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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole derivatives and evaluation of their antiglycation potential

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Abstract In the search of potent antidiabetic drug, we synthesized **1**–**25** 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole derivatives. First, we synthesized 2-methoxybenzohydrazide from methyl 2-methoxybenzoate which was treated with different arylaldehydes to afford **1**–**25** compounds. The synthesized compounds were evaluated for antiglycation activity. We found that **1**–**6** and **8** showed potent activity ranging from 160.2 to 290.17 μM better than standard drug rutin ($IC_{50} = 295.09 \pm 1.04$ μM). All the synthesized compounds were characterized by different spectroscopy methods. These compounds can further be studied to develop lead antidiabetic compounds.

Keywords
2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole · Antiglycation activity · Rutin · Diabetic

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Introduction

Oxidative stress and chronic hyperglycemia produce advanced glycation end-products. Amadori products formation starts by glycation process by the reaction of the amino group of proteins and sugar molecules. (Rojas and Morales, 2004). Carboxyl-methyllysine and carboxymethyl-hydroxylysine are AGEs formed through oxidative cleavage of Amadori adducts, while pentosidine results by crosslinking of lysine and arginine. It was observed that high level of glycation process occurs at aging and hyperglycemic patient as compared to healthy persons (Baral *et al.*, 2000). AGEs formation is further enhanced with oxidative stress (Wu and Yen, 2005). Diabetic complication like retinopathy, neuropathy, atherosclerosis and cataract has direct relevance with AGEs (Ahmed, 2005).

Some molecules have been reported that can break AGEPs crosslinks and possibly open the opportunity of reversing the slow process of diabetic complications (Vasan *et al.*, 2003). It has been found that AGE inhibits the formation of AGEPs in vitro and stops the formation of glycation-derived free radicals. *S*-Allylcysteine is an important component of AGE that acts as a potent antioxidant and thus inhibits the AGEPs formation (Hunt *et al.*, 1993; Ahmed and Ahmed, 2006). Aminoguanidine, an inhibitor of AGEPs formation, was found to prevent retinopathy in diabetic animals and protect them from developments of diabetic vascular complications. However, aminoguanidine has encountered some toxicity problems in phase III clinical trials (Gugliucci, 2000). Great struggles have been made nowadays to develop new and safe synthetic antiglycation agents (Singh *et al.*, 2001).

The heterocyclic compounds have wide range of biological application (Rahim *et al.*, 2015; Khan *et al.*, 2014,

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2015; Imran *et al.*, 2014, 2015a, b; Taha *et al.*, 2014a, b; Zawawi *et al.*, 2015). Great attention has been paid to the chemistry and biological activities of 1,3,4-oxadiazole nucleus. Numerous compounds having 1,3,4-oxadiazole scaffold have been freshly reported as potential antiproliferative agents (Gudipati *et al.*, 2011; Rashid *et al.*, 2012). Besides from anticancer potential, other biological activities have been reported for 1,3,4-oxadiazole derivatives such as antidiabetic (Hadady *et al.*, 2004), antitubercular (Ahsan *et al.*, 2011), antifungal (Liu *et al.*, 2008), anti-inflammatory (Jakubkiene *et al.*, 2002) and antibacterial activities (Desai *et al.*, 2013). 1,3,4-Oxadiazole, a fortunate structure, showed a key motif in heterocyclic chemistry and attracts a lot of interest in the fields of medicinal chemistry and synthetic study due to their competence to exhibit a wide range of pharmacological activities, such as antianxiety (Harfenist *et al.*, 1996) and antitubercular activities (Ahsan *et al.*, 2011). Literature survey revealed that minor modification in the structure of 1,3,4-oxadiazole/thiadiazole can lead to quantitative as well as qualitative changes in the biological activity (Aziz-Ur-Rehman *et al.*, 2012). There are several examples like, Raltegravir®, an antiretroviral drug and Zibotentan® an anticancer agent, while this scaffold, also a part of antibiotics such as furamizole etc. (Musmade *et al.*, 2015) (Fig. 1).

Results and discussion

The 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole derivatives synthesis begins with the synthesis of 2-methoxybenzohydrazide and then 2-methoxybenzohydrazide was treated with different arylaldehydes to produce 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole derivatives **1**–**25** Scheme 1. All the synthesized compounds **1**–**25** were characterized by diverse spectroscopy methods: ^{1}HNMR, EI, MS and elemental analysis (Table 1). The compounds **1**–**16**, **18**, **21** and **24** are new, and compounds **17**, **19**, **20**, **22**, **23** and **25** are known (Wang *et al.*, 2006; Khan *et al.*, 2005; Biju *et al.*, 2012; Roy *et al.*, 2005; Yi-Ming *et al.*, 2014).

Biological activity

It is reported that a Schiff base adduct between pyridoxal and aminoguanidine is responsible for inhibiting advanced glycation end-product (AGEPs) formation. In continuation of our study on activity of heterocyclic compounds bearing oxadiazole ring (Taha *et al.*, 2015a), we have synthesized 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole derivatives **1**–**25** to analyze for their antiglycation potential.

Bovine serum albumin, methyl glyoxal, various concentrations of the compounds and phosphate buffer (pH 7.4) containing sodium azide were mixed and incubated under aseptic conditions at 37 °C for 9 days. After 9 days, each sample was examined for the development of specific fluorescence. Rutin was used as a positive control (Khan *et al.*, 2011a, 2013a, b; Taha *et al.*, 2014a, b, 2015b; Khan *et al.*, 2009; Jamil *et al.*, 2015).

