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Structure–activity relationships of tyrosinase inhibitory combinatorial library of 2,5-disubstituted-1,3,4-oxadiazole analogues

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Abstract—Here the tyrosinase inhibition studies of library of 2,5-disubstituted-1,3,4-oxadiazoles have been reported and their structure–activity relationship (SAR) also have been discussed. The library of the oxadiazoles was synthesized under the microwave irradiation and was structures of these were characterized by different spectral techniques. From this study it could be concluded that for a better inhibition of tyrosinase, electronegative substitution is essential as most probably the active site of the enzyme contain some hydrophobic site and position is also very important for the inhibition purposes due to the conformational space. The electronegativity of the compounds is somewhat proportional to the inhibitory activity. The compound **3e** (3′-[5-(4′-bromophenyl)-1,3,4-oxadiazol-2-yl]pyridine) exhibited most potent (IC_{50} = 2.18 μM) inhibition against the enzyme tyrosinase which is more potent than the standard potent inhibitor L-mimosine (IC_{50} = 3.68 μM). This molecule can be the best candidate as a lead compound for further development of drug for the treatments of several skin disorders.

1. Introduction

Tyrosinase (E.C. 1.14.18.1), also known as polyphenol oxidase (PPO), is a multifunctional copper-containing enzyme, widely distributed in plants and animals. It catalyses the *o*-hydroxylation of monophenols and also the oxidation of *o*-diphenols to *o*-quinones. Tyrosinase is known to be a key enzyme for melanin biosynthesis in plants and animals. Therefore, tyrosinase inhibitors should be clinically useful for the treatment of some dermatological disorders associated with melanin hyperpigmentation and also important in cosmetics for whitening and depigmentation after sunburn. In addition, tyrosinase is known to be involved in the molting process of insect and adhesion of marine organisms.[1] In insects, several functions of this enzyme have been reported in the generation of *o*-diphenols and quinones for pigmentation, wound healing, parasite encapsulation, and sclerotization and the enzyme is an alternative target site for the control of insect pests. In food industry, tyrosinase is responsible for the enzymatic browning reactions in damaged fruits during post-harvest handling and processing. Control of enzymatic browning during processing is important in fruit pulp manufacturing. In addition, tyrosinase inhibitors are becoming important constituents of cosmetic products that relate to hyperpigmentation. Therefore, there is a concerted effort to search for naturally occurring tyrosinase inhibitors from plant, because plants constitute a rich source of bioactive chemicals and many of them are largely free from harmful adverse effects.[2]

In recent years numbers of potent tyrosinase inhibitors have been reported from our and other groups. Very recently, we have reported two long chain esters, methyl 2β(2*S*)-hydroxyl-7(*E*)-tritriacontenoate and methyl

Keywords: Tyrosinase inhibitor; 2,5-Disubstituted-1,3,4-oxadiazole library; Melanin; Vitiligo; Hyperpigmentation; Depigmentation.
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2β(2*S*)-*O*-β-D-galactopyranosyl-7(*E*)-tetratriacontenoate, showing strong to moderate inhibitory activities against tyrosinase.[3] In another paper we have reported that, (+)-androst-4-ene-3,17-dione and its five metabolic analogues having steroidal skeletons, namely androsta-1,4-diene-3,17-dione, 17β-hydroxyandrosta-1,4-dien-3-one, 11α-hydroxyandrost-4-ene-3,17-dione, 11α,17β-dihydroxyandrost-4-en-3-one and 15α-hydroxyandrosta-1,4-dien-17-one, exhibited moderate inhibitory activities against the enzyme.[4] Ahmad et al. in 2004 reported that, a new coumarinolignoid 8′-*epi*-cleomiscosin A together with the new glycoside 8-*O*-β-D-glucopyranosyl-6-hydroxy-2-methyl-4*H*-1-benzopyrane-4-one, exhibited strong inhibition against the enzyme tyrosinase, when compared to the standard tyrosinase inhibitors kojic acid and L-mimosine. The new coumarinolignoid exhibited two times more potency than that of the standard potent inhibitor L-mimosine.[5] Recently, Karbassi et al. reported the inhibition kinetics of two new synthetic bi-pyridine molecules, [1,4′]bipiperidinyl-1′-yl-naphthan-2-yl-methanone (**I**) and [1,4′]bipiperidinyl-1′-yl-4-methylphenyl-methane (**II**) of the catecholase activity of mushroom tyrosinase. The kinetics studies indicated that these are uncompetitive inhibitors and the values of the K_i are 5.87 and 1.31 μM for **I** and **II**, respectively, which showed high potency. Fluorescent studies confirmed the uncompetitive type of inhibition for these two inhibitors. They also suggested that, the inhibition mechanism presumably coming from the presence of a particular hydrophobic site which can accommodate these inhibitors. This site could be formed due to a probable conformational change that was induced by binding of substrate with the enzyme.[6]

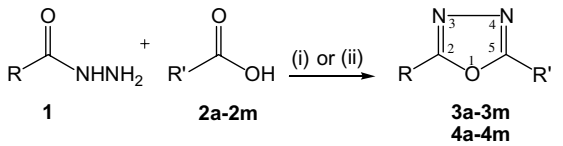
The microwave radiation endows with an unconventional to the usual heating as it employs the capability of liquids or solids to convert electromagnetic energy into heat. The exploitation of microwave radiations has commenced numerous innovative perceptions in chemistry, while the absorption and transmission of the energy is completely different from the conventional mode of heating. This technology has been applied to a number of useful research and development processes such as polymer technology, organic synthesis, application to waste treatment; drug release/targeting; ceramic and alkane decomposition.[7]

Here in this paper, we have discussed the tyrosinase inhibitory activities of a library of 26 analogues of 2,5-disubstituted-1,3,4-oxadiazoles, which were synthesized using microwave-assisted combinatorial synthetic approach and finally their structure–activity relationships (SAR) also have been discussed.

2. Results and discussion

2.1. General chemistry

The detailed chemistry and the synthetic parts of the compounds have been reported recently and discussed elsewhere.[7] Briefly, a number of commercially available hydrazides were treated with different carboxylic acids **2** (**a**–**m**) in the presence of phosphorous oxychloride to afford 2,5-disubstituted-1,3,4-oxadiazoles **3** (**a**–**m**) and **4** (**a**–**m**) (Scheme 1). To establish the general validity of our newly developed method, several selected one-pot microwave-assisted syntheses were carried out. The reaction was found to proceed smoothly under microwave irradiation within 6–16 min whereas under reflux conditions in 4–10 h (shown in Tables 1 and 2). The products were isolated by simple cold aqueous work-up followed by either solvent extraction or precipitation and were finally purified by column chromatography wherever necessary to afford pure 2,5-disubstituted-1,3,4-oxadiazole. This method appeared to be the rapid and economical with wide range of applications.[7]



Scheme 1. Reagents: (i) $POCl_3$; (ii) $POCl_3$, Al_2O_3.

