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Synthesis and biological evaluation of 1,2,4-oxadiazole linked imidazopyrazine derivatives as anticancer agents

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A series of new 1,2,4-oxadiazole linked imidazopyrazines (**10a-j**) were synthesized and evaluated for their cytotoxic activity against various human cancer cell lines, such as MCF-7 (breast), A-549 (lung), and A375 (melanoma). These compounds showed moderate to appreciable anticancer activities. Among them, compounds **10b** (MCF-7 = 0.68±0.03 μM, A-549 = 1.56±0.061 μM and A-375 = 0.79±0.033 μM)**, 10c** (MCF-7 = 2.11±0.14 μM, A-549 = 1.02±0.043 μM and A-375 = 0.34±0.016 μM)**, 10d** (MCF-7 = 1.45±0.06 μM, A-549 = 0.90±0.032 μM and A-375 = 2.18±0.112 μM)**, 10f** (MCF-7 = 1.35±0.058 μM, A-549 = 0.55±0.001 μM and A-375 = 1.67±0.06 μM) and **10i** (MCF-7 = 0.22±0.009 μM, A-549 = 1.09±0.041 μM and A-375 = 1.18±0.054 μM) were showed more potent activity than adriamycin (MCF-7 = 2.02±0.078 μM, A-549 = 2.18±0.081 μM and A-375 = 5.51±0.203 μM).

Keywords: Imidazo[1,2-*a*]pyrazine, phidianidines A, phidianidines B, cytotoxicity.

Introduction

Cancer is the second leading cause of death in both developing as well as undeveloped countries. It is very dangerous disease with rapid growth and uncontrolled spreading of abnormal cells. Cancer cell lines can be destroyed by three different ways such as surgery, radiation therapy and chemotherapy. Among them, chemotherapy is the potent treatment for the inhibition of cancer cell lines. Most of the nitrogen containing heterocyclic moieties are act as cytotoxic agents in cancer chemotherapy[1–20].

Imidazo[1,2-*a*]pyrazine (**1**) was a nitrogen containing heterocyclic's have been gain consideration in drug discovery realm especially as structural analogues of purines[21–23]. Imidazo[1,2-*a*]pyrazine derivatives were showed a different biological activities such as antiproliferative[24], Aurora-A kinase inhibitors[25], antiulcer[26], antibacterial[27], anti-inflammatory[28], uterine relaxing activity[29], antibronchospastic[30], cardiac stimulating[31], antidepressant[32], hypoglycemic activity[33], controlling allergic reactions[34]. Recently some of the imidazopyrazine derivatives were reported as anticancer activity[25].

1,2,4-Oxadiazoles are prominent targets for synthetic chemists due to their diverse and potent biological properties[35–39]. These have been showed a wide range of pharmaceutical activities including antitumor[40], antimicrobial[41], analgesic[42], antiasthmatic[43], diuretic[44], antidiabetic[45], anthelmintic[46], anti-inflammatory[47], anti-HIV[48] and antiparasitic[49] activities. Recently two novel 1,2,4-oxadiazole alkaloids, phidianidines A (**2**) and B (**3**) (Fig. 1), had been isolated from the shell-less marine opisthobranch mollusk *Phidiana militaris*[50] which were showed strong antitumor activity against C6 and HeLa cells with the IC_{50} values within nanomolar range[51–53].

Based on the potent biological importance of both imidazo[1,2-*a*]pyrazine and 1,2,4-oxadiazoles, we have design and synthesized a new series of 1,2,4-oxadiazole-linked imidazopyrazine derivatives and screened their anticancer activities against three human cancer cell lines such as MCF-7 (breast), A-549 (lung), and A-375 (melanoma) with MTT assay method.

