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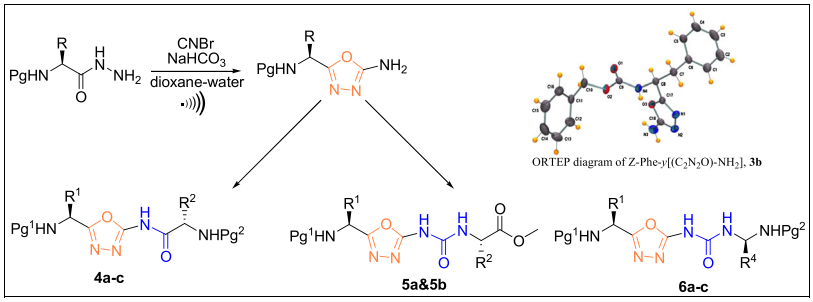

Synthesis of 2-amino-1,3,4-oxadiazole derivatives of N^{α}-Cbz(benzyloxycarbonyl)/Boc-protected amino/peptide acids under sonication is described. The conditions involved in the present protocol are simple, mild, and racemization free. The utility of 2-amino group in the substituted oxadiazoles for the incorporation of peptide and ureido bonds to obtain hybrid peptidomimetics is also delineated. The 2-amino-1,3,4-oxadiazole **3b** was obtained as a single crystal, and its molecular structure has been confirmed through X-ray crystallographic study.

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INTRODUCTION

Oxadiazoles are the important targets in the field of pharmacology and medicine [1]. They have often been described as bioisosteres of amides and esters [2]. 1,3,4-Oxadiazole is an important structural motif in the development of drug candidates such as tiodazosin [3], nesapidil [4], and furamizole (Fig. 1) [5]. It also has applications in diverse fields such as material science [6] and organic electronics [7]. The insertion of heterocyclic unit in a peptide introduces conformational constraint to the structure, which might enhance the activity and also alter the structure–activity relationships [8]. Several heterocycles such as triazole [9], oxazole [10], thiazole [11], and tetrazole [12] have been inserted *en route* to the design of new peptidomimetics [13].

The preparation and utility of 2-alkylamino-1,3,4-oxadiazole peptidomimetics is well known. Luthman et al. reported the synthesis of 1,3,4-oxadiazole containing enantiomerically pure Boc-Phe-Gly dipeptidomimetics with a methylene spacer (Fig. 2A) [14]. Batey et al. described a one-pot procedure for the synthesis of 1,3,

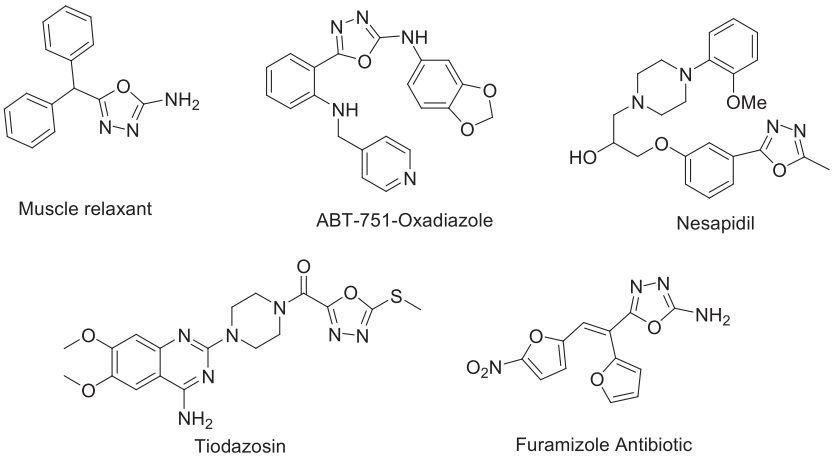
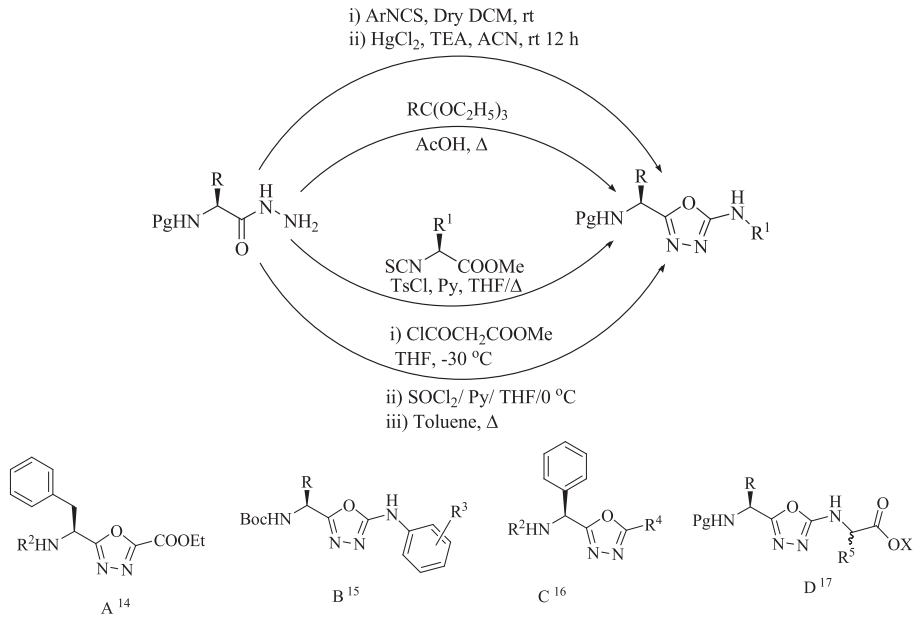


Figure 1. Structures of biologically active 1,3,4-oxadiazoles containing compounds.



