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Syntheses of Chiral *N*-(Protected) Tri- and Tetrapeptide Conjugates

Kiran Bajaj[1], Siva S. Panda[1], Claudia El-Nachef[1] and Alan R. Katritzky[1,2,*]

[1]*Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA*
[2]*Chemistry Department, King Abdulaziz University, Jeddah, 21589 Saudi Arabia*
**Corresponding author: Alan R. Katritzky, katritzky@chem.ufl.edu*

Cbz-(protected)-tri- and tetrapeptide conjugates with steroids, sugars, terpenes, and heterocycles were prepared using Cbz-(protected)-tri- and tetrapeptidoylbenzotriazoles as active intermediates.

Key words: chemical structure, heterocycles, peptide, steroids, terpenes

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Peptides and their derivatives such as hormones, neurotransmitters, and neuromodulators act as signal molecules in diverse biological and medicinal applications and thus have attracted considerable synthetic attention (1,2). Esterifications of amino acids and peptides for the protection of carboxylic acid functionality and for their activation to make peptide conjugates are well known (3–5).

Peptidyl steroids, with amino acid or peptide units linked to the steroidal frame, are important in living systems; examples such as cholyl glycine and cholyl taurine are found in the human body (6). Amino acid esters of hydroxylic terpenes, a class of peptide conjugate, are effective medicinal agents, for example, for atherosclerosis (7). *N*-protected α-aminoacyl esters derived from long-chain alkanols containing 12–22 carbon atoms and α-amino acids or peptides possess medicinal, nutritional and industrial utility (8). The combination of sugar moieties with peptides is important in biochemical processes ranging from cell growth regulation, immune responses, and binding of pathogens to intercellular communication, intercellular targeting, cancer cell metastasis, and inflammation (9–11).

Reported preparative methods for peptides and their conjugates include (i) activating the *C*-terminus with coupling reagents such as carbodiimides, (4) HOBt, and HOAt (3)-based uronium (12), phosphonium (13), and immonium salts (3) and (ii) procedures involving the isolated *C*-terminus-activated intermediates such as acyl halides (14–16), acylimidazoles (17), active alkyl and phenolic esters (18), and acyloxy boron intermediates (19).

Peptide conjugates with sugar, steroid, and heterocyclic moieties have previously been prepared (i) by solid-phase syntheses (20,21) and (ii) in solution phase by stepwise synthesis using regular coupling reagents like EDC, (22) TBTU, (23) DCC (24), and BOP (25). However, such methods suffer from difficulties in product purification and analysis by (HPLC): High Performance Liquid Chromatography, (20) coupling steps being sensitive to the environment and water, (20) and low yields (23), especially with glycine units (24).

We have already utilized *N*-acylbenzotriazoles extensively for *N*-(26,27), *C*- (28,29), *O*- (30), and *S*-acylations (31). Previously, we reported the facile synthesis of amino acid conjugates with steroids, terpenes, and sugars. (32) Herein, we present the extension of our methodology for the convenient and efficient formation of Cbz-protected tri- and tetrapeptide conjugates with sugars, steroids, terpenes, and heterocyclic nuclei of biological importance.

Methods and Materials

Melting points were determined on a hot-stage apparatus and are uncorrected. All reactions were carried out under nitrogen unless otherwise specified. All microwave-assisted reactions were carried out with a single-mode cavity Discover Microwave Synthesizer (CEM Corporation, Matthews, NC, USA). Column chromatography was conducted on flash silica gel (200–425 mesh). Visualization of TLC plates was *via* UV and phosphomolybdic acid staining. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were determined in $CDCl_3$ with TMS as the internal standard, $(CD_3)_2CO$ or DMSO-d_6.

General procedure for the synthesis of N-Cbz-(dipeptidoyl)benzotriazoles (1a–c)

The compounds were synthesized following our established procedure (32).

Benzyl((*S*)-1-(((*S*)-1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)carbamate (Cbz-Ala-Phe-Bt) (1a)

White microcrystals (93%); mp 148–150 °C; Lit mp 148–149 °C.

Benzyl((*S*)-1-(((*S*)-1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-1-oxo-3-phenylpropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Cbz-Val-Phe-Bt) (1b)

White microcrystals (93%); mp 188–190 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 8.7 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.68 (t,

J = 7.7 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.41–7.27 (m, 5H), 7.24–7.17 (m, 3H), 7.13–7.07 (m, 2H), 6.70 (d, *J* = 7.2 Hz, 1H), 6.30–6.20 (m, 1H), 5.31 (d, *J* = 8.4 Hz, 1H), 5.17–5.06 (m, 2H), 4.08 (t, *J* = 7.2 Hz, 1H), 3.47 (dd, *J* = 14.1, 5.1 Hz, 1H), 3.24 (dd, *J* = 14.0, 7.7 Hz, 1H), 2.19–2.02 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 170.4, 156.5, 146.2, 136.4, 135.0, 131.2, 131.0, 129.4, 129.0, 128.7, 128.4, 128.3, 127.7, 126.8, 120.6, 114.5, 67.4, 60.4, 54.2, 38.8, 31.1, 19.3, 17.9. Anal. Calcd for $C_{28}H_{29}N_5O_4$: C, 67.32; H, 5.85; N, 14.02; found: C, 67.44; H, 5.86; N, 14.09.

(*S*)-Benzyl(1-((2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-1-oxo-3-phenyl-propan-2-yl)carbamate (Cbz-Phe-Gly-Bt) (1c)

White microcrystals (85%); mp 169–171 °C; ^{1}H NMR (DMSO-d_6) δ 8.89 (t, *J* = 5.5 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.70–7.60 (m, 2H), 7.35–7.19 (m, 10H), 5.08–4.91 (m, 4H), 4.50–4.42 (m, 1H), 3.16 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.88–2.78 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 172.7, 168.5, 155.9, 145.3, 138.1, 137.0, 131.0, 130.6, 129.2, 128.3, 128.1, 127.6, 127.4, 126.6, 126.3, 120.1, 113.7, 65.2, 56.1, 42.7, 37.6. Anal. Calcd for $C_{25}H_{23}N_5O_4$: C, 65.64; H, 5.07; N, 15.31; found: C, 65.67; H, 5.00; N, 15.10.

General procedure for the synthesis of N-Cbz-tripeptides (2a–c)

The compounds were synthesized following our established procedure (33).

(5*S*,8*S*)-8-Benzyl-5-methyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (Cbz-Ala-Phe-Gly-OH) (2a)

White microcrystals (78%); mp 108–110 °C; ^{1}H NMR (DMSO-d_6) δ 8.35 (t, *J* = 5.7 Hz, 1H), 7.93–7.88 (m, 1H), 7.46–7.43 (m, 1H), 7.42–7.25 (m, 5H), 7.24–7.16 (m, 5H), 5.00 (s, 2H), 4.60–4.52 (m, 1H), 4.01 (q, *J* = 6.9 Hz, 1H), 3.78 (d, *J* = 5.7 Hz, 2H), 3.10–2.98 (m, 1H), 2.88–2.76 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.2, 171.3, 171.1, 155.2, 137.1, 136.5, 128.8, 127.9, 127.5, 127.3, 125.7, 65.0, 53.0, 49.8, 40.2, 37.2, 17.7. Anal. Calcd for $C_{22}H_{25}N_3O_6$. 0.5 H_2O: C, 60.54; H, 6.00; N, 9.63; found: C, 60.89; H, 5.83; N, 9.73.

(5*S*,8*S*)-8-Benzyl-5-isopropyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (Cbz-Val-Phe-Gly-OH) (2b)

White microcrystals (91%); mp 212–215 °C; ^{1}H NMR (DMSO-d_6) δ 8.36 (t, *J* = 5.7 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.40–7.28 (m, 5H), 7.27–7.11 (m, 6H), 5.02 (br s, 2H), 4.68–4.55 (m, 1H), 3.86–3.71 (m, 3H), 3.02 (dd, *J* = 13.5, 3.9 Hz, 1H), 2.78 (dd, *J* = 13.8, 9.9 Hz, 1H), 1.91–1.78 (m, 1H), 0.78–0.64 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 171.4, 171.0, 170.8, 156.0, 137.6, 137.0, 129.2, 128.4, 128.0, 127.8, 127.7, 126.2, 65.5, 60.4, 53.5, 40.7, 37.8, 30.4, 19.2, 18.1. Anal. Calcd for $C_{24}H_{29}N_3O_6$: C, 63.28; H, 6.42; N, 9.22; found: C, 63.48; H, 6.47; N, 9.20.

