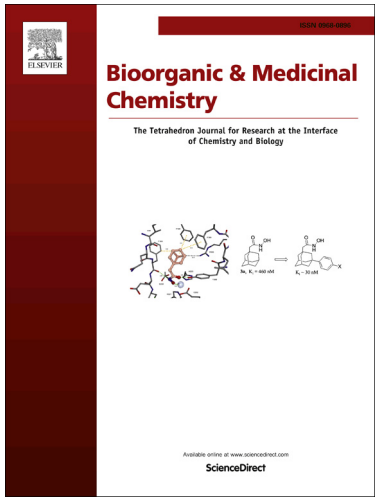

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Synthesis of New Oxadiazole Derivatives as α-Glucosidase Inhibitors

Muhammad Taha[*a,b], Nor Hadiani Ismail[a,b], Syahrul Imran[a,b], Muhammad Qamarruddin Bin Rokei[b], Syed Muhammad Saad[d], and Khalid Mohammed Khan[d]

[a]*Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300, Bandar Puncak Alam, Selangor, Malaysia.*

[b]*Faculty of Applied Science Universiti Teknologi MARA (UiTM), 40450, Shah Alam, Selangor, Malaysia* [c]*Integrative Pharmacogenomics Institute (iPROMISE), Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia.*

[d]*H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan.*

Abstract:

Oxadiazole derivatives (**6**-**28**) having hydrazone linkage, were synthesized through condensation reaction between benzohydrazide **5** with various benzaldehydes. The oxadiazoles derivatives (**6**-**28**) were evaluated for their α-glucosidase inhibitory activity. The IC_{50} values for inhibition activity vary in the range between 2.64 ± 0.05 to 460.14 ± 3.25 μM. The IC_{50} values were being compared to the standard acarbose (IC_{50} = 856.45 ± 5.60 μM) and it was found that compounds **6-9**, **12**, **13**, **16**, **18**, **20**, **22-28** were found to be more active than acarbose, while other compounds showed no activity. Structure-activity relationship (SAR) studies suggest that oxadiazole benzohydrazones (**6**-**28**) inhibitory potential is dependent on substitution of the *N*-benzylidene part. Compound **18** (IC_{50} = 2.64 ± 0.05 μM), which has trihydroxy substitution at C-2′, C-4′, and C-5′ on *N*-benzylidene moiety, recorded the highest inhibition activity that is three-hundred times more active than the standard drug, acarbose (IC_{50} = 856.45 ± 5.60 μM). Compound **23** (IC_{50} = 34.64 ± 0.35 μM) was found to be the most active among compounds having single hydroxyl substitution. Shifting hydroxyl from C-2′ to C-4′ (**6**) and C-3′ (**7**) reduces inhibitory activity significantly. Compounds with chlorine substituent (compounds **16**, **28**, and **27**) showed potent activities but lower as compared to hydroxyl analogs. Substituent like nitro or methyl groups at any position suppresses enzyme inhibition activity. This reveals the important presence of hydroxyl and halo groups to have enzyme inhibitory potential.

Keywords: Oxadiazole, benzohydrazone, antidiabetic, α-glucosidase inhibitors.

* Correspondence and reprints
E-mail: taha_hej@yahoo.com and muhamm9000@puncakalam.uitm.edu.my, Tel: 0060182901765

1. Introduction

Oxadiazole is a five membered furan type heterocyclic compound in which any two of four methines are replaced by the nitrogen atoms. Different position of nitrogen atoms in a ring yields four possible isomers of oxadiazole (Figure-1).

Insert figure 1 here

Among these four isomers, 1,3,4-oxadiazole is widely studied by the chemists because of its wide applicability in research[1]. A great number of pharmacological properties have been associated with this small but important nucleus such as anticancer [2], anti-HIV [3], antibacterial [4], anti-inflammatory [5], anticonvulsant [6], herbicidal [7], analgesic [8], and fungicidal [9].

Oxadiazole ring has been incorporated in drug discovery programs as an essential element of pharmacophore in contribution of ligand binding [10]. This nucleus has been revealed to function as an aromatic linker to position substituents in the right position [11]. Raltegravir® (Figure-2) which is a drug which contains oxadiazole as a core moiety had been used for treatment of HIV infection [12]. Two other drugs Zibotentan [13] (Figure-2) and Ataluren [14] (Figure-2), which have oxadiazole moiety, are in the late stages of clinical trial. Oxadiazoles have been used as bioisosteric replacements for different carbonylated compounds such as amides, carbamates, esters, and hydroxamic esters [15-17]

Insert figure 2 here

α-Glucosidase (EC 3.2.1.20) is a glycosidic hydrolase enzyme that hydrolyzes carbohydrates into glucose. α-Glucosidase, which is present in the brush border surface of intestinal cells, is essential in the release of monosaccharides from carbohydrates, as human intestine only absorbs monosacharides for blood circulation [18]. However, carbohydrate metabolism disorder results in increase of glucose level in blood. This complication gives birth to a disease called Diabetes Mellitus (DM) [19]. Diabetes Mellitus is managed by different classes of drugs [20,21] such as biguanides, sulfonylureas, thiazolidinediones, and α-glucosidase inhibitors. α-Glucosidase inhibitors work by decelerating the digestion rate in the intestine of polysaccharides into monosaccharides and thus lessen the level of glucose in blood stream [22]. These inhibitors have been comprehensively premeditated for the management of pre-diabetic conditions (impaired fasting glucose IFG and impaired glucose tolerance IGT) [23,24]. α-Glucosidase inhibitors like acarbose, voglibose, and miglitol, have been designed and instigated as drugs during last two decades [25,26]. Recently our research group has published an article revealing the α-glucosidase inhibitory potential of oxadiazoles along with thiadiazoles [27] and also benzohydrazide [28]. In continuation of exploring oxadiazoles as α-glucosidase inhibitors, we

have decided to synthesize a library of oxadiazole benzohydrazones (**6**-**28**) and evaluated these against *α*-glucosidase *in vitro*. Encouraging results were found and are discussed in forthcoming paragraphs.

2. Results and Discussion

2.1 Chemistry

The synthetic route of compounds **6**-**28** is shown in Scheme-1 and 2. Compound **2** was synthesized by treating methyl 2,4-dimethoxybenzoate with excess hydrazine hydrate. Compound **2** was reacted with methyl 4-formylbenzoate in methanol with catalytic amount of acetic acid to afford hydrazone **3**, which was then subjected through an oxidative cyclization using phenyliododiacetate ($PhI(OAc)_2$) in dry chloroform to form oxadiazole **4**. The ester functional group of compound **4** was further converted into hydrazide by treating with hydrazine hydrate to afford compound **5**.

Insert Scheme -1 here

In Scheme-2, hydrazide **5** was reacted with various benzaldehydes in the presence of acetic acid to form the targeted oxadiazole benzohydrazone derivatives **6**-**28** (Table-1). The structures of the oxadiazole benzohydrazones **6**-**28** were elucidated using spectroscopic techniques such as NMR, MS and were further confirmed using CHN analysis.

Insert Scheme 2 here

2.1. Enzyme Inhibitory Studies

Studies on structure-activity relationship (SAR) proposed that *α*-glucosidase inhibition active of oxadiazole benzohydrazones **6**-**28**, is mainly reliant upon variations in substitutions on the *N*-benzylidene part, attached to oxadiazole benzohydrazide.

