Functionalized Derivatives of Benzocrown Ethers, III[◇]

New Macrocyclic Derivatives Containing Chiral and Linear Lateral Amino-Acid Moieties

Mihai Barboiu*[ab], Nadine Hovnanian[c], Constantin Luca[b], Georgeta Popescu[a], and Louis Cot[c]

Research Centre of Macromolecular Materials and Membranes[a],
206, Spl. Independentei, P. O. Box 15-143, R-79611, Bucharest, Romania
Fax: (internat.) + 40(0)1/222-9131
E-mail: m-barboiu@chim.upb.ro

University "Politehnica" Bucharest, Department of Analytical Chemistry[b],
1, Polizu, R-78126, Bucharest, Romania

Laboratoire des Materiaux et Procedes Membranaires, Ecole Nationale Superieure de Chimie Montpellier,[c]
8, rue de l'Ecole Normale, F-34053 Montpellier, Cedex 1, France
E-mail: Impm@cit.enscm.fr

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We report the preparation of a new series of functionalized derivatives of dibenzo-18-crown-6, containing in second sphere of coordination lateral arms of different linear and chiral L-amino acids: glycine, β-alanine, 11-aminoundecanoic acid, L-cysteine, L-aspartic acid, L-phenylalanine, L-tryptophan, L-histidine. All these new derivatives were characterized by elemental analysis, IR and ^{1}H-NMR spectroscopy, and these data were in agreement with proposed molecular structures.

Molecular receptors are defined as organic structures held by covalent bonds, that are able to bind selectively ionic or molecular substrates by means of various intermolecular interactions, leading to an assembly of two or more species, a *supermolecule*.[1] Complexation of ionic substrates[1][2][3][4][5][6][7][8] was achieved by the simplest recognition with synthetic receptors such as crown ethers and their numerous derivatives, cryptates or polyaza- and polythia-macrocyclic ligands. Tetrahedral, trigonal or multiple recognition was extended for selective binding of molecular substrates.[9][10] Because of the important role played by substituted ammonium ions (i.e. amino acids, ephedrine, adrenaline etc.) in chemistry and in biology, the preparation of the optically active crown ethers **1**, **3**[11][12] or the tritopic selective receptor **2**[10], capable of selectively recognizing of such substrates, is of special interest (Figure1).

We previously reported the first ditopic receptors containing positively charged moieties in the second sphere of coordination[13][14] for which we expected a new kind of complexation behavior. For instance, amino acids are known to bind to crown ethers[4][6][15]; the ammonium moiety of complexed amino acids is able to interact with a crown ether cavity by three hydrogen bonds. The ditopic receptors are able to interact with the carboxylate anion (from the zwitterionic form of the amino acid) under specific conditions.[15][16] In this paper we describe the preparation of a new series of functionalized dibenzo-18-crown-6 ether derivatives containing linear or optically active L-amino acid moieties in the second sphere of coordination. The objective is to use these derivatives as polytopic receptors, as mobile carriers in liquid membrane separation, as analytical reagents for spectrophotometric determination of optically active compounds, as well as molecular models for enzymatic catalysis.[17][18][19] The selected macrocyclic receptor used in our syntheses was the commercially available dibenzo-18-crown-6 (**4**). The acylation reaction, using acetic acid, carried out in Eaton reagent (CH_3SO_3H/P_2O_5, 1:12 w/w)[20] yielded the 2,3,11,12-bis[4(5′)-acetyl]benzo-18-crown-6 derivatives **5a,b**.[14][20] Subsequent oxidation of crude **5a,b** with NaBrO/NaOH[22] led to 2,3,11,12-bis(4-carboxy)benzo-18-crown-6 (**6**; Figure 2).