$R^1 = R^5$ = amino acid side chain; R^2 = Ac/ Boc or H-Xaa ; R^3 = H, Me, Br, NO_2 etc.; R^4 = H, Me, Et, Ph; X = Me, Bn

Figure 2. Various approaches reported for the synthesis of 2-substituted-1,3,4-oxadiazole containing peptidomimetics.

4-oxadiazoles from Boc-protected amino acid hydrazides and arylisothiocyanates in the presence of $HgCl_2$ (Fig. 2B) [15]. Kudelko et al. reported the synthesis of 2-aminomethyl-1,3,4-oxadiazoles from N^{α}-Ac and N^{α}-Boc-protected phenylglycine hydrazide and triethyl orthoesters under reflux in AcOH (Fig. 2C) [16]. 2-Amino-5-substituted-1,3,4-oxadiazoles can be synthesized by the cyclization of corresponding diacylhydrazines or thiosemicarbazide (Fig. 2D) [17]. Few amino-acid-derived 2-amino-1,3,4-oxadiazoles are reported in the literature by the treatment of CNBr with hydrazide [18]. However, some of the these reported procedures for the synthesis of 2-amino-1,3,4-oxadiazoles require long reaction duration and harsh conditions. Because of the wide utility of 2-amino-1,3,4-oxadiazole moiety as a peptidomimetic, still there is continued interest in the synthesis of optically pure 2-amino-1,3,4-oxadiazoles and their hybrids.

Ultrasonic irradiation has been recognized as a powerful technique for the acceleration of organic transformations. Particularly, heterocyclic compounds including pyrazoles [19], 1,2,4-oxadiazoles [20], and triazoles [21] have been synthesized using ultrasonic chemistry, and it has proven to be highly reliable method when compared with conventional reflux or microware conditions. Recently, our group has also utilized ultrasonication for the synthesis of thiopeptides and selenazole-linked peptidomimetics, which has lead to significantly shorter reaction duration, as well to mild and cleaner reaction profile [22]. Also with our expertise in the heterocyclic peptidomimetics [23], we herein report the synthesis of 2-amino-1,3,4-oxadiazoles containing peptidomimetics and their utility for the synthesis of a variety of amide and urea hybrid peptidomimetics under mild conditions and ultrasonication as environmentally friendly energy source.

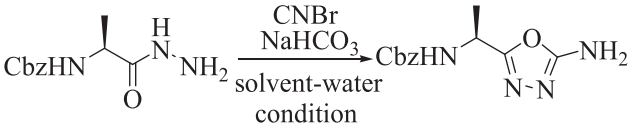
RESULTS AND DISCUSSION

In a model reaction, 2-amino-1,3,4-oxadiazole **3a** was synthesized by treating Cbz-Ala-$CONHNH_2$ **2a**, with CNBr and $NaHCO_3$ in THF–H_2O (5:2) at rt. The desired product **3a** was obtained with 64% yield in 6 h (Table 1, entry 1). In order to optimize the reaction, various conditions were screened including temperature and solvent (Table 1, entries 2–5). Increasing the temperature up to 80°C in solvent system THF–H_2O and dioxane–H_2O could yield 80–85% of the product. In an effort to make the protocol mild and facile, we then turned our attention to ultrasonication (Table 1, entries 6 and 7). It was found that the reaction of hydrazide **2a** (1.0 mmol) with CNBr and $NaHCO_3$ in dioxane–H_2O (5:2) performed at 25°C under ultasonication resulted in complete disappearance of hydrazide **2a** in 30 min as observed by TLC. After completion of reaction, the desired peptidomimetic **3a** (solid product) was filtered, washed with water, and recrystallized using MeOH–H_2O (1:1). Upon increasing the temperature, no appreciable change in the yield of **3a** (Table 1, entry 6) was observed.

In accordance with the optimized conditions, syntheses of several amino-acid-derived 2-amino-1,3,4-oxadiazoles **3b–g** were carried out (Scheme 1). Also, two peptidic

Table 1

Optimization of reaction conditions for the synthesis of **3a**.



Sl. No.	Condition	Solvent	Time	Yield (%)
1	rt	THF	6 h	64
2	Reflux, 60°C	THF	3 h	75
3	Heat, 60°C	Dioxane	2 h	80
4	Reflux, 80°C	THF	2 h	81
5	Reflux, 80°C	Dioxane	100 min	85
6	Sonication, rt	Dioxane	30 min	94
7	Sonication, rt	THF	30 min	86
8	Sonication, 50°C	Dioxane	30 min	94

hydrazides were converted to corresponding 2-amino-1,3,4-oxadiazoles **3h** and **3i**. All the products **3a–i** were isolated in good to excellent yields of 85–94% (Table 2), characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopic analyses.

During the course of the study, two enantiomeric N^{α}-protected 2-amino-1,3,4-oxadiazoles derived from Cbz-L-Ala-OH, **3a**, and its epimer Cbz-D-Ala-OH, **3a***, were prepared through optimized protocol and analyzed by chiral RP-HPLC for racemization. In the chiral HPLC profile, a single peak with retention times at $R_t = 18.30$ and 26.44 min was recorded for **3a** and **3a***, respectively. Also, an intentionally made equimolar mixture of **3a** and **3a*** exhibited two separate peaks corresponding to the D- and L-isomers ($R_t = 18.63$ and 26.84 min) (Fig. 3). This clearly confirms that the present protocol employed for synthesis of amino oxadiazole peptidomimetics is free from racemization [24].

