1,3-Cycloaddition synthesis of 1,2,3-triazole conjugates of betulonic acid with peptides*

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1,2,3-Triazole conjugates of betulonic acid with peptides were synthesized by 1,3-dipolar cycloaddition of azido peptides to *N*-(3-oxolup-20(29)-en-28-oyl)-4-ethynylaniline.

Key words: triterpenoids, betulonic acid, arylacetylenes, azides, peptides, 1,3-dipolar cycloaddition, 1,2,3-triazoles.

The most important trend of modern medicinal chemistry is the modification of metabolites isolated from various plants,[1] molecules of which bear two or more structural fragments of different type.[2] Synthetic transformations of metabolites into bioconjugates with various structural moieties are of growing interest.[3,4]

Efficiency of this approach was demonstrated on the example of triterpenoids by the introduction of 1,2,3-triazole moieties in their structures. Among previously synthesized 1,2,3-triazole derivatives of betulonic acid amides,[5] bioconjugates exhibiting strong anti-inflammatory and antioxidant properties were found. It is known[6,7] that the 1,2,3-triazole fragment is bioisosteric to the amide bond; this fact should be considered in the design of the bioconjugates.

In the present work, we described the synthesis of a new series of triterpene derivatives bearing fragments of 1,2,3-triazole-substituted peptides (Scheme 1). Synthetic strategy was based on the click chemistry concept. One of most popular reaction within the click chemistry is the Cu^{I} catalyzed 1,3-dipolar cycloaddition of azides to alkynes. The azide—alkyne assembling is very effective for combining different building blocks, including biologically active structural synthons. This reaction is simple and provides high yields, regio- and stereoselectivity, provides high atom economy, simple product isolation and can be performed under physiological conditions.[8—10]

The starting terminal acetylene **1** was synthesized earlier.[11] Peptides **2a—f** with azido group were prepared by the Ugi reaction (Scheme 2).

The Ugi four-component condensation[12—14] on the base of isonitriles is a versatile procedure towards the structural amino acid fragments, peptides and peptidomimetics.[15—20] Peptide analogs bearing azido moieties were prepared by the Ugi condensation using protected amino acids and chiral azido isonitriles[21] as the acid and isonitrile components, respectively.

The structures of the compounds synthesized were established on the base of analytical and spectral data (Table 1). The structures of amides of betulonic acid **3a—f** with 1,4-disubstututed 1,2,3-triazole fragments were confirmed experimentally by stereospecific formation of only 4-isomers (not 5-) of 1,2,3-triazolopeptides in the reaction of azides with terminal alkynes in the presence of Cu^{I}.[8] Moreover, data obtained by us previously[5] also unambiguously confirm selective formation of only 4-substituted 1,2,3-triazoles in the reactions of alkyl and aryl azides with terminal alkynes of the series of betulonic acid amides in the presence of CuCl.

A feature of the synthesized conjugates is the formation of stable hydrates, which was confirmed by elemental analysis. Earlier,[22] the similar property, namely, the formation of stable hydrates by hydrogen bonding between the nitrogen atoms and the oxygen atoms of the water molecules. Thus, according to the microanalysis data, compound **3d** is monohydrate (see Table 1), while for the sample dried *in vacuo* (2 Torr, 80 °C) over KOH

