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A new and efficient synthesis of 1,3,4-oxadiazole derivatives using TBTU

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Dedicated to Professor Firouz Matloubi Moghaddam on the occasion of his 60th birthday

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ABSTRACT

An efficient method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from isothiocyanates and hydrazides through cyclodesulfurization in the presence of (*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate) TBTU as an uronium coupling reagent has been developed. The present methodology offers several advantages, such as simple and easy work-up procedures, mild reaction conditions and it is environmentally benign.

1. Introduction

1,3,4-Oxadiazole is a versatile lead molecule for designing potential bioactive agents.[1] Due to the increased hydrolytic and metabolic stability of the oxadiazole ring, improved pharmacokinetic properties are often observed, which make this skeleton an important structural moiety for the pharmaceutical industry.[2] Consequently, 1,3,4-oxadiazoles have often been the target of numerous drug discovery programs as anti-inflammatory, analgesic, antibacterial, fungicidal, hyperglycaemic, antimalarial, antidepressant agents, and other activities.[3,4] Prescribed agents featuring the 1,3,4-oxadiazoles scaffold include the antiretroviral isentress,[5] AZD3988, which recently identified DGAT-1 inhibitors for the treatment of obesity and diabetes,[6] antihypertensive nesapidil and the antibiotic furamizole[7] (Fig. 1).

1,3,4-Oxadiazoles containing different functional groups have attracted a great deal of attention from synthetic and medicinal chemists that has led to production of novel compounds with unknown or improved pharmacological properties. For instance, compounds containing the 2-amino-1,3,4-oxadiazole possess biological activities such as muscle relaxants,[8] and anti-mitotics[9]

Therefore, there is a high demand for the development of easily accessible methods for the preparation of 1,3,4-oxadiazole derivatives.

The most straightforward synthetic route involves the cyclodehydration of semicarbazides, which typically requires harsh reagents such as $POCl_3$[10] or concentrated sulfuric acid.[11] Alternatively, phosphonium salts[7] and Burgess-type reagents[12] have been used to promote the cyclization. However, these reagents cause the formation of significant by-products and are only suitable for solid-phase synthetic strategies.

When thiosemicarbazides are used as oxadiazole precursors, H_2S scavengers, such as stoichiometric mercuric salts,[13] or lead oxide,[8] can be used to affect the cyclization. Other desulfurization reagents including I_2/NaOH[14] and tosyl chloride[7,14b] have been utilized, which often lead to inconvenient handling and undesirable by-products.

Selective activation of the sulfur moiety followed by cyclization has been achieved by carbodiimides (DCC,[15] EDC[15b,16]), polymer-supported DCC reagent[17] or PS-carbodiimides.[18]

Disadvantages and weaknesses of these reported methods are lack of generality, limited functional group tolerance, multistep synthesis sequences, and harsh reaction conditions.

This paper presents a continuation of our previous work, designing an efficient approach for the synthesis of 2,5-disubstituted

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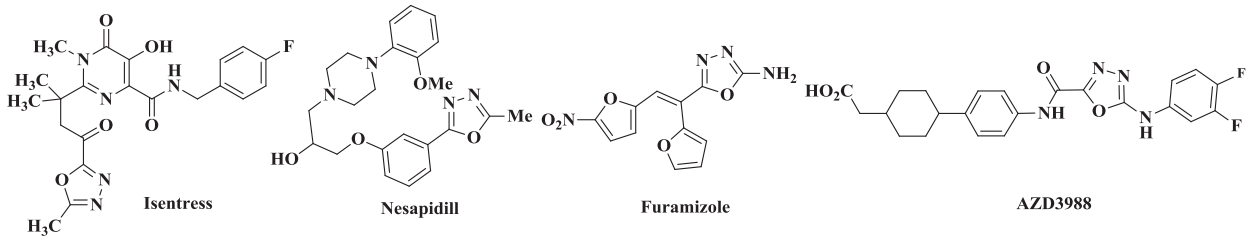
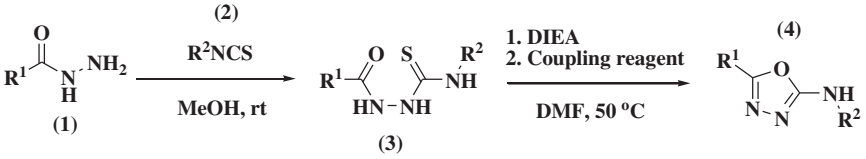


Fig. 1. Prescribed agents featuring the 1,3,4-oxadiazoles scaffold.