The current study is planned to explore potent antiglycating agents: Out of twenty-five (**25**) compounds, fourteen (14) analogs showed variable degree of antiglycation activities with IC_{50} values ranging between 160.2 ± 0.50 and 668.25 ± 3.74 μM, if compared with standard rutin (IC_{50} = 295.09 ± 1.04 μM) (Table 1). The standard

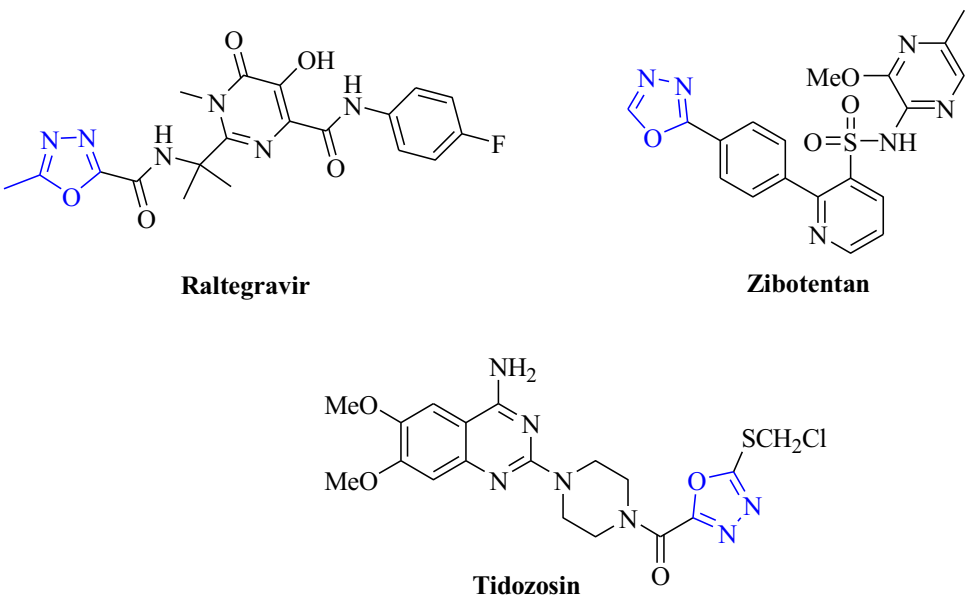
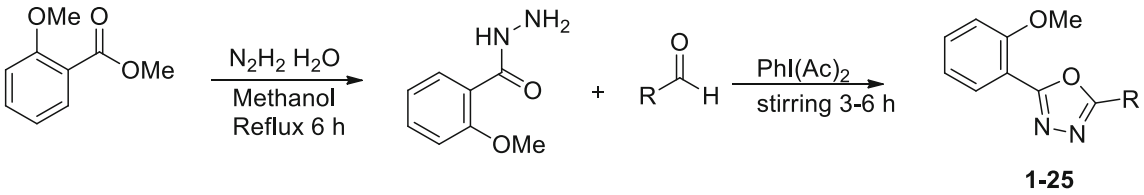


Fig. 1 Oxadiazole ring containing commercially available drugs



Scheme 1 Synthesis of oxadiazole 1–25

(rutin) is the choice because it is potent natural product. Compounds **1** ($IC_{50} = 160.2 \pm 0.50$ μM), **6** ($IC_{50} = 165.23 \pm 0.33$ μM), **5** ($IC_{50} = 185.41 \pm 0.43$ μM), **4** ($IC_{50} = 232.22 \pm 0.78$ μM), **2**($IC_{50} = 236.29 \pm 0.67$ μM), **3** ($IC_{50} = 280.24 \pm 0.88$ μM) and **8** ($IC_{50} = 290.17 \pm 1.05$ μM) showed excellent antiglycation potential, much better to the standard rutin ($IC_{50} = 295.09 \pm 1.04$ μM). Compounds **12** ($IC_{50} = 331.56 \pm 1.32$ μM) and **7** ($IC_{50} = 390.32 \pm 1.10$ μM) showed moderate to good antiglycation activity. However, compound **9** ($IC_{50} = 406.07 \pm 1.55$ μM), **23** ($IC_{50} = 475.89 \pm 1.89$ μM), **11** ($IC_{50} = 480.49 \pm 2.23$ μM), **10** ($IC_{50} = 495.26 \pm 2.04$ μM) and **14** ($IC_{50} = 668.25 \pm 3.74$ μM) are the weakly active among the series. Moreover, remaining compounds showed less than 50 % inhibition and were therefore not evaluated for IC_{50} values (Table 2).

Compound **1**, having a trihydroxyl group on the phenyl residue, is the most active analog of the series. Activity related to this compound may be due to the acetal formation by the reaction of hydroxy groups of this compound and the carbonyl group of methylglyoxal.

Compound **6** is the second most active compound among the series. It is a dihydroxylated analog. The minor differences in activity are due to the difference in number of the hydroxyl groups on the phenyl ring. Compounds **2**, **3**, **4** and **5** are the dihydroxylated analogs showing potent activities. There is a slight activity among these compounds. The activity difference among these compounds might be due to the position difference of hydroxyl group on the phenyl ring. The decline in activity is observed in compounds having single hydroxyl group. Finally, it becomes obvious from the experimental data that all compounds having hydroxyl group showed anti-glycation potential.

Conclusion

We synthesized **1**–**25** oxadiazole derivatives and evaluated antiglycation potential. Out of twenty-five compounds, only seven compounds **1**–**6** and **8** showed better activity than standard drug which can further be studied for lead compounds. Out of twenty-five compounds, 19 compounds are new.