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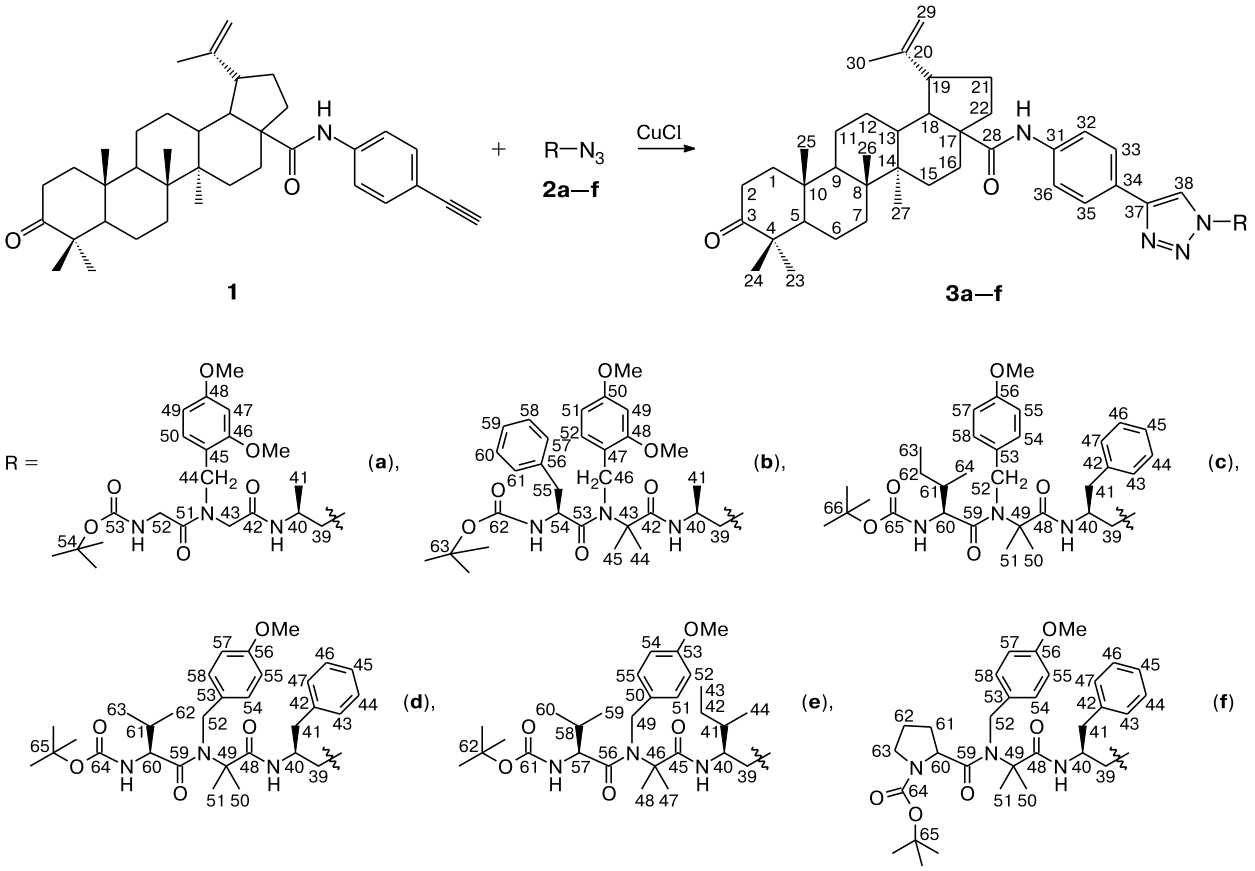
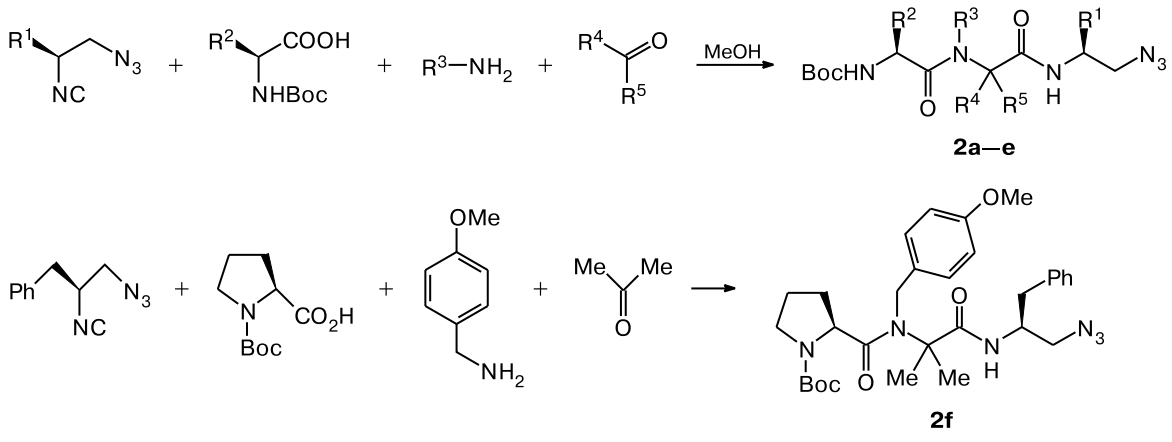
Scheme 1



