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Research Article

DESIGN, SYNTHESIS AND ANTICANCER ACTIVITY OF STRUCTURALLY MODIFIED 1, 3, 4-OXADIAZOLE INCORPORATED 2H-CHROMENE DERIVATIVES AS ANTICANCER AGENTS

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ABSTRACT

This paper reports the synthesis of a series of 1, 3, 4-oxadiazole incorporated chromene derivatives (9a-j) were synthesized and their chemical structures were firmed by ^{1}HNMR, ^{13}CNMR and mass spectral examination. Further, all these target compounds were investigated for their anticancer activity towards four human cancer cell lines including MCF-7: human breast, A549: human lung, DU-145: human prostrate and MDA MB-231: human breast, by using MTT assay method and obtained results were expressed in IC_{50} µM. Here etoposide used as standard drug and most of the compounds were showed good to moderate activity than positive control. Among all synthesized compounds, five compounds (9b, 9f, 9g, 9i and 9j) were displayed more potent activity than etoposide.

Keywords: Amlexanox, Zibotentan, 2*H*-chromene, 1, 3, 4-oxadiazole and anticancer activity.

INTRODUCTION

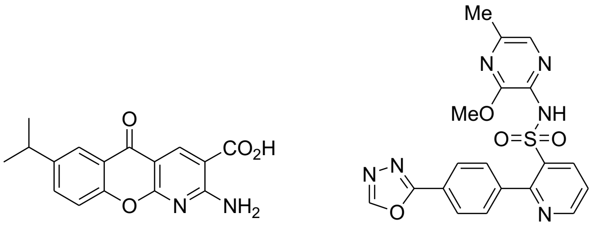
Generally, cancer is a genetic illness leading to death of human beings in developed, undeveloped countries[1] and it is characterized by uncontrolled cell development, tumour formation. Most of the cancers are occurred by cellular replication course of action goes out of control due to change of lifestyle, environmental, radiation and behavioural exposures.[2,3]

There are three types of cancers treatment are available like radiation therapy, surgery and chemotherapy. Among them, chemotherapy is the most distinguishable treatment for various cancers, in which anticancer agents are used. These anticancer agents are to destroy the cancer cells without harmful effect on normal cells.

The 2*H*-chromenes are a distinguish oxygen atom bearing fused-bicyclic heterocycles and core structural motifs of various natural products, biological active molecules.[4-6] These are used as key intermediates for the preparation of 7-diethylamino-4-methyl coumarin and biscarbazole alkaloids murrafoline.[7-9] They are possessed a variety of biological properties including antitumor[4] antiproliferative,[10] pigments,[11] anti-HIV,[12] antimicrobial,[13] laserdyes,[14] fungicidal,[15] cosmetics,[16] insecticidal,[17] antiviral,[18] antioxidant,[19] antibacterial,[20] anti acetylcholinesterase[21] and anti-inflammatory.[22] Because of its versatile biological activities that many researchers have put great attention on this chemistry. Amlexanox (1, Figure 1) is a chromene nucleus containing anti-inflammatory, anti-allergic drug as used for treatment of aphthous ulcers.[23,24]

Similarly, five-member 1, 3, 4-oxadiazole are most important heterocyclic compounds and are important building blocks in synthesis of natural products.[25,26] These are formed hydrogen bonding with suitable receptors due to it having azole functionality, which is responsible for increase of biological activity.[27] 1, 3, 4-Oxadiazole are displayed numerous biological activities such as anticancer,[28] tyrosinase inhibitor,[29] antioxidant,[30] anti-HCV,[31] antiviral,[32] anti-inflammatory,[33] anti-hypotensive,[34] antibacterial,[35] antifungal[36] and anticonvulsant.[37] The Zibotentan (2) is US FDA approved anticancer drug candidate and it bearing 1,3,4-oxadiazole unit as a part of the structure.[38]

In view of above biological information of chromenes and 1, 3, 4-oxadiazole moieties, it is worth full to combined these two moieties in the single frame work and to know the biological effects of these moieties. We have designed and synthesized a series of structurally modified 1, 3, 4-oxadiazole incorporated 2H-chromene derivatives (9a-j) and evaluated their anticancer activity against human cancer cell lines.



Amlexanox (1) **Zibotentan (2)**

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 Gemini Varian-VXR-unity (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 electro thermal melting point apparatus, and are uncorrected.