Compound **18** (IC_{50} = 2.64 ± 0.05 μM) was found to be the most active compound in the library oxadiazole benzohydrazones **6**-**28**, with three-hundred folds more active than the standard drug, acarbose (IC_{50} = 856.45 ± 5.60 μM). The trihydroxy substitutions at C-2′, C-4′, and C-5′, on the *N*-benzylidene moiety, must have been in the best hydrogen bonding mode with the amino acid residue of the enzyme, *α*-glucosidase, to inhibit it. This inhibitory trend lowered to eleven-folds when the hydroxy was moved from C-5′ to C-6′, as in compound **13** (IC_{50} = 29.68 ± 0.78 μM).

Dihydroxylation at C-3′ and C-4′, as in compound **8** (IC_{50} = 28.28 ± 0.25 μM), was found to have slightly better inhibitory activity than compound **13**, that had trihydroxylation at C-2′, C-4′, and C-6′. This reveals, how fruitful is the presence of two adjacent hydroxyl groups to interact with *α*-glucosidase enzyme. Di-substitution of hydroxyl groups, *para* to each other, as in compound **9** (IC_{50} = 87.64 ± 0.90 μM) lowered its activity up to three times w.r.t. its regio-isomer **8**.

Among the monohydroxylated versions, compound having hydroxy group installed at C-2′, as in compound **23** (IC_{50} = 34.64 ± 0.35 μM), was found to be the most active. The inhibitory activity

decreased to five- and six-folds when the hydroxy group shifted from C-2′ to C-4′ and C-3′, as in compounds **6** (IC_{50} = 180.46 ± 1.65 μM) and **7** (IC_{50} = 210.24 ± 1.95 μM), respectively.

Between the hydroxylated-cum-methoxylated analogs, compound **12** (IC_{50} = 146.146 ± 1.20 μM) took a lead over compound **20** (IC_{50} = 256.16 ± 2.25 μM). The *ortho* linkage of hydroxyl and methoxy groups must have made compound **12** almost doubly active than compound **20**, which had the *para* linkage.

Chlorinated analogs (compounds **16**, **28**, and **27**) also showed potent activities but lower than their hydroxylated analogs (compounds **23**, **6**, and **7**). Chlorine at C-2′, as in compound **16** (IC_{50} = 6.14 ± 0.15 μM), was found to be quadruple active than compound **28** (IC_{50} = 24.16 ± 0.28 μM), where the chlorine group moved to C-4′. Chlorine group at C-3′, further lowered the activity to eleven-folds, as in compound **27** (IC_{50} = 68.16 ± 0.53 μM). When chlorine, of compound **16**, was replaced with fluorine, as in compound in **25** (IC_{50} = 18.46 ± 0.28 μM), a three-fold decline in activity was observed. Fluorine at C-4′, as in compound **26** (IC_{50} = 48.16 ± 0.48 μM), was found to have two-folds less activity than its chlorinated analog (compound **28**).

Entry of nitro (as in compounds **19**, **10**, and **11**) or methyl (as in compounds **14**, **15**, and **17**) groups at any postion on *N*-benzylidene motif, made the compounds entirely inactive against enzyme inhibition. This reveals the important presence of hydroxyl and halo groups to have enzyme inhibitory potential.

Induction of pyridine ring showed different activities subjected to the position of ring nitrogen. Pyridin-2′-yl derivative, as in compound **24**, had an IC_{50} value of 25.16 ± 0.25 μM. This activity was decreased to eighteen-folds, when it replaced pyridin-2′-yl with pyridin-4′-yl, as in compound **22** (IC_{50} = 460.14 ± 3.25 μM). Pyridin-3′-yl derivative (compound **21**) was found to be unsuited to interact with the enzyme as it showed no activity at all.

Insert Table 1 here

3. Experimental

3.1 General

NMR experiments had been carried out using UltraShield Bruker FT NMR 500 MHz. Electron impact mass spectra (EI-MS) were recorded on a Finnegan MAT-311A, Germany. CHN analysis was performed on a Carlo Erba Strumentazion-Mod-1106, Italy. Reaction progress was monitored using thin layer chromatography (TLC) which was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm.

Baker's Yeast α-glucosidase inhibition assay

The enzyme inhibition was evaluated according to the method previously reported by Shibano et al. [29] with minor modification. Test sample (10 µl) was premixed with 95 µl of 50 mM phosphate buffer (pH 6.8), 25 µl of α-glucosidase solution (a stock solution of 1 mg/ml in phosphate buffer, was diluted to 0.0625 U/ml with the same buffer just before the assay) and pre-incubated at 37°C for 10 min. The reaction was initiated with the addition 25 µl of 5 mM PNPG (dissolve 1.5 mg in 1 ml of phosphate buffer) and absorbance at time 0 minutes was measured. The reaction mixture was then incubated at 37°C for 30 min and absorbance at time 30 minutes was measured. For negative control, the test samples were replaced with 10 µl of DMSO and acarbose was used as positive control. The enzymatic hydrolysis of the substrate was monitored based on the amount of p-nitrophenol released in the reaction mixture by observation at 405 nm using a microplate reader. All experiments were carried out in triplicate and the results are expressed as the mean ± S.D. of three determinations.

The percentage (%) inhibition of α-glucosidase inhibitory activity was calculated using the equation:

$$\% \text{ Inhibition} = \frac{(A^{30 \text{ minutes}} - A^{0 \text{ minute}})^{\text{control}} - (A^{30 \text{ minutes}} - A^{0 \text{ minute}})^{\text{experiment}}}{(A^{30 \text{ minutes}} - A^{0 \text{ minute}})^{\text{control}}} \times 100\ \%$$

3.2 Synthesis of 2,4-dimethoxybenzohydrazide (2)

Methyl 2-hydroxybenzoate (**1**) (7.60 g, 53 mmol) and 20 ml of hydrazine hydrate were mixed in methanol (50 mL). The mixture was refluxed for 6 hours. Methanol was then evaporated and the product formed was being rinsed with plenty of water to remove excess hydrazine hydrate. The product formed was left to dry at room temperature and yielded 7.21 g (94.9 %). White solid, m.p. 149 °C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta\delta$3.88 (s, 3H), 3.93 (s, 3H), 4.05 (s, 2H), 6.79 (dd, 1H, J = 2.0 Hz, 9.0 Hz), 6.84 (d, 1H, J = 2.0 Hz), 7.76 (d, 1H, J = 9.0 Hz); 9.40(s, 3H); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 165.17, 162.68, 159.84, 130.03, 117.10, 107.45, 99.78, 56.78, 56.03; Anal. Calcd for C9H12N2O3, C = 55.09; H = 6.16; N = 14.28, found C = 55.08; H = 6.17; N = 14.30; EI MS *m/z* (% rel. abund.): 196.22 (M+, 64)

3.4. Synthesis of (*E*)-methyl 4-((2-(2,4-dimethoxybenzoyl)hydrazono)methyl)benzoate (3)

A mixture of compound **2** (7.00 g, 46 mmol), methyl 4-formylbenzoate (7.56 g, 46 mmol) and catalytic amount of acetic acid in methanol (50 mL) was refluxed for 3 hours. The solvent was evaporated and the residue (**3**) was washed with diethyl ether, filtered, dried, and then crystallized from ethanol and gives white solid, (12.8 g, 93%). m.p. 275 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ3.91 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 6.77 (dd, 1H, J = 2.0 Hz, 9.0 Hz), 6.84 (d, 1H, J = 2.0 Hz), 7.76 (d, H, J = 9.0 Hz); 8.11 (d, H, J = 8.5 Hz), 8.18 (d, 2H, J = 8.0 Hz) 8.31 (s, 1H), 9.50 (s,1H); ^{13}C-NMR (150 MHz,

