Microwave Solvent Free Regioselective 1,3 Dipolar Cycloaddition in the Synthesis of 1,4 Substituted [1,2,3]-Triazoles as Amide Bond Isosteres

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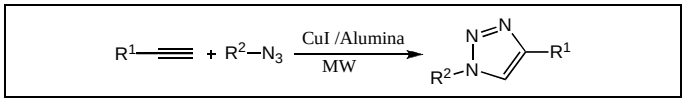

1,3 Dipolar cycloaddition of Fmoc-amino azides and acetylenic amides produces under solvent free irradiation a mixture of 1,4 or 1,5 substituted [1,2,3]-triazoles. The presence of copper (I) iodide, plays a central role on regioselectivity. Four Fmoc-amino azides characterized by different steric hindrance in side chains, and three different terminal alkynes, provided only the 1,4 substituted regioisomer under thermal microwave heating. Good yields, low consumption of organic solvents and short reaction times are the main aspects of our procedure. Reactions are compared to regioselective copper (I) catalysed solution synthesis performed at room temperature.

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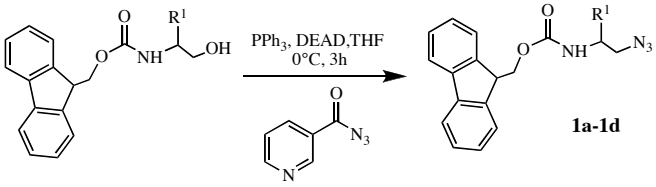
INTRODUCTION

Replacement of the amide moiety by non hydrolysable aromatic scaffolds and/or by isosters that introduce a different orientation of the amino acids side chains is currently an area of great interest in peptide and peptidomimetic chemistry [1]. 1,2,3-Substituted triazoles are characterized by the described properties and can be introduced in the syntheses of a great variety of peptides [2]; in fact, they have been previously used as anti-HIV agents [3], selective β_3 adrenergic receptor agonists [4], as antinflammatory agents [5] and more recently as inhibitors on a recombinant cysteine protease [6]. These scaffolds can be synthesized by linking propiolic acid to a N-terminal amino group, followed by 1,3 dipolar cycloaddiction with an Fmoc amino azide; the removal of the protecting group allows the peptide synthesis to continue [7]. The synthesis of 1,2,3-triazoles has been widely discussed in literature, both in solution and on solid phase or under solvent free conditions [7-8]. Thermal synthesis of 1,2,3-triazoles is described as non-regioselective [9], while the use of catalysts allows one to obtain a single isomer [10]. Copper (I) iodide for example, either in solution or on solid phase syntheses, generate 1,4 substituted triazoles without the formation of the 1,5 isomer. The reaction takes place in mild conditions and very high yields [11]. Since no examples were described in literature for the generation of just one isomer in a heated reaction, in order to reduce reaction times and to confirm the regioselectivity of the reaction, considering the importance of the described heterocyclic moiety in peptide chemistry, our attention has turned to improve the syntheses of these modified residues by new synthetic methodologies [12]. Our interests were mainly directed to the advances in the syntheses of peptidomimetics and particularly to the application of microwave irradiation in the field of peptide chemistry [12-13]. In fact, the application of microwave energy to organic compounds for conducting synthetic reactions at highly accelerated rates has become a well-known technique [14]. This paper describes the one pot regioselective and environmentally friendly synthesis of 1,4 substituted [1,2,3]-triazoles by application of microwave energy under solvent free condition obtained by reaction of four Fmoc-amino azides, characterized by different steric hindrance in side chains, and three different terminal alkynes in presence of copper (I) iodide and basic alumina.

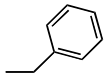
RESULTS AND DISCUSSION

The synthesis of Fmoc-amino azides, compounds **1a-1d**, was conducted through a nicotinoyl azide mediated Mitsunobu reaction, in according to that already described in literature [15], starting from the corresponding Fmoc amino alcohol; reagents and conditions are reported in Scheme I.

