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Synthesis of 2-amino-1,3,4-oxadiazoles from isoselenocyanates via cyclodeselenization

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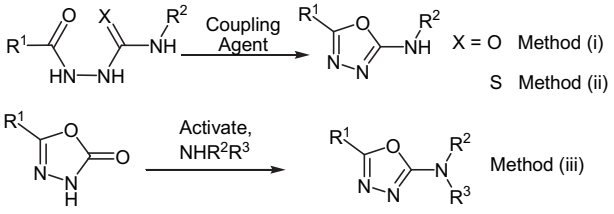
ABSTRACT

An efficient one-pot method to access 2-amino-1,3,4-oxadiazoles from isoselenocyanates and hydrazides or dihydrazides was developed via cyclodeselenization. Without any harsh reagents, various 2-amino-1,3,4-oxadiazoles were obtained in considerably high yields (82%–97%) and purities (>99%) directly with simple crystallization in ethanol. And the formed precipitated Se powder during the reaction could be recycled for preparation of isoselenocyanates efficiently. A plausible mechanism is proposed for the formation of the target products.

1. Introduction

Oxadiazoles are popular bioisosteres for the biologically active amides, esters and ureas.[1] In particular, 2-amino-1,3,4-oxadiazoles are present in a wide range of pharmaceutically potent agents,[2] generally including antimicrobial agents,[3] anticancer agents,[4] anti-inflammatory agents[5] and anticonvulsant agents.[6] In addition, they are utilized as intermediates to prepare various biologically important compounds.[7] As a result, a variety of approaches have been developed to obtain 2-amino-1,3,4-oxadiazoles (Scheme 1).

Generally, a large number of methods for the synthesis of 2-amino-1,3,4-oxadiazoles are available in the literatures, which could be broadly classified as, (i) cyclodehydration of semicarbazide derivatives,[8] (ii) cyclodesulfurization of thiosemicarbazide derivatives,[9] (iii) amination of oxadiazol-2-one at C2.[10] However, there are limitations to these methods, respectively. Method (i) frequently causes significant byproduct formation and gives poor yield, when $POCl_3$,[8a] tosyl chloride,[7] Burgess reagents[8b,c] and other harsh conditions[8d–g] were employed. For method (ii), various desulfurizing reagents have to be utilized, including I_2/NaOH,[9a] carbodiimides(DCC, EDC) or PS-carbodiimides,[9b–d] tosyl chloride[9e,f] and stoichiometric mercury salts,[9g,h] which often lead to inconvenient handling and undesirable byproducts. Although



Scheme 1. Literature methods for preparation of 2-amino-1,3,4-oxadiazoles.

method (iii) provides ready access to *N*,*N*-disubstituted 2-amino-1,3,4-oxadiazoles, it only prepares 2-arylamino-1,3,4-oxadiazoles in moderate yields.[10]

Isoselenocyanates are widely employed in the synthesis of selenium-containing heterocycles as a result of their convenient preparation, low toxicity, relative stability and excellent reactivity.[11] To the best of our knowledge, however, there are few studies on synthesis of non-selenium-containing compounds from isoselenocyanates.[11a] Therefore, we were attracted to prepare non-selenium-containing compounds from isoselenocyanates via deselenization processes. Very recently, we have reported efficient synthesis of 2-aminobenzimidazoles, 2-aminobenzoxazoles and 2-aminobenzothiazoles from isoselenocyanates via cyclodeselenization.[12] Herein, based on these results, we investigated the cyclodeselenization of selenosemicarbazide derivatives, which were obtained by the reaction of various isoselenocyanates with hydrazides.

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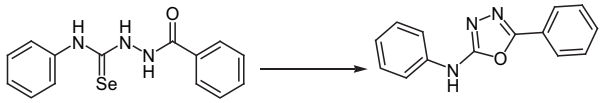
2. Results and discussion

Initially selenosemicarbazide[13] **1Aa** was selected to optimize the reaction conditions. The effects of different solvents, reaction temperatures and bases were investigated. The results were summarized in Table 1. Among the solvents, DMF was proved to be the optimal one, and the result might depend on the solubility of selenosemicarbazide. A variation of the reaction temperature from 50 to 100 °C causes positive effect on both reaction rate and yield. It was noteworthy, the yield was not improved when the reaction was carried out at 100 °C, compared with 90 °C. So the optimal reaction conditions were established as using DMF as solvent, with the temperature of 90 °C without addition of any base.

Table 1
Optimization of reaction conditions for the construction of 2-amino-1,3,4-oxadiazoles via cyclodeselenization



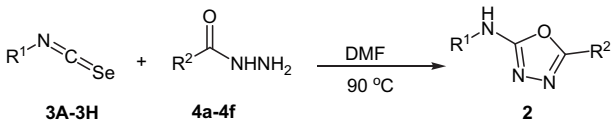
1Aa **2Aa**

Entry	Solvents	Base	Temp (°C)	Times[a] (h)	Yield[b] (%)
1	CH_2Cl_2	TEA	Reflux	48	None
2	EtOAc	TEA	Reflux	48	None
3	MeCN	TEA	Reflux	48	15
4	EtOH	TEA	Reflux	48	<10
5	THF	TEA	Reflux	10	75
6	THF	—	Reflux	48	10
7	DMF	TEA	90	3	95
8	DMF	—	50	24	85
9	DMF	—	70	10	88
10	DMF	—	90	4	95
11	DMF	—	100	3	95

[a] Monitored by TLC, until selenosemicarbazide **1Aa** was fully consumed.
[b] Isolated yield.

Considering that selenosemicarbazide (**1Aa**) could be prepared conveniently from isoselenocyanate **3A** and hydrazide **4a**, we thought the procedure could be simplified. Then one-pot reaction of isoselenocyanate **3A** and hydrazide **4a** was performed in DMF at 90 °C (Scheme 2). The result was exciting, and 2-amino-1,3,4-oxadiazole **2Aa** was still obtained in 95% yield (Table 2, entry 1), whereas the highest reported yield in the literature is 67%.[9b,d,10] It should be noted, the product could be conveniently afforded in high purity after simple crystallization process, and the selenium powder filtered off could be reused for preparing isoselenocyanates **3**.[11a]

Subsequently, the scope of the reaction substrates was investigated under the optimized conditions. Various isoselenocyanates **3** and hydrazides **4** were conducted in DMF at 90 °C, and the results were summarized in Table 2. A variety of 5-phenyl-2-arylamino-1,3,4-oxadiazoles **2** were obtained in excellent yields ranging from 90 to 97% when substituted isoselenocyanates **3** reacted with hydrazide **4a**. The nature of R^1 group on the isoselenocyanates **3** affected the reaction rate and yields a little.



