A convenient synthesis of chiral 1,2,4-oxadiazoles from N-protected (α-aminoacyl)benzotriazoles

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Dedicated to Vladimir I. Minkin on the occasion of his 70th anniversary

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Abstract

1,2,4-Oxadiazoles (**4a-k**, **6a-c, 7a-d**, and **11a-f**) derived from chiral α-amino acids were synthesized in 70–94% yields *via* a fast and easy procedure under mild conditions. They were shown to be at least 97% enantiomerically pure by HPLC and NMR.

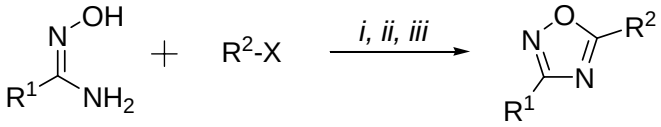
Keywords: Chiral 1,2,4-oxadiazole, *N*-aminoacylbenzotriazole, *N*-acylbenzotriazole, benzotriazole methodology

Introduction

1,2,4-Oxadiazole rings occur widely in biologically active synthetic compounds, and are often used in drug discovery as hydrolysis-resisting bioisosteric replacements for ester or amide functionalities.[1] Numerous 1,2,4-oxadiazoles have been suggested as potential agonists for cortical muscarinic,[1c,2] benzodiazepine,[3] and 5-HT_{1D} (5-hydroxytryptamine) receptors,[4] and as antagonists for 5-HT_3,[5] or histamine H_3 receptors.[6] They show activity as antirhinoviral agents,[1b] growth hormone secretagogues,[7] anti-inflammatory agents,[8] and antitumor agents.[9] They also inhibit the SH2 domain of tyrosine kinase,[10] monoamine oxidase,[11] human *nuetrophil* elastase,[12] and human DNA topoisomerases.[13] Finally, tropane derivatives of 1,2,4-oxadiazoles display high affininity for the cocaine binding site of the dopamine transporter.[14]

The most common routes to 1,2,4-oxadiazoles couple amidoximes with: (i) activated carboxylic acid derivatives such as acid chlorides,[15] fluorides,[16] anhydrides,[17] or active esters;[10a,b] (ii) carboxylic acids in the presence of coupling reagents including dicyclohexylcarbodiimide (DCC),[17b,18] 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC),[13,15a,17a] 2-(dimethylamino)isopropyl chloride (DIC)/HOBt,[19] bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl),[17b] 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU),[20]

or 1,1'-carbonyldiimidazole (CDI).[21] Other methods to obtain 1,2,4-oxadiazoles include reactions of amidoximes with aryl halides in the presence of palladium catalysts,[22] or with aldehydes followed by oxidation (Scheme 1).[23]



i: X = -C(O)Cl, -C(O)F, -C(O)O-C(O)R^2, -C(O)OSu
ii: X = -C(O)OH, coupling reagent = DCC, EDC, DIC, BOP-Cl, TBTU, CDI
iii, X = -Hal (R^2=Ar), -CHO, -CN, -NCO

Scheme 1

The synthesis of chiral 1,2,4-oxadiazoles from amino acids has attracted attention recently.[17b,10a,18,19c] *O*-Acylation of amidoximes with carboxylic acids or activated carboxylic acids occurs under mild conditions, but the cyclization of the intermediate *O*-(aminoacyl)amidoximes requires temperatures of 86–100 ^{o}C and reaction times of 2–12 hours.[18,19c]

We reported previously that N-protected (aminoacyl)benzotriazoles are stable, versatile peptide coupling reagents.[24] The reactions of *N*-(Boc-*α*-aminoacyl)benzotriazoles with chiral amines produced *N*-(Boc-α-amino)amides in 82–99% yields with no detectable racemization.[25] The peptide coupling of *N*-(Z-α-aminoacyl)benzotriazoles[26a] (Z-Ala-Bt, Z-Val-Bt, and Z-Phe-Bt) with unprotected amino acids in CH_3CN/H_2O occurred with complete preservation of the original chirality.[26b] Efficient preparations of functionalized *N*-(Z or Fmoc-α-aminoacyl)benzotriazoles derived from Tyr, Trp, Met, Cys, and Gln were followed by advantageous coupling with unprotected amino acids (*L*-Ala, *DL*-Ala, *L*-Phe, *DL*-Phe).[27] We herein demonstrate facile reactions for the preparation of 3,5-disubstituted-1,2,4-oxadiazoles derived from chiral α-amino acids utilizing *N*-(Boc, Z, and Fmoc-α-aminoacyl)benzotriazoles. We also report the preparation of 3,5-substituted-1,2,4-oxadiazoles utilizing *N*-acylbenzotriazoles in order to show the general applicability of the method.

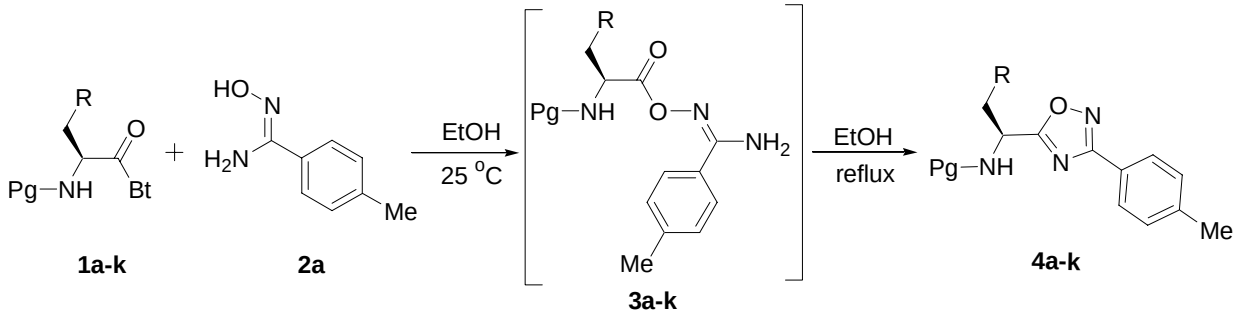
Results and Discussion

Preparation of 1,2,4-oxadiazoles (4a-k, 6a-c, 7a-d) using N-protected (α-aminoacyl) benzotriazoles (1a-k). Refluxing a symmetric Boc-amino acid anhydride and an amidoxime in pyridine provided one-pot preparations of chiral 1,2,4-oxadiazoles in 20–81% yield calculated on the amidoxime utilizing only 50% of the Boc-amino acid. Retention of chirality was proved by HPLC analysis.[17b] Recently, preparations of 1,2,4,-oxadiazoles from N-protected amino acids

were reported using DIC/HOBt or DCC as coupling reagents, followed by heating at 86–100 °C for 2–12 hours.[18,19c] Although these reaction procedures give reasonable yields (50–80%), carbodiimides (DIC and DCC) and their intermediates with HOBt are frequently moisture sensitive, and isolation and purification processes often involve column chromatography due to the formation of ureas from the coupling reagents.

N-Protected (α-aminoacyl)benzotriazoles (**1a-k**) are sufficiently reactive to form amide bonds at ambient temperature, but stable enough to resist side reactions such as hydrolysis.[26b] They are available directly from the corresponding N-protected amino acids and can be stored at room temperature without decomposition or racemization for months. We prepared 1,2,4-oxadiazoles **4a-k**, **6a-c**, and **7a-d** from (α-aminoacyl)benzotriazoles **1a-k** with *p*-tolyl (**2a**), 4-pyridinyl (**2b**), and benzyl (**2c**) amidoximes, respectively.

The *O*-acylation of **1** with *p*-tolyl amidoxime (**2a**) proceeded immediately after addition of 1 equivalent of Et_3N in EtOH at room temperature. Subsequent cyclization occurred surprisingly quickly (3–5 min) when the mixture was refluxed in EtOH in the presence of Et_3N (Scheme 2). These reactions were complete within 5 min, and the products **4a-k** were precipitated in 70–94% yield by adding water to the reaction mixture (Table 1). To support the proposed mechanism of the reaction (Scheme 2), intermediates **3c** and **3g** were isolated in 96, 97% yield by filtration from water-EtOH solution, and subjected to cyclization by heating under reflux in EtOH for 5 minutes to afford 1,2,4,-oxadiazoles **4c** and **4g** in 83 and 75% yields, respectively.