(5*S*,11*S*)-5-Benzyl-11-isobutyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oic acid (Cbz-Phe-Gly-Leu-OH) (2c)

White microcrystals (80%); mp 79–81 °C; ^{1}H NMR (DMSO-d_6) δ 8.34–8.30 (m, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.33–7.19 (m, 10H), 4.99–4.90 (m, 2H), 4.32–4.22 (m, 2H), 3.77 (d, *J* = 7.8 Hz, 2H), 3.08–3.00 (m, 1H), 2.80–2.71 (m, 1H), 1.68–1.60 (m, 1H), 1.55–1.50 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 174.0, 171.9, 168.6, 156.0, 138.2, 137.0, 129.2, 128.3, 128.1, 127.7, 127.5, 126.3, 65.3, 56.3, 50.2, 41.8, 40.3, 40.1, 37.3, 24.2, 22.8, 21.4. Anal. Calcd for $C_{25}H_{31}N_3O_6$: C, 63.95; H, 6.65; N, 8.95; found: C, 64.06; H, 6.75; N, 8.98.

General procedure for the synthesis of N-Cbz-tripeptidoylbenzotriazole (3a–c)

The compounds were synthesized following our established procedure (33).

Benzyl((*S*)-1-(((*S*)-1-((2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)carbamate(Cbz-Ala-Phe-Gly-Bt) (3a)

White microcrystals (92%); mp 182–185 °C; ^{1}H NMR (DMSO-d_6) δ 8.83–8.81 (m,1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.35–7.22 (m, 10 H), 5.02–4.96 (m, 4H), 4.70–4.68 (m, 1H), 4.03 (t, *J* = 6.9 Hz, 1H), 3.14–3.08 (m, 1H), 2.96–2.78 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.2, 168.4, 155.6, 145.2, 137.5, 131.0, 130.5, 129.2, 128.3, 128.0, 127.7, 126.6, 126.2, 120.1, 113.7, 65.4, 53.5, 50.2, 42.6, 37.7, 18.2. Anal. Calcd for $C_{28}H_{28}N_6O_5$: C, 63.63; H, 5.34; N, 15.90; found: C, 63.22; H, 5.37; N, 15.79.

Benzyl((*S*)-1-(((*S*)-1-((2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-1-oxo-3-phenyl-propan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (Cbz-Val-Phe-Gly-Bt) (3b)

White microcrystals (93%); mp 214–215 °C; ^{1}H NMR (DMSO-d_6) δ 8.84 (brs, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.25–7.15 (m, 11H), 5.10–4.90 (m, 4H), 4.85–4.68 (m, 1H), 3.84 (t, *J* = 7.5 Hz, 1H), 3.19–3.05 (m, 1H), 2.95–2.80 (m, 1H), 1.98–1.79 (m, 1H), 0.80–0.60 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 172.1, 170.9, 168.4, 156.0, 145.3, 137,6, 137.0, 131.0, 130.6, 129.2, 128.3, 128.0, 127.6, 126.2, 120.1, 113.7, 65.4, 60.4, 53.4, 42.6, 37.9, 30.4, 19.1, 18.1. Anal. Calcd for $C_{30}H_{32}N_6O_5$: C, 64.73; H, 5.79; N, 15.10; found: C, 64.60; H, 5.79; N, 15.01.

Benzyl((*S*)-1-((2-(((*S*)-1-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (Cbz-Phe-Gly-Leu-Bt) (3c)

White microcrystals (84%); mp 144–146 °C; ^{1}H NMR (DMSO-d_6) δ 8.81–8.77 (m, 1H), 8.42–8.38 (m, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 8.20

(d, J = 7.2 Hz, 1H), 8.10–8.06 (m, 1H), 7.80–7.77 (m, 1H), 7.65–7.59 (m, 1H), 7.39–7.12 (m, 10H), 4.94 (s, 2H), 4.51–4.45 (m, 1H), 4.29–4.25 (m, 1H), 3.88–3.74 (m, 2H), 3.08–3.03 (m, 1H), 2.80–2.72 (m, 1H), 1.80–1.65 (m, 1H), 1.60–1.50 (m, 2H), 0.99–0.87 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 173.7, 172.6, 169.3, 169.1, 156.6, 146.0, 138.9, 137.6, 131.7, 129.9, 129.0, 128.7, 128.4, 128.1, 127.3, 126.9, 120.9 114.5, 65.9, 56.9, 51.5, 43.2, 42.8, 38.0, 24.8, 23.8, 22.2. Anal. Calcd for $C_{31}H_{34}N_6O_5$: C, 65.25; H, 6.01; N, 14.73; found: C, 65.21; H, 5.85; N, 14.56.

General procedure for the synthesis of N-Cbz-tetrapeptides (4a–c)

The compounds were synthesized following our established procedure (33).

(5*S*,8*S*,14*S*)-8-Benzyl-5,14-dimethyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oic acid (Cbz-Ala-Phe-Gly-Ala-OH) (4a)

White microcrystals (74%); mp 184–186 °C; ^{1}H NMR (DMSO-d_6) δ 8.26 (t, J = 6.0 Hz, 1H), 8.08 (d, J = 6.9 Hz, 1H), 7.98 (d, J = 6.9 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.36–7.30 (m, 5H), 7.24–7.16 (m, 5H), 5.08–4.94 (m, 2H), 4.52–4.42 (m, 1H), 4.21 (quintet, J = 7.2 Hz, 1H), 4.08–3.96 (m, 1H), 3.73 (d, J = 5.7 Hz, 2H), 3.04 (dd, J = 13.5, 4.2 Hz, 1H), 2.88–2.78 (m, 1H), 1.28 (d, J = 7.2 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 173.9, 172.4, 171.1, 168.3, 155.6, 137.6, 136.9, 129.2, 128.3, 128.0, 127.7, 126.2, 65.4, 53.9, 50.1, 47.5, 41.7, 37.3, 18.0, 17.3. Anal. Calcd for $C_{25}H_{30}N_4O_7$: C, 60.23; H, 6.07; N, 11.24; found: C, 59.95; H, 6.04; N, 11.07.

(5*S*,8*S*)-8-Benzyl-5-methyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraaza-penta decan-15-oic acid (Cbz-Ala-Phe-Gly-Gly-OH) (4b)

White microcrystals (85%); mp 148–150 °C; ^{1}H NMR (DMSO-d_6) δ 8.88 (t, J = 5.4 Hz, 1H), 8.68 (t, J = 5.8 Hz, 1H), 8.57 (d, J = 7.5 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.04–7.94 (m, 5H), 7.88–7.78 (m, 5H), 5.63 (d, J = 12.6 Hz, A part of AB system, 1H), 5.57 (d, J = 12.9 Hz, B part of AB system, 1H), 5.16–5.04 (m, 1H), 4.68–4.57 (m, 1H), 4.38–4.24 (m, 4H), 3.66–3.61 (m, 1H), 3.46–3.22 (m, 1H), 1.71 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.4, 171.1, 171.1, 169.0, 155.7, 137.6, 136.9, 129.3, 128.3, 128.0, 127.8, 126.2, 65.5, 53.8, 50.2, 41.8, 40.6, 37.4, 18.1. Anal. Calcd for $C_{24}H_{28}N_4O_7$: C, 59.50; H, 5.82; N, 11.56; found: C, 59.12; H, 5.84; N, 11.88.

(5*S*,11*S*)-5-Benzyl-11-isobutyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraazapenta decan-15-oic acid (Cbz-Phe-Gly-leu-Gly-OH) (4c)

White microcrystals (88%); mp 109–110 °C; ^{1}H NMR (DMSO-d_6) δ 8.32–8.26 (m, 2H), 7.94 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.35–7.17 (m, 10H), 5.10–4.90 (m, 2H), 4.38–4.32 (m, 1H), 4.30–4.23 (m,1H), 3.80–3.72 (m, 4H), 3.10–3.00 (m, 1H), 2.80–2.70 (m, 1H), 1.65–1.60 (m, 1H), 1.51–1.45 (m, 2H), 0.88 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.3, 171.8, 171.1, 168.4, 155.9, 138.2, 136.9, 129.2, 128.3, 128.0, 127.7, 127.4, 126.2, 65.3, 56.2, 50.7, 42.0, 41.0, 40.6, 37.3, 24.1, 23.1, 21.6. Anal. Calcd for $C_{27}H_{34}N_4O_7$: C, 61.58; H, 6.51; N, 10.64; found: C, 61.69; H, 6.62; N, 10.48.

General procedure for the synthesis of N-Cbz-tetrapeptidoylbenzotriazole (5a–c)

The compounds were synthesized following our established procedure (33) (Table 1).

