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A XANTHONE-BASED MACROCYCLIC RECEPTOR AND ITS POSSIBLE APPLICATIONS

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Abstract – A macrocycle (**2**) based on xanthone units and diphenylethylenediamine is shown to present strong affinity for chloride ion; the extraction of sodium chloride from water to chloroform is possible in the presence of (**2**) and 18-crown-6 ether. Carboxylates also show strong affinities for (**2**) in MeOH, but no significant chiral recognition was detected for either naproxenate or ibuprofenate. Zwitterionic amino acids are also extracted from water to chloroform in the presence of 18-crown-6 ether. A modest degree of chiral discrimination was observed for phenylalanine, phenylglycine and *t*-leucine.

INTRODUCTION

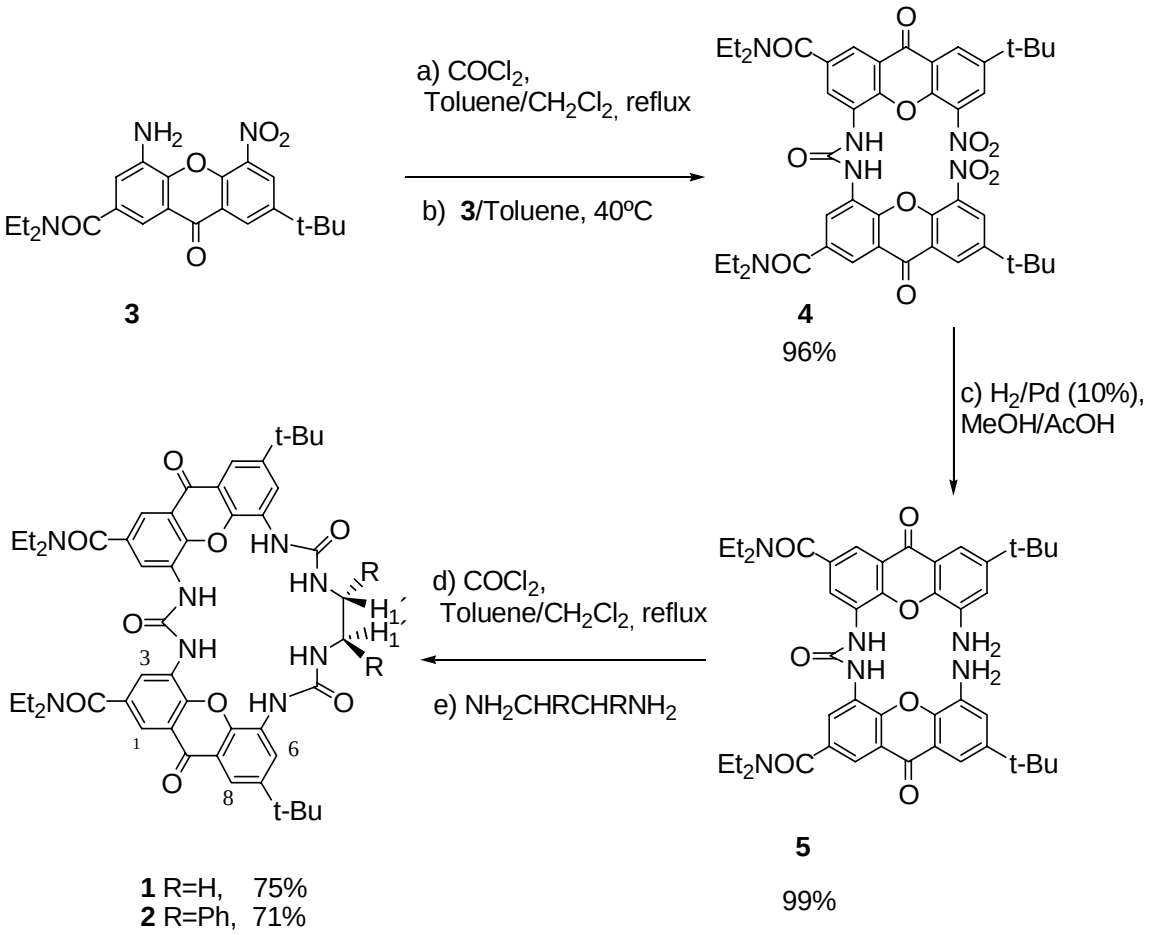
Although receptors for cations can be found extensively throughout the literature, the study for anion receptors has been started more recently, but has already shown promising results.[1]

Positively charged compounds are obvious receptors for anions, nevertheless neutral compounds capable to establish H-bonds,[2] like ureas,[3] can also be used to associate anions, and they offer many advantages. Cleft type receptors based on xanthones[4] and chromenones[5] have been shown to be successful for the association of anions, and especially for carboxylates. Macrocyclic receptors[6] offer the additional advantage of greater rigidity and therefore a smaller loss of entropy during complex formation.

