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ORIGINAL ARTICLE

Synthesis, characterization and biological evaluation of novel 2,5 substituted-1,3,4 oxadiazole derivatives

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MTT assay

Abstract In the present study, a series of 3-(5-cyclohexyl-1,3,4-oxadiazol-2-yl)-N-substituted aniline have been synthesized by multistep reaction scheme. Benzohydrazide was used as the starting material. The structures of all synthesized compounds are characterized and confirmed by FT-IR, ^{1}H and C^{13} NMR and mass spectral studies with the intention of developing the novel biologically active compounds. All title synthetic compounds were screened for their antidiabetic, anti-inflammatory and anticancer activities.

1. Introduction

Cancer is one of leading ailments in which abnormal cells grow and can occur in all the living cells at every stage of human life. Many of peoples are suffering from cancer disease in the globe (Rashid et al., 2015). Chemotherapy is considered as one of the important treatments against the cancer diseases. Nowadays, many researchers are interested to find *anti neoplastic* drugs with less harmful effects on the immune system.

On the other hand, Diabetes is a clinical syndrome characterized by high levels of blood glucose resulting as defects in insulin production, insulin action, or both. Type 2 diabetes mellitus is the fastest rising worldwide threat to public health. The diabetic cases were 171 million in 2000 and may be found to increase to 366 million in 2030 (Narender et al., 2013). α-Amylase and α-glycosidase are important enzymes involved in carbohydrates breakdown and intestinal absorption. Acarbose, miglitol, and voglibose are good synthetic antidiabetic agents but, usage of those can be reduced may induce side effects such as flatulence, abdominal cramps, vomiting, and diarrhoea. Because of a number new drugs are developed by the researcher, which induces no harmful side effects.

Recently, the oxadiazole chemistry has been developed extensively and is still developing. Most of the drugs are used clinically, which comprise oxadiazole moiety in association with various heterocyclic rings. 1,3,4-Oxadiazoles are important heterocyclic compounds, which are synthetically useful, and biologically active. Literature survey revealed that 1,3,4 oxadiazoles are related to a wide range of pharmacological activities. 2,5 Substituted oxadiazole derivatives have been reported to possess anticonvulsant activity and antifungal activity (Zhang et al., 2013). Oxadiazole moiety is also used

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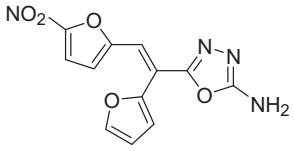
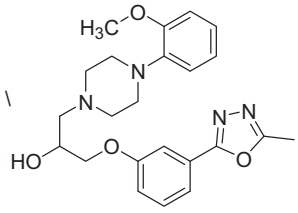
in material science in the field of photo sensitizer and liquid crystals and also a number of biological properties have been described: anticancer (Bondock et al., 2012; Salahuddin et al., 2014), antimicrobial (Aziz-ur-Rehman et al., 2015; Desai et al., 2011; Malladi et al., 2014), anti-inflammatory (Gadegoni and Manda, 2013), anticonvulsant (Harish et al., 2013), antioxidant (Musad et al., 2011), Anti-HIV (Hajimahdi et al., 2013), etc.

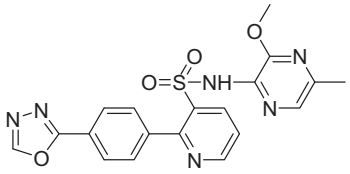
Keeping the view of this, we have synthesized 15 novel new oxadiazole derivatives carrying urea, amide, and sulphonamide groups to investigate their antidiabetic and anti-inflammatory. Further, we tested 1,3,4-oxadiazole derivatives against HeLa (cervical) and MCF-7 (breast) cancer cell lines using MTT assay.



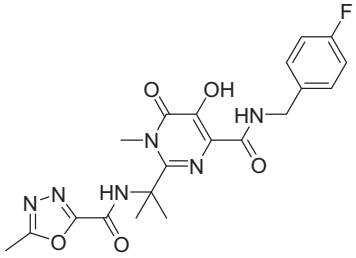
Furamizole
Antibiotic



Nesapidil
(Antihypertensive Drug)



Zibotentan (Anticancer drug)



Raltegravir(Antiretroviral)

Examples of 1,3,4-oxadiazole based drugs (Desai et al., 2013).

2. Experimental protocols

2.1. General

New synthetic approach for a novel series of 2,5 disubstituted 1,3,4-oxadiazole derivatives bearing urea, amide, sulphonamide is shown in Scheme 1. The starting material 2-cyclo hexyl-5-phenyl-1,3,4-oxadiazole was obtained by the reaction of cyclohexanoic acid with Benzohydrazide in $POCl_3$. The nitration reaction was carried out for 3 using KNO_3 and Con H_2SO_4 afforded 2-cyclohexyl-5-(3-nitrophenyl)-1,3,4-oxa diazole in 72% yield. The nitro compound (**4**) was changed to amine as parent compound (**5**) through tin chloride and Con HCl at room temperature. The desired 2,5 disubstituted 1,3,4 oxadiazole derivatives were bearing urea and amide, and sulphonamide functionalities were synthesized by reacting parent compound (**5**) with aryl isocyanates, acids, and aryl sulphonyl chloride respectively at rt with mild conditions. The purity of synthetic compounds was checked by TLC and proton, C^{13} NMR and IR also done for their proposed structures.