Benzyl((*S*)-1-(((*S*)-1-((2-(((*S*)-1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-1-oxopropan-2-yl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)carbamate (Cbz-Ala-Phe-Gly-Ala-Bt) (5a)

White microcrystals (72%); mp 200–202 °C; ^{1}H NMR (DMSO-d_6) δ 8.72–8.70 (m, 1H), 8.30 (d, J = 7.8 Hz, 2H), 8.22 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 6.9 Hz, 1H), 7.80 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.46–7.10 (m, 11H), 5.66–5.60 (m, 1H), 5.02–4.96 (m, 2H), 4.48–4.45 (m, 1H), 4.02–3.95 (m, 1H), 3.82 (d, J = 5.4 Hz, 2H), 3.10–2.97 (m, 1H), 2.86–2.80 (m, 1H), 1.56 (d, J = 6.9 Hz, 3H), 1.10 (d, J = 8.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.5, 171.8, 171.2, 169.1, 155.6, 145.3, 137.6, 136.9, 131.1, 130.6, 129.2, 128.3, 127.9, 127.7, 126.7, 126.2, 125.3, 120.2, 114.9, 113.9, 65.4, 53.9, 50.2, 48.5, 41.5, 37.3, 18.0, 16.7. Anal. Calcd for $C_{31}H_{33}N_7O_6$: C, 62.09; H, 5.55; N, 16.35; found: C, 62.12; H, 5.56; N, 15.98.

Benzyl((*S*)-1-(((*S*)-1-((2-((2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)carbamate (Cbz-Ala-Phe-Gly-Gly-Bt) (5b)

White microcrystals (62%); mp 144–145 °C; ^{1}H NMR (DMSO-d_6) δ 8.62–8.55 (m, 1H), 8.42–8.36 (m, 1H), 8.29 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.80 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 6.9 Hz, 1H), 7.43–7.30 (m, 5H),

Table 1: Preparation of *N*-Pg–tripeptidoylbenzotriazoles **3a–c** and tetrapeptidoylbenzotriazoles **5a–c**

Entry	Reactant	Product	Yield (%)	Mp(°C)
1	Z–L–Ala–L–Phe–Gly–OH **2a**	Z–L–Ala–L–Phe–Gly–Bt **3a**	92	180–182[a]
2	Z–L–Val–L–Phe–Gly–OH **2b**	Z–L–Val–L–Phe–Gly–Bt **3b**	93	214–215
3	Z–L–Phe–Gly-L–Leu-OH **2c**	Z–L–Phe–Gly-L–Leu-Bt **3c**	84	144–146
4	Z–L–Ala–L–Phe–Gly–L-Ala-OH **4a**	Z–L–Ala–L–Phe–Gly–L-Ala-Bt **5a**	72	200–202[b]
5	Z–L–Ala–L–Phe–Gly–Gly-OH **4b**	Z–L–Ala–L–Phe–Gly–Gly-Bt **5b**	62	144–145
6	Z–L–Phe–Gly–L-Leu–Gly-OH **4c**	Z–L–Phe–Gly–L–Leu–Gly-Bt **5c**	79	280–282

[a]Lit mp 186–187 °C (33), [b]Lit mp 212–214 °C (33).

7.24–7.22 (m, 5H), 5.02–4.96 (m, 4H), 4.62–4.50 (m, 1H), 4.10–3.99 (m, 1H), 3.94–3.86 (m, 2H), 3.10–3.05 (m, 1H), 2.87–2.80 (m, 1H), 1.13 (d, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.5, 171.3, 169.7, 168.5, 155.7, 145.3, 137.6, 136.9, 131.0, 130.6, 129.3, 128.3, 128.0, 127.8, 126.6, 126.2, 120.2, 113.7, 65.5, 53.8, 50.2, 42.6, 41.8, 37.3, 18.0. Anal. Calcd for $C_{30}H_{31}N_7O_6.0.5\ H_2O$: C, 60.60; H, 5.42; N, 16.49; found: C, 60.70; H, 5.26; N, 16.22.

Benzyl((*S*)-1-((2-(((*S*)-1-((2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (Cbz-Phe-Gly-Leu-Gly-Bt) (5c)

White microcrystals (79%); mp 194–195 °C; ^{1}H NMR (DMSO-d_6) δ 8.80–8.70 (m, 1H), 8.35–8.30 (m, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.66–7.55 (m, 2H), 7.33–7.19 (m, 10H), 4.97–4.90 (m, 4H), 4.55–4.46 (m, 1H), 4.32–4.22 (m, 1H), 3.89–3.72 (m, 2H), 3.08–3.02 (m, 1H), 2.80–2.50 (m, 1H), 1.70–1.66 (m, 1H), 1.60–1.56 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.9, 171.8, 168.5, 168.4, 155.9, 145.2, 138.1, 136.9, 131.0, 130.5, 129.2, 128.2, 128.0, 127.6, 127.4, 126.6, 126.2, 120.1, 113.7, 65.2, 56.2, 50.7, 42.5, 42.0, 41.0, 37.3, 24.1, 23.1, 21.6. Anal. Calcd for $C_{33}H_{37}N_7O_6$: C, 63.14; H, 5.94; N, 15.62; found: C, 62.88; H, 5.92; N, 15.46.

General procedure for O-acylation: synthesis of compounds (6a–f)

Compounds were prepared by using similar microwave conditions reported for *O*-acylation. (34) A dried heavy-walled Pyrex tube containing a small stir bar was charged with benzotriazole intermediate **3a–c** or **5b–c** (1 eq.), *O*-nucleophile (1.5 eq.), and base dimethylaminopyridine (DMAP) (0.1 eq.) dissolved in THF. The reaction mixture was exposed to microwave irradiation (100 W) at 70 °C for specified times. Each mixture was allowed to cool through an inbuilt system until the temperature had fallen below 30 °C (ca. 10 min). The reaction mixture was quenched with water, extracted with EtOAc, and the extracts were washed with (10%) Na_2CO_3, water, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column using EtOAc/hexane as an eluent to give the corresponding compound **6a–f**.

(5*S*,8*S*)-(8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl 8-benzyl-5-methyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (Cbz-Ala-Phe-Gly-*O*-Cholesterol) (6a)

White microcrystals (45%); mp 162–163 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–7.30 (m, 5H), 7.29–7.15 (m, 5H), 6.76 (d, J = 7.2 Hz, 1H), 6.70–6.60 (m, 1H), 5.38–5.34 (m,1H), 5.27 (d, J = 6.6 Hz, 1H), 5.14–5.00 (m, 2H), 4.80–4.70 (m,1H), 4.66–4.58 (m, 1H), 4.22–4.16 (m, 1H), 4.08–3.98 (m, 1H), 3.90–3.80 (m, 1H), 3.22–3.10 (m, 1H), 3.09–3.00 (m, 1H), 2.30 (d, J = 7.8 Hz, 2H), 2.01–1.93 (m, 2H), 1.90–1.78 (m, 4H), 1.62–1.40 (m, 8H), 1.36–1.28 (m, 2H), 1.27 (d, J = 7.2 Hz, 6H), 1.17–1.07 (m, 4H), 1.06–1.00 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 7.5 Hz, 6H), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.4, 171.0, 169.0, 156.4, 139.5, 136.6, 136.2, 129.4, 128.8, 128.5, 128.3, 127.2, 123.2, 75.6, 67.4, 56.9, 56.4, 54.3, 51.1, 50.2, 42.5, 41.7, 39.9, 39.7, 38.2, 37.1, 36.8, 36.4, 36.0, 32.1, 29.9, 28.4, 28.2, 27.9, 24.5, 24.1, 23.0, 22.8, 21.2, 19.5, 18.9, 18.4, 12.1. HRMS Calcd for $C_{49}H_{69}N_3O_6Na$ [M + Na]$^+$ 818.5079; found 818.5089.

(5*S*,8*S*)-(*E*)-3,7-Dimethylocta-2,6-dien-1-yl-8-benzyl-5-methyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (Cbz-Ala-Phe-Gly-*O*-Nerol) (6b)

White microcrystals (50%); mp 114–116 °C; ^{1}H NMR ($CDCl_3$) δ 7.36–7.28 (m, 5H), 7.26–7.12 (m, 5H), 7.02 (d, J = 7.5 Hz, 1H), 6.92–6.82 (m, 1H), 5.58 (d, J = 7.2 Hz, 1H), 5.30 (t, J = 7.2 Hz, 1H), 5.12–5.00 (m, 3H), 4.80 (q, J = 7.5 Hz, 1H), 4.59 (d, J = 7.5 Hz, 2H), 4.30–4.20 (m, 1H), 4.08–3.80 (m, 2H), 3.13 (dd, J = 13.8, 6.6 Hz, 1H), 3.01 (dd, J = 13.8, 7.2 Hz, 1H), 2.14–2.00 (m, 4H), 1.74 (s, 3H), 1.67 (s, 3H), 1.58 (s, 3H), 1.26 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.7, 171.2, 169.6, 156.3, 143.4, 136.6, 136.3, 132.4, 129.4, 128.7, 128.6, 128.3, 128.2, 127.0, 123.6, 118.7, 67.2, 62.1, 54.2, 50.9, 41.4, 38.3, 32.3, 26.7, 25.8, 23.6, 18.6, 17.8. Anal. Calcd for $C_{32}H_{41}N_3O_6$: C, 68.18; H, 7.33; N, 7.45; found: C, 68.28; H, 7.57; N, 7.50.