In the first step, a *cis*/*trans* mixture of diacylated compounds **5a,b** was obtained, which could not be purified by column chromatography or by fractional crystallization. In general, for similar systems the *cis* isomer is the predominant one.[20][21] Previously, the acylation reaction of benzocrown ethers with phthalimido-protected amino acids led to the same result.[15] Oxidation of the *cis*/*trans* derivatives **5a,b**[22] afforded a mixture of crude dicarboxylic acids, from which the *cis* product **6** was isolated by fractional crystallization from EtOH. Unfortunately, the *trans*-dicarboxylic acid (15% from crude mixture), could not be satisfactorily purified due to its low solubility. By reaction with $SOCl_2$, the *cis*-dicarboxylic acid led to the diacyl dichloride deriva-

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Figure 1. Selective macrocyclic receptors for biologically active ammonium substrates

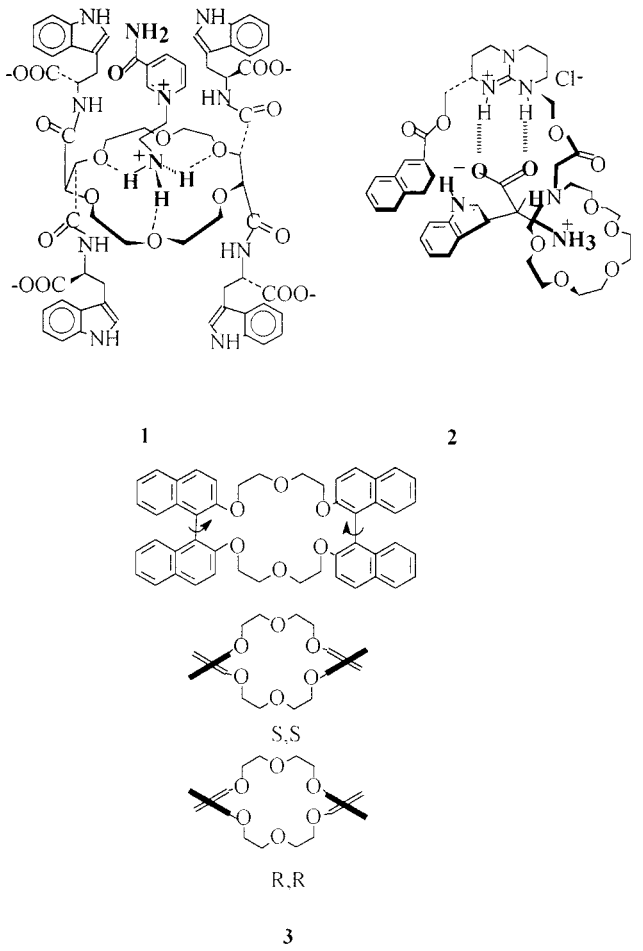
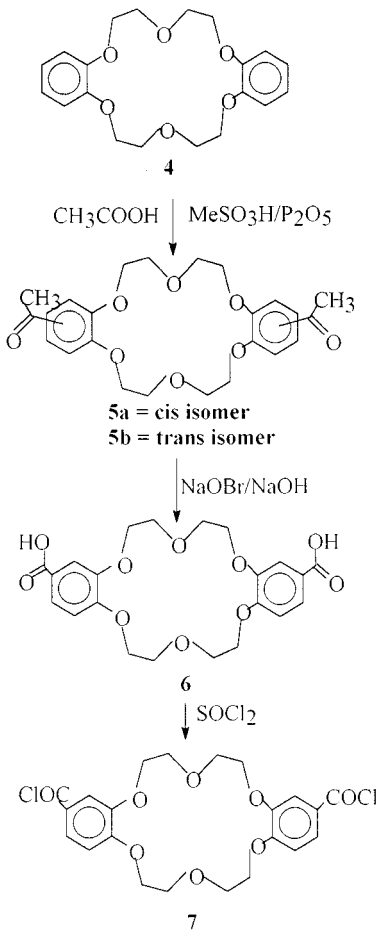


Figure 2. Acylation and oxidation reactions of dibenzo-18-crown-6



tive **7** (see Figure 2) which reacts with glycine (**8**), β-alanine (**9**), 11-aminoundecanoic acid (**10**), L-cysteine (**11**), L-aspartic acid (**12**), L-phenylalanine (**13**), L-tryptophan (**14**), L-histidine (**15**) (see Figure 3), to yield the ditopic macrocyclic derivatives **8**−**15**.