3A-3H **4a-4f** **2**

3A: R^1 = C_6H_5 ; **3B**: R^1 = 4-ClC_6H_4 ; **3C**: R^1 =4-$MeOC_6H_4$;
3D: R^1 = 2-MeC_6H_4; **3E**: R^1 = 2-EtC_6H_4 ; **3F**: R^1 = 3-MeC_6H_4 ;
3G: R^1 = 1-Naphthyl; **3H**: R^1=4-BrC_6H_4
4a: R^2 = C_6H_5; **4b:**R^2 = 4-BrC_6H_4; **4c**: R^2 = 4-$MeOC_6H_4$;
4d: R^2 = 4-MeC_6H_4; **4e**: R^2 = CH_3; **4f**: R^2 = 4-Pyridyl

Scheme 2. Preparation of 5-phenyl(alkyl)-2-arylamino-1,3,4-oxadiazoles **2** from isoselenocyanates **3**.

Table 2
Preparation of 5-phenyl(alkyl)-2-arylamino-1,3,4-oxadiazoles **2** from isoselenocyanates **3**[a]

Entry	R^1	R^2	Times[b] (h)	Products	Yield[c] (%)
1	C_6H_5	C_6H_5	4.0	**2Aa**	95, 91[d]
2	4-ClC_6H_4	C_6H_5	5.0	**2Ba**	93, 93[d]
3	4-$MeOC_6H_4$	C_6H_5	3.5	**2Ca**	97, 96[d]
4	2-MeC_6H_4	C_6H_5	5.0	**2Da**	92
5	2-EtC_6H_4	C_6H_5	5.5	**2Ea**	90
6	3-MeC_6H_4	C_6H_5	3.5	**2Fa**	95
7	1-Naphthyl	C_6H_5	5.0	**2Ga**	90
8	C_6H_5	4-BrC_6H_4	6.0	**2Ab**	94
9	4-ClC_6H_4	4-BrC_6H_4	6.5	**2Bb**	93
10	4-$MeOC_6H_4$	4-BrC_6H_4	5.0	**2Cb**	95
11	2-MeC_6H_4	4-BrC_6H_4	6.0	**2Db**	91
12	1-Naphthyl	4-BrC_6H_4	6.5	**2Gb**	90
13	C_6H_5	4-$MeOC_6H_4$	3.0	**2Ac**	96
14	4-ClC_6H_4	4-$MeOC_6H_4$	4.0	**2Bc**	94
15	4-$MeOC_6H_4$	4-$MeOC_6H_4$	3.0	**2Cc**	97
16	2-MeC_6H_4	4-$MeOC_6H_4$	3.5	**2Dc**	92
17	1-Naphthyl	4-$MeOC_6H_4$	3.5	**2Gc**	91
18	C_6H_5	4-MeC_6H_4	3.0	**2Ad**	95
19	4—$MeOC_6H_4$	4-MeC_6H_4	3.0	**2Cd**	97
20	2-MeC_6H_4	4-MeC_6H_4	3.0	**2Dd**	91
21	1-Naphthyl	4-MeC_6H_4	3.5	**2Gd**	90
22	4-BrC_6H_4	4-MeC_6H_4	3.5	**2Hd**	93
23	C_6H_5	CH_3	8.0	**2Ae**	87
24	4-ClC_6H_4	CH_3	8.5	**2Be**	85
25	4-$MeOC_6H_4$	CH_3	8.0	**2Ce**	88
26	2-MeC_6H_4	CH_3	8.0	**2De**	84
27	C_6H_5	4-Pyridyl	3.0	**2Af**	94
28	4-ClC_6H_4	4-Pyridyl	4.0	**2Bf**	92
29	4-$MeOC_6H_4$	4-Pyridyl	3.0	**2Cf**	95
30	2-MeC_6H_4	4-Pyridyl	3.0	**2Df**	92
31	1-Naphthyl	4-Pyridyl	3.5	**2Gf**	91

[a] Isoselenocyanates **3** (1 mmol) and hydrazides **4** (1 mmol) were heated at 90 °C in DMF.
[b] Monitored by TLC, until isoselenocyanate **3** was fully consumed.
[c] Isolated yield.
[d] Using reproduced isoselenocyanates.

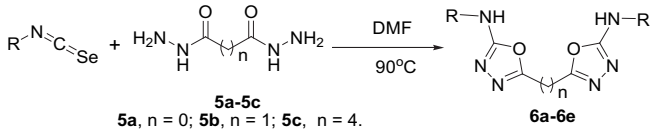
Electron-donating group (Table 2, entries 3 and 6) substituted compounds showed slightly higher reactivity with slightly higher yields than electron withdrawing group (Table 2, entry 2). However, when the methyl or ethyl group attached to the *ortho* position of the phenyl isoselenocyanate (Table 2, entries 4 and 5), the reaction yields were decreased due to the steric effect. Moreover, naphthyl isoselenocyanate was also an appropriate reactant for this reaction, providing the desired product in 90% yield (Table 2, entry 7).

The applicability of hydrazides **4** was also studied. Firstly, different *para*-substituted benzoyl hydrazines were treated with isoselenocyanates **3** under the optimized conditions, and the corresponding products were obtained in excellent yields (Table 2, entries 8–22). The yields could be affected slightly when the substituents were bonded to the *para* position of benzoyl hydrazine. Then acetyl hydrazine and isonicotinohydrazide were also investigated. 5-Methyl-2-phenylamino-1,3,4-oxadiazoles were obtained in satisfactory yields (Table 2, entries 23–26), though generally lower than those of 5-aryl-2-phenylamino-1,3,4-oxadiazoles. Isonicotinohydrazide also provided the desired products with excellent yields comparable to benzoyl hydrazines (Table 2, entries 27–31).

To further examine the generality of this procedure, the reaction of dihydrazides[14] with isoselenocyanates was also studied. Gratifyingly, the desired products bis(1,3,4-oxadiazoles) were also obtained in excellent yields under the standard reaction conditions(Table 3).