Scheme 2



2	R^1	R^2	R^3	R^4	R^5	**2**	R^1	R^2	R^3	R^4	R^5
a	Me	H	DMB	H	H	**d**	Bn	Pr^i	PMB	Me	Me
b	Me	Bn	DMB	Me	Me	**e**	But-2(*R*)-yl	Pr^i	PMB	Me	Me
c	Bn	But-2(*R*)-yl	PMB	Me	Me						

DMB — 2,4-dimethoxybenzyl, PMB — 4-methoxybenzyl

Table 1. Yields, melting points, elemental analysis data and IR spectra of triazole derivatives of betulonic acid **3a—f**

Compound	Yield (%)	M.p./°C	Found / Calculated (%)			Molecular formula	IR-spectra ($CHCl_3$), ν/cm^{-1}
			C	H	N		
3a	46	125—127	68.80	8.27	8.63	$C_{59}H_{83}N_7O_8 \cdot H_2O$	1701 (C=O),
			68.38	8.27	9.46		3438 (NH)
3b	45	115—117	69.86	8.16	7.90	$C_{68}H_{93}N_7O_8 \cdot 2H_2O$	1710 (C=O),
			69.65	8.34	8.36		3434 (NH)*
3c	49	140—143	72.00	8.33	8.14	$C_{70}H_{97}N_7O_7 \cdot H_2O$	1708 (C=O),
			72.07	8.55	8.40		3439 (NH)*
3d	48	138—140	71.92	8.69	7.96	$C_{69}H_{95}N_7O_7 \cdot H_2O$	1701 (C=O),
			71.90	8.48	8.51		3440 (NH)
			72.91	8.48	8.36	$C_{69}H_{95}N_7O_7$	
			73.05	8.44	8.64		
3e	57	133—135	70.86	8.85	8.77	$C_{66}H_{97}N_7O_7 \cdot H_2O$	1706 (C=O),
			70.87	8.92	8.23		3438 (NH)
3f	46	139—141	70.79	8.05	7.95	$C_{69}H_{93}N_7O_7 \cdot 2H_2O$	1672 (C=O),
			70.92	8.37	8.39		3442 (NH)

* In KBr pellets.

the elemental analysis data confirm the loss of the water molecule.

In summary, in the present work, the versatile synthetic procedure towards novel betulonic acid derivatives bearing 1,2,3-triazolylpeptide fragments were developed. The compounds synthesized currently tested for pharmacological activity.

Experimental

Melting points were determined on a Kofler apparatus. IR spectra were recorded on a Vector 22 spectrometer in the KBr pellets or in the $CHCl_3$ solutions. High resolution mass spectra (70 eV) were run on a DFS instrument (Thermo Electron Corporation). Elemental analyses were carried out on a CHN-analyzer (model 1106, Carlo Erba, Italy). NMR spectra were run on a Bruker AV-400 spectrometer (400.13 (^{1}H) and 100.61 MHz (^{13}C)) in $CDCl_3$. Chemical shifts are given in the δ scale relative to the solvent residual signal (δ_H 7.24 and δ_C 76.90). In the ^{13}C NMR spectra, signal multiplicities were determined using *J*-modulations of spin echoes (JMOD). Signals of the polycyclic framework in the ^{1}H and ^{13}C NMR spectra of compounds **3a—f** were assigned by the comparison with the corresponding signals of betulonic acid as the reference compound.[23] Only characteristic signals of the compounds in the ^{1}H NMR are given due to difficulties in attributing of all signals. The main part of the signals of the triterpenoid framework resonate in the region of δ 2.7—0.8.

Silica gel Kieselgel 60 (70—230 mesh) were used for the column chromatography.