Materials and methods

Experimental

General experimental

NMR experiments were performed on UltraShield Bruker FT NMR 500 MHz. IR experiments were performed on Perkin Elmer FT-IR and UV, Perkin Elmer Lambda 35 UV–Vis Spectrometer. CHN analysis was performed on a Carlo Erba Strumentazion-Mod-1106, Italy. Ultraviolet Electron impact mass spectra (EI MS) were recorded on a Finnigan MAT-311A, Germany. Thin layer chromatography (TLC) 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.

Assay protocol

Bovine serum albumin (BSA) was purchased from Merck Marker Pvt. Ltd. (Germany), rutin and methylglyoxal (MG) (40 % aqueous solution) were purchased from Sigma-Aldrich (Japan), sodium dihydrogen phosphate (NaH_2PO_4), disodium hydrogen phosphate (Na_2HPO_4) and sodium azide (NaN_3) were purchased from Scharlau Chemie, S. A. (Spain), while dimethyl sulphoxide (DMSO) was purchased from Fischer Scientific (UK). Bovine serum albumin (10 mg/mL), methyl glyoxal (14 mM), various concentrations of the compounds (prepared in DMSO, 10 % final concentration) and 0.1 M phosphate buffer (pH 7.4) containing sodium azide (30 mM) were incubated under aseptic conditions at 37 °C for 9 days. After 9 days, each sample was examined for the development of specific fluorescence (excitation, 330 nm; emission, 440 nm) against sample blank. Rutin was used as a positive control. The percent inhibition of AGE formation in the test sample versus control was calculated for each inhibitor compound by using the following formula: % inhibition = (1 − fluorescence of test

Table 1 Synthesis of 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole **1**–**25** and their % yields

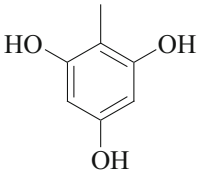
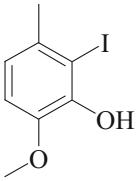
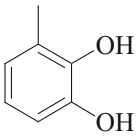
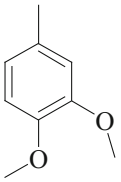
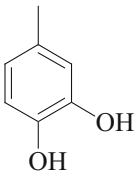
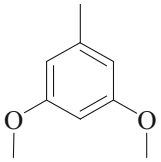
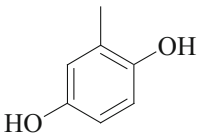
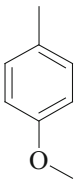
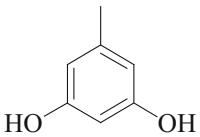
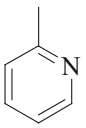
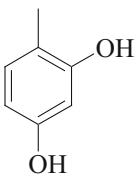
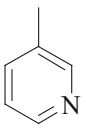
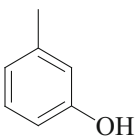
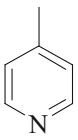
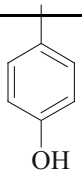
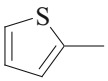
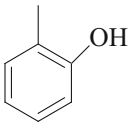
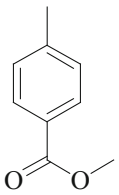
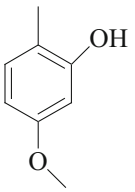
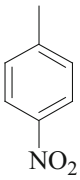
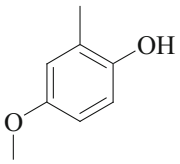
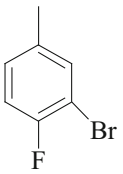
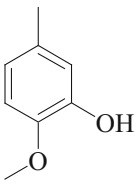
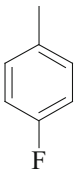
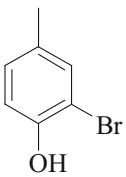
Comp. No.	*R*	Yield (%)	Comp. No.	*R*	Yield (%)
1		28	**14**		45
2		34	**15**		60
3		37	**16**		67
4		36	**17**		68
5		34	**18**		54
6		42	**19**		52
7		44	**20**		57

Table 1 continued

Comp. No.	*R*	Yield (%)	Comp. No.	*R*	Yield (%)
8		45	**21**		70
9		47	**22**		51
10		50	**23**		48
11		59	**24**		60
12		54	**25**		65
13		52		–	–

sample/Fluorescence of the control group) × 100 (Khan *et al.*, 2013a; Taha *et al.*, 2014a; Khan *et al.*, 2013c, 2011b).

*Synthesis 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (**1–25**)*

A mixture of 2-methoxybenzohydrazide and benzaldehyde derivatives (1 mmol) each and equivalent amount of $PhI(OAc)_2$ was stirred in dichloromethane (10 ml) at room temperature. The solvent was evaporated and the residue was washed with diethyl ether, filtered, dried and then crystallized from ethanol to afford desired compounds **1–25**.