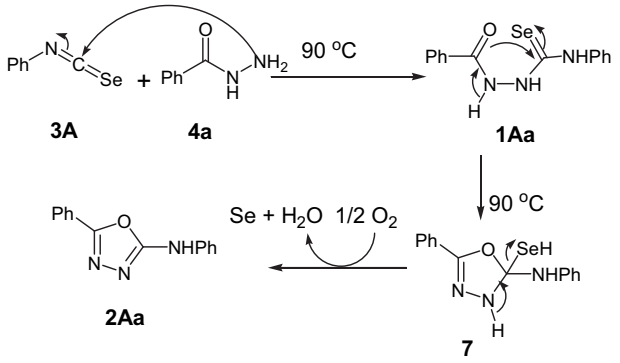
A plausible mechanism is proposed for the formation of 2-amino-1,3,4-oxadiazoles **2Aa** (Scheme 3). Firstly, selenosemicarbazide **1Aa** could be generated from isoselenocyanate **3A** and hydrazide **4a** rapidly. Subsequently, the intramolecular cyclization of **1Aa** produced the intermediate **7** via attack of oxygen atom on

Table 3
Preparation of bis(1,3,4-oxadiazoles) from isoselenocyanates and dihydrazides via cyclodeselenization[a]



Entry	R	Compounds **5**	Times[b] (h)	Products	Yield[c] (%)
1	4-ClC_6H_4	**5a**	4	**6a**	92
2	C_6H_5	**5b**	10	**6b**	82
3	C_6H_5	**5c**	6	**6c**	89
4	4-$MeOC_6H_4$	**5c**	5	**6d**	90
5	4-ClC_6H_4	**5c**	4	**6e**	93

[a] Isoselenocyanates **3** (1 mmol) and dihydrazides **5** (0.5 mmol) were heated at 90 °C in DMF.
[b] Monitored by TLC, until isoselenocyanate **3** was fully consumed.
[c] Isolated yield.



Scheme 3. Plausible mechanism for the formation of 2-amino-1,3,4-oxadiazoles **2**.

carbonyl to selenocarbonyl. The intermediate **7** was then converted to the 2-amino-1,3,4-oxadiazole **2Aa** via cyclodeselenization with the aid of oxygen. To confirm this process, the reaction was performed in a nitrogen-protected vessel, no desired product and selenium powder were detected. This result meant that oxygen was crucial to this reaction. The detailed discussion was appeared in our previous paper.[12]

3. Conclusion

In conclusion, a facile and efficient approach to the synthesis of 2-amino-1,3,4-oxadiazoles was developed via a one-pot cyclodeselenization reaction of easily available isoselenocyanates and hydrazides. Without using any deselenizing reagents, the desired products could be obtained with excellent yields, compared with the previous reported approaches. The products were purified easily by crystallization in ethanol, and the complicated purification procedures were avoided. In addition, the formed selenium powder during the reaction could be recycled for preparation of isoselenocyanates.

4. Experimental

4.1. General

Mp: *Büchi B*-540 apparatus; uncorrected. IR Spectra: *Nicolet Avatar*-370 spectrometer, in KBr; in cm^{-1}. ^1H and ^{13}C NMR Spectra: *Varian Mercury Plus*-400 instrument, in (d_6) DMSO at 400 and 100 MHz, resp.; δ in parts per million, J in hertz. ESI-MS: *Thermo Finnigan LCQ Advantage* instrument; in m/z. HRMS: *Agilent* 6210 *TOF* instrument.

4.2. General procedure for the synthesis of 2-amino-1,3,4-oxadiazoles 2

Phenyl isoselenocyanate **3A** (0.182 g, 1 mmol) and benzoyl hydrazine **4a** (0.136 g, 1 mmol) were added to DMF (10 mL) with magnetic stirring. The mixture was heated to 90 °C for 4 h. When the reaction was completed as monitored by TLC, the mixture was cooled to rt. The black selenium powder was filtered off and washed with CH_2Cl_2 (10 mL). The recovery rate of black selenium was around 95%. The combined filtrate was concentrated in vacuo. The residue was crystallized, filtered and washed by ethanol (10 mL) to give *N*,5-diphenyl-1,3,4-oxadiazol-2-amine **2Aa** (0.225 g, yield 95%, purity 99%) as white solid. Mp: 214.9–215.9 °C; lit. mp:[15] 215 °C; IR (KBr): ν_{max}=3262, 3053, 1620, 1604, 1579, 1501, 1243 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.69 (br, 1H, NH), 7.92–7.89 (m, 2H), 7.63 (d, J=8.4 Hz, 2H), 7.60–7.56 (m, 3H), 7.37 (t, J=7.6 Hz, 2H), 7.02 (t, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.9, 157.7, 138.6, 131.0, 129.4 (CH×2), 129.1 (CH×2), 125.5 (CH×2), 123.9, 121.9, 117.1 (CH×2); MS (EI): m/z (%)=237 (M^+, 86), 77 (100).

*4.2.1. N-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**2Ba**, Table 2)*[16]. Light yellow solid; mp: 137.1–138.6 °C; IR (KBr): ν_{max}=3274, 3067, 1642, 1587, 1488, 1227, 1045, 758 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.05 (br, 1H), 8.06 (d, J=8.0 Hz, 1H), 7.92–7.89 (m, 2H), 7.59–7.57 (m, 3H), 7.53 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.5, 158.5, 135.2, 131.1, 129.8, 129.3 (CH×2), 127.9, 125.6 (CH×2), 124.8, 123.9, 123.8, 122.1; MS (EI): m/z (%)=273 (M^++2, 17), 271 (M^+, 51), 77 (100).

*4.2.2. N-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**2Ca**, Table 2)*[16]. White solid; mp: 217.1–217.8 °C; IR (KBr): ν_{max}=3260, 3052, 1615, 1583, 1513, 1234, 1182, 1036, 827 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.46 (s, 1H), 7.90–7.88 (m, 2H), 7.58–7.57 (m, 3H), 7.54 (d, J=8.8 Hz, 2H), 6.96 (d, J=8.8 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.2, 157.5, 154.5, 131.9, 130.8, 129.3 (CH×2), 125.4 (CH×2), 124.0, 118.6 (CH×2), 114.3 (CH×2), 55.2; MS (EI): m/z (%)=267 (M^+, 100).