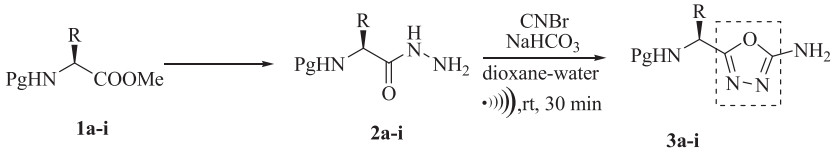
In recent years, hybrid peptides have been investigated using various types of non-amide bond tethers between two amino acid residues to gain detailed insight into structure–function relationships and to achieve improved properties such as pharmacological response, biodegradability, and bioavailability. The heterocycle-peptide hybrids have been screened for agonist activity by using human gel-filtered platelet aggregation [25]. A combination of urea-ester, peptide-urea hybrids [26] and aminoxy peptide hybrids [27] were also reported (Fig. 4), and their structure–aggregation relationships have been studied. Aminoxy peptide hybrids have been employed as novel foldamers, and they feature strong intramolecular hydrogen bonds between adjacent residues in peptidomimetics foldamers.

The presence of free 2-amino group in the amino-oxadiazole scaffold in the present case provides an opportunity for the diversification by insertion of other moieties leading to the hybrid peptidomimetics. Thus, we exploited the synthesized molecules for facile construction of 2-amino-1,3,4-oxadiazole-amide/urea containing hybrid peptidomimetics. These new functionalities are expected to provide valuable insights into structure–function relationships of a peptide. In the first part of the study, the utility of the 2-amino-1,3,4-oxadiazoles **3** in the synthesis of orthogonally protected 2-amino-1,3,4-oxadiazole-amide peptidomimetics **4a–c** was demonstrated. The requisite N-protected amino acid flourides were prepared from respective N-protected amino acids employing Deoxo-Fluor (Sigma-Aldrich, St. Louis, MO) in the presence of *N*-methylmorpholine, thus the reaction of **3** with N-protected amino acid fluorides in THF under ultrasonication. After consumption of the starting materials (TLC analysis), a simple work up lead to the oxadiazole-amide containing orthogonally protected peptidomimetics **4a–c** (Scheme 2).

In the next part, we used the oxadiazole **3** as a monomer for the construction of oxadizole-urea-linked dipeptidomimetics. Amino-acid-derived isocyanates were reacted with amino-oxadiazoles **3** under ultrasonication in THF at rt. The products were isolated after simple work-up followed by column purification using EtOAc/*n*-hexane (3:7; Scheme 3, Table 3).

X-ray crystallographic study of Cbz-Phe-ψ[(C_2N_2O)-NH_2] 3b, (CCDC No. 851895). One of the oxadiazole derivatives, Cbz-Phe-ψ[(C_2N_2O)-NH_2] **3b**, was obtained as a single crystal, and its molecular structure was determined by X-ray crystallography (Fig. 5). Oxadiazole **3b** has been crystallized in non-centrosymmetric $P2_1$ space group. The crystal structure is stabilized by strong intermolecular N–H···N and N–H···O bonds facilitated with weak intermolecular C–H···O bonds. The 1,3,4-oxadiazole moiety is involved in most of the interactions (for details, see the Supporting information).

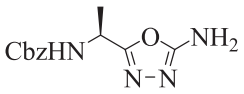
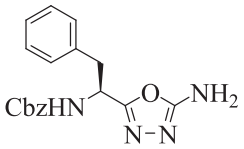
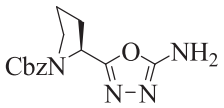
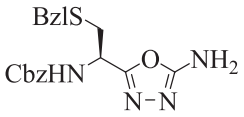
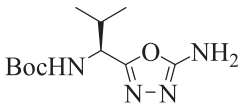
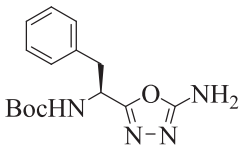
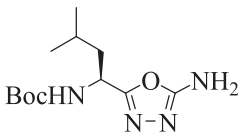
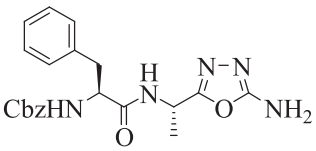
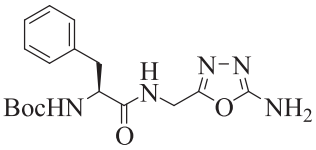
Scheme 1. Synthesis of amino acid derived 2-amino-1,3,4-oxadiazoles.



Pg = Cbz or Boc group

Table 2

List of 2-amino-1,3,4-oxadiazoles prepared.

Entry	Oxadiazole **3**	mp (°C)	Yield (%)	Mass calcd (obsd)
3a		219.0–220.0	94	262.1 (285.1)[a]
3b		146.0–147.0	91	338.1 (339.2)[b]
3c		Gum	86	288.15 (311.2)[a]
3d		138.0–139.0	85	384.1 (407.1)[a]
3e		178.0–179.0	87	256.2 (257.2)[b]
3f		175.0–176.0	90	304.2 (303.5)[c]
3g		173.0–175.0	88	270.1692 (271.1778)[d]
3h		180.0–182.0	91	409.18 (432.18)[a]
3i		100.0–101.0	87	362.1820 (362.1820)[d]

[a]LC-MS $[M+Na]^+$.
[b]LC-MS $[M+H]^+$.
[c]LC-MS $[M-H]^+$.
[d]HR-MS $[M+H]^+$.