DMSO-d6,): δ 167.85, 163.23, 160.73, 160.38, 149.73, 137.52, 134.59, 131.21, 128.34, 128.34, 127.62, 127.62, 116.85, 106.72, 100.62, 56.28, 56.56, 52.38; Anal. Calcd for C18H18N2O5, C = 63.15; H = 5.30; N = 8.18, found C = 63.14; H = 5.31; N = 8.20; EI MS m/z (% rel. abund.): 342.18 (M+, 61)

3.5 Synthesis of methyl 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)benzoate (4)

A mixture of compound **3** (11.0 g, 37 mmol) and equivalent amount of $PhI(OAc)_2$ was stirred in dichloromethane (100 ml) at room temperature overnight. The solvent was evaporated and the residue (**4**) was washed with diethyl ether, filtered, dried, and then crystallized from ethanol to gives white solid, (9.8 g, 89 %). m.p. 274 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.90 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 6.79 (dd, 1H, J = 2.5 Hz, 9.0 Hz), 6.84 (d, 1H, J = 2.0 Hz), 7.75 (d, H, J = 9.0 Hz); 8.12 (d, 2H, J = 8.5 Hz), 8.20 (d, 2H, J = 8.0 Hz); ^{13}C-NMR (150 MHz, DMSO-d6,): δ 167.74, 165.58, 161.41, 159.80, 156.31, 130.14, 129.74, 129.74, 129.24, 128.46, 125.42, 125.42, 116.67, 107.91, 101.55, 56.73, 56.43, 52.25; Anal. Calcd for C18H16N2O5, C = 63.52; H = 4.74; N = 8.23, found C = 63.54; H = 4.71; N = 8.24; EI MS *m/z* (% rel. abund.): 340.28 (M+, 74)

3.6 Synthesis of 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)benzohydrazide (5)

Compound **4** (9.00 g, 30 mmol) and 15 ml of hydrazine hydrate were mixed in methanol (50 mL). The mixture was refluxed for 6 hours. Methanol was then evaporated and the product formed was being rinsed with plenty of water to remove excess hydrazine hydrate. The product formed (**5**) was left to dry at room temperature and yielded 8.50 g (94 %). m.p. 291 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.90 (s, 3H), 3.93 (s, 3H), 4.08 (s, 2H), 6.76 (dd, 1H, J = 2.0 Hz, 9.0 Hz), 6.85 (d, 1H, J = 2.0 Hz), 7.75 (d, H, J = 9.0 Hz); 8.12 (d, H, J = 8.5 Hz), 8.19 (d, 2H, J = 8.0 Hz) 9.70 (s,1H); ^{13}C-NMR (150 MHz, DMSO-d6,): δ 167.62, 165.37, 161.48, 159.37, 156.64, 132.58, 132.26, 130.76, 127.23, 127.23, 126.45, 126.45, 116.18, 107.36, 101.47, 56.89, 56.13; Anal. Calcd for $C_{17}H_{16}N_4O_4$, C = 59.99, H = 4.74, N = 16.46, found C = 60.01, H = 4.75, N = 16.44; EI MS *m/z* (% rel. abund.): 340.12 9 (M+, 56)

3.6.1. General procedure for synthesis of oxadiazole benzohydrazones (6-28)

Equimolar quantities (1 mmol) of compound **5** and substituted benzaldehydes (1 mmol) in methanol (25 mL) were refluxed for 3 h, in the presence of catalytic amount of glacial acetic acid. The resulting solid was filtered and recrystallized from methanol in good yields.

3.6.1.1 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)- *N'*-(4-hydroxybenzylidene)benzohydrazide

Pale Yellow Solid; Yield: 60.5% ; M.p 140-142 °C; R_f = 0.25 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.89 (s, 3H), 3.96 (s, 3H), 6.77 (dd, 1H, *J* = 2.5 Hz, 9.0 Hz), 6.81 (d, 1H, *J* = 2.0 Hz), 6.85 (d, 2H, *J* = 8.0 Hz), 7.58 (d, 2H, *J* = 8.5 Hz), 6.77 (d, 1H, *J* = 8.5 Hz), 8.11 (d, 2H, *J* = 8.5 Hz), 8.19 (d, 2H, *J* = 8.0 Hz), 8.38 (s, 1H), 11.86 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.17, 164.35, 161.13, 159.40, 158.12, 156.74, 156.23, 133.52, 132.12, 130.51, 129.42, 129.42, 128.42, 128.42, 126.94, 126.94, 126.72, 116.11, 115.31, 115.31, 107.86, 101.25, 56.64, 56.15; IR (KBr, cm^{-1}): 3213 (N-H), 1658 (C = N), 1216 (C-O); Anal. Calcd for $C_{24}H_{20}N_4O_4$, C = 67.28; H = 4.71; N = 13.08, found C = 67.29; H = 4.73; N = 13.10; EI MS *m/z* (% rel. abund.): 444.21 (M+, 56)

3.6.1.2 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)- *N'*-(3-hydroxybenzylidene)benzohydrazide

White Solid; Yield: 33.3% ; M.p 238-240 °C; R_f = 0.35 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.89 (s, 3H), 3.95 (s, 3H), 6.75 (dd, 1H, *J* = 2.5 Hz, 8.5 Hz), 6.81 (s, 1H), 6.85 (d, 1H, *J* = 6.5 Hz), 7.13 (d, 1H, *J* = 7.5 Hz), 7.23 (s, 1H), 7.28 (t, 1H, *J* = 7.5 Hz), 7.98 (d, 1H, *J* = 8.5 Hz), 8.13 (d, 2H, *J* = 8.5 Hz), 8.21 (d, 2H, *J* = 8.5 Hz), 8.40 (s, 1H), 12.00 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.17, 164.39, 161.44, 159.75, 156.71, 156.34, 154.18, 137.33, 133.72, 132.49, 130.49, 130.66, 128.18, 128.18, 126.39, 126.39, 120.72, 119.68, 116.41, 114.53, 107.31, 101.38, 56.51, 56.14; IR (KBr, cm^{-1}): 3411 (N-H), 1658 (C = N), 1217 (C-O); Anal. Calcd for $C_{24}H_{20}N_4O_4$, C = 67.28; H = 4.71; N = 13.08, found C = 67.30; H = 4.69; N = 13.06; EI MS *m/z* (% rel. abund.): 444.38 (M+, 62)

3.6.1.3 *N'*-(3,4-dihydroxybenzylidene)-4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)benzohydrazide (3)

Yellow Solid; Yield: 67.3%; M.p 160-162 °C; R_f = 0.44 (Ethyl Acetate : Methanol, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.89 (s, 3H), 3.96 (s, 3H), 6.77 (dd, 1H, *J* = 2.0 Hz, 8.0 Hz), 6.79 (s, 1H), 6.81 (d, 1H, *J* = 2.0 Hz), 6.95 (dd, 1H, *J* = 2 Hz), 7.22 (d, 1H, *J* = 1.5 Hz), 7.94 (d, 1H, *J* = 9.0 Hz), 8.11 (d, 2H, *J* = 8.5 Hz), 8.19 (d, 2H, *J* = 8.5 Hz), 8.29 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.51, 164.12, 161.47, 159.41, 156.69, 154.25, 148.14, 145.36, 133.74, 132.35, 130.46, 128.47, 128.47,

