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Synthesis and Water Solubility of Adamantyl-OEG-fullerene Hybrids

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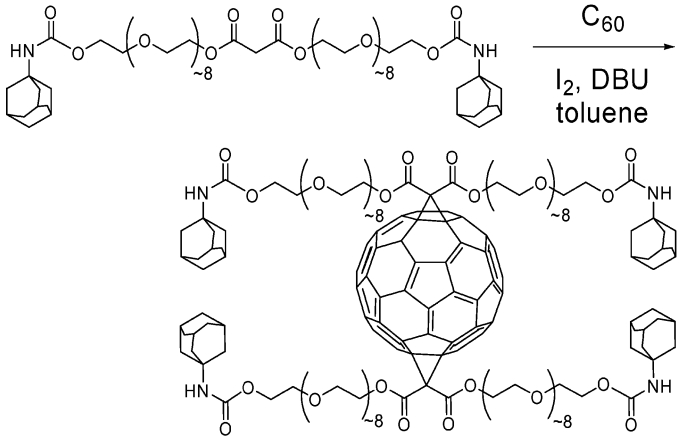

A series of new adamantyl-oligoethyleneglycol-fullerene hybrids was prepared via Bingel−Hirsch functionalization of the C_{60} fullerene with various adamantyl-oligoethyleneglycol malonates. As NMDA-targeted antioxidants, these compounds may have the potential to be developed as therapeutic agents for the treatment of neurological disorders.

During recent years, research in the field of water-soluble C_{60} fullerene derivatives has significantly increased due to a broad range of biological activity that was found for these compounds.[1] This includes antioxidant and neuroprotective properties,[2] inhibitory activity for various enzymes,[3] antiviral[4] and antibacterial properties,[5] and compounds with the potential to be developed as anticancer drugs[6] and imaging diagnostic agents.[7] One of the well-established approaches to overcome the lack of fullerenes' solubility in aqueous solutions is by chemical modification of fullerenes with polar groups such as polyols,[8] carboxylates,[9] polyethers,[10] and dendrons.[11]

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Further development of this concept led to the construction of hybrid systems in which a variety of functional moieties such as peptides,[12] oligonucleotides,[13] porphyrins,[14] flavonoids,[15] steroids,[16] and DNA-binding and protein-binding fragments[17] were attached to a fullerene core. Such dyad systems could amplify or alter biochemical characteristics of their components or even produce compounds with new biological properties.

Recently, preparation of novel fullerene hybrids bearing 1,4-dihydropyridin[18] and arylpiperazine[19] functional groups was described by Martin and co-workers. Although these materials combine components with very promising biological activity, their best solubility in a 10% DMSO aqueous solution was reported to be in the range of $\sim 10^{-5}$ M and could present a challenge in further preclinical development of these compounds.

Other promising candidates for the creation of new fullerene hybrids with improved therapeutic properties are adamantyl derivatives. Adamantyl-containing drugs have shown excellent efficacy as antiviral,[21] antiglycemic,[22] antiarrythmic,[23] antidepressant,[24] and antitumor agents.[25] Among a broad spectrum of adamantyl-containing therapeutic agents aminoadamantyl derivatives are particularly interesting since they are well-studied compounds that have an extensive array of clinical applications. These applications range from healing of viral infections[26] to treatment of neuroleptic extrapyramidal