2.2. Tyrosinase inhibition studies

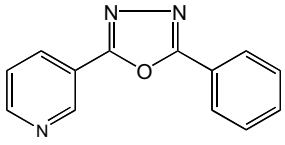
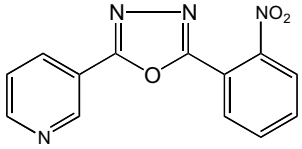
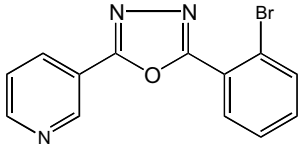
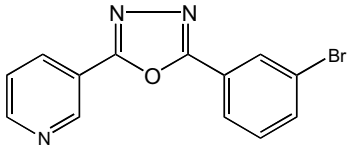
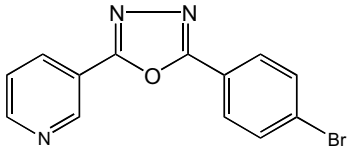
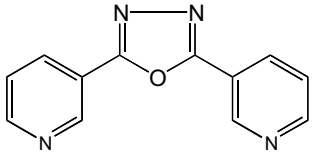
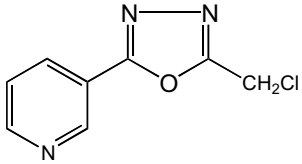
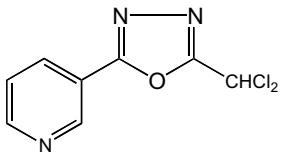
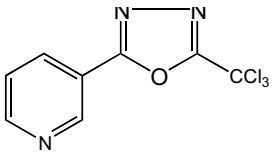
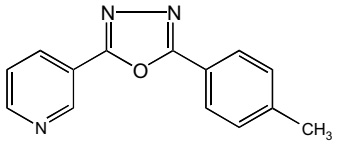
In the present studies, two types of 26 derivatives of the oxadiazole basic skeleton have been studied to explain their inhibition patterns and structure–activity relationships (SAR) against the enzyme tyrosinase, which is a multifunctional copper-containing enzyme, widely distributed in plants and animals and catalyses the *o*-hydroxylation of monophenols and also the oxidation of *o*-diphenols to *o*-quinones.[1]

In one type of compounds, substitutions were changing at different positions of the phenyl ring at C-5 while keeping the pyridine ring constant at C-2. In another type of compounds, substitutions were changing at different positions of the phenyl ring while keeping the *o*-methoxy phenyl ring constant at C-2 position.

In a previous report it was found that 3-hydroxypyridine-4-ones is showing inhibition against tyrosinase.[8] This was established that alkyl substitution at position 2 in the aromatic ring minimizes the interaction with tyrosinase. Several phenolic compounds have been reported to have potent tyrosinase inhibitory activity.[9–11]

Compound **3a** exhibited potent tyrosinase inhibition and the IC_{50} value is 5.15 μM, where the IC_{50} value of reference tyrosinase inhibitor kojic acids (KA) is 16.67 μM. This compound was totally unsubstituted. When C-2″ position was substituted with $-NO_2$ group the resulting **3b** was showing highly potent (IC_{50} = 3.18 μM) inhibition against tyrosinase, when compared with highly potent reference tyrosinase inhibitor L-mimosine (LM) (IC_{50} = 3.68 μM). Due to the substitution of this $-NO_2$ group the resulting compound exhibited potent inhibition. But when the same phenyl ring was found to have bromine atom at C-2″ (**3c**, IC_{50} = 5.23 μM) and C-3″ (**3d**, IC_{50} = 6.04 μM)

Table 1. Comparison between microwave-assisted and conventional method of synthesis of 2,5-disubstituted-1,3,4-oxadiazole **3** (**a**–**m**) in terms of time and yield

Sr.	R′	Structures	Microwave		Conventional	
			Time (min)	Yield (%)	Time (h)	Yield (%)
3a	C_6H_5		12	92	6	81
3b	*o*-$NO_2C_6H_4$		9	96	5	86
3c	*o*-BrC_6H_4		12	92	6	76
3d	*m*-BrC_6H_4		12	87	6	71
3e	*p*-BrC_6H_4		12	85	6	68
3f	3-Pyridinyl		12	89	9	75
3g	CH_2Cl		7	87	5	78
3h	$CHCl_2$		7	85	4	77
3i	CCl_3		6	91	4	76
3j	*p*-$CH_3C_6H_4$		13	81	7	69

(*continued on next page*)

Table 1 (*continued*)

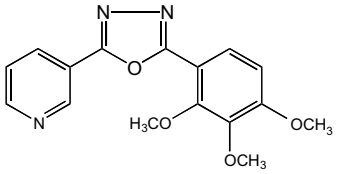
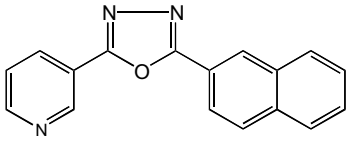
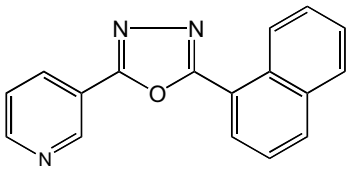
Sr.	R′	Structures	Microwave		Conventional	
			Time (min)	Yield (%)	Time (h)	Yield (%)
3k	3,4,5-Trimethoxybenzoyl		15	79	9	63
3l	1-$C_{10}H_7$		12	83	9	69
3m	2-$C_{10}H_7$		12	81	8	72

Table 2. Comparison between microwave-assisted and conventional method of synthesis of 2,5-disubstituted-1,3,4-oxadiazole **4** (**a**–**m**) in terms of time and yield

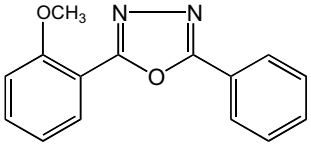
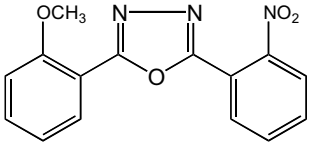
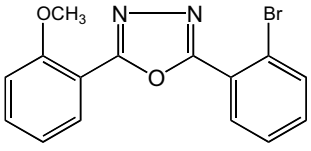
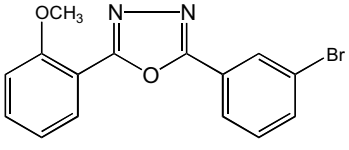
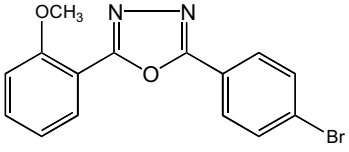
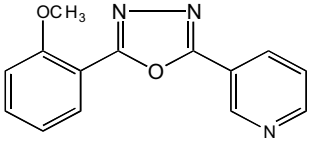
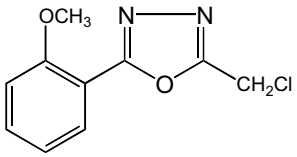
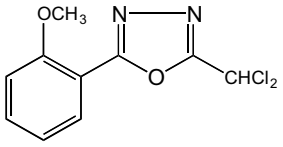
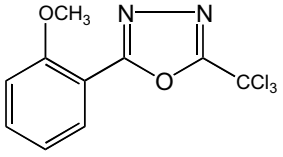
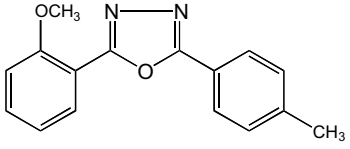
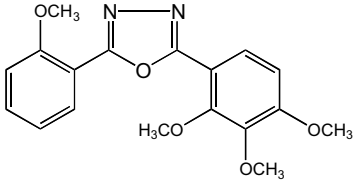
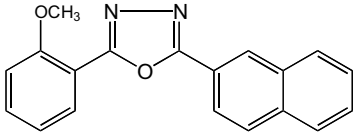
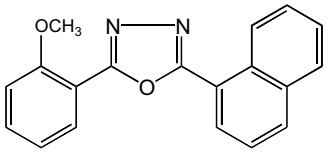
Sr.	R′	Structures	Microwave		Conventional	
			Time (min)	Yield (%)	Time (h)	Yield (%)
4a	C_6H_5		12	89	6	78
4b	*o*-$NO_2C_6H_4$		9	95	5	80
4c	*o*-BrC_6H_4		12	90	6	73
4d	*m*-BrC_6H_4		12	86	6	69
4e	*p*-BrC_6H_4		12	85	6	66
4f	3-Pyridinyl		12	87	9	74

Table 2 (*continued*)

