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Synthesis of 1-[(2-Methoxyethoxy)Methyl]-N^3-(Alkyl)-6-(Phenylthio)Thymine. Potential Anti-Hiv Agents

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SYNTHESIS OF 1-[(2-METHOXYETHOXY)METHYL]-N^3-(ALKYL)-6-(PHENYLTHIO)THYMINE. POTENTIAL ANTI-HIV AGENTS

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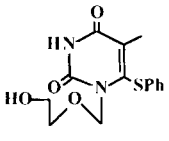
Abstract. The synthesis of six 1[(2-methoxyethoxy](methyl)-N^3-(alkyl)-6-(phenylthio)thymines **3a-f**, potential anti-HIV agents was carried out by two different synthetic routes.

Introduction

The Acquired Immunodeficiency Syndrome (AIDS) continues to be one of the most important unsolved health problems. Among the potential targets for antiviral chemotherapy, HIV-1 reverse transcriptase (HIV-1 RT) and, more recently, HIV-1 protease have been the only successful to date. Nucleoside analogues, such as 2',3'-dideoxynucleosides, are the principal agents against HIV-1 RT approved for clinical use. However, these compounds exhibit

significant toxicity and viral resistance.[1,2] Several years ago, the development of very specific and highly active non-nucleoside inhibitors of HIV-1 RT was envisioned to be the potential solution for HIV-1 infection. Nonetheless, these agents also failed to deal with viral resistance and, therefore, it is necessary to continue the search for new and more effective anti-HIV agents. Even the newly developed therapies which include a combination of drugs against both HIV-1 RT and HIV-1 protease do not represent the final solution to the problem.[3,6]

Within the group of non-nucleoside inhibitors of HIV-1 RT, 1[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine[7] (**1**, HEPT) is one of the potential candidates for further development in search for an effective drug. Structure-activity relationship studies have shown that 1[(2-methoxyethoxy)methyl]-6-(phenylthio)thymine **2** appeared to retain the activity accompanied by a slight increase in cytotoxicity.[8] We were interested in pursuing these family of compounds by synthesizing derivatives of **2** such as 1[(2-methoxyethoxy)methyl]-N^3-(alkyl)-6-(phenylthio)thymine **3** (Scheme 1). These derivatives are going to be evaluated for their in-vitro anti-HIV activity.



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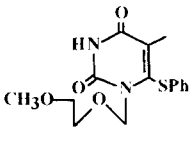

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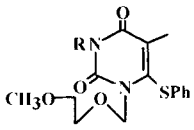


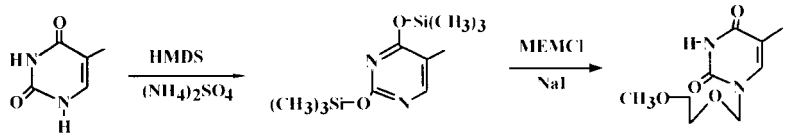
3a: R = methyl
b: R = ethyl
c: R = propargyl
d: R = allyl
e: R = prenyl
f: R = benzyl

Scheme 1

Results and Discussion

For the preparation of the target molecules **3a-f**, commercially available thymine **4** was first persilylated[9] with an excess of 1,1,1,3,3,3-

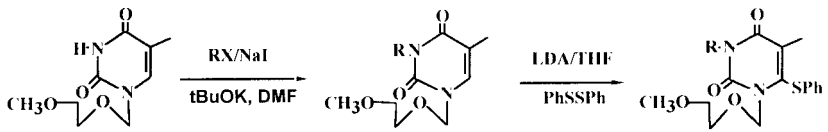
hexamethyldisilasane (HMDS) in the presence of catalytic amount of ammonium sulfate and then alkylated with one molar equivalent of 2-methoxyethoxymethyl chloride (MEMCl) and one molar equivalente of sodium iodide in dry 1,2-dichloroethane to furnish 1[(2-methoxyethoxy) methyl]thymine **5** as shown in Scheme 2.



4 **5**

Scheme 2

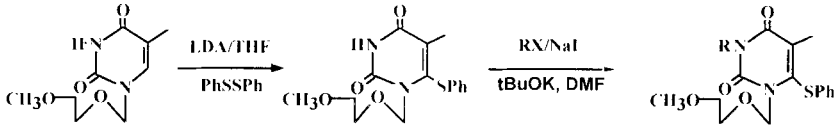
Compound **5** was allowed to react with potassium tertbutoxide in DMF with the appropriate alkyl halide[10] providing the N^3 alkylated thymine derivatives **6a, 6c, 6d, 6e**. Lithiation chemistry[11,12] was used for the C-6 functionalization of **6**. Therefore, 1[(2-methoxyethoxy)methyl]-N^3-(alkyl)thymine **6a, 6c, 6d, 6e** were treated with LDA in THF and then reacted with diphenyl disulfide, giving **3a, 3c, 3d, 3e** in a low yield (Scheme 3). Presumably the presence of an alkyl group at the position N^3 of 1[(2-methoxyethoxy)methyl]thymine **5** decreases the C-6 lithiation level.