Ethyl 2-hydroxy-2-methyl-2H-pyrano[3,2-b]pyridine-3-carboxylate (5)

To a mixture of 3-hydroxypyridine-2-carbaldehyde (3) (8 g, 0.064 mmol), ethyl acetoacetate (4) (3.7 ml, 0.128 mmol) in 30 mL of anhydrous ethanol was added piperidine (0.42 ml, 0.00426 mmol) dropwise at room temperature. The resulting mixture was stirred at reflux for 7 hours and then allowed to cool to room temperature. The ethanol was evaporated by vacuum and obtained crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound 5, 10.6 g in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, 3H), 1.62 (s, 3H), 4.36 (q, 2H), 3.90 (bs, 1H), 6.93 (d, 1H, J = 8.3 Hz), 7.46-7.50 (m, 1H), 8.08 (s, 1H), 8.22 (d, 1H, J = 8.3 Hz); MS (FAB): 236 $[M+H]^+$.

Ethyl 2-methoxy-2-methyl-2H-pyrano[3,2-b]pyridine-3-carboxylate (6)

A mixture of compound (5) (9 g, 0.038 mmol) and methyl iodide (1.8 mL, 0.057 mmol), K_2CO_3 (10.5 g, 0.076 mmol) in anhydrous THF and reaction mixture stirred at room temperature for 5 hours; after completion of reaction, K_2CO_3 was filtered and evaporated vacuum and extracted with dichloromethane. The solvent was distilled out by rotavapower and dried with Na_2SO_4, the crude product was purified with ethyl acetate/hexane (1;1) to afford compound 6, 8.7 g in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, 3H), 1.58 (s, 3H), 3.55 (s, 3H), 4.35 (q, 2H), 6.92 (d, 1H, J = 8.2 Hz), 7.47-7.51 (m, 1H), 8.07 (s, 1H), 8.22 (d, 1H, J = 8.2 Hz); MS (FAB): 250 $[M+H]^+$.

2-Methoxy-2-methyl-2H-pyrano[3,2-b]pyridine-3-carbohydrazide (7)

A mixture of compound (6) (7 g, 0.028 mmol) and hydrazine hydrochloride (5.9 g, 0.084 mmol) in ethanol and reaction mixture stirred at reflux for 4 hours. After completion of reaction, the crude product was obtained after distilling off the excess ethanol. Cooling filtering then washing with a little cold water, this product (7) was employed in the next step without further purification. 5.9 g, with 89% yield. ^{1}H NMR (300 MHz, DMSO-d6): δ 1.59 (s, 3H), 3.56 (s, 3H), 4.54 (s, 2H), 6.95 (d, 1H, J = 8.4 Hz), 7.46-7.50 (m, 1H), 8.08 (s, 1H), 8.23 (d, 1H, J = 8.4 Hz), 9.83 (bs, 1H); MS (ESI): 236 $[M+H]^+$.

2-Methoxy-2-methyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2H-pyrano[3,2-b]pyridine (9a)

Compound (7) (200 mg, 8.5 mmol) was dissolved in $POCl_3$ (10 mL) and added benzoic acid (8a) (0.082 ml, 8.5 mmol). The reaction mixture was reflux for 6 hours. After completion of reaction, it can be neutralized with Aq $NaHCO_3$ and then workup with ethyl acetate. The organic layer can be evaporated through rotavapor and dried it with Na_2SO_4. The crude compound was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound 9a, 106.3 mg in 39% yield. Mp: 146–148 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 3H), 3.56 (s, 3H), 6.96 (d, 1H, J = 8.5 Hz), 7.44-7.57 (m, 3H), 7.61 (t, 1H), 7.83 (d, 2H, J = 7.30 Hz), 8.10 (s, 1H), 8.23 (d, 1H, J = 8.5 Hz); ^{13}CNMR (300 MHz, $CDCl_3$): δ 26.4, 54.3, 111.6, 118.5, 124.6, 128.3, 129.4, 130.5, 131.3, 131.8, 135.4, 136.7, 144.7, 152.8, 159.6, 162.8; MS (ESI): 322 $[M+H]^+$.