Sr.	R′	Structures	Microwave		Conventional	
			Time (min)	Yield (%)	Time (h)	Yield (%)
4g	CH_2Cl		7	86	5	75
4h	$CHCl_2$		7	83	4	70
4i	CCl_3		6	88	4	73
4j	*p*-$CH_3C_6H_4$		13	79	7	67
4k	3,4,5-Trimethoxybenzoyl		15	76	9	60
4l	1-$C_{10}H_7$		12	79	9	67
4m	2-$C_{10}H_7$		12	76	8	69

positions, the activities were decreased although the potency was much better than the KA. Again when the bromination was done at C-4″ position, the resulting compound **3e** exhibited highest potency against the enzyme tyrosinase and IC_{50} value is 2.18 μM, which is 1.96 times more potent than the LM. We believe that 4′-bromophenyl group also has some extra effects on the tyrosinase inhibition. Recently Wang et al. reported that the 4-halobenzoic acids (4-fluorobenzoic acid, 4-chlorobenzoic acid and 4-bromobenzoic acid) can strongly inhibit both monophenolase activity and diphenolase activity of the enzyme, and the inhibition displays a reversible course, where the inhibition of 4-bromobenzoic acid is more potent than the other two. The kinetic analyses exhibited that the inhibition mechanism of all three 4-halobenzoic acids is noncompetitive inhibition to the diphenolase activity.[12]

When pyridine was attached at C-5 position, the resulting compound **3f** was showing highly potent (IC_{50} = 3.29 μM) inhibition against tyrosinase, even better than the LM.

When chloromethyl group was present at the C-5 position, the resulting compound **3g** was showing highly potent (IC_{50} = 4.18 μM) inhibition against tyrosinase, if compared with the KA, which is 3.99 times more potent. At the same position one more chlorine was attached, the resulting compound **3h** exhibited little more potency (IC_{50} = 4.01 μM) than the previous one. Finally when all chlorine atoms are attached, the resulting **3i** exhibited more potency (IC_{50} = 3.98 μM) than the previous two compounds. These compounds were proving that, for the better inhibition of tyrosinase, electronegativity is necessary and the tyrosinase inhibition is

directly proportional to the electronegativity of substituent(s).

Again when the compound has methyl group at C-4″ position, the resulting compound **3j** was showing less potency with IC_{50} = 10.40 μM, as compared to the unsubstituted one **3a** and with reference inhibitor KA. When the compound was substituted with 1″-naphthyl group at C-5 position, the resulting compound **3l** was showing potent (IC_{50} = 3.23 μM) inhibition, if compared with LM.

In the second series of the library of compounds, substitutions have been done at C-5 position of the oxadiazole ring, while keeping the methoxy group at C-2′. When bromine was present at C-3″ position, the resulting compound **4d** was showing potent inhibition (IC_{50} = 7.18 μM) when compared with KA. When bromine was present at C-4″ as in the case of compound **4e**, then the potency of the compound decreased (IC_{50} = 7.82 μM). Again it has been noted that when bromine is present at C-2″ rather than at C-3″, as in the case of compound **4c**, the potency has been found to increase (IC_{50} = 5.16 μM) and exhibit better inhibition than the **4d** and **4e**. When the bromine was totally replaced by phenyl ring, as in the case of compound **4a**, then the potency of the compound decreased (IC_{50} = 8.71 μM). It means that, the presence and the position of the –Br is essential for tyrosinase inhibition, which is also supporting the findings of Wang et al.[12]

When the tricholoromethyl group is present at C-5 position **4i** of oxadiazole ring the compound showed better inhibition (IC_{50} = 6.21 μM), when compared with the compound **4h** (IC_{50} = 7.28 μM), where one –Cl was replaced with proton. The compound **4j**, containing methyl group at aromatic ring, exhibited excellent potency (IC_{50} = 6.45 μM). The compound **4m**, having naphthyl group have IC_{50} = 7.81 μM.

All these studies are presented in tabular and graphical forms in Tables 3 and 4 and also graphically in Figures 1 and 2.

The inhibition mechanisms of the inhibitors most likely appearing from the presence of a particular hydrophobic site, which can accommodate these inhibitors which could be formed due to a probable conformational change that was induced by binding of substrate with the enzyme.[6] Unfortunately, the crystal structure of the enzyme mushroom tyrosinase has not yet been published. So we are unable to explain the probable binding interactions between the inhibitors and the protein in this stage, by taking the three-dimensional structure of the protein by molecular docking experiments. We are going to report the modeling of the enzyme through homology modeling approaches[13] and after validating properly of the model, especially solving the folding related problems we will further study the docking interactions.

In the near future we will communicate about the calculations of QSAR–QSPR molecular descriptors, molecular modeling, docking and 3D-QSAR (three-dimensional quantitative structure–activity relationships), like CoMFA, CoMSIA, Golpe, etc., studies of the same and similar tyrosinase inhibitors.

It can be concluded from this whole study that for the better inhibition of enzyme tyrosinase, electronegative changeover is crucial and the location of the group is also imperative in support of the inhibition. If the electronegativity is increased the inhibition also increases. The compound **3e** (3′-[5-(4′-bromophenyl)-1,3,4-oxadiazol-2-yl]pyridine) exhibited most potent inhibition against the enzyme tyrosinase, while compared with both of the reference inhibitors.

The molecule **3e** preserves the best candidature as a lead molecule for further development of drug for the treatments of several skin disorders.

Table 3. Tyrosinase inhibitory activities of the series **3** (**a**–**m**) as compared with the standard inhibitors

Compounds	IC_{50}(Mean ± SEM[a]) (μM)
3a	5.15 ± 0.02574
3b	3.18 ± 0.01774
3c	5.23 ± 0.023
3d	6.04 ± 0.00081
3e	2.18 ± 0.01774
3f	3.29 ± 0.02956
3g	4.18 ± 0.00293
3h	4.01 ± 0.0271
3i	3.98 ± 0.003112
3j	10.40 ± 0.01207
3k	ND[c]
3l	3.23 ± 0.01936
3m	ND[c]
Kojic acid[b]	16.67 ± 0.5190
L-Mimosine[b]	3.68 ± 0.02234

[a] SEM: Standard error of the mean.
[b] Standard inhibitors (KA and LM) of the enzyme tyrosinase.
[c] Not done.

Table 4. Tyrosinase inhibitory activities of the series **4** (**a**–**m**), as compared with the standard inhibitors

Compounds	IC_{50}(Mean ± SEM[a]) (μM)
4a	8.71 ± 0.022
4b	ND[c]
4c	5.16 ± 0.02371
4d	7.18 ± 0.513
4e	7.82 ± 0.563
4f	ND[c]
4g	ND[c]
4h	7.28 ± 0.0694
4i	6.21 ± 0.00371
4j	6.43 ± 0.1003
4k	ND[c]
4l	ND[c]
4m	7.81 ± 0.563
Kojic acid[b]	16.67 ± 0.5190
L-Mimosine[b]	3.68 ± 0.02234

[a] SEM: Standard error of the mean.
[b] Standard inhibitors (KA and LM) of the enzyme tyrosinase.
[c] Not done.

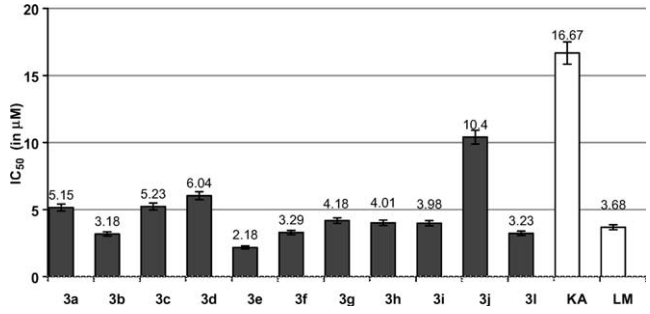


Figure 1. Graphical presentation of the comparative IC_{50} values of the series **3** (**a**–**m**) against the enzyme tyrosinase.