Scheme I

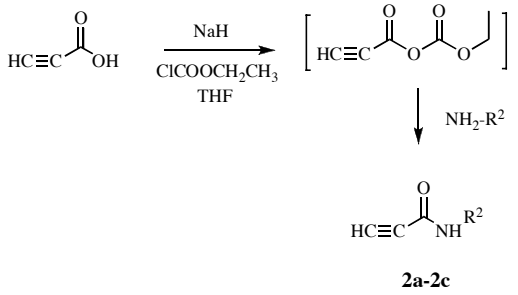


1a-1d

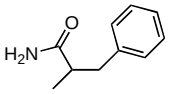
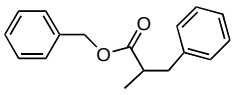
Compound	R^1
1a	H
1b	$-CH_3$
1c	
1d	

The synthesis of the amido alkynes was conducted, on the other hand, by reaction of propiolic acid and the desired amines following, with slight modifications of the mixed anhydride method described by Coppola *et al*. [16] yielding compounds **2a**-**2c**; the described procedure is summarized in Scheme II.

Scheme II

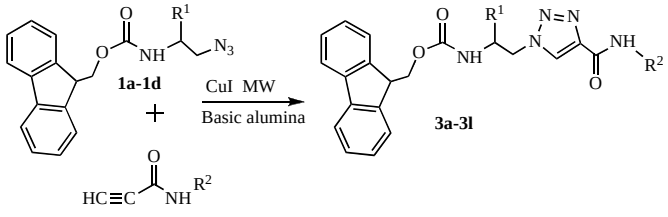


2a-2c

Compound	R^2
2a	
2b	
2c	

All synthesized compounds were obtained as white powders, with exception of compound **2c** that was obtained as yellow oil. The syntheses of 1,2,3-triazoles, summarized in Scheme 3, were performed using a microwave oven (ETHOS 1600, Milestone®) especially designed for organic synthesis. Fmoc amino-azides **1a**-**1d**, acetylenic amides **2a**-**2c**, and copper (I) iodide were mixed with the basic alumina in a 4:1 ratio.

Scheme III



The mixture was mixed for 5 min. The reaction mixture was then transferred into a sealed tube and irradiated by microwave for a total time of 20 min. The desired parameters (microwave power, temperature and time) were set as reported in Table 1. The main advantage of our procedure, in comparison to those already reported in literature [7-10], is that a short time of irradiation provided the final compounds **3a**-**3l** in good yields and overall without the presence of the 1,5 isomer. The copper (I) iodide catalyzed microwave assisted thermal synthesis is regioselective and not dependent on steric effects that, instead, play a central role in the uncatalyzed thermal rection, where the hindrance of substituents in the amino azide side chain can allow the obtaining of both the 1,4- and 1,5-substituted triazoles or completely inhibit the cycloaddition of the 1,5 substituted triazole. If the application of microwave energy was performed for longer time (> 20 min, Table 1) the reagents were not completely transformed in the corresponding 1,2,3-trizoles derivatives due to the decomposition of the starting reagents. In the same way, no further yield increasing was evidenced when the irradiation power was increased from 800W to 1600W (Table 1); this is again related to decomposition of the starting materials.

CONCLUSION

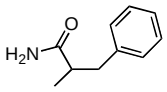
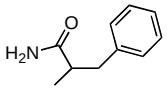
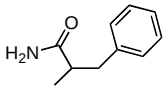
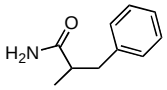
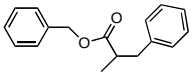
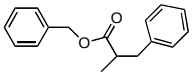
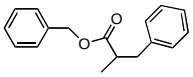
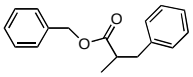
Final results obtained are summarized in Table 1. Interestingly, the best results were obtained with compounds **3i**-**3l** both in solution then under microwave solvent free synthesis; these results should probably be addressed to the terminal alkyne used that resulted in a liquid compound, considering its better distribution in the solid matrix. In conclusion, we have shown that the application of microwave irradiation in the solvent free catalyzed synthesis of 1,4 substituted 1,2,3-triazoles significantly reduces reaction times from 12-16 h to 20 minutes, without influencing significantly the obtained yields, preserving the regioselectivity of the reaction.

Abbreviations and symbols. We have followed the recommendations of the IUPAC-IUB Joint Commission on Biochemical Nomenclature (*Eur. J. Biochem.*, **138**, 9 (1984)). In addition the following abbreviations are used: DEAD, Diethyl azodicarboxylate; PPh_3, Triphenylphosphin.