Modelling studies show that the ring of receptor (**1**) (scheme 1) is essentially free of angular tension and we therefore expected a reasonably high yield in the synthesis. Scheme 1 shows the synthesis of receptors (**1**) and (**2**) starting with a xanthone derivative (**3**).[7]

RESULTS AND DISCUSSION

An initial attempt to carry out the cyclization of (**5**) with ethylenediamine afforded a good 75 % yield. We therefore also prepared the two enantiomers of receptor (**2**) (Scheme 1), making use of the commercially available (*R, R*)- and (*S, S*)- 1,2-diphenylethylenediamines. Figure 1 shows the aromatic region of its NMR spectrum in DMSO at 20˚C.



Scheme 1

Prior to complete purification, the negative ionization electrospray MS spectrum of receptor (**2**) showed a strong signal at m/z corresponding to an associate of receptor (**2**) and a chloride ion. The presence of this adduct could be due to a preference for the formation of the complex, and hence other halide ions were also tested to study the selectivity of host (**2**). Table 1 shows the results of this experiment, and the preference for chloride ion. The association of receptor (**2**) in deuterochloroform with tetraethylammonium chloride was also established. Job plots showed a 1/1 stoichiometry. Table 2 shows the chemical shifts of the free receptor and its associate. The K_{ass} in this solvent was too high for a direct NMR spectral measurement[8] and therefore MeOH was used. Conventional NMR titration[8] in this solvent afforded K_{ass} =4.0x10^4 M^{-1} while the same bromide salt offered a lower one: 4.7x10^3 M^{-1}.

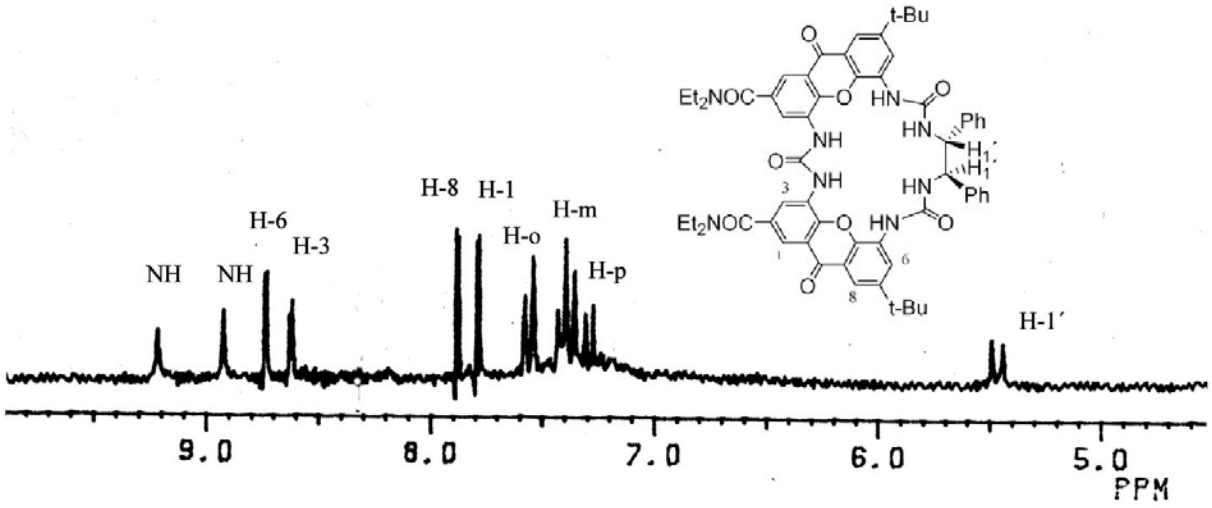


Figure 1. Aromatic region of the receptor (**2**) NMR spectrum in DMSO at 20˚C.