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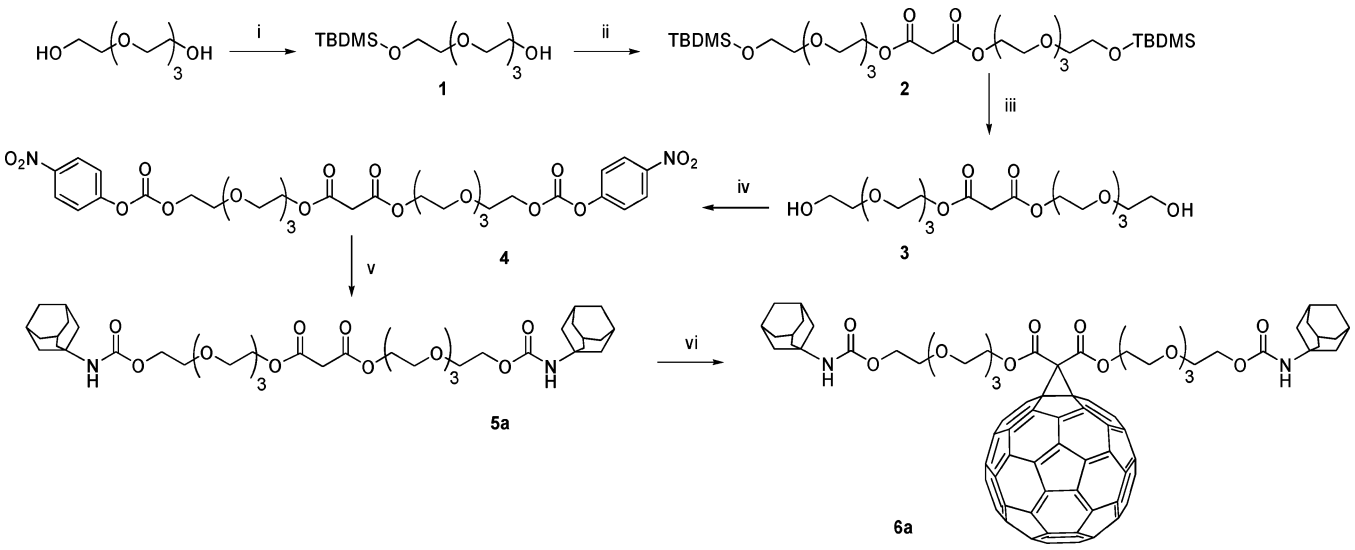

FIGURE 1. Synthesis of compound **6a**. Reagents and conditions: (i) *tert*-butyldimethylsilyl chloride, imidazole, DMF, 0 °C; (ii) malonic acid, DCC, acetonitrile; (iii) tetrabutylammonium fluoride, THF, 0 °C; (iv) *p*-nitrophenylchloroformate, triethylamine, THF, 0 °C; (v) aminoadamantane, triethylamine, DMF; (vi) C_{60}, I_2, DBU, toluene, rt.

movement disease,[27] depression,[28] and cocaine dependence.[29] Aminoadamantyl derivatives are especially effective in the treatment of fatigue associated with multiple sclerosis[30] and Parkinson's and Alzheimer's diseases.[31] On the molecular level, adamantyl derivatives were found to function as noncompetitive antagonists for the *N*-methyl-D-aspartate (NMDA) receptor.[32] As the latter contributes importantly to the etiology and progression of many neurological diseases states,[33] new adamantyl-fullerene hybrids may have potential to become therapeutic agents for treating these diseases.

In this work, we describe the preparation and characterization of new water-soluble adamantyl-oligoethyleneglycol-fullerene hybrids, in which adamantyl groups are connected to a carboxyfullerene moiety through oligoethyleneglycol (OEG) bridges of various lengths. In addition to water-solubility, incorporation of biocompatible and flexible OEG bridges between the two functional moieties should provide these compounds with improved NMDA receptor affinity characteristics since, in the described arrangement, receptor-binding moieties are not sterically hindered by a fullerene fragment. The described architecture and preparation methods of new compounds are very attractive, as they lay a platform for the synthesis of other target-specific fullerene derivatives.

The general synthetic strategy toward these materials was based on initial construction of malonate oligoethyleneglycol esters terminated with adamantylcarbamates that were further coupled to a C_{60} fullerene, following the Bingel–Hirsch methodology.[34] The synthetic route for the preparation of compound **6a** is outlined in Figure 1.

To avoid a possible polymerization reaction, which typically takes place in direct esterification of malonic acid with diols, one hydroxyl terminal of tetraethyleneglycol was protected by reaction with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) at 0 °C in DMF, using imidazole as a base. DCC-mediated coupling of monosilyl-protected tetraethyleneglycol **1**[35] with malonic acid in acetonitrile produced bis(TBDMS-tetraethyleneglycol)-malonate **2** in 81% yield, which was further converted to the corresponding diol **3** in 91% yield, by deprotection with tetrabutylammonium fluoride (TBAF) at 0 °C in THF. Bis-*p*-nitrophenyl carbonate **4** was obtained in 70% yield by reaction of diol **3** with *p*-nitrophenylchloroformate at 0 °C in THF, using triethylamine as a base. The synthesis of the target adamantyl-tetraethyleneglycol-fullerene hybrid **6a** was completed by coupling synthon **4** with 1-aminoadamantane in DMF to produce adamantylcarbamate-tetraethyleneglycol-malonic ester **5a** and its subsequent attachment to a C_{60} fullerene in 44% yield.