2-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)benzene-1,3,5-triol **(1)** Yield: 0.084 g (28 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.15 (s, 2H, −OH), 8.60 (s, 1H, −OH) 7.62 (dd, 1H, J = 8.5, 2.2 Hz, H-4), 7.50–7.46 (m, 1H, H-2),

Table 2 Evaluation of antiglycation potential of 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole derivatives **1–25**

Comp.	IC_{50} (μM ± SEM[a])	Comp.	IC_{50} (μM ± SEM[a])	Comp.	IC_{50} (μM ± SEM[a])
1	160.2 ± 0.50	**10**	495.26 ± 2.04	**19**	N.A.
2	236.29 ± 0.67	**11**	480.49 ± 2.23	**20**	N.A.
3	280.24 ± 0.88	**12**	331.56 ± 1.32	**21**	N.A.
4	232.22 ± 0.78	**13**	N.A.	**22**	N.A.
5	185.41 ± 0.43	**14**	668.25 ± 3.74	**23**	475.89 ± 1.89
6	165.23 ± 0.33	**15**	N.A.	**24**	N.A.
7	390.32 ± 1.10	**16**	N.A.	**25**	N.A.
8	290.17 ± 1.05	**17**	N.A.	Standard drug rutin	
9	406.07 ± 1.55	**18**	N.A.	295.09 ± 1.04 μM	

SEM[a] is the standard error of the mean; rutin is the standard drug

7.18 (d, 1H, $J = 8.0$ Hz, H-1), 7.02–6.96 (m, 1H, H-3), 6.67 (s, 2H, H-2′, H-4′), 3.88 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): 164.4 (C, 3′), 162.1 (C, 1′), 160.4 (C, 2), 160.0 (C, 4″), 158.4 (C, 2″), 158.3 (CH, 6″), 129.2 (CH, 4), 128.2 (CH, 6), 122.2 (CH, 1), 121.5 (CH, 4), 116.5 (CH, 3), 103.4 (C, 1″), 98.4 (CH, 3″), 98.4 (CH, 5″), 56.2 (OCH_3), Anal. Calcd for $C_{15}H_{12}N_2O_5$, C = 60.00, H = 4.03, N = 9.33, Found C = 60.02, H = 4.04, N = 9.34; EI MS *m/z* (% rel. abund.): 300.

3-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)benzene-1,2-diol **(2)** Yield: 0.097 g (34 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.42 (s, 1H, −OH), 8.23 (s, 1H, −OH), 7.96 (dd, 1H, $J = 8.5$, 2.0 Hz, H-4), 7.61–7.54 (m, 1H, H-2), 7.26 (d, 1H, $J = 8.5$ Hz, H-1), 7.14–7.09 (m, 1H, H-3), 6.94–6.89 (m, 2H, H-2′, H-3′), 6.82–6.75 (m, 1H, H-1′), 3.87 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C, 1′), 160.4 (C, 2), 145.2 (C, 3″), 143.4 (C, 2″),129.3 (CH, 4), 128.1 (CH, 6), 125.2 (C, 1″), 123.1 (CH, 5″), 122.2 (CH, 1), 121.3 (CH, 6″), 121.5 (CH, 5), 117.2 (CH, 3″), 114.7 (CH, 3), 56.2 (OCH_3), Anal. Calcd for $C_{15}H_{12}N_2O_4$, C = 63.38, H = 4.25, N = 9.85, Found C = 63.41, H = 4.27, N = 9.87; EI MS *m/z* (% rel. abund.): 284.

4-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)benzene-1,2-diol **(3)** Yield: 0.105 g (37 %), ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.24 (s, 2H, −OH), 7.61 (dd, 1H, $J = 7.5$, 2.0 Hz, H-4), 7.55–7.49 (m, 1H, H-4, H-2), 7.42 (d, 1H, $J = 2.0$ Hz, H-5′), 7.25 (d, 1H, $J = 8.0$ Hz, H-2′), 7.13–7.08 (m, 1H, H-1), 7.05–6.99 (m, 1H, H-3), 6.80 (d, 1H, $J = 7.5$ Hz, H-1′), 3.87 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C, 1′), 160.4 (C, 2), 145.1 (C, 3″), 144.4 (C, 4″), 130.2 (C, 1″), 129.5 (CH, 4), 128.3 (CH, 6), 122.2 (C, 1), 121.5 (CH, 6″), 121.4 (CH, 5), 117.5 (CH, 5″), 115.4 (CH, 2″), 114.7 (CH, 3), 56.2 (OCH_3), Anal. Calcd for $C_{15}H_{12}N_2O_4$, C = 63.38, H = 4.25, N = 9.85, Found C = 62.39, H = 4.27, N = 9.86; EI MS *m/z* (% rel. abund.): 284.

2-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)benzene-1,4-diol **(4)** Yield: 0.102 g (36 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.41 (s, 1H, −OH), 9.01 (s, 1H, −OH) 7.65 (dd, 1H, $J = 7.5$, 2.0 Hz, H-4), 7.50–7.46 (m, 1H, H-2), 7.15 (d, 1H, $J = 8.0$ Hz, H-1), 7.08–7.02 (m, 1H, H3), 6.90 (d, 1H, $J = 2.0$ Hz, H-1′), 6.74–6.70 (m, 2H, H-3′, H-4′), 3.88 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C, 1′), 160.4 (C, 2), 150.2 (C, 3″), 148.5 (C, 6″), 129.6 (CH, 4), 128.2 (CH, 6), 125.2 (C, 1″), 122.5 (C, 1), 121.2 (CH, 5), 117.4 (CH, 5″), 117.3 (CH, 4″), 115.4 (CH, 2″), 114.2 (CH, 3), 56.2 (OCH_3), Anal. Calcd for $C_{15}H_{12}N_2O_4$, C = 63.38, H = 4.25, N = 9.85, Found C = 62.37, H = 4.27, N = 9.84; EI MS *m/z* (% rel. abund.): 284.

