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EFFICIENT MICROWAVE-ASSISTED SYNTHESIS OF 1,2,4-TRIAZOLE-BASED PEPTIDOMIMETICS USING BENZOTRIAZOLE METHODOLOGY

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This work is submitted in honor of the 75th anniversary of Albert Padwa and his excellent chemistry

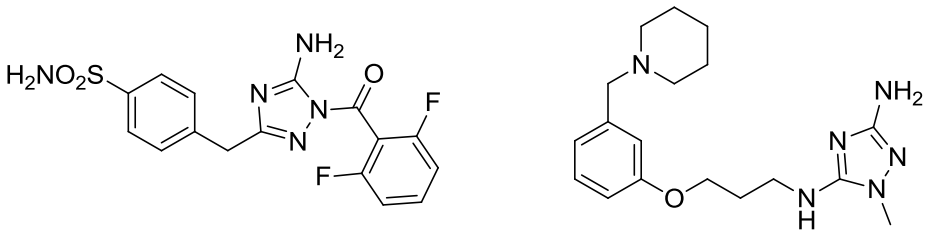
Abstract – A microwave-assisted three-step protocol allowed the rapid and convenient construction of a series of 1,2,4-triazole substituted amino acids and dipeptides as potential building blocks for peptidomimetics.

INTRODUCTION

The coupling of microwave-assisted reactions with traditional organic synthesis allows a large range of compounds to be synthesized in an efficient manner. By utilizing the strengths of both methods organic chemists can quickly create large libraries of molecules, which can lead to the expeditious discovery of novel drugs.[1-4]

1,2,4-Triazole derivatives have attracted considerable interest among medicinal chemists because of their versatile biological properties. For instance, 1,2,4-triazoles have been found to exhibit a wide range of antifungal and antibacterial activities.[5,6] The 1,2,4-triazole moiety was also found in potent CRF1 receptor antagonists,[7] H_2 receptor antagonists[8] and muscarinic receptor ligands.[9,10] Ring acylated 1,2,4-triazole derivatives have shown substantial inhibition of Janus associated kinases (TYK2 and JAKs1-3)[11] and cyclin-dependent kinases (CDKs, Figure 1).[12]

Various efficient methods for the preparation of 1,2,4-triazole-3,5-diamine derivatives have been published which involve the use of (i) *N*-cyanoguanidines,[13,14] (ii) *S*,*S*-dimethyl-*N*-cyanodithioimidocarbonate[15] and (iii) diphenyl cyanocarbonimidate.[16-19] However, due to limited scope method (i) does not show great versatility and diphenyl cyanocarbonimidate (method iii) is a relatively expensive starting material.



JNJ-7706621
(CDK inhibitor)

AH 22216
(H_2 receptor antagonist)

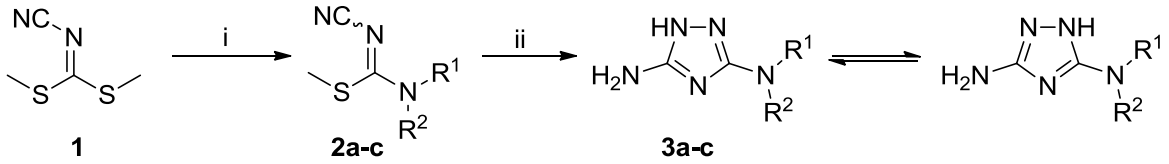
Figure 1. Selected Biologically Active 1,2,4-Triazole Derivatives

Recently discovered bioactive peptides play diverse roles, including functioning as hormones, enzyme inhibitors and neurotransmitters.[20,21] However, their clinical application has been limited due to their rapid hydrolysis by peptidase enzymes. One approach to overcome the drawbacks of natural peptides is the use of peptidomimetics. These are small protein-like molecules designed to mimic natural peptides or proteins.[22] Bioisosteric replacement of the amide bond is an important aspect in the design of peptidomimetics.[23] In particular 1,2,4-triazole derivatives were successfully utilized as amide bond mimetics with increased hydrolytic stability.[23,24]

N-Acylbenzotriazoles are stable solids, easy to handle and advantageous for N-, O-, C- and S-acylation.[25] We herein demonstrate a novel microwave-assisted approach for the synthesis of 1,2,4-triazole-based peptidomimetics using benzotriazole methodology and starting from inexpensive and versatile starting materials.

