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 confirmed by ¹HNMR, ¹³CNMR 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 prostate and MDA MB-231: human breast, by using MTT assay method and obtained results were expressed in IC₅₀ 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, 2H-chromene, 1, 3, 4-oxadiazole and anticancer activity.

INTRODUCTION

Generally, cancer is a genetic illness leading to death of human beings in developed, undeveloped countries¹ 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 2H-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 biscalbazole alkaloids murrarfoline.⁷⁻⁹ They are possessed a variety of biological properties including antitumor⁴ antiproliferative,¹⁰ pigments,¹¹ anti-HIV,¹² antimicrobial,¹³ laserdyes,¹⁴ fungicidal,¹⁵ cosmetics,¹⁶ insecticidal,¹⁷ antiviral,¹⁸ antioxidant,¹⁹ antibacterial,²⁰ anti acetylcholinesterase²¹ 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 antihypertensive,³⁴ antibacterial,³⁵ antifungal³⁶ 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.

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. ^1H and ^{13}C NMR spectra were recorded on Gemini Varian-VXR-unity (400 MHz, 300 MHz) instrument. Chemical shifts (δ) 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. ^1H 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 $[\text{M}+\text{H}]^+$.

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 rotavapor 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. ^1H 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 $[\text{M}+\text{H}]^+$.

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. ^1H NMR (300 MHz, DMSO- d_6): 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 $[\text{M}+\text{H}]^+$.

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, ^1H 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}C NMR (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 $[\text{M}+\text{H}]^+$.

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, ^1H 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, 1H), 8.22 (d, 1H, $J = 8.6$ Hz); ^{13}C NMR (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 $[\text{M}+\text{H}]^+$.

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, ^1H 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}C NMR (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 $[\text{M}+\text{H}]^+$.

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, ^1H 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}C NMR (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 $[\text{M}+\text{H}]^+$.

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, ^1H 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}C NMR

(300 MHz, CDCl₃): 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), POCl₃ (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 °C, ¹H NMR (400 MHz, CDCl₃): 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); ¹³CNMR (300 MHz, CDCl₃): 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), POCl₃ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound 9g, 151.7 mg in 52% yield. Mp: 173–175 °C, ¹H NMR (400 MHz, CDCl₃): 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); ¹³CNMR (300 MHz, CDCl₃): 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), POCl₃ (10 mL) and the crude product was purified by column chromatography with ethyl acetate/hexane (1:1) to afford pure compound 9h, 110.4 mg in 39% yield. Mp: 145–147 °C, ¹H NMR (400 MHz, CDCl₃): 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); ¹³CNMR (300 MHz, CDCl₃): 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), POCl₃ (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 °C, ¹H NMR (400 MHz, CDCl₃): 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); ¹³CNMR (300 MHz, CDCl₃): 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), POCl₃ (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 °C, ¹H NMR (400 MHz, CDCl₃): 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); ¹³CNMR (300 MHz, CDCl₃): 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 μ L of complete medium containing 1×10^4 cells. The plates were incubated at 37°C in a humidified 5% CO₂ incubator for 18 hours prior to the experiment. After medium removal, 100 μ L of fresh medium containing the test compounds and etoposide at different concentrations such as 0.5, 1, and 2 μ M were added to each well and incubated at 37°C for 24 hours. Then the medium was discarded and replaced with 10 μ L MTT dye. Plates were incubated at 37°C for 2 hours. The resulting formazan crystals were solubilized in 100 μ L extraction buffer. The optical density (O.D) was read at 570 nm with micro plate reader (Multi-mode Varioskan Instrument-Thermo 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 K₂CO₃ 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 POCl₃ at reflux for 6 hours to afford pure final compounds 9a-j in good yield.

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), prostate (DU-145) and breast (MDA MB-231) by using MTT assay. The obtained results were expressed in IC_{50} μ M, 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 μ M, A549 = 0.11 ± 0.065 μ M, DU-145 = 1.09 ± 0.22 μ M and MDA MB-231 = 0.27 ± 0.081 μ M. Where compound 9i with 3, 5-dimethoxy group has showed lower in activity (MCF-7

= 1.87 ± 0.35 μ M, A549 = 2.11 ± 1.44 μ M, DU-145 = 1.66 ± 0.29 μ M and MDA MB-231 = 1.31 ± 0.48 μ M) 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 μ M, A549 = 0.82 ± 0.085 μ M, DU-145 = 0.18 ± 0.051 μ M and MDA MB-231 = 0.19 ± 0.037 μ M) than all compounds. When compound 6c with 4-methoxy group has showed decreased activity on all cell lines (MCF-7 = 2.88 ± 1.65 μ M, A549 = 6.15 ± 3.28 μ M, DU-145 = 9.23 ± 4.19 μ M and MDA MB-231 = 2.66 ± 1.34 μ M). 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 μ M, A549 = 1.33 ± 0.76 μ M, DU-145 = 0.36 ± 0.054 μ M and MDA MB-231 = 1.98 ± 0.68 μ M), (MCF-7 = 1.25 ± 0.55 μ M, A549 = 1.60 ± 0.34 μ M, DU-145 = 1.42 ± 0.52 μ M and MDA MB-231 = 2.04 ± 1.09 μ M) respectively. Instead of 4-cyano group with 4-methyl group resulted compound 9h has showed poor activity (A549 = 14.32 ± 6.81 μ M, DU-145 = 3.25 ± 2.18 μ M and MDA MB-231 = 9.10 ± 3.87 μ M).

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

Compound	^a MCF-7	^d A549	^c 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

^aND = Not determined

^aEach data represents as mean $\pm$ S.D values. From three different experiments performed in triplicates. ^bMCF-7: human breast cancer cell line. ^dA549: human lung cancer cell line. ^cDU-145: human prostate cancer cell line. ^fMDA 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 ¹HNMR, ¹³CNMR 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 prostate and MDA MB-231: human breast, by using MTT assay method and obtained results were expressed in IC₅₀ 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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