2-Methoxy-3-(5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-2-methyl-2H-pyrano[3,2-b]pyridine (9b)

This compound 9b was prepared following the method described for the preparation of the compound 9a, employing 7 (200 mg, 8.5 mmol) with 3,4,5-trimethoxybenzoic acid (8b) (180 mg, 8.5 mmol), $POCl_3$ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (6:4) to afford pure compound 9b, 121.6 mg in 35% yield. Mp: 166–168 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 3H), 3.56 (s, 3H), 3.87 (s, 3H), 3.91 (s, 6H), 6.97 (d, 1H, J = 8.6 Hz), 7.45-7.50 (m, 1H), 7.63 (s, 2H), 8.09 (s, 1H0, 8.22 (d, 1H, J = 8.6 Hz); ^{13}CNMR (300 MHz, $CDCl_3$): δ 26.5, 54.4, 57.5, 61.3, 105.6, 111.8, 118.6, 124.5, 127.5, 128.3, 135.2, 136.5, 142.3, 144.6, 152.4, 155.8, 159.7, 162.8; MS (ESI): 412 $[M+H]^+$.

2-Methoxy-3-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-2-methyl-2H-pyrano[3,2-b]pyridine (9c)

This compound 9c was prepared following the method described for the preparation of the compound 9a, employing 7 (200 mg, 8.5 mmol) with 4-methoxybenzoic acid (8c) (129 mg, 8.5 mmol), $POCl_3$ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (6:4) to afford pure compound 9c, 113.4 mg in 39% yield. Mp: 152–154 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 3H), 3.57 (s, 3H), 3.85 (s, 3H), 6.94-7.11 (m, 3H), 7.46-7.51 (m, 1H), 7.68 (d, 2H, J = 7.31 Hz), 8.10 (s, 1H), 8.22 (d, 1H, J = 8.4 Hz); ^{13}CNMR (300 MHz, $CDCl_3$): δ 26.4, 54.5, 57.6, 111.7, 117.5, 118.6, 119.5, 124.7, 125.3, 128.7, 135.2, 136.8, 144.7, 152.4, 159.6, 161.5, 162.7; MS (ESI): 352 $[M+H]^+$.

3-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-2-methoxy-2-methyl-2H-pyrano[3,2-b]pyridine (9d)

This compound 9d was prepared following the method described for the preparation of the compound 9a, employing 7 (200 mg, 8.5 mmol) with 4-chlorobenzoic acid (8d) (133 mg, 8.5 mmol), $POCl_3$ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound 9d, 135.6 mg in 45% yield. Mp: 171–173 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 3H), 3.57 (s, 3H), 6.98 (d, 1H, J = 8.6 Hz), 7.47-7.52 (m, 1H), 7.62 (d, 2H, J = 7.32 Hz), 7.85 (d, 2H, J = 7.32 Hz), 8.11 (s, 1H), 8.22 (d, 1H, J = 8.6 Hz); ^{13}CNMR (300 MHz, $CDCl_3$): δ 26.5, 54.8, 111.6, 118.7, 124.5, 128.6, 129.3, 130.4, 131.6, 135.6, 136.4, 138.6, 144.6, 152.7, 159.8, 162.8; MS (ESI): 356 $[M+H]^+$.

3-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)-2-methoxy-2-methyl-2H-pyrano[3,2-b]pyridine (9e)

This compound 9e was prepared following the method described for the preparation of the compound 9a, employing 7 (200 mg, 8.5 mmol) with 4-bromobenzoic acid (8e) (171 mg, 8.5 mmol), $POCl_3$ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound 9e, 149.8 mg in 44% yield. Mp: 174–176 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 3H), 3.57 (s, 3H), 6.97 (d, 1H, J = 8.6 Hz), 7.46-7.52 (m, 1H), 7.66 (d, 2H, J = 7.33 Hz), 7.87 (d, 2H, J = 7.33 Hz), 8.13 (s, 1H), 8.22 (d, 1H, J = 8.6 Hz); ^{13}CNMR

(300 MHz, $CDCl_3$): δ 26.4, 54.7, 111.7, 118.5, 124.6, 126.4, 127.3, 128.5, 130.6, 133.4, 135.6, 136.8, 144.6, 152.7, 159.8, 162.8; MS (ESI): 400 $[M+H]^+$.