To evaluate the influence of OEG length on adamantyl-fullerene hybrids solubility in aqueous solutions, we prepared several compounds. A straightforward procedure for preparing target compounds **6a**–**c**, without the use of protection groups, was based on the reaction of tetraethyleneglycol, diethyleneglycol, or PEG-400 with adamantylisocyanate under reflux conditions in THF, to

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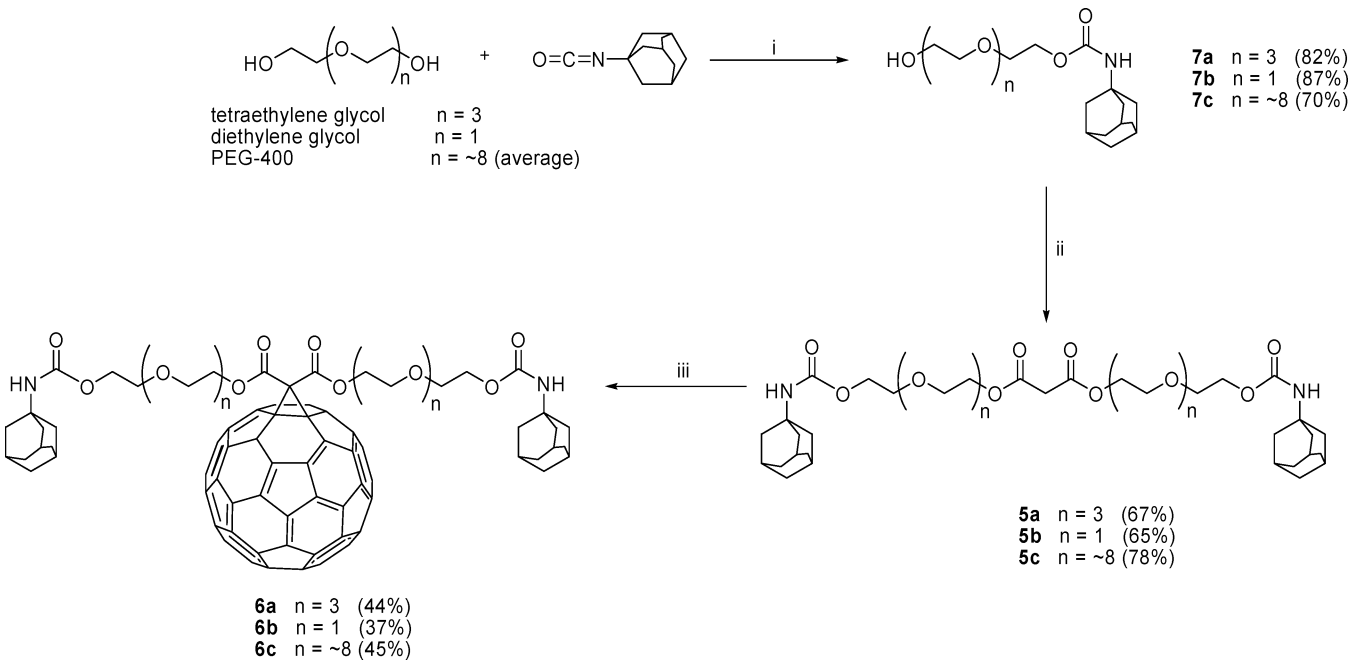

FIGURE 2. Synthesis of compounds **6a**−**c**. Reagents and conditions: (i) adamantylisocyanate, THF, reflux; (ii) malonic acid, DCC, acetonitrile; (iii) C_{60}, I_2, DBU, toluene, rt.