Table 1. Observed intensities for the receptor (**2**) halide adduct in the negative electrospray ionization MS spectrum-settings: negative ESI; capillary voltage: 2.50 KV; cone voltage: 4.0 V; extractor voltage: 5.0 V; source temperature: 120˚C; desolvation temperature: 200˚C; cone gas flow: 60 l/h; desolvation gas flow: 400 l/h-Receptor concentration $1.0x10^{-4}$ M. Halide concentration $2.5x10^{-4}$ M. Solvent: methanol.

Receptor (**2**)	F^-	Cl^-	Br^-	I^-
Intensity	$1.3x10^7$	$2.2x10^8$	$2.6x10^7$	$9.8x10^6$

Table 2. Observed changes in the chemical shift in ppm of the protons in the complexes of receptor (**2**) with tetraethylammonium and sodium chloride (complexes (**I**) and (**II**), respectively) in $CDCl_3$ at 20°C.

Proton	δ Receptor (**2**)	δ Complex (**I**)	Δδ	δ Complex (**II**)[a]	Δδ
H-1	7.71	7.87	0.16	8.05	0.34
H-3	8.39	8.73	0.34	8.75	0.36
H-6	8.55	8.81	0.26	8.93	0.38
H-8	7.87	8.03	0.16	7.87	0.00
H-1´	5.72	5.45	-0.27	5.48	-0.24
H-*ortho*	7.52	7.71	0.19	7.61	0.09
H-*meta*	7.31	7.33	0.02	7.33	0.02
H-*para*	7.21	7.24	0.03	7.24	0.03

[a]In presence of 18-crown-6 ether.

Halide sodium salts are not extracted by receptor (**2**) from water to chloroform. However, in the presence of 18-crown-6 ether extraction does take place. Table 2 also shows the chemical shifts of the associate

with sodium chloride. Figure 2 shows the aromatic region of NMR spectrum corresponding to this complex in presence of 18-crown-6 ether in $CDCl_3$ at 20˚C. The separation of chloride salts from seawater has been studied recently due to its important applications.[9]

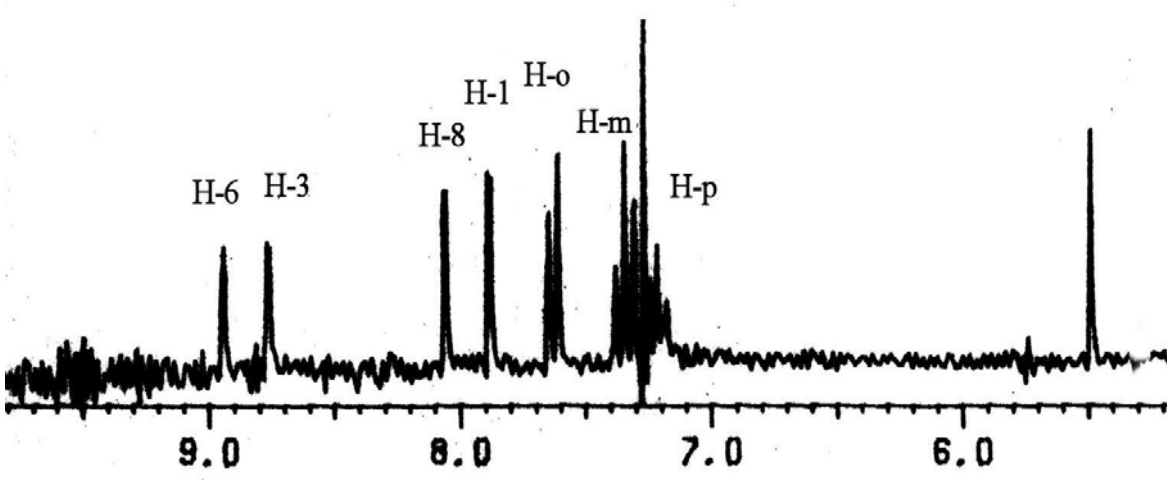


Figure 2. Aromatic region of the NMR spectrum of the ternary of receptor (**2**), sodium chloride and 18-crown-6 ether in $CDCl_3$ at 20˚C.

The interesting results obtained with halide ions suggested the use of mass spectrometry to study the different affinities of several carboxylates for host (**2**). The results are shown in Table 3 and point to high intensities for the associates with carboxylates with large residues, while small ones such as formate do not even show up in the spectrum.