*4.2.3. N-(2-Methylphenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**2Da**, Table 2).* White solid; mp: 164.0–165.6 °C; IR (KBr): ν_{max}=3284, 3060, 1646, 1601, 1585, 1491, 1245, 1051, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.67 (s, 1H), 7.88 (d, J=3.6 Hz, 2H), 7.79 (d, J=8.4 Hz, 1H), 7.56–7.55 (m, 3H), 7.23 (d, J=6.0 Hz, 2H), 7.04 (t, J=7.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.1, 158.0, 136.7, 130.9, 130.7, 129.3 (CH×2), 129.0, 126.6, 125.5 (CH×2), 124.0, 123.9, 121.0, 18.0; MS (EI): m/z (%)=251 (M^+, 100); HRMS-ESI: calcd for $C_{15}H_{14}N_3O$ $(M+H)^+$: 252.1137; found: 252.1147.

*4.2.4. N-(2-Ethylphenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**2Ea**, Table 2).* Light yellow solid; mp: 113.1–114.7 °C; IR (KBr): ν_{max}=3273, 3054, 1638, 1597, 1585, 1478, 1251, 1045, 747 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.63 (s, 1H), 7.87–7.84 (m, 2H), 7.73 (d, J=7.6 Hz, 1H), 7.56–7.54 (m, 3H), 7.25–7.20 (m, 2H), 7.09 (td, J_1=7.6 Hz, J_2=1.2 Hz, 1H), 2.71 (q, J=7.6 Hz, 2H), 1.16 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.2, 157.7, 135.7, 135.1, 130.6, 129.1 (CH×2), 128.6, 126.3, 125.2 (CH×2), 124.2, 123.8, 121.8, 23.7, 14.3; MS (EI): m/z (%)= 265 (M^+, 99), 145 (96), 77 (100); HRMS-ESI: calcd for $C_{16}H_{16}N_3O$ $(M+H)^+$: 266.1293; found: 266.1290.

*4.2.5. N-(3-Methylphenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**2Fa**, Table 2).* Yellow solid; mp: 149.3–152.0 °C; IR (KBr): ν_{max}=3166, 3056, 1665, 1601, 1585, 1506, 1246, 1052, 775, 692 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.59 (s, 1H), 7.89–7.87 (m, 2H), 7.58–7.54 (m, 3H), 7.43–7.40 (m, 2H), 7.23 (t, J=7.6 Hz, 1H), 6.82 (d, J=7.2 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.6, 157.4,

138.3, 138.1, 130.7, 129.1 (CH×2), 128.7, 125.3 (CH×2), 123.7, 122.5, 117.4, 114.1, 21.4; MS (EI): *m/z* (%)=251 (M^+, 100); HRMS-ESI: calcd for $C_{15}H_{14}N_3O$ $(M+H)^+$: 252.1137; found: 252.1134.

*4.2.6. N-(Naphthalen-1-yl)-5-phenyl-1,3,4-oxadiazol-2-amine (**2Ga**, Table 2)*[17]. Light yellow solid; mp: 192.0–193.0 °C; IR (KBr): ν_{max}=3146, 3057, 1648, 1621, 1597, 1577, 1491, 1242, 1056, 776 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.29 (br, 1H), 8.34 (d, *J*=8.8 Hz, 1H), 8.08 (d, *J*=7.6 Hz, 1H), 7.98–7.91 (m, 3H), 7.71 (d, *J*=8.4 Hz, 1H), 7.58–7.53 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.3, 158.2, 134.0, 133.9, 131.0, 129.4 (CH×2), 128.3, 126.2, 125.9 (CH×2), 125.8, 125.6 (CH×2), 124.0, 123.7, 122.2, 116.6; MS (EI): *m/z* (%)=287 (M^+, 67), 77 (100).

*4.2.7. 5-(4-Bromophenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**2Ab**, Table 2).* White solid; mp: 260.5–261.9 °C; IR (KBr): ν_{max}=3260, 3056, 1620, 1600, 1585, 1573, 1502, 1234, 1046, 830 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.72 (br, 1H), 7.82 (d, *J*=8.4 Hz, 2H), 7.77 (d, *J*=8.4 Hz, 2H), 7.61 (d, *J*=8.4 Hz, 2H), 7.36 (t, *J*=7.6 Hz, 2H), 7.02 (t, *J*=7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.1, 157.1, 138.5, 132.4 (CH×2), 129.1 (CH×2), 127.4 (CH×2), 124.3, 123.1, 122.0, 117.2 (CH×2); MS (EI): *m/z* (%)=317 (M^++2, 94), 315 (M^+, 100).

*4.2.8. 5-(4-Bromophenyl)-N-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine (**2Bb**, Table 2).* White solid; mp: 257.1–257.8 °C; IR (KBr): ν_{max}=3258, 3057, 1620, 1600, 1585, 1571, 1496, 1237, 1049, 833 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H, NH), 7.80 (d, *J*=8.8 Hz, 2H), 7.77 (d, *J*=8.8 Hz, 2H), 7.62 (d, *J*=8.8 Hz, 2H), 7.41 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 156.9, 137.2, 132.1 (CH×2), 128.7 (CH×2), 127.2 (CH×2), 125.3, 124.1, 122.7, 118.5 (CH×2); MS (EI): *m/z* (%)=353 (M^++4, 25), 351 (M^++2, 100), 349 (M^+, 84); HRMS-ESI: calcd for $C_{14}H_{10}BrClN_3O$ $(M+H)^+$: 349.9696; found: 349.9693.

*4.2.9. 5-(4-Bromophenyl)-N-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine (**2Cb**, Table 2).* White solid; mp: 262.0–263.2 °C; IR (KBr): ν_{max}=3264, 3060, 1617, 1600, 1588, 1573, 1513, 1235, 1068, 831 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 1H), 7.80 (d, *J*=9.2 Hz, 2H), 7.77 (d, *J*=8.8 Hz, 2H), 7.51 (d, *J*=9.2 Hz, 2H), 6.95 (d, *J*=8.8 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.0, 156.6, 154.2, 132.2 (CH×2), 131.5, 127.1 (CH×2), 124.0, 122.9, 118.5 (CH×2), 114.2 (CH×2), 55.2; MS (EI): *m/z* (%)=347 (M^++2, 94), 345 (M^+, 100); HRMS-ESI: calcd for $C_{15}H_{13}BrN_3O_2$ $(M+H)^+$: 346.0191; found: 346.0184.