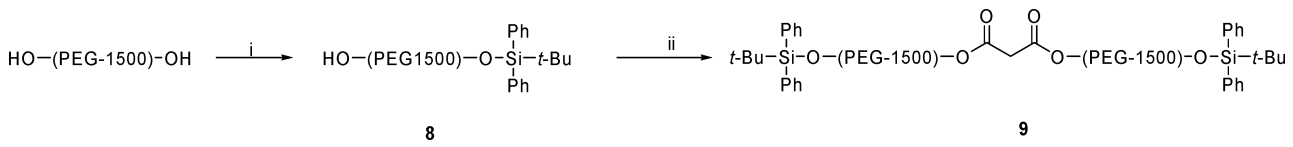

FIGURE 3. Synthesis of compound **9**. Reagents and conditions: (i) *tert*-butyldiphenylsilyl chloride, imidazole, DMF; (ii) malonic acid, DCC, acetonitrile.

produce a series of compounds **7a**−**c**. These reactions were followed by DCC-assisted coupling of **7a**−**c** with malonic acid in acetonitrile and by subsequently attaching the product to a C_{60} core (Figure 2).

However, attempts to achieve higher solubility of hybrids by incorporating PEG-1500 into their structures were less successful. Reaction of PEG-1500 with adamantylisocyanate produced an inseparable mixture of products, under all tested reaction and separation conditions. In an alternative approach, *tert*-butyldiphenylsilyl chloride (TBDPS-Cl) was used to protect one hydroxyl group of PEG-1500, utilizing DMF as a solvent and imidazole as a base (Figure 3).

Use of the bulky silyl protection group allowed obtaining purified **8** in 43% yield. A subsequent DCC-mediated coupling of **8** with malonic acid in acetonitrile resulted in a mixture of products, from which target bis(TBDPS-PEG-1500)-malonate **9** was separated in 15% yield, after several consecutive chromatographic steps. Further deprotection of **9**, with TBAF in THF, led to an inseparable mixture of products.

These results indicated that a more practical approach to the solubility improvement of adamantyl-fullerene hybrids would be the poly-substitution of a fullerene core, with purifiable OEG-derivatives, rather than the synthesis of monosubstituted fullerenes with longer OEG fragments. The synthesis of fullerene derivative **10** was achieved in 77% yield, by reacting 2 equiv of PEG-400-derived **5c** with a pristine C_{60} fullerene (Figure 4).[36]

Since, commercially available PEG-400 contains a mixture of oligoethyleneglycols, electrospray ionization mass spectrometry (ESI-MS) was found to be particularly useful in the analysis of this starting material and all subsequent derivatives, including **5c** and target fullerene hybrids **6c** and **10**, the typical ESI-MS spectra of which are shown in Figure 5. In this figure (top) ESI-MS spectra of **5c** clearly exhibit a typical distribution of molecular weights (44 *m/z* for each $-CH_2CH_2O-$ unit) around the average mass, due to a variability in the OEG chain lengths.

Solubility results of hybrids **6a**−**c** and **10** in DMSO aqueous solutions are summarized in Table 1 and Figure 6.

The solubility of **10** in 2% DMSO aqueous solution was found to be even higher, reaching maximum concentration of 5.15×10^{-4} M (1.6 mg/mL) and clearly exhibiting an overall validity of our approach.

The present work describes the preparation of new adamantyl-oligoethyleneglycol-fullerene hybrids and qualitative evaluation of the influence of the oligoethyleneglycol length on the solubility of these compounds in aqueous solutions. The developed methodology should provide a platform for the synthesis of other well-defined and targeted fullerene derivatives for a broad variety of biomedical applications.

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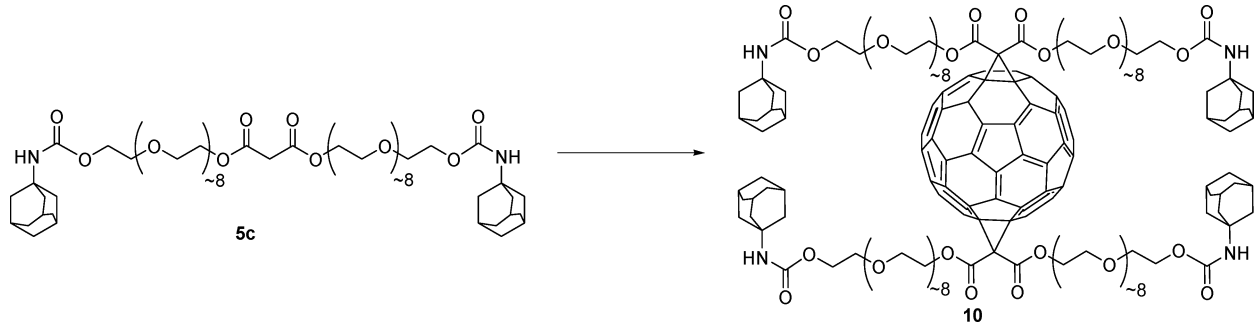

FIGURE 4. Synthesis of compound **10**. Reagents and conditions: 0.46 equiv of C_{60}, I_2, DBU, toluene.