The new compounds **5**−**15** were characterized by elemental analysis, IR and ^{1}H-NMR spectroscopy. The IR spectra of **5a,b** showed a broad ν_{CO} band at 1630−1674 cm^{-1}, probably due to the two isomers. After purification of the crude dicarboxylated compounds, the *cis* compound **6** presented two ν_{CO} bands at 1677 and 1730 cm^{-1}.[22] The *trans* product also shows two ν_{CO} bands at 1635 and 1730 cm^{-1}. The IR spectra of amino acid derivatives **8**−**15** showed the characteristic vibrations of the crown ether moiety: ν_{COCas} = 1267−1270 cm^{-1}, ν_{COCs} = 1131−1134 cm^{-1}, ν_{COCAr} = 1062 cm^{-1}, ν_{CCAr} = 1500−1509 cm^{-1}, $\nu_{Ar\ conj.}$ = 1588−1600 cm^{-1}, ν_{CH2s} = 2875−2886 cm^{-1}, ν_{CH2s} = 2923−2933 cm^{-1} and ν_{CHAr} = 3075−3086 cm^{-1}. The bands of the amide moiety were also detected: $\nu_{NHCO\ I}$ = 1630−1680 cm^{-1}, $\nu_{NHCO\ II}$ = 1451−1462 cm^{-1} and $\nu_{NHCO\ III}$ = 1341−1362 cm^{-1}. For the linear amino acid derivatives **8**−**10**, the $\nu_{NHCO\ I}$ and $\nu_{NHCO\ III}$ bands appeared at 1675−1682 cm^{-1} and 1356−1362 cm^{-1}, respectively, due to the non-associated amide moieties. For the optically active amino acid derivatives **11**−**15** the $\nu_{NHCO\ II}$ and $\nu_{NHCO\ III}$ bands were displaced to lower frequencies ($\nu_{NHCO\ II\ (NH)}$: 1550⇒1451 cm^{-1} and $\nu_{NHCO\ (CN)\ III}$: 1400⇒1350 cm^{-1}), probably due to intramolecular hydrogen bonding with amide, carboxylic or heterocyclic moieties (Figure 4).[23]

In the IR spectra of compounds **8**−**15** the carboxylic bands of the amino acids are present at ν_{CO} = 1710−1720 cm^{-1} and $\nu_{OH\ as}$ = 3200−3500 cm^{-1} and $\nu_{OH\ nonas}$ = 3610−3618 cm^{-1}. In the ^{1}H-NMR spectra of the synthesized compounds the following features were observed:

i) the proton signals of the ether bridges of the crown ether moieties appear as triplets at δ = 3.70−4.30 for the unsubstituted derivatives **5**,**6** and at δ = 3.83−4.11 for the amino acid compounds **8**−**15**;

ii) the signals of the aromatic protons of the acylated phenyl ring are observed at δ = 6.96−7.00 and at δ = 7.25−7.51;

iii) the carboxylic proton signals appear as a singlet at δ = 9.94−10.04;

iv) in the ^{1}H-NMR spectra of the chiral and linear amino acid derivatives the proton signals of the R groups were assigned (for details see Experimental Section);

v) in the ^{1}H-NMR spectra of the amides **8**−**10** the NH proton signals appear at δ = 8.11−8.28, and a considerable

Figure 3. Synthesis of macrocyclic amino acid derivatives **8**−**15** from diacyl dichloride **7**

