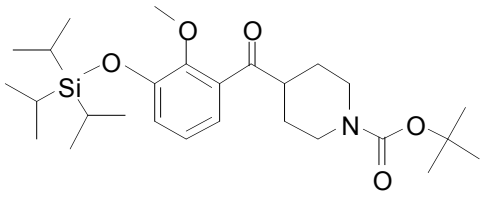
Supplementary Data

Synthesis and evaluation of dimeric derivatives of 5-HT_{2A} receptor (5-HT_{2A}R) antagonist M-100907

Authors
Matt Shashack, Kathryn A. Cunningham, Patricia K. Seitz, Andrew McGinnis, Thressa Smith, Cheryl S. Watson and Scott R. Gilbertson*

Experimental

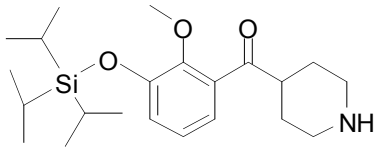
tert-butyl 4-(2-methoxy-3-(triisopropylsilyloxy)benzoyl)piperidine-1-carboxylate (7)



A solution of triisopropyl(2-methoxyphenoxy)silane (**6**) (8.0 g, 28.5 mmol) in 65 mL freshly distilled THF was cooled to -78˚ C. A solution of 2.5M nBuLi (63 mL, 156.8 mmol) was added dropwise and stirred an additional 10 minutes at -78 ˚C. The solution was stirred at 0˚ C for 2 hours, then warmed to room temperature and stirred an additional 2 hours. Next the solution was refluxed for 2 hours and cooled to -78˚ C. Tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (9.3 g, 34.2 mmol) in 10 mL of freshly distilled THF was added and the reaction mixture was warmed to room temperature. The reaction was stirred for 18 hours at room temperature, cooled to 0˚C, and quenched with aqueous NH_4Cl. The aqueous solution was extracted three times with CH_2Cl_2; the organic extracts were dried over $MgSO_4$ and concentrated. The crude reaction mixture was purified with flash chromatography (100% hexane to 20% EtOAc in

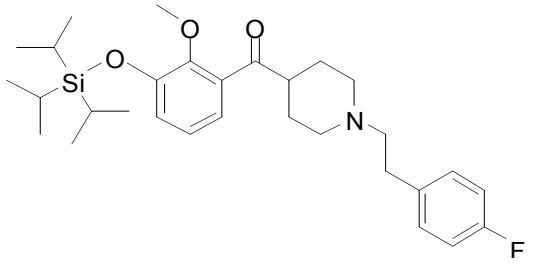
hexane) to afford 7.0 g of tert-butyl 4-(2-methoxy-3-(triisopropylsilyloxy)benzoyl)piperidine-1-carboxylate(**7**) as a yellow oil (50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99-6.93 (m, 3H), 4.06 (bs, 2H), 3.84 (s, 3H), 3.23 (tt, J = 3.7, 11.0 Hz, 1H), 2.84 (dd, J = 9.3, 12.4 Hz, 2H), 1.83 (d, J = 10.5 Hz, 2H), 1.63-1.53 (m, 2H), 1.45 (s, 9H), 1.30 (septet, J = 7.8 Hz, 3H), 1.11 (d, J = 7.3 Hz, 18H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 206.3, 154.8, 149.5, 134.8, 124.3, 123.4, 121.0, 79.6, 61.7, 48.0, 28.5, 27.9, 18.0, 12.9, 12.4

(2-methoxy-3-(triisopropylsilyloxy)phenyl)(piperidin-4-yl)methanone (8)



