-205[d]	A2780[e]
13a	3.700±0.890	11.600±3.560	13.9±4.350	Not active
13b	0.032±0.004	0.061±0.0076	0.25±0.025	0.022±0.005
13c	1.650±0.650	0.770±0.023	0.98±0.013	1.230±0.910
13d	2.100±1.230	1.280±0.440	1.55±0.510	1.960±0.270
13e	0.450±0.0440	0.120±0.035	0.18±0.017	0.280±0.059
13f	9.400±0.540	Not active	10.8±0.720	Not active
13g	0.390±0.630	0.010±0.003	0.10±0.032	0.510±0.088
13h	17.800±1.670	3.200±1.880	Not active	12.600±3.450
13i	12.300±0.660	15.700±4.380	23.7±3.720	Not active
13j	2.170±1.660	2.660±1.900	2.31±1.080	6.900±0.640
Etoposide	2.100±0.024	3.080±0.135	0.13±0.017	1.310±0.27

[a] Each data is presented as mean ±S.D values. [b] MCF-7: human breast cancer cell line. [c] A549: human lung cancer cell line. [d] Colo-205: human colon cancer cell line. [e] A2780: human ovarian cancer cell line.

activity. Its analogue **13c** with dimethoxyphenyl substituent was of lower activity. Significant loss of activity was determined by compound **13d** that contained only one 4-methoxy group on the phenyl ring. Upon replacement of the 4-methoxy group by chlorine in compound **13e** resulted in its improved activity against four cell lines, whereas its 4-bromo containing analogue demonstrated very poor activity. Presence of the 4-nitrophenyl substituent on triazole ring (**13g**) resulted in its excellent activity on all cell lines, but 3,4-dinitrophenyl derivative (**13h**) did not show the improved activity.

EXPERIMENTAL

All chemicals were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA) and Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and 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. Melting points were determined on an electro thermal melting point apparatus, and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a BRUKER NMR (300 MHz, 400 MHz) spectrometer using TMS as an internal standard and DMSO-d_6 as a solvent. ESI spectra were measured on a Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector.

(*E*)-3-(6-Bromo-3*H*-imidazo[4,5-*b*]pyridin-2-yl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (6). 6-Bromo-3*H*-imidazo[4,5-*b*]pyridine-2-carbaldehyde (**4**) (10 g, 0.0444 mmol) was dissolved in 30 mL of ethanol and mixed with 3,4,5-trimethoxyacetophenone (**5**) (9.3 g, 0.0444 mmol) and 3 drops of piperidine. The reaction mixture was refluxed for 6 h. After completion of reaction cold water (20 mL) was added slowly to it. The crystalline precipitate was filtered off and recrystallized. Yield 88%, mp 190–192°C. ^{1}H NMR spectrum, δ, ppm: 3.89 s (3H), 3.92 s (6H), 7.10 d (1H, J = 16.2 Hz), 7.31 s (2H), 8.38 s (1H), 8.62 d (1H, J = 16.2 Hz), 9.40 s (1H), 10.18 s (1H). MS (ESI): *m/z*: 418 $[M + H]^+$.

6-Bromo-2-(3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl)-3*H*-imidazo[4,5-b]pyridine (7). A mixture of compound **6** (15 g, 0.0359 mmol) with hydroxylamine hydrochloride (5 g, 0.0719 mmol) was dissolved in 40 mL of 2-propanol, 2 mL of pyridine were added, and the reaction mixture was stirred upon refluxing for 6 h. Upon completion of the reaction (TLC) the solvent was evaporated under reduced pressure. The precipitated was washed with water (3×20 mL), and the crude product was purified by column chromatography with ethyl acetate–hexane (4 : 6) to afford compound **7**. Yield 70%, mp 188–190°C. ^{1}H NMR spectrum, δ, ppm: 3.88 s (3H), 3.92 s (6H), 7.40 s (2H), 7.92 s (1H), 8.32 s (1H), 9.39 s (1H), 10.23 s (1H). MS (ESI): 433 $[M + H]^+$.