5 **6a, c, d, e** **3a, c, d, e**

Scheme 3

As an alternative way to synthesize **3a-f** the 1[(2-methoxyethoxy)methyl]-6-(phenylthio)thymine **7** was first prepared in high yield based on the lithiation of **5** and successive alkylation with methyl iodide, ethyl bromide, allyl bromide, propargyl bromide, benzyl bromide and prenyl bromide (Scheme 4).



5 7 3a-f

Scheme 4

Pharmacological evaluation of the compounds synthesized here are in progress, and will be published elsewhere.

Experimental

Melting points were determined on a Fisher-Jones apparatus and are uncorrected. Flash column chromatography was performed on silica gel (grade 60, Merck). Thin-layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, Merck). The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively on a Varian VXR-300 S spectrometer and the chemical shift data are reported in parts per million (δ) with tetramethylsilane as internal standard, coupling constants in hertz. Infrared (IR) spectra were recorded on a Nicolet 5-SX FT IR spectrophotometer. Elemental analyses were performed at Galbraith Laboratories, Inc, Knoxville, TN. Low-resolution mass spectra were determinated with Hewlet-Packard 5985B GC/MS mass spectrometer. High resolution mass spectra (HMRS) were obtained on a JEOL JMS-SX102A mass spectrometer.

1[(2-Methoxyethoxy)methyl]thymine 5. Thymine **4** (5g, 40 mmol) was refluxed with excess hexamethyldisilazane (HMDS) (80 mL) and catalytic amount of $(NH_4)_2SO_4$ until a clear solution was obtained. The excess of HMDS was removed by distillation in *vacuo* and 2-methoxyethoxymethyl chloride (MEMCl) (3.80 mL, 33 mmol) without solvent and (4.95g, 33 mmol) of sodium iodide dissolved in dry 1,2-dichloroethane was added. The mixture was refluxed for 3 h. Evaporation of the solvent to dryness in *vacuo* followed by purification of the residue by silica gel column chromatography (3.0 % ethyl

acetate in hexane) gave the 1[(2-methoxyethoxy)methyl]thymine **5** as a white crystalline solid, 4.73 g (80 %), mp 103-105 °C. I.R ($CHCl_3$) 3030, 1700, 1650,1430, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94 (d, 3H, J=1.20, 5-CH_3), 3.38 (s, 3H, OCH_3), 3.50 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 5.20 (s, 2H, OCH_2N), 7.17 (q, 1H, J=1.20, 6-H); MS: (CI) m/z 215 $(MH)^+$, 139, 89.

General preparation of the 1[(2-methoxyethoxy)methyl]-N^3(alkyl) thymine 6a,c,d,e.

Representative procedure for 1[(2-methoxyethoxy)methyl](methyl)-thymine 6a. To a solution of 1[(2-methoxyethoxy) methyl]thymine (150 mg, 0.701 mmol) **5** in DMF (20 mL) was added at 0 °C *t*- BuOK (172 mg, 1.54 mmol) methyl iodide (0.131 mL, 2.103 mmol). After 30 min, the solution was allowed to warm to room temperature and stirring was continued another 90 min under a nitrogen atmosphere to yield a cloudy solution of **6a.** The solvent was removed in *vacuo*, dichloromethane-MeOH 8:2 solution was added to the reaction mixture, and the suspension was filtered on a filter paper. The filtrate was evaporated to dryness *in vacuo* and the residue purified on a silica gel column eluted with dichloromethane-MeOH 9:1 to give the monoalkyl 1[(2-methoxyethoxy) methyl](methyl)thymine **6a** (70 mg, 0.30 mmol, 43%). Spectroscopic data for 1[(2-methoxyethoxy)methyl]-N^3-(alkyl)thymine **6a, c, f, g** follow.