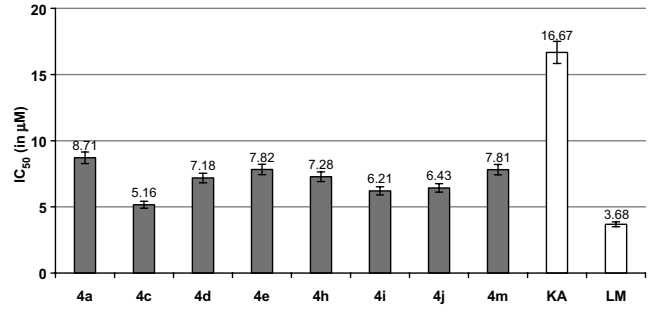


Figure 2. Graphical presentation of the comparative IC_{50} values of the series **4** (**a**–**m**) against the enzyme tyrosinase.

3. Materials and methods

3.1. General experimental

The ultraviolet spectra were measured in chloroform on a Lambda 5 UV/vis spectrophotometer (Perkin–Elmer). IR spectra (KBr discs or MeOH) were recorded on a Bruker FT-IR IFS48 spectrophotometer. EI mass spectra data were recorded with various MAT 711 (70 eV) spectrophotometers and data are tabulated as *m*/*z* ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using Bruker AC400 (500 and 400 MHz) spectrophotometer, respectively. Splitting patterns are as follows: s, singlet; d, doublet; dd, double doublets; t, triplet; m, multiplet. Chemical shifts are reported in δ (ppm) and coupling constants are given in hertz. The progress of all reactions was monitored by TLC, which was performed on 2.0×5.0 cm aluminum sheets precoated with silica gel $60F_{254}$ to a thickness of 0.25 mm (Merck). The chromatograms were visualized under ultraviolet light (254–366 nm) or iodine vapours.

The hydrazides used as intermediates for the title compounds were synthesized and characterized satisfactorily. Phosphorous oxychloride and all the carboxylic acids is commercially available (Flulka Aldrich).

3.2. Tyrosinase inhibition assay

Tyrosinase inhibition assays were performed in 96-well microplate format using SpectraMax® 340 (Molecular Devices, CA, USA) microplate reader according to the developed method earlier described by Hearing.[14]

First the compounds were screened for the *o*-diphenolase inhibitory activity of tyrosinase using L-DOPA as substrate. All the active inhibitors from the preliminary screening were subjected for IC_{50} studies. Briefly, all the compounds were dissolved in DMSO and finally the solvent mixture was 2.5%. Mushroom tyrosinase (30 units, 28 nM) was first preincubated with the compounds, in 50 nM Na–phosphate buffer (pH 6.8) for 10 min at 25 °C. Then the L-DOPA (0.5 mM) was added to the reaction mixture and the enzyme reaction was monitored by measuring the change in absorbance at 475 nm (at 37 °C) of the formation of the DOPA chrome for 10 min.

The percent inhibition of the enzyme and IC_{50} values of the active compounds were calculated using a program developed with JAVA and MACRO EXCEL® 2000 (Microsoft Corp., USA) for this purpose. The following equation has been followed:

$$\text{Percent inhibition} = [\text{ABS}_{\text{Blank}} - \text{ABS}_{\text{Sample}}/\text{ABS}_{\text{Blank}}] \times 100$$

Here the ABS_{Blank} and ABS_{Sample} are the absorbances for the blank and samples, respectively. All the studies have been done atleast in triplicates and the results here represents the Mean ± SEM. (standard error of the mean). All the regents, enzyme, substrate and reference compounds, were purchased from Sigma Chem. Co., MO, USA.

3.3. Spectral data of the compounds

3.3.1. 3′-(5-Phenyl-1,3,4-oxadiazol-2-yl)pyridine (3a). Yield 92%; mp 112–114 °C; $R_f = 0.34$ (ethyl acetate–acetone, 9:1); UV (methanol): λ_{max} (log ε) 256 (2.32) nm^{-1}; IR (KBr) ν_{max}: 3073 (C–H), 1667 (C=N), 1557 (C=C), 1287 (C–O), 832, 659 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (d, 1H, $J = 1.1$ Hz, H-2′), 9.13 (dd, 1H, $J_{6',5'} = 4.9$ Hz, H-6′), 8.81 (br d, $J_{4',5'} = 8.3$ Hz, 1H, H-4′), 8.59 (dd, 1H, $J_{5',6'} = 4.9$, $J_{5',4'} = 8.3$ Hz, H-5′), 7.63 (dd, 2H, $J_{2'',3''/6'',5''} = 7.8$, $J_{2'',4''/6'',4''} = 2.3$ Hz, H-2″/H-6″), 7.50 (t, 1H, $J = 7.8$ Hz, H-4″), 7.38 (t, 2H, J = 7.8, H-3″/5″); EI MS (*m*/*z*): 223 (M^+, 21), 145 (31), 106 (100), 77 (79), 78 (65), 68 (35), 51 (72). Anal. Calcd for $C_{13}H_9N_3O$: C, 9.95; H, 4.06; N, 18.82; O, 7.17. Found: C, 69.86; H, 3.97; N, 18.73; O, 7.08.

3.3.2. 3′-[5-(2″-Nitrophenyl)-1,3,4-oxadiazol-2-yl]pyridine (3b). Yield 96%; mp 89 °C; $R_f = 0.40$ (ethyl acetate–acetone, 8:2); UV (methanol): λ_{max} (log ε) 283 (3.00) nm^{-1}; IR (KBr) ν_{max}: 1563 (C=C), 3065 (C–H), 1667 (C=N), 1283 (C–O), 1545 (NO_2), 831, 651; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.23 (d, 1H, $J = 1.2$ Hz, H-2′), 9.16 (dd, 1H, $J = 4.9$ Hz, H-6′), 8.92 (dd, 1H, $J = 8.2$, $J = 1.7$ Hz, H-3″), 8.87 (t, 1H, $J = 7.8$, H-5″), 8.76 (br d, 1H, $J = 8.3$ Hz, H-4′), 8.60 (dd, 1H, $J = 4.9$, 8.3 Hz, H-5′), 8.13 (dd, 1H, $J = 7.8$, 1.8 Hz, H-6″), 7.85 (t, 1H, $J = 7.8$ Hz, H-4″); EI MS (*m*/*z*): 268 (M^+, 6), 223 (9), 147 (29), 106 (100), 93 (43), 78 (75), 68 (39), 51 (84). Anal. Calcd for $C_{13}H_8N_4O_3$: C, 58.21; H, 3.01; N, 20.89; O, 17.89. Found: C, 58.29; H, 3.08; N, 20.98; O, 17.97.

3.3.3. 3′-[5-(2″-Bromophenyl)-1,3,4-oxadiazol-2-yl]pyridine (3c). Yield 92%; mp 102–114 °C; $R_f = 0.38$ (ethyl acetate–acetone, 8:2); UV (methanol): λ_{max} ($\log\varepsilon$) 261 (2.28) nm^{-1}; IR (KBr) ν_{max}: 3069 (C–H), 1665 (C=N), 1561 (C=C), 1289 (C–O), 647 (C–Br); ^1H NMR (500 MHz, DMSO-d_6): δ 9.21 (d, 1H, $J = 1.1$ Hz, H-2′), 9.12 (br d, 1H, $J = 4.8$ Hz, H-6′), 8.59 (br d, 1H, $J = 8.3$ Hz, H-4′), 8.91 (dd, $J = 7.9$, 2.1 Hz, H-3″), 7.86 (dd, 1H, $J = 4.8$, 8.3 Hz, H-5′), 7.58 (t, 1H, $J = 7.9$ Hz, H-4″), 7.49 (dd, 1H, $J = 7.9$, 1.9 Hz, H-6″), 7.28 (t, 1H, $J = 7.9$ Hz, H-5″); EI MS (*m*/*z*): 303 (M^{+1}, 48), 301 (41), 223 (33), 157 (29), 106 (69), 78 (100), 68 (49), 51 (52). Anal. Calcd for $C_{13}H_8N_4O_3$: C, 58.21; H, 3.01; N, 20.89; O, 17.89. Found: C, 58.29; H, 3.08; N, 20.98; O, 17.97.