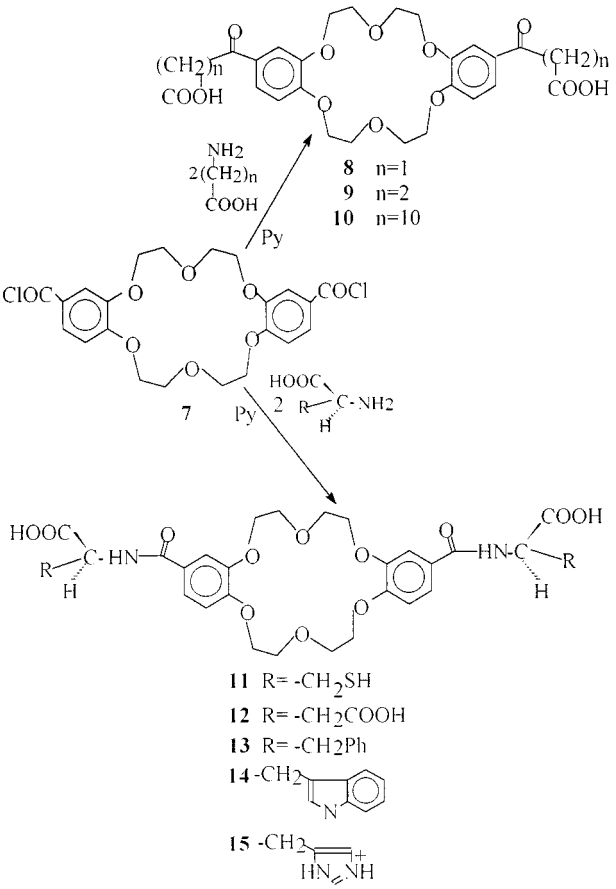
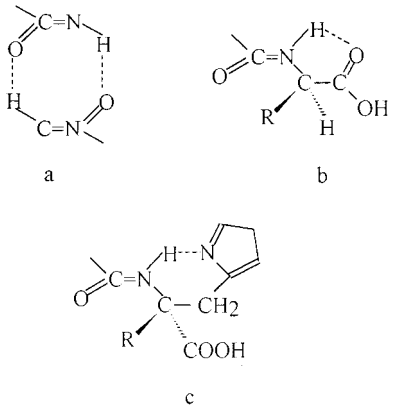


Figure 4. Hydrogen bonding of amide moieties with: a) the other amide moiety; b)carboxylic acid, or c) heterocyclic moiety from the amino acid group



downshift is observed for those protons (δ = 10.44−10.65) in the derivatives **11**−**15**,[24] indicating the formation of hydrogen bonds between amide groups and available moieties of the amino acid groups (see Figure 4).

Further enantioselective transport experiments with the amino acids using liquid membranes are currently under way.

Experimental Section

L-Amino acids, dibenzo-18-crown-6, methanesulfonic acid, and phosphorus pentoxide were purchased from Merck and were used without purification. All other reagents and solvents were of analytical grade and were used as received. − Melting points were determined with a heating-plate microscope and were not corrected. − IR spectra were recorded using KBr pellets with a Nicolet 2DXFT-IR spectrometer. − ^{1}H-NMR spectra were recorded with a Bruker AC 250-MHz spectrometer in [D$_6$]DMSO. Chemical shifts are reported as δ values relative to TMS as internal standard. − Elemental analysis was done by combustion with a Carlo Erba instrument CHNS Elemental Analyser Model 1106.

Preparation of of 2,3,11,12-Bis[4(5′)-acetyl]benzo-18-crown-6 (**5a**,**b**): 3 g ($8.33 \cdot 10^{-3}$ mol) of dibenzo-18-crown-6 (**4**) and 0.7 g (0.7 ml) of acetic acid were added to 15 ml of Eaton reagent.[20] The reaction mixture was stirred for 48 h at room temp., then for 20 min at 60°C. The reaction mixture was poured into 200 ml of water, causing precipitation of the desired product. After filtration, this was redissolved in 50 ml of $CHCl_3$ and the obtained solution was washed with diluted LiOH, then with water. The solvent was evaporated in vacuo and the separated products were recrystallized from *n*-hexane. (3.33 g, 90%). − M.p. 165−167°C from *n*-hexane. − IR (KBr): ν = 798, 1058, 1140, 1274, 1360, 1430, 1516, 1598, 1630−1674, 2880, 2932 cm^{-1}. − ^{1}H NMR ([D$_6$]DMSO): δ = 2,53 (s, 6 H,C*H*$_3$), 3.70−4.23 (m, 16 H, C*H*$_2$C*H*$_2$), 6.82−6.86 [m, 2 H, *m*-*H*-C$_6$H$_3$O(CO)], 7.49−7.52 [m, 4 H, *o*-*H*-C$_6$H$_3$O(CO)]. − $C_{24}H_{28}O_8$ (438.43): calcd. C 65.75, H 5.06, O 29.19; found C 65.52, H 5.49, O, 28.86.