5-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)benzene-1,3-diol **(5)** Yield: 0.098 g (34 %), ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.60 (s, 2H, −OH) 7.94 (dd, 1H, $J = 8.0$, $J = 2.0$ Hz, H-1), 7.55–7.51 (m, 1H, H-2), 7.23 (d, 1H, $J = 8.0$ Hz, H-1), 7.14–7.09 (m, 1H, H-3), 6.75 (d, 2H, $J = 2.0$ Hz, H-1′, H-5′), 6.30–6.26 (m, 1H, H-3′), 4.03 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C, 1′), 160.1 (C, 2), 159.5 (C, 5″), 159.3 (C, 3″), 139.2 (C, 1″), 129.6 (CH, 4), 128.2 (CH, 6), 122.2 (C, 1), 121.4 (CH, 5), 114.5 (CH, 3), 106.5 (CH, 6″), 106.4 (CH, 2″), 102.5 (CH, 4″), 56.1 (OCH_3), Anal. Calcd for $C_{15}H_{12}N_2O_4$, C = 63.38, H = 4.25, N = 9.85, Found C = 62.39, H = 4.24, N = 9.87; EI MS *m/z* (% rel. abund.): 284.

4-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)benzene-1,3-diol **(6)** Yield: 0.119 g (42 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.41 (s, 1H), 9.02 (s, 1H), 7.64 (dd, 1H, $J = 7.0$, 2.0 Hz, H-4), 7.50–7.47 (m, 1H, H-4, H-2), 7.29 (d, 1H, $J = 8.0$ Hz, H-4′), 7.20 (d, 1H, $J = 8.0$ Hz, H-1), 7.08–7.04 (m, 1H, H-3), 6.35 (dd, 1H, $J = 8.0$, $J = 2.0$ Hz, H-2′), 6.29 (d, 1H, $J = 2.0$ Hz, H-1′), 3.88 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): 164.4 (C, 3′), 162.1 (C, 1′), 160.4 (C, 2), 158.5 (C, 4″), 157.4 (C, 2″), 129.5

(CH, 4), 129.4 (CH, 6″), 128.1 (CH, 6), 122.5 (C, 1), 121.5 (CH, 5), 116.2 (C, 1″), 114.5 (CH, 3), 108.5 (CH, 5″), 103.3 (CH, 3″), 56.1 (OCH_3), Anal. Calcd for $C_{15}H_{12}N_2O_4$, C = 63.38, H = 4.25, N = 9.85, Found C = 62.36, H = 4.26, N = 9.86; EI MS *m/z* (% rel. abund.): 284.

3-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenol **(7)** Yield: 0.118 g (44 %), ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (s, 1H, −OH), 7.60 (dd, 1H, J = 8.0, 2.0 Hz, H-4), 7.51–7.49 (m, 1H, H-2), 7.27–7.23 (m, 1H, H-3), 7.17–7.11 (m, 4H, H-1, H-2′, H-3′, H-5′), 6.80 (dd, 1H, J = 7.0, 2.0 Hz, H-1′), 4.03 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C, 1′), 160.4 (C, 2), 157.3 (C, 3″), 130.5 (CH, 5″), 129.5 (CH, 4), 128.3 (CH, 6), 119.4 (CH, 6″), 122.4 (C, 1), 121.5 (CH, 5), 115.5 (CH, 4″), 114.6 (C, 1″), 114.4 (CH, 2″), 114.5 (CH, 3), 56.1 (OCH_3), Anal. Calcd for $C_{15}H_{12}N_2O_3$, C = 67.16, H = 4.51, N = 10.44, Found C = 67.15, H = 4.52, N = 10.43; EI MS *m/z* (% rel. abund.): 268.

4-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenol **(8)** Yield: 0.121 g (45 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.93 (s, 1H, −OH), 7.60 (dd, 1H, J = 7.0, J = 2.0 Hz, H-4), 7.50 (d, 2H, J = 8.5 Hz, H-2′, H-4′), 7.46 (ddd, 1H, J = 7.0, 6.0, 2.0 Hz, H-2), 7.14 (d, 1H, J = 8.0 Hz, H-1), 7.03 (t, 1H, J = 5.0 Hz, H-3), 6.81 (d, 2H J = 8.5 Hz, H-1′, H-5′), 3.87 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C, 1′), 160.6 (C, 2), 157.5 (C, 4″), 116.3 (C, 3″), 129.5 (CH, 4), 128.3 (CH, 6), 128.5 (CH, 6″), 129.6 (C, 1″), 128.4 (CH, 2″), 122.2 (C, 1), 121.5 (CH, 5), 116.3 (CH, 5″), 114.5 (CH, 3), 56.1 (OCH_3), Anal. Calcd for $C_{15}H_{12}N_2O_3$, C = 67.16, H = 4.51, N = 10.44, Found C = 67.14, H = 4.50, N = 10.45; EI MS *m/z* (% rel. abund.): 268.

2-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenol **(9)** Yield: 0.126 g (47 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.27 (s, 1H, −OH), 7.60 (dd, 1H, J = 7.0, 2.0 Hz, H-4), 7.52–7.50 (m, 2H, H-2, H-4′), 7.42–7.40 (m, 1H, H-3′), 7.16 (d, 1H, J = 8.0 Hz, H-1), 7.04–7.02 (m, 1H, H-3), 6.90–6.88 (m, 2H, H-1′, H-2′), 3.88 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C, 1′), 160.4 (C, 2), 155.4 (CH, 2″), 121.5 (CH, 5″), 129.4 (CH, 4), 6″), 129.5 (CH, 4″), 128.6 (CH, 6), 128.5 (CH, 123.6 (C, 1″), 122.6 (C, 1), 121.5 (CH, 5), 116.3 (CH, 3″), 114.5 (CH, 3), 56.2 (OCH_3), Anal. Calcd for $C_{15}H_{12}N_2O_3$, C = 67.16, H = 4.51, N = 10.44, Found C = 67.17, H = 4.52, N = 10.46; EI MS *m/z* (% rel. abund.): 268.