(5*S*,8*S*)-((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4′,5′-*d*]pyran-5-yl)methyl-8-benzyl-5-isopropyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (Cbz-Val-Phe-Gly-*O*-Glactopyranose) (6c)

White microcrystals (47%); mp 129–131 °C; ^{1}H NMR ($CDCl_3$) δ. 7.45–7.30 (m, 5H), 7.28–7.15 (m, 5H), 6.68–6.58 (m, 2H), 5.53 (d, J = 4.8 Hz, 1H), 5.27 (d, J = 7.5 Hz, 1H), 5.14–5.03 (m, 2H), 4.82–4.71 (m, 1H), 4.62 (dd, J = 8.0, 2.3 Hz, 1H), 4.35–4.19 (m, 4H), 4.11–3.88 (m, 4H), 3.20–3.10 (m, 1H), 3.08–2.98 (m, 1H), 2.14–2.00 (m, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.33 (s, 6H), 0.88 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 171.0, 169.4, 156.7, 136.6, 136.2, 129.4, 128.8, 128.5, 128.4, 127.2, 109.9, 109.0, 96.4, 71.1, 70.8, 70.6, 67.5, 66.0, 64.4, 60.9, 54.2, 41.5, 38.2, 30.8, 26.3, 26.1, 25.1, 24.7, 19.4, 17.7. Anal. Calcd for $C_{36}H_{47}N_3O_{11}$: C, 61.97; H, 6.79; N, 6.02; found: C, 61.78; H, 6.94; N, 5.91.

(5*S*)-(8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl-8-benzyl-5-isopropyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazadodecan-12-oate (Cbz-Val-Phe-Gly-*O*-estrone) (6d)

White flakes (35%); mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 7.38–7.30 (m, 6H), 7.28–7.22 (m, 2H), 7.22–7.16 (m, 4H), 6.87–6.78 (m, 2H), 6.60 (d, J = 7.8 Hz, 1H), 5.30–5.20 (m, 1H), 5.14–4.98 (m, 3H), 4.85–4.71 (m, 1H), 4.34–3.80 (m, 4H), 3.23–2.98 (m, 3H), 2.87 (dd, J = 8.9, 4.1 Hz, 1H), 2.58–1.91 (m, 4H), 1.70–1.35 (m, 5H), 0.90 (s, 3H), 0.87 (dd, J = 6.9, 3.3 Hz, 3H), 0.76 (dd, J = 6.6, 3.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 170.9, 169.5, 168.5, 156.9, 148.3, 138.3,

137.9, 136.6, 136.2, 129.4, 128.9, 128.8, 128.5, 128.4, 127.3, 126.7, 121.5, 118.6, 61.7, 61.1, 54.3, 50.6, 48.1, 44.3, 41.5, 38.2, 36.1, 31.8, 30.6, 29.6, 26.5, 26.0, 21.8, 19.4, 14.4, 14.1. HRMS Calcd for $C_{42}H_{49}N_3O_7Na$ $[M + Na]^+$: 730.3463; found: 730.3472.

(5*S*,8*S*)-(3a*R*,5*R*,6*R*,6a*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl-8-benzyl-5-methyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa -4,7,10,13-tetraazapentadecan-15-oate (Cbz-Ala-Phe-Gly-Ala-*O*-diacetoneglucose) (6e)

White microcrystals (58%); mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–7.29 (m, 7H), 7.26–7.09 (m, 6H), 5.86 (d, J = 3.6 Hz, 1H), 5.76 (d, J = 6.1 Hz, 1H), 5.27–5.25 (m, 1H), 5.10–5.00 (m, 2H), 4.78 (q, J = 7.2 Hz, 1H), 4.49 (d, J = 3.6 Hz, 1H), 4.40–4.34 (m, 1H), 4.24–4.1.8 (m, 2H), 4.16–3.99 (m, 4H), 3.98–3.80 (m, 2H), 3.12–2.95 (m, 2H), 1.50 (s, 3H), 1.38 (s, 3H), 1.30–1.25 (m, 9H), 0.92–0.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.1, 171.4, 169.4, 168.8, 156.5, 136.5, 136.3, 129.4, 128.8, 128.5, 128.2, 127.3, 112.5, 109.6, 105.2, 83.3, 79.8, 72.5, 67.4, 54.8, 51.1, 43.0, 41.4, 38.3, 27.1, 26.9, 26.4, 25.4, 18.6. Anal. Calcd for $C_{36}H_{46}N_4O_{12}$: C, 59.49; H, 6.38; N, 7.71; found: C, 59.26; H, 6.56; N, 7.35.

(5*S*,11*S*)-(1*S*,2*S*)-2-Isopropyl-5-methylcyclohexyl 5-benzyl-11-isobutyl-3,6,9,12-tetra oxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecan-15-oate (Cbz-Phe-Gly-Leu-Gly-*O*-menthol) (6f)

White microcrystals (42%); mp 104–106 °C; ^{1}H NMR ($CDCl_3$) δ. 7.40–7.06 (m, 13H), 5.79 (d, J = 6.6 Hz, 1H), 5.06 (d, A part of AB system, J = 12 .0 Hz, 1H), 4.98 (d, B part of AB system, J = 12.3 Hz, 1H), 4.76–4.51 (m, 3H), 4.04–3.83 (m, 4H), 3.14 (dd, J = 15.0, 5.4 Hz, 1H), 3.00–2.92 (m, 1H), 2.18–2.10 (m, 1H), 1.98–1.91 (m, 1H), 1.89–1.78 (m, 1H), 1.68–1.50 (m, 5H), 1.49–1.31 (m, 2H), 1.03–0.88 (m, 14), 0.71 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.5, 172.3, 169.7, 169.1, 156.5, 136.6, 136.2, 129.4, 128.8, 128.7, 128.4, 128.2, 127.2, 75.9, 67.3, 56.5, 51.9, 47.1, 43.4, 41.6, 41.2, 40.9, 38.4, 34.3, 31.5, 26.4, 24.9, 23.6, 23.1, 22.2, 22.1, 20.9, 16.5. HRMS Calcd for $C_{37}H_{52}N_4O_7Na$ $[M + Na]^+$: 687.3728; found: 687.3743.

General procedure for S-acylation: synthesis of compounds (7a–d)

Mercapto nucleophile (1 eq.) was dissolved in THF and triethyl amine (1.5 eq.). Benzotriazole intermediate (1 eq.) was added to the solution, and the mixture was stirred at room temperature for 1–2 h. The mixture was then acidified with 6 N HCl, concentrated, and then diluted with ethyl acetate. The organic layer was washed with 6 N HCl and dried over anhydrous $MgSO_4$, filtered, and then evaporated to give the desired compound.

(5*R*,8*R*)-*S*-Phenyl 8-benzyl-5-methyl-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triaza-dodecane-12-thioate (7a)

White microcrystals (78%); mp 146–147 °C; ^{1}H NMR (DMSO-d_6) δ 8.89–8.86 (m, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.47–7.25 (m, 16H), 5.02–4.90 (m, 2H), 4.63–4.59 (m, 1H), 4.13–4.05 (m, 2H), 4.06–4.01 (m, 1H), 3.19–3.08 (m, 1H), 2.91–2.82 (m, 1H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 196.2, 172.3, 171.9, 155.6, 137.6, 137.0, 134.5, 129.5, 129.4, 129.2, 128.3, 128.1, 127.7, 126.9, 126.3, 65.4, 53.7, 50.2, 48.8, 37.3, 18.2. Anal. Calcd for $C_{28}H_{29}N_3O_5S.H_2O$: C, 62.55; H, 5.81; N, 7.82; found: C, 62.85; H, 5.49; N, 7.46.

(5*S*,8*S*)-Methyl-8-benzyl-5-methyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-13-thia-4,7,10-triazapentadecan-15-oate (7b)

White powder (83%); mp 158–160 °C; ^{1}H NMR (DMSO-d_6) δ 8.85–8.82 (m, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.42–7.18 (m, 11H), 5.03–4.99 (m, 2H), 4.62–4.59 (m, 1H), 4.09–3.98 (m, 3H), 3.76 (s, 2H), 3.64 (s, 3H), 3.14–3.06 (m, 1H), 2.91–2.85 (m, 1H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 197.6, 172.3, 171.9, 168.9, 155.6, 137.6, 137.0, 129.2, 128.3, 128.1, 127.7, 126.3, 65.4, 53.7, 52.4, 50.1, 48.5, 37.3, 30.2, 18.2. Anal. Calcd for $C_{25}H_{29}N_3O_7S$: C, 58.24; H, 5.67; N 8.15; found: C, 58.08; H, 5.63; N, 8.04.