(1-*tert*-Butoxycarbonyl-L-prolyl)-N^1-[(2*S*)-1-azido-3-phenylprop-2-yl]-N^2-(4-methoxybenzyl)-2-methylalanineamide (2f). To a solution of acetone (0.058 g, 1 mmol) and 4-methoxybenzylamine (0.137 g, 1 mmol) in MeOH (5 mL), *N*-Boc-L-proline (0.216 g, 1 mmol) and 1-((*S*)-3-azido-2-isocyanopropyl)benzene (0.172 g, 1 mmol) were added. The solution was kept at ambient temperature for 24 h. The solvent was removed *in vacuo*, column chromatography of the residue (elution with hexane—ethyl acetate, 2 : 1) afforded the mixture of rotamers (3 : 1) in a yield of 0.35 g (61%), white solid, m.p. 77—78 °C, $[\alpha]_D^{25}$ −16.9 (*c* 1.0, MeOH). ^{1}H NMR, δ: 1.42, 1.47 (s, 9 H, Boc); 1.49 (s, 3 H, H(50)); 1.52 (s, 3 H, H(51)); 1.70—1.78 (m, 1 H, H(62)); 1.86—1.97 (m, 2 H, H(61), H(62)); 2.01—2.10 (m, 1 H, H(61)); 2.69—2.75, 2.82—2.87 (m, 1 H, H(41)); 2.99—3.09 (m, 1 H, H(41)); 3.28—3.45 (m, 3 H, H(63), H(39)); 3.51—3.60 (m, 1 H, H(39)); 3.83 (s, 3 H, OMe); 4.16—4.24, 4.26—4.34 (m, 1 H, H(60)); 4.37—4.45 (m, 1 H, H(40)); 4.59 (d, 1 H, H(52), $J_{AA'}$ = = 18.2 Hz); 4.70, 4.95 (d, 1 H, H(52), $J_{AA'}$ = 18.2 Hz); 5.75, 6.30 (d, 1 H, NH, *J* = 8.2 Hz); 6.93—6.97 (m, 2 H, H(55), H(57)); 7.19—7.33 (m, 5 H, H(43)—H(47)); 7.38—7.44 (m, 2 H, H(54), H(58)). ^{13}C NMR, δ: 24.02 (C(50)); 24.40 (C(51)); 24.50 (C(62)); 28.55 (3 CH_3, Boc); 30.42 (C(61)); 37.60 (C(41)); 47.29 (C(52)); 47.58 (C(63)); 51.03 (C(40)); 52.39 (C(39)); 55.27 (OMe); 57.30 (C(60)); 63.54 (C(49)); 79.50 (C(65)); 114.18, 114.31, 126.40, 127.27, 127.41, 128.45, 128.59, 129.29, 129.38, 130.78, 137.82 (C(42)—C(47), C(53)—C(55), C(57), C(58)); 154.65 (C(64)); 158.85 (C(56)); 174.34 (C(59)); 174.59, 174.64 (C(48)). Found (%): C, 64.21; H, 7.54; N, 14.33. $C_{31}H_{42}N_6O_5$. Calculated (%): C, 64.34; H, 7.32; N, 14.52.

Reaction of compound 1 with azides 2a—f (general procedure). A mixture of acetylene **1** (0.17 mmol), azide **2a—f** (0.17 mmol), CuCl (2 mg) in butan-1-ol (3—4 mL) was stirred at 110—115 °C for 4—9 h. After completion of the reaction, the mixture was diluted with toluene (10 mL) and washed with aqueous ammonia. The organic layer was dried with Na_2SO_4, filtered through the SiO_2 pad (1×1.5 cm). The solvent was removed *in vacuo*, the residue was triturated with hexane. The precipitate that formed was filtered off to give compounds **3a—f**.

(*N*-*tert*-Butoxycarbonylglycyl)-N^2-(2,4-dimethoxybenzyl)-N^1-((1*S*)-2-{4-[4-(3,28-dioxolup-20(29)-en-28-ylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}-1-methylethyl)glycineamide (3a). ^{1}H NMR, δ: 0.85—1.03 (m, 18 H, C(23)H_3—C(27)H_3, C(41)H_3); 1.42 (s, 9 H, Boc); 1.68 (s, 3 H, C(30)H_3); 3.17 (m, 1 H, H(19)); 3.75 (s, 6 H,