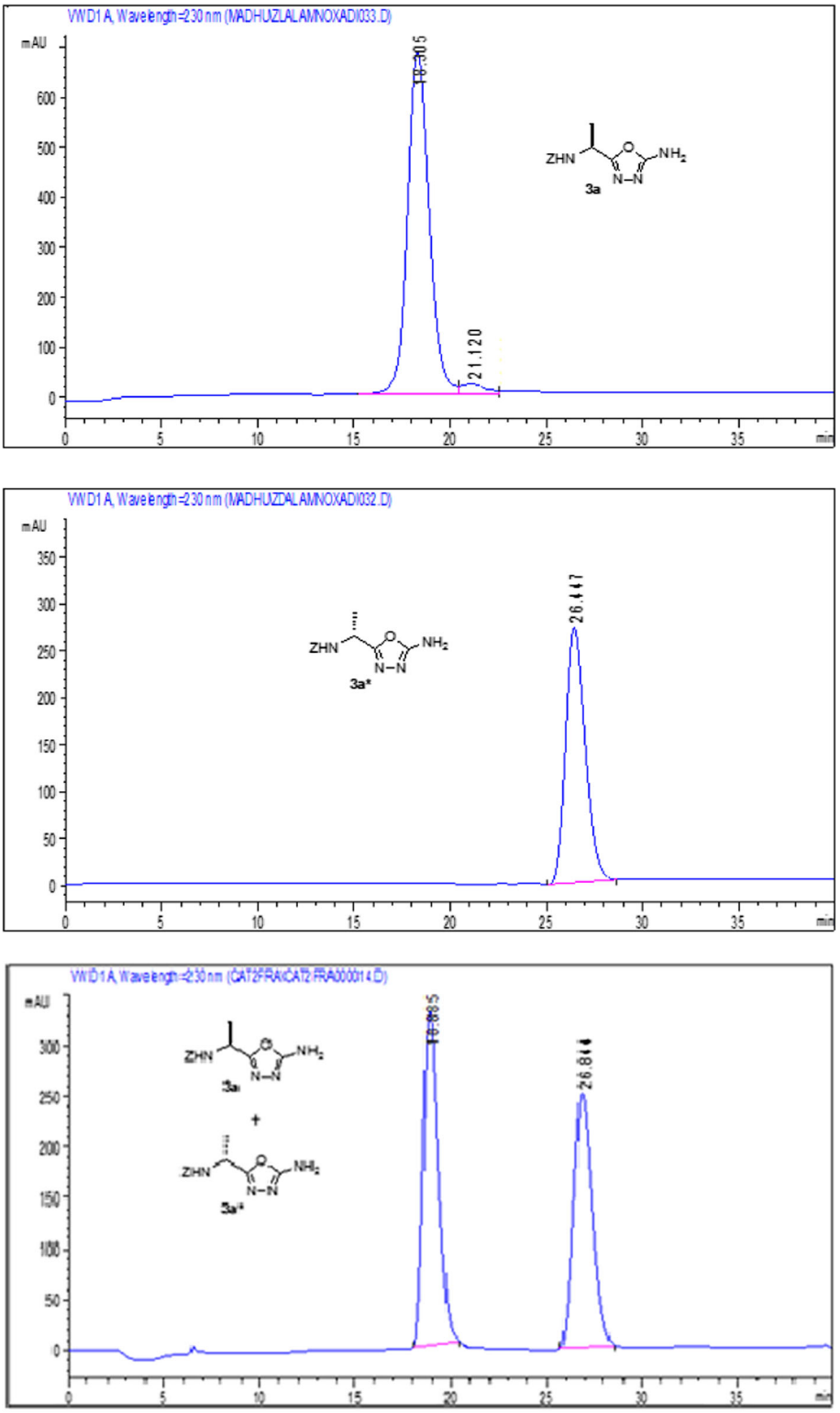


Figure 3. Chiral HPLC of **3a**, **3a*** and its racemic mixture. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

CONCLUSION

A simple and convenient method for the synthesis of amino/peptide acid derived 2-amino-1,3,4-oxadiazoles **3a–i** from corresponding acylhydrazides under ultrasonication is described. The presence of amino group facilitated the construction of 2-amino-1,3,4-oxadiazole-amide/urea containing hybrid peptidomimetics. The oxadiazole

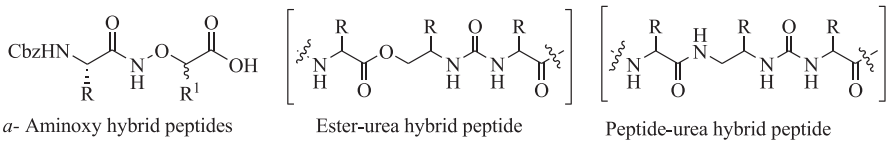
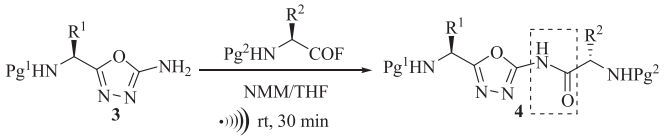


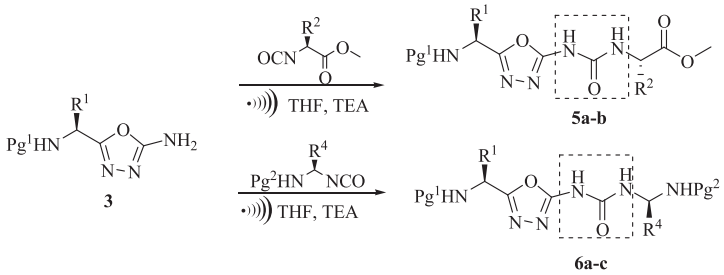
Figure 4. Structures of hybrid peptides.

Scheme 2. Synthesis of orthogonally protected 2-amino-1,3,4-oxadiazole-amide peptidomimetics.



	Pg^1	R^1	Pg^2	R^2
4a	Cbz	Me	Fmoc	$CH_2C_6H_5$
4b	Boc	$CH(Me)_2$	Cbz	Me
4c	Boc	$CH_2C_6H_5$	Fmoc	$CH(Me)_2$

Scheme 3. Synthesis of 2-amino-1,3,4-oxadiazole-urea tethered peptidomimetics.



Z-Phe-ψ[(C_2N_2O)-NH_2] **3b** was isolated as a single crystal, and its molecular structure was confirmed through X-ray crystallographic study.