*4.2.10. 5-(4-Bromophenyl)-N-(2-methylphenyl)-1,3,4-oxadiazol-2-amine (**2Db**, Table 2).* Grey solid; mp: 193.5–195.3 °C; IR (KBr): ν_{max}=3285, 1655, 1600, 1481, 1246, 1047, 835, 743 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.70 (s, 1H), 7.81–7.75 (m, 5H), 7.25–7.21 (m, 2H), 7.05 (td, J_1=7.6 Hz, J_2=1.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9, 157.0, 136.3, 132.2 (CH×2), 130.4, 128.9, 127.1 (CH×2), 126.3, 124.0, 123.8, 123.0, 120.9, 18.0; MS (EI): *m/z* (%)=331 (M^++2, 63), 329 (M^+, 66), 131 (100); HRMS-ESI: calcd for $C_{15}H_{13}BrN_3O$ $(M+H)^+$: 330.0242; found: 330.0238.

*4.2.11. 5-(4-Bromophenyl)-N-(naphthalen-1-yl)-1,3,4-oxadiazol-2-amine (**2Gb**, Table 2).* Red solid; mp: 223.7–225.1 °C; IR (KBr): ν_{max}=3198, 3010, 1636, 1602, 1573, 1481, 1270, 1068, 828 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, 1H), 8.32 (d, *J*=7.6 Hz, 1H), 8.06 (d, *J*=7.6 Hz, 1H), 7.96 (d, *J*=8.4 Hz, 1H), 7.84 (d, *J*=8.4 Hz, 2H), 7.79 (d, *J*=8.4 Hz, 2H), 7.72 (d, *J*=8.0 Hz, 1H), 7.59–7.53 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.5, 157.5, 133.8 (CH×2), 132.4 (CH×2), 128.3, 127.4 (CH×2), 126.3, 125.9 (CH×3), 124.3, 123.9, 123.2, 122.2, 116.8; MS (EI): *m/z* (%)=367 (M^++2, 92), 365 (M^+, 98), 123 (100); HRMS-ESI: calcd for $C_{18}H_{13}BrN_3O$ $(M+H)^+$: 366.0242; found: 366.0235.

*4.2.12. 5-(4-Methoxyphenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**2Ac**, Table 2).* White solid; mp: 204.9–205.5 °C; IR (KBr): ν_{max}=3256, 3052, 1624, 1609, 1580, 1501, 1254, 1030, 833 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 7.81 (d, *J*=9.2 Hz, 2H), 7.60 (d, *J*=8.8 Hz, 2H), 7.34 (dd, J_1=7.6 Hz, J_2=8.8 Hz, 2H), 7.10 (d, *J*=9.2 Hz, 2H), 6.99 (t, *J*=7.6 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 159.2, 157.4, 138.5, 128.9 (CH×2), 127.1 (CH×2), 121.5, 116.8 (CH×2), 116.1, 114.6 (CH×2), 55.4; MS (EI): *m/z* (%)=267 (M^+, 100); HRMS-ESI: calcd for $C_{15}H_{14}N_3O_2$ $(M+H)^+$: 268.1086; found: 268.1082.

*4.2.13. N-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine (**2Bc**, Table 2).* Grey solid; mp: 277.1–278.9 °C; IR (KBr): ν_{max}=3266, 3072, 1626, 1610, 1576, 1487, 1243, 1025, 840 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.76 (s, 1H), 7.81 (d, *J*=8.8 Hz, 2H), 7.62 (d, *J*=8.8 Hz, 2H), 7.40 (d, *J*=8.8 Hz, 2H), 7.11 (d, *J*=8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 159.0, 157.6, 137.5, 128.7 (CH×2), 127.2 (CH×2), 125.1, 118.3 (CH×2), 116.0, 114.6 (CH×2), 55.4; MS (EI): *m/z* (%)=303 (M^++2, 24), 301 (M^+, 72), 133 (100); HRMS-ESI: calcd for $C_{15}H_{13}ClN_3O_2$ $(M+H)^+$: 302.0696; found: 302.0704.

*4.2.14. N,5-Bis(4-methoxyphenyl)-1,3,4-oxadiazol-2-amine (**2Cc**, Table 2).* Grey solid; mp: 171.7–172.4 °C; IR (KBr): ν_{max}=3255, 3057, 1610, 1580, 1501, 1250, 1052, 833 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.34 (s, 1H), 7.80 (d, *J*=8.8 Hz, 2H), 7.51 (d, *J*=8.8 Hz, 2H), 7.10 (d, *J*=8.8 Hz, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 3.83 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9, 159.5, 157.1, 154.1, 131.8, 127.0 (CH×2), 118.2 (CH×2), 116.2, 114.6 (CH×2), 114.1 (CH×2), 55.4, 55.2; MS (EI): *m/z* (%)=297 (M^+, 100); HRMS-ESI: calcd for $C_{16}H_{16}N_3O_3$ $(M+H)^+$: 298.1192; found: 298.1187.

*4.2.15. 5-(4-Methoxyphenyl)-N-(2-methylphenyl)-1,3,4-oxadiazol-2-amine (**2Dc**, Table 2).* Grey solid; mp: 153.8–154.4 °C; IR (KBr): ν_{max}=3289, 3044, 1658, 1616, 1602, 1504, 1253, 1045, 842 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.54 (s, 1H), 7.81–7.77 (m, 3H), 7.23–7.20 (m, 2H), 7.10 (d, *J*=9.2 Hz, 2H), 7.01 (td, J_1=7.2 Hz, J_2=1.2 Hz, 1H), 3.83 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9, 160.3, 157.6, 136.5, 130.4, 128.5, 127.0 (CH×2), 126.3, 123.4, 120.5, 116.2, 114.6 (CH×2), 55.4, 18.0; MS (EI): *m/z* (%)=281 (M^+, 69), 135 (100); HRMS-ESI: calcd for $C_{16}H_{16}N_3O_2$ $(M+H)^+$: 282.1243; found: 282.1239.