Pg = Boc, Z, Fmoc
Amino acid with R: alanine, valine, phenylalanine, methionine, tryptophan, and glutamine
Bt = benzotriazol-1-yl

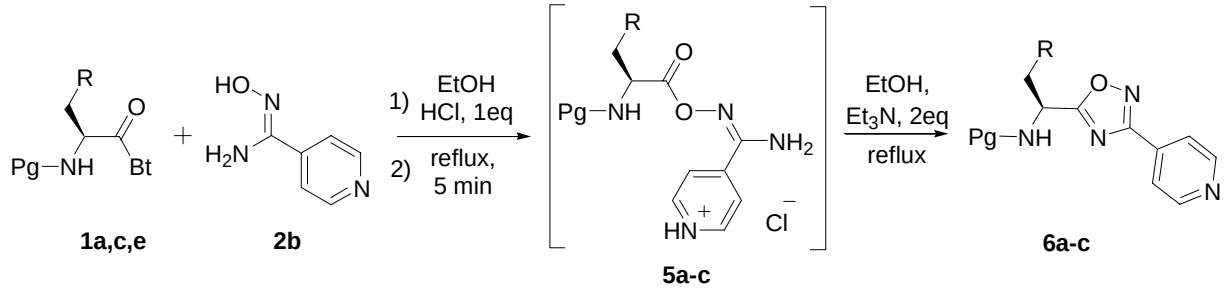
Scheme 2

Table 1. Synthesis of 1,2,4-oxadiazoles **4a-k** from N-protected (α-aminoacyl) benzotriazoles **1a-k** utilizing *p*-tolyl amidoxime (**2a**)

Entry	RCOBt	Time (min)	Product[a] (% yield)
1	Z-*L*-Ala-Bt (**1a**)	5	**4a** (83)
2	Z-*D*-Ala-Bt (**1b**)	5	**4b** (84)
3	Z-*L*-Val-Bt (**1c**)	5	**4c** (70)[b]
4	Boc-*L*-Phe-Bt (**1d**)	5	**4d** (79)
5	Z-*L*-Phe-Bt (**1e**)	5	**4e** (91)
6	Z-*D*-Phe-Bt (**1f**)	5	**4f** (93)
7	Fmoc-*L*-Phe-Bt (**1g**)	3	**4g** (71)[c]
8	Z-*L*-Met-Bt (**1h**)	5	**4h** (94)
9	Fmoc-*L*-Met-Bt (**1i**)	3	**4i** (89)
10	Fmoc-*L*-Trp-Bt (**1j**)	3	**4j** (92)
11	Z-*L*-Gln-Bt (**1k**)	5	**4k** (87)

[a] Isolated yield. [b] **4c** in 83% yield was obtained by cyclization of **3c.** [c] **4g** in 75% yield was obtained by cyclization of **3g**.

Utilizing conditions similar to those described for the preparation of **4a-k,** the synthesis of **6c** was first attempted by reaction of **1e** with 4-pyridinyl amidoxime (**2b**). However, **6c** was obtained along with *N*,*O*-disubstituted amidoxime as by-product formed by a reaction of **2b** with two molecules of **1e**. This result can be explained by the higher reactivity of amidoxime **2b** compared to **2a**. To overcome this problem, **2b** was initially converted into the hydrochloric salt by adding 1 equivalent of HCl (10% aq.) and then coupled with **1a**,**c**,**e** under refluxing EtOH to give the intermediates **5a-c**, which were cyclized to give **6a-c** by heating under reflux in EtOH in the presence of two equivalents of Et_3N. The products **6a-c** were isolated in 90–93% yield after column chromatography, and fully characterized by NMR and elemental analysis (Scheme 3, Table 2).

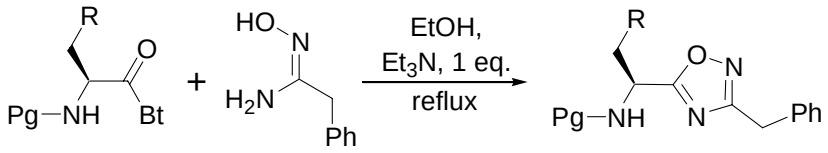


Scheme 3

Table 2. Synthesis of 1,2,4-oxadiazoles **6a-c** from N-protected (α-aminoacyl) benzotriazoles **1a**,**c**,**e** utilizing 4- pyridinyl amidoxime (**2b**)

Entry	RCOBt	Time (min)	Product (% yield)
1	Z-*L*-Ala-Bt (**1a**)	10	**6a** (91)
2	Z-*L*-Val-Bt (**1c**)	10	**6b** (93)
3	Z-*L*-Phe-Bt (**1e**)	10	**6c** (90)

We also investigated the preparation of 1,2,4-oxadiazoles derived from benzyl amidoxime (**2c**) (Scheme 4) to produce **7a-d** in 83–89% yields following the procedure used for preparation of **4a-l**, but with extended refluxing times (Table 3). When the conditions for the preparation of **4** were applied, yields of **7** did not exceed 10%, presumably due to the lower reactivity of **2c** compared to **2a**.



1a,e,h,i **2c** **7a-d**

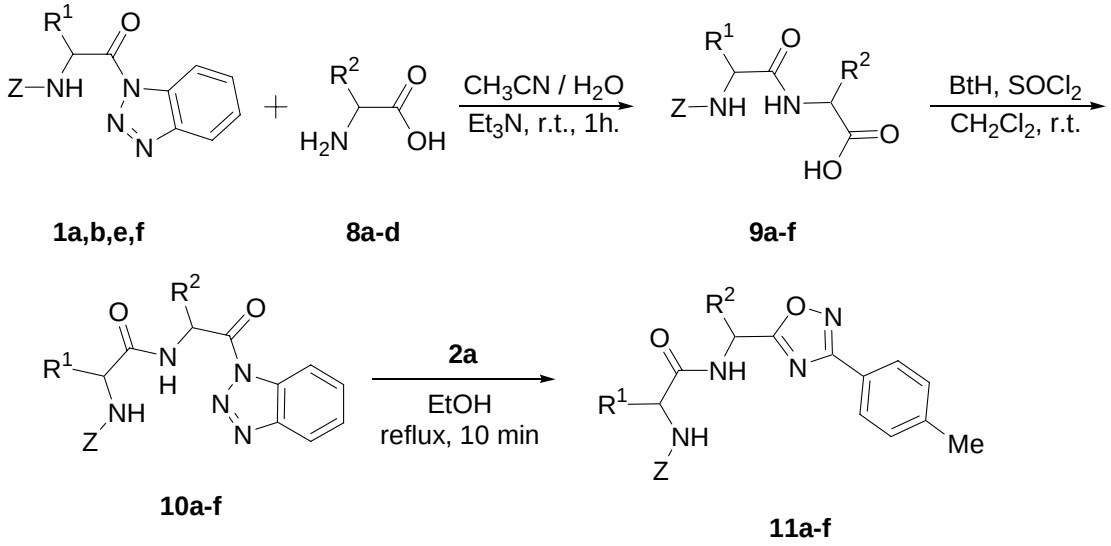
Scheme 4

Table 3. Synthesis of 1,2,4-oxadiazoles **7a-d** from N-protected (α-aminoacyl) benzotriazoles **1a**,**e**,**h**,**i** utilizing *N*-benzyl amidoxime (**2c**)

Entry	RCOBt	Time (hours)	Product (% yield)
1	Z-*L*-Ala-Bt (**1a**)	1.5	**7a** (87)
2	Z-*L*-Phe-Bt (**1e**)	1.5	**7b** (83)
3	Z-*L*-Met-Bt (**1h**)	1.5	**7c** (89)
4	Fmoc-*L*-Met-Bt (**1i**)	1.0	**7d** (85)

Stereochemistry

Dipeptides and tripeptides prepared from N-protected (α-aminoacyl)benzotriazoles were previously shown to be more than 97% enantiomerically pure by HPLC analysis and NMR spectra.[28] We have now made N-protected diastereomers of peptidolylbenzotriazoles **10a-f** from **1a**,**b**,**e**,**f** and amino acid **8a-d**. The extent of racemization during 1,2,4-oxadiazole ring-formation was then checked by NMR and HPLC of products **11a-f** from reactions of **10a-f** with **2a** (Scheme 5).