1,3,4-oxadiazole via a desulfurization reaction of thiosemicarbazides in the presence of coupling reagents. Thiosemicarbazide intermediates are obtained via reaction of hydrazides and isothiocyanates (Scheme 1).



Scheme 1. The overall sequence to prepare 2,5-disubstituted 1,3,4-oxadiazoles.

Different coupling reagents are used for the final cyclization including DIC, DCC as carbodiimides, TBTU as uronium coupling reagent. TBTU is an uronium salt that acts as a highly efficient coupling reagent commonly used in peptide chemistry for a wide variety of peptide sequences, including the synthesis of some pharmaceutical peptides. From an industrial and environmental point of view, an effective coupling reagent should have the following characteristics: (a) high efficiency, (b) works in stoichiometric quantities, and (c) solubility in the currently used solvents. Considering these characteristics, TBTU is one of the common coupling reagents and additives used in peptide chemistry.[19]

2. Results and discussion

We began our investigation with thiosemicarbazide **3a**, which was synthesized via reaction of benzohydrazide and phenylisothiocyanate. Thiosemicarbazides were prepared in good to high yields (75–88%) by mixing equimolar amounts of the corresponding hydrazides and isothiocyanate derivatives in MeOH at room temperature for 4 h, in some cases, the products were obtained under solvent-free conditions. The mixture was heated at 50 °C in DMF in the presence of DIEA as base and DIC, DCC, CDI, or TBTU as coupling reagents producing the desired 2-amino-1,3,4-oxadiazole in 85, 50, 63, 85% yields, respectively. According to these results, TBTU was selected as the best coupling reagent for the synthesis of 1,3,4-oxadiazoles. The results are summarized in Table 1.

Alternatively, other desulfurizing agents such as tosyl chloride, mercury acetate, zinc acetate, copper acetate were examined under the same conditions. The results are summarized in Table 2.

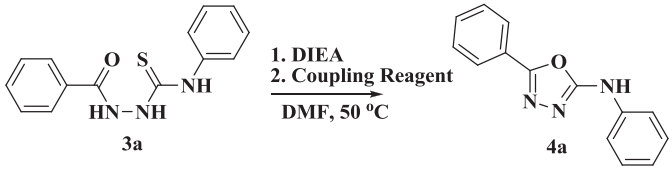
Using toxic materials such as $Hg(OAc)_2$ is highly undesirable. Meanwhile, the yield of the desired product (**3a**) was low compared to TBTU as coupling reagent. According to these results, TBTU was selected as the best reagent for the cyclization. After finding suitable conditions, the scope and limitations of this reaction were explored by using different hydrazides **1a**–**e** and isothiocyanates **2a**–**g**. The results are summarized in Table 3.

The presence of electron-donating groups on the benzhydrazide ring showed higher activity with higher yields (Table 3, **4d** and **4h**) compared to electron-withdrawing groups. The structures of the products **4a**–**l** were deduced from their HR-ESI mass spectrometry and NMR spectroscopic data. Meanwhile, X-ray crystallographic analysis confirmed the structure of the product (**4c**) and showed the intermolecular hydrogen bonding between the oxadiazole rings. Fig. 2 shows the ORTEP structure of compound **4c**.

It has been reported that, the presence of amide bonds in the structure of molecule could affect its biological activity,[20] to reach this aim, benzoyl isothiocyanate was selected as starting material, and the desired 1,3,4-oxadiazoles were synthesized, which contain the amide moiety (compounds **4l** and **4k**).

The possible mechanism for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles is shown in Scheme 2. This conversion involves the initial reaction of the sulfur of thiosemicarbazide with the uronium salt to form the desired intermediate (**A**), then the subsequent cyclization of intermediate (**A**) followed by the elimination of the tetramethythiourea group leads to the desired product. On the basis of the established chemistry of TBTU, it is reasonable to assume that its activation has an essential role in the cyclization reaction. Meanwhile, the same activation could be done using carbodiimides, but in this case, urea derivatives are generated as by-products.