*4.2.16. 5-(4-Methoxyphenyl)-N-(naphthalen-1-yl)-1,3,4-oxadiazol-2-amine (**2Gc**, Table 2).* White solid; mp: 231.9–232.8 °C; IR (KBr): ν_{max}=3223, 3052, 1633, 1611, 1578, 1503, 1256, 1032, 793 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.38 (br, 1H, NH), 8.33–8.30 (m, 1H), 8.06 (d, *J*=7.6 Hz, 1H), 7.95–7.93 (m, 1H), 7.84 (d, *J*=8.8 Hz, 2H), 7.68 (d, *J*=8.0 Hz, 1H), 7.57–7.51 (m, 3H), 7.12 (d, *J*=9.2 Hz, 2H), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 160.6, 157.9, 133.9, 133.6, 128.1, 127.2 (CH×2), 126.0, 125.7, 125.6, 125.4, 123.3, 122.0, 116.2, 116.1, 114.6 (CH×2), 55.4; MS (EI): *m/z* (%)=317 (M^+, 100); HRMS-ESI: calcd for $C_{19}H_{16}N_3O_2$ $(M+H)^+$: 318.1243; found: 318.1243.

*4.2.17. 5-(4-Methylphenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**2Ad**, Table 2)*[18]. Pink solid; mp: 224.8–225.2 °C; lit. mp:[5] 226–227 °C; IR (KBr): ν_{max}=3287, 1619, 1577, 1500, 1247, 1048, 821, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.60 (s, 1H); 7.76 (d, *J*=8.4 Hz, 2H); 7.59 (dd, J_1=8.8 Hz, J_2=1.2 Hz, 2H); 7.37–7.32 (m, 4H); 6.99 (t, *J*=7.6 Hz, 1H); 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 157.5, 140.7, 138.4, 129.6 (CH×2), 128.8 (CH×2), 125.3 (CH×2), 121.6,

120.9, 116.8 (CH×2), 21.1; MS (ESI): *m/z* (%)=250 (M^-−1, 100); HRMS-ESI: calcd for $C_{15}H_{14}N_3O$ $(M+H)^+$ 252.1137; found: 252.1131.

*4.2.18. N-(4-Methoxyphenyl)-5-(4-methylphenyl)-1,3,4-oxadia-zol-2-amine (**2Cd**, Table 2).* White solid; mp: 213.2–213.9 °C; IR (KBr): ν_{max}=3259, 3063, 1613, 1578, 1501, 1232, 1040, 827 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.39 (br, 1H, NH), 7.75 (d, *J*=8.0 Hz, 2H), 7.51 (d, *J*=9.2 Hz, 2H), 7.35 (d, *J*=8.0 Hz, 2H), 6.94 (d, *J*=9.2 Hz, 2H), 3.73 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.7, 157.3, 154.1, 140.6, 131.7, 129.6 (CH×2), 125.2 (CH×2), 121.0, 118.4 (CH×2), 114.2 (CH×2), 55.2, 21.1; MS (EI): *m/z* (%)=281 (M^+, 100); HRMS-ESI: calcd for $C_{16}H_{16}N_3O_2$ $(M+H)^+$: 282.1243; found: 282.1241.

*4.2.19. N-(2-Methylphenyl)-5-(4-methylphenyl)-1,3,4-oxadiazol-2-amine (**2Dd**, Table 2).* Yellow solid; mp: 158.8–159.3 °C; IR (KBr): ν_{max}=3444, 3163, 1655, 1606, 1584, 1489, 1296, 1048, 819, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.59 (s, 1H), 7.78–7.75 (m, 3H), 7.36 (d, *J*=8.0 Hz, 2H), 7.23–7.21 (m, 2H), 7.02 (t, *J*=8.0 Hz, 1H), 2.38 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.6, 157.8, 140.5, 136.5, 130.4, 129.6 (CH×2), 128.7, 126.3, 125.2 (CH×2), 123.5, 121.0, 120.7, 21.1, 17.9; MS (ESI): *m/z* (%)=264 (100, M^-−1); HRMS-ESI: calcd for $C_{16}H_{16}N_3O$ $(M+H)^+$ 266.1293; found: 266.1288.

*4.2.20. N-(Naphthalen-1-yl)-5-(4-methylphenyl)-1,3,4-oxadiazol-2-amine (**2Gd**, Table 2).* White solid; mp: 184.3–183.9 °C; IR (KBr): ν_{max}=3445, 3044, 1651, 1623, 1596, 1578, 1501, 1313, 1016, 821 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.43 (s, 1H), 8.33–8.30 (m, 1H), 8.06 (d, *J*=7.6 Hz, 1H), 7.96–7.94 (m, 1H), 7.79 (d, *J*=8.0 Hz, 2H), 7.69 (d, *J*=8.0 Hz, 1H), 7.59–7.52 (m, 3H), 7.38 (d, *J*=8.4 Hz, 2H), 2.39 (s, 3H), ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.8, 158.0, 140.7, 133.8, 133.6, 129.7 (CH×2), 128.0, 126.0, 125.7, 125.6, 125.5, 125.3 (CH×2), 123.4, 122.0, 121.0, 116.3, 21.1; MS (ESI): *m/z* (%)=300 (100, M^-−1); HRMS-ESI: calcd for $C_{19}H_{16}N_3O$ $(M+H)^+$ 302.1293; found: 302.1289.

*4.2.21. N-(4-Bromophenyl)-5-(4-methylphenyl)-1,3,4-oxadiazol-2-amine (**2Hd**, Table 2).* White solid; mp: 286.0–287.0 °C; IR (KBr): ν_{max}=3252, 3065, 1620, 1605, 1574, 1503, 1234, 1051, 826 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.81 (s, 1H), 7.77 (d, *J*=8.0 Hz, 2H), 7.57 (d, *J*=9.2 Hz, 2H), 7.52 (d, *J*=9.2 Hz, 2H), 7.37 (d, *J*=8.0 Hz, 2H), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.1, 157.7, 140.8, 137.8, 131.6 (CH×2), 129.7 (CH×2), 125.4, 120.8, 118.8 (CH×2), 113.1, 21.1; MS (EI): *m/z* (%)=331 (M^++2, 67), 329 (M^+, 75), 159 (100); HRMS-ESI: calcd for $C_{15}H_{12}BrN_3NaO$ $(M+Na)^+$: 352.0061; found: 352.0057.