EXPERIMENTAL

Microwave equipment and conditions. The synthetic steps performed by microwave irradiation were carried out using a microwave oven (ETHOS 1600, Milestone®) especially designed for organic synthesis. The experimental conditions used during microwave application were similar, with the same concentration of starting materials, to those used in solvent catalyzed reaction performed at room temperature. In this latter, anyway, THF was used as solvent and N-ethyldiisopropylamine was used instead of basic alumina. Basic alumina was selected as solid support for the solvent free synthesis because of its basic features, a necessary condition to the cycloaddition; on the other hand, neat reaction was not successful. Microwave reactions were performed in sealed tubes and a microwave program that was composed by appropriate ramping and holding steps was

Table 1

Compd	R^1	R^2	Room temperature		Solvent free microwave irradiation[b]			
			Yield [a] (%)	Time (h)	Solid support	Time (min.)	Temp. (°C)	Yield (%)
3a	-H	$-CH_2C_6H_5$	58	16	Basic alumina	5	60	48
						10	100	
						5	100	
3b	$-CH_3$	$-CH_2C_6H_5$	68	16	Basic alumina	5	60	64
						10	100	
						5	100	
3c	$-CH_2CH(CH_3)_2$	$-CH_2C_6H_5$	62	16	Basic alumina	5	60	71
						10	100	
						5	100	
3d	$-CH_2C_6H_5$	$-CH_2C_6H_5$	34	12	Basic alumina	5	50	30
						10	85	
						5	85	
3e	-H		50	16	Basic alumina	5	60	46
						10	100	
						5	100	
3f	$-CH_3$		57	16	Basic alumina	5	60	68
						10	100	
						5	100	
3g	$-CH_2CH(CH_3)_2$		30	16	Basic alumina	5	60	26
						10	100	
						5	100	
3h	$-CH_2C_6H_5$		42	12	Basic alumina	5	50	38
						10	85	
						5	85	
3i	-H		66	12	Basic alumina	5	50	58
						10	85	
						5	85	
3j	$-CH_3$		50	12	Basic alumina	5	50	55
						10	85	
						5	85	
3k	$-CH_2CH(CH_3)_2$		56	12	Basic alumina	5	50	60
						10	85	
						5	85	
3l	$-CH_2C_6H_5$		61	12	Basic alumina	5	50	60
						10	85	
						5	85	

[a] all the reactions were performed 3 times and the reaction time and yields given are the average values [b] the power used was 800 W

selected. The temperature of the stirred reaction mixture was monitored directly by a microwave-transparent fluoroptic probe inserted into the reaction mixture; irradiation time and power were monitored with the "easyWAVE" software package. Pressure was not monitored because the compounds in the reaction were all solids.

Chemistry. All reactions were followed by thin layer chromatography carried out on Merck silica gel 60 F_{254} plates with fluorescent indicator and the plates were visualized with UV light (254 nm). Preparative chromatographic purifications were performed using silica gel column (Kieselegel 60). Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba model 1106. The structures were verified spectroscopically by proton ^{1}H-NMR and ESI-MS. Spectra were recorded on a Varian Mercury Plus 400 MHZ instrument. Chemical shifts are given as δ with references to Me_4Si. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet). Mass spectra of the final products were performed on LCQ Thermoquest-Ion trap mass spectrometry.

General procedure for the synthesis of 1,2,3-triazoles derivatives under solvent free conditions. Fmoc-amino azide (0.314 mmol), acetylenic amide (1 equiv.) and copper (I) iodide (1 equiv.) were mixed with the neutral alumina in a 4:1 ratio. The mixture was shaken for 5 min. The reaction mixture was then transferred into a sealed vial and irradiated by microwave for 20 min. The desired parameters (microwave power, temperature and time) were set as reported in Table 1. After irradiation the solid was extracted in dichloromethane and purified by silica gel chromatography.

(9*H*-fluoren-9-yl)methyl-2-(4-(benzylcarbamo-yl)-1*H*-1,2,3-triazol-1-yl)ethylcarbamate (3a). White powder, mp 178-180 °C; R_f 0.45 (dichlorometane/methyl alcohol 9.5/0.5); ^{1}H NMR (400 MHz, DMSO-d6): δ 3.43 (t, 2H), 4.15 (t, 1H), 4.22 (d, 2H), 4.45 (d, 2H), 4.52 (t, 2H), 7.25 (m, 8H), 7.35 (t, 2H), 7.42 (s, NH), 7.62 (d, 2H), 7.84 (d, 2H), 8.51 (s, 1H), 8.89 (s, NH); ^{13}C NMR (DMSO-d6): δ 38.0, 43.8, 47.0, 51.6, 67.4, 124.2, 126.8, 127.0, 128.2, 128.4, 128.6, 128.8, 131.9, 141.0, 141.7, 143.1, 143.6, 156.0, 161.1 ms: 468 (MH^+), 490 (M-Na), 507(M-K). *Anal.* Calcd. for $C_{27}H_{25}N_5O_3$: C, 69.36; H, 5.39; N, 14.98; O, 10.27. Found: C, 69.51; H, 5.44; N, 14.94; O, 10.34.