127.79 126.41, 126.41, 121.13, 116.83, 116.07, 115.62, 107.73, 101.61, 56.58, 56.21; IR (KBr, cm^{-1}): 3409 (N-H), 1654 (C = N), 1214 (C-O); Anal. Calcd for $C_{24}H_{20}N_4O_6$, C = 62.60; H = 4.38; N = 12.17, found C = 62.61; H = 4.39; N = 12.15; EI MS *m/z* (% rel. abund.): 460.13 (M+, 73)

***N'*-(2,5-dihydroxybenzylidene)-4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)benzohydrazide (4)**

Yellow Solid; Yield: 67.3%; M.p 160-162 °C; R_f = 0.44 (Ethyl Acetate : Methanol, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.85 (s, 3H), 3.88 (s, 3H), 6.76-6.84 (m, 4H), 6.86 (d, 1H, *J* = 2.0 Hz), 6.92 (d, 1H, *J* = 3.0 Hz), 7.92 (dd, 1H, *J* = 8.5 Hz), 8.15 (d, 2H, *J* = 8.0 Hz), 8.20 (d, 2H, *J* = 8.0 Hz), 8.61 (s, 1H), 10.40 (s, 1H), 12.05 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.62, 164.26, 161.70, 159.24, 156.14, 154.80, 148.39, 145.24, 133.38, 132.62, 130.94, 128.57, 128.57, 127.72, 126.67, 126.67, 121.56, 116.84, 116.03, 115.51, 107.82, 101.48, 56.38, 56.12; IR (KBr, cm^{-1}): 3413 (N-H), 1656 (C = N), 1217 (C-O); Anal. Calcd for $C_{24}H_{20}N_4O_6$, C = 62.60; H = 4.38; N = 12.17, found C = 62.62; H = 4.36; N = 12.15; EI MS *m/z* (% rel. abund.): 460.37 (M+, 68)

3.6.1.5 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)- *N'*-(4-nitrobenzylidene)benzohydrazide (9)

Pale Yellow Solid; Yield: 70.9%; M.p 247-249 °C; R_f = 0.41 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.89 (s, 3H), 3.96 (s, 3H), 6.75 (dd, 1H, *J* = 2.0 Hz, 8.5 Hz), 6.81 (d, 1H, *J* = 2.5 Hz), 7.49 (d, 1H, *J* = 8.5 Hz), 8.02 (d, 2H, *J* = 6.5 Hz), 8.12 (d, 2H, *J* = 8.5 Hz), 8.22 (d, 2H, *J* = 8 Hz), 8.31 (d, 2H, *J* = 8.5 Hz), 8.59 (s, 1H), 10.02 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.64, 164.81, 161.41, 159.71, 156.91, 156.17, 148.56, 139.74, 133.87, 132.46, 130.73, 128.52, 128.52, 127.95, 127.95, 126.46, 126.46, 124.72, 124.72, 116.15, 107.46, 101.28, 56.38, 56.05; IR (KBr, cm^{-1}): 3399 (N-H), 1676 (C = N), 1216 (C-O); Anal. Calcd for $C_{24}H_{19}N_5O_6$, C = 60.89; H = 4.05; N = 14.79, found C = 60.87; H = 4.06; N = 14.78; EI MS *m/z* (% rel. abund.): 473.36 (M+, 49)

3.6.1.6 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)- *N'*-(3-nitrobenzylidene)benzohydrazide (10)

White Solid; Yield: 59.2% ; M.p 253-255 °C; R_f = 0.39 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.89 (s, 3H), 3.96 (s, 3H), 6.75 (dd, 1H, *J* = 2.5 Hz, 9.0 Hz), 6.80 (d, 1H, *J* = 2.5 Hz), 6.81 (d, 1H, *J* = 2.0 Hz), 7.78 (t, 1H, *J* = 8.0 Hz), 7.94 (d, 1H, *J* = 8.5 Hz), 8.15-8.24 (m, 5H), 8.28 (d, 1H, *J* = 8.5 Hz), 8.59 (s, 1H), 8.61 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.72, 164.52, 161.69, 159.82, 156.32, 154.23, 147.25, 137.74, 133.25, 132.85, 132.09, 130.62, 129.39, 128.66, 128.66, 128.14, 126.77, 126.77, 126.47, 124.72, 122.47, 116.26, 107.17, 101.37, 56.84, 56.13; IR

(KBr, cm^{-1}): 3290 (N-H), 1675 (C = N), 1209 (C-O); Anal. Calcd for $C_{24}H_{19}N_5O_6$, C = 60.89; H = 4.05; N = 14.79, found C = 60.88; H = 4.04; N = 14.81; EI MS *m/z* (% rel. abund.): 473.44 (M+, 62)

3.6.1.4 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)- *N'*-(3-hydroxy-4-methylbenzylidene)benzohydrazide

White Solid; Yield: 70.1%; M.p 251-253 °C; R_f = 0.35 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.82 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 6.75 (dd, 1H, *J* = 2.0 Hz, 8.5 Hz), 6.80 (d, 1H, *J* = 2.0 Hz), 7.00 (t, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 2.0 Hz), 7.96 (d, 1H, *J* = 8.5 Hz), 8.11 (d, 2H, *J* = 8.5 Hz), 8.19 (d, 2H, *J* = 8.0 Hz), 8.33 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.17, 164.61, 161.14, 159.48, 156.36, 155.27, 154.68, 133.79, 133.09, 132.71, 132.03, 130.82, 128.61, 128.61, 128.29, 126.89, 126.89, 119.83, 117.51, 116.63, 107.83, 101.24, 56.51, 56.07, 15.86; IR (KBr, cm^{-1}): 3192 (N-H), 1652 (C = N), 1217 (C-O); Anal. Calcd for $C_{25}H_{22}N_4O_5$, C = 65.49; H = 4.84; N = 12.22, found C = 65.47; H = 4.85; N = 12.21; EI MS *m/z* (% rel. abund.): 458.27 (M+, 36)

3.6.1.7 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)- *N'*-(2,4,6-trihydroxybenzylidene)benzohydrazide

Brown Solid; Yield: 73.4% ; M.p 202-204 °C; R_f = 0.36 (Ethyl Acetate : Methanol, 95 : 5); ^{1}H NMR (500 MHz, DMSO-d_6): 3.89 (s, 3H), 3.96 (s, 3H), 5.87 (s, 2H), 6.75 (dd, 1H, *J* = 2.5 Hz, 9.0 Hz), 6.80 (d, 1H, *J* = 2.5 Hz), 7.95 (d, 1H, *J* = 8.5 Hz), 8.13 (d, 2H, *J* = 8.5 Hz), 8.20 (d, 2H, *J* = 8.0 Hz), 8.84 (s, 1H), 9.89 (s, 1H), 11.12 (s, 2H), 12.08 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.37, 164.82, 163.52, 161.68, 161.68, 161.33, 159.50, 156.24, 149.81, 133.61, 132.61, 130.83, 128.38, 128.38, 126.89, 126.89, 116.57, 107.48, 106.71, 101.41, 95.82, 95.82, 56.48, 56.21; IR (KBr, cm^{-1}): 3214 (N-H), 1652 (C = N), 1214 (C-O); Anal. Calcd for $C_{24}H_{20}N_4O_7$, C = 60.50; H = 4.23; N = 11.76, found C = 60.48; H = 4.24; N = 11.74; EI MS *m/z* (% rel. abund.): 476.44 (M+, 81)

3.6.1.8 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)- *N'*-(2-methylbenzylidene)benzohydrazide