RESULTS AND DISCUSSION

Isothiourea derivatives **2a-c** were prepared by reacting commercially available *S*,*S*-dimethyl-*N*-cyanodithioimidocarbonate (**1**) with primary or secondary amines according to literature procedures (63-89% yield, Scheme 1, Table 1).[15,26,27] However, the preparation of **2a-c** under conventional conditions required relatively long reaction times (4-5 h, 63-89% yield). Therefore, we repeated the synthesis of **2a-c** using microwave irradiation. Under microwave heating, significant reduction in reaction times were observed, which provided the isothiourea derivatives **2a-c** within 5-30 minutes in comparable or greater yields (61-86%, Table 1).



i: amine (1 equiv.)
ii: hydrazine hydrate (2 equiv.)

Scheme 1. Synthesis of 1,2,4-Triazole Intermediates **3a-c**

Table 1. Isothioureas **2a-c** Synthesized

Entry	*R^1*	*R^2*	*Product*	*Conv. Method*		*Microwave*		*Mp (°C)*
				Time (min)	Yield (%)	Time (min)	Yield (%)	
1	$-(CH_2)_2O(CH_2)_2-$		**2a**	240	63[a]	5	76[d]	131-132
2	$PhCH_2$	H	**2b**	300	89[b]	5	86[d]	158-161
3	Ph	H	**2c**	240	63[c]	30	61[e]	195-198

[a] $CHCl_3$, reflux[15]
[b] Et_2O, RT[26]
[c] EtOH, reflux[27]
[d] Et_2O, MW, 45 °C, 50 W
[e] EtOH, MW, 90 °C, 100 W

Treatment of isothioureas **2a-c** with hydrazine hydrate (2 equiv.) in refluxing ethanol furnished the 1,2,4-triazole-3,5-diamine derivatives **3a-c** in 75-90% yield within 4-5 hours (Scheme 1, Table 2). Furthermore, the reaction conditions were optimized using microwave irradiation to shorten reaction times and to improve yields. The microwave-assisted preparation (80 °C, 100 W) afforded **3a-c** within 5-10 minutes in significantly higher yields (89-95%, Scheme 1, Table 2).

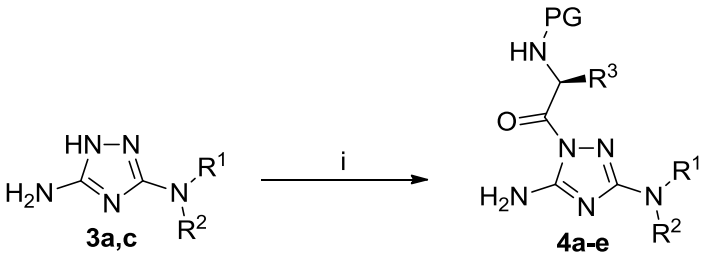
Table 2. 1,2,4-Triazole Intermediates **3a-c** Prepared

Entry	*R^1*	*R^2*	*Product*	*Conv. heating*[a]		*Microwave*[b]		*Mp (°C)*
				Time (min)	Yield (%)	Time (min)	Yield (%)	
1	$-(CH_2)_2O(CH_2)_2-$		**3a**	240	83	5	89	165-166
2	$PhCH_2$	H	**3b**	300	75	10	90	147-148
3	Ph	H	**3c**	240	90	10	95	166-169

[a] EtOH, reflux
[b] EtOH, MW, 80 °C, 100 W

We then investigated the preparation of the desired 1,2,4-triazole substituted amino acids and dipeptides. In initial experiments the reaction of **3a** with Cbz-L-Ala-Bt (Bt = benzotriazol-1-yl) was incomplete after heating the reaction mixture under reflux for 12 hours. Subsequently, we studied the microwave-assisted *N*-acylation of **3a,c**. Interestingly, the reaction of **3a,c** with *N*-(protected α-aminoacyl)benzotriazoles under microwave irradiation (70 °C, 100 W) was complete after 30 minutes and afforded the ring acylated products **4a-e** (65-95% yield, Table 3).

