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ARTICLE *in* ORGANIC LETTERS · MARCH 2002

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2002
Vol. 4, No. 4
549−552

Synthesis of Cyclic Prodrugs of Aggrastat and Its Analogue with a Modified Phenylpropionic Acid Linker

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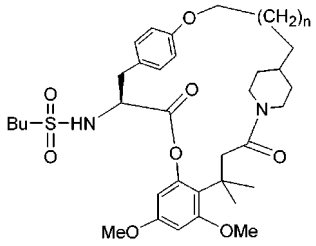
Received December 3, 2001

ABSTRACT



1a, n=2; **1b**, n=1

The objective of this work was to synthesize cyclic prodrugs 1a and 1b from Aggrastat 2a and its analogue 2b, respectively, to improve their membrane permeation. Cyclic prodrugs 1a and 1b were formed using an ester bond between the -COOH group of Aggrastat or its analogue and the phenylpropionic acid linker 3 and an amide bond between the piperidinylamine and the -COOH group of the linker 3, respectively, as outlined in Scheme 4.

In recent years, RGD (Arg-Gly-Asp) peptidomimetics, such as Aggrastat and SC-57101, have been used clinically to treat thrombosis because they have potent antiplatelet aggregation activity.[1−6] Most of these RGD-peptidomimetics have been used only for intravenous applications because, due to their unfavorable physicochemical properties (i.e., charge, hydrogen-bonding potential, conformation), they have poor oral bioavailability for crossing cell membranes in the intestinal mucosa. However, forming cyclic prodrugs of Aggrastat and its analogue can transiently alter these physicochemical properties.[7−9] We and other groups have shown that cyclic prodrugs of peptides formed with acyloxyalkoxy[10−12] and phenylpropionic acid[13−15] linkers have improved membrane permeation. However, cyclic prodrugs containing a phenylpropionic acid linker (**1c**, Scheme 1) have low water solubility. Therefore, there is a need to modify linker **1c** by

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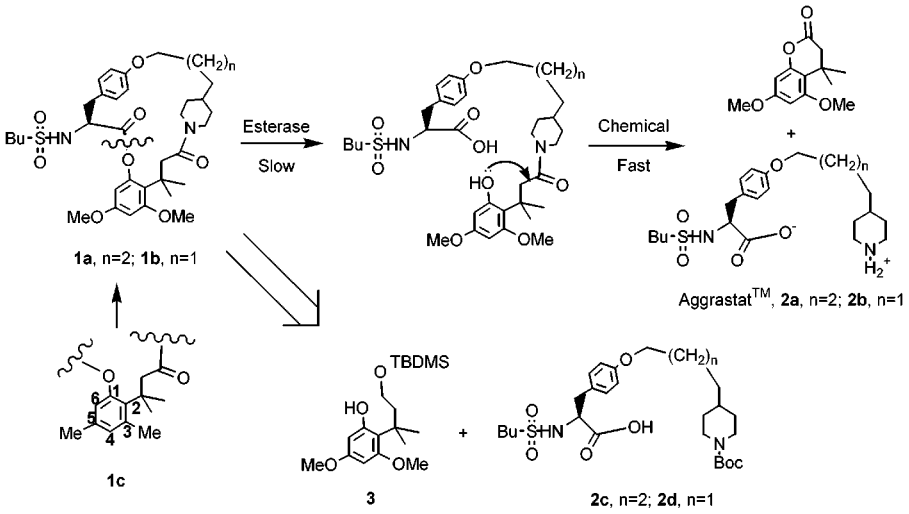
10.1021/ol010282n CCC: $22.00
Published on Web 01/19/2002