(9*H*-Fluoren-9-yl)methyl-1-(4-(benzylcarbamo-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-ylcarbamate (3b). White powder, mp 228-230 °C; R_f 0.15 (ethyl acetate/hexane 1/1); ^{1}H NMR (400 MHz, DMSO-d6): δ 1.05 (d, 3H), 3.18 (d, 2H), 3.88 (m, 1H), 4.18 (t, 1H), 4.20 (d, 1H), 4.24 (d, 1H), 4.42 (d, 2H), 7.15 (s, NH), 7.25 (m, 8H), 7.42 (t, 1H), 7.58 (d, 2H), 7.84 (d, 2H), 8.48 (s, 1H), 8.88 (s, NH); ^{13}C NMR (DMSO-d6): δ 18.5, 43.1, 43.6, 44.2, 47.0, 60.7, 67.4, 125.6, 126.8, 127.1, 128.0, 128.5, 128.8, 129.2, 131.9, 141.0, 141.7, 143.6, 155.7, 161.1 ms: 482 (MH^+), 504 (M-Na), 520 (M-K). *Anal.* Calcd. for $C_{29}H_{29}N_5O_3$: C, 70.28; H, 5.90; N, 14.13; O, 9.69. Found: C, 70.35; H, 5.98; N, 14.16; O, 9.83.

(9*H*-Fluoren-9-yl)methyl-1-(4-(benzylcarbamo-yl)-1*H*-1,2,3-triazol-1-yl)-4-methylpentan-2-ylcarbamate (3c). White powder, mp 167-169°C; R_f 0.20 (ethyl acetate/hexane 1/1); ^{1}H NMR (400 MHz, DMSO-d6): δ 1.02 (dd, 2H), 1.05 (m, 1H), 1.21 (m, 1H), 1.35 (d, 6H), 4.14 (m, 1H), 4.42 (d, 1H), 4.46 (d, 1H), 4.60 (d, 2H), 4.78 (d, 2H), 7.18 (s, NH), 7.28 (m, 8H), 7.37 (t, 1H), 7.40 (d, 2H), 7.68 (d, 2H), 8.02 (s, 1H), 8.12 (s, NH); ^{13}C NMR (DMSO-d6): δ 23.5, 25.4, 30.9, 40.4, 42.0, 47.0, 48.1, 67.4, 126.8, 127.7, 128.2, 128.4, 128.8, 129.3, 129.7, 131.0, 134.0, 135.7, 141.0, 143.6, 156.0, 169.9 ms: 524 (MH^+), 546 (M-Na), 572 (M-K). *Anal.* Calcd. for $C_{32}H_{35}N_5O_3$: C, 71.49; H, 6.56; N, 13.03; O, 8.93. Found: C, 71.63; H, 6.71; N, 13.07; O, 8.99.

(9*H*-Fluoren-9-yl)methyl-1-(4-(benzylcarbamo-yl)-1*H*-1,2,3-triazol-1-yl)-3-phenylpropan-2-ylcarbamate (3d). White powder, mp 235-237 °C; R_f 0.43 (ethyl acetate/ hexane 6/4); ^{1}H NMR (400 MHz, DMSO-d6): δ 2.85 (d, 1H), 2.88 (d, 1H), 3.15 (d, 1H), 3.18 (d, 1H), 3.78 (m, 1H), 4.22 (t, 1H), 4.62 (d, 2H), 5.09 (d, 2H), 7.02 (s, NH), 7.28 (m, 12H), 7.47 (t, 2H), 7.61 (d, 2H), 7.83 (d, 2H), 8.47 (s, 1H), 8.75 (s, NH); ^{13}C NMR (DMSO-d6): δ 35.8, 40.4, 41.3, 47.0, 47.4, 67.4, 125.6, 126.8, 127.7, 127.9, 128.2, 128.4, 128.6, 128.8, 129.3, 129.8, 131.0, 134.0, 135.7, 140.4, 141.0, 143.6, 156.0, 169.9 ms: 558 (MH^+), 580 (M-Na), 596 (M-K). *Anal.* Calcd. for $C_{34}H_{31}N_5O_3$: C, 73.23; H, 5.60; N, 12.56; O, 8.61. Found: C, 73.34; H, 5.73; N, 12.65; O, 8.72.