These differences probably do not reflect the true affinities for the carboxylates[10] since experiments in solution afforded similar K_{ass} between receptor (**2**) and these guests. For example, conventional titrations of tetramethylammonium salts in MeOH give K_{ass} =8.4x10^3 M^{-1} for acetate, K_{ass} =6.4x10^3 M^{-1} for benzoate and K_{ass} =2.0x10^4 M^{-1} for phenylacetate. Different desolvation energies during the ionization may account for the mass spectrum results.[10]

Since this kind of effect does not interfere in the case of enantiomers, the chiral recognition of receptor (**2**) was studied with mass spectrometry. However, no significant differences were found between the guest enantiomers when naproxenate or ibuprofenate were tested.

Table 3. Observed intensities for the receptor (**2**) carboxylate adducts in the negative electrospray ionization mass spectrum-settings: negative ESI; capillary voltage: 2.50 KV; cone voltage: 4.0 V; extractor voltage: 5.0 V; source temperature: 120˚C; desolvation temperature: 200˚C; cone gas flow: 60 l/h; desolvation gas flow: 400 l/h-Receptor concentration $2.5x10^{-4}$ M. Carboxylate concentration $5.0x10^{-4}$ M. Solvent: methanol.

Carboxylate	Intensity
Naproxenate	$6.9x10^{8}$
Diphenylacetate	$2.0x10^{8}$
Ibuprofenate	$2.4x10^{8}$
Mandelate	$6.4x10^{7}$
Phenylacetate	$1.2x10^{8}$
Benzoate	$4.1x10^{7}$
Acetate	Not observed
Formate	Not observed

Host (**2**) showed the best results in the association of amino acids. Zwitterionic amino acids are not directly associated by receptor (**2**), probably because the ammonium hydrogen bonds cannot be fully saturated in this type of complex. To provide a more suitable environment for this group, 18-crown-6 ether was included and, in the presence of this ether, successful extraction was achieved. In general, the complex ^{1}H-NMR spectrum of host (**2**) does not allow easy identification of the amino acids used as guests; an exception is phenylalanine. The aromatic signals of this guest appear strongly shielded; integration of these signals showed a 1:1 ratio of extraction of the amino acid with the receptor. When racemic phenylalanine was used as the guest with (1*R* 2*R*) receptor (**2**), two different sets of signal could be assigned due to the formation of diastereomeric complexes in the solution at 6.96 ppm (*ortho*), 6.69 ppm (*meta*), 6.59 ppm (*para*) corresponding to the (1*R* 2*R*, *R*) associate and 6.74 ppm (*ortho*), 6.51 ppm (*meta*), and 6.51 ppm (*para*) for the (1*R* 2*R*, *S*) complex. Since the last set of signals shows double intensity, a chiral recognition of 2 must be taking place. Figure 3 shows the proposed geometry for the most stable associate, in which the smallest steric hindrance between the amino acid side chain and the receptor aromatic ring takes place.

Phenylglycine provides a similar situation. In the ^{1}H-NMR spectrum, extraction of the racemic amino acid with the (1*S* 2*S*) receptor showed broad signals for the aromatic protons (7.24 ppm and 6.61 ppm for the (*S*)-guest and 7.02 ppm and 6.58 ppm for the (*R*)-guest) and two singlets corresponding to the amino acid α protons at 4.38 ppm and 4.47 ppm, the last signal corresponding to the (*R*)-phenylglycine, which is

1.6 times larger. Again, the (1*S* 2*S*, *R*) configuration was the most stable. The receptor also extracts *t*-leucine. Integration of the *t*-butyl groups of the diastereomeric complexes reveals a ratio of 1.5.