1a,b,e,f **8a-d** **9a-f**

10a-f **11a-f**

R^1, R^2 = $PhCH_2$-, Me_2CH-, Me-

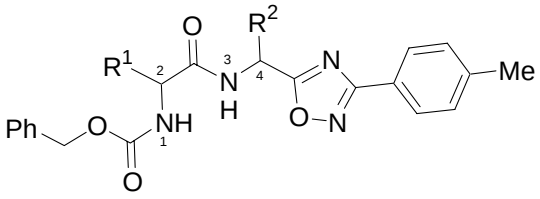
Scheme 5

According to HPLC analysis, compounds **11a**,**b**,**e**,**f** are single isomers (Table 4), and no peaks corresponding to another diastereomer were detected. The ^{1}H NMR spectra of compounds **11a-f** contain signals of –NH protons as doublets, which resonate in different positions for each pair of diastereomers (Table 5). On Chirobiotic T column, retention times for diastereomers **11a** and **11b** were 24.2 and 27.0 minutes, respectively. Signals of the NH protons *β* to the oxadiazole ring for **11a** and **11b** appeared as doublets at 6.93 ppm (J = 6.5 Hz) and 6.76 ppm (J = 6.6 Hz), respectively. Using similar conditions, diastereomers **11c** and **11d** could not be separated on Chirobiotic T column. However, the ^{1}H NMR spectra of **11c** and **11d** showed significant difference in their N^3H proton shifts as described in Table 5. Diastereomers **11e** and **11f** were observed in HPLC at 24.4 and 20.3 minutes, and demonstrated different values for N^3H proton shifts at 6.89 ppm and 7.08 ppm, respectively. The ^{1}H NMR and ^{13}C NMR spectra of **11a-f** indicated the absence of the peaks expected from racemization. Thus, HPLC and NMR analyses indicated less than 3% of racemization for 1,2,4-oxadiazoles **11a**,**b**,**e**,**f**, and the racemization of the orginal chirality in **11c** and **11d** was illustrated by NMR to be less than 5%.

Table 4. Synthesis of 1,2,4-oxadiazoles **11a-f** containing two centers of chirality

Entry	RCOBt	Time (min.)	Product (% yield)	HPLC analysis		
				Solvents ratio	Flow rate (mL/min)	Retention time (min.)
1	Z-*L*-Phe-*L*-Ala-Bt (**10 a**)	10	**11a** (83)	EtOH(65%)/ H_2O (35%)	0.85	24.2
2	Z-*D*-Phe-*L*-Ala-Bt (**10 b**)	10	**11b** (79)	EtOH(65%)/ H_2O (35%)	0.85	27.0
3	Z-*L*-Ala-*L*-Val-Bt (**10 c**)	10	**11c** (87)	EtOH(65%)/ H_2O (35%)	1.00	24.0
4	Z-*D*-Ala-*L*-Val-Bt (**10 d**)	10	**11d** (85)	EtOH(65%)/ H_2O (35%)	1.00	24.0
5	Z-*L*-Ala-*L*-Phe-Bt (**10e**)	10	**11e** (91)	EtOH(65%)/ H_2O (35%)	1.00	24.4
6	Z-*L*-Ala-*D*-Phe-Bt (**10f**)	10	**11f** (94)	EtOH(65%)/ H_2O (35%)	1.00	20.3

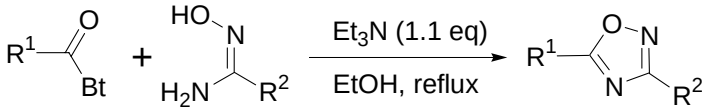
Table 5. Characteristic ^{1}H NMR signals of compounds **11a-f**



Product	N^1H (d)	N^3H (d)	C^2H (m)	C^4H (m)	Ar-Me (s)	Ph-CH_2-O- (s)
11a	5.65	6.93	4.50-4.57	5.31-5.42	2.40	5.04
11b	5.62	6.76	4.53-4.58	5.27-5.39	2.38	5.05
11c	5.53	7.08	4.41-4.48	5.33 (dd)	2.46	5.18
11d	5.59	7.23	4.42-4.52	5.32 (dd)	2.44	5.18
11e	5.31	6.89	4.28-4.40	5.66-5.75	2.47	5.15
11f	5.50	7.08	4.29-4.33	5.64 (dd)	2.39	5.10

Preparation of 1,2,4-oxadiazoles (13a-d) utilizing aromatic *N*-acylbenzotriazoles (12a-c). To extend the synthetic possibilities, we introduced the reaction of amidoximes **2a**,**b** with aromatic *N*-acylbenzotriazoles **12a-c** (Scheme 6). Compounds **12a-c** were prepared directly from carboxylic acids according to the procedures developed in our group.[29] 1,2,4-Oxadiazoles **13a-d** were synthesized in 73–82% yields following the procedure illustrated for the preparation of compounds **4a-l**. The starting materials **12a-c** were less reactive in the cyclization reactions than

their aliphatic analogues **1a-l** and hence required longer refluxing times (Table 6). Since many previously reported methods for the synthesis of 1,2,4-oxadiazole require acyl halides, our method offers advantages, especially where acyl halides are not readily available or stable.



12a-c **2a,c** **13a-d**

R^1 = Ph-, 4-MeO-C_6H_4-, 2-indolyl;

R^2 = *p*-tolyl, benzyl.

Scheme 6

Table 6. Synthesis of 1,2,4-oxadiazoles **13a-d** utilizing *N*-acylbenzotriazoles **12a-c**

R^1	R^2	Time (h)	Product (% yield)
C_6H_5 (**12a**)	*p*-tolyl (**2a**)	7	**13a** (77)
4-$MeOC_6H_4$ (**12b**)	*p*-tolyl (**2a**)	7	**13b** (82)
2-indolyl (**12c**)	*p*-tolyl (**2a**)	7	**13c** (73)
C_6H_5 (**12a**)	benzyl (**2c**)	7	**13d** (74)

Conclusions

In summary, a convenient method for the preparation of 1,2,4-oxadiazoles utilizing N-protected (α-aminoacyl)benzotriazoles and aromatic *N*-acylbenzotriazoles has been developed. The reactions were demonstrated to give 1,2,4-oxadiazoles in high yields under mild conditions together with a simple process for isolation and purification. During the whole process, the original chirality has been preserved in >97% enantiomerically pure products, as demonstrated by HPLC and NMR analysis.

Experimental Section

General Procedures. Melting points were determined on a capillary point apparatus equipped with a digital thermometer. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS for ^1H (300 MHz) and ^{13}C (75 MHz) as the internal reference. *N*-Boc-, Z- and Fmoc-amino acids purchased from Fluka and amino acids purchased from Acros, were used without further purification. Optical rotation values were measured at the sodium D line. CH_2Cl_2 was distilled in the presence of CaH_2 under N_2 immediately prior to use. HPLC analyses were performed on

Beckman system gold programmable solvent module 126 using Chirobiotic T column (4.6×250 mm), detection at 254 nm.

General procedure for compounds 1a-k, 10a-f, and 12 a-c

Thionyl chloride (2.0 mmol) was added dropwise to a solution of 1*H*-benzotriazole (8.0 mmol) in CH_2Cl_2 (60 mL), and reaction mixture was heated under reflux for 30 minutes. The solution was cooled in an ice bath, and the corresponding carboxylic acid (2.0 mmol) was added in one portion. After stirring for 2 hours at room temperature, the reaction mixture was washed with aq 5% Na_2CO_3 (3×30 mL), aq sat. NH_4Cl (30 mL), and dried ($MgSO_4$). After evaporation of the solvent and recrystallization from CH_2Cl_2/hexanes, *N*-acylbenzotriazoles **1a-k**, **10a-f**, and **12a-c** were obtained in 67–95% yield.

(*S*)-Benzyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxopropan-2-ylcarbamate (1a). Yield: 90%; colorless microcrystals from CH_2Cl_2-hexanes; mp 113–114 °C (Lit.[26b,c] mp 114–115 °C).

(*R*)-Benzyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxopropan-2-ylcarbamate (1b). Yield: 91%; colorless microcrystals from CH_2Cl_2-hexanes; mp 114–115 °C, $[\alpha]_D^{23}$ = +37.8 (*c* 2.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.69 (d, *J* = 7.0 Hz, 3H), 5.13–5.15 (m, 2H), 5.67 (d, *J* = 7.3 Hz, 1H), 5.79–5.83 (m, 1H), 7.12–7.41 (m, 5H), 7.50–7.55 (m, 1H), 7.63–7.69 (m, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 19.1, 50.7, 67.4, 114.5, 120.5, 126.6, 128.3, 128.4, 128.7, 130.9, 131.3, 136.2, 146.1, 155.8, 172.4. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.79; H, 4.89; N, 17.23.

(*S*)-Benzyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (1c). Yield: 87%; colorless microcrystals from CH_2Cl_2-hexanes; mp 73–74 °C (Lit.[26b,c] mp 73–74 °C).

(*S*)-*tert*-Butyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamate (1d). Yield: 89%; colorless microcrystals from CH_2Cl_2-hexanes; mp 144–145 °C (Lit.[26a] mp 144–145 °C). **(*S*)-Benzyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamate (1e).** Yield: 93%; colorless microcrystals from CH_2Cl_2- hexanes; mp 149–150 °C (Lit.[26b] mp 151–152 °C).

