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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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1,3,4-Oxadiazole;
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Antiinflammatory;
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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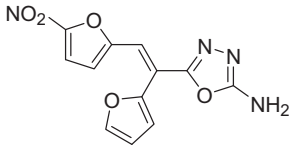
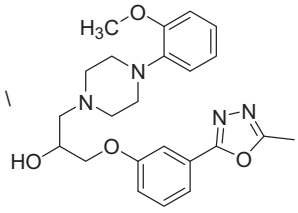
in material science in the field of photo sensitizer and liquid crystals and also a number of biological properties have been described: anticancer (Bondock et al., 2012; Salahuddin et al., 2014), antimicrobial (Aziz-ur-Rehman et al., 2015; Desai et al., 2011; Malladi et al., 2014), anti-inflammatory (Gadegoni and Manda, 2013), anticonvulsant (Harish et al., 2013), antioxidant (Musad et al., 2011), Anti-HIV (Hajimahdi et al., 2013), etc.

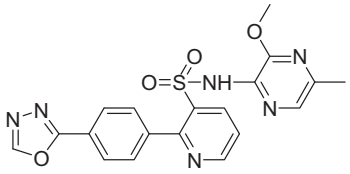
Keeping the view of this, we have synthesized 15 novel new oxadiazole derivatives carrying urea, amide, and sulphonamide groups to investigate their antidiabetic and anti-inflammatory. Further, we tested 1,3,4-oxadiazole derivatives against HeLa (cervical) and MCF-7 (breast) cancer cell lines using MTT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



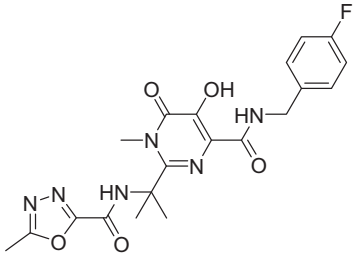
Furamizole
Antibiotic



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).