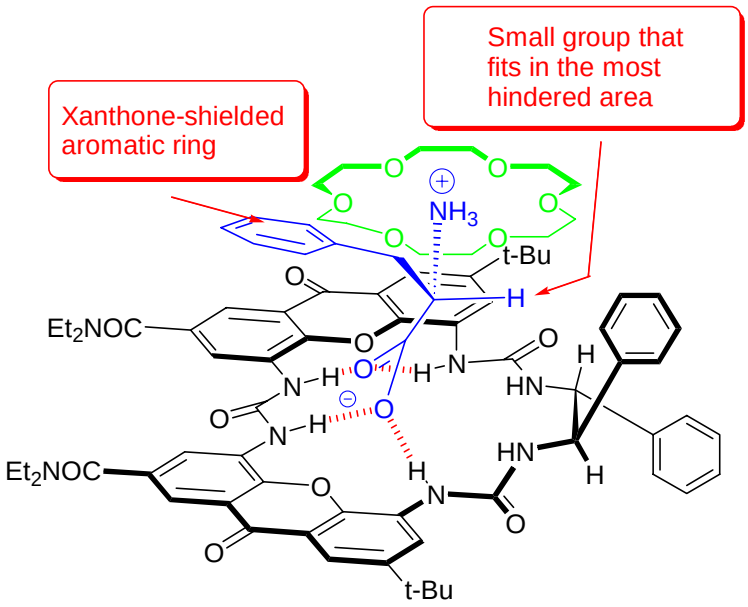


Figure 3. Proposed structure for the (1*R* 2*R*, *S*) complex of receptor (**2**) and phenylalanine. The most stable complex shows a geometry in which the interaction between the crown ether and the ethylenediamine phenyl group is minimized.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Advance DRX 400 MHz spectrometer and Bruker WP 200MHz SY. MS spectrometric data were obtained with a VG. MOD. TS-250 and Waters ZQ-4000. IR spectra were recorded on a BONEN MB-100FT IR spectrophotometer. Melting points were obtained with a Stuart Scientific SMP3 Apparatus. Rotatory power was measured with a Perkin Elmer 341 polarimeter.

Bis 4-(7-*tert*-butyl-2-diethylcarboxamido-5-nitro-9-oxo-9*H*-xanthyl)urea (4). A solution of phosgene (0.2 mL) in toluene (20%) was added to compound (**3**) (100 mg, 0.24 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was refluxed for 30 min and the solvent was eliminated under vacuum. Compound (**3**) (100 mg, 0.24 mmol) in toluene (3 mL) was then added and the solution was warmed at 40˚C for 5 min. Cooling down and adding petroleum ether precipitate the urea which after filtration yielded compound (**4**) (200 mg), 96%. Recrystallization from MeOH afforded the pure compound. mp: 192-194˚C. IR ν (cm^{-1}): 3337, 2969, 2876, 2672, 1622, 1539, 1462, 1362, 1285, 1215, 826, 791, 750. ^{1}H NMR (200 MHz, $CDCl_3$)

δ (ppm): 1.25 (m, 8H), 1.46 (s, 18H), 3.34 (m, 6H), 3.54 (m, 6H), 7.97 (d, 2H, J=2 Hz), 8.22 (s, 2H), 8.58 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 31.0 (6C), 35.0 (2C), 118.0 (2C), 120.8 (2C), 122.6 (2C), 125.2 (2C), 128.9 (2C), 129.0 (2C), 133.9 (2C), 137.8 (2C), 146.0 (2C), 147.7 (2C), 151.8, 169.3 (2C), 174.4 (2C), 198.6 (2C). MS (FAB): 850 (M^+-2), 776, 438, 339, 154.

Bis 4-(5-amino-7-*tert*-butyl-2-diethylcarboxamido-9-oxo-9*H*-xanthyl)urea (5). Compound (**4**) (2.0 g, 2.35 mmol) in AcOH/MeOH 1/1 (20 mL) was treated with 10% Pd/C (200 mg) and hydrogen at 4 atm. After 3 h the catalyst was filtered and concentration of the reaction mixture yielded the yellow crystalline compound (**5**) (1.83 g), 99%. Recrystallization from MeOH afforded the pure compound. mp: 307-309˚C. IR ν (cm^{-1}): 3420, 3316, 3618, 1539, 1279, 1215, 868, 789. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.15 (m, 12H), 1.33 (s, 18H), 3.42 (m, 8H), 7.35 (d, 2H, J=2.6 Hz), 7.24 (d, 2H, J=2.6 Hz), 7.76 (d, 2H, J=2.0 Hz), 8.57 (d, 2H, J=2.0 Hz). ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm): 36.2 (6C), 39.5 (2C), 112.8 (2C), 121.5 (2C), 125.8 (2C), 126.5 (2C), 133.7 (2C), 137.3 (2C), 142.7 (2C), 146.7 (2C), 150.5 (2C), 152.6 (2C), 157.2 (2C), 174.0 (2C), 181.3 (1C), 199.0 (2C). HRMS (FAB): calcd for $C_{45}H_{53}N_6O_7$: 789. 3897, found: 789. 3983.