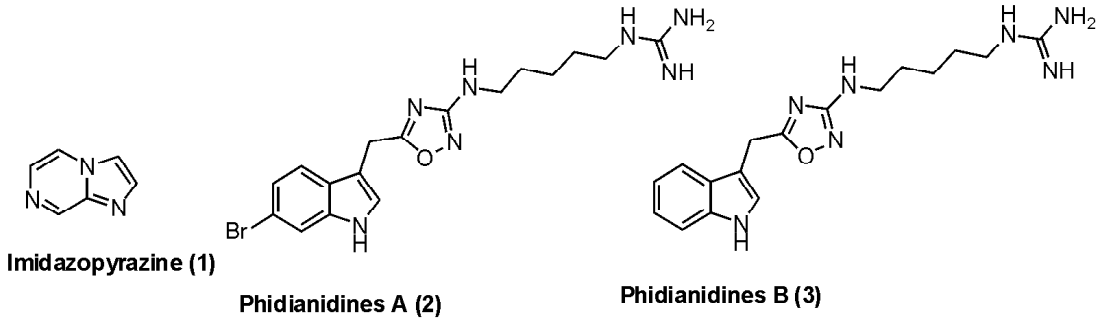


Fig. 1. Structures of imidazopyrazine, phidianidines A and phidianidines B.

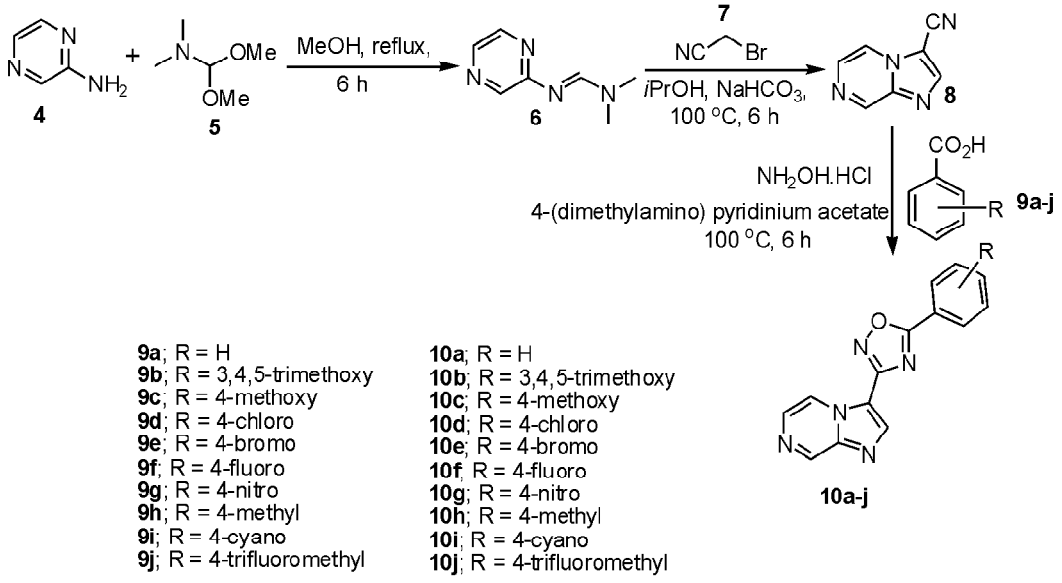
Results and discussion

The synthesis of 1,2,4-oxadiazole linked imidazopyrazine derivatives (**10a-j**) were shown in Scheme 1. Pyrazin-2-amine (**4**) was reacted with dimethoxy-N,N-dimethylmethanamine (DMF-DMA) (**5**) in methanol solvent under reflux conditions for 6 h time period then afford pure (*E*)-N,N-dimethyl-N′-(pyrazin-2-yl)formamidine (**6**) in good yield. This intermediate **6** was cyclized with 2-bromoacetonitrile (**7**) in the presence of isopropanol and $NaHCO_3$ at 100°C for 6 h then gave imidazo[1,2-*a*]pyrazine-3-carbonitrile (**8**). The cyano intermediate (**8**) was cyclized with different substituted aromatic carboxylic acids (**9a-j**) in 4-(dimethylamino)pyridinium acetate, $NH_2OH.HCl$ at 100°C for 6 h to afford 1,2,4-oxadiazole linked imidazopyrazine derivatives[54] **10a-j** in good yields.