EXPERIMENTAL

General information. All solvents were freshly distilled before use. Amino acids were used as received from Sigma-Aldrich Company. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AMX 300 and 100 MHz instrument (Ramrod Scientifics, Waterford Street, Gardner, MA) with TMS as internal standard. Mass spectra were recorded on HR-MS Q-Tof micro mass spectrometer. All the reactions were monitored using TLCs with pre-coated silica gel plates purchased from Merck (Whitehouse Station, NJ). Column chromatography was performed with Merck silica gel (200–300 mesh) at normal atmospheric pressure. The ultrasound bath (Elma, T 310/H) was German made and operated at 35 kHz.

General procedure for the synthesis of N^{α}-protected amino acid/peptide acid derived 2-amino-1,3,4-oxadiazoles 3a–i. To a solution of N^{α}-protected amino alkyl hydrazide/peptide hydrazide (10 mmol) in dioxane–H_2O (10:4 mL), a solution of $NaHCO_3$ (12 mmol) and CNBr (12 mmol) was added at rt, and the reaction was subjected to sonication for about 30 min. After the completion of the reaction as indicated by TLC, the solid product was filtered, washed with water, and recrystallized using MeOH–H_2O (1:1) to obtain the analytically pure product.

General procedure for the synthesis of orthogonally protected dipeptidyl 2-amino-1,3,4-oxadiazoles, 4a–c. To a solution of N^{α}-protected amino acid fluoride (10 mmol) and *N*-methylmorpholine (1.2 mmol) in dry THF, a solution of 2-amino-1,3,4-oxadiazole (12 mmol) in THF was added, and the reaction mixture was subjected to ultrasonication at rt. After the completion of the reaction as monitored by TLC (30 min), the solvent was evaporated, and the crude was extracted into EtOAc. The organic layer was washed with 5% citric acid (10 mL × 2), 5% Na_2CO_3 (10 mL × 2), water, and brine. The solvent was dried over anhydrous Na_2SO_4, evaporated, and purified through column chromatography (hexane/EtOAc 7:3) to obtain the orthogonally protected dipeptidyl 2-amino-1,3,4-oxadiazole.

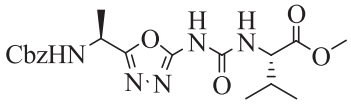
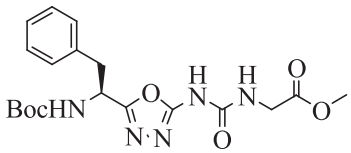
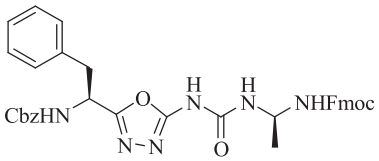
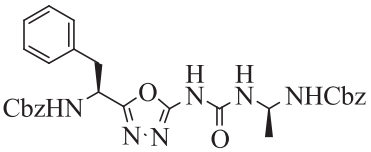
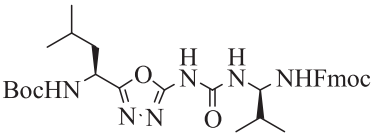
General procedure for the synthesis of 2-amino-1,3,4-oxadiazole-urea tethered peptidomimetics (5a,b and 6a–c) under ultrasonication. To a solution of N-protected amino acid derived 2-amino-1,3,4-oxadiazole (10 mmol) in THF, TEA (11 mmol, 1.54 mL) and N^{α}-protected amino alkyl isocyanate (11 mmol) in THF were added. The reaction was subjected to ultrasonication at rt, and progress of the reaction was monitored through TLC analysis. After the completion of the reaction, the solvent was evaporated, and the crude was extracted into EtOAc. The organic layer was washed with 5% citric acid (10 mL × 2), water, and brine, dried over Na_2SO_4, and evaporated under *vacuo*, which afforded the ureido product. The crude product was subjected to silica gel column chromatography to obtain the pure product.

Spectral data

Cbz-Ala-ψ[(C_2N_2O)-NH_2] (3a). White solid (94%); mp 219–220°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (d, 3H,

Table 3

List of 2-amino-1,3,4-oxadiazole-urea tethered peptidomimetics prepared.

Entry	Compound	Time (min)	Yield (%)[a]	Mass calcd (obsd)[b]
5a		25	79	419.18 (442.08)
5b		32	76	419.18 (442.24)
6a		28	83	646.25 (669.23)
6b		30	81	558.22 (581.13)
6c		30	86	606.32 (629.24)

[a]Yields reported after column chromatographic purification.
[b]ESI-MS $[M+Na]^+$.

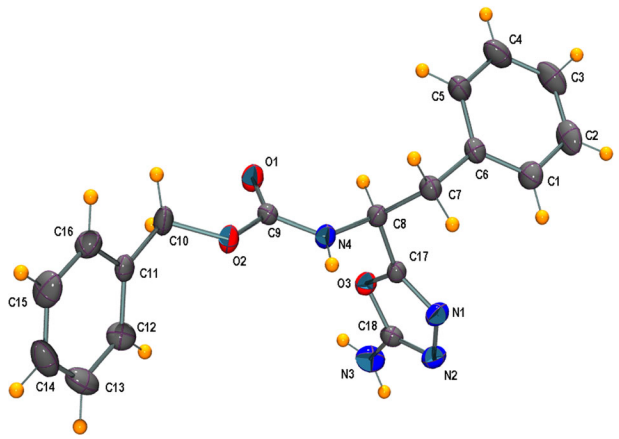


Figure 5. ORTEP diagram of Z-Phe-ψ[(C_2N_2O)-NH_2], **3b**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$J = 6.8$ Hz), 4.70–4.75 (m, 1H), 4.9 (br, 2H), 5.32 (s, 2H), 7.18–7.22 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.3 (CH_3), 50.1 (CH), 64.3 (CH_2), 126.5 (CH), 127.1 (CH), 128.7 (CH), 141.2 (C), 156.2 (C═O).169.8 (C-5 Oxadiazole), 170.6 (C-2 Oxadiazole); LC-MS Calcd for $C_{12}H_{14}N_4O_3$ *m/z*: 262.1, found 285.1$(M+Na)^+$.