1[(2-Methoxyethoxy)methyl]-3-(methyl)thymine 6a. Colorless oil, yield 43 %. IR ($CHCl_3$) 1705, 1645, 1468, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (d, 3H, J=1.5, 5-Me), 3.32 (s, 3H, N-CH_3), 3.33 (s, 3H, OCH_3), 3.50 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 3.50 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 5.18 (s, 2H, OCH_2N), 7.11 (q, 1H, J=1.20, 6-H); ^{13}CNMR ($CDCl_3$) δ 12.954, 27.885, 58.978, 68.757, 71.541, 110.553, 136.894, 151.948, 163.758; MS: (CI) m/z 228 $(M)^+$, 169, 153, 140, 89, 59. Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.75; H, 6.87; N, 12.41.

1[(2-Methoxyethoxy)methyl]-3-(propargyl)thymine 6c. Colorless oil, yield 37 %. IR ($CHCl_3$) 3309, 1711, 1671, 1656, 1449, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (d, 3H, J=1.2, 5-Me), 2.17 (t, 1H, J-2.4, $\underline{H}C{\equiv}CCH_2$), 3.32 (s, 3H, OCH_3), 3.50 (m, 2H, $CH_3OC\underline{H_2}CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2C\underline{H_2}OCH_2N$), 4.68 (d, 2H, J=2.4, $HC{\equiv}CC\underline{H_2}N$), 5.18 (s, 2H, OCH_2N), 7.13 (d, 1H, J=1.20, 6-H); ^{13}CNMR ($CDCl_3$) δ 12.831, 30.407, 58.931, 68.896, 70.529, 71.464, 110.737, 137.371, 151.041, 162.512; MS: (CI) m/z 252 $(M)^+$, 193, 177, 164, 110, 89, 59. Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.01; H, 6.27; N, 10.92.

1[(2-Methoxyethoxy)methyl]-3-(allyl)thymine 6d. Colorless oil, yield 39 %. IR ($CHCl_3$) 1705, 1673, 1651, 1450, 1089 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (d, 3H, J=1.5, 5-Me), 3.33 (s, 3H, OCH_3), 3.50 (m, 2H, $CH_3OC\underline{H_2}CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2C\underline{H_2}OCH_2N$), 4.52 (dt, 2H, J=1.5, 5.7, $CH{=}C\underline{H_2}N$), 5.17 (s, 2H, OCH_2N), 7.17 (q, 1H, J=1.20, 6-H); ^{13}CNMR ($CDCl_3$) δ 12.923, 43.339, 58.962, 66.804, 71.510, 76.584, 110.753, 117.826, 131.666, 137.140, 151.548, 163.220; MS: (CI) m/z 254 $(M)^+$, 195, 178, 89, 59. Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.91; H, 6.96; N, 11.22.

1[(2-Methoxyethoxy)methyl]-3-(prenyl)thymine 6e. Colorless oil, yield. IR ($CHCl_3$) 1705, 1671, 1646, 1449, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (d, 3H, J=1.2, $C\underline{H_3}C{=}CH$), 1.82 (d, 3H, J= 0.9, $C\underline{H_3}C{=}CH$), 1.94 (d, 3H, J=1.2, 5-Me), 3.37 (s, 3H, OCH_3), 3.50 (m, 2H, $CH_3OC\underline{H_2}CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2C\underline{H_2}OCH_2N$), 4.54 (d, 2H, J=6.9, $C{=}CCH_2\underline{N}$), 5.24 (m, 1H, $(CH_3)_2C{=}C\underline{H}$), 5.00 (s, 2H, OCH_2N), 7.12 (d, 1H, J=1.20, 6-H); MS: (CI) m/z 282 $(M)^+$, 206, 110, 89, 59. Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.63; H, 7.55; N, 9.93.

1[(2-Methoxyethoxy)methyl]-6-(phenylthio)thymine 7. LDA (3.7 g, 35.04 mmol) in THF (20mL) was placed in a three-necked flask fifted with a nitrogen inlet adapter, a thermometer, and a rubber septum. To this solution, under a nitrogen atmosphere 1[(2-methoxyethoxy)methyl]thymine **5** (2.5 g, 11.68 mmol) dissolved in THF (30 mL) was added at a rate such that the temperature

did not exceed -70 °C. After the mixture had been stirred for 1.5 h, diphenyl disulfide (6.07 g, 29.22 mmol) in THF (25 mL) was added maintaining the temperature below -70 °C. The mixture was stirred for 30 min below -70 °C, then quenched with AcOH (4.2 mL), and allowed to warm to room temperature. The whole was evaporated to dryness, and the residue was purified by chromatography EtOAc-hexane (7:3) gave the 1[(2-methoxyethoxy)methyl]-6-(phenylthio)thymine **7** as a white crystalline solid, 2.25 g (59 %), mp 101-103 °C. (Lit.[13] 102'104°C) I.R ($CHCl_3$) 3187, 1683, 1442,1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H, 5-CH_3), 3.31 (s, 3H, OCH_3), 3.40 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 5.60 (s, 2H, OCH_2N), 7.20 (m, 5H, SPh); MS: (CI) m/z 322 $(M)^+$, 234, 123, 109, 89, 59.