(5*S*,8*S*,14*R*)-8-Benzyl-5,14-dimethyl-3,6,9,12,15-pentaoxo-1-phenyl-2-oxa-16-thia-4,7,10,13-tetraazaoctadecan-18-oic acid (7c)

Off-white microcrystals (70%); mp 103–105 °C; ^{1}H NMR (DMSO-d_6) δ. 8.52 (d, J = 7.2 Hz, 1H), 8.36–8.28 (m, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.38–7.30 (m, 5H), 7.25–7.18 (m, 5H), 5.07–4.94 (m, 2H), 4.55–4.38 (m, 2H), 4.07–3.97 (m, 1H), 3.78 (t, J = 5.6 Hz, 1H), 3.62 (s, 2H), 3.08–3.00 (m, 1H), 2.88–2.78 (m, 1H), 1.28 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 200.9, 172.4, 171.2, 169.6, 169.0, 155.6, 137.6, 136.9, 129.2, 128.3, 128.0, 127.7, 126.2, 65.4, 54.5, 53.9, 50.1, 41.8, 37.3, 30.9, 18.0, 17.3. HRMS Calcd for $C_{27}H_{32}N_4O_8NaS$ $[M + Na]^+$: 595.1833; found: 595.1835.

(5*S*,11*S*)-S-Benzyl-5-benzyl-11-isobutyl-3,6,9,12-tetraoxo-1-phenyl-2-oxa-4,7,10,13-tetraazapentadecane-15-thioate (7d)

White microcrystals (94%); mp 186–187 °C; ^{1}H NMR (DMSO-d_6) δ 8.67 (t, J = 5.56 Hz, 1H), 8.32 (t, J = 5.1 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.39–7.19 (m, 15H), 4.95 (s, 2H), 4.42–4.22 (m, 2H), 4.10 (s, 2H), 4.05–4.00 (m, 2H), 3.81–3.74 (m, 2H), 3.09–3.00 (m, 1H), 2.81–2.70 (m, 1H), 170–1.60 (m, 1H), 1.59–1.49 (m, 2H), 0.89 (d, J = 6.3 Hz, 3H), 0.85 (d, J = 6.0 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 197.8, 172.7, 171.8, 168.6, 155.9, 138.2, 137.7, 136.9, 129.2, 128.7, 128.5, 128.3, 128.0, 127.7, 127.4, 127.1, 126.2, 65.3, 56.2, 50.9, 48.7, 42.0, 40.6, 37.3, 31.7, 24.1, 23.0, 21.5. Anal. Calcd for $C_{34}H_{40}N_4O_6S$: C, 64.54; H, 6.37; N 8.85; found: C, 64.50; H, 6.50; N, 8.48.

General procedure for N-acylation: synthesis of compounds (8a, 8d)

N-nucleophile (1 eq.) was dissolved in THF and triethylamine (1.5 eq.). The benzotriazole intermediate (1 eq.) was added to the solution, and the mixture was stirred at room temperature for 1 h. The mixture was acidified with 6 N HCl and then diluted with ethyl acetate. The organic layer was washed with 6 N HCl and dried over anhydrous $MgSO_4$, and filtered and evaporated to give the desired compound.

Benzyl((*S*)-1-(((*S*)-1-((2-((3-(1*H*-imidazol-1-yl)propyl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)carbamate (8a)

White microcrystals (75%); mp 134–137 °C; ^{1}H NMR (DMSO-d_6) δ 8.30–8.20 (m, 1H), 8.08 (d, J = 7.2 Hz, 1H), 7.78–7.72 (m, 1H), 7.61 (s, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.38–7.30 (m, 5H), 7.23–7.20 (m, 5H), 7.16 (s, 1H), 6.88 (s, 1H), 5.02–4.88 (m, 2H), 4.52–4.40 (m, 1H), 4.08–3.90 (m, 3H), 3.79–3.68 (m, 1H), 3.66–3.54 (m, 1H), 3.08–2.99 (m, 3H), 2.92–2.78 (m, 1H), 1.92–1.78 (m, 2H), 1.12 (d, J = 6.9 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.7, 171.2, 168.6, 155.7, 137.6, 137.3, 136.9, 129.2, 128.3, 128.0, 127.7, 126.2, 119.3, 65.5, 54.2, 50.2, 43.4, 42.2, 37.1, 35.7, 30.7, 17.9. Anal. Calcd for $C_{28}H_{34}N_6O_5$: C, 62.91; H, 6.41; N 15.72; found: C, 62.56; H, 6.46; N, 15.52.

Benzyl ((*S*)-1-((2-(((*S*)-4-methyl-1-((2-(4-methylpiperazin-1-yl)-2-oxoethyl)amino)-1-oxopentan-2-yl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (8d)

White microcrystals (68%); mp 181–183 °C; ^{1}H NMR (DMSO-d_6) δ 8.29 (t, J = 5.7 Hz, 1H), 8.01 (t, J = 5.3 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.34–7.18 (m, 10H), 4.95–4.89 (m, 2H), 4.42–4.34 (m, 1H), 4.30–4.22 (m, 1H), 3.91 (d, J = 5.4 Hz, 2H), 3.76 (t, J = 5.7 Hz, 2H), 3.41–3.36 (m, 4H), 3.04 (dd, J = 13.6, 3.9 Hz, 1H), 2.75 (dd, J = 13.5, 11.1 Hz, 1H), 2.27–2.22 (m, 4H), 2.15 (s, 3H), 1.65–1.58 (m, 1H), 1.51–1.45 (m, 2H), 0.87 (dd, J = 6.3 Hz, 3H), 0.83 (d, J = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.0, 171.8, 168.5, 166.6, 156.0, 138.2, 137.0, 129.2, 128.3, 128.1, 127.7, 127.5, 126.3, 65.3, 56.3, 54.6, 54.2, 51.0, 45.7, 43.9, 42.1, 41.3, 41.0, 37.3, 24.1, 23.1, 21.6. Anal. Calcd for $C_{32}H_{44}N_6O_6$: C, 63.14; H, 7.29; N 13.81; found: C, 62.84; H, 7.38; N, 13.68.

General procedure for N-acylation: synthesis of compounds (8b–c)

Compounds were prepared by using similar reaction condition reported for (α-aminoacyl)benzotriazoles. (35) A dried heavy-walled Pyrex tube containing a small stir bar was charged with benzotriazole intermediate (1 eq.), and *N*-nucleophile (1 eq.) was dissolved in DMF. The reaction mixture was exposed to microwave irradiation (60 W) at 65 °C temperature for specified times. Each mixture was allowed to cool through an inbuilt system until the temperature had fallen below 30 °C (ca. 10 min). Each reaction mixture was quenched with water, and the solid obtained was filtered and washed with 10% Na_2CO_3 and water to give the desired compound.

Benzyl((*S*)-3-methyl-1-oxo-1-(((*S*)-1-oxo-1-((2-oxo-2-(pyridin-2-ylamino)ethyl)amino)-3-phenylpropan-2-yl)amino)butan-2-yl)carbamate (8b)

White microcrystals (68%); mp 214–215 °C; ^{1}H NMR (DMSO-d_6) δ 10.47 (s, 1H), 8.50–8.30 (m, 2H), 8.05 (d, J = 8.1 Hz, 2H), 7.85–7.72 (m, 1H), 7.50–7.05 (m, 12H), 5.02 (s, 2H), 4.72–4.58 (m, 1H), 4.10–3.90 (m, 2H), 3.82 (t, J = 7.2 Hz, 1H), 3.15–3.00 (m, 1H), 2.90–2.75 (m, 1H), 1.99–1.72 (m, 1H), 0.80–0.61 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 171.5, 170.9, 168.3, 156.0, 151.7, 148.0, 138.2, 137.7, 137.0, 129.2, 128.3, 128.0, 127.6, 126.2, 119.4, 113.4, 65.5, 60.4, 53.6, 42.7, 37.7, 30.4, 19.1, 18.0. HRMS Calcd for $C_{29}H_{34}N_5O_5$ [M + H]$^+$: 532.2554; found: 532.2572.