3.3.4. 3′-[5-(3″-Bromophenyl)-1,3,4-oxadiazol-2-yl]pyridine (3d). Yield 87%; mp 127–130 °C; $R_f = 0.31$ (ethyl acetate–acetone, 8:2); UV (methanol): λ_{max} ($\log\varepsilon$) 263 (2.29) nm^{-1}; IR (KBr) ν_{max} : 3069 (ArC–H), 1664 (C=N), 1565 (C=C), 1289 (C–O), 829, 653 (C–Br); ^1H NMR (500 MHz, DMSO-d_6): δ 9.22 (d, 1H, $J = 1.1$ Hz, H-2′), 9.11 (br d, 1H, $J = 4.9$ Hz, H-6′), 8.84 (br d, 1H, $J = 8.3$ Hz, H-4′), 8.58 (dd, 1H, $J = 4.9$, 8.3 Hz, H-5′), 7.78 (d, 1H, $J = 1.7$ Hz, H-2″), 7.68 (dd, $J = 8.3$, 1.7 Hz, H-4″), 7.46 (dd, 1H, $J = 7.8$, $J = 1.7$ Hz, H-6″), 7.41 (dd, 1H, $J = 8.3$, $J = 7.8$ Hz, H-5″); EI MS (*m*/*z*): 303 (M+2, 43), 301 (M^+, 48), 223 (33), 157 (27), 106 (59), 78 (100), 77 (69), 68 (53), 51 (78). Anal. Calcd for $C_{13}H_8BrN_3O$: C, 51.68; H, 2.67; Br, 26.45; N, 13.91; O, 5.30. Found: C, 51.61; H, 2.74; Br, 26.39; N, 13.97; O, 5.31.

3.3.5. 3′-[5-(4″-Bromophenyl)-1,3,4-oxadiazol-2-yl]pyridine (3e). Yield 85%; mp 199–102 °C; $R_f = 0.37$ (ethyl acetate–acetone, 8:2); UV (methanol): λ_{max} ($\log\varepsilon$) 262 (2.30) nm^{-1}; IR (KBr) ν_{max}: 3067 (C–H), 1662 (C=N), 1568 (C=C), 1283 (C–O), 821, 656 (C–Br); ^1H NMR (400 MHz, $CDCl_3$): δ 9.20 (d, 1H, $J = 1.1$ Hz, H-2′), 9.10 (dd, 1H, $J = 4.9$, 1.6 Hz, H-6′), 8.83 (br d, 1H, $J = 8.3$ Hz, H-4′), 8.59 (dd, 1H, $J = 4.9$, 8.3 Hz, H-5′), 7.76 (dd, 2H, $J = 8.4$, 1.2 Hz, H-3″/5″), 7.57 (dd, 2H, $J = 8.4$, 1.3 Hz, H-2″/6″); EIMS (*m*/*z*): 303 (M+2, 48), 301 (M^+, 50), 223 (39), 157 (31), 106 (76), 78 (100), 68 (43), 51 (59). Anal. Calcd for $C_{13}H_8BrN_3O$: C, 51.68; H, 2.67; Br, 26.45; N, 13.91; O, 5.30. Found: C, 51.58; H, 2.77; Br, 26.37; N, 13.99; O, 5.31.

3.3.6. 3′-[5-(3″-Pyridinyl)-1,3,4-oxadiazol-2-yl]pyridine (3f). Yield 89%; mp 124–126 °C; $R_f = 0.43$ (ethyl acetate–acetone, 8:2); UV (methanol): λ_{max} ($\log\varepsilon$) 208 (2.41) nm^{-1}; IR (KBr) ν_{max}: 3061 (C–H), 1659 (C=N), 1563 (C=C), 1286 (C–O), 831, 625; ^1H NMR (500 MHz, DMSO-d_6): δ 9.22 (d, 2H, $J = 1.1$ Hz, H-2′/2″), 9.11 (br d, 2H, $J = 4.9$ Hz, H-6′/6″), 8.84 (br d, 2H, $J = 8.3$ Hz, H-4′/4″), 8.63 (dd, 1H, $J = 4.9$, 8.3 Hz, H-5′/5″); EI MS (*m*/*z*): 303 (M^+, 12), 146 (9), 106 (100), 78 (80), 51 (66). Anal. Calcd for $C_{12}H_8N_4O$: C, 64.28; H, 3.60; N, 24.99; O, 7.14. Found: C, 64.19; H, 3.69; N, 24.88; O, 7.27.

3.3.7. 3′-[5-(Chloromethyl)-1,3,4-oxadiazol-2-yl]pyridine (3g). Yield 87%; mp 112–114 °C; $R_f = 0.34$ (ethyl acetate–acetone, 9:1); UV (methanol): λ_{max} ($\log\varepsilon$) 207 (2.41) nm^{-1}; IR (KBr) ν_{max}: 3059 (C–H), 2993 (C–H), 1667 (C=N), 1561 (C=C), 1285 (C–O), 741 (C–Cl), 610; ^1H NMR (500 MHz, DMSO-d_6): δ 9.19 (d, 1H, $J = 1.1$ Hz, H-2′), 9.11 (dd, 1H, $J = 4.9$, 1.7 Hz, H-6′), 8.89 (br d, 1H, $J = 8.3$ Hz, H-4′), 8.67 (dd, 1H, $J = 4.9$, 8.3 Hz, H-5′), 3.21 (s, 2H, H-1″); EI MS (*m*/*z*): 197 (M+2, 4), 195 (M^+, 13), 159 (29), 146 (35), 78 (100), 68 (33), 51 (78). Anal. Calcd for $C_8H_6ClN_3O$: C, 49.12; H, 3.09; Cl, 18.12; N, 21.48; O, 8.18. Found: C, 49.01; H, 3.20; Cl, 18.19; N, 21.41; O, 8.19.

3.3.8. 3′-[5-(Dichloromethyl)-1,3,4-oxadiazol-2-yl]pyridine (3h). Yield 85%; mp 145–147 °C; $R_f = 0.34$ (ethyl acetate–acetone, 9:1); UV (methanol): λ_{max} ($\log\varepsilon$) 209 (2.42) nm^{-1}; IR (KBr) ν_{max}: 3061 (C–H), 2998 (C–H), 1664 (C=N), 1564 (C=C), 1281 (C–O), 757 (C–Cl), 612; ^1H NMR (500 MHz, DMSO-d_6): δ 9.20 (d, 1H, $J = 1.1$ Hz, H-2′), 9.12 (br d, 1H, $J = 4.9$ Hz, H-6′), 8.87 (br d, 1H, $J = 8.3$ Hz, H-4′), 8.69 (dd, 1H, $J = 8.3$, 4.9 Hz, H-5′), 3.39 (s, 1H, H-1″); EI MS (*m*/*z*): 234 (M+4, 6), 232 (M+2, 19), 230 (M^+, 29), 194 (66), 159 (29), 146 (63), 106 (73), 78 (100), 51 (85). Anal. Calcd for $C_8H_5Cl_2N_3O$: C, 41.77; H, 2.19; Cl, 30.82; N, 18.27; O, 6.95. Found: C, 41.86; H, 2.10; Cl, 30.77; N, 18.32; O, 6.94.