Receptors (1) and (2). A suspension of diamine (**5**) (100 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was reacted with a solution of phosgene (0.5 mL) in toluene (20%) at reflux for 30 min. After vacuum distillation the residue was dissolved in toluene (100 mL) and a small excess of the suitable diamine was slowly added in toluene (20 mL). Evaporation of the solvent and recrystallization from EtOH/H_2O (9:1) yielded the pure compounds, yield: 83.3 mg, (75%) for **1** and 94.4 mg (71%) for **2**.

(1) mp: 304-306˚C. IR ν (cm^{-1}): 3356, 3314, 2965, 1699, 1663, 1551, 1464, 1221, 1103, 897, 789. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.17 (t, 8H, J=6.8 Hz), 1.36 (s, 18H), 3.42 (m, 12H), 4.04 (s, 4H), 4.57 (t, 2H, J=3.5 Hz), 7.77 (d, 2H, J=2.4 Hz), 7.83 (d, 2H, J=2.0 Hz), 8.56 (d, 2H, J=2.4 Hz), 8.75 (d, 2H, J=1.7 Hz), 8.93 (s, 1H), 9.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm): 12.8 (2C), 14.0 (2C), 30.7 (2C), 31.0 (6C), 34.6 (2C), 38.9 (2C), 43.2 (2C), 47.7 (2C), 113.5 (2C), 117.0 (2C), 120.2 (2C), 121.0 (2C), 123.0 (2C), 123.7 (2C), 128.2 (2C), 128.6 (2C), 132.4 (2C), 143.4 (2C), 145.1 (2C), 146.7 (2C), 153.7 (2C), 168.7 (2C), 175.6 (1C), 198.8 (2C). MS (FAB): 900 (M^+), 335, 136; (ESI) 923 (M^++23). Anal. Calcd for $C_{49}H_{56}N_8O_9$: C, 65.32; H, 6.26; N, 12.44. Found: C, 65.05; H, 6.02; N, 12.71.
(2) mp: 279-281˚C. Rotatory power: (1*R* 2*R*) $[\alpha]_D^{20}$=67˚ (c=0.6%, $CDCl_3$); (1S2S) $[\alpha]_D^{20}$=-66˚ (c=0.6%, $CDCl_3$). IR ν (cm^{-1}): 3335, 2967, 1701, 1667, 1607, 1543, 1468, 1219, 1103, 791, 700. ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm): 1.17 (t, 6H, J=7.0 Hz), 1.32 (s, 18H), 3.43 (m, 8H), 5.46 (d, 2H, J=10.1 Hz), 7.26 (t, 2H, J=7.1 Hz), 7.38 (t, 4H, J=7.0 Hz), 7.54 (t, 4H, J=7.4 Hz), 7.77 (d, 2H, J=2.5 Hz), 7.86 (d, 2H,

J=2.1 Hz), 8.61 (d, 2H, J=2.3 Hz), 8.72 (d, 2H, J=2.0 Hz), 8.91 (s, 2H), 9.20 (s, 2H). ^{13}C NMR (100 MHz, DMSO- d_6) δ (ppm): 31.0 (8C), 34.6 (2C), 39.1 (2C), 113.5 (2C), 117.4 (2C), 120.2 (4C), 121.1 (2C), 122.2 (2C), 124.3 (2C), 126.4 (2C), 126.5 (2C), 127.3 (2C), 128.0 (2C), 128.6 (2C), 128.7 (2C), 132.3 (2C), 142.3 (2C), 143.2 (2C), 145.5 (2C), 146.9 (2C), 153.8 (2C), 168.7 (2C), 175.7 (1C), 199.0 (2C). MS (FAB) 1053 (M^+), 816, 742, 307, 154; HRMS (FAB): calcd for $C_{61}H_{65}N_8O_9$: 1053.4875, found: 1053.4823. Anal. Calcd for $C_{61}H_{64}N_8O_9$: C, 69.54; H, 6.12; N, 10.64. Found: C, 69.72; H, 6.35; N, 10.47.

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