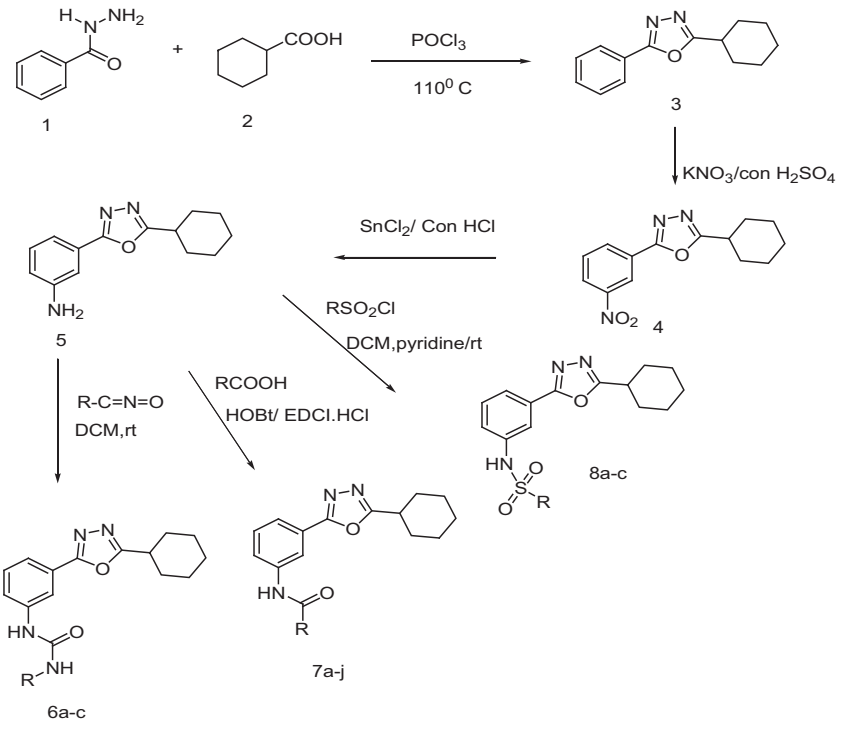
2.2. Chemicals

All the chemical reagents and solvents of analytical grade were purchased from the local supplier and Sigma Aldrich. Silica-coated TLC plates were used with petroleum ether and Ethyl acetate as the solvent system. ^{1}H NMR spectra were recorded by utilizing 400 and 300 MHz Bruker spectrometers indicating chemical shift value on ppm scale and TMS was taken as an internal reference. Perkin Elmer RXI was utilized for IR spectra by using KBr pellet method. Thermo LCQ Deca XP MAX spectrometer was utilized for mass spectra. The thin layer chromatography (TLC) analysis was carried out for synthesis using 5 × 20 cm plate coated with silica gel GF254.

2.3. Synthesis of 2-cyclohexyl-5-phenyl-1,3,4-oxadiazole

2-Cyclohexyl-5-phenyl-1,3,4-oxadiazole was synthesized according to the procedure by Chandrakantha et al. (2010) with minor modification. An equimolar mixture of Benzohydrazide with cyclohexanoic acid was refluxed with phosphorous oxychloride (7 vol) at 110 °C for 2–3 h. The reaction mixture was distilled off, the residue was quenched with ice water, and the solid was separated, filtered off, and washed with water repeatedly. Toluene was added to the mixture and it was concentrated through rotovap to afford the product as white solid.

M.p. 102 °C; Yield 83%. IR (KBr, cm^{-1}): 2933, 2855 (CH_2 Str), 1590 (C═N), 1506, 1496, 1442 (for oxadiazole), 1018 (C─O─C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24–1.46 (m, 3H), 1.62–1.72 (m, 3H), 1.86–1.93 (m, 2H), 2.13–2.18 (m, 2H), 2.93–3.01 (m, 1H), 7.45–7.49 (m, 3H), 7.92 (d, 2H, J = 8.1 Hz). ^{13}NMR ($CDCl_3$ 300 MHz); δ 170, 164.3, 131.3, 128.9, 126.7, 124.2, 35.2, 30.1, 29.2, 25.4. LC/ESI-MS: m/z value 229 (M + 1).



Scheme 1 Synthesis of 2,5- substituted 1,3,4- Oxadiazole derivatives.

2.4. Synthesis of 2-cyclohexyl-5-(3-nitrophenyl)-1,3,4-oxadiazole

Concentrated sulphuric acid (5 mL, 26 N) was taken into a flask at 0 °C. 2-Cyclohexyl-5-phenyl-1,3,4-oxadiazole (1 mmol) was added dropwise to the flask while stirring. To this cold solution of Potassium nitrate (16 mmol) in concentrated sulphuric acid was added. The mixture was stirred for 30 min at 0 °C and further for 1 h at room temperature. The reaction progress was monitored by TLC (Petroleum ether and ethyl acetate 8:2). The reaction mixture was quenched with ice water and extracted using ethyl acetate, washed with water, 10% $NaHCO_3$, brine water and dried over sodium sulphate. The organic mixture was concentrated and purified by silica column chromatography to afford nitro compound as light yellow solid. M.p. 74 °C; Yield 65%.

IR (KBr, cm^{-1}): 2935, 2856 (CH_2 Str), 1590 (C═N), 1531 (Ar—NO_2), 1515, 1486, 1441 (for oxadiazole), 1016 (C—O—C). (^{1}H NMR, $CDCl_3$, 400 MHz): δ 1.33–1.50 (m, 3H), 1.66–1.79 (m, 3H), 1.87–1.92 (m, 2H), 2.14–2.19 (m, 2H), 2.99–3.07 (m, 1H), 7.73 (t, 2H, J = 8.4 Hz), 8.37–8.43 (m, 1H) 8.84 (t, 1H, J = 1.6 Hz). ^{13}NMR ($CDCl_3$ 400 MHz); δ 170.8, 162.5, 148.6, 132.3, 130.2, 127.6, 125.8, 124.2, 35.3, 30.1, 29.1, 25.4. LC/ESI-MS: m/z value 274 (M + 1).

2.5. Synthesis of 3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl amine

2-Cyclohexyl-5-(3-nitrophenyl)-1,3,4-oxadiazole (1 Equi) was taken in a round bottom flask. Concentrated hydrochloric acid (4 vol) and tin chloride (4 Equi) were added in portionwise. The reaction was carried out for one hour at room temperature with calcium chloride tube. The reaction mixture was poured into ice water and basified with 40% sodium hydroxide. The mixture was extracted with ethyl acetate, washed with water, $NaHCO_3$ and brine water and dried over sodium sulphate. The mixture was purified by silica column chromatography to afford amino compound as light yellow solid. M.p; 118 °C Yield 69%. IR (KBr, cm^{-1}): 3440, 3362 (NH Stretch), 2927, 2856 (CH_2 Str), 1597 (C═N), 1564, 1469, 1412 (for oxadiazole), 1076 (C—O—C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27–1.36 (m, 2H), 1.41–1.48 (m, 2H), 1.63–1.76 (m, 2H), 1.84–1.90 (m, 2H), 2.13–2.18 (m, 2H), 2.94–3.01 (m, 1H), 3.82 (s, 2H), 6.80 (dd, 1H, J = 2.2 Hz), 6.82 (dd, 1H, J = 2.2 Hz), 7.40 (t, 1H, J = 1.2 Hz), 7.37 (dt, 1H). ^{13}NMR ($CDCl_3$ 400 MHz); δ 169.8, 164.5, 146.8, 129.9, 125, 117.9, 116.8, 112.7, 35.2, 30.1, 25.5, 27.4. LC/ESI-MS: m/z value 244 (M + 1).