3.3.9. 3′-[5-(Trichloromethyl)-1,3,4-oxadiazol-2-yl]pyridine (3i). Yield 91%; mp 127–129 °C; $R_f = 0.34$ (ethyl acetate–acetone, 9:1); UV (methanol): λ_{max} ($\log\varepsilon$) 207 (2.41) nm^{-1}; IR (KBr) ν_{max}: 1562 (C=C), 3059 (C–H), 1663 (C=N), 1283 (C–O), 781 (C–Cl), 613; ^1H NMR (500 MHz, DMSO-d_6): δ 9.23 (d, 1H, $J = 1.1$ Hz, H-2′), 9.12 (br d, 1H, $J = 4.9$ Hz, H-6′), 8.86 (br d, 1H, $J = 8.3$ Hz, H-4′), 8.63 (dd, 1H, $J = 4.9$, 8.3 Hz, H-5′); EI MS (*m*/*z*): 270 (M+6, 1), 268 (M+4, 6), 266 (M+2, 18), 264 (M^+, 13), 158 (29), 118.5 (39), 106 (43), 78 (100), 68 (49), 51 (41). Anal. Calcd for $C_8H_4Cl_3N_3O$: C, 36.33; H, 1.52; Cl, 40.21; N, 15.89; O, 6.05. Found: C, 36.45; H, 1.40; Cl, 40.14; N, 15.96; O, 6.06.

3.3.10. 3′-[5-(4″-Methylphenyl)-1,3,4-oxadiazol-2-yl]pyridine (3j). Yield 81%; mp 102–104 °C; $R_f = 0.43$ (ethyl acetate–acetone, 9:1); UV (methanol): λ_{max} ($\log\varepsilon$) 206 (2.41) nm^{-1}; IR (KBr) ν_{max}: 3063 (C–H), 2912 (C–H), 1663 (C=N), 1561 (C=C), 1283 (C–O), 608; ^1H NMR (500 MHz, DMSO-d_6): δ 9.14 (d, 1H, $J = 1.1$ Hz, H-2′), 9.04 (br d, 1H, $J = 4.9$ Hz, H-6′), 8.78 (br d, 1H, $J = 8.3$ Hz, H-4′), 8.54 (dd, 1H, $J = 4.9$, 8.3 Hz, H-5′), 7.49 (br d, 2H, $J = 7.8$ Hz, H-2″/6″), 7.32 (d, 2H, $J = 7.8$ Hz, H-3″/5″); EI MS (*m*/*z*): 237 (M^+, 13), 222 (28), 146 (58), 106 (43), 78 (100), 77 (62), 68 (47). Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71; O, 6.74. Found: C, 70.79; H, 4.75; N, 17.63; O, 6.69.

3.3.11. 3′-[5-(3″,4″,5″-Trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine (3k). Yield 79%; mp 137–140 °C; $R_f = 0.39$ (ethyl acetate); UV (methanol): λ_{max} ($\log\varepsilon$) 283 (3.17) nm^{-1}; IR (KBr) ν_{max}: 3059 (C–H), 1665 (C=N), 1562 (C=C), 1284 (C–O), 1198 (Ph–O–Me), 619; ^1H NMR (400 MHz, MeOD-d_4): δ 9.20 (d, 1H, $J = 1.1$ Hz, H-2′), 9.13 (br d, 1H, $J = 4.9$ Hz, H-6′), 8.87 (br d, 1H, $J = 8.3$ Hz, H-4′), 8.65 (dd, 1H,

J = 4.9, 8.3 Hz, H-5′), 7.49 (s, 2H, H-2″/6″), 3.93 (s, 6H, –OCH_3), 3.88 (s, 3H, OCH_3); EI MS (*m*/*z*): 313 (M^+, 9), 282 (11), 251 (13), 220 (18), 146 (37), 106 (73), 78 (100), 77 (53), 68 (38), 51 (79). Anal. Calcd for $C_{16}H_{15}N_3O_4$: C, 61.34; H, 4.38; N, 13.41; O, 20.43. Found: C, 61.27; H, 4.45; N, 13.34; O, 20.51.

3.3.12. 3′-[5-(1″-Naphthyl)-1,3,4-oxadiazol-2-yl]pyridine (3l). Yield 83%; mp 125–127 °C; R_f = 0.34 (ethyl acetate–acetone, 8:2); UV (methanol): λ_{max} (log ε) 289 (3.17) nm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 9.22 (d, 1H, J = 1.1 Hz, H-2′), 9.15 (br d, 1H, J = 4.9 Hz, H-6′), 8.89 (br d, 1H, J = 8.3 Hz, H-4′), 8.60 (dd, 1H, J = 4.9, 8.3 Hz, H-5′), 8.46 (dd, 1H, J = 8.4, 1.3 Hz, H-8″), 8.38 (dd, 1H, J = 8.4, 1.4 Hz, H-4″), 8.29 (dd, 1H, J = 8.0, 1.3 Hz, H-2″), 8.19 (t, 1H, J = 8.0 Hz, H-3″), 7.68 (t, 1H, J = 8.4 Hz, H-7″), 7.60 (dd, 1H, J = 7.8, 1.4 Hz), 7.51 (t, 1H, J = 8.4 Hz, H-6″); EI MS (*m*/*z*): 273 (M^+, 57), 146 (47), 106 (77), 78 (100), 77 (63), 68 (49), 51 (67); IR (KBr) ν_{max}: 3063 (C–H), 1561 (C=C), 1661 (C=N), 1281 (C–O), 637, 609. Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 74.71; H, 4.06; N, 15.38; O, 5.85. Found: C, 74.65; H, 4.12; N, 15.31; O, 5.92.

3.3.13. 3′-[5-(2″-Naphthyl)-1,3,4-oxadiazol-2-yl]pyridine (3m). Yield 81%; mp 166–169 °C; R_f = 0.34 (ethyl acetate–acetone, 9:1); UV (methanol): λ_{max} (log ε) 288 (3.17) nm^{-1}; IR (KBr) ν_{max}: 1567 (arom. C=C), 3062 (C–H), 1662 (C=N), 628, 603; ^1H NMR (500 MHz, DMSO-d_6): δ 9.25 (d, 1H, J = 1.1 Hz, H-2′), 9.16 (br d, 1H, J = 4.9, 1.3 Hz, H-6′), 8.71 (br d, 1H, J = 8.3 Hz, H-4′), 8.49 (dd, 1H, J = 4.9, 8.3 Hz, H-5′), 8.32 (br s, 1H, H-1″), 8.13 (d, 1H, J = 8.1 Hz, H-4″), 8.03 (br d, J = 8.1, H-3″), 7.82 (dd, 1H, J = 7.8, 1.6 Hz, H-5″), 7.76 (dd, 1H, J = 7.9, 1.6 Hz, H-8″), 7.54 (t, J = 7.9 Hz, H-7″), 7.45 (t, J = 7.9 Hz, H-6″); EI MS (*m*/*z*): 273 (M^+, 57), 146 (47), 106 (76), 78 (100), 77 (63), 68 (49), 51 (67). Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 74.71; H, 4.06; N, 15.38; O, 5.85. Found: C, 74.65; H, 4.12; N, 15.31; O, 5.92.

3.3.14. Methyl 2-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl ether (4a). Yield 89%; UV (methanol): λ_{max} (log ε) 290 (3.19) nm^{-1}; IR (KBr) ν_{max}: 1568 (arom. C=C), 1662 (C=N), 1267 (C–O), 619, 601; ^1H NMR (400 MHz, DMSO-d_6): δ 8.19 (overlapped, 2H, H-2″/H-6″), 7.91 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.49 (overlapped, 3H, H-3″,4″,5″), 7.00 (t, J = 7.6 Hz, H-5′), 7.41 (br t, 1H, J = 8.4 Hz, H-4′), 7.11 (d, 1H, J = 8.4 Hz, H-3′), 3.88 (s, 3H, –OCH_3); EI MS (*m*/*z*): 252 (M^+, 8), 175 (136), 135 (47), 107 (100), 77 (81), 68 (29). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79, N, 11.10; O, 12.68. Found: C, 71.40; H, 4.81, N, 11.18; O, 12.60.