4-[2-(3-(3,4,5-Trimethoxyphenyl)isoxazol-5-yl]-3*H*-imidazo[4,5-b]pyridin-6-yl)benzenamine (9). The mixture of compound **7** (9 g, 0.0208 mmol) with Pd(dppf)Cl_2 (7.6 g, 0.0104 mmol) and 4-aminophenylboronic acid hydrochloride **8** (5.4 g, 0.0312 mmol) was dissolved in THF (50 mL). An aqueous solution of Na_2CO_3 (5 mL) was added to it upon stirring, and the reaction mixture was heated at 80°C for 4 h. After cooling, Et_2O (25 mL) was added, and the organic solution was washed with brine (2×30 mL), dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by column chromatography (ethyl acetate–hexane 8 : 2) to afford compound **9**. Yield 80%, mp 213–215°C. ^{1}H NMR spectrum, δ, 3.89 s (3H), 3.92 s (6H), 6.27 br.s (2H), 6.93 d (2H, *J* = 7.6 Hz), 7.39 s (2H), 7.70 d (2H, *J* = 7.6 Hz), 7.93 s (1H), 8.15 s (1H), 9.28 s (1H), 10.22 s (1H). MS (ESI): *m/z*: 444 $[M + H]^+$.

2-Azido-*N*-{4-[2-(3-{3,4,5-trimethoxyphenyl)-isoxazol-5-yl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl)phenyl}-acetamide (11). The mixture of compound **9** (7 g, 0.0158 mmol) with EDCI (3.7 g, 0.0237 mmol) and HOBt (1.2 g, 0.0079 mmol) was dissolved in 30 mL of anhydrous dichloromethane and stirred at 0°C for 1 h. 2-Azidoacetic acid **10** (1.5 mL, 0.0205 mmol) was then added to the mixture and stirred at room temperature for 12 h. Upon completion of the process, the mixture was washed with saturated sodium bicarbonate solution. The organic layer was separated and evaporated under reduced pressure to afford compound **11**. Yield 89%, mp 226–228°C. ^{1}H NMR spectrum, δ, ppm: 3.89 s (3H), 3.92 s (6H), 4.82 s (2H), 7.38 s (2H), 7.74 d (2H, *J* = 7.8 Hz), 7.80 d (2H, *J* = 7.8 Hz), 7.93 s (1H), 8.29 s (1H), 9.34 s (1H), 10.22 s (1H), 12.42 br.s (1H). MS (ESI): *m/z*: 527 $[M + H]^+$.

***N*-(4-{2-[3-(3,4,5-Trimethoxyphenyl)isoxazol-5-yl]-3*H*-imidazo[4,5-b]pyridin-6-yl}phenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide (13a).** A solution of azide **11** (500 mg, 9.5 mmol) and 1-ethynylbenzene (**12a**) (0.64 mL, 9.5 mmol) in anhydrous THF (15 mL) was mixed with CuI (90 mg, 5 mol%, 4.75 mmol). The mixture was stirred vigorously at room temperature for 16 h. After completion of the process (THF) the solvent was evaporated in vacuum and the crude product was dissolved in ethyl acetate (3×30 mL). The organic phase was washed with water and dried over Na_2SO_4. After evaporation of the solvent in vacuum the crude product was purified by column chromatography (ethyl acetate–hexane 7 : 3) to obtain compound **13a.** Yield 52%, mp 257–259°C. ^{1}H NMR spectrum, δ, ppm: 3.89 s (3H), 3.92 s (6H), 5.10 s (2H), 7.39 s (2H), 7.60–7.76 m (5H), 7.93 s (1H), 8.10 s (1H), 8.31 s (1H), 9.38 s (1H), 10.22 s (1H), 12.47 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 50.4, 57.5, 61.8, 102.3, 107.6, 114.5, 116.2, 125.3, 125.7, 126.3, 127.5, 127.8, 128.3, 129.4, 130.5, 131.4, 134.6, 136.2, 139.6, 141.8, 142.3, 143.8, 147.3, 148.4, 156.2, 167.9. MS (ESI): *m/z*: 629 $[M + H]^+$.

Compounds **13b**–**13j** were synthesized according to the above method developed for compound **13a**.

2-(4-(3,4,5-Trimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-{2-[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]-3H-imidazo[4,5-*b*]pyridin-6-yl}phenyl)acetamide (13b). Yield 45%, mp 283–285°C. ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H), 3.89 s (3H), 3.92 s (6H), 3.94 s (6H), 5.06 s (2H), 7.39 s (2H), 7.41 s (2H), 7.93 s (1H), 8.11 s (1H), 8.30 s (1H), 9.38 s (1H), 10.23 s (1H), 12.45 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 50.4, 57.6, 58.3, 61.5, 61.9, 102.4, 107.6, 110.5, 114.8, 116.3, 125.4, 125.8, 127.3, 127.8, 128.3, 129.2, 134.3, 136.5, 139.4, 141.6, 142.3, 144.8, 147.4, 147.9, 148.4, 155.6, 156.9, 167.9. MS (ESI): *m/z*: 719 $[M + H]^+$.