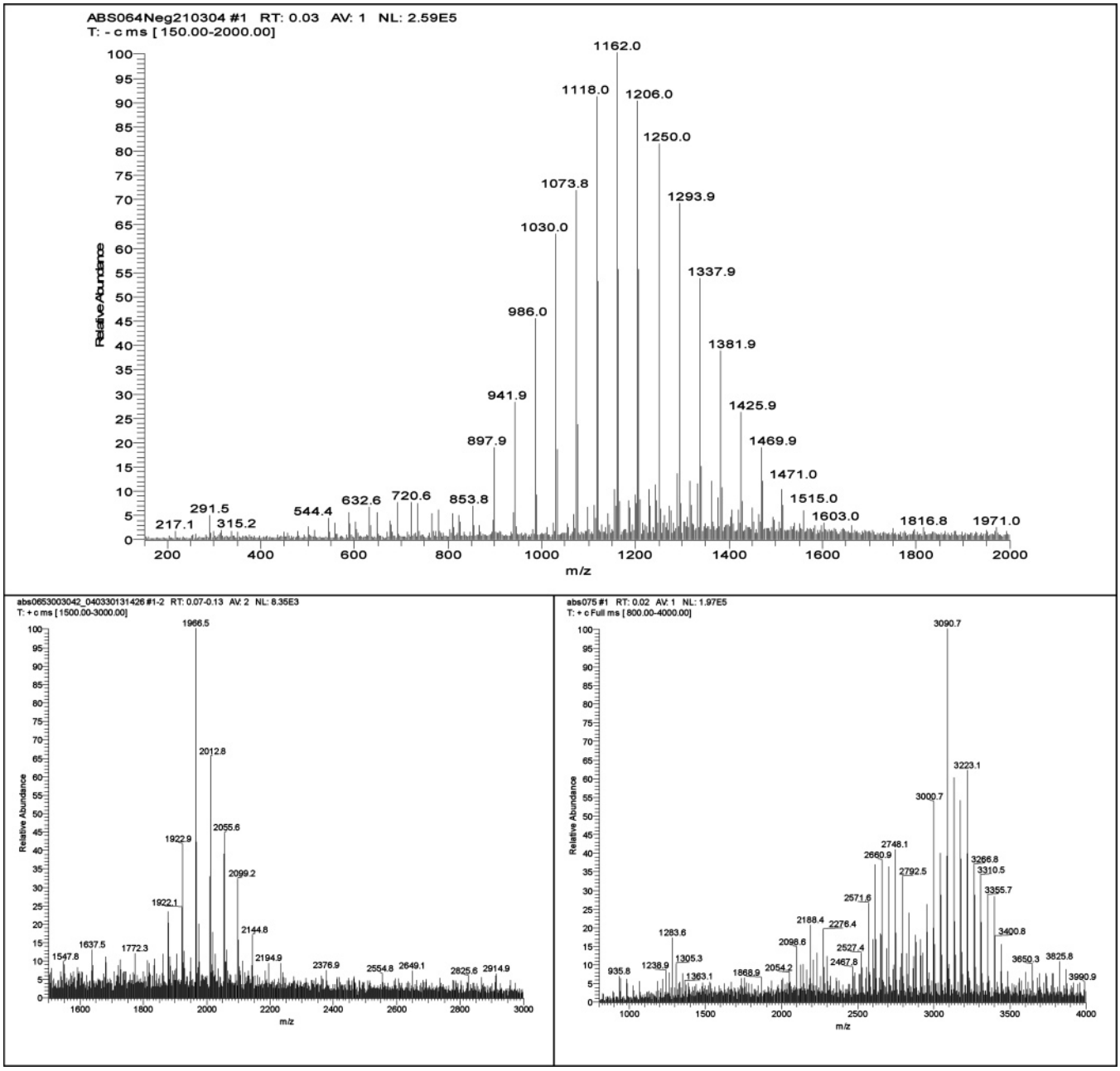

FIGURE 5. ESI-MS spectra of compounds **5c** (top), **6c** (bottom, left), and **10** (bottom, right).