2-Methoxy-2-methyl-3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2H-pyrano[3,2-b]pyridine (9f)

This compound 9f was prepared following the method described for the preparation of the compound 9a, employing 7 (200 mg, 8.5 mmol) with 4-nitrobenzoic acid (8f) (142 mg, 8.5 mmol), $POCl_3$ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound 9f, 164.2 mg in 53% yield. Mp: 167–169 ᵒC, ^1H NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 3H), 3.58 (s, 3H), 6.99 (d, 1H, J = 8.7 Hz), 7.48-7.53 (m, 1H), 7.89 (d, 2H, J = 7.35 Hz), 8.15 (s, 1H), 8.22 (d, 1H, J = 8.7 Hz), 8.31 (d, 2H, J = 7.35 Hz); ^{13}CNMR (300 MHz, $CDCl_3$):δ 26.5, 54.7, 111.8, 118.6, 124.8, 125.9, 126.7, 128.6, 135.4, 136.5, 137.8, 144.6, 149.7, 152.5, 159.8, 162.9; MS (ESI): 367 $[M+H]^+$.

4-(5-(2-Methoxy-2-methyl-2H-pyrano[3,2-b]pyridin-3-yl)-1,3,4-oxadiazol-2-yl)benzonitrile (9g)

This compound 9g was prepared following the method described for the preparation of the compound 9a, employing 7 (200 mg, 8.5 mmol) with 4-cyanobenzoic acid (8g) (125 mg, 8.5 mmol), $POCl_3$ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound 9 g, 151.7 mg in 52% yield. Mp: 173–175 ᵒC, ^1H NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 3H), 3.58 (s, 3H), 6.98 (d, 1H, J = 8.6 Hz), 7.46-7.51 (m, 1H), 7.92 (d, 2H, J = 7.36 Hz), 8.16 (s, 1H), 8.22 (d, 1H, J = 8.6 Hz), 8.36 (d, 2H, J = 7.36 Hz); ^{13}CNMR (300 MHz, $CDCl_3$):δ 26.5, 54.8, 111.7, 115.8, 118.7, 119.5, 124.8, 128.6, 129.7, 134.6, 135.7, 136.3, 136.9, 144.6, 152.7, 160.4, 162.8; MS (ESI): 347 $[M+H]^+$.

2-Methoxy-2-methyl-3-(5-p-tolyl-1,3,4-oxadiazol-2-yl)-2H-pyrano[3,2-b]pyridine (9h)

This compound 9h was prepared following the method described for the preparation of the compound 9a, employing 7 (200 mg, 8.5 mmol) with 4-methylbenzoic acid (8h) (116 mg, 8.5 mmol), $POCl_3$ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound 9 h, 110.4 mg in 39% yield. Mp: 145–147 ᵒC, ^1H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 3H), 2.46 (s, 3H), 3.54 (s, 3H), 6.97 (d, 1H, J = 8.3 Hz), 7.38 (d, 2H, J = 7.29 Hz), 7.46-7.52 (m, 1H), 7.65 (d, 2H, J = 7.29 Hz), 8.10 (s, 1H), 8.22 (d, 1H, J = 8.3 Hz); ^{13}CNMR (300 MHz, $CDCl_3$):δ 23.7, 24.6, 54.8, 111.7, 118.6, 124.6, 126.7, 128.6, 129.5, 130.6, 135.8, 136.3, 141.7, 144.7, 152.8, 159.7, 162.8; MS (ESI): 336 $[M+H]^+$.

2-Methoxy-3-(5-(3,5-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-2-methyl-2H-pyrano[3,2-b]pyridine (9i)

This compound 9i was prepared following the method described for the preparation of the compound 9a, employing 7 (200 mg, 8.5 mmol) with 3,5-dimethoxybenzoic acid (8i) (155 mg, 8.5 mmol), $POCl_3$ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (6:4) to afford pure compound 9i, 129.6 mg in 40% yield. Mp: 177–179 ᵒC, ^1H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 3H), 3.56 (s, 3H), 3.82 (s, 6H), 6.85-6.96 (m, 2H), 7.47-7.51 (m, 1H), 7.65 (s, 2H), 8.10 (s, 1H), 8.23 (d, 1H, J = 8.4 Hz); ^{13}CNMR (300 MHz, $CDCl_3$):δ 26.5, 54.7, 57.5, 104.7, 105.8, 111.8, 118.6, 124.5, 128.7, 133.6, 135.8, 136.5, 144.7, 152.4, 159.5, 162.7, 163.8; MS (ESI): 382 $[M+H]^+$.