Table 3. Microwave-Assisted Acylation of 3,5-Diamino-1,2,4-triazoles **3a,c**



i: *N*-(protected α-aminoacyl)benzotriazoles, THF, MW (100 W, 70 °C, 30 min)

Entry	*4*	*R*[1]	*R*[2]	*R*[3]	*PG*	*Yield (%)*	*Mp (°C)*
1	**4a**	-$(CH_2)_2O(CH_2)_2$-		Me	Cbz	95	205-207
2	**4b**	-$(CH_2)_2O(CH_2)_2$-		H	Fmoc	70	211-214
3	**4c**	-$(CH_2)_2O(CH_2)_2$-		$PhCH_2$	Cbz	95	217-218
4	**4d**	-$(CH_2)_2O(CH_2)_2$-		H	Boc	73	212-215
5	**4e**	Ph	H	H	Boc	65	230-233

Acylation of the ring nitrogen was confirmed by observation of an amino signal (2H) in the ^{1}H NMR spectrum. The downfield shift of the amino group signal (> 7ppm) indicates clearly that the ring acylation has taken place at the N^1 position proximal to the amino group consistent with the findings by Reiter *et al.*,[15] who showed that the exocyclic amino group proximal to the methyl substituted ring nitrogen in 1-methyl-1*H*-1,2,4-triazole-3,5-diamine induced a downfield shift whereas the distal exocyclic amino group was shifted upfield by ca. 2 ppm.[15] D'Andrea *et al.* found a similar trend with an analog of compound JNJ-7706621, from which the chemical shift of the amino group upon acylation at N^2 was upfield (6.25 ppm) whereas acylation at N^1 showed a significant downfield shift (7.95 ppm).[11] Our compounds share this chemical shift pattern where the downfield shift of the amino group indicates acylation of the ring nitrogen (N^1) proximal to the primary amino group (Figure 2).

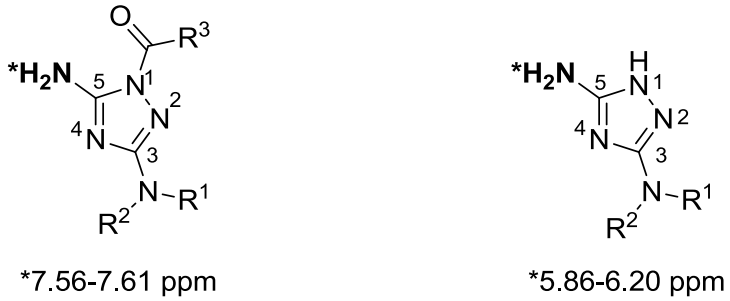
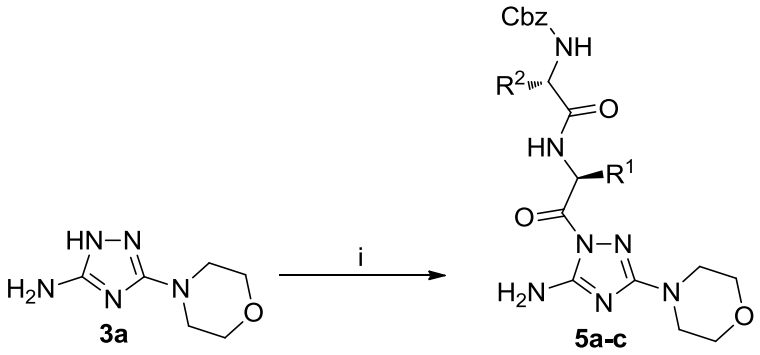


Figure 2. ^{1}H NMR shifts due ring acylation position

The microwave-assisted reactions of **3a** with *N*-(protected dipeptidoyl)benzotriazoles similarly furnished ring acylated dipeptidoyl 1,2,4-triazole derivatives **5a-c** in 76-95% yield. Again, the exocyclic amino group shows a ^{1}H NMR spectra shift in the region of >7ppm as seen in compounds **4a-e**.