(*R*)-Benzyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-ylcarbamate (1f). Yield: 91%; colorless microcrystals from CH_2Cl_2-hexanes; mp 152–153 °C, $[\alpha]_D^{23}$ = –24.0 (*c* 2.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 3.29 (dd, *J* = 13.9, 7.7Hz, 1H), 3.48–3.61 (m, 1H), 5.15 (s, 2H), 5.62 (d, *J* = 8.0Hz, 1H), 6.08–6.21 (m, 1H), 7.09–7.43 (m, 10H), 7.56–7.65 (m, 1H), 7.69–7.78 (m, 1H), 8.21 (d, *J* = 8.1Hz, 1H), 8.30 (d, *J* = 8.2Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 39.1, 55.9, 67.5, 114.5, 120.6, 126.8, 127.6, 128.4, 128.4, 128.7, 129.0, 129.5, 131.0, 131.2, 135.2, 136.2, 146.2, 155.9, 171.0. Anal. Calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 69.30; H, 5.02; N, 14.06.

(*S*)-(9*H*-Fluoren-9-yl)methyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenyl propan-2-ylcarbamate (1g). Yield: 84%; colorless microcrystals from CH_2Cl_2-hexanes; mp 137–138 °C, (Lit.[30] mp 136–137 °C).

(*S*)-Benzyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-4-(methylthio)-1-oxobutan-2-ylcarbamate (1h). Yield: 92%; colorless microcrystals from CH_2Cl_2-hexanes; mp 107–109 °C, $[\alpha]_D^{23}$ = –32.9 (*c* 2.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.11 (s, 3H), 2.21–2.23 (m, 1H), 2.48–2.50 (m, 1H), 2.74 (t, *J* = 7.8 Hz, 2H), 5.19 (s, 2H), 5.96 (s, 2H), 7.40 (br. s, 5H), 7.55–7.61 (m, 1H), 7.69–7.74 (m, 1H), 8.18 (d, *J* = 8.2Hz, 1H), 8.29 (d, *J* = 8.1Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 15.5, 30.2, 32.5, 54.4, 67.6, 114.5, 120.5, 126.8, 128.4, 128.4, 126.1, 128.7, 131.0, 131.2, 146.2, 156.2, 171.4. Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 59.36; H, 5.24; N, 14.57. Found: C, 59.42; H,5.24; N, 14.59.

(*S*)-(9*H*-Fluoren-9-yl)methyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-4-(methylthio)-1-oxobutan-2-ylcarbamate (1i). Yield: 89%; colorless microcrystals from CH_2Cl_2-hexanes; mp 100–101 °C (Lit.[27] mp 98–100 °C).

(*S*)-(9*H*-Fluoren-9-yl)methyl 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-3-(1*H*-indol-3-yl)-1-oxopropan-2-ylcarbamate (1j). Yield: 87%; colorless microcrystals from CH_2Cl_2-hexanes; mp 93–94 °C (Lit.[27] mp 88–90 °C).

(*S*)-Benzyl 5-amino-1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1,5-dioxopentan-2-ylcarbamate (1k). Yield: 67%; colorless microcrystals from CH_2Cl_2-hexanes; mp 160–161 °C (Lit.[27] mp 161–162 °C).

Benzyl (*S*)-1-((*S*)-1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxopropan-2-ylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (10a). Yield: 87%; colorless microcrystals from CH_2Cl_2-hexanes; mp 180–181 °C (Lit.[26a] mp 180–181 °C).

Benzyl (*R*)-1-((*S*)-1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxopropan-2-ylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (10b). Yield: 90%; colorless microcrystals from CH_2Cl_2-hexanes; mp 135–136 °C, $[\alpha]_D^{23}$ = –45.4 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.47 (d, *J* = 7.1 Hz, 3H), 3.04–3.19 (m, 2H), 4.54–4.59 (m, 1H), 5.10 (s, 2H), 5.51 (d, *J* = 6.9 Hz, 1H), 5.80–5.90 (m, 1H), 6.67 (d, *J* = 5.5 Hz, 1H), 7.21–7.35 (m, 10H), 7.47–7.54 (m, 1H), 7.60–7.67 (m, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 8.7, 38.9, 49.1, 67.3, 69.8, 114.5, 120.5, 126.7, 127.3, 128.2, 128.4, 128.7, 129.0, 129.6, 130.9, 131.3, 131.9, 136.3, 136.4, 146.2, 170.8, 171.6. Anal. Calcd for $C_{26}H_{25}N_5O_4$: C, 66.23; H, 5.34; N, 14.85. Found: C, 65.75; H, 5.31; N, 15.08.

Benzyl (*S*)-1-((*S*)-1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-3-methyl-1-oxobutan-2-ylamino)-1-oxopropan-2-ylcarbamate (10c). Yield: 84%; colorless microcrystals from CH_2Cl_2-hexanes; mp 131–132 °C, $[\alpha]_D^{23}$ = –62.9 (*c* 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.95 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H), 1.41 (d, *J* = 7.0 Hz, 3H), 2.46–2.57 (m, 1H), 4.39–4.48 (m, 1H), 5.15 (s, 2H), 5.53 (d, *J* = 7.3 Hz, 1H), 5.94 (dd, *J* = 8.2, 5.2 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.27–7.40 (m, 5H), 7.49–7.56 (m, 1H), 7.63–7.70 (m, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 7.4, 19.8, 31.8, 50.6, 57.8, 67.3, 114.6, 120.5, 126.7, 128.2, 128.4, 128.7, 130.9, 131.2, 135.2, 136.3, 146.2, 171.2, 172.8. Anal. Calcd for $C_{22}H_{25}N_5O_4$: C, 62.40; H, 5.95; N, 16.54. Found: C, 62.41; H, 5.98; N, 16.39.

Benzyl (*R*)-1-((*S*)-1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-3-methyl-1-oxobutan-2-ylamino)-1-oxopropan-2-ylcarbamate (10d). Yield: 81%; colorless microcrystals from CH_2Cl_2-hexanes; mp 103–104 °C, $[\alpha]_D^{23}$ = +6.9 (*c* 2.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.93 (d, *J* = 6.0 Hz,

3H), 1.07 (d, *J* = 4.9 Hz, 3H), 1.46 (d, *J* = 6.9 Hz, 3H), 2.44–2.56 (m, 1H), 4.42–4.55 (m, 1H), 5.15 (s, 2H), 5.49–5.67 (m, 1H), 5.97 (dd, *J* = 8.5 Hz, *J* = 5.1 Hz, 1H), 7.25–7.39 (m, 5H), 7.46–7.52 (m, 1H), 7.59–7.65 (m, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 17.3, 19.9, 31.8, 50.7, 57.7, 67.3, 114.5, 120.5, 126.6, 128.2, 128.3, 128.7, 130.8, 131.2, 136.4, 146.2, 171.2, 172.9. Anal. Calcd for $C_{22}H_{25}N_5O_4$: C, 62.40; H, 5.95; N, 16.54. Found: C, 62.33; H, 5.99; N, 16.56.

Benzyl (*S*)-1-((*S*)-1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-ylamino)-1-oxopropan-2-ylcarbamate (10e). Yield: 95%; colorless microcrystals from CH_2Cl_2-hexanes; mp 148–149 °C (Lit.[26b] mp 148–149 °C).

Benzyl (*S*)-1-((*R*)-1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-ylamino)-1-oxopropan-2-ylcarbamate (10f). Yield: 93%; colorless microcrystals from CH_2Cl_2-hexanes; mp 97–98 °C, $[\alpha]_D^{23}$ = –37.4 (*c* 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.35 (d, *J* = 6.9 Hz, 3H), 3.20 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.51 (dd, *J* = 13.7, 4.3 Hz, 1H), 4.35–4.54 (m, 1H), 5.15 (s, 2H), 5.72, (d, *J* = 7.2 Hz, 1H), 6.25–6.35 (m, 1H), 7.17–7.30 (m, 5H), 7.30–7.41 (m, 6H), 7.42–7.51 (m, 1H), 7.51–7.62 (m, 1H), 7.62–7.75 (m, 1H), 8.10–8.22 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 18.6, 38.6, 50.6, 54.2, 67.2, 114.4, 120.5, 126.0, 126.7, 127.5, 128.1, 128.3, 128.7, 128.8, 129.4, 130.9, 131.1, 135.4, 146.1, 156.4, 170.6, 172.8. Anal. Calcd for $C_{26}H_{25}N_5O_4$: C, 66.23; H, 5.34; N, 14.85. Found: C, 66.31; H, 5.40; N, 14.80.

(1*H*-Benzo[d][1,2,3]triazol-1-yl)(phenyl)methanone (12a). Yield: 93%; colorless microcrystals from CH_2Cl_2-hexanes; mp 122–123 °C (Lit.[29] mp 116–117 °C).