2.5.1. General procedure for the synthesis of urea derivatives

Amine (1 Equi) was taken in dichloromethane (10 mL) at room temperature and added the substituted aromatic isocyanates (1 Equiv) at 0 °C. Then, the reaction mixture was allowed to room temperature for 1–2 h. The reaction progress was checked by TLC in petroleum ether and ethyl acetate (6:4). The resulting organic mixture was concentrated under reduced pressure to afford the product, which was purified by washing with petroleum ether (Toche and Janrao, 2015).

2.5.2. General procedure for the synthesis of amide derivatives

To the solution of amine (1 Equiv), aromatic or aliphatic acids (1.2 Equiv), HOBt (1 Equi) in dichloro methane was added EDCI. HCl at 0 °C. Then, triethylamine (4 Equiv) was added dropwise and kept overnight at room temperature. The product was diluted with ethyl acetate, washed with water, 2 N HCl, 5% $NaHCO_3$, and brine water, dried over anhydrous

Na_2SO_4 and concentrated by the rotary evaporator to get residue as solid.

2.5.3. General procedure for the synthesis of sulphonamide derivatives

To a solution of amine (1 Equi) dichloro methane was added to pyridine (4 Equi) followed by aromatic sulphonyl chloride (1 Equi) added dropwise at 0 °C. The reaction mixture was gradually brought to room temperature, and stirred for 2 h. The mixture was diluted with ethyl acetate, and washed with water, 2 N HCl, 10% $NaHCO_3$, brine water, and dried over sodium sulphate. It was concentrated by rotary evaporator to obtain sulphonamide as product (Toche and Janrao, 2015; Dogruer et al., 2010).

2.5.4. Spectral data of synthesized compounds

*2.5.4.1. 1-[3-(5-Cyclohexyl-[1,3,4] oxadiazol-2-yl)-phenyl]-3-(4-fluoro-phenyl)-urea (**6a**).* Yield 81%, M.p. 121; IR (KBr, cm^{-1}) 2933, 2856 (CH_2 Str), 1698 (C═O), 3344 (NH), 1300 (C─F), 3058 (CH), 1560 (C═N), 1033 (C─O─C), ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.33–1.46 (m, 3H), 1.54–1.67 (m, 3H), 1.74–1.78 (m, 2H), 2.04–2.080 (dd, 2H), 2.99–3.06 (m, 1H), 7.14–7.09 (m, 2H), 7.45–7.49 (m, 1H), 7.58–7.54 (m, 1H), 8.23 (s, 1H), 8.73 (s, 1H), 8.98 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm; 169.4, 163.6, 158.6, 156.2, 152.5, 140.5, 135.7, 129.8, 124.0, 121.1, 120.2, 119.5, 115.3, 34.1, 29.5, 25.1, 24.6. LC/ESI-MS: *m/z* value; 381.1 (M + 1).

*2.5.4.2. 1-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3-p-tolyl-urea (**6b**).* Yield 85%. M.p 185; IR (KBr, cm^{-1}) 2930, 2851 (CH_2 Str), 1647 (NH─C═O), 3321 (NH), 3039 (CH Str), 1414 (C═N), 1037 (C─O─C). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.20–1.41 (m, 4H), 1.56–1.68 (m, 2H), 1.80–1.86 (m, 2H), 2.01–2.12 (m, 2H), 2.65 (s, 3H), 2.88–2.98 (m, 1H), 6.59–6.6 (m, 2H), 6.64 (t, 1H, *J* = 2.4 Hz), 6.95 (s, 1H), 7.07 (t, 1H, *J* = 7.8 Hz), 7.37 (d, 1H, *J* = 8.1 Hz), 8.07 (dd, 1H, *J* = 7.8 Hz), 8.53 (d, 1H, *J* = 1.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 169.6, 164.1, 152.8, 140.2, 136.2, 131.7, 129.2, 129, 124.2, 121.1, 119.9, 111.8, 116, 39.4, 34.9, 29.8, 25, 20.4. LC/ESI-MS: *m/z* value; 377 (M + 1).

*2.5.4.3. 1-[3-(5-Cyclohexyl-[1,3,4] oxadiazol-2-yl)-phenyl]-3-(3-methoxy-phenyl)-urea (**6c**).* Yield 78%, M.p 156, IR (KBr, cm^{-1}): 2931, 2854 (CH_2 Str), 1703 (NH─C═O), 3339 (NH), 3089 (CH Ar), 1472 (C═N), 1040 (C─O─C). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.18–1.42 (m, 4H), 1.64–1.70 (m, 2H), 1.77–1.82 (m, 2H), 2.05–2.11 (d, 2H), 2.92–3.02 (m, 1H), 3.72 (s, 3H), 6.54 (dd, 1H, *J* = 9 Hz), 6.92 (d, 1H, *J* = 8.1 Hz), 7.16 (d, 1H, *J* = 1.2 Hz) 7.17–7.19 (m, 1H), 7.36 (t, 1H *J* = 8.1 Hz), 7.50 (d, 1H *J* = 8.1 Hz), 7.9 (s, 1H), 8.05 (d, 1H, *J* = 7.2 Hz), 8.32 (s, 1H) 8.66 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 170.5, 164.7, 160.2, 153.5, 140.1, 139.7, 129.6, 123.9, 123.6, 121, 117.2, 112.3, 108.9, 105.9, 55.2, 35.4, 30.2, 27.3, 25.4. LC/ESI-MS: *m/z* value; 393 (M + 1).