Table 4. Microwave-Assisted Preparation of Dipeptidoyl 1,2,4-Triazole Derivatives **5a-c**

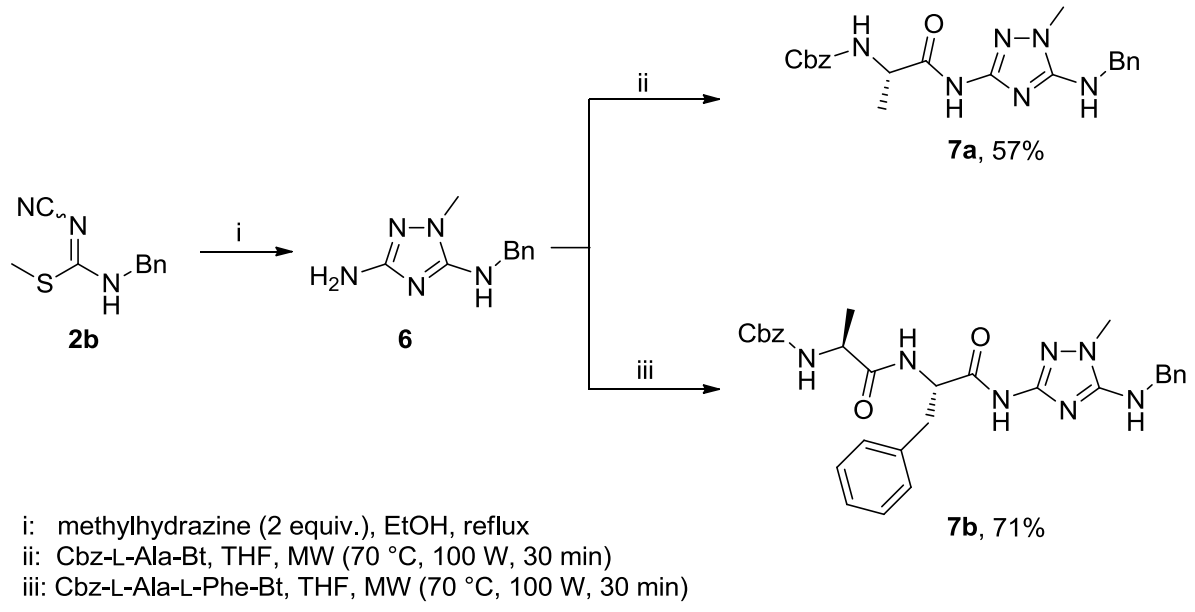


i: *N*-(protected dipeptidoyl)benzotriazoles, THF, MW (100 W, 70 °C, 30 min)

Entry	*5*	R^1	R^2	*Yield (%)*	*Mp (°C)*
1	**5a**	Me	$PhCH_2$	95	188-190
2	**5b**	$PhCH_2$	Me	86	194-195
3	**5c**	^{i}Bu	H	76	102-106

We observed exclusive ring acylation of triazoles **3a,c** with *N*-(protected α-aminoacyl)benzotriazoles and *N*-(protected dipeptidoyl)benzotriazoles yielding compounds of type **4** and **5**. It was therefore decided to study the acylation of the exocyclic amino group. To this end we required a substrate with a ring-substituted nitrogen to prevent any possible ring acylation. Thus, N^5-benzyl-1-methyl-1*H*-1,2,4-triazole-3,5-diamine **6** was prepared in 51% yield by treatment of isothiourea **2b** with 2 equiv. of methylhydrazine according to a literature procedure[15] (Scheme 2). The 1-methylsubstituted triazole compound **6** was conveniently acylated at the exocyclic NH_2 group using a

microwave-assisted protocol (70 °C, 100 W, 30 min) to afford the desired 3,5-diamino-1,2,4-triazole derivatives **7a** and **7b** in 57% and 71% yield, respectively (Scheme 2).



Scheme 2. Microwave-Assisted Acylation of the Exocyclic Amino Group of 3,5-Diamino-1,2,4-triazole **6**

CONCLUSIONS

In conclusion, we have developed an efficient, fast and convenient method for the microwave-assisted preparation of 1,2,4-triazole substituted amino acids and dipeptides, which can be considered as potential building blocks for peptidomimetics as well as prospective biologically active compounds. Our method offers short reaction times, good to excellent yields and is compatible with a variety of protecting groups.