(1*H*-Benzo[d][1,2,3]triazol-1-yl)(4-methoxyphenyl)methanone (12b). Yield: 92%; colorless microcrystals from CH_2Cl_2-hexanes; mp 102–103 °C (Lit.[30] mp 104 °C).

(1*H*-Benzo[d][1,2,3]triazol-1-yl)(1*H*-indol-2-yl)methanone (12c). Yield: 95%; colorless microcrystals from CH_2Cl_2-hexanes; mp 214–215 °C (Lit.[29] mp 213–215 °C).

General procedure for amidoximes 2a-c

A mixture of a nitrile (0.1 mol), hydroxylamine hydrochloride (0.13 mol), and sodium carbonate (0.13 mol) were heated under reflux in ethanol (300 mL). After 6 hours, the reaction mixture was added another portion of hydroxylamine hydrochloride (0.13 mol) and sodium carbonate (0.13 mol), and then refluxed for another 14 hours. After cooling to room temperature, inorganic salts were filtered off, and the filtrate was concentrated in vacuum. Resulting white precipitate was filtered and washed on filter with water and small amount of ethanol to give amidoximes **2a-c** in 88–95% yield. Amidoximes **2a-c** were used without further purification.

***N*-Hydroxy-4-methylbenzenecarboximidamide (2a).** Yield: 91%; colorless microcrystals, mp 147–148 °C (Lit.[15c] mp 148–149 °C).

***N*-Hydroxy-4-pyridinecarboximidamide (2b).** Yield: 88%; colorless microcrystals, mp 205–206 °C (Lit.[32] mp 207–208 °C).

***N*-Hydroxy-benzeneethanimidamide (2c).** Yield: 95%; colorless microcrystals, mp 67–68 °C (Lit.[33] mp 68 °C).

General procedure for 1,2,4-oxadiazoles 4a-k

A mixture of *N*-hydroxy-4-methylbenzenecarboximidamide (**2a**) (1 mmol) and *N*-acylbenzotriazole **1a-k** (1 mmol) was heated under reflux in ethanol (30 mL) for 5 minutes in the presence of Et_3N (1 mmol) (in case of Fmoc-protected *N*-(aminoacyl) benzotriazoles **1g**,**i** refluxing time was reduced to 3 minutes and only catalytic amount of Et_3N was used to avoid deprotection). Completion of the reaction was monitored by TLC. The reaction mixture was cooled down to room temperature and quenched with water to form a white precipitate, which was filtered and subsequently washed on the filter with aq 5% Na_2CO_3 (10 mL), water (10 mL), EtOH/H_2O 50% mixture (2×10 mL), and hexanes (10 mL) to give oxadiazoles **4a-k** in 70–94% yield. **4a-k** were further purified by recrystallization from EtOH-hexanes.

(*S*)-Benzyl 1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethylcarbamate (4a). Yield: 83%; colorless microcrystals from EtOH–hexanes; mp 89–90 °C, $[\alpha]_D^{23}$ = –52.1 (*c* 3.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.65 (d, *J* = 7.1 Hz, 3H), 2.41 (s, 3H), 5.15 (s, 2H), 5.20–5.26 (m, 1H), 5.21 (d, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.31–7.40 (m, 5H), 7.94 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 20.3, 21.8, 45.0, 67.5, 109.7, 123.8, 127.6, 128.4, 128.5, 128.8, 129.8, 141.9, 168.5, 176.7, 179.6. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 68.01; H, 5.69; N, 12.56.

(*R*)-Benzyl 1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethylcarbamate (4b). Yield: 84%; colorless microcrystals from EtOH–hexanes; mp 89–90 °C, $[\alpha]_D^{23}$ = +52.4 (*c* 2.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.63 (d, *J* = 7.0 Hz, 3H), 2.40 (s, 3H), 5.14 (s, 2H), 5.20–5.23 (m, 1H), 5.57 (d, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.35–7.36 (m, 5H), 7.94 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 20.3, 21.8, 44.9, 67.5, 109.5, 123.8, 127.6, 128.4, 128.5, 128.8, 129.7, 141.8, 155.6, 168.5, 179.6. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.98; H, 5.66; N, 12.53.

(*S*)-Benzyl 2-methyl-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)propylcarbamate (4c). Yield: 70%; colorless microcrystals from EtOH–hexanes; mp 68–69 °C, $[\alpha]_D^{23}$ = –45.7 (*c* 1.5, DMF). ^{1}H NMR (DMSO-d_6): δ 0.92 (d, *J* = 6.6Hz, 3H), 1.00 (d, *J* = 6.6Hz, 3H), 2.19–2.35 (m, 1H), 2.39 (s, 3H), 4.73–4.83 (m ,1H), 5.09 (s, 2H), 7.29–7.42 (m, 7H), 7.91 (d, *J* = 8.0 Hz, 2H), 8.29 (d, *J* = 8.0Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 18.5, 18.7, 21.1, 31.0, 54.4, 65.8, 123.3, 127.0, 127.8, 127.9, 128.4, 129.8, 136.8, 141.6, 156.3, 167.5, 179.6. Anal. Calcd for $C_{21}H_{23}N_3O_3$: N, 11.50. Found: N, 11.24.

(*S*)-*tert*-Butyl 2-phenyl-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethylcarbamate (4d). Yield: 79%; colorless microcrystals from EtOH–hexanes; mp 117–118 °C, $[\alpha]_D^{23}$ = –0.72 (*c* 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.49 (s, 9H), 2.47 (s, 3H), 3.34–3.38 (m, 2H), 5.25–5.28 (m, 1H), 5.42–5.45 (m, 1H), 7.15–7.18 (m, 2H), 7.29–7.32 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H) 8.0 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.8, 28.5, 40.2, 49.7, 80.7, 123.9, 127.5, 127.6, 128.9, 129.5, 129.7, 130.3, 135.3, 141.8, 168.4, 178.6. Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.38; H, 6.75; N, 11.02.

(*S*)-Benzyl 2-phenyl-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethylcarbamate (4e). Yield: 91%; colorless microcrystals from EtOH–hexanes; mp 98–99 °C, $[\alpha]_D^{23}$ = –30.4 (*c* 1.8, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.39 (s, 3H), 3.26–3.31 (m, 2H), 5.10 (s, 2H), 5.43–5.47 (m, 1H), 5.53 (d, *J* = 8.5 Hz, 1H), 7.03–7.07 (m, 2H), 7.20–7.34 (m, 10H), 7.92 (*d*, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.7, 39.9, 50.0, 67.4, 123.7, 127.5, 127.6, 128.3, 128.4, 128.7, 128.9, 129.4, 129.7, 135.0, 136.2, 141.8, 155.7, 168.4, 178.3. Anal. Calcd for $C_{25}H_{23}N_3O_3$: C, 72.62; H, 5.61; N, 10.16. Found: C, 72.19; H, 5.56; N, 10.07.

(*R*)-Benzyl 2-phenyl-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethylcarbamate (4f). Yield: 93%; colorless microcrystals from EtOH–hexanes; mp 99–98 °C, $[\alpha]_D^{23}$ = +29.8 (*c* 2.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.42 (s, 3H), 3.29–3.34 (m, 2H), 5.13 (s, 2H), 5.40–5.57 (m, 2H), 7.08–7.12 (m, 2H), 7.23–7.37 (m, 10H), 7.95 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.7, 40.0, 50.1, 67.5, 123.8, 127.6, 127.7, 128.3, 128.4, 128.7, 128.9, 129.5, 129.7, 135.0, 136.2, 141.9, 155.7, 168.4, 178.4. Anal. Calcd for $C_{25}H_{23}N_3O_3$: C, 72.62; H, 5.61; N, 10.16. Found: C, 72.20; H, 5.56; N, 10.11.

(*S*)-(9*H*-Fluoren-9-yl)methyl 2-phenyl-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethyl carbamate (4g). Yield: 71% (isolated yield), 75% (from **3g**); colorless microcrystals from EtOH–hexanes; mp 102–103 °C, $[\alpha]_D^{23}$ = –33.0 (*c* 2.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H), 3.29–3.33 (m, 2H), 4.20 (t, *J* = 6.3 Hz, 1H), 4.41–4.43 (m, 2H), 5.43–5.47 (m, 2H), 7.06 (d, *J* = 5.2 Hz, 2H), 7.22–7.32 (m, 7H), 7.37–7.41 (m, 2H), 7.53–5.57 (m, 2H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.8, 39.4, 47.3, 50.0, 67.3, 120.2, 123.8, 125.2, 127.3, 127.6, 127.7, 127.9, 128.9, 129.5, 129.8, 135.0, 141.5, 141.9, 143.8, 155.6, 168.4, 178.3. Anal. Calcd for $C_{32}H_{27}N_3O_3$: C, 76.63; H, 5.43; N, 8.38. Found: C, 76.28; H, 5.57; N, 7.94.