Benzyl ((*S*)-1-(((*S*)-1-((2-(((*S*)-1-((6-methoxybenzo[d]thiazol-2-yl)amino)-1-oxo propan -2-yl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)carbamate (8c)

White microcrystals (60%); mp 148–150 °C; ^{1}H NMR (DMSO-d_6) δ 8.28–8.22 (m, 1H), 8.00 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.58–7.52 (m, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.36–7.30 (m, 5H), 7.26–7.18 (m, 6H), 7.06–6.90 (m, 1H), 5.02–4.92 (m, 2H), 4.58–4.42 (m, 2H), 4.01 (t, J = 7.2 Hz, 1H), 3.84–3.62 (m, 5H), 3.08–2.98 (m, 1H), 2.88–2.68 (m, 1H), 1.35 (d, J = 7.2 Hz, 3H), 1.11 (d, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 172.1, 172.0, 171.2, 168.7, 156.1, 142.6, 137.6, 137.0, 132.8, 129.2, 128.3, 128.0, 127.7, 126.2, 121.1, 114.9, 104.7, 65.5, 55.6, 53.9, 50.7, 48.6, 41.7, 37.3, 22.7, 18.1, 17.6 Anal. Calcd for $C_{33}H_{36}N_6O_7S$: C, 59.99; H, 5.49; N 12.72; found: C, 59.61; H, 5.50; N, 12.50.

General procedure for C-acylation: synthesis of compounds (9a–b)

A solution of benzotriazole intermediate **3a**, **5c** (1eq.), *C*-nucleophile (1eq.), and DMAP (1eq.) in THF (5 mL), was added to a dried heavy-walled Pyrex tube with a small stir bar. This reaction mixture was exposed to microwave irradiation (70 °C, 50 W) for specified time with a simultaneous cooling. After the reaction was completed (monitored by TLC), the THF was evaporated, and the solution was acidified and then extracted with ethyl acetate. The solvent was removed under reduced pressure, and the residue was purified by recrystallization from ethyl acetate to give the corresponding product **9a** and **9b**.

Benzyl-((*S*)-1-(((*S*)-1-((2-(4,4-dimethyl-2,6-dioxocyclohexylidene)-2-hydroxyethyl) amino)-1-oxo-3-phenylpropan-2-yl)amino)-1-oxopropan-2-yl)carbamate (9a)

White microcrystals (69%); mp 103–105 °C; ^{1}H NMR (DMSO-d_6) δ 8.78–8.60 (m, 1H), 8.40–8.26 (m, 1H), 7.84–7.55 (m, 11H), 5.38 (br s, 2H), 5.05–4.82 (m, 2H), 4.94–4.81 (m, 2H), 4.43–4.40 (m, 1H), 4.20–4.16 (m, 1H), 3.45–3.38 (m, 1H), 3.26–3.18 (m, 1H), 2.89 (s, 4H), 1.50 (d, J = 7.5 Hz, 3H), 1.40–1.30 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 200.6, 195.2, 172.1, 171.3, 171.1, 155.5, 137.6, 136.9, 129.2, 128.3, 127.9, 127.7, 126.2, 111.1, 65.4, 53.5, 50.2, 47.5, 37.7, 30.7, 27.5, 18.1. HRMS Calcd for $C_{30}H_{35}N_3O_7Na$ [M + Na]$^+$ 572.2367; found 572.2377.

Benzyl-((*S*)-1-((2-(((*S*)-1-((2-(2,6-dioxocyclohexyl)-2-oxoethyl)amino)-4-methyl-1-oxo-pentan-2-yl)amino)-2-oxoethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (9b)

White microcrystals (69%); mp 103–105 °C; ^{1}H NMR (DMSO-d_6) δ 8.37–8.26 (m, 1H), 8.22–8.15 (m, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.36–7.18 (m, 10H), 5.02–4.88 (m, 2H), 4.50–4.20 (m,

4H), 3.88–3.67 (m, 2H), 3.07–2.98 (m, 1H), 2.80–2.65 (m, 2H), 2.55–2.27 (m, 3H), 1.95–1.44 (m, 5H), 0.89 (d, J = 6.0 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 201.1, 172.3, 171.8, 168.5, 155.9, 138.2, 136.9, 129.2, 128.3, 128.0, 127.7, 127.4, 126.2, 112.1, 65.2, 56.2, 50.8, 47.6, 42.0, 41.0, 37.3, 24.1, 23.1, 21.6, 18.7. HRMS Calcd for $C_{33}H_{41}N_4O_8$ $[M + H]^+$ 621.2919; found 621.2931. HRMS Calcd for $C_{33}H_{41}N_4O_8Na$ $[M + Na]^+$ 643.2738; found 643.2757.

Results and Discussion

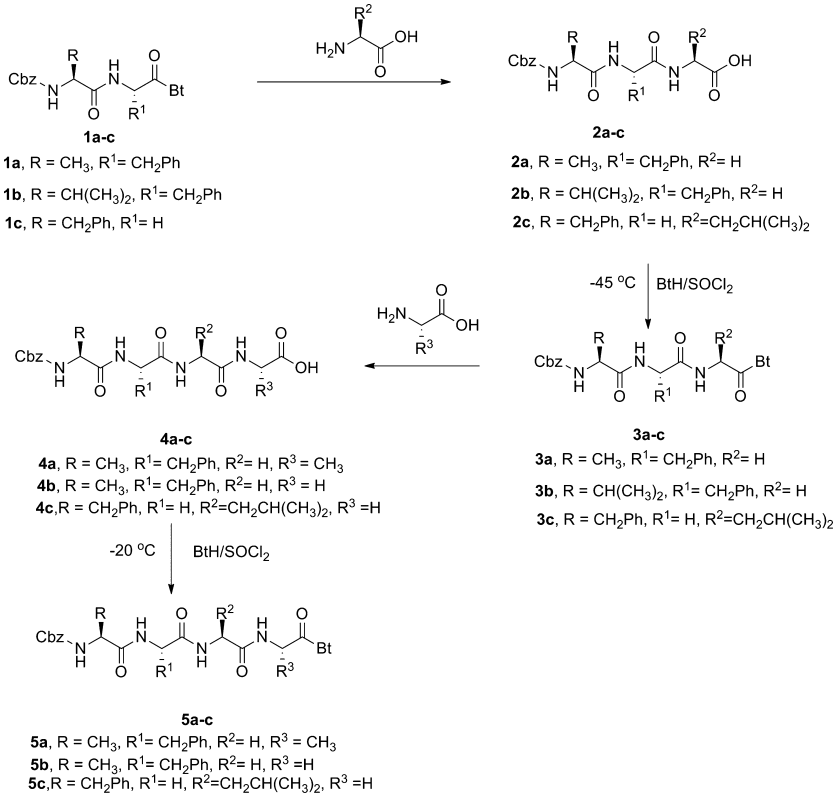
Syntheses of Cbz-protected-tripeptidoylbenzotriazole and tetrapeptidoylbenzotriazole

The Cbz-protected tripeptides **2a–c** and tetrapeptides **4a**–**c** were synthesized by our previously reported method by stepwise coupling (33) of amino acids with subsequent benzotriazole-activated *N*-protected amino acid analogs in solution phase in good yields (67–91%). Compounds **2a–c** and **4a**–**c** were further activated by benzotriazole to obtain known intermediates **3a**, **5a** and novel intermediates **3b–c** and **5b–c** in good yields (62–93%). These tripeptidoylbenzotriazoles **3a–c** and tetrapeptidoylbenzotriazoles **5a–c** were used as active intermediates to prepare peptide conjugates (Scheme 1, Table 1).

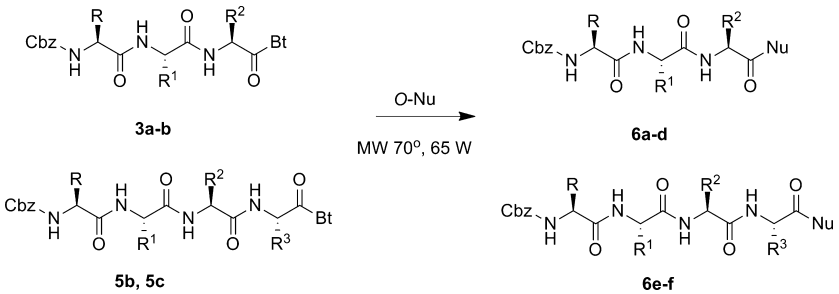
O-Acylations carried out by tri- and tetrapeptidoylbenzotriazoles

Compounds **3a–b, 5b,** and **5c** were reacted with a variety of steroids, terpenes, and sugar derivatives in the presence of catalytic amount of DMAP under microwave irradiations at 70 °C and 65 W power for 1.5–3 h to afford novel peptide conjugates **6a–f** in yields of 35–58% (Scheme 2, Table 2).

Compounds **6a–f** were fully characterized by ^{1}H NMR and ^{13}C NMR and elemental analysis. The tri- and tetrapeptide conjugates



Scheme 1: Syntheses of benzotriazole derivatives of tri- and tetrapeptides.



Scheme 2: *O*-Acylation of *N*–Pg-tri- and tetrapeptidoylbenzotriazoles.