EXPERIMENTAL

Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on Gemini or Varian NMR operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C with TMS as an internal standard. Elemental analyses were performed on a Carlo Erba-1106 instrument. All microwave assisted reactions were carried out with a single mode cavity Discover Microwave Synthesizer (CEM Corporation, NC). The reaction mixtures were transferred into a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation (Discover mode; run time: 60 sec.; PowerMax-cooling mode). All *N*-(protected α-aminoacyl)-benzotriazoles and *N*-(protected dipeptidoyl)benzotriazoles used have been prepared according to our previously published methods.[25]

General Procedure for the Microwave-assisted Preparation of Isothioureas 2a-c. A mixture of

dimethyl cyanodithioiminocarbonate (0.44 g, 3 mmol) and the respective primary or secondary amine (3 mmol) in Et_2O (5 mL) or EtOH (5 mL) was subjected to microwave irradiation (see Table 1). Compounds **2a,b** precipitated from the reaction mixture and were filtered, washed with Et_2O (2 x 5 mL) and dried under vacuum. Compound **2c** was crystallized from EtOH:hexanes, filtered, washed with hexanes (2 x 5 mL) and dried under vacuum.

Methyl *N*-cyanomorpholine-4-carbimidothioate (2a). White microcrystals, 76% yield, mp 131-132 °C (lit.[28] mp 125-126 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (t, J = 4.7 Hz, 4H), 3.70 (t, J = 4.7 Hz, 4H), 2.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 114.9, 66.4, 48.7, 16.3. Anal. Calcd for $C_7H_{11}N_3OS$: C 45.39; H 5.99; N 22.68. Found: C 45.24; H 5.96; N 22.64.

Methyl *N*-benzyl-*N*'-cyanocarbamimidothioate (2b). White microcrystals, 86% yield, mp 158-161 °C (lit.[29] mp 156-157 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.91 (s, 1H), 7.38-7.25 (m, 5H), 4.50 (s, 2H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.3, 137.4, 128.4, 127.3, 127.2, 115.8, 46.2, 14.1. Anal. Calcd for $C_{10}H_{11}N_3S$: C 58.51; H 5.40; N 20.47. Found: C 58.13; H 5.29; N 20.68.

Methyl *N*'-cyano-*N*-phenylcarbamimidothioate (2c). White microcrystals, 61% yield, mp 195-198 °C (lit.[27] mp 194-196 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.16 (s, 1H), 7.52-7.18 (m, 5H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.2, 137.2, 128.8, 126.4, 124.2, 114.8, 14.9. Anal. Calcd for $C_9H_9N_3S$: C 56.52; H 4.74; N 21.97. Found: C 56.25; H 4.60; N 21.95.

General Procedure for Microwave Assisted Synthesis of 1,2,4-Triazoles 3a-c. A reaction mixture of the appropriate isothiourea **2a-c** (2 mmol) and 72% hydrazine hydrate (0.2 g, 4 mmol) in EtOH (5 mL) was subjected to microwave irradiation (80 °C, 100 W, 5-10 min). On completion of the reaction (TLC), the solvent was removed under reduced pressure and the residue was crystallized from $CHCl_3$:hexanes.

3-Morpholino-1*H*-1,2,4-triazol-5-amine (3a). White microcrystals, 89% yield, mp 165-166 °C (lit.[15] mp 167-168 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.90 (br s, 1H), 5.99 (br s, 2H), 3.66 (t, J = 4.4 Hz, 4H), 3.15 (t, J = 4.4 Hz, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1, 156.9, 66.3, 47.4.

***N*^{3}-Benzyl-1*H*-1,2,4-triazole-3,5-diamine (3b).** White microcrystals, 90% yield, mp 147-148 °C (lit.[15] mp 151-153 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.47-7.10 (m, 5H), 6.20 (s, 1H), 5.42 (s, 2H), 4.23 (d, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.1, 157.8, 141.1, 128.0, 127.2, 126.4, 46.2.

***N*^{3}-Phenyl-1*H*-1,2,4-triazole-3,5-diamine (3c).** White microcrystals, 95% yield, mp 166-169 °C (lit.[15]

mp 161-162 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.20 (br s, 1H), 8.62 (s, 1H), 7.49 (d, J = 7.9 Hz, 2H), 7.15 (t, J = 7.8 Hz, 2H), 6.71 (t, J = 7.3 Hz, 1H), 5.87 (br s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.6, 155.6, 142.6, 128.4, 118.3, 115.5. Anal. Calcd for $C_8H_9N_5$: C 54.85; H 5.18; N 39.98. Found: C 54.48; H 5.08; N 39.81.