3-(5-(4-Bromo-3,5-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-2-methoxy-2-methyl-2H-pyrano[3,2-b]pyridine (9j)

This compound 9j was prepared following the method described for the preparation of the compound 9a, employing 7 (200 mg, 8.5 mmol) with 4-bromo-3,5-dimethoxybenzoic acid (8j) (247 mg, 8.5 mmol), $POCl_3$ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (6:4) to afford pure compound 9j, 144.2 mg in 37% yield. Mp: 182–184 ᵒC, ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 3H), 3.58 (s, 3H), 3.93 (s, 6H), 6.98 (d, 1H, J = 8.5 Hz), 7.47-7.52 (m, 1H), 7.66 (s, 2H), 8.12 (s, 1H), 8.22 (d, 1H, J = 8.5 Hz); ^{13}CNMR (300 MHz, $CDCl_3$):δ 26.4, 54.7, 108.6, 110.6, 111.8, 118.6, 124.5, 128.7, 133.7, 135.8, 136.9, 152.7, 159.7, 162.8, 163.9; MS (ESI): 460 $[M+H]^+$.

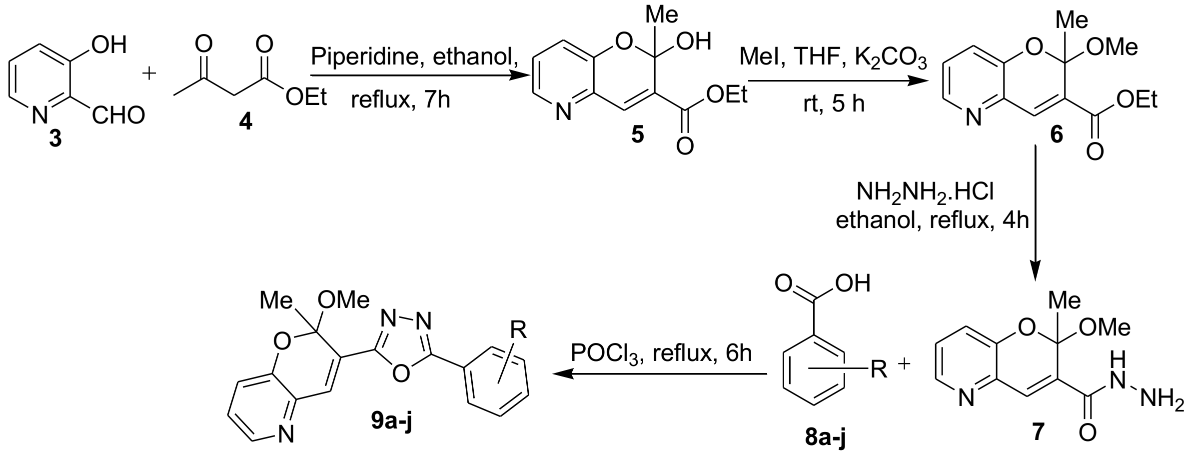
MTT assay

Individual wells of a 96-well tissue culture micro titre plate were inoculated with 100 µL of complete medium containing 1×10^4 cells. The plates were incubated at 37ᵒC in a humidified 5% CO_2 incubator for 18 hours 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 37ᵒC for 24 hours. Then the medium was discarded and replaced with 10 µL MTT dye. Plates were incubated at 37ᵒC for 2 hours. 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%.

RESULTS AND DISCUSSION

Chemistry

The synthetic route of 1,3,4-oxadiazole incorporated chromene derivatives (9a-j) as illustrated in Scheme 1. Accordingly, 3-hydroxypyridine-2-carbaldehyde (3) was subjected to cyclization reaction with ethyl 3-oxobutanoate (4) in presence of piperidine in absolute ethanol at reflux for 7 h to obtain intermediate 5 in 69% yield. Then the resulting intermediate 5 was treated with methyl iodide in the presence of K_2CO_3 in anhydrous THF at room temperature for 5 hours to afford methylated compound 6 in 92% yield. Next, this methylated intermediate 6 was reacted with hydrazine hydrochloride in ethanol at reflux for 4 hours to afford pure acid hydrazide intermediate 7. Further, this intermediate was subjected to cyclization reaction with substituted aromatic carboxylic acids (8a-j) in the presence of $POCl_3$ at reflux for 6 hours to afford pure final compounds 9a-j in good yield.