Table 1
Conversion of thiosemicarbazide (**3a**) to *N*,5-diphenyl-2-amino-1,3,4-oxadiazole (**4a**) mediated by coupling reagents



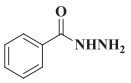
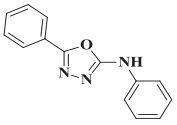
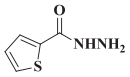
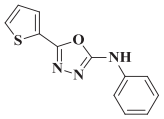
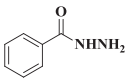
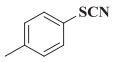
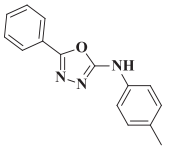
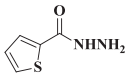
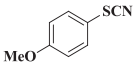
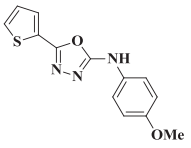
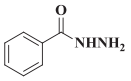
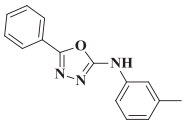
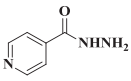
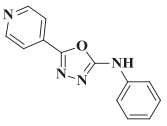
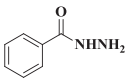
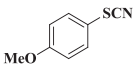
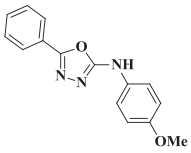
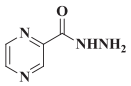
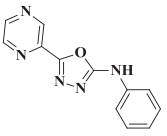
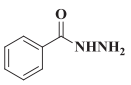
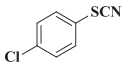
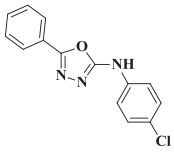
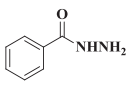
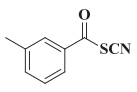
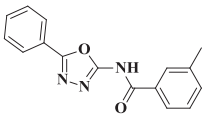
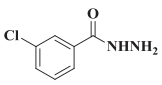
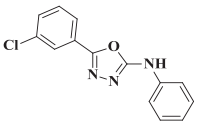
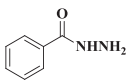
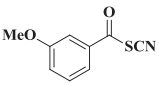
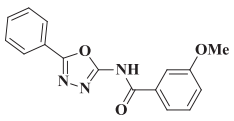
Coupling reagent	Time (h)	Yield (%)
DIC	20	85
DCC	24	50
CDI	24	63
TBTU	12	85

DIC: *N,N′*-diisopropylcarbodiimide.
DCC: *N,N′*-dicyclohexylcarbodiimide.
CDI: *N,N′*-carbonyldiimidazole.
TBTU: *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate.

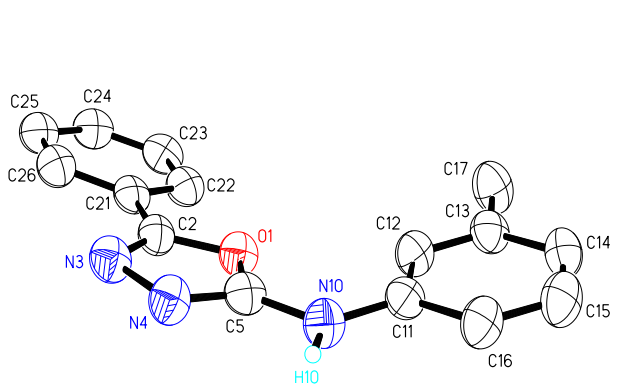
Table 2
Results of cyclization of thiosemicarbazide (**3a**) via metal desulfurizing reagents

Desulfurizing agent	Time (h)	Yield (%)
$Hg(OAc)_2$	12	75
$Zn(OAc)_2$	24	—
$Cu(OAc)_2$	24	Trace
p-TsCl/Pyr	24	50

Table 3
Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

Hydrazide	Isothiocyanate	Product	Hydrazide	Isothiocyanate	Product
 **1a**	 **2a**	 **4a(85%)**	 **1c**	 **2a**	 **4g(87%)**
 **1a**	 **2b**	 **4b(87%)**	 **1c**	 **2d**	 **4h(92%)**
 **1a**	 **2c**	 **4c(86%)**	 **1d**	 **2a**	 **4i(70%)**
 **1a**	 **2d**	 **4d(90%)**	 **1e**	 **2a**	 **4j(66%)**
 **1a**	 **2e**	 **4e(55%)**	 **1a**	 **2f**	 **4k(70%)**
 **1b**	 **2a**	 **4f(40%)**	 **1a**	 **2g**	 **4l**(80%)

Reaction conditions: hydrazide (1 mmol), isothiocyanate derivatives (1 mmol), coupling reagent (1.5 mmol), DIEA (1 mmol).