5-Methoxy-2-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenol **(10)** Yield: 0.148 g (50 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.57 (s, 1H, −OH) 7.60 (dd, 1H, J = 8.0, J = 2.0 Hz, H-4), 7.51–7.49 (m, 1H, H-2), 7.37 (d, 1H, J = 8.0 Hz, H-1′), 7.16 (d, 1H, J = 8.0 Hz, H-1), 7.05–7.03 (m, 1H, H-3), 6.51–6.48 (m, 2H, H-2′, H-4′), 3.89 (s, 3H, $-OCH_3$), 3.79 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 163.5 (C, 4″), 162.1 (C, 1′), 160.5 (C, 2), 156.4 (C, 2″), 129.5 (CH, 4), 129.4 (CH, 6″), 128.1 (CH, 6), 122.5 (C, 1), 121.5 (CH, 5), 116.2 (C, 1″), 114.5 (CH, 3), 107.5 (CH, 5″), 101.3 (CH, 3″), 56.1 (OCH_3), Anal. Calcd for $C_{16}H_{14}N_2O_4$, C = 64.42, H = 4.73, N = 9.39, Found C = 64.44, H = 4.72, N = 9.38,; EI MS *m/z* (% rel. abund.): 298.

4-Methoxy-2-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenol **(11)** Yield: 0.176 (59 %), ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.48 (s, 1H, −OH), 7.92 (dd, 1H, J = 8.0, J = 2.0 Hz, H-4), 7.58–7.56 (m, 1H, H-2), 7.20 (d, 1H, J = 8.5 Hz, H-1), 7.11–7.09 (m, 1H, H-3), 7.08 (d, 1H, J = 2.0 Hz, H-4′), 6.91 (dd, 1H, J = 8.0, 2.0 Hz, H-3′), 6.84 (d, 1H, J = 8.0 Hz, H-5′), 3.90 (s, 3H, $-OCH_3$), 3.84 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.2 (C, 1′), 160.6 (C, 2), 155.5 (C, 5″), 148.4 (C, 6″), 148.4 (C, 2″), 129.6 (CH, 4), 128.1 (CH, 6), 122.4 (C, 1), 124.2 (C, 1″), 121.5 (CH, 5), 117.3 (CH, 3″), 115.5 (CH, 4″), 114.5 (CH, 3), 56.1 (OCH_3), Anal. Calcd for $C_{16}H_{14}N_2O_4$, C = 64.42, H = 4.73, N = 9.39, Found C = 64.43, H = 4.71, N = 9.36; EI MS *m/z* (% rel. abund.): 298.

2-Methoxy-5-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenol **(12)** Yield: 0.161 g (54 %), ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.33 (s, 1H), 7.60 (dd, 1H, J = 7.0, 2.0 Hz, H-4), 7.53–7.51 (m, 1H, H-2), 7.24 (d, 1H, J = 2.0 Hz, H-5′), 7.15 (d, 1H, J = 8.0 Hz, H–H-1), 7.06–7.04 (m, 2H, H-3, H-2′), 6.96 (d, 1H, J = 8.0 Hz, H-1′), 3.89 (s, 3H, $-OCH_3$), 3.85 (s, 3H, OCH_3); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.2 (C, 1′), 160.6 (C, 2), 116.5 (CH, 5″), 120.4 (CH, 6″), 115.4 (CH, 2″), 129.6 (CH, 4), 128.1 (CH, 6), 122.4 (C, 1), 130.1 (C, 1″), 121.4 (CH, 5), 143.3 (C, 3″), 149.5 (C, 4″), 114.5 (CH, 3), 56.1 (OCH_3), Anal. Calcd for $C_{16}H_{14}N_2O_4$, C = 64.42, H = 4.73, N = 9.39, Found C = 64.40, H = 4.72, N = 9.37; EI MS *m/z* (% rel. abund.): 298.

2-Bromo-4-(5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenol **(13)** Yield: 0.180 g (52 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.39 (s, 1H, −OH), 7.80 (d, 1H, J = 2.0 Hz, H-5′), 7.61 (dd, 1H, J = 7.0, 2.0 Hz, H-4), 7.52 (dd, 1H, J = 8.0, J = 2.0 Hz, H-1′), 7.50–7.48 (m, 1H, H-2), 7.14 (d, 1H, J = 8.0 Hz, H-1), 7.04–7.01 (m, 1H, H-3), 6.98 (d, 1H, J = 8.0 Hz, H-2′), 3.88 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.2 (C, 1′), 160.5 (C, 4″), 160.4 (C, 2), 131.4 (CH, 2″), 131.1 (C, 1″), 129.6 (CH, 4), 128.1 (CH, 6),118.5 (CH, 5″), 127.5 (CH, 6″), 122.4 (C, 1), 121.5 (CH, 5), 114.5 (CH, 3), 110.3 (C, 3″), 56.1 (OCH_3), Anal. Calcd for $C_{15}H_{11}BrN_2O_3$, C = 51.90, H = 3.19, N = 8.07, Found C = 51.92, H = 3.18, N = 8.09; EI MS *m/z* (% rel. abund.): (M + 2) 348, 346.