3.3.15. 2-(2-Methoxyphenyl)-5-(2-nitrophenyl)-1,3,4-oxadiazole (4b). Yield 95%; UV (methanol): λ_{max} (log ε) 291 (3.19) nm^{-1}; IR (KBr) ν_{max}: 1563 (arom. C=C), 3069 (C–H), 1658 (C=N), 1265 (C–O), 627, 598; ^1H NMR (400 MHz, DMSO-d_6): δ 8.87 (dd, 1H, J = 7.8, 1.7 Hz, H-3″), 8.79 (t, 1H, J = 7.8 Hz, H-5″), 8.3 (dd, 1H, J = 7.8, J = 1.4 Hz, H-6″), 8.08 (t, 1H, J = 7.8 Hz, H-4″), 7.98 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.44 (br t, 1H, J = 8.4 Hz, H-4′), 7.15 (d, 1H, J = 8.4 Hz, H-3′), 7.00 (t, J = 7.6 Hz, H-5′), 3.88 (s, 3H, –OCH_3); EI MS (*m*/*z*): 297 (M^+, 8), 251 (44), 266 (32), 122 (56), 107 (23), 68 (39), 77 (100). Anal. Calcd for $C_{15}H_{11}N_3O_4$: C, 60.61; H, 3.73; N, 14.14; O, 21.53. Found: C, 60.67; H, 3.67; N, 14.21; O, 21.46.

3.3.16. 2-(2-Bromophenyl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole (4c). Yield 90%; UV (methanol): λ_{max} (log ε) 273 (3.17) nm^{-1}; IR (KBr) ν_{max}: 1568 (aromatic C=C), 1662 (C=N), 1267 (C–O), 619, 601; ^1H NMR (400 MHz, DMSO-d_6): δ 8.03 (dd, 1H, J = 8.1, J = 1.1 Hz, H-6′), 7.87 (br d, J = 7.9 Hz, H-3″), 7.60 (t, 1H, J = 7.9 Hz, H-4″), 7.92 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.34 (t, 1H, J = 7.9 Hz, H-5″), 7.44 (br t, 1H, J = 8.4 Hz, H-4′), 7.15 (d, 1H, J = 8.4 Hz, H-3′), 7.00 (t, J = 7.6 Hz, H-5′), 3.88 (s, 3H, –OCH_3); EI MS (*m*/*z*): 330 (M^+, 18), 332 (M+2, 16), 300 (39), 251 (100), 136 (59), 107 (62), 81 (6), 79 (17), 77 (71), 68 (46). Anal. Calcd for $C_{15}H_{11}N_2O_2Br$: C, 54.40; H, 3.35; Br, 24.13; N, 8.46; O, 9.66. Found: C, 54.45; H, 3.30; Br, 24.23; N, 8.38; O, 9.63.

3.3.17. 2-(3-Bromophenyl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole (4d). Yield 86%; R_f = 0.34 (ethyl acetate–acetone, 9:1); UV (methanol): λ_{max} (log ε) 273 (3.17) nm^{-1}; IR (KBr) ν_{max}: 1564 (arom. C=C), 1659 (C=N), 1285 (C–O), 621, 609; ^1H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, 1H, J = 1.7 Hz, H-2″), 7.91 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.89 (dd, 1H, J = 8.2 Hz, H-4″), 7.79 (dd, 1H, J = 7.8, 1.7 Hz, H-6″), 7.55 (dd, 1H, J = 8.2, 7.8 Hz, H-5″), 7.44 (br t, 1H, J = 8.4 Hz, H-4′), 7.11 (d, 1H, J = 8.4 Hz, H-3′), 7.00 (t, J = 7.6 Hz, H-5′), 3.88 (s, 3H, –OCH_3); EI MS (*m*/*z*): 330 (M^+, 20), 332 (M+2, 19), 300 (48), 251 (100), 136 (27), 107 (69), 81 (8), 79 (6), 77 (76), 68 (31). Anal. Calcd for $C_{17}H_{11}N_3O$: C, 54.40; H, 3.35; Br, 24.13; N, 8.46; O, 9.66. Found: C, 54.44; H, 3.31; Br, 24.19; N, 8.40; O, 9.66; O, 9.66.

3.3.18. 2-(4-Bromophenyl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole (4e). Yield 85%; R_f = 0.31 (ethyl acetate–acetone, 9:1); UV (methanol): λ_{max} (log ε) 275 (3.17) nm^{-1}; IR (KBr) ν_{max}: 1567 (arom. C=C), 1661 (C=N), 1279 (C–O), 626, 611; ^1H NMR (400 MHz, DMSO-d_6): δ 7.89 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.74 (dd, 2H, J = 8.4, J = 1.3 Hz, H-3″/5″), 7.54 (dd, 2H, J = 8.4, J = 1.3, H-2″/6″), 7.42 (br t, 1H, J = 8.4 Hz, H-4′), 7.02 (t, J = 7.6 Hz, H-5′), 7.16 (d, 1H, J = 8.4 Hz, H-3′), 3.87 (s, 3H, –OCH_3); EI MS (*m*/*z*): 330 (M^+, 20), 332 (M+2, 19), 300 (48), 251 (100), 136 (27), 107 (69), 81 (8), 79 (6), 77 (76), 68 (31). Anal. Calcd for $C_{15}H_{11}N_2O_2Br$: C, 54.40; H, 3.35; Br, 24.13; N, 8.46. Found: C, 54.47; H, 3.28; Br, 24.20; N, 8.38; O, 9.66.

3.3.19. Methyl 2-[5-(3-pyridinyl)-1,3,4-oxadiazol-2-yl]-phenyl ether (4f). Yield 87%; UV (methanol): λ_{max} (log ε) 273 (3.17) nm^{-1}UV (methanol): λ_{max} (log ε) 251 (3.15) nm^{-1}; IR (KBr) ν_{max}: 1571 (arom. C=C), 1661 (C=N), 1269 (C–O), 625, 607; ^1H NMR (400 MHz, DMSO-d_6): δ 9.21 (d, 1H, J = 0.98 Hz, H-2″), 9.11 (dd, 1H, J = 4.9, 1.6 Hz, H-6″), 8.87 (dd, 1H, J = 4.9,

8.3 Hz, H-5″), 8.54 (br d, 1H, J = 8.3 Hz, H-4″), 7.95 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.48 (br t, 1H, J = 8.4 Hz, H-4′), 7.16 (d, 1H, J = 8.4 Hz, H-3′), 7.05 (t, J = 7.6 Hz, H-5′), 3.88 (s, 3H, –OCH_3); EI MS (*m*/*z*): 253 (M^+, 18), 175 (66), 135 (35), 107 (48), 78 (100), 68 (38). Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59; O, 12.63. Found: C, 66.48; H, 4.30; N, 16.62; O, 12.60.

3.3.20. 2-(Chloromethyl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole (4g). Yield 86%; UV (methanol): λ_{max} (log ε) 235 (2.46) nm^{-1}; IR (KBr) ν_{max}: 1571 (arom. C=C), 1661 (C=N), 1269 (C–O), 764 (C–Cl), 625, 607; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.43 (br t, 1H, J = 8.4 Hz, H-4′), 7.15 (d, 1H, J = 8.4 Hz, H-3′), 7.04 (t, J = 7.6 Hz, H-5′), 3.86 (s, 3H, –OCH_3), 3.21 (s, 2H, H-1″); EI MS (*m*/*z*): 224 (M^+, 21), 226 (M+2, 7), 189 (8), 209 (25), 181 (43), 175 (31), 105 (52), 135 (100), 77 (68), 51 (29). Anal. Calcd for $C_{10}H_9N_2O_2Cl$: C, 53.47; H, 4.04; Cl, 15.78; N, 12.47; O, 14.24. Found: C, 53.52; H, 3.99; Cl, 15.76; N, 12.49; O, 14.25.