(9*H*-Fluoren-9-yl)methyl-2-(4-(1-carbamoyl-2-phenyl-ethyl-carbamoyl)-1*H*-1,2,3-triazol-1-yl)ethyl-carbamate (3e). White powder, mp 242-244 °C; R_f 0.71 (dichlorometane/methyl alcohol 9.5/0.5); ^{1}H NMR (400 MHz, DMSO-d6): δ 3.02 (d,1H), 3.08 (d, 1H), 3.42 (d, 2H), 4.18 (t, 1H), 4.23 (d, 2H), 4.43 (t, 2H), 4.65 (q, 1H), 7,29 (m, 10H), 7.38 (t, 2H), 7.52 (t, 1H), 7.58 (s NH_2), 7.83 (d, 2H), 8.45 (s, 1H); ^{13}C NMR (DMSO-d6): δ 37.3, 38.0, 47.0, 51.6, 55.5, 67.4, 126.0, 126.8, 127.8, 128.2, 128.4, 128.8, 129.0, 131.9, 139.5, 141.0, 143.1, 143.6, 156.0, 160.8, 177.4 ms: 525 (MH^+), 547 (M-Na), 563(M-K). *Anal.* Calcd. for $C_{29}H_{28}N_6O_4$: C, 66.40; H, 5.38; N, 16.02; O, 12.20. Found: C, 66.51; H, 5.43; N, 16.12; O, 12.28.

(9*H*-Fluoren-9-yl)methyl-1-(4-(1-carbamoyl-2-phenyl-ethyl-carbamoyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl-carbamate (3f). White powder, mp 137-139 °C; R_f 0.23 (ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d6): δ 1.02 (d, 3H), 2.64 (d, 1H), 2.68 (d, 1H), 2.82 (m, 1H), 2.84 (d, 1H), 2.88 (d, 1H), 3.82 (t, 1H), 4.15 (q, 1H), 5.73 (d, 2H), 7.12 (s, NH_2), 7.16 (d, 2H), 7.18 (d, 2H), 7.22 (t, 1H), 7.28 (m, 8H), 7.32 (s, NH), 8.21 (s, 1H), 8.88 (s, NH); ^{13}C NMR (DMSO-d6): δ 17.8, 31.3, 37.3, 42.4, 47.0, 53.5, 55.5, 55.7, 67.4, 126.0, 126.8, 127.8, 128.2, 128.4, 128.7, 128.8, 131.9, 139.5, 141.0, 143.1, 143.6, 155.7, 160.8, 177.4 ms: 581 (MH^+), 603 (M-Na), 619 (M-K). *Anal.* Calcd. for $C_{33}H_{36}N_6O_4$:C, 68.26; H, 6.25; N, 14.47; O, 11.02 Found: C, 68.44; H, 6.13; N, 14.88; O,11.32.

(9*H*-Fluoren-9-yl)methyl-1-(4-(1-carbamoyl-2-phenyl-ethyl-carbamoyl)-1*H*-1,2,3-triazol-1-yl)propan-2-yl-carbamate (3g). White powder, mp 154-156 °C; R_f 0.26 (ethyl acetate/ hexane 9/1); ^{1}H NMR (400 MHz, DMSO-d6): δ 0.80 (d, 3H), 0.84 (d, 3H), 1.18 (dd, 2H), 1.38 (m, 1H), 3.15 (d, 1H), 3.18 (d, 1H), 3.62 (m, 1H), 4.16 (d, 1H), 4.18 (d, 1H), 4.24 (d, 1H), 4.76 (q, 1H), 5.09 (d, 2H), 7.04 (s, NH), 7.26 (m, 8H), 7.47 (t, 2H), 7.62 (d, 2H), 7.82 (d, 2H), 8.04 (s, NH), 8.45 (s, 1H); ^{13}C NMR (DMSO-d6): δ 18.5, 37.3, 43.2, 47.0, 55.5, 60.7, 67.4, 126.0, 126.8, 127.8, 128.2, 128.4, 128.7, 128.8, 131.9, 139.5, 141.0, 143.1, 143.6, 155.7, 160.8, 177.4 ms: 538 (MH^+), 560 (M-Na), 576 (M-K). *Anal.* Calcd. for $C_{30}H_{30}N_6O_4$: C, 66.90; H, 5.61; N, 15.60; O, 11.88. Found: C, 66.78; H, 5.73; N, 15.32; O, 11.57.