*2.5.4.4. 4-Chloro-N-[3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzamide (**7a**).* Yield 79%, M.p 143, IR (KBr, cm^{-1}); 2923, 2854 (CH_2 Str), 1646 (C═O), 3281 (NH), 3089 (CH), 1472 (C═N), 1095 (C─O─C), 727 (C─Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.32–1.37 (m, 3H), 1.60–1.77 (m, 3H), 1.78–1.81 (m, 2H), 2.03–2.07 (d, 2H), 2.82–2.92 (m, 1H), 7.40–7.44 (m, 2H), 7.47 (s, 1H), 7.74 (s, 1H), 7.76–7.81 (m, 2H), 7.92 (d, 1H, *J* = 8.4 Hz), 8.11 (s, 1H), 8.21 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm; 169.6, 165, 163.9, 139.3, 137.4, 132.9, 129.1, 128.1, 124, 123.2, 121.8, 118.3, 39.7, 34.8, 29.7, 26.6, 24.9. LC/ESI-MS: *m/z* value; 382 (M + 1).

*2.5.4.5. N-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-4-methyl-benzamide (**7b**).* Yield 58%, M.p 188, IR (KBr, cm^{-1}); 2923, 2852 (CH_2 Str), 1648 (C═O), 3293 (NH), 3031 (CH), 1562 (C═N), 1029 (C─O─C). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.22–1.41 (m, 4H), 1.54–1.69 (m, 2H), 1.78–1.86 (m, 2H), 2.03–2.10 (m, 2H), 2.84–2.94 (m, 1H), 2.37 (s, 3H), 7.23 (t, 2H, *J* = 8.1 Hz), 7.43 (t, 1H, *J* = 8.1 Hz), 7.74 (d, 2H, *J* = 8.1 Hz), 7.89–7.91 (m, 1H), 8.03 (t, 1H, *J* = 2.7 Hz), 8.18 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 170.2, 166, 164.1, 142.6, 139, 131.6, 129.4, 127.2, 124.7, 123.1, 122.5, 120, 118.2, 35.2, 30.1, 27.3, 25.4, 21.5. LC/ESI-MS: *m/z* value; 362 (M + 1).

*2.5.4.6. N-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-2-(2-fluoro-phenyl)acetamide (**7c**).* Yield 67%, M.p 118. IR (KBr, cm^{-1}); 2929, 2855 (CH_2 Str), 1648 (C═O), 3308 (NH), 3069 (CH), 1488 (C═N), 1028 (C─O─C). 998 (C─F). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.32–1.41 (m, 4H), 1.53–1.69 (m, 2H), 1.77–1.82 (m, 2H), 1.98–2.11 (m, 2H), 2.84–2.94 (m, 1H) 3.72 (s, 2H), 7.04–7.19 (m, 2H), 7.23–7.36 (m, 3H),7.40 (d, 2H, *J* = 6.3 Hz), 7.68–7.72 (m, 2H), 7.99 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 170.2, 168.5, 164.1, 162.6, 159.3, 138.6, 131.6, 129.7, 127.6, 124.7, 122.9, 122.5, 121.4, 117.9, 111.5.8, 37.7, 35.3, 30.1, 29.7, 25.3, 25.3, 22.7. LC/ESI-MS: *m/z* value; 380 (M + 1).

*2.5.4.7. N-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3,5-difluoro-benzamide (**7d**).* Yield 63%, M.p 110. IR (KBr, cm^{-1}); 2927, 2857 (CH_2 Str), 1660 (C═O), 3323 (NH), 3028 (CH, Ar), 1471 (C═N), 985 (C─O─C), 794 (Di fluoro). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.14–1.21 (m, 1H), 1.24–1.38 (m, 3H), 1.50–1.65 (m, 2H), 1.76–1.78 (m, 2H), 1.98–2.04 (m, 2H), 2.79–2.90 (m, 1H), 6.95 (td, 1H, *J* = 8.4 Hz), 7.37–7.43 (m, 2H), 7.45 (d, 1H, *J* = 8.1 Hz), 7.74 (d, 1H *J* = 7.8 Hz), 7.96 (d, 1H, *J* = 8.2 Hz), 8.28 (s, 1H), 8.44 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 170.3, 164.6, 164.1, 161.1, 138.6, 138, 129.7, 124.6, 123.8, 122.9, 119.0, 110.7, 107.2, 35.2, 30.1, 29.7, 25.3. LC/ESI-MS: *m/z* value; 384 (M + 1).

*2.5.4.8. Pyrazine-2-carboxylic acid [3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-amide (**7e**).* Yield 72%, M.p 138. IR (KBr, cm^{-1}); 2928, 2853 (CH_2 Str), 1682 (C═O), 3320 (NH), 3056 (CH, Ar), 1470 (C═N), 1020 (C─O─C). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.19–1.44 (m, 4H), 1.60–1.70 (m, 2H), 1.79–1.83 (m, 2H), 2.07–2.12 (m, 2H), 2.88–2.98 (m, 1H), 7.48 (t, 1H, *J* = 8.1 Hz), 7.81 (d, 1H, *J* = 7.8 Hz), 7.97 (d, 1H, *J* = 8.1 Hz), 8.30 (s, 1H), 8.56 (s, 1H), 8.78 (d, 1H, *J* = 2.1 Hz), 9.47 (s, 1H), 9.77 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm; 170.2, 163.9, 160.9, 147.8, 144.7, 144, 142.4, 137.9, 130, 125.1, 123.0, 122.5, 117.7, 35.3, 30.1, 25.4, 27.4. LC/ESI-MS: *m/z* value; 350 (M + 1).