General preparation of the 1[(2-methoxyethoxy)methyl]-N^3-(alkyl)-6-(phenylthio)thymine 3a-f.

Representative procedure for 1[(2-methoxyethoxy)methyl]-N^3-(allyl)-6-(phenylthio)thymine 3d. To a solution of 1[(2-methoxyethoxy) methyl]thymine (500 mg, 1.53 mmol) **7** in DMF (20 mL) was added at 0 °C *t*- BuOK (250 mg, 2.29 mmol,) allyl bromide (0.397 mL, 4.59 mmol) with one molar equivalent of sodium iodide. After 30 min, the solution was allowed to warm to room temperature and stirring was continued another 90 min under a nitrogen atmosphere to yield a cloudy solution of **3d**. Evaporation of the solvent to dryness in *vacuo* followed by purification of the residue by silica gel column chromatography (EtOAc-hexane 6:4) gave the monoalkyl 1[(2-methoxyethoxy)methyl]-N^3-(allyl)-6-(phenylthio) thymine **3d** (529 mg, 1.46 mmol, 95.4 %). Spectroscopic data for 1[(2-methoxyethoxy)methyl]-N^3-(alkyl)-6-(phenylthio)thymine **3a, b, c, d, e, f** follow.

1[(2-Methoxyethoxy)methyl]-N^3-(methyl)-6-(phenylthio)thymine 3a.
Colorless oil, yield 82 %. IR ($CHCl_3$) 2925, 1702, 1654, 1452, 1092, 1023 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, 5-Me), 3.32 (s, 3H, NCH_3), 3.40 (s, 3H, OCH_3), 3.40 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 5.65 (s, 2H, OCH_2N), 7.20 (m, 5H, SPh); ^{13}CNMR

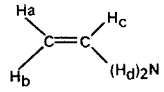
($CDCl_3$) δ 14.479, 28.542, 58.811, 68.624, 71.548, 76.045, 119.117, 127.093, 127.752, 129.565, 132.986, 143.716, 152.078, 162.345; MS: (CI) m/z 336 $(M)^+$, 261, 248, 123, 109, 89, 59. Anal. Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33. Found: C, 56.97; H, 6.09; N, 8.57. HRMS Calcd for $C_{16}H_{20}N_2O_4S$ m/z 336.1144. Found m/z 336.1143.

1[(2-Methoxyethoxy)methyl]-N^3-(ethyl)-6-(phenylthio)thymine 3b. Colorless oil, yield 85 %. IR ($CHCl_3$) 1702, 1652, 1443, 1093, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, J=7.14, $C\underline{H}_3CH_2$), 2.08 (s, 3H, 5-Me), 3.33 (s, 3H, OCH_3), 3.50 (m, 2H, $CH_3OC\underline{H}_2CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2C\underline{H}_2OCH_2N$), 4.05 (q, 2H, J=7.14, $NC\underline{H}_2CH_3$) 5.64 (s, 2H, OCH_2N), 7.20 (m, 5H, SPh); ^{13}CNMR ($CDCl_3$) δ 12.603, 14.434, 37.255, 58.911, 68.620, 71.553, 75.995, 119.316, 127.068, 127.76, 129.562, 133.014, 143.670, 151.703, 161.935; MS: (CI) m/z 350 $(M)^+$, 275, 262, 123, 110, 89, 59. Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 7.99. Found: C, 58.46; H, 6.43; N, 7.81. HRMS Calcd for $C_{17}H_{22}N_2O_4S$ m/z 350.1300. Found m/z 350.1318.