Experimental Section

Compound 1. A solution of imidazole (7.0 g, 102.8 mmol) and tetraethyleneglycol (30.0 g, 154.4 mmol) in dry DMF (70 mL) was cooled to 0 °C and stirred for 30 min under argon. To this solution was added *tert*-butyldimethylsilyl chloride (15.5 g, 102.8 mmol) in dry DMF (50 mL) dropwise. After 2 h at 0

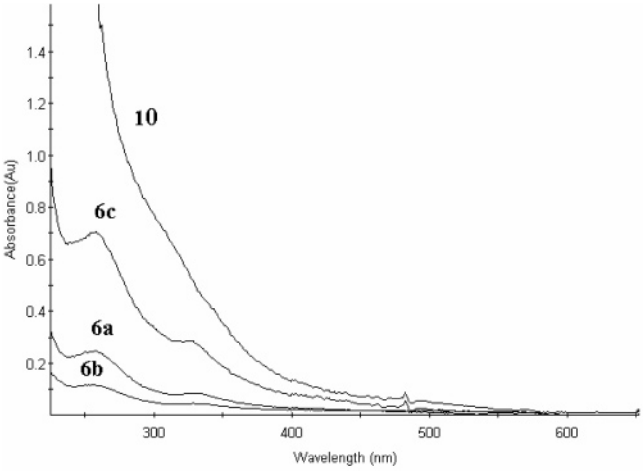

FIGURE 6. UV−vis spectra of compounds **6a**−**c** and **10** measure in 0.1% DMSO aqueous solution.

TABLE 1. Maximum Concentrations Measured for 6a−c and 10 Hybrids in DMSO Aqueous Solutions

conc of DMSO in water (%)	**6a** (10^{-5} M)	**6b** (10^{-5} M)	**6c** (10^{-5} M)	**10** (10^{-5} M)
0.1	1.18	0.07	1.17	1.80
0.5	1.38	0.35	5.12	14.0
1.0	3.14	1.40	6.97	27.0

°C, the reaction mixture was allowed to warm to rt. Water (900 mL) was added, and the resulting solution was extracted with ethyl acetate (4 × 400 mL). The combined organic extracts were washed with brine. After solvent evaporation, the crude product was purified by flash chromatography (SiO_2; ethyl acetate) to yield **1** as a light yellow oil (19.2 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (m, 16 H), 0.86 (s, 9 H), 0.03 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.0, 72.8, 71.0, 70.9, 63.0, 62.0, 26.2, 18.6, −5.0. IR (neat): 778, 836, 943, 1107, 1253, 1355, 1467, 1648, 2860, 2930, 3445 cm^{-1}. MS (CI$^+$): *m/z* 309.2 (MH$^+$).

Compound 2. To a solution of malonic acid (0.31 g, 2.9 mmol) and **1** (2.0 g, 6.5 mmol) in dry acetonitrile (9 mL) was added a solution of DCC (1.4 g, 6.5 mmol) in dry acetonitrile (7 mL) dropwise over 20 min under argon. The reaction mixture was stirred for an additional 20 min during which time a white precipitate was formed. The precipitate was filtered and washed with CH_2Cl_2 (3 × 20 mL), and combined organic fractions were evaporated. The crude product was purified by flash chromatography (SiO_2; ethyl acetate/hexanes, 65:35) to yield **2** as a light yellow oil (1.61 gr, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (t, J = 4.8 Hz, 4 H), 3.76 (t, J = 5.6 Hz, 4 H), 3.70 (t, J = 4.8 Hz, 4 H), 3.64 (m, 16 H), 3.55 (t, J = 5.6 Hz, 4 H), 3.44 (s, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 72.9, 71.0, 70.9, 69.1, 64.8, 63.0, 41.5, 26.2, 18.6, −5.0. IR (neat): 774, 837, 947, 1108, 1253, 1466, 1744, 2860, 2933 cm^{-1}. MS (CI): *m/z* 685.3 (MH$^+$). HRMS (MALDI-TOF): calcd for $C_{31}H_{64}O_{12}NaSi_2$ 707.3829, found 707.3821.