Cbz-Phe-ψ[(C_2N_2O)-NH_2] (3b). White solid (91%); mp 146–148ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (br, 2H), 3.15 (d, 2H, $J = 6.8$ Hz), 5.09–5.16 (m, 1H), 5.38 (s, 2H), 5.60 (br, 1H), 7.11–7.38 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 39.1 (CH2), 48.6 (CH), 67.1 (CH_2(Cbz)), 127.1 (CH), 128.0 (CH), 128.2 (CH), 128.54 (CH), 128.6 (CH), 129.3 (CH), 135.5 (C-Cbz), 136.0 (C-Ph), 155.6 (C═O), 170.9 (C-5 Oxadiazole), 171.6 (C-2 Oxadiazole); LC-MS Calcd for $C_{18}H_{18}N_4O_3$ *m/z*: 338.1, found 339.2 $(M+H)^+$.

Cbz-Pro-ψ[(C_2N_2O)-NH_2] (3c). White solid (86%); gum; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52–1.57 (m, 2H), 1.91–1.98 (m, 2H), 3.25 (t, 2H, $J = 5.4$ Hz), 4.81 (t, 2H, $J = 4.8$ Hz), 5.27 (s, 2H), 5.41 (br, 2H), 6.3 (br, 1H), 7.19–7.22 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.8 (CH_2-3 pro), 34.1 (CH_2-2 pro), 47.9 (CH_2-4 pro), 56.1 (CH-1 pro), 67.0 (CH_2-), 126.8 (CH), 127.0 (CH), 128.3 (CH), 140.3 (C-Cbz), 157.2 (C═O), 170.2 (C-5 Oxadiazole), 171.1 (C-2 Oxadiazole); LC-MS Calcd for $C_{14}H_{17}N_4O_3$ *m/z*: 288.15, found 311.2 $(M+Na)^+$.

Cbz-Cys(sBzl)-ψ[(C_2N_2O)-NH_2] (3d). White solid (85%); mp 138–139°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (d, 2H, J = 6.8 Hz), 3.62 (s, 2H), 5.1 (t, 1H, J = 5.6 Hz), 5.23 (s, 2H), 5.8 (br, 2H), 7.15–7.23 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) 33.9 (S-CH_2), 38.4 (S-CH_2-Ph), 54.1 (CH), 66.7 (CH_2), 126.8 (CH), 127.0 (CH), 127.3 (CH), 128.1 (CH), 128.2 (CH), 136.1 (C-ph), 140.5 (C-Cbz), 156.7 (C═O), 170.2 (C-5 Oxadiazole), 171.5 (C-2 Oxadiazole); LC-MS Calcd for $C_{19}H_{20}N_4O_3S$ *m/z*: 384.1, found 407.1 $(M + Na)^+$.

Boc-Val-ψ[(C_2N_2O)-NH_2] (3e). White solid (87%); mp 178–179°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (d, 6H, J = 7.2 Hz), 1.37 (s, 9H), 2.72–2.78 (m, 1H), 4.79 (d, 1H, J = 6.8 Hz), 5.35 (br, 2H), 6.84 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 16.8 (CH_3), 28.3 (3CH_3-Boc), 34.1 (CH), 59.7 (CH), 79.2 (C-Boc), 155.8 (C═O), 170.9 (C-5 Oxadiazole), 171.4 (C-2 Oxadiazole); LC-MS Calcd for $C_{11}H_{20}N_4O_3$ *m/z*: 256.2, found 257.2$(M + H)^+$.

Boc-Phe-ψ[(C_2N_2O)-NH_2] (3f). White solid (90%); mp 175–176°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.35 (s, 9H), 3.23–3.27 (m, 2H), 3.8 (br, 2H), 4.90–4.95 (m, 1H), 5.84 (s, 2H), 6.3 (br, 1H), 7.14–7.27 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.2 (3CH_3- Boc), 39.5 (CH_2), 48.1 (CH), 78.3 (C-Boc), 127.1 (CH), 128.6 (CH), 129.4 (CH), 135.6 (C-Ph), 156.1 (C═O), 170.1 (C-5 Oxadiazole), 171.5 (C-2 Oxadiazole); LC-MS Calcd for $C_{15}H_{20}N_4O_3$ *m/z*: 304.2, found 303.5 $(M - H)^+$.

Boc-Leu-ψ[(C_2N_2O)-NH_2] (3g). White solid (88%); mp 173–175°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (d, 6H, J = 7.2 Hz), 1.35 (s, 9H), 1.79–1.82 (m, 3H), 4.91 (t, 1H, J = 4.4 Hz), 5.6 (br, 2H), 6.3 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 21.9 (2CH_3), 23.4 (CH), 28.1 (3CH_3-Boc), 45.7 (CH_2), 49.6 (CH), 78.1 (C-Boc), 155.3 (C═O), 170.3 (C-5 Oxadiazole), 171.6 (C-2 Oxadiazole); HRMS Calcd for $C_{12}H_{22}N_4O_3$ *m/z*: 270.1692, found 271.1778 $(M + H)^+$.

Z-Phe-Ala-ψ[(C_2N_2O)-NH_2] (3h). White solid (91%); mp 180–182°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48 (d, 3H, J = 6.8 Hz), 3.13 (d, 2H, J = 6.2 Hz), 4.93–4.98 (m, 2H), 5.25 (s, 2H), 5.8 (br, 2H), 6.3 (br, 1H), 7.12–7.21 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) 20.8 (CH_3), 37.1 (CH_2), 51.7 (CH), 54.2 (CH), 66.6 (CH_2-Cbz), 126.4 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 128.3 (CH), 129.1 (CH), 138.7 (C-Ph), 141.4 (C-Cbz), 156.7 (C═O), 168.9 (O═C–NH), 170.8 (C-5 Oxadiazole), 171.2 (C-2 Oxadiazole); LC-MS Calcd for $C_{21}H_{23}N_5O_4$ *m/z*: 409.18, found 432.18 $(M + Na)^+$.