2-[4-(3,5-Dimethoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-*N*-(4-{2-[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl}-3*H*-imidazo[4,5-*b*]pyridin-6-yl}phenyl)acetamide (13c). Yield 39%, mp 275–277°C. ^{1}H NMR spectrum, δ, ppm: 3.76 s (6H), 3.89 s (3H), 3.92 s (6H), 4.98 s (2H), 7.10 s (1H), 7.27 s (2H), 7.39 s (2H), 7.94 s (1H), 8.12 s (1H), 8.32 s (1H), 9.40 s (1H), 10.24 s (1H), 12.48 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 50.6, 57.8, 58.3, 61.9, 99.4, 102.6, 107.6, 110.5, 114.2, 116.4, 125.3, 125.7, 127.4, 127.8, 129.4, 132.5, 134.6, 136.8, 139.7, 141.4, 145.6, 147.5, 147.8, 148.4, 156.5, 163.7, 168.3. MS (ESI): *m/z*: 689 $[M + H]^+$.

2-[4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-*N*-(4-{2-[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl}phenyl)acetamide (13d). Yield 35%, mp 293–295°C. ^{1}H NMR spectrum, δ, ppm: 3.68 s (3H), 3.89 s (3H), 3.92 s (6H), 5.03 s (2H), 7.13 d (2H, *J* = 7.7 Hz), 7.40 s (2H), 7.66 d (2H, *J* = 7.7 Hz), 7.94 s (1H), 8.14 s (1H), 8.34 s (1H), 9.42 s (1H), 10.25 s (1H), 12.50 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 50.7, 57.6, 58.5, 61.8, 102.5, 107.6, 114.5, 115.8, 116.8, 124.6, 125.4, 125.8, 127.4, 127.8, 128.4, 129.5, 134.6, 136.2, 139.6, 141.5, 142.3, 143.7, 147.3, 147.6, 148.6, 156.7, 160.5, 168.3. MS (ESI): *m/z*: 659 $[M + H]^+$.

2-[4-(4-Chlorophenyl)-1*H*-1,2,3-triazol-1-yl]-*N*-(4-{2-[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]-3*H*-

imidazo[4,5-*b*]pyridin-6-yl}phenyl)acetamide (13e). Yield 45%, mp 304–306°C. ^{1}H NMR spectrum, δ, ppm: 3.90 s (3H), 3.93 s (6H), 5.20 s (2H), 7.40 s (2H), 7.56 d (2H, *J* = 8.02 Hz), 7.73 d (2H, *J* = 8.02 Hz), 7.94 s (1H), 8.17 s (1H), 8.35 s (1H), 9.44 s (1H), 10.25 s (1H), 12.56 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 50.7, 57.8, 61.6, 102.5, 107.8, 114.5, 116.8, 125.4, 126.8, 127.6, 127.8, 128.6, 129.7, 130.6, 130.9, 133.5, 134.8, 136.8, 139.7, 141.5, 142.3, 143.8, 148.7, 156.8, 168.4. MS (ESI): *m/z*: 663 $[M + H]^+$.

2-[4-(4-Bromophenyl)-1*H*-1,2,3-triazol-1-yl]-*N*-(4-{2-[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl}phenyl)acetamide (13f). Yield 41%, mp 310–312°C. ^{1}H NMR spectrum, δ, ppm: 3.90 s (3H), 3.93 s (6H), 5.22 s (2H), 7.40 s (2H), 7.53 d (2H, *J* = 8.05 Hz), 7.75 d (2H, *J* = 8.05 Hz), 7.94 s (1H), 8.19 s (1H), 8.36 s (1H), 9.45 s (1H), 10.24 s (1H), 12.58 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 50.8, 57.9, 61.9, 102.6, 107.8, 114.6, 116.8, 122.5, 125.6, 125.8, 127.3, 127.8, 128.5, 129.5, 130.4, 132.5, 134.8, 136.8, 139.6, 141.5, 142.8, 143.8, 147.4, 147.8, 148.7, 156.9, 168.3. MS (ESI): *m/z*: 707 $[M + H]^+$.