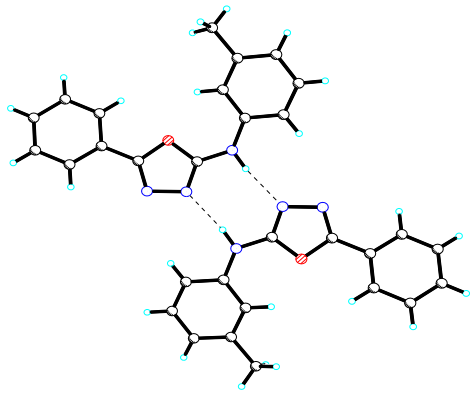
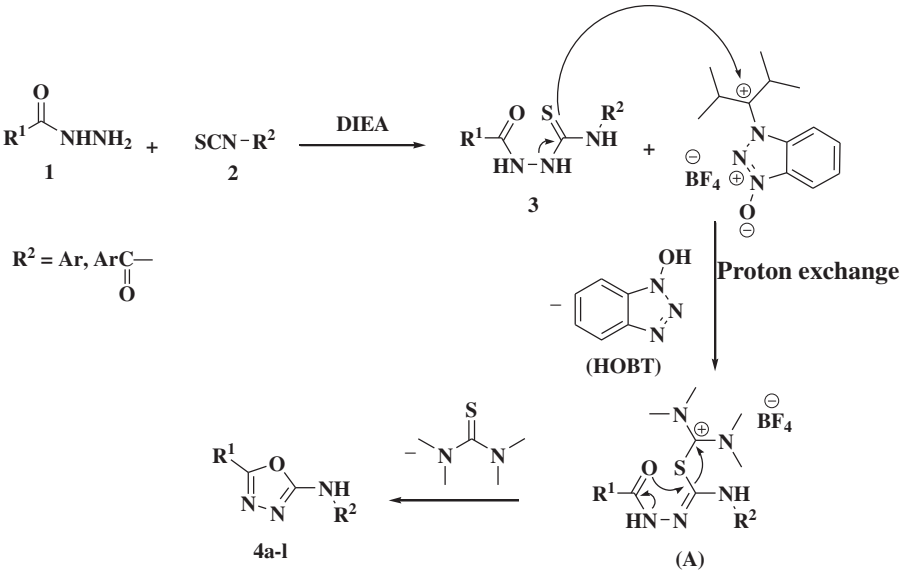


Fig. 2. The ORTEP structure of compound **4c**.



Scheme 2. The possible mechanism for the synthesis of **4a–l**.

3. Conclusion

In conclusion, a facile and efficient approach to the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles through the cyclodesulfurization reaction of thiosemicarbazides in the presence of TBTU as an uronium coupling reagent has been developed. The present methodology offers several advantages, such as simple and easy work-up procedure, mild reaction conditions and in environmentally benign compared to other reported methods.

4. Experimental section

4.1. General

Commercially available materials were used without further purification. Melting points were determined on an *Electrothermal* 9100 apparatus and are uncorrected. IR spectra were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on Bruker DRX-500 AVANCE and Bruker DRX-300 AVANCE spectrometers at 500 and 300 MHz for ^{1}H NMR, and 125 and 75 MHz for ^{13}C NMR. DMSO was used as the solvent. High-resolution mass spectra were recorded on Mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer.

4.2. General procedure for the synthesis of 2-aryl-*N*-arylhydrazinecarbothioamide and *N*-(2-benzoylhydrazinecarbonothioyl)benzamide (3a–l)

Arylhydrazide (1 mmol) and arylisothiocyanate (1 mmol) were combined in MeOH (4 mL) in a 20-mL round-bottom flask at room temperature and stirred for 4 h. The resultant precipitate was collected by filtration, washed with MeOH and dried.

4.3. General procedure for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles (4a–l)

Thiosemicarbazide (1 mmol), DIEA (1 mmol) and coupling reagent (1.5 mmol) were added to DMF (3 mL) with magnetic stirring. The mixture was heated 50 °C. When the reaction was completed as monitored by TLC, the mixture was cooled to room temperature. The solvent was removed in vacuo and the residue was extract with water. The solid formed was isolated by filtration, washed with MeOH and dried. The product was further purified by recrystallization from MeOH.