Scheme 1

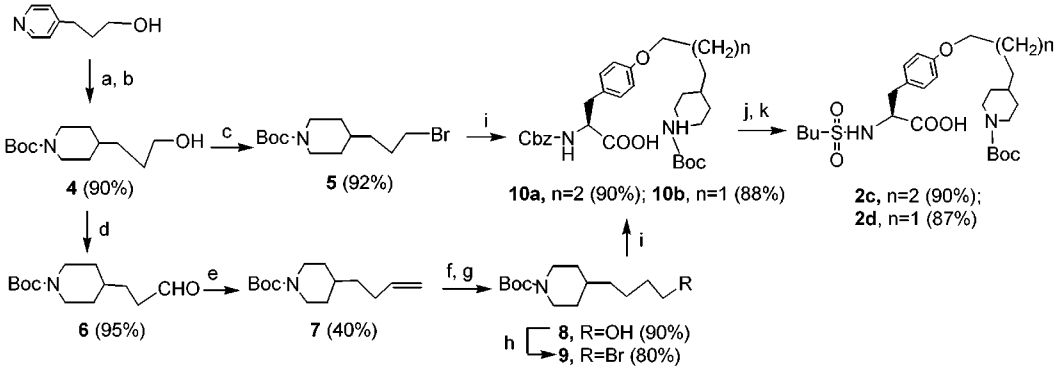


adding several polar groups to improve the solubility of the cyclic prodrugs without compromising the membrane permeation. To increase the polarity of phenylpropionic acid linker **1c**, the dimethyl groups at positions 3 and 5 of linker **1c** were substituted with dimethoxy groups in **1a** or **1b** (Scheme 1). This substitution does not affect the prodrug to drug conversion by esterase (unpublished data). Furthermore, this methoxy group can be utilized as a handle for other functional groups to balance solubility and membrane permeation of the prodrugs.

Here, we apply this new linker to make cyclic prodrugs **1a**,**b** from Aggrastat **2a** and its analogue **2b** (Scheme 1). The synthesis was accomplished by conjugating intermediate **3** and Boc-protected RGD-peptidomimetics **2c**,**d**. The synthesis of compounds **2c**,**d** is shown in Scheme 2. The synthesis of **2c** was started from 4-pyridinylpropanol; the pyridine ring was reduced with hydrogenation in the presence of Pd/C to give 4-piperidinylpropanol in 90% yield.[16,17] Treatment of 4-piperidinylpropanol with $(Boc)_2O$ in the presence of 1 N NaOH in dioxane produced *N*-Boc-protected alcohol **4** in 92% yield. Halogenation of the primary alcohol of compound **4** was carried out with CBr_4/PPh_3 in CH_2Cl_2 to give bromide **5** in 80% yield. Nucleophilic displacement of the bromide atom in **5** by phenolic oxygen of Cbz-Tyr-OH produced intermediate **10b** in 88% yield. Removal of the Cbz group in **10b** by hydrogenation gave an amine in 95% yield, which was reacted with Bu-SO_2-Cl to give the desired intermediate **2d** in 87% yield.

The intermediate **2c** was synthesized from alcohol **4**, which upon Swern oxidation produced aldehyde **6** in 95% yield. A Wittig reaction of aldehyde **6** with $CH_2{=}PPh_3$ generated in situ in dry THF resulted in compound **7** in 40% yield. Treatment of the alkene group in **7** with $BH_3{\cdot}$THF followed by H_2O_2/NaOH gave alcohol **8** in 90% yield. Bromination of alcohol **8** with CBr_4/PPh_3 gave compound **9** in 80% yield. Reaction of compound **9** and Cbz-Tyr-OH in the presence of NaH produced compound **10a** in 90% yield. Deprotection of the Cbz group in **10a** yielded an amine compound, which

Scheme 2[a]

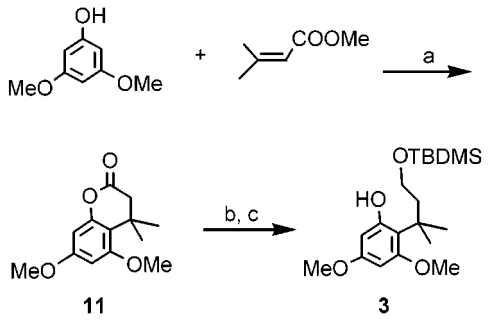


[a] Reagents and conditions: (a) 50 psi H_2, 10% Pd/C, AcOH, rt; (b) $(Boc)_2O$, NaOH, dioxane; (c) CBr_4, PPh_3, CH_2Cl_2; (d) ClCOCOCl, DMSO, CH_2Cl_2, −78 °C; (e) $CH_2{=}PPh_3$, THF; (f) $BH_3{\cdot}$THF; (g) H_2O_2/NaOH; (h) CBr_4, PPh_3, CH_2Cl_2; (i) Cbz-Tyr-OH, NaH, DMF; (j) H_2, 10% Pd/C, EtOH; (k) Bu-SO_2-Cl.

was reacted with Bu-SO_2-Cl to give compound **2c** in 90% yield.