***N*-(4-{2-[3-(3,4,5-Trimethoxyphenyl)isoxazol-5-yl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl}phenyl)-2-[4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl]acetamide (13g).** Yield 57%, mp 320–322°C. ^{1}H NMR spectrum, δ, ppm: 3.90 s (3H), 3.93 s (6H), 5.24 s (2H), 7.41 s (2H), 7.62 d (2H, *J* = 8.10 Hz), 7.77 d (2H, *J* = 8.10 Hz), 7.95 s (1H), 8.21 s (1H), 8.38 s (1H), 9.46 s (1H), 10.26 s (1H), 12.63 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 50.7, 57.8, 61.9, 102.7, 107.8, 114.7, 116.8, 125.6, 125.9, 126.4, 127.5, 127.8, 129.5, 130.4, 134.5, 135.6, 136.7, 139.7, 141.3, 142.7, 143.8, 147.6, 147.9, 148.3, 148.7, 156.8, 168.5. MS (ESI): *m/z*: 674 $[M + H]^+$.

***N*-(4-{2-[3-(3,4,5-Trimethoxyphenyl)isoxazol-5-yl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl}phenyl)-2-[4-(3,5-dinitrophenyl)-1*H*-1,2,3-triazol-1-yl]acetamide (13h).** Yield 47%, mp 345–347°C. ^{1}H NMR spectrum, δ, ppm: 3.90 s (3H), 3.93 s (6H), 5.34 s (2H), 7.41 s (2H), 7.95 s (1H), 8.26 s (1H), 8.41 s (1H), 8.62 s (2H), 9.17 s (1H), 9.48 s (1H), 10.26 s (1H), 12.69 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 50.7, 57.8, 61.9, 102.6, 107.6, 114.9, 116.8, 118.5, 125.4, 125.8, 127.6, 127.8, 129.5, 133.6, 133.8, 134.5, 136.8, 139.7, 141.4, 142.3, 147.6, 147.2, 148.7, 149.3, 156.7, 168.6. MS (ESI): *m/z*: 719 $[M + H]^+$.

***N*-(4-{2-[3-(3,4,5-Trimethoxyphenyl)isoxazol-5-yl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl}phenyl)-2-(4-*p*-tolyl-1*H*-1,2,3-triazol-1-yl)acetamide (13i).** Yield 39%, mp 266–268°C. ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H), 3.90 s (3H), 3.93 s (6H), 4.98 s (2H), 7.40 s (2H), 7.51–7.65 m (4H), 7.94 s (1H), 8.15 s (1H), 8.36 s (1H), 9.42 s (1H), 10.22 s (1H), 12.39 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 24.6, 50.4, 57.8, 61.6, 102.5, 107.6, 114.3, 116.8, 125.4, 125.8, 127.4, 127.7, 128.3, 129.4, 130.5, 134.6, 136.8, 138.6, 139.5, 141.6, 142.8, 143.7, 147.6, 147.9, 148.4, 156.8, 167.4. MS (ESI): *m/z*: 643 $[M + H]^+$.

***N*-(4-{2-[3-(3,4,5-Trimethoxyphenyl)isoxazol-5-yl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl}phenyl)-2-[4-(3,5-dimethylphenyl)-1*H*-1,2,3-triazol-1-yl]acetamide (13j).** Yield 37%, mp 270–272°C. ^{1}H NMR spectrum, δ, ppm: 2.45 s (6H), 3.89 s (3H), 3.92 s (6H), 4.99 s (2H), 6.92 s (2H), 7.23 s (1H), 7.39 s (2H), 7.93 s (1H), 8.13 s (1H), 8.35 s (1H), 9.41 s (1H), 10.22 s (1H), 12.37 br.s (1H). ^{13}C NMR spectrum, δ, ppm: 25.6, 50.5, 57.6, 61.6, 102.7, 107.4, 114.5, 116.7, 125.6, 125.8, 127.4, 127.8, 129.3, 129.7, 131.5, 134.6, 135.2, 136.5, 139.7, 140.5, 141.6, 142.8, 146.5, 147.3, 147.7, 148.5, 156.7, 167.5. MS (ESI): *m/z*: 657 $[M + H]^+$.

MTT assay. Individual wells of a 96-well tissue culture micro titer 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 (Eto) at a concentration 0.5, 1 or 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 (O.D) 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

Design and synthesis of new 1,2,3-triazole linked 1,2-isoxazole-pyridobenzimidazoles **13a**–**13j** have been carried out. The compounds are tested for their anticancer activity against four human cancer cell lines: MCF-7 (breast cancer), A549 (lung cancer), Colon-205 (colon cancer), and A2780 (ovarian cancer) by the MTT assay and with IC_{50} values ranging from 0.01±0.003 to 23.7±3.72 μM. Etoposide is used as a standard drug (IC_{50} values range from 0.13±0.017 to 3.08±0.135 μM). Six synthesized compounds are identified to be of high activity.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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