Table 2: *O*-Acylation with *N*–Pg-tri- and tetrapeptidoylbenzotriazoles

Product	Reactant	Reactant	Time	Yield (%)	Mp(°C)
6a	Z–L–Ala–L–Phe–Gly–Bt **3a**	Cholesterol	1 h 45 min	45	162–163
6b	Z–L–Ala–L–Phe–Gly–Bt **3a**	Nerol	1 h 30 min	50	114–116
6c	Z–L–Val–L–Phe–Gly–Bt **3b**	Galactopyranose	1 h 30 min	47	129–132
6d	Z–L–Val–L–Phe–Gly–Bt **3b**	Estrone	2 h 15 min	35	151–153
6e	Z–L–Ala–L–Phe–Gly–Gly-Bt **5b**	Diacetone glucose	1 h 45 min	58	102–104
6f	Z–L–Phe–Gly–L–Leu–Gly-Bt **5c**	Menthol	1 h 45 min	42	104–106

are at least 95% chirally pure as supported by the NMR spectra of **6a–f,** which showed no duplication of signals (Appendix S1).

S-Acylation with tri- and tetrapeptidoylbenzotriazoles

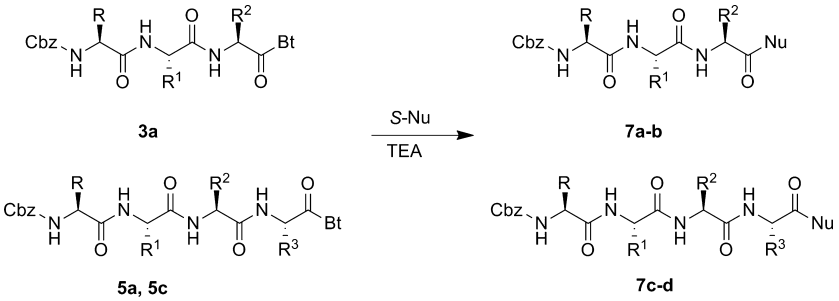
Compounds **3a, 5a** and **5c** were reacted with *S*-nucleophiles in the presence of triethylamine at room temperature for 2 h to give their corresponding *S*-acylated tripeptide conjugates **7a–b** (78–83%) and tetrapeptide conjugates **7c**–**d** (68–94%) (Scheme 3, Table 3). The chiral purity of **7a–d** was supported by their ^{1}H NMR and ^{13}C NMR spectra, which showed no evidence of epimerization in their *S*-acylated tri- and tetrapeptide conjugates (Appendix S1).

The ^{1}H NMR spectra of compounds **7a** and **7b** showed prominent doublets for the methyl protons of alanine unit at 1.14 ppm, and ^{13}C NMR showed prominent signals for all carbonyls of the tripeptide unit in the range of 196.2–155.6 ppm. Duplicate signals are absent in the ^{13}C NMR spectra of compounds **7a–b**. Compound **7c** showed sharp singlets of CH_2 protons of mercaptoacetic acid unit and Cbz group at 3.62 and 4.99 ppm, respectively, with no other repetition of signals in the NMR spectrum. Compound **7d** also showed singlet of CH_2 protons of benzyl group and Cbz group at 4.10 and 4.95 ppm, respectively, with no other repeated signals confirming the formation of chirally pure **7c** and **7d**.

N-Acylation with tri- and tetrapeptidoylbenzotriazoles

Compounds **3a–b** and **5a**, **5c** were reacted with different *N*-nucleophiles in the presence of base to give the corresponding chirally pure *N*-acylated tripeptides **8a–b** and tetrapeptides **8c–d** (Scheme 4, Table 4). Compounds **3a** and **5c** were reacted with *N*-nucleophiles in the presence of triethylamine at 20 °C for 1 h to give the corresponding tripeptide conjugate **8a** (75%) and tetrapeptide conjugate **8d** (68%). Compounds **3b** and **5b** reacted with heterocyclic *N*-nucleophiles under microwave irradiation at 65 °C for 30 min in DMF to give the corresponding chirally pure peptide conjugates **8b** (68%) and **8c** (60%). Compounds **8a–d** were fully characterized by NMR spectroscopy and elemental analysis (Appendix S1).

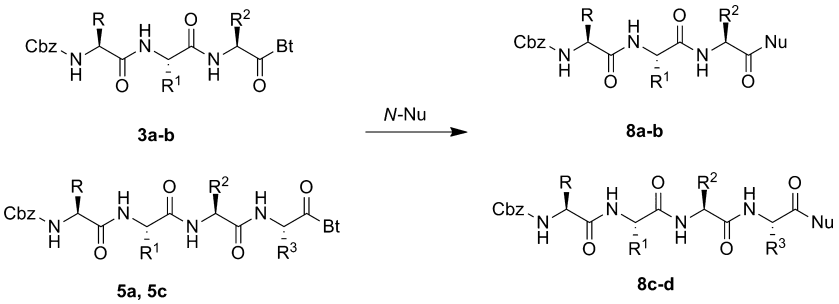
The chiral purity of compounds **8a–d** was confirmed by ^{1}H NMR and ^{13}C NMR. Tripeptide conjugate **8a** and tetrapeptide conjugate **8c** showed doublets for the methyl protons of the alanine unit at δ 1.12 ppm (**8a**) and 1.35, 1.12 ppm (**8c**) with no duplication of signals in ^{1}H NMR and ^{13}C NMR spectra. Compound **8b** showed prominent singlet of NH proton of aminopyridine unit at 10.47 ppm, and compound **8d** showed sharp singlet for the methyl protons of the *N*-methylpiperazine unit at 2.15 ppm with no other duplication of signals in ^{1}H NMR and ^{13}C NMR spectra, which confirms the formation of chirally pure **8b** and **8d**.



Scheme 3: *S*-Acylation of *N*–Pg-tri- and tetrapeptidoylbenzotriazoles.

Table 3: *S*-Acylation with *N*–Pg-tri- and tetrapeptidoylbenzotriazoles

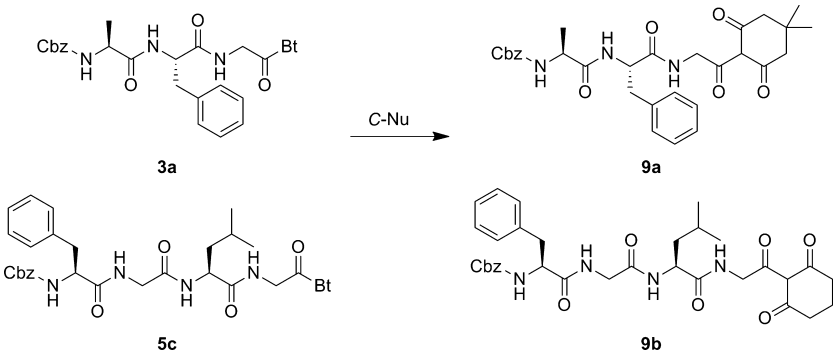
Product	Reactant	Reactant	Yield (%)	Mpt(°C)
7a	Z–L–Ala–L–Phe–Gly–Bt **3a**	Thiophenol	78	146–148
7b	Z–L–Ala–L–Phe–Gly–Bt **3a**	Methylmercaptoacetate	83	158–160
7c	Z–L–Ala–L–Phe–Gly–L-Ala-Bt **5a**	Mercaptoacetic acid	68	103–105
7d	Z–L–Phe–Gly–L–Leu–Gly-Bt **5c**	Benzyl mercaptan	94	186–187



Scheme 4: *N*-Acylation of *N*–Pg-tri- and tetrapeptidoylbenzotriazoles.

Table 4: *N*-Acylation with *N*–Pg-tri- and tetrapeptidoylbenzotriazoles

Product	Reactant	Reactant	Conditions	Yield (%)	Mpt(°C)
8a	Z–L–Ala–L–Phe–Gly–Bt **3a**	*N*-(3-Amino-propyl)-imidazole	THF, TEA, 1 h, RT	75	65–69
8b	Z–L–Val–L–Phe–Gly–Bt **3b**	2-Aminopyridine	DMF, 65°, MW, 0.5 h	68	214–215
8c	Z–L–Ala–L–Phe–Gly–L-Ala-Bt **5a**	2-Amino-6-methoxy-benzothiazole	DMF, 65°, MW, 0.5 h	60	148–150
8d	Z–L–Phe–Gly–L–Leu–Gly-Bt **5c**	*N*-Methylpiperazine	THF, TEA, 1 h, RT	68	181–183



Scheme 5: *C*-Acylation of *N*–Pg-tri- and tetrapeptidoylbenzotriazoles.