*4.3.1. N,5-Diphenyl-1,3,4-oxadiazol-2-amine (**4a**).* White solid (201 mg, 85%); mp: 194–196 °C; R_f (25% EtOAc/hexane) 0.42; ν_{max} (KBr): 1572, 1666, 3222 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.00 (t, 1H, *J* 3.7 Hz, H–Ar), 7.35 (t, 2H, *J* 7.7 Hz, H–Ar), 7.54–7.55 (m, 3H, H–Ar), 7.61 (d, 2H, *J* 8.0 Hz, H–Ar), 7.88–7.93 (m, 2H, H–Ar), 10.62 (s, 1H, NH); δ_C (125 MHz, DMSO): 117.0, 121.8, 123.8, 125.5, 129.0, 129.3, 130.9, 138.6, 157.7, 159.9; HR-mass (ESI) calcd for $C_{28}H_{23}N_6O_2$ $[2M+H]^+$ 475.1877, found 475.1877.

*4.3.2. 5-Phenyl-N-p-tolyl-1,3,4-oxadiazol-2-amine (**4b**).* White solid (218 mg, 87%); mp: 193–196 °C; R_f (25% EtOAc/hexane) 0.45; ν_{max} (KBr): 1617, 3257 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 2.24 (s, 3H, $-CH_3$), 7.15 (d, 2H, *J* 8.3 Hz, H–Ar), 7.50 (d, 2H, *J* 8.4 Hz, H–Ar), 7.54–7.56 (m, 3H, H–Ar), 7.87–7.89 (m, 2H, H–Ar), 10.53 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 20.3, 117.1, 123.9, 125.4, 129.2, 129.4, 130.7, 130.8, 136.1, 157.6, 160.0; HR-mass (ESI) calcd for $C_{15}H_{14}N_3O$ $[M+H]^+$ 252.1133, found 252.1133.

*4.3.3. 5-Phenyl-N-m-tolyl-1,3,4-oxadiazol-2-amine (**4c**).* White solid (215 mg, 86%); mp: 192–193 °C; R_f (25% EtOAc/hexane) 0.55; ν_{max} (KBr): 1594, 1665, 3316 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 2.30 (s, 3H, $-CH_3$), 6.82 (d, 1H, *J* 7.5 Hz, H–Ar), 7.23 (t, 1H, *J* 7.8 Hz, H–Ar), 7.40–7.43 (m, 2H, H–Ar), 7.55–7.57 (m, 3H, H–Ar), 7.87–7.93 (m, 2H, H–Ar), 10.61 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 21.2, 114.2, 117.5, 122.6, 123.8, 125.5, 128.9, 129.3, 130.9, 138.3, 138.5, 157.6, 159.9; HR-mass (ESI) calcd for $C_{15}H_{14}N_3O$ $[M+H]^+$ 252.1131, found 252.1130, calcd for $C_{15}H_{13}N_3NaO$ $[M+Na]^+$ 274.0949, found 274.0945, calcd for $C_{15}H_{13}KN_3O$ $[M+K]^+$ 290.0689, found 290.0689. Colourless crystal (needle), dimensions 0.75×0.10×0.02 mm^3, crystal system monoclinic, space group $P2_1/c$, Z=4, a=13.192(6) Å, b=5.700(3) Å, c=17.232(8) Å, α=90°, β=93.888(11)°, γ=90°, V=1292.9(11) Å^3, ρ=1.291 g/cm^3, T=200(2) K, θ_{max}=23.25°, radiation Mo Kα, λ=0.71073 Å, 0.3° omega-scans with CCD area detector, covering a whole sphere in reciprocal space, 8356 reflections measured, 1856 unique (R(int)=0.0823), 1206 observed ($I>2s(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[21a] based on the Laue symmetry of the reciprocal space, μ=0.08 mm^{-1}, T_{min}=0.94, T_{max}=1.00, structure solved by direct methods and refined against F^2 with a full-matrix

least-squares algorithm using the SHELXTL (Version 2008/4) software package,[21b] 177 parameters refined, hydrogen atoms were treated using appropriate riding models, except of H10, which was refined isotropically, goodness of fit 0.97 for observed reflections, final residual values $R1(F)$=0.061, $wR(F^2)$=0.146 for observed reflections, residual electron density −0.25 to 0.24 e Å^{-3}. CCDC 900992 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*4.3.4. N-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**4d**).* White solid (240 mg, 90%); mp: 214–217 °C; R_f (25% EtOAc/hexane) 0.34; ν_{max} (KBr): 1617, 3257 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 3.72 (s, 3H, −OCH_3), 6.94 (d, 2H, *J* 9.1 Hz, H–Ar), 7.52 (d, 2H, *J* 2.1 Hz, H–Ar), 7.53–7.56 (m, 3H, H–Ar), 7.86–7.88 (m, 2H, H–Ar), 10.45 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 55.2, 114.3, 118.5, 123.9, 129.3, 130.8, 131.8, 154.4, 157.4, 160.1; HR-mass (ESI) calcd for $C_{30}H_{27}N_6O_4$ $[2M+H]^+$ 535.2092, found 535.2091.