Compound 3. To a solution of **2** (6.53 g, 9.5 mmol) in THF (50 mL) was added a solution of tetrabutylammonium fluoride in THF (24 mL of 1 M solution) by syringe at 0 °C. After 2 h at 0 °C, the reaction mixture was allowed to warm to rt and stirred at rt for an additional 30 min. CH_2Cl_2 (400 mL) was added, and the resulting solution was washed with a saturated Na_2SO_4 aqueous solution (3 × 50 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL), combined organic fractions were evaporated, and the crude residue was purified by flash chromatography (SiO_2; CH_2Cl_2/CH_3OH, 9:1) to yield **3** as a light yellow oil (0.27 gr, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (t, J = 4.8 Hz, 4 H), 3.61 (m, 4 H), 3.61 (m, 4 H), 3.56 (m, 16 H), 3.49 (t, J = 5.2 Hz, 4 H), 3.36 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 72.7, 70.7, 70.6, 70.5, 64.6, 61.6, 41.3. IR (neat): 940, 1104, 1283, 1340, 1458, 1636, 1743, 2876, 3387 cm^{-1}. MS (CI): *m/z* 457.1 (MH$^+$).

Compound 4. A solution of **3** (1.10 g, 2.41 mmol) and triethylamine (1.9 mL) in dry THF (100 mL) was cooled to 0 °C under argon. To this solution was added *p*-nitrophenylchloroformate (1.07 g, 5.30 mmol) in dry THF (40 mL) dropwise during 1 h. After the end of addition, the reaction mixture was allowed to warm to rt, stirred for 2 h, and monitored by TLC (SiO_2; ethyl acetate). The formed precipitate was filtered out, and after solvent evaporation, the crude product was purified by flash chromatography (SiO_2; ethyl acetate) to yield **4** as yellow oil (1.33 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 9.2 Hz, 2 H), 7.35 (d, J = 9.2 Hz, 4 H), 4.39 (t, J = 4.4 Hz, 4 H), 4.25 (t, J = 4.8 Hz, 4 H), 3.77 (t, J = 4.8 Hz, 4 H), 3.67 (m, 12 H), 3.61 (m, 8 H), 3.40 (s, 2 H).^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 155.7, 152.7, 145.6, 125.5, 122.0, 70.9, 70.81, 70.76, 69.0, 68.8, 68.5, 64.7, 41.4. IR (neat): 664, 774, 860, 1214, 1349, 1491, 1524, 1592, 1615, 1753 cm^{-1}. MS (CI): *m/z* 787.0 (MH$^+$). HRMS (MALDI-TOF): calcd for $C_{33}H_{42}N_2O_{20}Na$ 809.2223, found 809.2232.

Compound 5a (Procedure A). To a solution of 1-adamantylamine (0.634 g, 4.19 mmol) in dry DMF (8 mL) were added triethylamine (2 mL) and **4** (1.5 g, 1.9 mmol) at rt. The reaction progress was monitored by TLC (SiO_2; CH_2Cl_2/CH_3OH, 95:5; R_f = 0.6). After reaction completion, DMF was removed under reduced pressure, and the crude product was purified by flash chromatography (SiO_2; CH_2Cl_2/CH_3OH, 95:5) to yield **5a** as a light yellow oil (1.14 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 (broad s, 2 H), 4.23 (t, J = 4.8 Hz, 4H), 4.08 (t, J = 4.0 Hz, 4 H), 3.65 (t, J = 5.2 Hz, 4 H) 3.59 (m, 20 H), 3.39 (s, 2 H), 2.00 (m, 6 H), 1.86 (d, J = 2.8 Hz, 12 H), 1.60 (t, J = 2.8 Hz, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 154.4, 70.7, 70.6, 69.9, 69.0, 64.7, 63.2, 50.8, 41.9, 41.4, 36.5, 29.6. IR ($CHCl_3$): 1067, 1139, 1277, 1295, 1456, 1508, 1723, 2853, 2912 cm^{-1}. MS (FAB$^+$): *m/z* 833.5 (MNa$^+$), 849.0 (MK$^+$).