*4.2.22. 5-Methyl-N-phenyl-1,3,4-oxadiazol-2-amine (**2Ae**, Table 2)[19].* Light yellow solid; mp: 172.9–173.8 °C; lit. mp:[6] 174–175 °C; IR (KBr): ν_{max}=3252, 1638, 1579, 1500, 1242, 1058, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.30 (s, 1H), 7.54 (d, *J*=8.4 Hz, 2H), 7.32 (t, *J*=7.6 Hz, 2H), 6.97 (t, *J*=7.2 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4, 156.6, 138.7, 128.8 (CH×2), 121.3, 116.6 (CH×2), 10.5; MS (EI): *m/z* (%)=175 (M^+, 100).

*4.2.23. N-(4-Chlorophenyl)-5-methyl-1,3,4-oxadiazol-2-amine (**2Be**, Table 2).* White solid; mp: 195.1–196.2 °C; IR (KBr): ν_{max}=3253, 3054, 1644, 1612, 1581, 1572, 1496, 1245, 1093, 835 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 1H), 7.54 (d, *J*=8.8 Hz, 2H), 7.36 (d, *J*=8.8 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.2, 156.9, 137.6, 128.7 (CH×2), 124.9, 118.1 (CH×2), 10.4; MS (EI): *m/z* (%)=211 (M^++2, 33), 209 (M^+, 100).

*4.2.24. N-(4-Methoxyphenyl)-5-methyl-1,3,4-oxadiazol-2-amine (**2Ce**, Table 2).* Grey solid; mp: 135.9–136.5 °C; IR (KBr): ν_{max}=3258, 3058, 1650, 1609, 1587, 1576, 1512, 1234, 1043, 825 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.03 (s, 1H), 7.43 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.8 Hz, 2H), 3.71 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.7, 156.3, 153.9, 132.0, 118.1 (CH×2), 114.1 (CH×2), 55.2, 10.5; MS (EI): *m/z* (%)=205 (M^+, 100); HRMS-ESI: calcd for $C_{10}H_{12}N_3O_2$ $(M+H)^+$: 206.0930; found: 206.0932.

*4.2.25. 5-Methyl-N-(2-methylphenyl)-1,3,4-oxadiazol-2-amine (**2De**, Table 2).* Light yellow solid; mp: 179.0–179.9 °C; IR (KBr): ν_{max}=3241, 3034, 1659, 1594, 1482, 1233, 1065, 759 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.26 (br, 1H), 7.70 (dd, J_1=8.4 Hz, J_2=1.2 Hz, 1H), 7.19–7.15 (m, 2H), 6.98 (td, J_1=7.2 Hz, J_2=1.2 Hz, 1H), 2.38 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.5, 156.8, 136.7, 130.3, 128.2, 126.2, 123.1, 120.2, 17.9, 10.5; MS (EI): *m/z* (%)=189 (M^+, 94), 131 (100); HRMS-ESI: calcd for $C_{10}H_{12}N_3O$ $(M+H)^+$: 190.0980; found: 190.0976.

*4.2.26. N-Phenyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (**2Af**, Table 2)[20].* White solid; mp: 217.6–218.8 °C; lit. mp:[5] 216–218 °C; IR (KBr): ν_{max}=3263, 3058, 1617, 1586, 1501, 1242, 1052, 750 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.77 (d, *J*=6.0 Hz, 2H), 7.79 (d, *J*=6.0 Hz, 2H), 7.62 (d, *J*=7.6 Hz, 2H), 7.37 (t, *J*=7.6 Hz, 2H), 7.03 (t, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.2, 155.9, 150.4 (CH×2), 138.1, 130.5, 128.8 (CH×2), 121.9, 118.9 (CH×2), 117.1 (CH×2); MS (EI): *m/z* (%)=238 (M^+, 100).

*4.2.27. N-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (**2Bf**, Table 2)[21].* White solid; mp: 292.8–293.8 °C; lit. mp:[7] 291–292 °C; IR (KBr): ν_{max}=3268, 3060, 1632, 1609, 1591, 1571, 1494, 1253, 1053, 817 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.04 (br, 1H), 8.78 (d, *J*=6.0 Hz, 2H), 7.80 (d, *J*=6.0 Hz, 2H), 7.64 (d, *J*=9.2 Hz, 2H), 7.43 (d, *J*=9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.3, 156.4, 150.8 (CH×2), 137.3, 130.7, 129.0 (CH×2), 125.9, 119.3 (CH×2), 118.9 (CH×2); MS (EI): *m/z* (%)=274 (M^++2, 33), 272 (M^+, 100).

*4.2.28. N-(4-Methoxyphenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (**2Cf**, Table 2)[21].* Yellow solid; mp: 231.3–232.3 °C; lit. mp:[7] 233–234 °C; IR (KBr): ν_{max}=3282, 2963, 1645, 1600, 1574, 1511, 1239, 1038, 817 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.76 (d, *J*=6.0 Hz, 2H), 7.77 (d, *J*=6.0 Hz, 2H), 7.53 (d, *J*=9.2 Hz, 2H), 6.95 (d, *J*=9.2 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.4, 155.6, 154.3, 150.4 (CH×2), 131.3, 130.6, 118.9 (CH×2), 118.6 (CH×2), 114.1 (CH×2), 55.2; MS (EI): *m/z* (%)=268 (M^+, 100).

*4.2.29. N-(2-Methylphenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (**2Df**, Table 2)[21].* White solid; mp: 171.0–171.8 °C; lit. mp:[7] 179–180 °C; IR (KBr): ν_{max}=3226, 3052, 1620, 1588, 1488, 1254, 1050, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 9.87 (br, 1H), 8.76 (d, *J*=6.0 Hz, 2H), 7.77–7.73 (m, 3H), 7.25–7.22 (m, 2H), 7.06 (td, J_1=7.6 Hz, J_2=1.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.5, 156.1, 150.5 (CH×2), 136.0, 130.6, 130.4, 129.3, 126.3, 124.1, 121.4, 118.8 (CH×2), 17.9; MS (EI): *m/z* (%)=252 (M^+, 100); HRMS-ESI: calcd for $C_{14}H_{13}N_4O$ $(M+H)^+$: 253.1089; found: 253.1085.