*2.5.4.9. N-[3-(5-Cyclohexyl-[1,3,4] oxadiazol-2-yl)-phenyl]-2-(1H-indol-3-yl)-acetamide (**7f**).* Yield 78%, M.p 162. IR (KBr, cm^{-1}); 2926, 2853 (CH_2 Str), 1660 (C═O), 3256 (NH 2^0-Amide), 3086 (CH, Ar), 1566 (C═N), 1038 (C─O─C). 1314 (N─N). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.18–1.41 (m, 4H), 1.57–1.69 (m, 2H), 1.76–1.80 (m, 2H), 1.98–2.06 (d, 2H), 2.83–2.93 (m, 1H), 3.87 (s, 2H), 7.12 (t, 1H, J = 7.2 Hz), 7.19–7.22 (m, 1H),7.31 (t, 1H, J = 8.1 Hz),7.39 (d,1H, J = 8.4 Hz), 7.54 (t, 2H, J = 7.8 Hz), 7.64 (dd, 2H, J = 7.8 Hz), 7.80 (t, 1H, J = 1.8 Hz), 8.36 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 170.2, 164.1, 141.3, 138.4, 136.5, 129.6, 126.8, 124.5, 124.1, 122.9, 122.4, 120.3, 118.5, 117.8, 108.1, 102.8, 35.2, 34.5, 30.1, 29.7, 25.3. LC/ESI-MS: m/z value; 431 (M + 1).

*2.5.4.10. Cyclopentane carboxylic acid [3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-amide (**7g**).* Yield 69%, M.p 144. IR (KBr, cm^{-1}); 2930, 2857 (CH_2 Str), 1689 (C═O), 3303 (NH), 3053 (CH, Ar), 1468 (C═N), 995 (C─O─C). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.56–1.63 (m, 9H), 1.66–1.98 (m, 9H), 2.61–2.71 (q, 1H), 2.85–2.95 (m, 1H), 7.37 (t, 2H, J = 7.8 Hz), 7.71 (t, 2H, J = 8.1 Hz), 8.11 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm: 175.2, 170.1, 164.2, 139.2, 129.6, 124.6, 122.7, 122.7, 122.1, 117.8, 46.7, 35.3, 30.2, 26, 25.4, 22.4. LC/ESI-MS: m/z value; 340 (M + 1).

*2.5.4.11. Furan-2-carboxylic acid [3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-amide (**7h**).* Yield 61%, M.p 121. IR (KBr, cm^{-1}); 2927, 2857 (CH_2 Str), 1660 (C═O), 3323 (NH), 3028 (CH, Ar), 1471 (C═N), 1005 (C─O─C). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.21–1.43 (m, 4H), 1.64–1.70 (m, 2H), 1.78–1.84 (m, 2H), 2.06–2.10 (d, 2H), 2.87–2.96 (m, 1H), 6.52 (dd, 1H, J = 3.6 Hz), 7.21 (t, 1H, J = 3.6 Hz), 7.43 (t, 1H, J = 8.1 Hz), 7.48 (s, 1H), 7.77 (d, 1H, J = 7.8 Hz), 7.85 (d, 1H, J = 8.1 Hz), 7.97 (d, 1H, J = 8.7 Hz), 8.16 (s, 1H), 8.19 (t, 1H, J = 1.8 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 170.2, 164., 156.2, 147.4, 144.5, 138.1, 136.7, 129.8, 124.9, 122.7, 117.8, 115.7, 112.7, 35.3, 30.1, 29.6, 25.4. LC/ESI-MS: m/z value; 338 (M + 1).

*2.5.4.12. N-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3-furan-2-yl-acrylamide (**7i**).* Yield 78%, mp 162, IR (KBr, cm^{-1}): 2927, 2857 (CH_2 Str), 1660 (C═O), 3323 (NH), 3028 (CH, Ar), 1471 (C═N), 989 (C─O─C). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.168–1.275 (m, 2H), 1.325–1.417 (m, 4H), 1.773–1.826 (m, 2H), 1.981–2.162 (d, 2H), 2.891–2.979 (m, 1H), 6.413–6.442 (m, 1H), 6.492 (s, 1H), 6.55 (d, 1H, J = 3.3 Hz), 7.40 (t, 2H, J = 8.4 Hz), 7.52 (d, 1H, J = 8.1 Hz), 7.70 (d, 1H, J = 7.8 Hz), 7.91 (d, 2H, J = 8.1 Hz), 8.23 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm; 169.2, 163.9, 163.5, 150.7, 143.4, 139.4, 128.7, 127.3, 123.7, 121.8, 120.8, 118.7, 116.9, 113.3, 111.6, 39.3, 34.4, 29.4, 24.5. LC/ESI-MS: m/z value; 364 (M + 1).

*2.5.4.13. N-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-4-methyl-benzenesulphonamide (**8a**).* Yield 72%, mp 182, IR (KBr, cm^{-1}): IR (KBr, cm^{-1}): 2921, 2849 (CH_2 Str), 3430 (NH), 3053 (CH, Ar), 1471 (C═N), 1158 (SO_2 Str), 990 (C─O─C). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.19–1.44 (m, 3H), 1.55–1.70 (m, 3H), 1.78–1.83 (m, 2H), 2.04–2.09 (dd, 2H), 2.28 (s, 3H), 2.90–3.0 (m, 1H), 7.16 (t, 2H, J = 7.8 Hz), 7.28–7.37 (m, 2H), 7.54 (d, 1H, J = 5.1 Hz), 7.62 (d, 2H, J = 8.4 Hz), 7.87 (d, 1H, J = 1.5 Hz), 10.3 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 170.6, 163.8, 143.8, 138.2, 136.2, 129.9, 129.7, 127.2, 124.9, 123.4, 122.6, 119.5, 35.3, 30.2, 27.4, 25.4, 21.5. LC/ESI-MS: m/z value; 398 (M + 1).

*2.5.4.14. 4-tert-Butyl-N-[3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulphonamide (**8b**).* Yield 70%, mp 151, IR (KBr, cm^{-1}); 2926, 2855 (CH_2 Str), 3423 (NH), 3051 (CH, Ar), 1472 (C═N), 1162 (SO_2 Str), 983 (C─O─C), ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.24–1.50 (m, 8H), 1.54–1.68 (m, 5H), 1.73–1.77 (m, 3H), 2.01–2.05 (d, 3H), 2.97–3.05 (m, 1H), 7.33–7.36 (m, 2H), 7.46 (t, 1H, J = 7.8 Hz), 7.72–7.78 (m, 4H), 7.85 (d, 1H, J = 8.7 Hz), 10.6 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 169.1, 163.1, 156.1, 141, 138.8, 136.5, 130.4, 127.7, 126.2, 124.4, 118.9, 116.7, 39, 34, 31, 29.5, 25.1, 24.6. LC/ESI-MS: m/z value; 440 (M + 1).