2 OMe); 4.07—4.48 (m, 9 H, 2 H(39), H(40), 2 H(43), 2 H(44), 2 H(52)); 4.59, 4.74 (both s, 1 H each, H(29)); 5.50—5.52 (m, 1 H, NH); 6.30 (d, 1 H, NH, J = 7.5 Hz); 6.37—6.39 (m, 2 H, H(47), H(49)); 6.97 (d, 1 H, H(50), J = 8.3 Hz); 7.33 (br.s, 1 H, NH); 7.54 (d, 2 H, H(32), H(36), J = 8.5 Hz); 7.81 (d, 2 H, H(33), H(35), J = 8.5 Hz); 7.87 (s, 1 H, H(38)). ^{13}C NMR, δ: 14.14 (C(27)); 16.40 (C(26)); 16.65 (C(25)); 19.24 (C(6)); 19.56 (C(30)); 20.89 (C(24)); 22.66 (C(11)); 25.48 (C(12)); 27.08 (C(23)); 28.41 (3 CH_3, Boc); 29.84 (C(21)); 30.47 (C(15)); 33.70 (C(16)); 34.03 (C(7)); 34.48 (C(2)); 36.95 (C(22)); 37.79 (C(13)); 38.19 (C(10)); 40.72 (C(1)); 41.65 (C(8)); 42.30 (C(14)); 17.54, 42.69, 43.74, 45.33, 53.53 (C(41), C(40), C(52), C(44), C(43)); 46.61 (C(19)); 47.72 (C(4)); 50.37 (C(18)); 50.74 (C(9)); 55.37 (C(5)); 55.45 (2 OMe); 56.54 (C(17)); 62.04, 79.65, 98.89, 104.13, 115.13 (C(39), C(54), C(47), C(49), C(45)); 109.57 (C(29)); 120.19 (C(32), C(36)); 120.60 (C(38)); 126.31 (C(33), C(35), C(50)); 130.66 (C(34)); 138.22 (C(31)); 147.39 (C(37)); 150.73 (C(20)); 156.09, 158.62, 161.30, 168.58, 170.35 (C(46), C(48), C(53), C(51), C(42)); 176.97 (C(28)); 218.20 (C(3)).

(*N*-*tert*-Butoxycarbonyl-L-phenylalanyl)-N^2-(2,4-dimethoxybenzyl)-N^1-((1*S*)-2-{4-[4-(3,28-dioxolup-20(29)-en-28-ylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}-1-methylethyl)-2-methylalanineamide (3b). ^{1}H NMR, δ: 0.91—1.03 (m, 15 H, C(23)H_3—C(27)H_3); 1.35 (s, 15 H, Boc, C(44)H_3, C(45)H_3); 1.68 (s, 3 H, C(30)H_3); 3.13—3.17 (m, 1 H, H(19)); 3.76 (s, 6 H, 2 OMe); 4.08—4.61 (m, 8 H, H(29), 2 H(39), H(40), H(54), H(46), 2 H(55)); 4.76 (s, 1 H, H(29)); 5.11 (d, 1 H, NH, J = 9.9 Hz); 5.82 (d, 1 H, NH, J = 8.5 Hz); 6.40—6.43 (m, 2 H, H(49), H(51)); 7.04—7.09 (m, 2 H, H(52), NH); 7.23—7.24 (m, 4 H, H(57), H(58), H(60), H(61)); 7.30—7.32 (m, 1 H, H(59)); 7.56 (d, 2 H, H(32), H(36), J = 8.5 Hz); 7.82 (d, 2 H, H(33), H(35), J = 8.5 Hz); 8.18 (s, 1 H, H(38)). ^{13}C NMR, δ: 13.66, 17.42 (C(41), C(44), C(45)); 14.64 (C(27)); 15.85 (C(26)); 16.51 (C(25)); 19.16 (C(30)); 19.43 (C(6)); 20.77 (C(24)); 23.46 (C(11)); 25.32 (C(12)); 26.94 (C(23)); 28.15 (3 CH_3, Boc); 29.70 (C(21)); 30.41 (C(15)); 30.69 (C(16)); 33.93 (C(7)); 34.33 (C(2)); 36.55 (C(22)); 37.66 (C(13)); 38.07 (C(10)); 39.90 (C(1)); 41.51 (C(8)); 42.55 (C(14)); 46.48 (C(19)); 48.34 (C(4)); 50.23 (C(18)); 50.58 (C(9)); 43.60, 45.78, 52.93, 53.55 (C(46), C(40), C(55), C(54)); 55.14 (C(5)); 55.22 (2 OMe); 56.46 (C(17)); 62.71, 65.30, 79.53, 98.43, 104.12, 118.04 (C(43), C(39), C(63), C(49), C(51), C(47)); 109.42 (C(29)); 120.09 (C(32), C(36)); 121.02 (C(38)); 126.09 (C(33), C(35)); 126.39 (C(34)); 126.72, 128.34, 129.49, 136.45 (C(59), C(58), C(60), C(57), C(61), C(56)); 137.95 (C(31)); 147.04 (C(37)); 150.59 (C(20)); 154.70, 156.94, 160.10, 172.99, 174.25 (C(62), C(48), C(50), C(53), C(42)); 176.84 (C(28)); 217.71 (C(3)).