*4.2.30. N-(Naphthalen-1-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (**2Gf**, Table 2).* Yellow solid; mp: 207.9–208.5 °C; IR (KBr): ν_{max}=3222, 3044, 1631, 1605, 1594, 1582, 1502, 1238, 1076 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.77 (d, *J*=6.0 Hz, 2H), 8.30–8.27 (m, 1H), 8.02 (d, *J*=7.2 Hz, 1H), 7.97–7.94 (m, 1H), 7.80 (d, *J*=6.0 Hz, 2H), 7.73 (d, *J*=8.0 Hz, 1H), 7.58–7.53 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.8, 156.4, 150.6 (CH×2), 133.6, 133.4, 130.7, 128.1, 126.1, 125.9, 125.8, 125.7, 124.0, 122.0, 119.0 (CH×2), 117.2; MS (EI): *m/z* (%)=288 (M^+, 100).

4.3. General procedure for the synthesis of bis(1,3,4-oxadiazoles) 6. (Take 6a, for example)

Oxalyl dihydrazide **5a** (0.059 g, 0.5 mmol) and 1-chloro-4-isoselenocyanatobenzene **3B** (0.217 g, 1.0 mmol) were added to

DMF (10 mL) with magnetic stirring. The mixture was heated to 90 °C for 4 h. When the reaction was completed as monitored by TLC, the mixture was cooled to rt. The black selenium powder was filtered off and washed with ethanol (10 mL). The combined filtrate was concentrated in vacuo. The residue was crystallized, filtered and washed by ethanol (10 mL) to give N^5,$N^{5\prime}$-bis(4-chlorophenyl)-2,2′-bi(1,3,4-oxadiazole)-5,5′-diamine **6a** (0.186 g, yield 96%) as a white solid.

*4.3.1. N^5,$N^{5\prime}$-Bis(4-chlorophenyl)-2,2′-bi(1,3,4-oxadiazole)-5,5′-diamine (**6a**, Table 3)*[22]. White solid; mp: 326.1–327.0 °C; IR (KBr): ν_{max}=3268, 3074, 1619, 1578, 1546, 1490, 1242, 1050, 830 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.24 (s, 2H), 7.62 (d, J=8.8 Hz, 4H), 7.45 (d, J=8.8 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.1 (CH×2), 146.9 (CH×2), 136.9 (CH×2), 129.0 (CH×4), 126.2 (CH×2), 119.0 (CH×4); MS (ESI): m/z (%)=389 (M^-+1, 65), 388 (M^-, 25), 387 (M^--1, 100); HRMS-ESI: calcd for $C_{16}H_9Cl_2N_6O_2$ $(M-H)^-$: 387.0164; found: 387.0164.

*4.3.2. 5,5′-Methylenebis(N-phenyl-1,3,4-oxadiazol-2-amine) (**6b**, Table 3)*[23]. White solid; mp: 250.1–250.7 °C; lit. mp: 205 °C; IR (KBr): ν_{max}=3240, 3051, 1639, 1580, 1500, 1247, 1053, 752, 691 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 2H), 7.53 (d, J=7.6 Hz, 4H), 7.34–7.30 (m, 4H), 6.98 (t, J=7.6 Hz, 2H), 4.57 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.0 (CH×2), 153.9 (CH×2), 138.3 (CH×2), 128.8 (CH×4), 121.6 (CH×2), 116.7 (CH×4), 22.2; MS (ESI): m/z (%)=335 (M^++1, 100); HRMS-ESI: calcd for $C_{17}H_{13}N_6O_2$ $(M-H)^-$: 333.1100; found: 333.1095.

*4.3.3. 5,5′-(1,4-Butanediyl)bis(N-phenyl-1,3,4-oxadiazol-2-amine) (**6c**, Table 3)*[22]. White solid; mp: 244.0–244.8 °C; lit. mp: 230 °C; IR (KBr): ν_{max}=3289, 3059, 1630, 1607, 1573, 1551, 1504, 1242, 1055, 756, 690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.34 (s, 2H), 7.52 (d, J=7.6 Hz, 4H), 7.30 (t, J=7.6 Hz, 4H), 6.95 (t, J=7.6 Hz, 2H), 2.83–2.80 (m, 4H), 1.80–1.76 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.4 (CH×2), 159.3 (CH×2), 138.6 (CH×2), 128.8 (CH×4), 121.3 (CH×2), 116.7 (CH×4), 25.1 (CH×2), 24.0 (CH×2); MS (ESI): m/z (%)=377 (M^++1, 40); HRMS-ESI: calcd for $C_{20}H_{21}N_6O_2$ $(M+H)^+$: 377.1726; found: 377.1718.

*4.3.4. 5,5′-(1,4-Butanediyl)bis(N-(4-methoxyphenyl)-1,3,4-oxa-diazol-2-amine) (**6d**, Table 3).* White solid; mp: 249.8–250.3 °C; IR (KBr): ν_{max}=3296, 3064, 1630, 1600, 1574, 1547, 1515, 1236, 1033, 829 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.10 (s, 2H), 7.43 (d, J=8.8 Hz, 4H), 6.89 (d, J=8.8 Hz, 4H), 3.70 (s, 6H), 2.81–2.78 (m, 4H), 1.78–1.74 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.6 (CH×2), 159.1 (CH×2), 153.9 (CH×2), 131.9 (CH×2), 118.1 (CH×4), 114.1 (CH×4), 55.3 (CH×2), 25.2 (CH×2), 24.1 (CH×2); MS (ESI): m/z (%)=437 (M^++1, 100); HRMS-ESI: calcd for $C_{22}H_{25}N_6O_4$ $(M+H)^+$: 437.1937; found: 437.1932.

*4.3.5. 5,5′-(1,4-Butanediyl)bis(N-(4-chlorophenyl)-1,3,4-oxadia-zol-2-amine) (**6e**, Table 3).* White solid; mp: 272.1–273.0 °C; IR (KBr): ν_{max}=3268, 3210, 3011, 1632, 1601, 1570, 1494, 1246, 1093, 831 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 2H), 7.55 (d, J=8.8 Hz, 4H), 7.36 (d, J=8.8 Hz, 4H), 2.83–2.80 (m, 4H), 1.79–1.76 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.6 (CH×2), 159.1 (CH×2), 137.6 (CH×2), 128.7 (CH×4), 124.9 (CH×2), 118.1 (CH×4), 25.1 (CH×2), 24.0 (CH×2); MS (ESI): m/z (%)=445 (M^-+1, 18), 444(M^-, 7), 443 (M^--1, 30); HRMS-ESI: calcd for $C_{20}H_{17}Cl_2N_6O_2$ $(M-H)^-$: 443.0790; found: 443.0772.

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Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.05.100.

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