Biological evaluation:

In vitro cytotoxicity:

The newly synthesized 1,2,4-oxadiazole linked imidazopyrazine derivatives (**10a-j**) were screened for their *in vitro* anticancer activity against a panel of three human cancer cell lines, such as MCF-7 (breast), A-549 (lung), and A-375 (melanoma) with MTT assay method by taking adriamycin as positive control. The obtained results were summarized in Table 1 and expressed as IC_{50} (μM) values. Among them, compounds **10b, 10c, 10d, 10f** and **10i** were showed more potent activity than adriamycin. Further, all these derivatives were examined for structure-activity relationship (SAR) analysis and results revealed that the compound **10b** with electron donating substituent (3,4,5-trimethoxy) on the phenyl



9a; R = H
9b; R = 3,4,5-trimethoxy
9c; R = 4-methoxy
9d; R = 4-chloro
9e; R = 4-bromo
9f; R = 4-fluoro
9g; R = 4-nitro
9h; R = 4-methyl
9i; R = 4-cyano
9j; R = 4-trifluoromethyl

10a; R = H
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10i; R = 4-cyano
10j; R = 4-trifluoromethyl

Scheme 1. Synthesis of 1,2,4-oxadiazole linked imidazopyrazine derivatives.

ring, displayed more potent anticancer activity with IC_{50} values of 0.68±0.03 μM, 1.56±0.061 μM, 0.79±0.033 μM against MCF-7, A-549 and A-375 cell lines respectively. When, compound **10c** having only 4-methoxy group have showed decrease of activity with IC_{50} values of 2.11±0.14 μM, 1.02±0.043 μM and 0.34±0.016 μM against MCF-7, A-549 and A-375 cell lines respectively compared to **10b.** Where, introducing of electron withdrawing group (4-chloro) resulted the compound **10d** was exhibited improved anticancer activities against MCF-7, A-549 and A-375 cancer cell lines with IC_{50} values of 1.45±0.06 μM, 0.90±0.032 μM and 2.18±0.112 μM respectively. Replacement of 4-chloro group with 4-fluoro group gave the compound **10f** which exhibit more potent activities than **10d** with IC_{50} values of 1.35±0.058 μM, 0.55±0.001 μM and 1.67±0.06 μM against MCF-7, A-549 and A-375 respectively. Interestingly, compound **10i** with 4-cyano substituent on the phenyl ring has possessed highest activity against MCF-7, A-549 and A-375 with corresponding IC_{50} values of 0.22±0.009 μM, 1.09±0.041 μM and 1.18±0.054 μM respectively.

Table 1. Cytotoxic activity (IC_{50} μM) of compounds **10a-j**

Compd.	MCF-7	A-549	A-375
10a	2.10±0.15	3.56±0.18	4.90±0.27
10b	0.68±0.03	1.56±0.061	0.79±0.033
10c	2.11±0.14	1.02±0.043	0.34±0.016
10d	1.45±0.06	0.90±0.032	2.18±0.112
10e	19.7±0.83	14.6±0.86	21.5±0.688
10f	1.35±0.058	0.55±0.001	1.67±0.06
10g	12.3±0.43	5.3±0.25	4.8±0.218
10h	10.6±0.53	13.4±0.68	8.6±0.52
10i	0.22±0.009	1.09±0.041	1.18±0.054
10j	2.44±0.12	3.89±0.151	10.5±0.56
Doxorubicin	2.02±0.078	2.18±0.081	5.51±0.203

where, MCF-7: human breast cancer cell line; A-549: human lung cancer cell line; A-375: human melanoma cancer cell line.

Experimental

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. ^1H and ^{13}C NMR spectra were recorded on Bruker UXNMR/XWIN-NMR (500 MHz, 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.

*(E)-N,N-Dimethyl-N′-(pyrazin-2-yl)formamidine (**6**):*

N,N-Dimethyl formamide dimethyl acetal (8.3 ml, 63.15 mmol) was added to a solution of pyrazine-2-amine (5 g, 52.6 mmol) in methanol (30 ml), and the mixture was refluxed for 6 h. The reaction mixture was cooled to room temperature, concentrated and evaporated to afford pure compound **6** in 7.82 g with 99% yield. ^1H NMR (500 MHz, $CDCl_3$): δ 3.10 (s, 6H), 8.06 (d, 1H, *J* 2.7 Hz), 8.10 (dd, 1H, *J* 2.7 Hz), 8.27 (d, 1H, *J* 1.4 Hz), 8.41 (s, 1H); MS (ESI): 151 $[M+H]^+$.