(*N*-*tert*-Butoxycarbonyl-L-isoleucyl)-N^1-((2*S*)-1-{4-[4-(3,28-dioxolup-20(29)-en-28-ylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}-3-phenylprop-2-yl)-N^2-(4-methoxybenzyl)-2-methylalanineamide (3c). ^{1}H NMR, δ: 0.90—1.03 (m, 27 H, C(23)H_3—C(27)H_3, C(50)H_3, C(51)H_3, C(63)H_3, C(64)H_3); 1.38 (s, 9 H, Boc); 1.68 (s, 3 H, C(30)H_3); 3.16—3.19 (m, 1 H, H(19)); 3.76 (s, 3 H, OMe); 4.48—4.59 (m, 6 H, H(29), H(39), 2 H(52), H(60), H(40)); 4.74 (s, 1 H, H(29)); 4.98 (d, 1 H, NH, J = 9.2 Hz); 5.89 (d, 1 H, NH, J = 7.0 Hz); 6.85 (d, 2 H, H(55), H(57), J = 8.4 Hz); 7.20—7.32 (m, 7 H, H(43)—H(47), H(54), H(58)); 7.54 (d, 2 H, H(32), H(36), J = 8.6 Hz); 7.78 (d, 2 H, H(33), H(35), J = 8.6 Hz); 8.07 (s, 1 H, H(38)). ^{13}C NMR, δ: 11.08, 15.52, 23.97 (C(63), C(64), C(50), C(51)); 13.62 (C(27)); 14.45 (C(26)); 14.65 (C(25)); 19.15 (C(6)); 19.38 (C(30)); 23.71 (C(24)); 23.71 (C(11)); 25.49 (C(12)); 26.43 (C(23)); 28.16 (3 CH_3, Boc); 29.47 (C(21)); 30.41 (C(15)); 30.66, 38.32 (C(62), C(61)); 33.56 (C(16)); 33.77 (C(7)); 34.05 (C(2)); 37.11 (C(22)); 37.53 (C(13)); 38.05 (C(10)); 39.53 (C(1)); 40.58 (C(8)); 42.50 (C(14)); 46.36 (C(19)); 47.24 (C(4)); 49.90 (C(18)); 50.08 (C(9)); 46.81, 48.33, 50.87, 54.91 (C(42), C(52), C(40), C(60)); 55.15 (OMe); 55.47 (C(5)); 56.46 (C(17)); 62.73, 65.30, 79.50, 114.09 (C(49), C(39), C(66), C(55), C(57)); 109.50 (C(29)); 120.11 (C(32), C(36)); 121.33 (C(38)); 126.09 (C(33), C(35)); 126.29 (C(34)); 126.86, 127.53, 128.66, 129.21, 129.83, 136.74 (C(45), C(43), C(47), C(54), C(58), C(46), C(48), C(53), C(42)); 137.99 (C(31)); 147.01 (C(37)); 150.51 (C(20)); 155.29, 158.81, 173.42, 174.31 (C(65), C(56), C(59), C(48)); 176.83 (C(28)); 218.08 (C(3)).