General Procedure for Microwave Assisted Synthesis of Compounds 4a-e. A mixture of the respective *N*-(protected α-aminoacyl)benzotriazole (1 mmol) and 1,2,4-triazole **3a,c** (1 mmol) in dry THF (3 mL) was subjected to microwave irradiation (70 °C, 100 W, 30 min). The products were isolated and purified according to the following procedures. The reaction mixtures of compounds **4a,c** were quenched with water (2 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with aqueous Na_2CO_3 solution (10% w/w, 3 x 20 mL), water (3 x 20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residues were recrystallized from CH_2Cl_2:hexanes to give the desired products **4a,c**. In case of compounds **4b,d** the reaction mixtures were evaporated under reduced pressure and the crude products were recrystallized from MeOH. The reaction mixture of compound **4e** was allowed to cool to room temperature and crystallized from a mixture of THF, CH_2Cl_2 and hexanes. The precipitate was collected, washed with CH_2Cl_2 (2 x 10 mL) and dried under vacuum.

(*S*)-Benzyl (1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-1-oxopropan-2-yl)carbamate (4a). White microcrystals, 95% yield, mp 205-207 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85 (d, J = 7.2 Hz, 1H), 7.61 (br s, 2H), 7.39-7.31 (m, 5H), 5.04-5.01 (m, 2H), 4.91-4.81 (m, 1H), 3.67-3.62 (m, 4H), 3.31-3.24 (m, 4H), 1.35 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.5, 163.0, 157.2, 155.9, 136.9, 128.4, 127.9, 65.6, 49.4, 45.6, 34.4, 16.2. HRMS calcd. for $C_{17}H_{22}N_6O_4$ $[M+H]^+$: 375.1775. Found $[M+H]^+$: 375.1786.

(9*H*-Fluoren-9-yl)methyl (2-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-2-oxoethyl)carbamate (4b). White microcrystals, 70% yield, mp 211-214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, J = 7.2 Hz, 2H), 7.84-7.67 (m, 3H), 7.58 (br s, 2H), 7.48-7.30 (m, 4H), 4.44-4.09 (m, 5H), 3.63 (br s, 4H), 3.28 (br s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ169.3, 163.7, 157.5, 157.3, 144.4, 141.4, 128.3, 127.7, 125.9, 120.8, 66.5, 66.2, 47.3, 46.2, 44.0. Anal. Calcd for $C_{23}H_{24}N_6O_4$: C 61.60; H 5.39; N 18.74. Found: C 61.91; H 5.53; N 18.53.

(*S*)-Benzyl (1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (4c). White microcrystals, 95% yield, mp 217-218 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88 (d, J = 7.2 Hz, 2H), 7.76-7.75 (m, 4H) 7.57 (br s, 2H), 7.45-7.40 (m 4 H), 4.34-4.30 (m, 2H), 4.27-4.21 (m, 2H),

3.63 (d, *J* = 4.8 Hz, 4H), 3.28 (d, *J* = 4.8 Hz, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.7, 163.0, 156.8, 156.6, 143.8, 140.7, 127.6, 127.0, 125.2, 120.1, 65.8, 65.5, 46.6, 45.5, 43.4. Anal. Calcd for $C_{23}H_{26}N_6O_4$: C 61.32; H 5.82; N 18.65. Found: C 61.44; H 5.45; N 18.28.

tert-Butyl (2-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-2-oxoethyl)-carbamate (4d). White microcrystals, 73% yield, mp 212-215 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (br s, 2H), 7.14 (t, *J* = 6.1 Hz, 1H), 4.14 (d, *J* = 6.1 Hz, 2H), 3.64 (t, *J* = 4.7 Hz, 4H), 3.27 (t, *J* = 4.7 Hz, 4H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.0, 163.0, 156.8, 155.9, 78.2, 65.6, 45.5, 43.0, 28.2. Anal. Calcd for $C_{13}H_{22}N_6O_4$: C 47.84; H 6.79; N 25.75. Found: C 48.17; H 6.97; N 25.95.

tert-Butyl (2-(5-amino-3-(phenylamino)-1*H*-1,2,4-triazol-1-yl)-2-oxoethyl)-carbamate (4e). White microcrystals, 65% yield, mp 230-233 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.65 - 7.52 (m, 4H), 7.29 - 7.17 (m, 3H), 6.85 (t, *J* = 7.2 Hz, 1H), 4.27 (d, *J* = 6.0 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.9, 158.4, 155.8, 140.9, 128.6, 120.0, 116.7, 78.3, 43.2, 28.2. Anal. Calcd for $C_{15}H_{20}N_6O_3$: C 54.21; H 6.07; N 25.29. Found: C 54.43; H 6.23; N 24.57.