Intermediate **3** was assembled by alkylating dimethoxyphenol with 3,3-dimethylacrylate in CH_3SO_3H to make lactone **11** in 40% yield using a procedure of isolation simpler than that previously reported (Scheme 3).[18−20] The

Scheme 3[a]



11 **3**

[a] Reagents and conditions: (a) CH_3SO_3H, 70 °C, 3 h, 40%; (b) $LiAlH_4$, THF, 70%; (c) TBDMS-Cl, Et_3N, CH_2Cl_2, 78%.

alkylation method using H_2SO_4 in toluene that was previously used to make linker **1c** produced only a 20% yield of compound **11**. Increasing the reaction temperature or time failed to improve this yield. Lactone **11** was then reduced to a diol in 70% yield using $LiAlH_4$ in THF. The primary alcohol was selectively protected by a TBDMS group using a standard procedure to give compound **3** in 78% yield.[13,21]

The syntheses of cyclic prodrugs **1a** and **1b** were initialized by coupling linker **3** and compounds **2c** and **2d** to yield intermediates **12a** (73%) and **12b** (67%), respectively.[22] The TBDMS-protected group was removed using AcOH/H_2O in THF; the resulting alcohols **13a**,**b** were oxidized to yield aldehydes **14a**,**b** (not shown in Scheme 4), which were further oxidized to acids **15a**,**b** in an overall yield of 30−33% determined from the starting materials **12a**,**b**. Removal of the Boc group in **15a**,**b** with TFA/CH_2Cl_2 produced the final linear precursors **16a**,**b**.[23] Cyclization of **16a**,**b** to give cyclic prodrugs **1a**,**b** was done using HBTU and DIEA in a highly dilute solution of DMF. Compounds **1a**,**b** were purified by column chromatography to give a 9−12% yield.[24]

In summary, we have developed a strategy to prepare cyclic prodrugs of Aggrastat and its analogue via a modified phenylpropionic acid linker with the aim of balancing the solubility and hydrophobicity of the cyclic prodrugs to obtain optimal physicochemical properties for membrane permeation through the intestinal mucosa. These cyclic prodrugs

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(19) **Experimental procedure:** Methanesulfonic acid (50 mL) was heated to 70 °C in an oil bath, and methyl 3,3-dimethylacrylate (5.7 g, 50.0 mmol) and 3,5-dimethoxyl phenol (6.65 g, 40.0 mmol) were added all at once with stirring. Stirring was continued at 70 °C for 3 h, and the reaction mixture was diluted to 500 mL with water and extracted with ethyl acetate (3 × 50 mL). The extracts were washed with water, saturated $NaHCO_3$, and NaCl solutions and dried over $MgSO_4$. Solvent removal with a rotary evaporator gave a brown solid, which was purified on a silica gel column (15:85, ethyl acetate/hexane) to give the light brown solid product **11** (3.78 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, 2 H, J = 10.3 Hz), 3.82 (s, 3 H), 3.79 (s, 3 H), 2.59 (s, 2 H), 1.42 (s, 6 H); MS (FAB) m/z 237 ($M^+ + 1$).