Preparation of 2,3,11,12-Bis(4-carboxy)benzo-18-crown-6 (**6**): A mixture of the *cis*- and *trans* isomers of *2,3,11,12-bis[4(5′)-acetyl]-benzo-18-crown-6* (**5a**,**b**) (3 g, $6.75 \cdot 10^{-3}$ mol), was suspended in 100 ml of distilled water, and 150 ml of an aqueous solutions of NaOH (44 g) and 14 ml of bromine water (276 mmol Br_2) were added at 0−10°C within 2 h; then the solution was stirred at 20°C for 24 h. After extraction of unreacted **5a**,**b** with chloroform (200 ml), the aqueous solution was acidified with hydrochloric acid (2 N). The product precipitated. Recrystallization from EtOH led to the *cis* isomer of *2,3,11,12-bis[4(5′)-carboxy]benzo-18-crown-6* (**6**) (2.42 g, 80%), whereas the insoluble residue contained a small quantity of the *trans* product.

General Procedure for the Preparation of the Amino Acid Derivatives **8**−**15**: 0.9 g ($2 \cdot 10^{-3}$ mol) of dicarboxylic acid **6** was suspended in 100 ml of freshly distilled benzene. Then 30 mmol of $SOCl_2$ was added and the reaction mixture was refluxed for 5 h. After cooling, the solvents were removed under vacuum and the crude diacyl dichloride **7** was dissolved in 50 ml of dry pyridine. A stoichiometric amount of the amino acid was added at 0−10°C during 30 min, and then the reaction mixture was refluxed for 1 h. The reaction mixture was poured into 200 ml of ice-cold water and the resulting product [0.92 g of **8** (80%), 0.94 g of **9** (79%), 1.14 g of **10** (70%), 0.94 g of **11** (72%), 0.82 g of **12** (60%), 1.19 g of **13** (75%), 1.13 g of **14** (78%), 1.32 g of **15** (80%),] was recrystallized from acetic acid.

2,3,11,12-Bis[4-carboxyl]benzo-18-crown-6 (**6**): M.p. > 250°C from EtOH. − IR (KBr): ν = 884, 957, 1067, 1131, 1204, 1267, 1367, 1456, 1504, 1598, 1677, 1730, 2875, 2928, 3432, 3621 cm^{-1}. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.82−4.20 (m, 16 H, C*H*$_2$C*H*$_2$), 7.02−7.06 [m, 2 H, *m*-*H*-C$_6$H$_3$O(CO)], 7.20−7.54 [m, 4 H, *o*-*H*-C$_6$H$_3$O(CO)], 10.04 (s, 2 H, COO*H*). − $C_{22}H_{24}O_{10}$ (448.43): calcd. C 58.93, H 5.39, O 35.68; found C 58.65, H 5.49, O 35.77.

Glycine Derivative **8**: M.p. 195−197°C from AcOH. − IR (KBr): ν = 875, 960, 1060, 1132, 1204, 1270, 1361, 1452, 1500, 1600, 1680, 1720, 1750, 2883, 2885, 2924, 3080, 3400, 3610 cm^{-1}. − ^{1}H NMR ([D$_6$] DMSO): δ = 3.88−4.11 (m, 16 H,C*H*$_2$C*H*$_2$), 5.60 (m, 4 H,

HNCH_2COOH), 7.00 [m, 2 H, *m*-*H*-C_6H_3O(CO)], 7.21−7.52 [m, 4 H, *o*-*H*-C_6H_3O(CO)], 8.28 (m, 2 H, *H*NCO), 10.01 (s, 2 H, COO*H*). − $C_{26}H_{30}N_2O_{12}$ (562.53): calcd. C 55.51, H 5.38, N 4.98, O 34.13; found C 55.16; H 5.79, N 4.91, O 34.16.