2-Iodo-6-methoxy-3-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)phenol **(14)** Yield: 0.191 g (45 %), ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.65 (s, 1H, −OH), 7.51 (dd, 1H, J = 7.0, 2.0 Hz, H-4), 7.50–7.48 (m, 1H, H-2), 7.43 (d, 1H, J = 8.0 Hz, H-2′), 7.13 (d, 1H, J = 8.0 Hz, H-1), 7.04 (d, 1H, J = 8.0 Hz, H-1′), 7.05–7.02 (m, 1H, H-3), 3.89 (s, 3H, $-OCH_3$), 3.87 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.5 (C, 3′), 162.1 (C, 1′), 160.5 (C, 2), 152.3 (C, 3″), 150.5 (C, 4″), 139.5 (C, 1″), 129.4 (CH, 4), 128.3 (CH, 6), 122.5 (CH, 6″), 122.6 (C, 1), 121.5 (CH, 5), 114.5 (CH, 5″), 114.4 (CH, 3), 84.2 (C, 2″), 56.6 (OCH_3), 56.4 (OCH_3), Anal. Calcd for $C_{16}H_{13}IN_2O_4$, C = 45.30, H = 3.09, N = 6.60, Found C = 45.31, H = 3.08, N = 6.62; EI MS *m/z* (% rel. abund.): 424.

2-(3,4-Dimethoxyphenyl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole **(15)** Yield: 0.187 g (60 %), ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.92 (dd, 1H, J = 7.0, J = 2.0 Hz, H-1′), 7.74 (d, 1H, J = 2.0 Hz, H-4), 7.55–7.53 (m, 1H, H-2), 7.20–7.18 (m, 2H, H-1, H-5′), 7.11–7.08 (m, 1H, H-3), 6.98 (d, 1H, J = 8.5 Hz, H-2′), 3.92 (s, 3H, $-OCH_3$), 3.90 (s, 3H, $-OCH_3$), 3.89 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C,1′), 160.5 (C, 2), 148.3 (C, 3″), 147.5 (C, 4″), 129.5 (C, 1″), 129.3 (CH, 4), 128.1 (CH, 6), 120.5 (CH, 6″), 122.6 (C, 1), 121.4 (CH, 5), 115.5 (CH, 5″), 114.4 (CH, 3), 113.4 (C, 2″), 56.6 (OCH_3), 56.6 (OCH_3), 56.3 (OCH_3) Anal. Calcd for $C_{17}H_{16}N_2O_4$, C = 65.38, H = 5.16, N = 8.97, Found C = 65.39, H = 5.15, N = 8.99; EI MS *m/z* (% rel. abund.): 312.

2-(3,5-Dimethoxyphenyl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole **(16)** Yield: 0.210 g (67 %), ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.60 (dd, 1H, J = 7.0, 2.0 Hz, H-4), 7.51–7.49 (m, 1H, H-2), 7.16 (d, 1H, J = 8.0 Hz, H-1), 7.02 (t, 1H, J = 7.0 Hz, H-3), 6.87 (d, 2H, J = 2.0 Hz, H-1′, H-5′), 6.56–6.53 (m, 1H), 3.89 (s, 3H, $-OCH_3$), 3.84 (s, 6H, OCH_3); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 163.3 (C, 3″), 163.3 (C, 5″), 162.1 (C, 1′), 160.5 (C, 2), 138.5 (C, 1″), 129.3 (CH, 4), 128.1 (CH, 6), 122.6 (C, 1), 121.4 (CH, 5), 114.4 (CH, 3), 104.5 (CH, 6″), 104.5 (CH, 2″), 99.5 (CH, 4″), 56.6 (OCH_3), 56.6 (OCH_3), 56.4 (OCH_3) Anal. Calcd for $C_{17}H_{16}N_2O_4$, C = 65.38, H = 5.16, N = 8.97, Found C = 65.37, H = 5.17, N = 8.96; EI MS *m/z* (% rel. abund.): 312.

2-(2-Methoxyphenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole **(17)** M.p. 262 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.94 (dd, 1H, J = 7.5, 2.0 Hz, H-4), 7.81 (dd, 2H, J = 8.5 Hz, H-1′, H-5′), 7.60–7.58 (m, 1H, H-2), 7.21 (dd, 1H, J = 8.5 Hz, H-1), 7.16–7.14 (m, 1H, H-3), 7.02 (dd, 2H, J = 8.5 Hz, H-2′, H-4′), 4.03 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); [20].

2-(2-Methoxyphenyl)-5-(pyridin-2-yl)-1,3,4-oxadiazole **(18)** Yield: 0.137 g (54 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.60–8.58 (m, 1H, H-4′), 7.96 (d, 1H, J = 8.5 Hz, H-3′), 7.88–7.86 (m, 1H, H-2′), 7.62 (dd, 1H, J = 8.5, 2.0 Hz, H-4), 7.50–7.47 (m, 1H, H-2), 7.30–7.28 (m, 1H, H-1′), 7.16 (d, 1H, J = 8.0 Hz, H-1′), 7.08–7.06 (m, 1H, H-3), 3.89 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C, 1′), 160.5 (C, 2), 157.5 (C, 1″), 150.3 (CH, 3″), 136.3 (CH, 5″), 129.4 (CH, 4), 128.3 (CH, 6), 122.5 (CH, 6″), 122.4 (C, 1), 121.4 (CH, 5), 120.6 (CH, 4″), 114.4 (CH, 3), 56.6 (OCH_3), Anal. Calcd for $C_{14}H_{11}N_3O_2$, C = 66.40, H = 4.38, N = 16.59, Found C = 66.42, H = 4.39, N = 16.60; EI MS *m/z* (% rel. abund.): 253.