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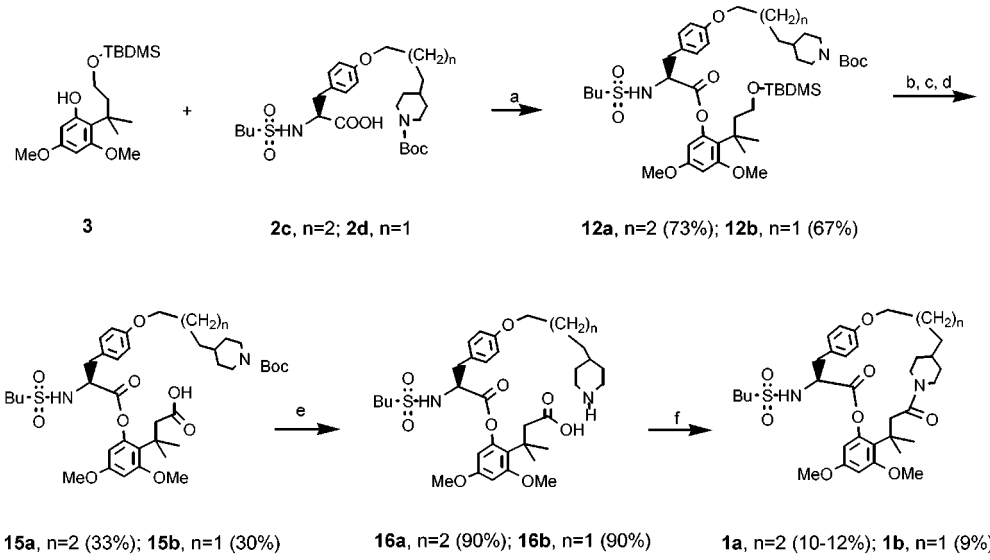
(21) Data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (br, 1 H), 6.06 (d, 2 H, J = 2.6 Hz), 5.98 (d, 1 H, J = 2.6 Hz), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.60 (t, 2 H, J = 6.8 Hz), 2.05 (t, 2 H, J = 6.8 Hz), 1.53 (s, 6 H), 0.86 (s, 9 H), 0.01 (s, 6 H); MS (FAB) m/z 355 ($M^+ + 1$).

(22) **Typical procedure:** Compound **2c** (1.44 g, 2.67 mmol) was dissolved in dry dichloromethane (DCM) (10.0 mL), and the solution was cooled to 0 °C. To this clear solution was added 1,3-dicyclohexylcarbodiimide (DCC) (0.66 g, 3.2 mmol), and the reaction mixture was stirred at 0 °C for 10 min. Compound **3** (0.945 g, 2.67 mmol) in dry DCM (5.0 mL) was added to the reaction followed by the addition of DMAP (0.39 g, 3.2 mmol). The reaction mixture was stirred for 2 h at 0 °C and for 20 h at room temperature. The resulting white precipitate was removed by filtration. Solvent removal with a rotary evaporator gave a yellow oil residue, which was dissolved in ethyl acetate (30 mL). The ethyl acetate solution was washed with 5% aqueous $NaHCO_3$, 5% aqueous citric acid, H_2O, and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a light yellow oil, which was purified on a silica gel column (50:50, ethyl acetate/hexane) to give the light yellow oil product **12a** (1.71 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 8.5 Hz), 6.88 (d, 2 H, J = 8.6 Hz), 6.37 (d, 1 H, J = 2.6 Hz), 5.86 (d, 1 H, J = 2.6 Hz), 4.96 (d, 1 H, 9 Hz), 4.50 (m, 1 H), 4.15 (m, 2 H), 3.95 (t, 2 H, J = 6.4 Hz), 3.81 (s, 3 H), 3.72 (s, 3 H), 3.47 (t, 2 H, J = 7.2 Hz), 3.32 (dd, 1 H, J = 4.9, 4.8 Hz), 3.10 (dd, 1 H, J = 7.9, 7.9 Hz), 2.80 (t, 2 H, J = 8.1 Hz), 2.70 (t, 2 H, J = 13.0 Hz), 2.08 (m, 2 H), 1.61−1.82 (m, 8 H), 1.47 (s, 8 H), 1.42 (s, 9 H), 1.30 (m, 5 H), 1.13 (m, 2 H), 0.87 (s, 9 H), 0.87 (t, 3 H, J = 7.3 Hz), 0.00 (s, 6 H); MS (FAB) m/z 775 (M^+ − Boc). Data for **12b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 8.5 Hz), 6.87 (d, 2 H, J = 8.6 Hz), 6.37 (d, 1 H, J = 2.6 Hz), 5.86 (d, 1 H, J = 2.6 Hz), 4.93 (d, 1 H, 9 Hz), 4.51 (m, 1 H), 4.15 (m, 2 H), 3.95 (t, 2 H, J = 6.4 Hz), 3.80 (s, 3 H), 3.73 (s, 3 H), 3.47 (t, 2 H, J = 7.2 Hz), 3.34 (dd, 1 H, J = 4.9, 4.8 Hz), 3.08 (dd, 1 H, J = 7.8, 7.8 Hz), 2.80 (t, 2 H, J = 8.1 Hz), 2.70 (t, 2 H, J = 13.0 Hz), 2.07 (m, 2 H), 1.82 (m, 2 H), 1.70 (m, 2 H), 1.61 (m, 4 H), 1.47 (s, 8 H), 1.41 (s, 9 H), 1.30 (m, 1 H), 1.13 (m, 2 H), 0.86 (s, 9 H), 0.86 (t, 3 H, J = 8.0 Hz), 0.00 (s, 6 H); MS (FAB) m/z 647 (M^+ − Boc − TBDMS + 1).