White Solid; Yield: 61.5% ; M.p 179-181 °C; R_f = 0.56 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 2.48 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 6.76 (dd, 1H, *J* = 2.0 Hz, 8.5 Hz), 6.81 (s, 1H), 7.28-7.35 (m, 3H), 7.87 (d, 1H, *J* = 7.0 Hz), 7.95 (d, 1H, *J* = 8.5 Hz), 8.15 (d, 2H, *J* = 8.0 Hz), 8.28 (d, 2H, *J* = 8.0 Hz), 8.79 (s, 1H), 12.01 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.67, 164.51, 161.74, 159.82, 156.51, 151.38, 136.94, 133.16, 133.58, 132.30, 130.27, 130.15, 128.49, 128.49, 128.16, 126.69, 126.69, 126.19, 125.69, 116.67, 107.36, 101.75, 56.86, 56.03, 18.05; IR (KBr,

cm^{-1}): 3235 (N-H), 1651 (C = N), 1213 (C-O); Anal. Calcd for $C_{25}H_{22}N_4O_4$, C = 67.86; H = 5.01; N = 12.66, found C = 67.84; H = 5.03; N = 12.64; EI MS *m/z* (% rel. abund.): 442.47 (M+, 63)

3.6.1.9 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)- *N'*-(3-methylbenzylidene)benzohydrazide

White Solid; Yield: 69.2% ; M.p 179-181 °C; R_f = 0.56 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 2.38 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 6.76 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz), 6.81 (d, 1H, *J* = 2 Hz), 7.27 (d, 1H, *J* = 7.5 Hz), 7.37 (t, 1H, *J* = 7.5 Hz), 7.54 (d, 1H, *J* = 7.5 Hz), 7.59 (s, 1H), 7.95 (d, 1H, *J* = 8.5 Hz), 8.14 (d, 2H, *J* = 8.5 Hz), 8.21 (d, 2H, *J* = 8.0 Hz), 8.46 (s, 1H), 12.02 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.41 7, 164.85, 161.52, 159.72, 156.83, 151.62, 136.95, 133.13, 133.78, 132.20, 130.58, 130.03, 128.43, 128.43, 128.16, 126.62, 126.62, 126.31, 125.52, 116.64, 107.37, 101.82, 56.66, 56.23, 18.35; IR (KBr, cm^{-1}): 3421 (N-H), 1658 (C = N), 1222 (C-O); Anal. Calcd for $C_{25}H_{22}N_4O_4$, C = 67.86; H = 5.01; N = 12.66, found C = 67.84; H = 4.99; N = 12.68; EI MS *m/z* (% rel. abund.): 442.47 (M+, 47)

3.6.1.10 *N'*-(2-chlorobenzylidene)-4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)benzohydrazide

White Solid; Yield: 44.1% ; M.p 179-181 °C; R_f = 0.68 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.90 (s, 3H), 3.97 (s, 3H), 6.76 (dd, 1H, *J* = 2.5 Hz, *J* = 8.5 Hz), 6.81 (d, 1H, *J* = 2.5 Hz), 7.46 (d, 2H, *J* = 7.0 Hz), 7.55 (d, 1H, *J* = 7.0 Hz), 7.95 (d, 1H, *J* = 9.0 Hz), 8.06 (d, 1H, *J* = 7.0 Hz), 8.16 (d, 2H, *J* = 8.5 Hz), 8.22 (d, 2H, *J* = 8.5 Hz), 8.91 (s, 1H), 12.26 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.67, 164.22, 161.61, 159.80, 156.34, 155.67, 133.21, 132.89, 132.19, 131.37, 130.93, 130.66, 128.87, 128.28, 127.53, 127.26, 126.29, 116.57, 107.76, 101.25, 56.48, 56.13; IR (KBr, cm^{-1}): 3429 (N-H), 1658 (C = N), 1215 (C-O); Anal. Calcd for $C_{24}H_{19}ClN_4O_4$, C = 62.27; H = 4.14; N = 12.10, found C = 62.25; H = 4.12; N = 12.08; EI MS *m/z* (% rel. abund.): 462.89 (M+, 68.3), 464.33 (M+2, 18.9)

3.6.1.11 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N'*-(4-methylbenzylidene)benzohydrazide

White Solid; Yield: 62.6% ; M.p 119-121 °C; R_f = 0.58 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 2.38 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 6.76 (dd, 1H, *J* = 2.5 Hz, *J* = 8.5 Hz), 6.82 (d, 1H, *J* = 2.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 7.65 (d, 2H, *J* = 7.5 Hz), 7.95 (d, 1H, *J* = 8.0 Hz), 8.13 (d, 2H, *J* = 8.0 Hz), 8.21 (d, 2H, *J* = 8.5 Hz), 8.47 (s, 1H), 11.97 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.87, 164.23, 161.75, 159.63, 156.96, 156.38, 138.83, 133.64, 132.26, 131.24, 130.58, 129.68, 129.68, 128.58, 128.58, 127.75, 127.75, 126.49, 126.49, 116.17, 107.56, 101.55, 56.38, 56.13,

19.52; IR (KBr, cm^{-1}): 3233 (N-H), 1660 (C = N), 1222 (C-O); Anal. Calcd for $C_{25}H_{22}N_4O_4$, C = 67.86; H = 5.01; N = 12.66, found C = 67.88; H = 5.02; N = 12.67; EI MS *m/z* (% rel. abund.): 442.19 (M+, 51)

3.6.1.12 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N'*-(2,4,5-trihydroxybenzylidene)benzohydrazide

Brown Solid; Yield: 88.8% ; M.p 282-284 °C; R_f = 0.68 (Ethyl Acetate : Methanol, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.90 (s, 3H), 3.97 (s, 3H), 6.35 (d, 1H, *J* = 4.5 Hz), 6.75 (dd, 1H, *J* = 2.0 Hz, *J* = 8.5 Hz), 6.82 (d, 1H, *J* = 2 Hz), 6.93 (d, 1H, *J* = 8 Hz), 7.95 (d, 1H, *J* = 8.5 Hz), 8.13 (d, 2H, *J* = 8.5 Hz), 8.20 (d, 2H, *J* = 8.5 Hz), 8.51 (s, 1H), 8.57 (s, 1H), 9.57 (s, 1H), 10.54 (s, 1H), 11.98 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.71, 164.52, 161.45, 159.72 156.67, 155.22, 153.45, 150.63, 140.81, 133.31, 132.19, 130.53, 128.41, 128.41, 126.42, 126.42, 117.29, 116.47, 112.71, 107.91, 102.70, 101.35, 56.73, 56.13; IR (KBr, cm^{-1}): 3219 (N-H), 1635(C = N), 1205 (C-O); Anal. Calcd for $C_{24}H_{20}N_4O_7$, C = 60.50; H = 4.23; N = 11.76, found C = 60.51; H = 4.25; N = 11.77; EI MS *m/z* (% rel. abund.): 476.26 (M+, 29)

3.6.1.17 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N'*-(2-nitrobenzylidene)benzohydrazide

Yellow Solid; Yield: 57.8% ; M.p 243-245 °C; R_f = 0.50 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.90 (s, 3H), 3.97 (s, 3H), 6.76 (dd, 1H, *J* = 2.0 Hz, 9.0 Hz), 6.81 (d, 1H, *J* = 2.0 Hz), 7.71 (s, 1H), 7.85 (s, 1H), 7.95 (d, 1H, *J* = 8.5 Hz), 8.10-8.23 (m, 6H), 8.92 (s, 1H), 12.38 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.37, 164.37, 161.63, 159.50, 156.69, 147.86, 147.11, 133.85, 133.21, 132.06, 130.86, 130.27, 129.35, 128.58, 128.58, 128.10, 126.83, 126.83, 125.73, 116.47, 107.56, 101.75, 56.58, 56.27; IR (KBr, cm^{-1}): 3290 (N-H), 1675 (C = N), 1209 (C-O); Anal. Calcd for $C_{24}H_{19}N_5O_6$, C = 60.89; H = 4.05; N = 14.79, found C = 60.90; H = 4.07; N = 14.80; EI MS *m/z* (% rel. abund.): 473.41 (M+, 31)