*4.3.5. N-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**4e**).* White solid (149 mg, 55%); mp: 229–230 °C; R_f (25% EtOAc/hexane) 0.55; ν_{max} (KBr): 1586, 1603, 3203 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.40 (d, 2H, *J* 8.6 Hz, H–Ar), 7.55–7.56 (m, 3H, H–Ar), 7.63 (d, 2H, *J* 8.7 Hz, H–Ar), 7.88 (m, 2H, H–Ar), 10.82 (s, 1-H, NH); δ_C (125 MHz, DMSO-d_6): 118.6, 123.7, 125.4, 125.5, 128.9, 129.3, 131.0, 137.6, 157.8, 159.6; HR-mass (ESI) calcd for $C_{14}H_{11}N_3O^{35}Cl$ $[M+H]^+$ 272.0587, found 272.0586, calcd for $C_{14}H_{10}N_3NaO^{35}Cl$ $[M+Na]^+$ 294.0406, found 294.0406.

*4.3.6. 5-(3-Chlorophenyl)-N-phenyl-1,3,4-oxadiazole-2-amine (**4f**).* White solid (108 mg, 40%); mp: 188–191 °C; R_f (25% EtOAc/hexane) 0.45; ν_{max} (KBr): 1578, 1615, 3266 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.00 (t, 2H, *J* 7.3 Hz, H–Ar), 7.35 (t, 2H, *J* 7.9 Hz, H–Ar), 7.54–7.65 (m, 4H, H–Ar), 7.82 (s, 1H, H–Ar), 7.84 (br s, 1H, H–Ar), 10.74 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 116.7, 117.1, 122.0, 124.1, 125.0, 125.7, 128.9, 129.1, 130.6, 131.3, 133.9, 138.4, 156.5, 160.1; HR-mass (ESI) calcd for $C_{14}H_{11}N_3O^{35}Cl$ $[M+H]^+$ 272.0585, found 272.0585.

*4.3.7. N-Phenyl-5-(thiophene-2-yl)-1,3,4-oxadiazol-2-amine (**4g**).* White solid (211 mg, 87%); mp: 187–188 °C; R_f (25% EtOAc/hexane) 0.40; ν_{max} (KBr): 1581, 1673 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.00 (t, 1H, *J* 7.4 Hz, H–Ar), 7.24 (dd, 1H, *J* 4.9, 3.8 Hz, H–Ar), 7.35 (t, 2H, *J* 8.4 Hz, H–Ar), 7.59 (d, 2H, *J* 7.8 Hz, H–Ar), 7.63 (dd, 1H, *J* 3.7, 1.1 Hz, H–Ar), 7.83 (dd, 1H, *J* 5.0, 1.1 Hz, H–Ar), 7.93 (s, 1-H, NH); δ_C (125 MHz, DMSO-d_6): 117.0, 121.9, 124.9, 128.2, 128.5, 129.0, 129.8, 138.5, 154.1, 159.3; HR-mass (ESI) calcd for $C_{12}H_{10}N_3OS$ $[M+H]^+$ 244.0541, found 244.0541.

*4.3.8. N-(4-Methoxyphenyl)-5-(thiophen-2-yl)-1,3,4-oxadiazol-2-amine (**4h**).* White solid (251 mg, 92%); mp: 200–203 °C; R_f (25% EtOAc/hexane) 0.35; ν_{max} (KBr): 1586, 1683, 3290 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 3.71 (s, 3H, −OCH_3), 6.93 (d, 2H, *J* 7.6 Hz, H–Ar), 7.23 (br s, 1H, thienyl), 7.49 (d, 2H, *J* 7.6 Hz, H–Ar), 7.50 (d, 2H, *J* 7.6 Hz, H–Ar), 7.60 (br s, 1H, H-thienyl), 7.81 (br s, 1H, thienyl), 10.46 (br s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 55.2, 114.3, 118.6, 125.1, 128.1, 128.4, 129.6, 131.8, 153.9, 154.5, 159.6; HR-mass (ESI) calcd for $C_{13}H_{12}N_3O_2S$ $[M+H]^+$ 274.0643, found 274.0643, calcd for $C_{13}H_{11}N_3NaO_2S$ $[M+Na]^+$ 296.0462, found 296.0462.