*Imidazo[1,2-a]pyrazine-3-carbonitrile (**8**):*

7 g of (*E*)-N,N-dimethyl-N′-(pyrazin-2-yl)formamidine **(6)** (46.6 mmol) was dissolved in 30 mL isopropanol solvent. To this, 3.2 mL of 2-bromoacetonitrile (46.6 mmol) and 23.4 g of $NaHCO_3$ (279 mmol) was added. Now, the reaction mass was heated at 100°C for 6 h. The reaction mixture was cooled to room temperature, concentrated and evaporated and this crude compound was purified by column chromatography with ethyl acetate/hexane (3:7) to afford pure compound **8** in 4.6 g with 68% yield. ^1H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, 1H, *J* 8.2 Hz), 8.21 (d, 1H, *J* 8.2 Hz), 8.28 (s, 1H), 8.37 (s, 1H); MS (ESI): 145 $[M+H]^+$.

*General procedure for synthesis of 1,2,4-oxadiazole linked imidazopyrazines (**10a-j**):*

In a 5-mL round-bottom flask, imidazo[1,2-*a*]pyrazine-3-carbonitrile **(8)** (300 mg, 2.08 mmol), hydroxylamine hydrochloride (144 mg, 2.08 mmol), and benzoic acid (**9a-j**) (2.08 mmol) were added to 4-(dimethylamino)pyridinium acetate (760 mg, 4.16 mmol). The reaction mixture was heated to 100°C for 6 h. The mixture cooled to room temperature. 1 mL ethanol was added to this reaction mass and allowed for stirring over a time period of 30 min. Further, this reaction mass was dissolved in 5 mL water and filtered. The solid products were collected and washed twice with water (2×5 mL). The crude product was purified by column chromatography with hexanes/ethyl acetate then afforded pure compounds (**10a-j**).

*3-(5-Phenyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyrazine (**10a**):*

57% yield. m.p. 138–140°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38–7.49 (m, 3H), 7.56 (d, 1H, *J* 8.1 Hz), 7.69 (d, 1H, *J* 8.1 Hz), 7.85 (d, 2H, *J* 8.3 Hz), 8.29 (s, 1H), 8.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 90.3, 116.4, 117.6, 126.5, 127.6, 129.4, 131.4, 132.5, 134.6, 138.7, 139.8, 143.5, 160.5; MS (ESI): 264 $[M+H]^+$.

*3-(5-(3,4,5-Trimethoxyphenyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyrazine (**10b**):*

44% yield. m.p. 162–164°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H), 3.94 (s, 6H), 7.55 (d, 1H, *J* 8.1 Hz), 7.69 (d, 1H, *J* 8.1 Hz), 7.74 (s, 2H), 8.29 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 58.5, 62.7, 90.4, 104.6, 116.7, 117.6, 126.4, 128.6, 132.6, 138.6, 139.6, 143.5, 145.8, 154.8, 160.6; MS (ESI): 354 $[M+H]^+$.

*3-(5-(4-Methoxyphenyl)-1,2,4-oxadiazol-3-yl)imidazo [1,2-a]pyrazine (**10c**):*

54% yield. m.p. 147–149°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H), 7.23 (d, 2H, *J* 8.3 Hz), 7.57 (d, 1H, *J* 8.1 Hz), 7.69 (d, 1H, *J* 8.1 Hz), 7.86 (d, 2H, *J* 8.3 Hz), 8.29 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.5, 90.5, 114.7, 116.7, 117.9, 126.7, 127.7, 131.6, 132.6, 138.6, 138.9, 143.7, 160.6, 163.7; MS (ESI): 294 $[M+H]^+$.

*3-(5-(4-Chlorophenyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyrazine (**10d**):*

57% yield. m.p. 163–165°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58 (d, 1H, *J* 8.1 Hz), 7.63 (d, 2H, *J* 8.3 Hz), 7.70 (d, 1H, *J* 8.1 Hz), 7.82 (d, 2H, *J* 8.3 Hz), 8.30 (s, 1H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 90.7, 116.8, 117.8, 126.7, 127.6, 129.6, 132.5, 134.5, 135.7, 138.6, 139.6, 143.6, 160.8; MS (ESI): 298 $[M+H]^+$.