3.6.1.15 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N'*-(2-hydroxy-5-methoxybenzylidene)benzohydrazide

Yellow Solid; Yield: 62.4% ; M.p 251-253 °C; R_f = 0.35 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.75 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 6.76 (dd, 1H, *J* = 2.0 Hz, 8.5 Hz), 6.83 (d, 1H, *J* = 2.0 Hz), 6.88 (d, 1H, *J* = 9.0 Hz), 6.93 (d, 1H, *J* = 8.5 Hz), 7.17 (d, 1H, *J* = 3.0 Hz), 7.95 (d, 1H, *J* = 8.5 Hz), 8.16 (d, 2H, *J* = 8.0 Hz), 8.22 (d, 2H, *J* = 8.0 Hz), 8.68 (s, 1H), 10.62 (s, 1H), 12.25 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.67, 164.71, 161.46, 159.74, 156.42, 155.75, 154.35, 154.15, 133.61, 132.29, 130.76, 128.18, 128.18, 126.49, 126.49, 121.19, 116.53, 116.38, 116.07, 112.62, 107.14, 101.28, 56.38, 56.28; IR (KBr, cm^{-1}): 3192 (N-H), 1652 (C = N), 1217 (C-O);

Anal. Calcd for $C_{25}H_{22}N_4O_6$, C = 63.29; H = 4.67; N = 11.81, found C = 63.31; H = 4.68; N = 11.82; EI MS *m/z* (% rel. abund.): 474.37 (M+, 63)

3.6.1.16 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N'*-(pyridin-3-ylmethylene)benzohydrazide

Dark Green Solid; Yield: 70.9% ; M.p 220-222 °C; R_f = 0.44 (Ethyl Acetate : Methanol, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.901 (s, 3H), 3.971 (s, 3H), 6.76 (dd, 1H, *J* = 2.0 Hz, 8.5 Hz), 6.81 (d, 1H, *J* = 2 Hz), 7.52 (t, 1H, *J* = 7.5 Hz), 7.95 (d, 1H, *J* = 8.5 Hz), 8.14-8.23 (m, 5H), 8.56 (s, 1H), 8.64 (d, 1H, *J* = 3.5 Hz), 8.90 (s, 1H), 12.20 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.67, 164.39, 161.45, 159.60, 156.54, 154.86, 149.65, 146.39, 135.61, 133.74, 133.45, 132.39, 130.29, 128.48, 128.48, 126.69, 126.69, 124.71, 116.19, 107.96, 101.73, 56.48, 56.13; IR (KBr, cm^{-1}): 3412 (N-H), 1653 (C = N), 1215 (C-O); Anal. Calcd for $C_{23}H_{19}N_5O_4$, C = 64.33; H = 4.46; N = 16.31, found C = 64.32; H = 4.44; N = 16.30; EI MS *m/z* (% rel. abund.): 429.25 (M+, 73)

3.6.1.14 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N'*-(pyridin-4-ylmethylene)benzohydrazide

Brick Red Solid; Yield: 67.5% ; M.p 231-232 °C; R_f = 0.51 (Ethyl Acetate : Methanol, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.89 (s, 3H), 3.96 (s, 3H), 6.77 (dd, 1H, *J* = 2.5 Hz, 8.5 Hz), 6.81 (d, 1H, J = 2.0 Hz), 7.72 (d, 2H, J = 8.0 Hz), 7.95 (d, 1H, *J* = 8.5 Hz), 8.15 (d, 2H, *J* = 7.5 Hz), 8.23 (d, 2H, *J* = 8.0 Hz), 8.49 (s, 1H), 8.69 (s, 2H), 12.32 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.43, 164.22, 161.73, 159.30, 156.64, 156.22, 150.29, 150.29, 140.31, 133.15, 132.03, 130.36, 128.39, 128.39, 126.59, 126.59, 122.25, 122.25, 116.15, 107.56, 101.35, 56.78, 56.23; IR (KBr, cm^{-1}): 3400 (N-H), 1669 (C = N), 1220 (C-O); Anal. Calcd for $C_{23}H_{19}N_5O_4$, C = 64.33; H = 4.46; N = 16.31, found C = 64.34; H = 4.47; N = 16.32; EI MS *m/z* (% rel. abund.): 429.42 (M+, 36)

3.6.1.18 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N'*-(2-hydroxybenzylidene)benzohydrazide

Brownish yellow solid; Yield: 69.1% ; M.p 218-220 °C; R_f = 0.40 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.90 (s, 3H), 3.971 (s, 3H), 6.783 (dd, 1H, *J* = 2.5 Hz, 8.5 Hz), 6.950 (t, 2H, *J* = 8 Hz), 7.32 (s, 1H), 7.58 (d, 1H, *J* = 7.0 Hz), 8.16 (d, 2H, *J* = 8.5 Hz), 8.22 (d, 2H, *J* = 8.5 Hz), 8.70 (1H, s), 11.21 (s, 1H), 12.28 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.73, 164.52, 161.47, 159.50, 158.72, 157.27, 156.84, 133.21, 132.39, 130.76, 129.35, 128.54, 128.54, 128.28,

126.59, 126.59, 121.13, 120.32, 117.57, 116.44, 107.33, 101.65, 56.38, 56.13; IR (KBr, cm^{-1}): 3218 (N-H), 1652 (C = N), 1218 (C-O); Anal. Calcd for $C_{24}H_{20}N_4O_4$, C = 67.28; H = 4.71; N = 13.08, found C = 67.26; H = 4.70; N = 13.07; EI MS *m/z* (% rel. abund.): 444.16 (M+, 68)

3.6.1.19 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N*'-(pyridin-2-ylmethylene)benzohydrazide

Dark Green Solid; Yield: 75.9% ; M.p 120-122 °C; R_f = 0.65 (Ethyl Acetate : Methanol, 95 : 5); ^{1}H NMR (500 MHz, DMSO-d_6): 3.90 (s, 3H), 3.97 (s, 3H), 6.76 (dd, 1H, *J* = 2.5 Hz, 8.5 Hz), 6.81 (d, 1H, *J* = 2.0Hz), 7.45 (t, 1H, *J* = 6.0 Hz), 7.91 (t, 1H, *J* = 7.5 Hz), 7.95 (d, 1H, *J* = 7.5 Hz), 8.01 (d, 1H, *J* = 8.0 Hz), 8.15 (d, 2H, *J* = 8.0 Hz), 8.22 (d, 2H, *J* = 8.0 Hz), 8.52 (s, 1H), 8.64 (d, 1H, *J* = 3.5 Hz), 12.23 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.62, 164.34, 161.48, 159.63, 156.51, 154.83, 149.61, 146.35, 135.67, 133.72, 133.35, 132.31, 130.24, 128.58, 128.58, 126.63, 126.63, 124.61, 116.23, 107.83, 101.63, 56.78, 56.33; IR (KBr, cm^{-1}): 3468 (N-H), 1659 (C = N), 1217 (C-O); Anal. Calcd for $C_{23}H_{19}N_5O_4$, C = 64.33; H = 4.46; N = 16.31, found C = 64.35; H = 4.48; N = 16.29; EI MS *m/z* (% rel. abund.): 429.49 (M+, 72.6)