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

8a; R = H
8b; R = 3,4,5-trimethoxy
8c; R = 4-methoxy
8d; R = 4-chloro
8e; R = 4-bromo
8f; R = 4-nitro
8g; R = 4-cyano
8h; R = 4-methyl
8i; R = 3,5-dimethoxy
8j; R = 4-bromo-3,5-dimethoxy

Scheme 1

Biological evaluation

In vitro cytotoxicity

The new 1,3,4-oxadiazole incorporated chromene derivatives (9a-j) were investigated for their in vitro cytotoxic potential towards selected human cancer cell lines of breast (MCF-7), lung (A549), prostrate (DU-145) and breast (MDA MB-231) by using MTT assay. The obtained results were expressed in IC_{50} µM, as summarised in Table 1 and etoposide was used as a reference standard. The results indicated that most of the compounds were good activity on all cell lines. Among the synthesized compounds, five compounds (9b, 9f, 9g, 9i and 9j) were displayed more potent activity compare with standard. Further, these compounds were examine for structure-activity relationship (SAR) analysis that the results revealed that compound 9b as contained electron-donating group (3,4,5-trimethoxy) on the phenyl ring has showed good activity on four cell lines MCF-7 = 0.34 ± 0.098 µM, A549 =0.11 ± 0.065 µM, DU-145 = 1.09 ± 0.22 µM and MDA MB-231 = 0.27 ± 0.081 µM. Where compound 9i with 3, 5-dimethoxy group has showed lower in activity (MCF-7 = 1.87 ± 0.35 µM, A549 = 2.11 ± 1.44µM, DU-145 = 1.66 ± 0.29 µM and MDA MB-231 = 1.31 ± 0.48 µM) to compare with 9b. Whereas, compound 9j having 4-bromo-3, 5-dimethoxy group has exhibited most promising activity (MCF-7 = 0.10 ± 0.062 µM, A549 = 0.82 ± 0.085 µM, DU-145= 0.18 ± 0.051 µM and MDA MB-231 = 0.19 ± 0.037 µM) than all compounds. When compound 6c with 4-methoxy group has showed decreased activity on all cell lines (MCF-7 = 2.88 ± 1.65 µM, A549 = 6.15 ± 3.28 µM, DU-145= 9.23 ± 4.19 µM and MDA MB-231 = 2.66 ± 1.34 µM). The replacement of 4-methoxy group with 4-chloro (9d), 4-bromo (9e) electron-withdrawing groups on the phenyl ring have showed moderate activity on four cell lines. Interestingly, compounds 9f, 9g having 4-nitro, 4-cyano groups have exhibited very good activity on all cell lines (MCF-7 = 1.49 ± 0.98 µM, A549 = 1.33 ± 0.76 µM, DU-145 = 0.36 ± 0.054 µM and MDA MB-231 = 1.98 ± 0.68 µM), (MCF-7 = 1.25 ± 0.55 µM, A549 = 1.60 ± 0.34 µM, DU-145 = 1.42 ± 0.52 µM and MDA MB-231 = 2.04 ± 1.09 µM) respectively. Instead of 4-cyano group with 4-methyl group resulted compound 9h has showed poor activity (A549 = 14.32 ± 6.81 µM, DU-145= 3.25 ± 2.18 µM and MDA MB-231 = 9.10 ± 3.87 µM).

Table 1: *In vitro* cytotoxicity of newly synthesized compounds 9a-j with IC_{50} µM

Compound	[c]MCF-7	[d]A549	[e]DU-145	[f]MDA MB-231
9a	3.80 ± 2.76	2.13 ± 1.23	5.67 ± 3.01	ND
9b	0.34 ± 0.098	0.11 ± 0.065	1.09 ± 0.22	0.27 ± 0.081
9c	2.88 ± 1.65	6.15 ± 3.28	9.23 ± 4.19	2.66 ± 1.34
9d	7.43 ± 3.70	ND	ND	10.4 ± 4.55
9e	13.2 ± 6.21	8.45 ± 4.05	19.4 ± 8.43	ND
9f	1.49 ± 0.98	1.33 ± 0.76	0.36 ± 0.054	1.98 ± 0.68
9g	1.25 ± 0.55	1.60 ± 0.34	1.42 ± 0.52	2.04 ± 1.09
9h	ND	14.32 ± 6.81	3.25 ± 2.18	9.10 ± 3.87
9i	1.87 ± 0.35	2.11 ± 1.44	1.66 ± 0.29	1.31 ± 0.48
9j	0.10 ± 0.062	0.82 ± 0.085	0.18 ± 0.051	0.19 ± 0.037
Etoposide	2.11 ± 0.024	3.08 ± 0.135	1.97 ± 0.45	1.91 ± 0.84