(*S*)-Benzyl 3-(methylthio)-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)propylcarbamate (4h). Yield: 94%; colorless microcrystals from EtOH–hexanes; mp 59–60 °C, $[\alpha]_D^{23}$ = –27.8 (*c* 1.8, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.08 (s, 3H), 2.17–2.21 (m, 1H), 2.29–2.31 (m,1H), 2.39 (s, 3H), 2.58 (t, *J* = 7.1 Hz, 2H), 5.14 (s, 2H), 5.29–5.33 (m, 1H), 5.81 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.31–7.35 (m, 5H), 7.93 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 15.5, 21.7, 29.8, 33.3, 48.2, 67.5, 123.7, 127.6, 128.3, 128.4, 128.7, 129.7, 136.1, 141.8, 155.9, 168.4, 178.5. Anal. Calcd for $C_{21}H_{23}N_3O_3S$: C, 63.45; H, 5.83; N, 10.57. Found: C, 63.73; H, 5.93; N, 10.46.

(*S*)-(9*H*-Fluoren-9-yl)methyl 3-(methylthio)-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)propyl carbamate (4i). Yield: 89%; colorless microcrystals from EtOH–hexanes; mp 88–89 °C, $[\alpha]_D^{23}$ = –45.2 (*c* 1.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 2.08 (s, 3H), 2.17–2.19 (m, 1H), 2.29–2.31 (m, 1H), 2.39 (s, 3H), 2.56 (t, *J* = 6.9 Hz, 2H), 4.21 (t, *J* = 6.7 Hz, 1H), 4.46 (d, *J* = 6.7 Hz, 2H), 5.29–5.33 (m, 1H), 5.72 (d, *J* = 8.8 Hz, 1H), 7.22–7.41 (m, 6H), 7.57–7.59 (m, 2H), 7.73 (d, *J* = 7.4 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 15.6, 21.7, 29.9, 33.3, 47.3, 48.2, 67.3, 120.1, 123.7, 125.1, 127.2, 127.6, 127.9, 129.7, 141.4, 141.9, 143.7, 143.9, 155.9, 168.5, 178.5. Anal. Calcd for $C_{28}H_{27}N_3O_3S$: C, 69.25; H, 5.60; N, 8.65. Found: C, 69.19; H, 5.76; N, 8.33.

(*S*)-(9*H*-Fluoren-9-yl)methyl 2-(1*H*-indol-3-yl)-1-(3-p-tolyl-1,2,4-oxadiazol-5-yl)ethyl carbamate (4j). Yield: 92%; colorless microcrystals from EtOH–hexanes; mp 169–170 °C, $[\alpha]_D^{23}$ = –7.7 (*c* 1.3, DMF). ^1H NMR (DMSO-d_6): δ 2.39 (s, 3H), 3.31–3.55 (m, 2H), 4.18–4.39 (m, 3H), 5.13–

5.28 (m, 1H), 6.92–7.0.5 (m, 1H), 7.05–7.15 (m, 1H), 7.21 (s, 1H), 7.25–7.46 (m, 7H), 7.56–7.72 (m, 3H), 7.84–7.96 (m, 4H), 8.44 (d, *J* = 7.8Hz, 1H), 10.92 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 21.1, 28.3, 46.6, 49.5, 65.8, 109.0, 111.5, 118.1 , 118.5, 120.1, 120.4, 121.1, 123.3, 124.1, 125.2, 127.0, 127.6, 129.8, 136.1, 140.7, 141.6, 143.7, 148.2, 155.8, 167.5, 180.0. Anal. Calcd for $C_{34}H_{28}N_4O_3$: C, 75.54; H, 5.22; N, 10.36. Found: C, 75.12; H, 5.16; N, 10.30.

(*S*)-Benzyl 4-amino-4-oxo-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)butylcarbamate (4k). Yield: 87 %; colorless microcrystals from EtOH–hexanes; mp 181–182 °C, $[\alpha]_D^{23}$ = –22.4 (*c* 1.5, DMF). ^{1}H NMR (DMSO-d_6): δ 1.98–2.13 (m, 1H), 2.13–2.31 (m, 3H), 2.39 (s, 3H), 4.91–5.04 (m, 1H), 5.09 (s, 2H), 6.87 (s, 1H), 7.20 (s, 1H), 7.38 (s, 7H), 7.89 (d, *J* = 7.7 Hz, 2H), 8.27 (d, *J* = 7.6Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 21.1, 27.7, 30.6, 48.1, 65.8, 123.3, 127.0, 127.8, 127.9, 128.4, 129.8, 136.8, 141.6, 156.0, 167.6, 173.1, 180.1. Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.95; H, 5.62; N, 14.20. Found: C, 63.97; H, 5.64; N, 14.19.

Stepwise procedure for 4c and 4g

A mixture of *N*-hydroxy-4-methylbenzenecarboximidamide (**2a**) (1 mmol) and *N*-acylbenzotriazole **1c** (1 mmol) was stirred at room temperature in ethanol (30 mL) for 15 min in the presence of Et_3N (1 mmol). The reaction mixture was quenched with water and a white precipitate was filtered and subsequently washed on the filter with aq 5% Na_2CO_3 (10 mL), water (10 mL), EtOH/H_2O 50% mixture (2×10 mL), and hexanes (10 mL) to give compound **3c** in 96% yield. Following the above method, **3g** was obtained in 97% yield. Without further purification intermediate **3a**,**g** were converted to **4c** and **4g**, respectively, by refluxing in ethanol for 5 minutes in the presence of catalytic amount of Et_3N and following workup procedure described for preparation of **4a-k**.

(*S*)-Benzyl 1-(amino(*p*-tolyl)methyleneamino)-3-methyl-1-oxobutan-2-ylcarbamate (3c). Yield: 96%; colorless microcrystals from EtOH; mp 152–153 °C, $[\alpha]_D^{23}$ = –3.2 (*c* 1.8, DMF). ^{1}H NMR (DMSO-d_6): δ 1.12 (d, *J* = 6.6 Hz, 3H) 1.13 (d, *J* = 6.6 Hz, 3H), 1.10–1.15 (m, 6H), 2.28–2.36 (m, 1H), 2.55 (s, 3H), 4.37 (dd, *J* = 8.9, 6.9 Hz, 1H), 5.28 (s, 2H), 7.04 (br s, 2H), 7.43–7.50 (m, 5H), 7.46 (d, *J* = 8,1 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 8.04 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 18.2, 19.0, 20.9, 30.3, 59.5, 65.6, 126.6, 127.7, 127.8, 128.4, 128.6, 128.9, 136.9, 140.2, 156.4, 156.8, 168.7. Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.76; H, 6.65; N, 10.98.

(*S*)-(9*H*-Fluoren-9-yl)methyl 1-(amino(*p*-tolyl)methyleneamino)-1-oxo-3-phenylpropan-2-ylcarbamate (3g). Yield: 97%; colorless microcrystals from EtOH; mp 144–145 °C, $[\alpha]_D^{23}$ = –25.9 (*c* 1.5, DMF). ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H), 2.88–2.97 (m, 1H), 3.22 (dd, *J* = 13.5, 4.0 Hz, 1H), 4.12–4.27 (m, 3H), 4.50–4.60 (m, 1H), 6.87 (br s, 2H), 7.20–7.44 (m, 11H), 7.61–7.69 (m, 4H), 7.88 (d, *J* = 7.4 Hz, 2H), 7.98 (d, *J* = 8.9 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 20.9, 36.8, 46.5, 55.0, 65.8, 120.1, 125.3, 126.5, 126.7, 127.1, 127.6, 128.2, 128.5, 129.0, 129.3, 137.7, 140.3, 140.7, 143.7, 156.0, 157.1, 169.3. Anal. Calcd for $C_{32}H_{29}N_3O_4$: C, 73.97; H, 5.63; N, 8.09. Found: C, 73.90; H, 5.58; N, 8.14.

General procedure for 1,2,4-oxadiazoles 6a-c

To a solution of *N*-hydroxy-4-pyridinecarboximidamide (**2b**) (1 mmol) and aq 10% HCl (1 eq.) in EtOH (30 mL), N-acylbenzotriazole **1a**,**c**,**e** (1mmol) was added. After a reaction mixture was refluxed for 20 minutes, Et_3N (2 mmol) was added and the mixture was refluxed additional 10 minutes. After cooling to a room temperature, EtOH was evaporated under reduced pressure, and CH_2Cl_2 (40 mL) was added to the reaction mixture. The organic solution was consequently washed with aq 5% Na_2CO_3 (3×30 mL), aq sat. NH_4Cl (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was subjected to column chromatography to give oxadiazoles **6a-c** in 90–93% yield.