β-Alanine Derivative **9**: M.p. 198−198°C from AcOH. − IR (KBr): ν = 878, 957, 1062, 1131, 1204, 1272, 1362, 1436, 1451, 1504, 1588, 1688, 1698, 2886, 2923, 3086, 3422, 3620 cm^{-1}. − ^1H NMR ([D$_6$]DMSO): δ = 2.15 (t, 4 H, CH_2COOH), 3.18 (t, 4 H, CH_2NHCO), 3.88−4.11 (m, 16 H, CH_2CH_2), 7.01 [m, 2 H, *m*-*H*-C_6H_3O(CO)], 7.20−7.56 [m, 4 H, *o*-*H*-C_6H_3O(CO)], 8.29 (m, 2 H, *H*NCO), 10.06 (s, 2 H, COO*H*). − $C_{26}H_{30}N_2O_{12}$ (562.53): calcd. C 55.51, H 5.38, N 4.98, O 34.13; found C 55.16, H 5.79, N 4.91, O 34.16.

11-Aminoundecanoic Acid Derivative **10**: M.p. 135−137°C from AcOH. − IR (KBr): ν = 757, 878, 1062, 1136, 1204, 1267, 1356, 1451, 1504, 1588, 1640, 1682, 1724, 2602, 2849, 2933, 3080, 3306, 3411, 3616 cm^{-1}. − ^1H NMR ([D$_6$] DMSO): δ = 1.24−1.47 [m, 32 H,(CH_2)$_8$], 2.14 (t, 4 H, CH_2COOH) 3.23 (t, 4 H, CH_2NHCO), 3.82−4.34 (m, 16 H, CH_2CH_2), 6.96 [m, 2 H, *m*-*H*-C_6H_3O(CO)], 7.25−7.51 [m, 4 H, *o*-*H*-C_6H_3O(CO)], 8.28 (m, 2 H, *H*NCO), 10.05 (s, 2 H, COO*H*). − $C_{44}H_{66}N_2O_{12}$ (815.01): calcd. C 64.84, H 8.16, N 3.44, O 23.56; found C 64.58, H 8.39, N 3.51, O 23.16.

L-Cysteine Derivative **11**: M.p. 188−189°C from AcOH. − IR (KBr): ν = 768, 878, 1062, 1136, 1204, 1267, 1351, 1430, 1456, 1504, 1604, 1635, 1720, 1750, 2883, 2885, 2924, 3080, 3400, 3610 cm^{-1}. − ^1H NMR ([D$_6$]DMSO): δ = 2.61 (d, 4 H, CH_2SH), 3.78 [t, 2 H, HOOC*CH*(R)NHCO], 3.82−4.11 (m, 16 H, CH_2CH_2), 7.04 [m, 2 H, *m*-*H*-C_6H_3O(CO)], 7.24−7.75 [m, 4 H, *o*-*H*-C_6H_3O(CO)], 10.02 (s, 2 H, COO*H*), 10.44 (m, 2 H, *H*NCO). − $C_{26}H_{30}N_2O_{12}S$ (650.67): calcd. C 51.69, H 4.65, N 4.31, O 29.51, S 9.85; found C 51.32, H 4.79, N 4.14, O 29.44, S 9.99.