*2.5.4.15. 3,5-Dichloro-N-[3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulphonamide (**8c**).* Yield 76%, mp 176, IR (KBr, cm^{-1}) 2924, 2853 (CH_2 Str), 3440 (NH), 3050 (CH, Ar), 1471 (C═N), 1169 (SO_2 Str), 939 (C─O─C),779 (C─Cl). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.17–1.43 (m, 2H), 1.47–1.52 (m, 2H), 1.60–1.69 (m, 2H), 1.74–1.91 (m, 2H), 2.02–2.06 (d, 2H), 2.98–3.07 (m, 1H),7.19–7.29 (m, 1H),7.32–7.39 (m, 2H),7.65 (t, 3H),7.75 (s, 1H), 11.0–11.3 (m, 1H) ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 169.6, 163, 142.5, 137.1, 134.3, 133.1, 131.7, 129.7, 124.5, 121.2, 117.9, 115.3, 40.1, 34.1, 29, 25.1. LC/ESI-MS: m/z value; 453 (M + 1).

2.6. α-Amylase assay

Phosphate buffer saline (PBS, 0.02 mol/L, pH 6.8) was used to dissolve the enzyme α-amylase at a concentration of 0.1 mg/mL. Sample solutions having different concentrations (0.25 mL) were mixed with the α-amylase solution (0.25 mL) and incubated at 37 °C for 5 min. The reaction mixture was initiated by the addition of 0.5 mL 1.0% (w/v) starch substrate solution to the incubation medium. After the elapsed time, the reaction was stopped by adding 0.5 mL DNS reagent (1% Dinitrosalicylic acid, 0.05% Na_2SO_3 and 1% NaOH solution) and heated at 100 °C for 5 min. Then the reaction mass is cooled to room temperature. After cooling the absorbance (Abs) at 540 nm was recorded using a spectrophotometer (Balan et al., 2015; Tegginamath et al., 2011).

2.7. In vitro anti-inflammatory activity (Anti-denaturation assay)

Newly synthesized fifteen compounds were evaluated for their anti-inflammatory activity by albumin denaturation method. The experiment was done by small modification (Priya et al., 2011; Lavanya et al., 2015). The sample and standard were dissolved in minimum amount of DMF and diluted in phosphate buffer (0.2 M, PH 7.4). Finally, DMF concentration in all solutions was used less than 2.5%. 1 mL of 1 mM albumin solution in phosphate buffer was mixed with test solution (4 mL) containing different concentrations of drug and incubated at 37 °C for 15 min. The reaction mixture was Denaturized by keeping at 70 °C for 15 min. After cooling, the turbidity was measured at 660 nm. Percentage of Inhibition

of denaturation was calculated from control where no drug was added. The diclofenac sodium was used as standard drug. The percentage inhibition was calculated by using the following empirical formula:

$$\% \text{ of Inhibition} = 100 \times (\text{At} - \text{Ac})/\text{At}$$

$$\text{At} = \text{O.D. of test solution Ac} = \text{O.D. of control}$$

2.8. In vitro anticancer activity

The human cervical cancer cell lines (HeLa) were obtained from National Centre for Cell Science (NCCS), Pune, and grown in Eagles Minimum Essential Medium containing 10% foetal bovine serum (FBS). The cells were maintained at 37 °C, 5% CO2, 95% air and 100% relative humidity. Maintenance cultures were passaged weekly, and the culture medium was changed twice a week.

The monolayer cells were isolated with trypsin-ethylenedia minetetraacetic acid (EDTA) to make single cell suspensions and viable cells. Further, it was counted using a hemocytometer, and diluted with medium containing 5% FBS to give the final density of 1×10^5 cells/ml. One hundred microlitres per well of cell suspension were seeded into 96-well plates, at the density of 10,000 cells/well plates and incubated to the cell attachment at 95% air, 37 °C, 5% CO_2, and 100% relative humidity. After 24 h, the cells were treated with serial concentrations of the test samples. They were initially dissolved in neat dimethylsulphoxide (DMSO), and an aliquot of the sample solution was diluted twice for maximum test concentration, with serum-free medium. In addition, to those four serial dilutions were made to provide a total of five sample concentrations (6.25 µM, 12.5 µM, 25 µM, 50 µM, 100 µM). Aliquots of 100 µl of these sample dilutions were added to the suitable wells, which contains 100 µl of medium. After addition, the plates were incubated for another 48 h at 37 °C, 5% CO_2, 95% air and 100% relative humidity. The medium containing without samples was called as control and triplicate were maintained for all the concentrations.

After 48 h of incubation, 15 µl of MTT (5 mg/ml) in PBS was added to all well and incubated at 37 °C for 4 h. The medium with MTT was then flicked off and the produced formazan crystals were solubilized in 100 µl of DMSO and measured the absorbance at 570 nm by microplate reader. The % cell inhibition was determined using the following formula (Monks et al., 1991):

$$\% \text{ Cell Inhibition} = 100 - \text{Abs (sample)}/\text{Abs (control)} \times 100.$$

Nonlinear regression graph was plotted between % Cell inhibition and Log concentration and IC_{50} was determined using Graph Pad Prism software.

3. Result and discussion

3.1. Chemistry

Benzohydrazide was refluxed with cyclohexanoic acid in the presence of phosphorous oxychloride afforded 2-cyclohexyl-5 -phenyl-1,3,4-oxadiazole. Subsequently, it was carried out nitration by KNO_3/H_2SO_4, followed by reduction with tin chloride/Con HCl to give 3-(5-cyclohexyl-1,3,4-oxadiazol-2-y l) aniline. Furthermore, 3-(5-cyclohexyl-1,3,4-oxadiazol-2-yl) aniline was used as key intermediate (**6a-c**), (**7a-i**), (**8a-c**) respectively. All the newly synthesized compounds were characterized by IR, NMR and Mass spectra and elemental studies.