"ND" = Not determined

[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]DU-145: human prostate cancer cell line. [f]MDA MB-231: human breast cancer cell line

CONCLUSION

In conclusion, we have design and synthesis a series of 1, 3, 4-oxadiazole incorporated chromene derivatives (9a-j) and their chemical structures were confirmed by ^{1}HNMR, ^{13}CNMR and mass spectral analysis. Further, all these target compounds were investigated for their anticancer activity against four human cancer cell lines such as MCF-7: human breast, A549: human lung, DU-145: human prostrate and MDA MB-231: human breast, by using MTT assay method and obtained results were expressed in IC_{50} μM. Here etoposide used as standard drug and most of the compounds were showed good to moderate activity than positive control. Among all synthesized compounds, five compounds (9b, 9f, 9g, 9i and 9j) were displayed more potent activity than etoposide.

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REFERENCES

1. Garcia M, Jemal A, Ward EM, Center MM, Hao Y, Siegel RL, Thun MJ. Global cancer facts and figures. American Cancer Society, Atlanta; 2007.
2. Anand P, Kunnumakara AB. Cancer is a preventable disease that requires major lifestyle changes. Pharmacy Research 2008; 25: 2097–2116.
3. Kenneth W, Bert V. The genetic basis of human cancer, McGraw-Hill, Medical Publishing Division; 2005.
4. Reddy BVS, Divya B, Swain M, Rao TP, Yadav JS, Vishnu Vardhan MVPS. A domino Knoevenagel hetero-Diels–Alder reaction for the synthesis of polycyclic chromene derivatives and evaluation of their cytotoxicity. Bioorganic and Medicinal Chemistry Letters 2012; 22: 1995-1999.
5. Yeom HS, Li H, Tang Y, Hsung RP. Total Syntheses of Cannabicyclol, Clusiacyclol A and B, Iso-Eriobrucinol A and B, and Eriobrucinol. Organic Letters 2013; 15: 3130-3133.
6. Gumula I, Alao JP, Ndiege IO, Sunnerhagen, P, Yenesew A, Erdélyi M. Flemingins G–O, Cytotoxic and Antioxidant Constituents of the Leaves of *Flemingia grahamiana*. J. Nat. Prod. 2014; 77: 2060-2067.
7. Zhang X, Huang P, Li Y, Duan C. A mild and fast continuous-flow trifluoromethylation of coumarins with the CF3 radical derived from CF3SO2Na and TBHP. Organic and Biomolecular Chemistry 2015; 13: 10917-10922.
8. Kumar VP, Gruner KK, Kataeva O, Knölker HJ. Total Synthesis of the Biscarbazole Alkaloids Murrafoline A–D by a Domino Sonogashira Coupling/Claisen Rearrangement/Electrocyclization Reaction. Angewandte Chemie International Edition 2013; 52: 11073-11077.
9. Zheng P, Somersan-Karakaya S, Lu S, Roberts J, Pingle M. Synthetic Calanolides with Bactericidal Activity against Replicating and Nonreplicating *Mycobacterium tuberculosis*. Journal of Medicinal Chemistry 2014; 57: 3755-3772.
10. Mao WW, Wang TT, Zeng HP, Wang ZY, Chen JP, Shen JG. Synthesis and evaluation of novel substituted 5-hydroxycoumarin and pyranocoumarin derivatives exhibiting significant antiproliferative activity against breast cancer cell lines. Bioorganic and Medicinal Chemistry Letters 2009; 19: 4570–4573.
11. Kiyani H, Ghorbani F. Potassium phthalimide: an efficient and simple organocatalyst for the one-pot synthesis of dihydropyrano [3,2-c] chromenes in aqueous media. Research on Chemical Intermediates 2015; 41: 4031-4046.