(9*H*-Fluoren-9-yl)methyl-1-(4-(1-carbamoyl-2-phenyl-ethyl-carbamoyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-propan-2-ylcarbamate (3h). White powder, mp 212-214 °C; R_f 0.35 (chloroform/ethyl alcohol 9,5/0,5); ^{1}H NMR (400 MHz, DMSO-d6): δ 2.64 (d,1H), 2.68 (d, 1H), 2.84 (d, 1H), 2.88 (d, 1H), 3.01 (m, 1H), 3.16 (d, 1H), 3.21 (d, 1H), 3.82 (d, 1H), 3.86 (d, 1H), 4.42 (t, 1H), 4.48 (q, 1H), 5.02 (d, 2H), 7.02 (s, NH_2), 7.26 (m, 14H), 7.47 (t, 2H), 7.82 (d, 2H), 8.04 (s, NH), 8.45 (s, 1H); ^{13}C NMR (DMSO-d6): δ 37.3, 40.6, 47.0, 48.8, 55.5, 58.1, 67.4, 126.1, 126.2, 126.8, 127.8, 127.9, 128.2, 128.4, 128.7, 128.8, 130.1, 131.9, 138.1, 139.5, 141.0, 143.1, 143.6, 155.7, 160.8, 177.4 ms: 615 (MH^+), 637 (M-Na), 653 (M-K). *Anal.* Calcd. for $C_{36}H_{34}N_6O_4$: C, 70.34; H, 5.58; N, 13.67; O, 10.41 Found: C, 70.56; H, 5.73; N, 13.46; O, 10.51.

(9*H*-Fluoren-9-yl)methyl-2-(4-(benzyl-2-carbamoyl-3-phenyl-propanoate)-1*H*-1,2,3-triazol-1-yl)ethyl-carbamate (3i). White powder, mp 173-175 °C; R_f 0.41 (ethyl acetate/ hexane 6/4); ^{1}H NMR (400 MHz, DMSO-d6): δ 3.16 (t, 2H), 3.42 (d, 1H), 3.46 (d, 1H), 4.22 (t, 1H), 4.26 (t, 2H), 4.42 (d, 2H), 4.74 (q, 1H), 5.18 (d, 2H), 7.28 (m, 12H), 7.42 (t, 2H), 7.46 (s, NH), 7.62 (d, 2H), 7.82 (d, 2H), 8.64 (s, 1H), 8.77(s, NH); ^{13}C NMR (DMSO-d6): δ 37.0, 38.0, 47.0, 51.6, 53.1, 67.4, 68.5, 126.0, 126.8, 127.2, 127.7, 127.8, 128.2, 128.4, 128.7, 128.8, 129.0, 131.9, 139.5, 141.0, 141.2, 143.1, 143.6, 156.0, 160.8, 171.6 ms: 616 (MH^+), 638 (M-Na), 654 (M-K). *Anal.* Calcd. for $C_{36}H_{33}N_5O_5$: C, 70.23; H, 5.40; N, 11.38; O, 12.99 Found: C, 70.46; H, 5.68; N, 11.23; O, 13.12.