(*N*-*tert*-Butoxycarbonyl-L-valyl)-N^1-((2*S*)-1-{4-[4-(3,28-dioxolup-20(29)-en-28-ylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}-3-phenylprop-2-yl)-N^2-(4-methoxybenzyl)-2-methylalanineamide (3d). ^{1}H NMR, δ: 0.90 (s, 3 H, C(25)H_3); 0.96 (s, 3 H, C(24)H_3); 0.98 (s, 6 H, C(26)H_3, C(27)H_3); 1.03 (s, 3 H, C(23)H_3); 1.38 (s, 9 H, Boc); 1.68 (s, 3 H, C(30)H_3); 3.17 (dt, 1 H, H(19), J_1 = 4.0 Hz, J_2 = 11.0 Hz); 3.76 (s, 3 H, OMe); 4.31—4.35 (m, 1 H, H(39)); 4.47—4.56 (m, 3 H, H(39), H(40), H(60)); 4.59 (br.s, 3 H, H(29), 2 H(52)); 4.74 (s, 1 H, H(29)); 5.03 (d, 1 H, NH, J = 9.7 Hz); 5.88 (d, 1 H, NH, J = 6.8 Hz); 6.85 (d, 2 H, H(55), H(57), J = 8.3 Hz); 7.22—7.33 (m, 7 H, H(43)—H(47), H(54), H(58)); 7.54 (d, 2 H, H(32), H(36), J = 8.6 Hz); 7.78 (d, 2 H, H(33), H(35), J = 8.6 Hz); 8.08 (s, 1 H, H(38)). ^{13}C NMR, δ: 14.46 (C(27)); 15.82 (C(26)); 15.88 (C(25)); 17.11, 23.68 (C(62), C(63), C(50), C(51)); 19.39 (C(30)); 19.49 (C(6)); 20.91 (C(24)); 21.32 (C(11)); 25.48 (C(12)); 26.43 (C(23)); 28.17 (3 CH_3, Boc); 29.47 (C(21)); 30.66 (C(15)); 33.56 (C(16)); 33.77 (C(7)); 34.05 (C(2)); 31.86, 36.81 (C(41), C(61)); 37.11 (C(22)); 37.53 (C(13)); 38.05 (C(10)); 39.53 (C(1)); 40.58 (C(8)); 42.50 (C(14)); 46.36 (C(19)); 47.24 (C(4)); 49.90 (C(18)); 50.08 (C(9)); 46.78, 50.80, 51.26 (C(52), C(40), C(49)); 54.92 (C(5)); 55.15 (OMe); 56.46 (C(17)); 56.06, 62.72, 79.50, 114.13 (C(60), C(39), C(65), C(55), C(57)); 109.50 (C(29)); 120.11 (C(32), C(36)); 121.33 (C(38)); 126.09 (C(33), C(35)); 126.29 (C(34)); 126.86, 127.53, 128.66, 129.21, 129.67, 136.69 (C(45), C(43), C(47), C(54), C(58), C(44), C(46), C(53), C(42)); 137.99 (C(31)); 147.01 (C(37)); 150.51 (C(20)); 155.41, 158.85, 173.21 (C(64), C(56), C(48)); 174.33 (C(28)); 218.07 (C(3)).

(*N*-*tert*-Butoxycarbonyl-L-valyl)-N^1-((2*S*,3*S*)-1-{4-[4-(3,28-dioxolup-20(29)-en-28-ylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}-3-methylpent-2-yl)-N^2-(4-methoxybenzyl)-2-methylalanineamide (3e). ^{1}H NMR, δ: 0.90—1.03 (m, 27 H, C(23)H_3—C(27)H_3, C(51)H_3, C(52)H_3, C(64)H_3, C(65)H_3); 1.39 (s, 9 H, Boc); 1.67 (s, 3 H, C(30)H_3); 3.16—3.19 (m, 1 H, H(19)); 3.75 (s, 3 H, OMe); 4.06—4.18 (m, 1 H, H(40)); 4.48—4.59 (m, 6 H, H(29), 2 H(39), 2 H(51), H(57)); 4.74 (s, 1 H, H(29)); 5.10 (d, 1 H, NH, J = 9.8 Hz); 5.66 (d, 1 H, NH, J = 7.7 Hz); 6.85 (d, 2 H, H(52), H(54), J = 8.1 Hz); 7.26 (d, 2 H, H(51), H(55), J = 8.1 Hz); 7.34 (s, 1 H, NH); 7.51 (d, 2 H, H(32), H(36), J = 7.9 Hz); 7.72 (d, 2 H, H(33), H(35), J = 7.9 Hz); 8.01 (s, 1 H, H(38)). ^{13}C NMR, δ: 10.83, 15.51, 17.11, 24.14, 24.93, 32.09, 35.61 (C(43), C(44), C(59), C(60), C(47), C(48), C(42), C(58), C(41)); 13.61 (C(27)); 16.26 (C(26)); 16.52 (C(25)); 19.15 (C(6)); 19.45 (C(30)); 23.47 (C(11)); 23.76 (C(24)); 25.33 (C(12)); 26.94 (C(23)); 28.16 (3 CH_3, Boc); 29.65 (C(21)); 30.43 (C(15)); 30.70 (C(16)); 33.89 (C(7)); 34.34 (C(2)); 36.55 (C(22)); 37.68 (C(13)); 38.14 (C(10)); 41.51 (C(1)); 42.55 (C(8)); 43.59 (C(14)); 46.48 (C(19)); 46.82 (C(4)); 50.22 (C(18)); 50.59 (C(9)); 48.33, 50.72,