3.3.21. 2-(Dichloromethyl)-5-(2-methoxyphenyl)-1,3,4-oxadiazole (4h). Yield 83%; UV (methanol): λ_{max} (log ε) 235 (2.46) nm^{-1}; IR (KBr) ν_{max}: 1571 (arom. C=C), 1661 (C=N), 1269 (C–O), 769 (C–Cl), 625, 607; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.46 (br t, 1H, J = 8.4 Hz, H-4′), 7.15 (d, 1H, J = 8.4 Hz, H-3′), 7.02 (t, J = 7.6 Hz, H-5′), 3.88 (s, 3H, –OCH_3), 3.38 (s, 1H, H-1″); EI MS (*m*/*z*): 262 (M+4, 3), 260 (M+2, 9), 258 (M^+, 28), 225 (M+2, 11), 223 (31), 175 (48) 135 (29), 107 (58), 83 (27), 85 (8), 87 (3), 68 (69). Anal. Calcd for $C_{10}H_8N_2O_2Cl_2$: C, 46.36; H, 3.11; Cl, 27.37; N, 10.81; O, 12.35. Found: C, 46.39; H, 3.08; Cl, 27.43; N, 10.79; O, 12.31.

3.3.22. 2-(2-Methoxyphenyl)-5-(trichloromethyl)-1,3,4-oxadiazole (4i). Yield 88%; UV (methanol): λ_{max} (log ε) 232 (2.46) nm^{-1}; IR (KBr) ν_{max}: 1566 (arom. C=C), 1661 (C=N), 1269 (C–O), 751 (C–Cl), 614, 597; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.47 (br t, 1H, J = 8.4 Hz, H-4′), 7.16 (d, 1H, J = 8.4 Hz, H-3′), 7.01 (t, J = 7.6 Hz, H-5′), 3.88 (s, 3H, –OCH_3); EI MS (*m*/*z*): 299 (M+6, 0.20), 297 (M+4, 6), 295 (M+2, 15), 293 (M^+, 18), 174 (68), 135 (69), 107 (100), 68 (51), 118 (16), 120 (M+2, 12), 122 (M+4, 3), 124 (M+6, 0.10). Anal. Calcd for $C_{10}H_7N_2O_2Cl_3$: C, 40.92; H, 2.40; Cl, 36.23; O, 10.90. Found: C, 40.88; H, 2.44; Cl, 36.27; O, 10.86.

3.3.23. 2-(2-Methoxyphenyl)-5-(4-methylphenyl)-1,3,4-oxadiazole (4j). Yield 79%; UV (methanol): λ_{max} (log ε) 267 (3.11) nm^{-1}; IR (KBr) ν_{max}: 1573 (arom. C=C), 1663 (C=N), 1276 (C–O), 618, 595; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (br d, 2H, J = 7.8, H-2″/6″), 7.90 (dd, 1H, J = 7.6, J = 1.5 Hz, H-6′), 8.17 (br d, 2H, J = 8.6 Hz, H-2″/H-6″), 7.42 (overlapped, 3H, H-4′/3″/5″), 7.15 (d, 1H, J = 8.4 Hz, H-3′), 7.00 (t, J = 7.6 Hz, H-5′), 3.80 (s, 3H, OCH_3), 2.1 (s, 3H, CH_3); EI MS (*m*/*z*): 266 (M^+, 7), 175 (54), 135 (34), 105 (61), 91 (46), 77 (100). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52; O, 12.02. Found: C, 72.20; H, 5.26; N, 10.49; O, 12.05.

3.3.24. 2,3-Dimethoxy-5-[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl methyl ether (4k). Yield 76%; UV (methanol): λ_{max} (log ε) 261 (2.49) nm^{-1}; IR (KBr) ν_{max}: 1576 (arom. C=C), 1658 (C=N), 1264 (C–O), 629, 597; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (dd, 1H, J = 7.6, J = 1.5 Hz, H-6′), 7.41 (br t, 1H, J = 8.4 Hz, H-4′), 7.12 (d, 1H, J = 8.4 Hz, H-3′), 6.99 (t, J = 7.6 Hz, H-5′), 6.58 (s, 2H, H-2″/6″), 3.95 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3); FD MS (*m*/*z*): 342 (M^+). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18; O, 23.37. Found: C, 63.19; H, 5.26; N, 8.23; O, 23.32.

3.3.25. 3′-[5-(1″-Naphthyl)-1,3,4-oxadiazol-2-yl]pyridine (3l). Yield 83%; mp 125–127 °C; R_f = 0.34 (ethyl acetate–acetone, 8:2); UV (methanol): λ_{max} (log ε) 289 (3.17) nm^{-1}; 7.44 (br t, 1H, J = 8.4 Hz, H-4′), 7.15 (d, 1H, J = 8.4 Hz, H-3′), 7.00 (t, J = 7.6 Hz, H-5′), 3.88 (s, 3H, –OCH_3); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.22 (d, 1H, J = 1.1 Hz, H-2′), 9.15 (br d, 1H, J = 4.9 Hz, H-6′), 8.89 (br d, 1H, J = 8.3 Hz, H-4′), 8.60 (dd, 1H, J = 4.9, 8.3 Hz, H-5′), 8.46 (dd, 1H, J = 8.4, J = 1.3 Hz, H-8″), 8.38 (dd, 1H, J = 8.4, 1.4 Hz, H-4″), 8.29 (dd, 1H, J = 8.0, 1.3 Hz, H-2″), 8.19 (t, 1H, J = 8.0 Hz, H-3″), 7.68 (t, 1H, J = 8.4 Hz, H-7″), 7.60 (dd, 1H, J = 7.8, 1.4 Hz), 7.51 (t, 1H, J = 8.4 Hz, H-6″); EI MS (*m*/*z*): 273 (M^+, 57), 146 (47), 106 (77), 78 (100), 77 (63), 68 (49), 51 (67); IR (KBr) ν_{max}: 3063 (C–H), 1561 (C=C), 1661 (C=N), 1281 (C–O), 637, 609. Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 74.71; H, 4.06; N, 15.38; O, 5.85. Found: C, 74.65; H, 4.12; N, 15.31; O, 5.92.

3.3.26. 2-(2-Methoxyphenyl)-5-(2-naphthyl)-1,3,4-oxadiazole (4m). Yield 79%; UV (methanol): λ_{max} (log ε) 294 (2.49) nm^{-1}; IR (KBr) ν_{max}: 1568 (arom. C=C), 1662 (C=N), 1267 (C–O), 619, 601; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (br s, 1H, H-1″), 8.10 (d, 1H, J = 8.1 Hz, H-4″), 8.02 (br d, 1H, J = 8.1 Hz, H-3″), 7.91 (dd, 1H, J = 7.6, 1.5 Hz, H-6′), 7.80 (dd, 1H, J = 8.2, 1.1 Hz, H-5″), 7.73 (dd, 1H, J = 8.3, 1.3 Hz, H-8″), 7.50 (t, 1H, J = 8.3 Hz, H-7″), 7.41 (t, 1H, J = 8.0 Hz, H-6″), 7.44 (br t, 1H, J = 8.4 Hz, H-4′), 7.15 (d, 1H, J = 8.4 Hz, H-3′), 7.00 (t, J = 7.6 Hz, H-5′), 3.88 (s, 3H, –OCH_3); EI MS (*m*/*z*): 302 (M^+, 12), 195 (54), 175 (29), 127 (24), 107 (32), 68 (79), 76 (100). Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27; O, 10.58. Found: C, 75.51; H, 4.64; N, 9.21; O, 10.64.

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