*3-(5-(4-Bromophenyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyrazine (**10e**):*

50% yield. m.p. 161–163°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.59 (d, 1H, *J* 8.2 Hz), 7.65–7.84 (m, 3H), 8.30 (s, 1H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 90.8, 116.8, 117.9, 124.7, 126.7, 127.9, 132.6, 133.5, 133.8, 138.6, 139.7, 143.6, 160.7; MS (ESI): 343 $[M+H]^+$.

*3-(5-(4-Fluorophenyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyrazine (**10f**):*

58% yield. m.p. 144–146°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 (d, 2H, *J* 8.3 Hz), 7.58 (d, 1H, *J* 8.1 Hz), 7.68 (d, 1H, *J* 8.1 Hz), 7.81 (d, 2H, *J* 8.3 Hz), 7.28 (s, 1H), 8.41 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 90.5, 116.8, 117.7, 119.7, 126.7, 128.6, 128.9, 130.7, 132.7, 138.5, 139.8, 143.6, 154.8, 160.5; MS (ESI): 282 $[M+H]^+$.

*3-(5-(4-Nitrophenyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyrazine (**10g**):*

64% yield. m.p. 170–172°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.59 (d, 1H, *J* 8.2 Hz), 7.69 (d, 1H, *J* 8.2 Hz), 7.73 (d, 2H, *J* 8.3 Hz), 7.79 (d, 2H, *J* 8.3 Hz), 8.30 (s, 1H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 90.8, 116.8, 117.9, 125.8, 126.7, 127.8, 132.6, 138.6, 139.8, 141.6, 143.5, 148.7, 160.8; MS (ESI): 309 $[M+H]^+$.

*3-(5-p-Tolyl-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyrazine (**10h**):*

55% yield. m.p. 137–139°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.54 (s, 3H), 7.19 (d, 2H, *J* 8.2 Hz), 7.57 (d, 1H, *J* 8.1 Hz), 7.67 (d, 1H, *J* 8.1 Hz), 7.76 (d, 2H, *J* 8.2 Hz), 8.28 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.6, 90.4, 116.5, 117.6, 125.6, 126.7, 127.6, 132.5, 133.6, 137.6, 138.5, 139.6, 143.5, 160.3; MS (ESI): 278 $[M+H]^+$.

*4-(3-(Imidazo[1,2-a]pyrazin-3-yl)-1,2,4-oxadiazol-5-yl)benzonitrile (**10i**):*

70% yield. m.p. 164–166°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (d, 1H, *J* 8.2 Hz), 7.69 (d, 1H, *J* 8.2 Hz), 7.78 (d, 2H, *J* 8.3 Hz), 7.83 (d, 2H, *J* 8.3 Hz), 8.30 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 90.7, 114.5, 116.7, 117.8, 119.7, 125.7, 126.8, 132.6, 136.7, 138.6, 139.8, 140.6, 143.6, 160.8l; MS (ESI): 289 $[M+H]^+$.

*3-(5-(4-(Trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)imidazo[1,2-a]pyrazine (**10j**):*

46% yield. m.p. 156–158°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.57 (d, 1H, *J* 8.1 Hz), 7.67 (d, 1H, *J* 8.1 Hz), 7.74 (d, 2H, *J* 8.2 Hz), 7.82 (d, 2H, *J* 8.2 Hz), 8.27 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 90.6, 114.6, 116.7, 117.9, 126.8, 127.9, 128.6, 132.5, 133.5, 135.6, 138.6, 139.8, 143.6, 160.7; MS (ESI): 332 $[M+H]^+$.

MTT assay:

The cytotoxic activity of the compounds was determined by using MTT assay. Each data represents as mean ±S.D. values. From three different experiments performed in triplicates. 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 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 h. 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.

Conclusion

In conclusion, we have been synthesized a series of 1,2,4-oxadiazole linked imidazopyrazine derivatives (**10a-j**) and characterized by ^{1}H NMR, ^{13}C NMR and mass spectral data. Futher, these compounds were evaluated for their anticancer activities against three different human cancer cell lines such as MCF-7 (breast), A-549 (lung), and A-375 (melanoma). Among them, compounds **10b**, **10c**, **10d**, **10f** and **10i** were showed more potent activity than adriamycin.

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