53.26 (C(49), C(40), C(57)); 55.16 (OMe); 55.94 (C(5)); 56.47 (C(17)); 61.89, 62.86, 79.39, 114.22 (C(46), C(39), C(62), C(52), C(54)); 109.42 (C(29)); 120.08 (C(32), C(36)); 120.50 (C(38)); 126.05 (C(33), C(35)); 126.27 (C(34)); 127.57, 129.83 (C(51), C(55), C(50)); 137.97 (C(31)); 147.09 (C(37)); 150.58 (C(20)); 155.27, 158.91, 173.01, 174.30 (C(61), C(53), C(56), C(45)); 176.83 (C(28)); 217.48 (C(3)).

(1-*tert*-Butoxycarbonyl-L-prolyl)-N^1-((2*S*)-1-{4-[4-(3,28-dioxolup-20(29)-en-28-ylamino)phenyl]-1*H*-1,2,3-triazol-1-yl}-3-phenylprop-2-yl)-N^2-(4-methoxybenzyl)-2-methylalanineamide (3f). ^{1}H NMR, δ: 0.83—1.01 (m, 21 H, C(23)H_3—C(27)H_3, C(50)H_3, C(51)H_3); 1.40 (s, 9 H, Boc); 1.68 (s, 3 H, C(30)H_3); 3.11—3.41 (m, 6 H, H(19), 2 H(63), 2 H(41), H(61)); 3.76 (s, 3 H, OMe); 3.79 (s, 2 H, H(52)); 4.48—4.59 (m, 6 H, H(29), 2 H(39), H(49), H(61), H(40)); 4.74 (s, 1 H, H(29)); 6.63 (d, 1 H, NH, J = 8.4 Hz); 6.85 (d, 2 H, H(55), H(57), J = 8.6 Hz); 7.25—7.33 (m, 7 H, H(43)—H(47), H(54), H(58)); 7.51 (d, 2 H, H(32), H(36), J = 8.5 Hz); 7.74 (d, 2 H, H(33), H(35), J = 8.5 Hz); 7.89 (s, 1 H, H(38)). ^{13}C NMR, δ: 13.66 (C(27)); 14.01 (C(26)); 14.64 (C(25)); 19.15 (C(6)); 19.42 (C(30)); 20.76, 22.53, 30.57 (C(50), C(51), C(62), C(61)); 24.10 (C(24)); 24.40 (C(11)); 25.34 (C(12)); 26.94 (C(23)); 28.16 (3 CH_3, Boc); 29.69 (C(21)); 30.41 (C(15)); 30.71 (C(16)); 31.46 (C(7)); 31.56 (C(2)); 33.90 (C(22)); 34.34 (C(13)); 38.08 (C(10)); 41.52 (C(1)); 42.55 (C(8)); 43.60 (C(14)); 46.49 (C(19)); 47.20 (C(4)); 47.66, 48.33, 51.24, 51.75 (C(41), C(52), C(63), C(40)); 50.23 (C(18)); 50.60 (C(9)); 55.18 (OMe); 56.47 (C(17)); 57.23 (C(5)); 61.91, 63.47, 65.29, 79.60, 114.18 (C(60), C(39), C(49), C(65), C(55), C(57)); 109.42 (C(29)); 120.04 (C(32), C(36)); 120.69 (C(38)); 126.15 (C(33), C(35)); 126.39 (C(34)); 126.64, 127.00, 128.55, 129.23, 130.49, 137.98 (C(45), C(43), C(47), C(53), C(54), C(58), C(44), C(46), C(42)); 137.25 (C(31)); 146.96 (C(37)); 150.60 (C(20)); 154.66, 158.69, 174.72, 174.94 (C(64), C(56), C(59), C(48)); 176.84 (C(28)); 217.56 (C(3)).

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