(23) Data for **15a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, 2 H, J = 8.3 Hz), 6.87 (d, 2 H, J = 8.3 Hz), 6.36 (d, 1 H, J = 2.4 Hz), 5.92 (d, 1 H, J = 2.5 Hz), 5.21 (d, 1 H, J = 8.9 Hz), 4.48 (m, 1 H), 3.93 (t, 2 H, J = 6.3 Hz), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.28 (dd, 1 H, J = 4.7, 4.7 Hz), 3.15 (dd, 1 H, J = 7.5, 7.3 Hz), 2.87 (q, 2 H, J = 5.8, 4.7 Hz), 2.78 (t, 2 H, J = 7.3 Hz), 2.68 (t, 2H, J = 11.0 Hz), 1.76 (m, 7 H), 1.67 (m, 2 H), 1.52 (m, 8 H), 1.47 (s, 9 H), 1.32−1.45 (m, 5 H), 1.12 (m, 2 H), 0.84 (t, 3 H, J = 7.4 Hz); MS (FAB) m/z 677 (M^+ − Boc + 2). Data for **15b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2 H, J = 8.4 Hz), 6.88 (d, 2 H, J = 8.6 Hz), 6.37 (d, 1 H, J = 2.7 Hz), 5.92 (d, 1 H, J = 2.5 Hz), 5.15 (d, 1 H, J = 8.9 Hz), 4.48 (m, 1 H), 3.94 (t, 2 H, J = 6.3 Hz), 3.81 (s, 3 H), 3.72 (s, 3 H), 3.30 (dd, 1 H, J = 4.7, 4.7 Hz), 3.10 (dd, 1 H, J = 7.7, 7.6 Hz), 2.88 (q, 2 H, J = 5.8, 4.7 Hz), 2.80 (t, 2 H, J = 8.1 Hz), 2.70 (t, 2H, J = 12.0 Hz), 1.81 (m, 2 H), 1.71 (m, 3 H), 1.60 (m, 2 H), 1.54 (d, 6 H, J = 9.3 Hz), 1.47 (s, 9 H), 1.35−1.45 (m, 4 H), 1.25 (m, 2 H), 1.14 (m, 3 H), 0.84 (t, 3 H, J = 7.4 Hz); MS (FAB) m/z 763 ($M^+ + 1$). Data for **16a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.7 (br, 1 H), 8.45 (br, 1 H), 8.10 (br, 1 H), 7.90 (d, 1 H, 9.3 Hz), 7.30 (d, 2 H, J = 8.5 Hz), 6.88 (d, 2 H, J = 8.5 Hz), 6.46 (d, 1 H, J = 2.4 Hz), 5.94 (d, 1 H, J = 2.3 Hz), 4.27 (m, 1 H), 3.99 (t, 2 H, J = 6.1 Hz), 3.78 (s, 3 H), 3.68 (s, 3 H), 3.40 (m, 2 H), 3.28 (d, 2 H, J = 9.3 Hz), 3.20 (dd, 1 H, J = 4.7, 4.7 Hz), 2.85 (m, 3 H), 2.70 (m, 2 H), 2.60 (m, 2 H), 1.80 (d, 2 H, J = 10.0 Hz), 1.70 (m, 2 H), 1.52 (m, 1 H), 1.39 (s, 6 H), 1.20−1.35 (m, 5 H), 1.12 (m, 2 H), 0.75 (t, 3 H, J = 7.2 Hz); MS (FAB) m/z 677 ($M^+ + 1$). Data for **16b**: ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.89 (m, 1 H), 8.20 (m, 1 H), 7.26 (d, 2 H, J = 8.4 Hz), 6.86 (d, 2 H, J = 8.4 Hz), 6.36 (d, 1 H, J = 2.4 Hz), 5.87 (d, 1 H, 2.4 Hz), 5.50 (m, 1 H), 4.48 (m, 1 H), 3.99 (t, 2 H, J = 6.0 Hz), 3.80 (s, 3 H), 3.72 (s, 3 H), 3.40 (m, 2 H), 3.29 (dd, 2 H, J = 4.7, 4.7 Hz), 3.15 (dd, 1 H, J = 7.5, 7.3 Hz), 2.85 (m, 5 H), 2.70 (m, 2 H), 1.80 (m, 2 H), 1.60 (m, 2 H), 1.50 (d, 6 H, J = 8.7 Hz), 1.41 (m, 5 H), 1.30 (m, 2 H), 0.87 (t, 3 H, J = 7.2 Hz); MS (FAB) m/z 663 ($M^+ + 1$).