General Procedure for Microwave Assisted Synthesis of Compounds 5a-c. A mixture of the appropriate *N*-(protected dipeptidoyl)benzotriazole (1 mmol) and 3-morpholino-1*H*-1,2,4-triazol-5-amine (0.169 g, 1 mmol) in dry THF (3 mL) was subjected to microwave irradiation (70 °C, 100 W, 30 min). The reaction mixtures were allowed to cool to room temperature and evaporated to give crude products. Compound **5a** was dissolved in EtOAc (30 mL), washed with aqueous Na_2CO_3 solution (10% w/w, 3 x 20 mL), water (3 x 20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the desired product. Compound **5b** was recrystallized from MeOH. Compound **5c** was recrystallized from Et_2O:hexanes. The precipitates were collected, washed with hexanes (2 x 5 mL) and dried under vacuum.

Benzyl ((*S*)-1-(((*S*)-1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-1-oxopropan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (5a). White microcrystals, 95% yield, mp 188-190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (d, *J* = 6.5 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.71 (d, *J* = 7.7 Hz, 2H), 7.57 (m, 3H), 7.46-7.28 (m, 6H), 5.10-5.00 (m, 1H), 4.30-4.17 (m, 3H), 3.68-3.62 (m, 6H), 3.32-3.24 (m, 4H), 1.36 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.9, 169.0, 162.9, 157.1, 156.4, 143.8, 140.7, 127.6, 127.1, 125.2, 120.1, 65.7, 65.6, 47.6, 46.6, 45.5, 42.9, 16.3. Anal. Calcd for $C_{26}H_{31}N_7O_5$: C 59.87; H 5.99; N 18.80. Found: C 60.21; H 5.60; N 18.42.

Benzyl ((*S*)-1-(((*S*)-1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-1-oxo-3-phenylpropan-2-yl)-amino)-1-oxopropan-2-yl)carbamate (5b). White microcrystals, 86% yield, mp 194-195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (d, J = 7.7 Hz, 1H), 7.56 (br s, 2H), 7.40-7.20 (m, 10H), 7.19-7.11 (m, 1H), 5.28-5.05 (m, 1H), 4.93 (d, J = 2.6 Hz, 2H), 4.12-3.96 (m, 1H), 3.67-3.54 (m, 4H), 3.37-3.22 (m, 4H), 3.14 (dd, J = 13.6, 3.3 Hz, 1H), 2.81 (dd, J = 13.8, 9.8 Hz, 1H), 1.14 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 170.6, 163.0, 157.1, 155.5, 137.6, 137.0, 129.0, 128.3, 128.2, 127.8, 126.5, 65.6, 65.3, 53.8, 49.7, 45.5, 35.7, 18.2. Anal. Calcd for $C_{26}H_{31}N_7O_5$: C 59.87; H 5.99; N 18.80. Found: C 59.72; H 6.04; N 18.92.

(*S*)-Benzyl (2-((1-(5-amino-3-morpholino-1*H*-1,2,4-triazol-1-yl)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)carbamate (5c). White microcrystals, 76% yield, mp 102-106 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (d, J = 8.0 Hz, 1H), 7.57 (br s, 2H), 7.43 (t, J = 6.2 Hz, 1H), 7.39-7.29 (m, 5H), 5.18-5.07 (m, 1H), 5.02 (s, 2H), 3.74-3.58 (m, 6H), 3.31-3.22 (m, 4H), 1.79-1.36 (m, 3H), 0.97-0.78 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.9, 169.4, 162.8, 157.1, 156.4, 137.0, 128.3, 127.7, 65.5, 65.4,50.3, 45.5, 43.1, 24.6, 23.2, 20.9. Anal. Calcd for $C_{22}H_{31}N_7O_3$: C 55.80; H 6.60; N 20.71. Found: C 55.86; H 6.55; N 20.33.