3.6.1.20 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N*'-(2-fluorobenzylidene)benzohydrazide

Brownish Solid; Yield: 54.6% ; M.p 208-210 °C; R_f = 0.57 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.90 (s, 3H), 3.97 (s, 3H), 6.76 (dd, 1H, *J* = 2.0 Hz, 9.0 Hz), 6.81 (d, 1H, *J* = 2.0 Hz), 7.31 (s, 1H), 7.59-7.62 (m, 3H), 7.95 (d, 1H, *J* = 8.5 Hz), 8.14 (d, 2H, *J* = 8.0 Hz), 8.21 (d, 2H, *J* = 8.5 Hz), 8.51 (s, 1H), 12.16 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.67, 164.52, 161.64, 159.68, 159.32, 156.67, 154.62, 154.53, 133.45, 132.23, 130.72, 130.45, 130.16, 129.47, 129.14, 128.43, 128.43, 126.72, 126.72, 125.55, 125.28 124.73, 124.24, 117.44, 117.25, 116.12, 107.76, 101.28, 56.73, 56.13; IR (KBr, cm^{-1}): 3401 (N-H), 1657 (C = N), 1214 (C-O); Anal. Calcd for $C_{24}H_{19}FN_4O_4$, C = 64.57; H = 4.29; N = 12.55, found C = 64.58; H = 4.31; N = 12.56; EI MS *m/z* (% rel. abund.): 446.43 (M+, 48.5)

3.6.1.13 *N*'-(4-chlorobenzylidene)-4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)benzohydrazide

White Solid; Yield: 66.2% ; M.p 179-181 °C; R_f = 0.56 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.90 (s, 3H), 3.96 (s, 3H), 6.75 (dd, 1H, *J* = 2.5 Hz, *J* = 8.0 Hz), 6.81 (d, 1H, *J* = 2.0 Hz), 7.54 (d, 2H, *J* = 8.5 Hz), 7.78 (d, 2H, *J* = 8.5 Hz), 7.95 (d, 1H, *J* = 8.5 Hz), 8.14 (d, 2H, *J* = 8.0 Hz), 8.22 (d, 2H, *J* = 8.0 Hz), 8.49 (s, 1H), 12.11 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.77, 164.36, 161.47, 159.74, 156.54, 156.15, 135.18, 134.30, 133.61, 132.06, 130.36, 129.72,

129.72, 129.26, 129.26, 128.28, 128.28, 126.86, 126.86, 116.27, 107.76, 101.28, 56.58, 56.23; IR (KBr, cm^{-1}): 3400 (N-H), 1665 (C = N), 1220 (C-O); Anal. Calcd for $C_{24}H_{19}ClN_4O_4$, C = 62.27; H = 4.14; N = 12.10, found C = 62.29; H = 4.13; N = 12.09; EI MS *m/z* (% rel. abund.): 462.89 (M+, 52.7), 464.89 (M+2, 15.6)

3.6.1.21 4-(5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-*N'*-(2-methoxybenzylidene)benzohydrazide

Brownish Solid; Yield: 54.5% ; M.p 107-109 °C; R_f = 0.48 (Ethyl Acetate : Hexane, 90 : 10); ^{1}H NMR (500 MHz, DMSO-d_6): 3.83 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 6.76 (dd, 1H, *J* = 2.5 Hz, 8.5 Hz), 6.81 (d, 1H, *J* = 2.0 Hz), 7.54 (d, 2H, *J* = 8.5 Hz), 7.79 (d, 2H, *J* = 8.0 Hz), 7.95 (d, 1H, *J* = 8.0 Hz), 8.13 (d, 2H, *J* = 8.0 Hz), 8.21 (d, 2H, *J* = 8.0 Hz), 8.50 (s, 1H), 12.11 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.57, 164.42, 161.41, 159.79, 159.67, 156.69, 156.27, 133.44, 132.39, 130.57, 128.58, 128.58, 128.23, 127.85, 126.69, 126.69, 125.41, 121.58, 116.27, 113.79, 107.96, 101.15, 56.58, 56.18 (s).IR (KBr, cm^{-1}): 3411 (N-H), 1660 (C = N), 1215 (C-O); Anal. Calcd for $C_{25}H_{22}N_4O_5$, C = 65.49; H = 4.84; N = 12.22, found C = 65.51; H = 4.86; N = 12.23; EI MS *m/z* (% rel. abund.): 458.47 (M+, 71)

Acknowledgements

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Figure caption

Figure-1: Four Possible Isomers of Oxadiazole

Figure-2: Drugs containing oxadiazole skeleton

Scheme-1 Synthesis of oxadiazoles hydrazide (**5**) through four steps

Scheme-2 Synthesis of oxadiazoles derivatives (**6-28**)