IR spectrum of compound 1 shows absorption band at 2933, 2855 cm^{-1} due to the aliphatic stretching. An absorption band at 1590 cm^{-1} assignable for C═N group and the region at 1018 cm^{-1} is due to stretching of oxadiazole ring. The absence of peaks for hydrazide. So, it confirms the oxadiazole formation. The IR Spectra of Compound 2 showed the peak at 1531 cm^{-1} due to NO_2. IR spectrum of Compound 3 showing absorption peak at 3440 and 3362 cm^{-1} due to the amine. IR spectrum of compounds (**6a-c**) showed absorption bands at around 3344, 3058, 2935, 1593, 1037 cm^{-1} which were due to the N—H (amide), C—H (Aromatic), CH_2 (Aliphatic), C═N, and C—O—C groups, respectively. The IR spectra of oxadiazole derivatives (**7a-i**) showed peaks at region of 1646 cm^{-1} due to C═O and 3281 cm^{-1} cm assignable for NH. Similarly, IR spectrum of compounds (**8a-c**) exhibited absorption bands at 2546 cm due to SO_2 and peak at region 3355 cm^{-1}.

H^1 NMR spectra of urea derivatives (**6a-c**) showed the presence of two singlets appeared at around δ 8.53–8.73 ppm. The C^{13} NMR spectra of urea derivatives (**6a-c**) indicated the presence of carbonyl group appeared at around δ 169.5 ppm. A signal at around 2.37 ppm was assigned to the methylene proton. The singlet at around 3.72 and 3.83 ppm was assigned to the methoxy and amino protons, respectively. The peaks at around 30.1 and 55.2 ppm were assigned to the methylene and methoxy carbon atoms. The H^1 NMR spectra of amide derivatives (**7a-i**) indicated the presence of one singlet appeared at around 8.1 ppm for NH proton attached to the carbonyl group. C^{13} NMR spectra revealed that the presence of carbonyl carbon showed at around δ 170 ppm. Furthermore, the H^1 NMR spectrum of sulphonamide derivatives (**8a-c**) showed broad downfield singlet appeared at around δ 10.64–11.25 ppm for sulphonamide NH proton. The IR, ^1H and C^{13} NMR and mass spectral data were found in good agreement with the newly synthesized compounds (see Fig. 1).

3.2. SAR studies

1. The anticancer activity results showed that the presence of urea moiety with electron releasing group (methyl, methoxy) may enhance cytotoxicity of the synthesized 1,3,4 oxadiazole derivatives. The electron releasing groups are playing important role for improving anticancer activity (Kumar et al., 2014).
2. The results also indicated that 1,3,4 oxadiazole ring attached to the substituted benzene sulphonamide increased cytotoxicity potential of tested compounds against MCF7 cell line, whereas, substituted benzamide unit attached to 1,3,4 oxadiazole derivatives decreased anticancer activity against both MCF7 and He La cell lines.
3. SAR analysis indicated that presence of electron donating groups on p-position of both urea and sulphonamide unit with 1,3,4 oxadiazole ring may increase anti-inflammatory and anticancer activity.

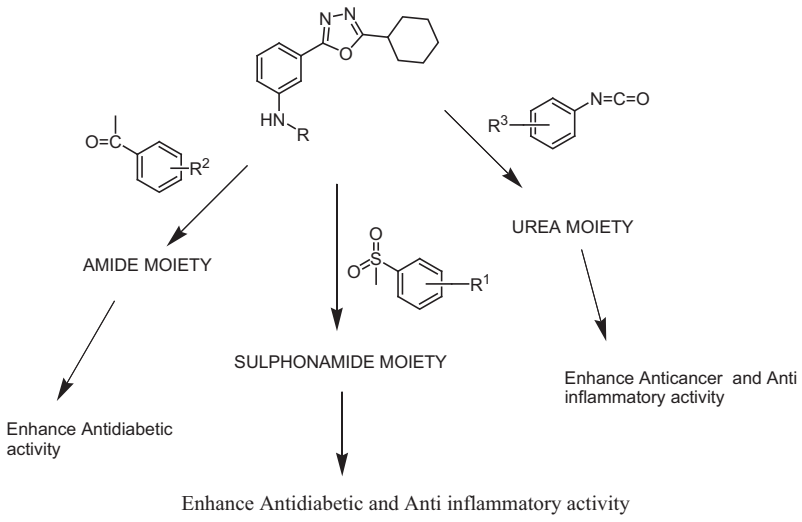


Figure 1 Structure activity relationship for synthesized 1,3,4 oxadiazole derivatives.

4. Most of the synthesized compounds indicated moderate to good activity against anti diabetic studies. Furthermore, **6f** showed high anti diabetic activity.

3.3. Antidiabetic activity

In the present study, it has been evaluated the inhibitory effects of synthesized compounds against α-amylase activity. Synthesized compounds were checked with five different concentrations (50, 100, 250, 500, and 1000 μm) and acarbose was used as a standard drug. The compounds (**7f** and **8c**) showed stronger inhibitory activity against α-amylase when compared to the acarbose inhibitor, whereas, the compounds **6a**, **6b**, **7d**, **7e**, and **7g** exhibited moderate activities and other the compounds have exposed weak activity. The bar graph representation of antidiabetic activities of title compounds (**6a-c**, **7a-i**, and **8a-c**) is shown in Fig. 2.

3.3. In-vitro Anti-inflammatory activity data

Anti-inflammatory activity was carried out by Serum albumin denaturation method with four different concentrations such as 50 μm, 100 μm, 300 μm, and 500 μm respectively. All the synthesized compounds (**6a-c**, **7a-i**, **8a-c**) were screened for their anti-inflammatory activity. Within series, Compounds **6a**, **6c**, and **8b** having urea and sulphonamide unit showed good activity, while, Compounds **6b**, **7a**, **7c**, **7g**, and **7i** showed moderate activity. Remaining compounds exhibited mild activity against the standard drug. The results of the anti-inflammatory activity of the newly synthesized compounds are shown in Fig. 3.

3.4. Anticancer activity

All newly synthesized 1,3,4-Oxadiazole derivatives were evaluated for their anticancer activity towards two cell lines using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cis plastin was used as a standard drug. Anticancer activities of all compounds were indicated by IC_{50} values and were calculated by linear regression analysis. Cisplatin was used as a standard and among all the synthesized compounds **6a**, **6b**, **6c**, **7c**, **7d**, and **8b** showed cytotoxicity on two cell lines after 48 h exposures. The results showed that the compounds **6b** and **6c** of 1,3,4 oxadiazole derivatives showed significant activity against MCF-7 and HeLa cells. For these compounds, IC_{50} values are in the range of 23.5–45.6 μM.