(*S*)-Benzyl 1-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)ethylcarbamate (6a). Yield: 91%; colorless microcrystals from EtOH–hexanes; mp 112–113 °C, $[\alpha]_D^{23}$ = –50.8 (*c* 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.65 (d, *J* = 7.0 Hz, 3H), 5.15 (s, 2H), 5.23–5.29 (m, 1H), 6.05 (d, *J* = 7.1 Hz, 1H), 7.25–7.40 (m, 5H), 7.89 (d, *J* = 5.4 Hz, 2H), 8.75 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 19.9, 44.9, 67.5, 121.4, 128.3, 128.4, 128.7, 134.1, 136.1, 150.7, 155.7, 166.9, 180.9. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.71; H, 5.05; N, 16.52.

(*S*)-Benzyl 2-methyl-1-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)propylcarbamate (6b). Yield: 93%; colorless microcrystals from EtOH–hexanes; mp 78–79 °C, $[\alpha]_D^{23}$ = –49.6 (*c* 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.06 (d, *J* = 6.9 Hz, 6H), 2.35–2.39 (m, 1H), 5.10–5.20 (m, 3H), 5.93 (d, *J* = 9.1 Hz, 1H), 7.55–7.92 (m, 5H), 7.96 (d, *J* = 5.5 Hz, 2H), 8.81 (d, *J* = 5.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 18.1, 18.8, 32.7, 54.4, 67.6, 121.4, 128.4, 128.5, 128.7, 134.1, 136.1, 150.8, 156.2, 166.8, 179.9. Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.51; H, 5.69; N, 15.65.

(*S*)-Benzyl 2-phenyl-1-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)ethylcarbamate (6c). Yield: 90%; colorless oil, $[\alpha]_D^{23}$ = –48.3 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 3.30–3.34 (m, 2H), 5.11 (s, 2H), 5.45–5.49 (m, 1H), 5.77 (d, *J* = 8.4 Hz, 1H), 7.05–7.10 (m, 2H), 7.21–7.38 (m, 8H), 7.88 (d, *J* = 5.6 Hz, 2H), 8.74 (d, *J* = 5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 39.8, 50.1, 67.5, 121.4, 127.7, 128.3, 128.5, 128.7, 129.0, 129.4, 134.0, 134.8, 136.1, 150.8, 155.8, 166.9, 179.6. Anal. Calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 68.73; H, 5.16; N, 13.79.

General procedure for 1,2,4-oxadiazole 7a-d

A mixture of *N*-hydroxy-benzeneethanimidamide (**2c**) (1 mmol) and *N*-protected (aminoacyl) benzotriazole **1a**,**e**,**h**,**i** (1 mmol) was heated under reflux in ethanol (30 mL) for 1.5 hours in the presence of Et_3N (1 mmol) (In case of Fmoc-protected *N*-acylbenzotriazole **1i**, refluxing time was reduced to 1 hour, and only catalytic amount of Et_3N was used to avoid deprotection.). After cooling to room temperature, EtOH was evaporated under reduced pressure and CH_2Cl_2 (40 mL) was added to the reaction mixture. The organic solution was consequently washed with aq 5% Na_2CO_3 (3×30 mL), aq sat. NH_4Cl (30 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was subjected to column chromatography to give oxadiazoles **7a-d** in 83–89% yield.

(*S*)-Benzyl 1-(3-benzyl-1,2,4-oxadiazol-5-yl)ethylcarbamate (7a). Yield: 87%; yellowish oil, $[\alpha]_D^{23}$ = –19.3 (*c* 4.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.50 (d, *J* = 7.0 Hz, 3H), 4.02 (s, 2H), 5.02–5.14 (m, 3H), 5.74 (d, *J* = 7.8 Hz, 1H), 7.18–7.33 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 19.9, 32.3, 44.7, 67.3, 127.2, 128.3, 128.4, 128.6, 128.8, 129.1, 135.3, 136.1, 155.6, 169.5, 179.9. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.31; H, 5.91; N, 12.07.

(*S*)-Benzyl 1-(3-benzyl-1,2,4-oxadiazol-5-yl)-2-phenylethylcarbamate (7b). Yield: 83%; colorless microcrystals from EtOH–hexanes; mp 71–72 °C, $[\alpha]_D^{23}$ = –19.7 (*c* 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 3.17–3.22 (m, 2H), 4.02 (s, 2H), 5.07, 5.08 (AB q, *J* = 2.5 Hz, 2H), 5.35–5.39 (m, 2H), 6.93 (d, *J* = 5.1 Hz, 2H), 7.14–7.32 (m, 13H). ^{13}C NMR ($CDCl_3$): δ 32.3, 40.0, 50.0, 67.5, 127.3, 127.5, 128.3, 128.4, 128.7, 128.9, 129.1, 129.4, 134.8, 135.4, 136.1, 155.6, 169.5, 178.5. Anal. Calcd for $C_{25}H_{23}N_3O_3$: C, 72.62; H, 5.61; N, 10.16. Found: C, 72.75; H, 5.63; N, 10.20.

(*S*)-Benzyl 1-(3-benzyl-1,2,4-oxadiazol-5-yl)-3-(methylthio)propylcarbamate (7c). Yield: 89%; colorless oil, $[\alpha]_D^{23}$ = –34.7 (*c* 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.00–2.23 (m, 5H), 2.44–2.55 (m, 2H), 4.02 (s, 2H), 5.08 (s, 2H), 5.14–5.25 (m, 1H), 5.81 (d, *J* = 8.2Hz, 1H), 7.18–7.38 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 15.4, 29.7, 32.2, 33.0, 48.0, 67.4, 127.2, 128.2, 128.3, 128.6, 128.7, 129.0, 135.2, 136.2, 155.8, 169.5, 178.8. HRMS *m/z* calcd for $C_{21}H_{23}N_3O_3S$ 398.1538 ($M+H^+$), found 398.1523.

(*S*)-(9*H*-Fluoren-9-yl)methyl 1-(3-benzyl-1,2,4-oxadiazol-5-yl)-3-(methylthio)propyl carbamate (7d). Yield: 85%; colorless oil, $[\alpha]_D^{23}$ = –23.8 (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H), 2.14–2.34 (m, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 4.12 (s, 2H), 4.27 (t, *J* = 6.6 Hz, 1H), 4.51 (d, *J* = 6.7 Hz, 2H), 5.30 (dd, *J* = 13.9, 5.9 Hz, 1H), 5.69 (d, *J* = 8.6 Hz, 1H), 7.28–7.41 (m, 7H), 7.43–7.50 (m, 2H), 7.62–7.68 (m, 2H), 7.82 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 15.5, 29.8, 32.3, 33.1, 47.2, 48.1, 67.3, 120.1, 125.1, 127.2, 127.3, 127.9, 128.8, 129.1, 135.2, 141.4, 143.7, 143.9, 155.8, 169.6, 178.8. Anal. Calcd for $C_{28}H_{27}N_3O_3S$: C, 69.25; H, 5.60; N, 8.65. Found: C, 69.37; H, 5.63; N, 8.58.

General procedure for 1,2,4-oxadiazoles 11a-f

A mixture of *N*-hydroxy-4-methylbenzenecarboximidamide (**2a**) (1 mmol) and *N*-acylbenzotriazole **10a-f** (1 mmol) was heated under reflux in ethanol (30 mL) for 10 minutes in the presence of Et_3N (1 mmol). The reaction mixture was cooled down to room temperature and quenched with water. Resulting white precipitate was filtered and subsequently washed on the filter with aq 5% Na_2CO_3 (10 mL), water (10 mL), EtOH/H_2O 50% mixture (2×10 mL), and hexanes (10 mL) to give 1,2,4-oxadiazoles **11a-f** in 79–94 yield. Recrystallization from EtOH-hexanes, or column chromatography was used for purification.

Benzyl (*S*)-1-oxo-3-phenyl-1-((*S*)-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethylamino) propan-2-ylcarbamate (11a). Yield: 83%; colorless microcrystals from EtOH–hexanes; mp 141–142 °C, $[\alpha]_D^{23}$ = –16.3 (*c* 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.51 (d, *J* = 6.9 Hz, 3H), 2.40 (s, 3H), 3.06 (d, *J* = 6.9 Hz, 2H), 4.50–4.57 (m, 1H), 5.04 (s, 2H), 5.31–5.42 (m, 1H), 5.65 (d, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 6.5 Hz, 1H), 7.08–7.38 (m, 12H), 7.91 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ

19.6, 21.7, 38.9, 42.8, 56.4, 67.3, 123.8, 127.2, 127.6, 128.1, 128.4, 128.7, 128.8, 129.4, 129.7, 136.2, 141.8, 156.2, 168.4, 170.8, 178.9. Anal. Calcd for $C_{28}H_{28}N_4O_4$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.02; H, 5.83; N, 11.28.