*4.3.9. N-Phenyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (**4i**).* White solid (166 mg, 70%); mp: 214–217 °C; R_f (25% EtOAc/hexane) 0.45; ν_{max} (KBr): 1565, 1615, 3267 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.02 (br s, 1H, H–Ar), 7.36 (br s, 2H, H–Ar), 7.61 (d, 2H, *J* 6.9 Hz, H–Ar), 7.78 (br s, 2H, H–Ar), 8.76 (br s, 2H, H–Ar), 10.85 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 117.2, 119.1, 122.2, 129.1, 130.7, 138.3, 150.8, 156.2, 160.5; HR-mass (ESI) calcd for $C_{13}H_{11}N_4O$ $[M+H]^+$ 239.0926, found 239.0926, calcd for $C_{13}H_{10}N_4NaO$ $[M+Na]^+$ 261.0746, found 261.0746.

*4.3.10. N-Phenyl-5-(pyrazin-2-yl)-1,3,4-oxadiazole-2-amine (**4j**).* Brown solid (157 mg, 66%); mp: 219–220 °C; R_f (25% EtOAc/hexane) 0.35; ν_{max} (KBr): 1622, 3290 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.02 (s, 1H, H–Ar), 7.36 (s, 2H, H–Ar), 7.61 (s, 2H, H–Ar), 8.77 (s, 2H, H–Ar), 9.25 (s, 1H, H–Ar), 10.93 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 117.2, 122.2, 129.1, 138.2, 139.3, 142.6, 144.7, 145.8, 155.8, 160.8; HR-mass (ESI) calcd for $C_{12}H_{10}N_5O$ $[M+H]^+$ 240.0879, found 240.0879, calcd for $C_{12}H_9N_5NaO$ $[M+Na]^+$ 262.0697, found 262.0698.

*4.3.11. 3-Ethyl-N-(5-phenyl-1,3,4-oxadiazol-2-yl)benzamide (**4k**).* White solid (179 mg, 70%); mp: 217–219 °C; R_f (25% EtOAc/hexane) 0.40; ν_{max} (KBr): 1583, 1630, 1716 cm^{-1}; δ_H (500 MHz, DMSO-d_6): 2.38 (s, 3H, H–Ar), 7.41–7.46 (m, 2H, H–Ar), 7.59–7.60 (m, 3H, H–Ar), 7.82–7.86 (m, 2H, H–Ar), 7.95–7.97 (m, 2H, H–Ar), 12.12 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 20.8, 123.3, 125.4, 126.0, 128.4, 128.7, 129.3, 131.6, 132.3, 133.4, 137.9, 158.0, 160.9, 165.3; HR-mass (ESI) calcd for $C_{16}H_{14}N_3O_2$ $[M+H]^+$ 280.1080, found 280.1080, calcd for $C_{16}H_{12}N_3NaO_2$ $[M+Na]^+$ 302.0900, found 302.0900.

*4.3.12. 3-Methoxy-N-(5-phenyl-1,3,4-oxadiazol-2-yl)benzamide (**4l**).* White solid (236 mg, 80%); mp: 149–150 °C; R_f (25% EtOAc/hexane) 0.35; ν_{max} (KBr): 1631, 1708, 3213 cm^{-1}; δ_H (300 MHz, DMSO-d_6): 3.83 (s, 3H, H–OMe), 7.21–7.22 (m, 1H, H–Ar), 7.47–7.61 (m, 6H, H–Ar), 7.96 (br s, 2H, H–Ar), 12.17 (br s, 1H, NH); δ_C (125 MHz, DMSO-d_6): 55.4, 113.0, 119.0, 120.0, 123.3, 126.0, 129.4, 129.8, 131.7, 133.6, 158.1, 159.2, 165.5; HR-mass (ESI) calcd for $C_{16}H_{14}N_3O_3$ $[M+1]^+$ 296.1032, found 296.1031, calcd for $C_{16}H_{13}N_3NaO_3$ $[M+Na]^+$ 318.0851, found 318.0852.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.11.071.