Table 5: *C*-Acylation with *N*–Pg-tri- and tetrapeptidoylbenzotriazoles

Product	Reactant	Reactant	Yield (%)	Mpt(°C)
9a	Z–L–Ala–L–Phe–Gly–Bt **3b**	Dimedone	69	135–137
9b	Z–L–Phe–Gly–L–Leu–Gly-Bt **5c**	1,3 Cyclohexanedione	61	188–190

C-Acylation using tri- and tetrapeptidoylbenzotriazoles

Compounds **3a** and **5a** were reacted with different *C*-nucleophiles in the presence of 1 equivalent of DMAP in MW at 70 °C under 50 W irradiation power to give the corresponding tripeptide conjugate **9a** (69%) and tetrapeptide conjugate **9b** (61%) (Scheme 5, Table 5). Compounds **9a** and **9b** were fully characterized by NMR and HRMS analysis. No evidence for epimerization was found in the ^{1}H NMR and ^{13}C NMR spectra of **9a** and **9b**.

Conclusion

In conclusion, *N*-(Pg-α-tripeptidoyl)benzotriazoles and *N*-(Pg-α-tetrapeptidoyl)benzotriazoles are convenient coupling reagents, sufficiently reactive to form amide and ester bonds at ambient temperature. They offer an efficient preparation of chirally pure *N*-protected tri- and tetrapeptide conjugates with sugars, steroids, terpenes, and different heterocycles by *O*-, *S*-, *N*-, and *C*-acylations in synthetically useful yields without detectable racemization.

Acknowledgments

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References

1. Ghose A.K., Viswanadhan V.N., Wendoloski J.J. (1999) A knowledge-based approach in designing combinatorial or medicinal

chemistry libraries for drug discovery. 1. a qualitative and quantitative characterization of known drug databases. J Comb Chem;1:55–68.
2. Gill I., Lopez-Fandino R., Jorba X., Vulfson E.N. (1996) Biologically active peptides and enzymatic approaches to their production. Enzyme Microb Technol;18:162–183.
3. Han S.-Y., Kim Y.-A. (2004) Recent development of peptide coupling reagents in organic synthesis. Tetrahedron;60:2447–2467.
4. Montalbetti C.A.G.N., Falque V. (2005) Amide bond formation and peptide coupling. Tetrahedron;61:10827–10852.
5. Iorga B., Campagne J.-M. (2004) Ethyl propiolate: a simple and convenient peptide coupling reagent. Synlett;10:1826–1828.
6. Matsumoto T., Watanabe M., Mataka S., Thiemann T. (2003) Estrano[17,16-*e*]pyrimidine-peptide conjugates. Steroids;68:751–757.
7. Laruelle C., Lepant M. (1992) Process for preparation of pure isomeric forms of 3,3,5-trimethylcyclohexanone and 3,3,5-trimethylcyclohexyl amino acid esters. FR Patent 19912654338, 1991; Chem Abstr;116:67183.
8. Penney C.L., Shah P., Landi S. (1985) A simple method for the synthesis of long-chain alkyl esters of amino acids. J Org Chem;50:1457–1459.
9. Varki A. (1993) Biological roles of oligosaccharides: all of the theories are correct. Glycobiology;3:97–130.
10. Dwek R.A. (1996) Glycobiology: toward understanding the function of sugars. Chem Rev;96:683–720.
11. Kobata A. (1993) Glycobiology: an expanding research area in carbohydrate chemistry. Acc Chem Res;26:319–324.
12. Albericio F., Bofill J.M., El-Faham A., Kates S.A. (1998) Use of onium salt-based coupling reagents in peptide synthesis. J Org Chem;63:9678–9683.
13. Klose J., El-Faham A., Henklein P., Carpino L.A., Bienert M. (1999) Addition of HOAt dramatically improves the effectiveness of pentafluorophenyl-based coupling reagents. Tetrahedron Lett;40:2045–2048.
14. Carpino L.A., Beyermann M., Wenschuh H., Bienert M. (1996) From α-amino acids to peptides: all you need for the journey. Acc Chem Res;29:268–274.
15. Carpino L.A., Sadat-Aalaee D., Chao H.G., Desselms R.H. (1990) (9-Fluorenylmethyl)oxy]carbonyl (FMOC) amino acid fluorides. Convenient new peptide coupling reagents applicable to the FMOC/tert-butyl strategy for solution and solid-phase syntheses. J Am Chem Soc;112:9651–9652.
16. DalPozzo A., Ni M., Muzi L., Caporale A., de Castiglione R., Kaptein B., Broxterman Q.B., Formaggio F. (2002) Amino acid bromides: their *N*-protection and use in the synthesis of peptides with extremely difficult sequences. J Org Chem;67:6372–6375.
17. Saha A.K., Schultz P., Rapoport H. (1989) 1,1′-Carbonylbis(3-methylimidazolium) triflate: an efficient reagent for aminoacylations. J Am Chem Soc;111:4856–4859.
18. Bodanszky M., Klausner Y.S., Ondetti M.A. (1976) Peptide Synthesis, 2nd edn. New York, USA: Wiley & Sons;224 p.
19. Ishihara K., Ohara S., Yamamoto H. (2000) Direct polycondensation of carboxylic acids and amines catalyzed by 3,4,5-trifluorophenylboronic acid. Macromolecules;33:3511–3513.
20. Reczek J.J., Rebolini E., Urbach A.R. (2010) Solid-phase synthesis of peptide-viologen conjugates. J Org Chem;75:2111–2114.
21. Yasukata T., Shindo H., Yoshida O., Sumino Y., Munekage T., Narukawa Y., Nishitiani Y. (2002) An efficient and practical method for solid-phase synthesis of tripeptide-bearing glycopeptide antibiotics: combinatorial parallel synthesis of carboxamide derivatives of chloroorienticin B. Bioorg Med Chem Lett;12:3033–3036.
22. Kachalova A.V., Stetsenko D.A., Gait M.J., Oretskaya T.S. (2004) Synthesis of oligonucleotide 2′-conjugates via amide bond formation in solution. Bioorg Med Chem Lett;14:801–804.
23. Jeric I., Horvat S. (2001) Novel ester-linked carbohydrate-peptide adducts: effect of the peptide substituent on the pathways of intramolecular reactions. Eur J Org Chem; 1533–1539.
24. Matsumoto T., Shiine K., Mataka S., Thiemann T. (2009) Estrano[17,16-*e*]pyrimidine-amino acid and estrano[17,16-*e*]pyrimidine-peptide conjugates. J Chem Res;39:1–396.
25. Coutrot F., Grison C., Coutrot P. (2004) A route to new galactosyl peptides: application to the synthesis of a galactosyl pentapeptide analogue of Leu-enkephalin. C R Chim;7:3–13.
26. Katritzky A.R., He H.-Y., Suzuki K. (2000) *N*-Acylbenzotriazoles: neutral acylating reagents for the preparation of primary, secondary, and tertiary amides. J Org Chem;65:8210–8213.
27. Katritzky A.R., Wang M., Zhang S. (2001) One-pot synthesis of cinnamoyl hydrazides. Arkivoc;ix:19–23.
28. Katritzky A.R., Abdel-Fattah A.A.A., Wang M. (2003) Expedient acylations of primary and secondary alkyl cyanides to α-substituted β-ketonitriles. J Org Chem;68:4932–4934.
29. Katritzky A.R., Suzuki K., Singh S.K., He H.-Y. (2003) Regiospecific c-acylation of pyrroles and indoles using *N*-acylbenzotriazoles. J Org Chem;68:5720–5723.
30. Katritzky A.R., Tala S.R., Abo-Dya N.E., Abdel-Samii Z.K. (2009) Efficient synthesis of azo dye labeled terpenes, sugars, and steroids using *N*-(4-arylazobenzoyl)-1*H*-benzotriazoles. Synthesis;10:1708–1714.
31. Katritzky A.R., Abo-Dya N.E., Tala S.R., Ghazvini-Zadeh E.H., Bajaj K., El-Feky S.A. (2010) Efficient and selective syntheses of *S*-acyl and *N*-acyl glutathiones. Synlett;9:1337–1340.
32. Katritzky A.R., Angrish P., Todadze E. (2009) Chiral acylation with *N*-(protected α-aminoacyl)benzotriazoles for advantageous syntheses of peptides and peptide conjugates. Synlett;15:2392–2411.
33. Abdelmajeid A., Tala S.R., Amine M.S., Katritzky A.R. (2011) Tri-, tetra- and pentapeptidoylbenzotriazoles: Novel synthetic intermediates. Synthesis;18:2995–3005.
34. Katritzky A.R., Angrish P. (2006) Convenient and efficient preparation of *N*-protected (α-aminoacyl)oxy-substituted terpenes and alkanes. Synthesis;24:4135–4142.
35. Katritzky A.R., El-gendy B.E., Todadze E., Abdel-Fattah A.A.A. (2008) (α-Aminoacyl)amino-substituted heterocycles and related compounds. J Org Chem;73:5442–5445.

Supporting Information

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

Appendix S1. ^{1}H NMR and ^{13}C NMR spectra for **1b–c**, **2a–c**, **3a–c**, **4a–c**, **5a–c**, **6a–f**, **7a–d**, **8a–d**, **9a–b**.

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