Scheme 4[a]



[a] Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2; (b) AcOH/H_2O/THF (3:1:1); (c) PCC, CH_2Cl_2; (d) $KMnO_4$, acetone, 30−33% overall yield starting from **12**; (e) TFA/CH_2Cl_2 (1:1); (f) HBTU, DIEA, DMF.

can be converted to the drugs by esterase in the blood stream. The oral bioavailability of these cyclic prodrugs will be evaluated in vitro and in vivo.

Acknowledgment. Financial support was provided by NIH Grant HL-59931 and a Self-Faculty Scholar Award to T.J.S. from The University of Kansas. We thank Dr. Todd Williams, Mr. Robert Drake, and Ms. Homigol Biesada at the Mass Spectroscopy Laboratory for their technical support.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) **Typical procedure for cyclic prodrug 1a:** Compound **16a** (0.12 g, 0.18 mmol) was dissolved in DMF (300 mL), and HBTU (0.34 g, 0.9 mmol) was added. The reaction mixture was stirred at room temperature for 30 min under N_2 followed by the addition of DIEA (0.23 g, 1.8 mmol). The reaction solution was stirred for 20 h. The solvent then was removed under reduced pressure to give a light brown solid, which was purified on a silica gel column (50:50, ethyl acetate/hexane) to give the desired white solid product **1a** (11 mg, 10%). ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.05 (d, 1 H, J = 8.8 Hz), 7.31 (d, 2 H, J = 8.2 Hz), 6.90 (d, 2 H, J = 8.1 Hz), 6.41 (d, 1 H, J = 2.4 Hz), 5.39 (d, 1 H, J = 2.2 Hz), 4.25 (m, 3 H), 3.90 (m, 1 H), 3.78 (s, 3 H), 3.68 (s, 3 H), 3.15 (m, 4 H), 2.92 (m, 2 H), 2.70 (s, 1 H), 2.33 (s, 1 H), 2.22 (m, 2 H), 1.70 (m, 4 H), 1.60 (m, 1 H), 1.40 (m, 8 H), 1.10−1.30 (m, 6 H), 0.89 (t, 3 H, J = 7.3 Hz), 0.82 (m, 1 H), 0.65 (m, 1 H); MS (FAB) m/z 659 ($M^+ + 1$). Data for **1b**: ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.09 (d, 1 H, J = 8.9 Hz), 7.31 (d, 2 H, J = 8.4 Hz), 6.92 (d, 2 H, J = 8.4 Hz), 6.42 (d, 1 H, J = 2.6 Hz), 5.29 (d, 1 H, J = 2.6 Hz), 4.30 (m, 3 H), 4.10 (m, 1 H), 3.78 (s, 3 H), 3.73 (d, 1 H, J = 6.7 Hz), 3.65 (s, 3 H), 3.18 (m, 5 H), 2.92 (m, 2 H), 2.25 (m, 1 H), 1.90 (d, 1 H, J = 13.1 Hz), 1.70 (m, 3 H), 1.40 (m, 5 H), 1.32 (s, 6 H), 1.20 (m, 2 H), 1.02 (m, 1 H), 0.87 (t, 3 H, J = 7.3 Hz), 0.85 (m, 1 H); MS (FAB) m/z 645 ($M^+ + 1$).