(9*H*-Fluoren-9-yl)methyl-1-(4-(benzyl-2-carbamoyl-3-phenyl-propanoate)-1*H*-1,2,3-triazol-1-yl)propan-2-yl-carbamate (3j). White powder, mp 182-184 °C; R_f 0.29 (ethyl acetate/hexane 1/1); ^{1}H NMR (400 MHz, DMSO-d6): δ 1.02 (d, 3H), 3.18 (d, 2H), 3.88 (t, 1H), 4.18 (d.1H), 4.22 (d,1H), 4.28 (m, 1H), 4.38 (d, 1H), 4.42 (d, 1H), 4.75 (q, 1H), 5.15 (d, 2H), 7.24, (s, NH), 7.28 (m, 12H), 7.58 (t, 2H), 7.62 (d, 2H), 7.84 (d, 2H), 8.44 (s, 1H), 8.78 (s, NH); ^{13}C NMR (DMSO-d6): δ 18.5, 37.0, 43.2, 47.0, 53.1, 60.7, 67.4, 68.5, 126.0, 126.8, 127.2, 127.7, 127.8, 128.2, 128.4, 128.8, 129.0, 131.9, 139.5, 141.0, 141.2, 143.1, 143.6, 155.7, 160.8, 171.9 ms: 630 (MH^+), 652 (M-Na), 668 (M-K). *Anal.* Calcd. for $C_{37}H_{35}N_5O_5$: C, 70.57; H, 5.60; N, 11.12; O, 12.70 Found: C, 70.56; H, 5.49; N, 11.24; O, 12.42.

(9*H*-Fluoren-9-yl)methyl-4-methyl-1-(4-(benzyl-2-carbamoyl-3-phenylpropanoate)-1*H*-1,2,3-triazol-1-yl)pentan-2-ylcarbamate (3k). White powder, mp 179-181°C; R_f 0.52 (ethyl acetate/hexane 1/1); ^{1}H NMR (400 MHz, DMSO-d6): δ 0.79 (d, 3H), 0.82 (d, 3H), 1.19 (dd, 2H), 1.27 (m, 1H), 3.15 (d, 2H), 4.15 (d, 1H), 4.22 (d, 1H), 4.24 (t, 1H), 4.25 (d, 1H), 4.27 (d, 1H), 4.32 (dd, 1H), 4.75 (q, 1H), 5.09 (d, 2H), 7.28 (m, 12H), 7.60 (t, 2H), 7.64 (d, 2H), 7.82 (d, 2H), 8.20 (s, NH), 8.42 (s, 1H), 8.70 (s, NH); ^{13}C NMR (DMSO-d6): δ 22.8, 23.2, 37.2, 42.4, 43.9, 47.0, 53.1, 58.8, 67.4, 68.5, 126.0, 126.8, 127.2, 127.7, 127.8, 128.2, 128.4, 128.7, 128.8, 129.0, 131.9, 139.5, 141.0, 141.2, 143.1, 143.6, 155.7, 160.8, 171.6 ms: 672 (MH^+), 694 (M-Na), 710 (M-K). *Anal*. Calcd. for $C_{40}H_{41}N_5O_5$: C, 71.52; H, 6.15; N, 10.43; O, 11.91 Found: C, 71.56; H, 6.22; N, 10.25; O, 13.36.

(9*H*-Fluoren-9-yl)methyl-3-phenyl-1-(4-(benzyl-2-carbamoyl-3-phenylpropanoate)-1*H*-1,2,3-triazol-1-yl)propan-2-ylcarbamate (3l). White powder, mp 199-201 °C; R_f 0.44 (ethyl acetate/hexane 6/4); ^{1}H NMR (400 MHz, DMSO-d6): δ 2.85 (d, 1H), 2.88 (d, 1H), 3.07 (d, 1H), 3.10 (d, 1H), 3.15 (d, 1H), 3.18 (d, 1H), 3.22 (m, 1H), 4.22 (t, 1H), 4.75 (q, 1H), 4.87 (s, 2H), 5.02 (d, 2H), 7.04 (s, NH), 7.22 (t, 2H), 7.26 (d, 2H), 7.31 (m, 12H), 7.37 (t, 1H), 7.47 (t, 2H), 7.62 (d, 2H), 7.84 (d, 2H), 8.44 (s, 1H), 8.53 (s, NH); ^{13}C NMR (DMSO-d6): δ 37.0, 40.6, 47.0, 48.8, 53.1, 58.1, 67.4, 68.5, 126.0, 126.1, 126.8, 127.2, 127.7, 127.8, 128.2, 128.3, 128.4, 128.7, 128.8, 128.9, 129.0, 131.9, 138.1, 139.5, 141.0, 141.2, 143.1, 143.6, 155.7, 160.8, 171.6 ms: 706 (MH^+), 728 (M-Na), 744 (M-K). *Anal*. Calcd. for $C_{43}H_{39}N_5O_5$: C, 73.17; H, 5.57; N, 9.92; O, 11.33 Found: C, 73.06; H, 5.23; N, 9.60; O, 11.47.

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