Benzyl (*R*)-1-oxo-3-phenyl-1-((*S*)-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethylamino) propan-2-ylcarbamate (11b). Yield: 79%; colorless microcrystals from EtOH–hexanes; mp 101–102 °C, $[\alpha]_D^{23}$ = –12.1 (*c* 2.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.40 (d, *J* = 6.9 Hz, 3H), 2.38 (s, 3H), 3.02–3.18 (m, 2H), 4.53–4.58 (m, 1H), 5.05 (s, 2H), 5.27–5.39 (m, 1H), 5.62 (d, *J* = 6.9 Hz, 1H), 6.76 (d, *J* = 6.6 Hz, 1H), 7.14–7.34 (m, 12H), 7.87 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 19.5, 21.7, 38.8, 42.8, 56.3, 67.3, 123.8, 127.3, 127.6, 128.2, 128.4, 128.7, 128.9, 129.5, 129.7, 136.2, 136.4, 141.8, 156.2, 168.4, 170.7, 179.0. Anal. Calcd for $C_{28}H_{28}N_4O_4$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.05; H, 5.94; N, 11.43.

Benzyl (*S*)-1-((*S*)-2-methyl-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)propylamino)-1-oxopropan-2-ylcarbamate (11c). Yield: 87%; colorless microcrystals from EtOH–hexanes; mp 101–102 °C, $[\alpha]_D^{23}$ = –37.6 (*c* 2.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.99 (d, *J* = 6.7 Hz, 6H), 1.46 (d, *J* = 7.0 Hz, 3H), 2.31–2.39 (m, 1H), 2.46 (s, 3H), 4.41–4.48 (m, 1H), 5.18 (s, 2H), 5.33 (dd, *J* = 8.9, 5.9 Hz, 1H), 5.53 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.29–7.42 (m, 7H), 8.00 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 18.0, 18.8, 21.7, 32.7, 50.7, 52.3, 67.4, 123.9, 127.6, 128.2, 128.4, 128.7, 129.7, 136.3, 141.8, 156.4, 168.4, 172.4, 178.3. Anal. Calcd for $C_{24}H_{28}N_4O_4$: C, 66.04; H, 6.47; N, 12.83. Found: C, 65.81; H, 6.61; N, 12.47.

Benzyl (*R*)-1-((*S*)-2-methyl-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)propylamino)-1-oxopropan-2-ylcarbamate (11d). Yield: 85%; colorless microcrystals from EtOH–hexanes; mp 94–95 °C, $[\alpha]_D^{23}$ = –20.6 (*c* 3.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.01 (d, *J* = 6.3 Hz, 6H), 1.49 (d, *J* = 7.0 Hz, 3H), 2.31–2.39 (m, 1H), 2.44 (s, 3H), 4.42–4.52 (m, 1H), 5.18 (s, 2H), 5.32 (dd, *J* = 8.9, 6.0 Hz, 1H), 5.59 (d, *J* = 6.7 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.25–7.40 (m, 7H), 7.97 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 18.1, 18.6, 18.9, 21.7, 32.7, 50.8, 52.2, 67.4, 123.9, 127.6, 128.2, 128.4, 128.7, 129.7, 136.2, 141.8, 156.4, 168.3, 172.5, 178.3. Anal. Calcd for $C_{24}H_{28}N_4O_4$: C, 66.04; H, 6.47; N, 12.83. Found: C, 66.05; H, 6.67; N, 12.51.

Benzyl (*S*)-1-oxo-1-((*S*)-2-phenyl-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethylamino) propan-2-ylcarbamate (11e). Yield: 91%; colorless microcrystals from EtOH–hexanes; mp 133–134 °C, $[\alpha]_D^{23}$ = –5.6 (*c* 2.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.41 (d, *J* = 7.0 Hz, 3H), 2.47 (s, 3H), 3.26–3.44 (m, 2H), 4.28–4.40 (m, 1H), 5.15 (AB q, *J* = 12.1 Hz, 2H), 5.31 (d, *J* = 5.9 Hz, 1H), 5.66–5.75 (m, 1H), 6.89 (d, *J* = 6.9 Hz, 1H), 7.09–7.17 (m, 2H), 7.25–7.47 (m, 10H), 7.97 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 18.3, 21.8, 39.6, 48.1, 50.6, 67.4, 123.8, 127.6, 127.7, 128.3, 128.5, 128.8, 128.9, 129.5, 129.8, 134.3, 135.0, 141.9, 168.4, 169.7, 172.1, 178.0. Anal. Calcd for $C_{28}H_{28}N_4O_4$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.05; H, 5.91; N, 11.43.

Benzyl (*S*)-1-oxo-1-((*R*)-2-phenyl-1-(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)ethylamino) propan-2-ylcarbamate (11f). Yield: 94%; colorless microcrystals from EtOH–hexanes; mp 122–123 °C, $[\alpha]_D^{23}$ = 21.3 (*c* 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.28 (d, *J* = 7.0 Hz, 3H), 2.39 (s, 3H), 3.18–3.36 (m, 2H), 4.31 (m, 1H), 5.1 (s, 2H), 5.50 (d, *J* = 7.3 Hz, 1H), 5.64 (dd, *J* = 14.3, 7.3 Hz, 1H), 7.08 (d, *J* = 5.9 Hz, 1H), 7.18–7.29 (m, 12H), 7.89 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ

18.7, 21.7, 39.5, 47.9, 50.6, 67.3, 123.7, 126.8, 127.5, 127.6, 128.2, 128.4, 128.7, 128.9, 129.5, 129.7, 135.1, 136.2, 141.9, 168.4, 172.3, 178.1. Anal. Calcd for $C_{28}H_{28}N_4O_4$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.11; H, 5.86; N, 11.43.

General procedure for 1,2,4-oxadiazoles 13a-d

A mixture of amidoxime (**2a,c**) (1 mmol) and *N*-acylbenzotriazole (**12a-c**) (1 mmol) was heated under reflux in ethanol (30 mL) for 7 hours in the presence of Et_3N (1 mmol). Completion of the reaction was monitored by TLC (AcOEt/hexanes = 1/2). The reaction mixture was cooled down to room temperature and quenched with water. Resulting white precipitate was filtered and subsequently washed on the filter with aq 5% Na_2CO_3 (10 mL), water (10 mL), EtOH/H_2O 50% mixture (2×10 mL), and hexanes (10 mL) to give oxadiazoles **13a-d** in 73–82% yield.

3-(4-Methylphenyl)-5-phenyl-1,2,4-oxadiazole (13a). Yield: 77%; colorless microcrystals from EtOH-hexanes; mp 101–102 °C (Lit.[15c] mp 105–106 °C). ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.50–7.59 (m, 3H), 8.06 (d, *J* = 8.1 Hz, 2H), 8.20 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.8, 124.3, 124.6, 127.6, 128.3, 129.2, 129.7, 132.8, 141.7, 169.1, 175.7.

5-(4-Methoxyphenyl)-3-(4-methylphenyl)-1,2,4-oxadiazole (13b). Yield: 82%; colorless microcrystals from EtOH-hexanes; mp 109–110 °C (Lit.[34] mp 110 °C). ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H), 3.87 (s, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 8.1 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.8, 55.7, 114.6, 117.1, 124.5, 127.6, 129.7, 130.2, 141.5, 163.3, 169.0, 175.6.

2-[3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl]-1*H*-indole (13c). Yield: 73%; colorless microcrystals from EtOH–hexanes; mp 149–150 °C. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H), 7.17–7.21 (m, 1H), 7.27–7.46 (m, 5H), 7.72 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 9.22 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 21.8, 108.4, 112.0, 121.5, 121.8, 122.6, 124.0, 125.9, 127.6, 128.1, 129.8, 137.6, 141.9, 168.8, 170.0. Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 73.85; H, 4.86; N, 14.96.

3-Benzyl-5-phenyl-1,2,4-oxadiazole (13d). Yield: 74%; colorless microcrystals from EtOH-hexanes; mp 79–80 °C (Lit.[35] mp 81–83 °C). ^{1}H NMR ($CDCl_3$): δ 4.22 (s, 2H), 7.30–7.65 (m, 8H), 8.15–8.20 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 32.6, 124.4, 127.2, 128.2, 128.8, 129.1, 129.2, 132.8, 135.7, 170.2, 175.9.

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