References and notes

1. Chandrakantha, B.; Shetty, P.; Nambiyar, V.; Isloor, N.; Isloor, A. M. *Eur. J. Med. Chem.* **2010**, *45*, 1206–1210.
2. Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csoeregh, I.; Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112–3120.
3. Khan, M. T. H.; Choudhary, M. I.; Khan, K. M.; Rani, M. *Bioorg. Med. Chem.* **2005**, *13*, 3385–3395.
4. Ramazani, A.; Rezaei, A. *Org. Lett.* **2010**, *12*, 2852–2855.
5. Laufer, R.; Paz, O. G.; Di Marco, A.; Bonelli, F.; Monteagudo, E.; Summa, V.; Rowley, M. *Drug Metab. Dispos.* **2009**, *37*, 873–883.
6. McCoull, W.; Addie, M. S.; Birch, A. M.; Birtles, S.; Buckett, L. K.; Butlin, R. J.; Bowker, S. S.; Boyd, S.; Chapman, S.; Davies, R. D. M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3873–3878.
7. Dolman, S. J.; Gosselin, F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2006**, *71*, 9548–9551.
8. Yale, H. L.; Losee, K. *J. Med. Chem.* **1966**, *9*, 478–483.
9. Kiselyov, A. S.; Semenova, M. N.; Chernyshova, N. B.; Leitao, A.; Samet, A. V.; Kislyi, K. A.; Raihstat, M. M.; Oprea, T.; Lemcke, H.; Lantow, M. *Eur. J. Med. Chem.* **2010**, *45*, 1683–1697.
10. Al-Talib, M.; Tashtoush, H.; Odeh, N. *Synth. Commun.* **1990**, *20*, 1811–1817.
11. Sharma, S.; Srivastava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2002**, *37*, 689–697.
12. Brain, C. T.; Paul, J. M.; Loong, Y.; Oakley, P. J. *Tetrahedron Lett.* **1999**, *40*, 3275–3278.
13. (a) Rostom, S. A. F.; Shalaby, M. A.; El-Demellawy, M. A. *Eur. J. Med. Chem.* **2003**, *38*, 959–974; (b) Wang, X.; Li, Z.; Wei, B.; Yang, J. *Synth. Commun.* **2002**, *32*, 1097–1103.
14. (a) Omar, F. A.; Mahfouz, N. M.; Rahman, M. A. *Eur. J. Med. Chem.* **1996**, *31*, 819–825; (b) Gosselin, F.; Britton, R. A.; Davies, I. W.; Dolman, S. J.;

Gauvreau, D.; Hoerrner, R. S.; Hughes, G.; Janey, J.; Lau, S.; Molinaro, C.; Nadeau, C.; O'Shea, P. D.; Palucki, M.; Sidler, R. *J. Org. Chem.* **2010**, *75*, 4154–4160.
15. (a) Labouta, I. M.; Hassan, A. M. M.; Aboulwafa, O. M.; Kader, O. *Monatsh. Chem. (Chemical Monthly)* **1989**, *120*, 571–574; (b) Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Gong, Y.-D. *J. Comb. Chem.* **2005**, *7*, 816–819.
16. (a) Piatnitski Chekler, E. L.; Elokdah, H. M.; Butera, J. *Tetrahedron Lett.* **2008**, *49*, 6709–6711; (b) Severinsen, R.; Kilburn, J. P.; Lau, J. F. *Tetrahedron* **2005**, *61*, 5565–5575.
17. Baxendale, I. R.; Ley, S. V.; Martinelli, M. *Tetrahedron* **2005**, *61*, 5323–5349.
18. Coppo, F. T.; Evans, K. A.; Graybill, T. L.; Burton, G. *Tetrahedron Lett.* **2004**, *45*, 3257–3260.
19. Jakubke, H. D.; Sewald, N. *Peptides Chemistry and Biology*; Wiley-VCH: Weinheim, 2002; p 202.
20. (a) Pellei, M.; Gandin, V.; Marinelli, M.; Marzano, C.; Yousufuddin, M.; Dias, H. V. R.; Santini, C. *Inorg. Chem.* **2012**, *51*, 9873–9882 and references cited therein; (b) Murakami, N.; Wang, W.; Ohyabu, N.; Ito, T.; Tamura, S.; Aoki, S.; Kobayashi, M.; Kitagawa, I. *Tetrahedron* **2000**, *56*, 9121–9128.
21. (a) Sheldrick, G. M. Bruker Analytical X-ray-Division: Madison, WI, 2008. (b) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.