1[(2-Methoxyethoxy)methyl]-N^3-(propargyl)-6-(phenylthio)thymine 3c. Yellow oil, yield 85 %. IR ($CHCl_3$) 3262, 2126, 1705, 1652, 1435, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H, 5-Me), 2.21 (t, 1H, J=2.46, HC≡C), 3.33 (s, 3H, OCH_3), 3.40 (m, 2H, $CH_3OC\underline{H}_2CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2C\underline{H}_2OCH_2N$), 4.76 (d, 2H, J=2.48, $HC{\equiv}CC\underline{H}_2N$), 5.66 (s, 2H, OCH_2N), 7.20 (m, 5H, SPh); ^{13}CNMR ($CDCl_3$) δ 14.418, 31.106, 58.883, 68.736, 70.812, 71.479, 76.109, 119.057, 127.226, 127.952, 129.590, 132.698, 144.645, 151.159, 161.135; MS: (CI) m/z 360 $(M)^+$, 285, 272, 123, 109, 89, 59. Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 60.21; H, 5.67; N, 7.91. HRMS Calcd for $C_{18}H_{20}N_2O_4S$ m/z 360.1144. Found m/z 360.1154.

1[(2-Methoxyethoxy)methyl]-N^3-(allyl)-6-(phenylthio)thymine 3d. Yellow oil, yield 95 %. IR ($CHCl_3$) 3080, 1702, 1652, 1650, 1437, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (s, 3H, 5-Me), 3.33 (s, 3H, OCH_3), 3.40 (m, 2H,

$CH_3OCH_2CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 4.60 (dt, 2H, J=6.0, 1.2, Hd)*, 5.21 (dq, 1H, J=10.2, 1.5, Ha)*, 5.29 (dq, 1H, J=17.4, 1.5, Hb)*, 5.64 (s, 2H, OCH_2N), 5.92 (dqt, 1H, J=6.0, 10.2, 16.4, Hc)*, 7.30 (m, 5H, SPh); ^{13}CNMR ($CDCl_3$) δ 14.411, 44.029, 58.884, 71.494, 118.152, 119.197, 127.102, 127.809, 129.562, 131.315, 144.018, 151.645, 161.764; MS: (CI) m/z 362 $(M)^+$, 278, 274, 123, 109, 89, 59. Anal. Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.47; H, 6.38; N, 7.88. HRMS Calcd for $C_{18}H_{22}N_2O_4S$ m/z 362.1300. Found m/z 362.1297.



1[(2-Methoxyethoxy)methyl]-N^3-(prenyl)-6-(phenylthio)thymine 3e. Yellow oil, yield 94 %. IR ($CHCl_3$) 1704, 1652, 1652, 1440, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.72 (d, 3H, J=0.88, MeC=CH), 1.83 (d, 3H, J=0.82, MeC=CH), 2.07 (s, 3H, 5-Me), 3.32 (s, 3H, OCH_3), 3.50 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 4.56 (d, 2H, J=6.96, C=CHCH$_2$N), 5.26 (t, 1H, J=1.98, Me_2C=CH), 5.63 (s, 2H, OCH_2N), 7.20 (m, 5H, SPh); ^{13}CNMR ($CDCl_3$) δ 14.522, 18.050, 25.693, 40.320, 58.936, 68.627, 71.570, 76.042, 118.127, 119.376, 127.093, 127.905, 129.594, 133.059, 137.156, 143.723, 151.850, 162.037; MS: (CI) m/z 390 $(M)^+$, 314, 223, 123, 110, 89, 59. Anal. Calcd for $C_{20}H_{26}N_2O_4S$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.63; H, 6.59; N, 7.23. HRMS Calcd for $C_{20}H_{26}N_2O_4S$ m/z 390.1613. Found m/z 390.1633.

1[(2-Methoxyethoxy)methyl]-N^3-(benzyl)-6-(phenylthio)thymine 3f. Yellow oil, yield 60 %. IR ($CHCl_3$) 3062, 1701, 1652, 1652, 1439, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, 5-Me), 3.30 (s, 3H, OCH_3), 3.40 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 3.70 (m, 2H, $CH_3OCH_2CH_2OCH_2N$), 5.16 (s, 2H, CH_2Ph), 5.63 (s, 2H, OCH_2N), 7.20 (m, 8H, SPh, CH_2Ph), 7.50 (dd, 2H, J=1.8, 8.1, CH_2Ph); ^{13}CNMR ($CDCl_3$) δ 14.565, 45.198, 58.195, 68.634, 71.495, 76.108, 119.000, 127.132, 127.655, 127.871, 128.363, 129.101, 129.593, 132.884, 136.482, 144.141, 152.045, 162.133; MS: (CI) m/z 412 $(M)^+$, 336, 324, 233, 123, 91, 89, 59. Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06;

H, 5.86; N, 6.79. Found: C, 64.25; H, 5.69; N, 6.67. HRMS Calcd for $C_{22}H_{24}N_2O_4S$ m/z 412.1457. Found m/z 412.1461.

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