Boc-Phe-Gly-ψ[(C_2N_2O)-NH_2] (3i). White solid (87%); mp 100–101°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (s, 9H), 2.9 (d, 2H, J = 7.2 Hz), 3.9 (br, 2H), 4.3 (s, 2H), 4.71–4.76 (m, 1H), 6.3 (br, 2H), 7.12–7.21 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.1 (3CH_3-Boc), 35.3 (CH_2), 43.4 (CH_2-Gly), 54.8 (CH), 76.5 (C-Boc), 127.4 (CH), 128.1 (CH), 129.3 (CH), 136.2 (C-Ph), 155.5 (C═O), 169.8 (O═C–NH), 170.6 (C-5 Oxadiazole), 171.2 (C-2 Oxadiazole); HRMS Calcd for $C_{17}H_{23}N_5O_4$ *m/z*: 361.1828, found 362.1820 $(M + H)^+$.

Cbz-Ala ψ[(C_2N_2O)NH-CO-Phe-NH-Fmoc (4a). White solid (73%), ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.51 (d, 3H, J = 7.6 Hz), 3.07 (d, 2H, J = 5.8 Hz), 4.48 (t, 1H, J = 5.2 Hz), 4.64 (d, 2H, J = 5.8 Hz), 4.73 (t, 1H, J = 4.8 Hz), 5.10–5.14 (m, 1H), 5.23 (s, 2H), 5.1 (br, 1H), 6.3 (br, 1H), 6.69 (br, 1H), 7.12–7.74 (m, 18H). ^{13}C NMR (100 MHz, DMSO-d_6) 21.4 (CH_3), 36.1 (CH_2), 48.2 (CH), 49.4 (CH-Fmoc), 53.7 (CH), 66.1 (CH_2), 67.9 (CH_2-Fmoc), 126.1 (CH), 126.4 (CH), 126.9 (CH), 127.2 (CH), 127.8 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 139.3 (C-Ph), 141.0 (C-Cbz), 141.4 (C-Fmoc), 144.5 (C-Fmoc), 156.3 (C═O), 156.8 (C═O), 167.2 (NH–C═O), 170.1 (C-5 Oxadiazole), 172.1 (C-2 Oxadiazole). ESI-MS Calcd for $C_{36}H_{33}N_5O_6$ *m/z*: 631.24, found 654.2 $(M + Na)^+$.

Boc-Val ψ[(C_2N_2O)NH-CO-Ala-NH-Cbz (4b). White solid (78%), ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (d, 6H, J = 7.2Hz), 1.36 (s, 9H), 1.53 (d, 3H, J = 6.4 Hz), 3.21–3.25 (m, 1H), 4.54–4.59 (m, 2H), 5.24 (s, 2H), 6.3 (br, 1H), 7.24 (s, 5H), 7.4 (br, 1H), 7.83 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.4 (2CH_3), 17.9 (CH_3), 27.9 (3CH_3-Boc), 36.1 (CH), 47.3 (CH), 61.7 (CH), 67.8 (CH_2-Cbz), 80.5 (C-Boc), 126.9 (CH), 127.4 (CH), 129.6 (CH), 140.3 (C-Cbz), 153.7 (C═O), 157.9 (C═O), 161.2 (NH–C═O), 163.7 (C-5 Oxadiazole), 170.9 (C-2 Oxadiazole); ESI-MS Calcd for $C_{22}H_{31}N_5O_6$ *m/z*: 461.23, found 485.3 $(M + Na)^+$.

Boc-Phe ψ[(C_2N_2O)NH-CO-Val-NH-Fmoc (4c). White solid (81%), ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (d, 6H, J = 7.2 Hz), 1.37 (s, 9H), 2.83–2.87 (m, 3H), 4.41 (t, 1H, J = 5.4 Hz), 4.53 (d, 1H, J = 4.8 Hz), 4.72 (d, 2H, J = 5.6 Hz), 5.23 (t, 1H, J = 4.8 Hz), 6.4 (br, 1H), 6.83 (br, 1H), 7.15–7.72 (m, 13H); ^{13}C NMR (100 MHz, DMSO-d_6) 17.3 (2CH_3), 28.1 (3CH_3-Boc), 30.8 (CH), 41.4 (CH_2), 47.3 (CH-Fmoc), 55.4 (CH), 58.1 (CH), 66.7 (CH_2-Fmoc), 78.2 (C-Boc), 126.7 (CH), 127.1 (CH), 127.5 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 138.7 (C-Ph), 140.9 (C-Fmoc), 143.3 (C-Fmoc), 155.8 (C═O), 156.0 (C═O), 168.2 (NH–C═O), 170.7 (C-5 Oxadiazole), 171.8 (C-2 Oxadiazole); ESI-MS Calcd for $C_{35}H_{39}N_5O_6$ *m/z*: 625.29, found 648.3 $(M + Na)^+$.