Compound 5a (Procedure B). To a solution of malonic acid (0.25 g, 2.45 mmol) and **7a** (2.0 g, 5.4 mmol) in dry acetonitrile (20 mL) was added a solution of DCC (1.10 g, 5.4 mmol) in dry acetonitrile (7 mL) dropwise over 20 min under argon. The reaction mixture was stirred for an additional 20 min during which time a white precipitate was formed. The precipitate was filtered and washed with CH_2Cl_2 (3 × 20 mL), and combined organic fractions were evaporated. The crude product was purified by flash chromatography (SiO_2; CH_2Cl_2/CH_3OH, 95:5) to yield **5a** as a light yellow oil (1.32 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.70 (broad s, 2 H), 4.23 (t, J = 4.8 Hz, 4H), 4.08 (t, J = 4.0 Hz, 4 H), 3.65 (t, J = 5.2 Hz, 4 H) 3.59 (m, 20 H), 3.39 (s, 2 H), 2.00 (m, 6 H), 1.86 (d, J = 2.8 Hz, 12 H), 1.60 (t, J = 2.8 Hz, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 154.4, 70.7, 70.6, 69.9, 69.0, 64.7, 63.2, 50.8, 41.9, 41.4, 36.5, 29.6. IR ($CHCl_3$): 1067, 1139, 1277, 1295, 1456, 1508, 1723, 2853, 2912 cm^{-1}. MS (FAB$^+$): *m/z* 833.5 (MNa$^+$), 849.0 (MK$^+$).

Compound 6a. DBU (0.47 g, 3.08 mmol) in 30 mL of toluene was added to a stirred solution of **5a** (1.0 g, 1.23 mmol), C_{60} (0.9 g, 1.23 mmol), and I_2 (0.3 g, 1.23 mmol) in 310 mL of toluene, and the mixture was stirred for 36 h under an argon atmosphere. The reaction mixture was loaded on top of a short SiO_2 flash chromatography column and eluted with toluene to remove the unreacted fullerene. Further elution with toluene/2-propanol (99:1) afforded **6a** as dark brown solid (0.83 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (broad s, 2 H), 4.63 (t, J = 4.8 Hz, 4H), 4.11 (t, J = 4.0 Hz, 4 H), 3.85 (t, J = 4.8 Hz, 4 H) 3.62 (m, 20 H), 2.03 (m, 6 H), 1.88 (d, J = 2.4 Hz, 12H), 1.62 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 154.5, 145.6, 145.5, 145.2, 145.0, 144.9, 144.2, 143.4, 143.3, 143.2, 142.5, 142.2, 141.2, 139.4, 71.8, 71.01, 71.00, 70.9, 70.8, 69.1, 66.6, 63.4, 51.0, 42.1, 36.6, 29.7. IR (KBr): 524, 704, 804,

1025, 1098, 1263, 1449, 1714, 2907, 2963 cm^{-1}. HRMS (MALDI-TOF): calcd for $C_{101}H_{64}N_2O_{14}Na$ 1551.4250, found 1551.4174. $\lambda_{max}(CHCl_3)$: 257, 326, 424, 475, 683 nm.

Compound 7a. A mixture of 1-adamantylisocyanate (2.0 g, 11.3 mmol) and tetraethyleneglycol (4.4 g, 22.6 mmol) in dry THF (30 mL) was refluxed for 20 h under argon. After the mixture was cooled to rt, the solvent was evaporated and the crude product was purified by flash chromatography (SiO_2; CH_2Cl_2/CH_3OH, 92:8) to yield **7a** as a colorless oil (3.46 g, 82%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.14 (t, J = 8.8 Hz, 2 H), 3.72 (t, J = 4.0 Hz, 2 H), 3.67 (m, 10 H), 3.61 (t, J = 4.0 Hz, 2 H), 2.06 (m, 3 H), 1.91 (d, J = 2.8 Hz, 6 H), 1.65 (t, J = 2.8 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 72.8, 70.7, 70.6, 70.5, 70.4, 69.9, 63.2, 61.8, 50.8, 41.9, 36.5, 29.6. IR (neat): 943, 1067, 1232, 1360, 1455, 1535, 1708, 2852, 2902, 3437 cm^{-1}. MS (FAB^+): *m/z* 372.2 (MH^+), 394.2 (MNa^+), 410.0 (MK^+). HRMS (ESI): calcd for $C_{19}H_{33}NO_6Na$ 394.2200, found 394.2077.

Compounds **5b**,**c**, **6b**,**c**, **7b**,**c**, and **8**−**10** were prepared following described above procedures. The products were characterized by their ^1H NMR, ^{13}C NMR, MS, and IR spectra (see the Supporting Information).

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Supporting Information Available: Experimental details, characterization data, and ^1H NMR, ^{13}C NMR, and MS spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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