2-(2-Methoxyphenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole **(19)** M.p. 260 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.60 (d, 1H, J = 6.0 Hz, H-5′), 7.97 (d, 1H, J = 8.0 Hz, H-3), 7.93–7.91 (m, 1H, H-2′), 7.61 (dd, 1H, J = 7.5, 2.0 Hz, H-4), 7.56–7.54 (m, 1H, H-2), 7.47–7.44 (m, 1H, H-1′), 7.19 (d, 1H, J = 8.0 Hz, H-1), 7.11–7.09 (m, 1H, H-3), 3.88 (s, 3H, $-OCH_3$); [20].

2-(2-Methoxyphenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole **(20)** M.p. 280 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.60 (d, 2H, J = 5.5 Hz, H-2′, H-4′), 7.62 (d, 2H, J = 6.0 Hz, H-1′, H-5′), 7.60 (dd, 1H, J = 7.5, 1.5 Hz, H-4), 7.54–7.52 (m, 1H, H-2), 7.19 (d, 1H, J = 8.0, H-1), 7.11–7.08 (m, 1H, H-3), 3.88 (s, 3H, $-OCH_3$); [20].

2-(2-Methoxyphenyl)-5-(thiophen-2-yl)-1,3,4-oxadiazole **(21)** Yield: 0.183 g (70 %); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.64 (d, 1H, J = 5.5 Hz, H-3′), 7.56 (dd, 1H, J = 7.0, 2.0 Hz, H-4), 7.50–7.48 (m, 1H, H-2), 7.41–7.38 (d, 1H, J = 3.0 Hz, H-2′), 7.14 (d, 1H, J = 8.0, H-1), 7.14–7.16 (m, 1H, H-1′), 7.05–7.02 (m, 1H, H-3), 3.89 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C, 1′), 160.4 (C, 2), 142.5 (C, 1″), 129.4 (CH, 4), 128.3 (CH, 6), 127.6 (CH, 4″), 125.4 (CH, 3″), 122.4 (C, 1), 122.3 (CH, 5″), 121.4 (CH, 5), 114.4 (CH, 3), 56.6 (OCH_3), Anal. Calcd for $C_{13}H_{10}N_2O_2S$, C = 60.45, H = 3.90, N = 10.85, Found C = 60.46, H = 3.92, N = 10.84; EI MS *m/z* (% rel. abund.): 258.

Methyl 4-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)benzoate **(22)** M.p. 290 °C. 1H NMR (500 MHz, DMSO-d_6): δ 8.10 (d, 2H, J = 8.0 Hz, H-2′, H-4′), 7.97 (d, 2H, J = 8.0 Hz, H-1′, H-5′), 7.92 (dd, 1H, J = 7.5, 2.0 Hz, H-4), 7.57 (ddd, 1H, J = 7.5, 6.5, 2.0 Hz, H-2), 7.24 (d, 1H, J = 8.5 Hz, H-1), 7.09 (t, 1H, J = 8.5, H-3), 3.89 (s, 3H, $-OCH_3$), 3.86 (s, 3H, $-COOCH_3$); [20].

2-(2-Methoxyphenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole **(23)** M.p. 285 °C. 1H NMR (500 MHz, DMSO-d_6): δ 8.30 (d, 2H, J = 8.5 Hz, H-2′, H-4′), 7.92 (d, 2H, J = 8.5 Hz, H-1′, H-5′), 7.62 (dd, 1H, J = 7.5, 1.5 Hz, H-4), 7.54 (m, 1H, H-2), 7.19 (d, 1H, J = 8.5 Hz, H-1), 7.09 (m, 1H, H-3), 3.88 (s, 3H, $-OCH_3$); [20].

2-(3-Bromo-4-fluorophenyl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole **(24)** Yield: 0.208 g (60 %); 1H NMR (500 MHz, DMSO-d_6): δ 8.20 (d, 1H, $J = 2.0$ Hz, H-5′), 7.90 (dd, 1H, $J = 8.0$, 2.0 Hz, H-1′), 7.82–7.79 (m, 1H, H-2′), 7.54–7.51 (m, 1H, H-4), 7.29–7.26 (m, 1H, H-2), 7.22 (d, 1H, $J = 8.0$ Hz, H-1), 7.17–7.15 (m, 1H, H-3), 3.90 (s, 3H, $-OCH_3$); C-NMR: (75 MeOD-d_4): δ 164.4 (C, 3′), 162.1 (C,1′), 160.5 (C, 2), 165.5 (C, 4″), 134.5 (C, 1″), 131.4 (C, 2″), 129.4 (CH, 4), 128.2 (CH, 6), 127.5 (CH, 6″), 122.6 (C, 1), 121.4 (CH, 5), 115.5 (CH, 5″), 114.4 (CH, 3), 110.3 (C, 3″), 56.6 (OCH_3), Anal. Calcd for $C_{15}H_{10}BrFN_2O_2$, C = 51.60, H = 2.89, N = 8.02, Found C = 51.61, H = 2.90, N = 51.61; EI MS *m/z* (% rel. abund.): 350 ($M^+ + 2$, 30), 348 (M^+, 28).

2-(4-Fluorophenyl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole **(25)** M.p. 265 °C. 1H NMR (500 MHz, DMSO-d_6): δ 7.82–7.79 (m, 2H, H-2′, H-4′), 7.64 (dd, 1H, $J = 7.5$, 1.5 Hz, H-4), 7.56–7.53 (m, 1H, H-2), 7.32 (m, 2H, H-1′, H-5′), 7.18 (d, 1H, $J = 7.5$ Hz, H-1), 7.10–7.08 (m, 1H, H-3), 3.88 (s, 3H, $-OCH_3$) [20].

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