***N*^{5}-Benzyl-1-methyl-1*H*-1,2,4-triazole-3,5-diamine (6)**. Methyl *N*-benzyl-*N*'-cyanocarbamimidothioate (2.0 g, 10 mmol) and methylhydrazine (1.1 mL, 20 mmol) was refluxed in EtOH (50 mL) for 4 hours. The solvent was removed under reduced pressure and the crude residue was recrystallized from MeCN/hexanes. White microcrystals, 51% yield, mp 159-162 °C (lit.[15] mp 159-161 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.40-7.16 (m, 5H), 6.74 (t, J = 6.0 Hz, 1H), 4.90 (br s, 2H), 4.39 (d, J = 6.0 Hz, 2H), 3.34 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.2, 154.8, 140.4, 128.2, 127.1, 126.7, 46.6, 32.5.

(*S*)-Benzyl (1-((1-methyl-5-(phenylamino)-1*H*-1,2,4-triazol-3-yl)amino)-1-oxopropan-2-yl)-carbamate (7a). A mixture of Cbz-L-Ala-Bt (0.32 g, 1 mmol) and N^5-benzyl-1-methyl-1*H*-1,2,4-triazole-3,5-diamine (0.20 g, 1 mmol) in dry THF (3 mL) was subjected to microwave irradiation (70 °C, 100 W, 30 min). The reaction was quenched with water (2 mL), and extracted with EtOAc (3 x 10 mL). The combined organics were washed with aqueous Na_2CO_3 solution (10% w/w, 3 x 20 mL), water (3 x 20 mL) and dried over $MgSO_4$. The solvent was then removed under reduced pressure and the residue was recrystallized from CH_2Cl_2/hexanes. White microcrystals, 57% yield, mp 184-185 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.47 (d, J = 7.6 Hz, 1H), 7.38-7.29 (m, 11H), 7.28-7.18 (br s, 1H), 5.00 (s, 2H), 4.41 (d, J = 5.9 Hz, 2H), 4.14 (d, J = 1.3 Hz, 1H), 3.48 (s, 3H), 1.21 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.6, 154.7, 140.0, 128.3, 128.2, 127.7, 127.0, 126.7, 65.3, 46.4, 33.0, 18.0. Anal.

Calcd for $C_{21}H_{24}N_6O_3$: C 61.75; H 5.92; N 20.57. Found: C 61.37; H 5.92; N 20.63.

Benzyl ((*S*)-1-(((*S*)-1-((5-(benzylamino)-1-methyl-1*H*-1,2,4-triazol-3-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)carbamate (7b). A mixture of Cbz-L-Ala-L-Phe-Bt (0.48 g, 1 mmol) and N^5-benzyl-1-methyl-1*H*-1,2,4-triazole-3,5-diamine (0.20 g, 1 mmol) in dry THF (3 mL) was subjected to microwave irradiation (70 °C, 100 W, 30 min). The reaction was quenched with water (2 mL), and extracted with EtOAc (3 x 10 mL). The combined organics were washed with aqueous Na_2CO_3 solution (10% w/w, 3 x 20 mL), water (3 x 20 mL) and dried over $MgSO_4$. The solvent was then removed under reduced pressure and the residue was recrystallized from CH_2Cl_2/hexanes. White microcrystals, 71% yield, mp 107-109 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.27 (br s, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.45-7.14 (m, 16H), 7.07 (br s, 1H), 5.06-4.91 (m, 2H), 4.72-4.51 (m, 1H), 4.42 (d, J = 6.0 Hz, 2H), 4.10-3.94 (m, 1H), 3.50 (s, 3H), 3.09-2.93 (m, 1H), 2.89-2.68 (m, 1H), 1.12 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 169.5, 156.2, 155.3, 152.4, 140.6, 138.1, 137.6, 130.0, 129.0, 128.9, 128.6, 128.4, 127.7, 127.4, 126.9, 66.1, 54.7, 50.7, 47.1, 38.2, 33.7, 18.9. Anal. Calcd for $C_{30}H_{33}N_7O_4$: C 64.85; H 5.99; N 17.65. Found: C 64.55; H 6.04; N 17.55.

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