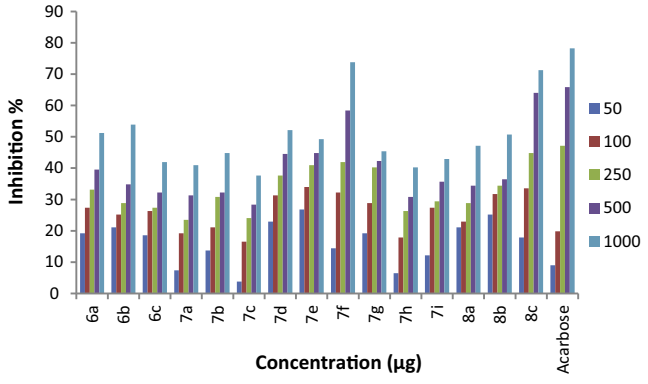


Figure 2 α-Amylase activity of synthesized compounds.

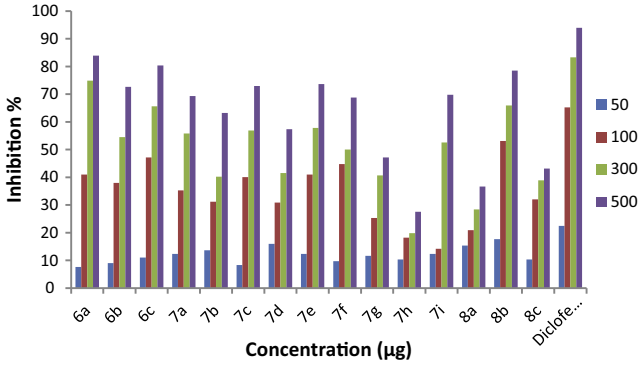


Figure 3 Anti-inflammatory activities of synthesized compounds.

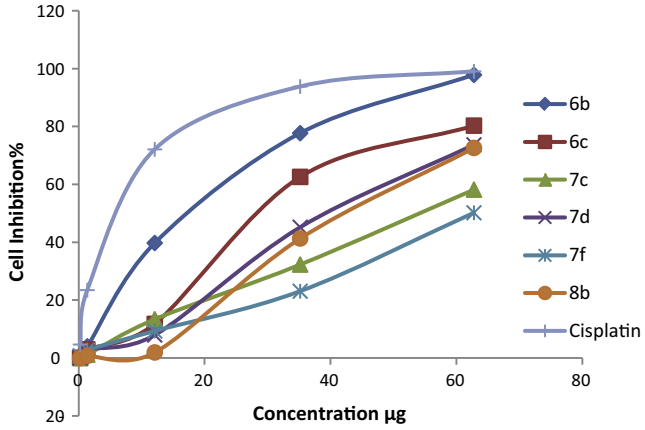


Figure 4 In vitro anticancer screening of the Compounds **6b**, **6c**, **7c**, **7d**, **7f** and **8b** against HeLa cell lines after 48 h exposure.

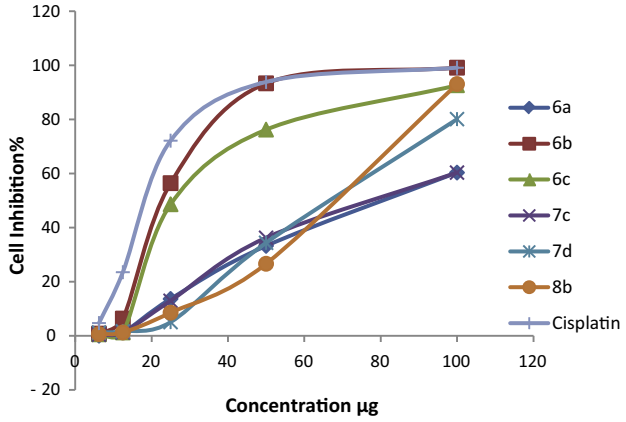


Figure 5 In vitro anticancer screening of the Compounds **6a**, **6b**, **6c**, **7c**, **7d** and **8b** against MCF7 cell lines after 48 h exposure.

Table 1 Preliminary cytotoxicity screening and antidiabetic activities of synthesized 1,3,4 oxadiazole derivatives.

Entry	IC_{50} µM		
	HeLa	MCF-7	Antidiabetic
6a	79.7	81.6	5.09
6b	30.4	23.5	5.29
6c	45.6	28.6	6.93
7a	⩾100	⩾100	6.22
7b	⩾100	⩾100	5.927
7c	80.1	78.3	6.510
7d	58.8	62.4	4.717
7e	⩾100	⩾100	4.947
7f	100.3	⩾100	3.40
7g	⩾100	⩾100	5.249
7h	⩾100	⩾100	6.213
7i	⩾100	⩾100	5.935
8a	⩾100	⩾100	6.008
8b	62.9	60.9	5.561
8c	⩾100	⩾100	3.268
Standard	3.5	3.5	2.09

Further derivatives **6a**, **7c**, **7d**, and **8b** also showed good activity against both cell lines compared with the standard. From the data, compound **6b** may be the powerful anticancer agent and the rest of other compounds did not show cytotoxic effects on cell lines. The results of the anticancer activity of synthesized compounds are shown in Figs. 4, 5 and Table 1.

4. Conclusion

A series of new 2,5-disubstituted 1,3,4-oxadiazole derivatives bearing urea, amide, and sulphonamide were synthesized, and their antidiabetic, anti-inflammatory, anticancer activities were evaluated in vitro. The fifteen synthesized compounds showed moderate to good activity against anti diabetic, anti-inflammatory and anticancer activities. Among them, compound **6b** was found to be effective anticancer agents. The antidiabetic activity of **7f** and **8c** was better than all other compounds. The result revealed that introduction of urea and sulphonamide group in oxadiazole enhances activities. Based on the above results, the current research is considered to synthesize 1,3,4 oxadiazole derivatives for their improvement of the biological activity.

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