L-Aspartic Acid Derivative **12**: M.p. 220−222°C from AcOH. − IR (KBr): ν = 873, 962, 1062, 1131, 1204, 1272, 1350, 1451, 1514, 1598, 1682, 1714, 1756, 2613, 2870, 2923, 3080, 3442, 3627 cm^{-1}. − ^1H NMR ([D$_6$]DMSO): δ = 2.39 (d, 4 H, CH_2COOH), 3.8 [m, 2 H, HOOCC*H*(R)NHCO], 3.89−4.11 (m, 16 H, CH_2CH_2), 7.00 [m, 2 H, *m*-*H*-C_6H_3O(CO)], 7.20−7.66 [m, 4 H, *o*-*H*-C_6H_3O(CO)], 10.26 (s, 2 H, COO*H*), 10.47 (s, 2 H, COO*H*), 10.58 (m, 2 H, *H*NCO). − $C_{30}H_{34}N_2O_{16}$ (678.60): calcd. C 53.10, H 5.05, N 4.13, O, 37.72; found C 53.35, H, 4.95, N 4.00, O 37.64.

L-Phenylalanine Derivative **13**: M.p. 185−187°C from AcOH. − IR (KBr): ν = 705, 747, 957, 1062, 1131, 1204, 1267, 1341, 1451, 1498, 1604, 1640, 1709, 2108, 2592, 2881, 2928, 3028, 3075, 3411, 3610 cm^{-1}. − ^1H NMR ([D$_6$]DMSO): δ = 3.15 (d, 4 H, CH_2C$_6$H$_5$), 3.78 [m, 2 H, HOOCC*H*(R)NHCO], 3.83−4.11 (m, 16 H, CH_2CH_2), 7.01 [m, 2 H, *m*-*H*-C_6H_3O(CO)], 7.21−7.57 [m, 16 H, *o*-*H*-C_6H_3O(CO) and $C_6H_5CH_2$], 10.02 (s, 2 H, COO*H*), 10.44 (m, 2 H, *H*NCO). − $C_{40}H_{42}N_2O_{12}$ (742.78): calcd. C 64.64, H 5.70, N 3.77, O 25.85; found C 64.22, H 5.91, N 4.02, O 25.65.

L-Histidine Derivative **14**: M.p. 177−179°C from AcOH. − IR (KBr): ν = 884, 957, 1062, 1136, 1204, 1272, 1360, 1435, 1462, 1509, 1593, 1680, 1709, 1740, 2602, 2875, 2933, 3075, 3417, 3632 cm^{-1}. − ^1H NMR ([D$_6$]DMSO): δ = 3.06 (d, 4 H, CH_2R), 3.78 [m, 2 H, HOOCC*H*(R)NHCO], 3.88−4.13 (m, 16 H, CH_2CH_2), 7.02 [m, 2 H, *m*-*H*-C_6H_3O(CO)], 7.21−7.70 [m, 12 H, *o*-*H*-C_6H_3O(CO) and the aromatic protons of histidine residues], 8.44 (m, 2 H, *H*NCO), 9.94 (s, 2 H, COO*H*). − $C_{34}H_{38}N_6O_{12}$ (722.71): calcd. C 56.51, H 5.30, N 11.63, O 26.57; found C 56.89, H 5.11, N 11.35, O 25.38.

L-Tryptophan Derivative **15**: M.p. 181−183°C from AcOH. − IR (KBr): ν = 873, 962, 1062, 1136, 1204, 1267, 1341, 1435, 1456, 1504, 1598, 1640, 1703, 2613, 2875, 2928, 3080, 3243, 3411, 3616 cm^{-1}. − ^1H NMR ([D$_6$]DMSO): δ = 3.37 (d, 4 H, CH_2Ar), 3.78 [m, 2 H, HOOCC*H*(R)NHCO], 3.83−4.11 (m, 16 H, CH_2CH_2), 6.44−7.01 [m, 4 H, *m*-*H*-C_6H_3O(CO) and the aromatic protons of tryptophan moieties], 7.10−7.57 [m, 14 H, *o*-*H*-C_6H_3O(CO) and the aromatic protons of tryptophan moieties], 10.02 (s, 2 H, COO*H*), 10.1 (m, 2 H, *H*N of tryptophan moieties), 10.54 (m, 2 H, *H*NCO). − $C_{44}H_{66}N_4O_{12}$ (843.03): calcd. C 62.69; H 7.89, N 6.65, O 22.77; found C 62.32, H 7.91, N 6.82, O 23.00.

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