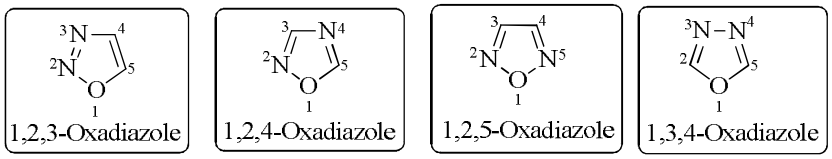


Figure-1: Four Possible Isomers of Oxadiazole

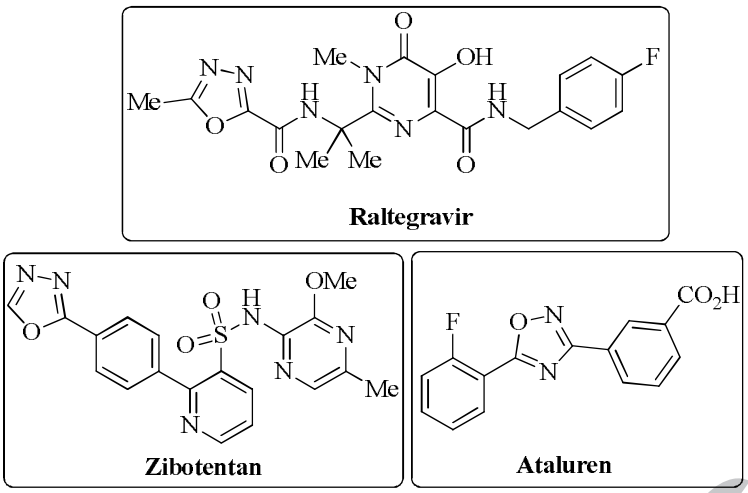
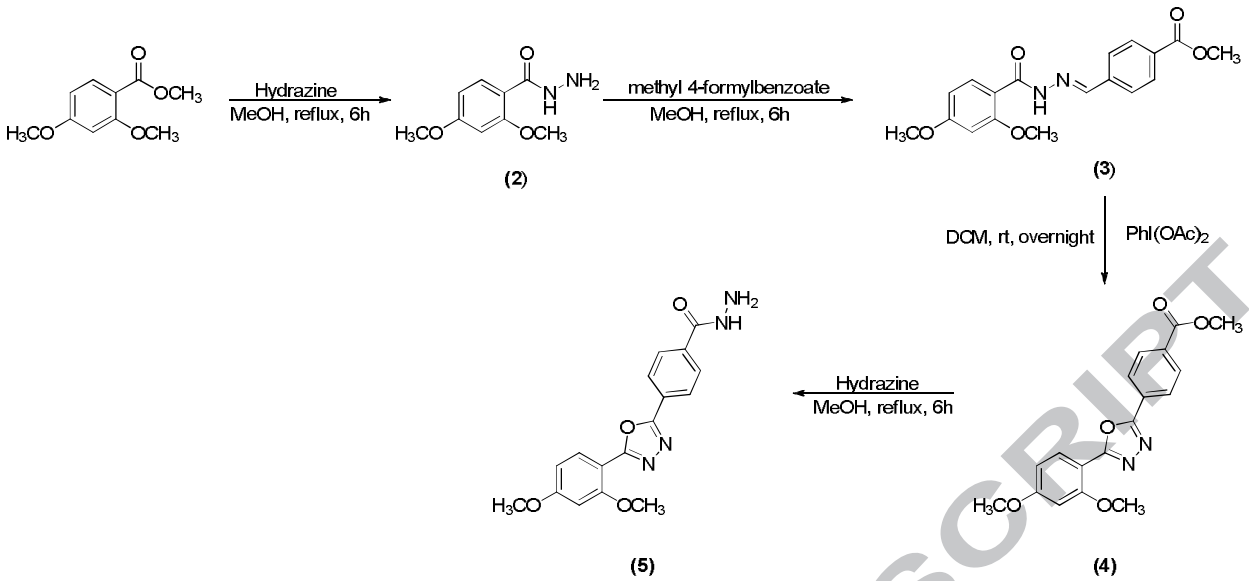
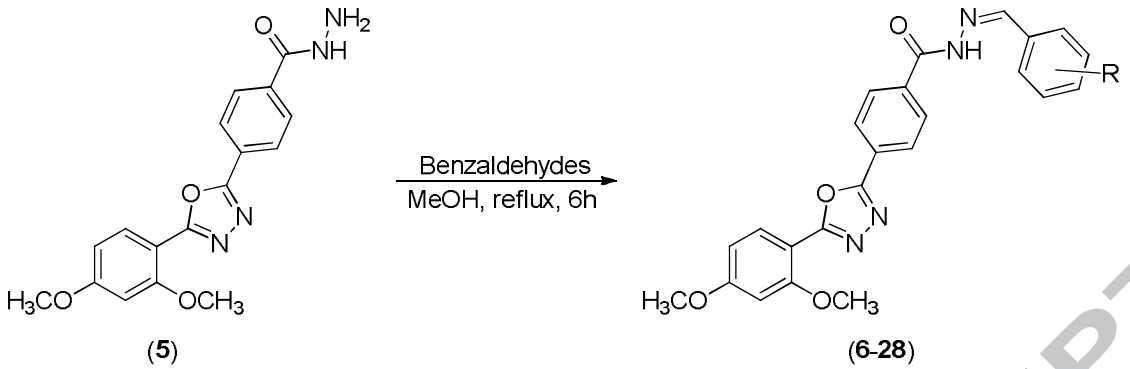


Figure-2: Drugs containing oxadiazole skeleton

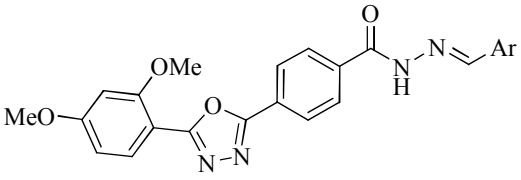


Scheme-1 Synthesis of oxadiazoles hydrazide (**5**) through four steps

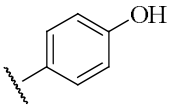
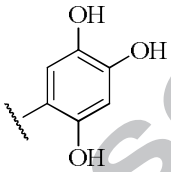
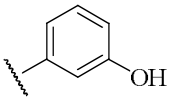
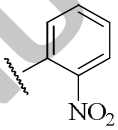
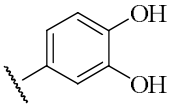
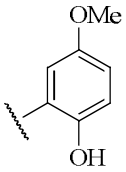
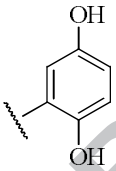
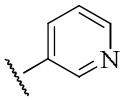
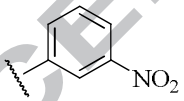
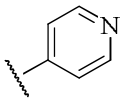
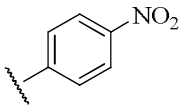
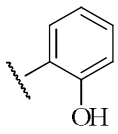
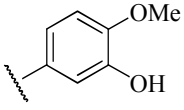
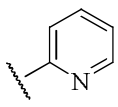


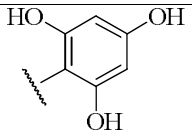
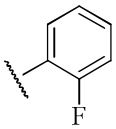
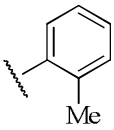
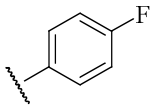
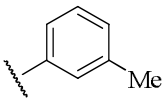
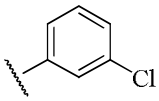
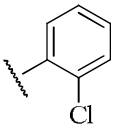
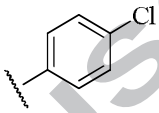
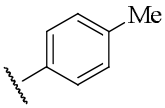
Scheme-2 Synthesis of oxadiazoles derivatives (**6-28**)

Table-1. Synthesis of Oxadiazole Benzohydrazones **6-28** and evaluation of their α-glucosidase inhibitory potential



6-28

Comp.	Ar	$IC_{50} \pm SEM^a$ [μM]	Comp.	Ar	$IC_{50} \pm SEM^a$ [μM]
6		180.46 ± 1.65	**18**		2.64 ± 0.05
7		210.24 ± 1.95	**19**		N.A.
8		28.28 ± 0.25	**20**		256.16 ± 2.25
9		87.64 ± 0.90	**21**		N. A.
10		N.A.	**22**		460.14 ± 3.25
11		N. A.	**23**		34.64 ± 0.35
12		146.46 ± 1.20	**24**		25.16 ± 0.25

13		29.68 ± 0.78	**25**		18.46 ± 0.28
14		N. A.	**26**		48.16 ± 0.48
15		N. A.	**27**		68.16 ± 0.53
16		6.14 ± 0.15	**28**		24.16 ± 0.28
17		N. A.	**Acarbose (Standard Drug)**		856.45 ± 5.60

Graphical Abstract

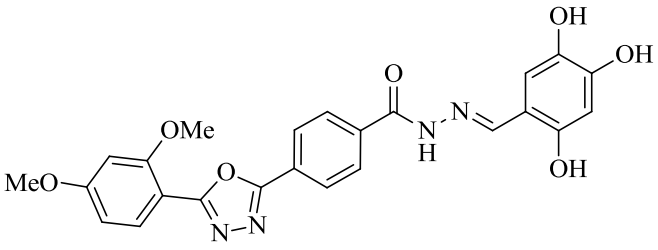
Synthesis of New Oxadiazole Derivatives as α-Glucosidase Inhibitors

Muhammad Taha[*a,b], Nor Hadiani Ismail[a,b], Syahrul Imran[a,b], Muhammad Qamarruddin Bin Rokei[b], Syed Muhammad Saad[d], and Khalid Mohammed Khan[d]

[a]Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300, Bandar Puncak Alam, Selangor, Malaysia.

[b]Faculty of Applied Science Universiti Teknologi MARA (UiTM), 40450, Shah Alam, Selangor, Malaysia [c]Integrative Pharmacogenomics Institute (iPROMISE), Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia.

[d]H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan.



18 (IC50 = 2.64 ± 0.05 µM)