Cbz-Ala-ψ[(C_2N_2O)-{NH-CO-NH}]-Val-COOMe (5a). White solid (79%), ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (d, 6H, J = 7.2 Hz), 1.47 (d, 3H, J = 6.8 Hz), 3.10–3.16 (m, 1H), 3.53 (s, 3H), 4.28 (d, 1H, J = 5.6 Hz), 4.93–4.97 (m, 1H), 5.27 (s, 2H), 5.7 (br, 1H), 6.3 (br, 1H,), 6.85 (br, 1H), 7.18–7.22 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) 17.8 (2CH_3), 22.1 (CH_3-Ala), 30.7 (CH), 48.4 (CH), 52.1 (OCH_3), 56.4 (CH), 65.3 (CH_2-Cbz), 127.3 (CH), 127.8 (CH), 128.5 (CH), 140.8 (C-Ph), 153.9 (C═O urea), 156.1 (C═O), 168.1 (C═O ester), 169.5 (C-5 Oxadiazole), 171.4 (C-2 Oxadiazole); ESI-MS Calcd for $C_{19}H_{25}N_5O_6$ *m/z*: 419.18, found 442.08 $(M + Na)^+$.

Boc-Phe-ψ[(C_2N_2O)-{NH-CO-NH}]-Gly-COOMe (5b). White solid (76%), ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (s, 9H), 2.95 (t, 2H, J = 5.4 Hz), 3.58 (s, 3H), 4.12 (s, 2H), 5.2 (br, 1H), 5.6 (br, 1H), 6.4 (br, 1H), 7.12–7.21 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) 27.9 (3CH_3-Boc), 40.8 (CH_2), 43.1(CH_2), 52.3 (OCH_3), 56.2 (CH), 79.4 (C-Boc), 126.8 (CH), 127.5 (CH), 128.4 (CH), 139.8 (C-Ph), 153.5 (C═O urea), 156.1 (C═O), 169.4 (C═O ester), 169.9 (C-5 Oxadiazole), 170.8 (C-2 Oxadiazole); ESI-MS Calcd for $C_{19}H_{25}N_5O_6$ *m/z*: 419.18, found 442.24 $(M + Na)^+$.

Cbz-Phe-ψ[(C_2N_2O)-{NH-CO-NH}]-Ala-NH-Fmoc (6a). White solid (83%);^{1}H NMR (300 MHz, DMSO-d_6) δ 1.4 (d, 3H, J = 6.4 Hz), 3.1 (d, 2H, J = 7.0 Hz), 4.5 (s, 2H), 4.75 (t, 1H, J = 5.6 Hz), 4.83–4.87 (m, 1H), 5.15 (s, 2H), 5.51–5.56 (m, 1H), 5.91 (br, 1H), 6.20 (br, 1H), 7.12–7.84 (m, 18H), 7.95 (br, 1H), 10.58 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.8 (CH_3), 40.9 (CH_2), 46.3 (CH-Fmoc), 55.9 (CH), 58.7 (CH), 66.4 (CH_2-Cbz), 68.1 (CH2-Fmoc), 125.9 (CH), 126.3 (CH), 127.4 (CH), 127.8 (CH), 128.5 (CH), 128.9 (CH), 139.5 (C-Ph), 141.7 (C-Fmoc), 143.5 (C-Fmoc), 155.9 (C═O urea), 156.7 (C═O), 157.4 (C═O, Fmoc), 170.8 (C-5 Oxadiazole), 171.4 (C-2 Oxadiazole); ESI-MS Calcd for $C_{36}H_{34}N_6O_6$ *m/z*: 646.25, found 669.23 $(M + Na)^+$.

Cbz-Phe-ψ[(C$_2$N$_2$O)-{NH-CO-NH}]-Ala-NH-Cbz (6b). White solid (81%), ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48 (d, 3H, J = 6.8 Hz), 2.81 (d, 2H, J = 5.4 Hz), 5.1 (t, 1H, J = 4.6 Hz), 5.27 (s, 2H), 5.31 (br, 1H), 5.67–5.71 (m, 1H), 6.42 (br, 1H), 7.14–7.19 (m, 15H); ^{13}C NMR (100 MHz, DMSO-d_6) 20.7 (CH_3), 41.4 (CH_2), 54.9 (CH), 59.1 (CH), 65.4 (CH_2-Cbz), 125.3 (CH), 126.9 (CH), 127.4 (CH), 127.8 (CH), 128.5 (CH), 128.6 (CH), 138.9 (C-ph), 141.7 (C-Cbz), 154.8 (C═O, urea), 156.7 (C═O), 158.5 (C═O), 169.7 (C-5 Oxadiazole), 170.3 (C-2 Oxadiazole); ESI-MS Calcd for $C_{29}H_{30}N_6O_6$ *m/z*: 558.22, found 581.13 $(M + Na)^+$.

Boc-Leu-ψ[(C$_2$N$_2$O)-{NH-CO-NH}]-Val-NH-Fmoc (6c). White solid (86%), ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (d, 6H, J = 7.2 Hz), 1.15 (d, 6H, J = 6.8 Hz), 1.36 (s, 9H), 1.81 (m, 3H), 4.41 (t, 1H, J = 5.4 Hz), 4.62 (d, 2H, J = 6.8 Hz), 4.78 (t, 1H, J = 5.2 Hz), 5.31 (d, 1H, J = 5.6 Hz), 5.47 (br, 1H), 5.83 (br, 2H), 6.3 (br, 1H), 7.21–7.78 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) 17.1 (2CH3), 22.5 ($2CH_3$), 23.5 (CH), 27.9 ($3CH_3$-Boc), 32.2 (CH), 47.5 (CH_2), 48.4 (CH-Fmoc), 51.2 (CH), 66.7 (CH_2-Fmoc), 68.0 (CH), 79.4 (C-Boc), 126.9 (CH), 127.4 (CH), 128.1 (CH), 128.6 (CH), 141.7 (C-Fmoc), 144.1 (C-Fmoc), 154.2 (C═O urea), 156.3 (C═O), 156.8 (C═O), 165.3 (C-5 Oxadiazole), 169.1 (C-2 Oxadiazole); ESI-MS Calcd for $C_{32}H_{42}N_6O_6$ *m/z*: 606.32, found 629.24 $(M + Na)^+$.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.