12. Engler T.A, La Tessa KO, Iyengar R, Chai W, Agrios K. Stereo selective syntheses of substituted pterocarpans with anti-HIV activity, and 5-aza-/5-thia-pterocarpan and 2-aryl-2,3-dihydrobenzofuran analogues. Bioorganic and Medicinal Chemistry 1996; 4: 1755.
13. Sangani C, Mungra D, Patel M, Patel R. Open Chemistry 2011; 9: 635-647.
14. Reynolds GA, Drexhage KH. Optics Communications 1975; 13: 222-225.
15. Lago JHG, Ramos CS, Casanova DCC, Morandim AA, Bergamo DCB, Cavalheiro AJ, Bolzani VS, Furlan M, Guilharaes EF, Young MCM, Kato MJ. Benzoic Acid Derivatives from *Piper* Species and Their Fungi toxic Activity against Cladosporium cladosporioides and *C. sphaerospermum*. Journal of Natural Product 2004; 67: 1783.
16. Hafez EAA, Elnagdi MH, Elagamey AGA, El-Taweel FMAA, Galil FMA, Riad BY, Elnagdi MH. Heterocycles 1987; 26: 903-1126.
17. Bernard CB, Krishnamurty HG, Chauret D, Durst T, Philogene BJR, Sanchez Vindas P, Hasbun C, Poveda L, San Roman L, Arnason JT. Journal of Chemical Ecology 1995; 21: 801.
18. Hwu JR, Lin SY, Tsay SC, Clercq ED, Leyssen P, Neyts J. Journal of Medicinal Chemistry 2011; 54: 2114-2126.
19. Sabry NM, Mohamed HM, Khattab ESAEH, Motlaq SS, El-Agrody AM. European Journal of Medicinal Chemistry 2011; 46: 765-772.
20. Singh I, Kaur H, Kumar S, Kumar A, Lata S, Kumar A. International Journal of Chem Tech Research 2010; 2: 1745-1752.
21. Shen Q, Peng Q, Shao J, Liu X, Huang Z, Pu X, Ma L, Li YM, Chan ASC, Gu L. European Journal of Medicinal Chemistry 2005; 40: 1307-1315.
22. More DH, Mahulikar PP. Indian Journal of Chemistry 2011; 50B: 745–747.
23. Bell J. Clinical Drug Investigation 2005; 25: 555–566.
24. Amlexanox. MeSH. U.S. National Library of Medicine; 2009.
25. Sears JE, Barker TJ, Boger DL. Organic Letters 2015; 17: 5460.
26. Kato D, Sasaki Y, Boger DL. Journal of American Chemical Society 2010; 132: 3685.
27. Guimaraes CRW, Boger DL, Jorgensen WL. Journal of American Chemical Society 2005; 127: 17377–17384.
28. Shepard DR, Dreicer R. Expert Opinion on Investigational Drugs 2010; 19: 899-908.
29. Khan HMT, Choudhary MI, Khan MK, Rani M, Rahman A. Bioorganic and Medicinal Chemistry 2005; 13: 3385.
30. Gong XR, Xi GL, Liu ZQ. Tetrahedron Letters 2015; 56: 6257–6261.
31. Sherif AR, Manal AS, Maha AE. European Journal of Medicinal Chemistry 2003; 38: 959.
32. Wu W, Chen Q, Tai A, Jiang G, Ouyang G. Bioorganic and Medicinal Chemistry Letters 2015; 25: 2243–2246.
33. Banerjee AG, Das N, Shengule SA, Srivastava RS, Srivastava SK. European Journal of Medicinal Chemistry 2015; 101: 81-95.
34. Turner S, Myers M, Gadie B. Journal of Medicinal Chemistry 1988; 31: 907.
35. Krishna C, Bhargavi MV, Rao CP, Krupadanam GLD. Medicinal Chemistry Research 2015; 24: 3743–3751.
36. Wani MY, Ahmad A, Shiekh RA, Al-Ghamdi KJ, Sobral AJFN. Bioorganic and Medicinal Chemistry 2015; 23: 4172–4180.
37. Zarghi A, Tabatabai SA, Faizi M, Ahadian A, Navabi P, Zanganesh V, Shafiee A. Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-

oxadiazoles, Bioorganic and Medicinal Chemistry Letters 2005; 15: 1863.
38. James ND, Growcott JW, Zibotentan. Zibotentan. Endothelin ET_A receptor antagonist, Oncolytic. Drugs Future 2009; 34: 624–633.
39. Helen Tomkinson, John Kemp, Stuart Oliver, Helen Swaisland, Maria Taboada, Thomas Morris, BMC Clinical Pharmacology 2011; 11: 3. Pharmacokinetics and tolerability of zibotentan (ZD4054) in subjects with hepatic or renal impairment: two open-label comparative studies.

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