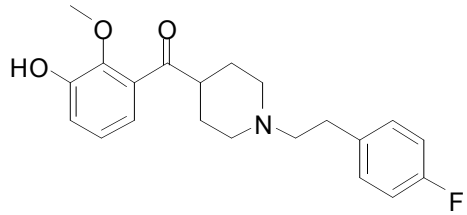
Tert-butyl 4-(2-methoxy-3-(triisopropylsilyloxy)benzoyl)piperidine-1-carboxylate (**7**) (7.5 g, 15.3 mmol) was cooled to 0˚ C and 40 mL TFA (58 g, 505 mmol) was added dropwise with stirring. The reaction was warmed to room temperature and stirred an additional 2 hours then cooled to 0˚C and quenched with 6 M NaOH. The neutralized reaction was extracted three times with CH_2Cl_2 and the combined extracts were dried over $MgSO_4$ and concentrated to afford 5.6 g of (2-methoxy-3-(triisopropylsilyloxy)phenyl)(piperidin-4-yl)methanone (**8**) as a red oil (94%). ^{1}H NMR (500MHz, $CDCl_3$) δ 6.98-6.93 (m, 3H), 3.84 (s, 3H), 3.24 (tt, J = 3.7, 11.0 Hz, 1H), 3.16 (dt, J = 3.7, 12.8 Hz, 2H), 2.74 (td, J = 2.7, 11.5 Hz, 2H), 1.90 (dd, J = 2.7, 13.7 Hz, 2H), 1.63 (qd, J = 4.1, 11.4 Hz, 2H), 1.35-1.25 (m, 3H), 1.11 (d, J = 7.3 Hz, 18H); ^{13}C NMR (500MHz, $CDCl_3$) δ 206.3, 149.5, 148.9, 134.7, 124.3, 123.3, 121.0, 61.7, 47.6, 45.5, 28.4, 18.0, 12.9

(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3(triisopropylsilyloxy)phenyl)-methanone(9)



A solution of 2-methoxy-3-(triisopropylsilyloxy)phenyl)(piperidin-4-yl)methanone (**8**) (822 mg, 2.1 mmol), 4-fluorophenethyl 4-methylbenzenesulfonate (550 mg, 2.5 mmol), and DIEA (650 mg, 5.0 mmol) in 12 mL CH_3CN was refluxed for 24 hours and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was taken up in a saturated solution of $NaHCO_3$. The aqueous solution was extracted three times with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified with flash chromatography (100% $CH_2Cl_2$to 10% MeOH in CH_2Cl_2) to afford 631 mg of (1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(triisopropylsilyloxy)phenyl)methanone(**9**) as an orange oil (60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, J = 5.2, 5.7 Hz, 2H), 6.99-6.93 (m, 5H), 3.83 (s, 3H), 3.08 (tt, J = 4.0, 10.9 Hz, 1H), 2.97 (d, J = 11.4 Hz, 2H), 2.76 (dd, J = 7.5, 8.6 Hz, 2H), 2.55 (dd, J = 8.0, 8.6 Hz, 2H), 2.13 (dd, J = 9.7, 11.5 Hz, 2H), 1.90 (d, J = 11.5 Hz, 2H), 1.75 (qd, J = 3.5, 11.4 Hz, 2H), 1.30 (septet, J = 7.4 Hz, 3H), 1.12 (d, J = 7.5 Hz, 18H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 206.7, 162.3, 160.4, 149.4, 148.8, 136.1, 136.1, 135.0, 130.5, 130.1, 130.0, 124.2, 123.1, 120.9, 115.3, 115.2, 115.0, 63.5, 61.2, 60.8, 53.5, 53.3, 47.9, 38.5, 32.9, 28.1, 17.9, 13.1, 12.9, 12.6

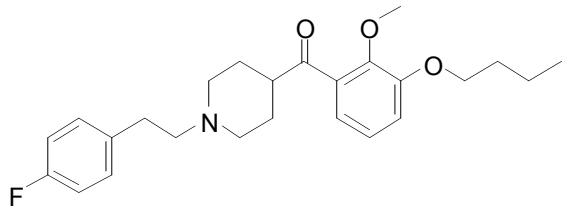
(1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (**10**)



1M TBAF (1.3 mL, 1.3 mmol) was added dropwise over 5 minutes to a solution of (1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(triisopropylsilyloxy)phenyl)methanone (**9**) (500 mg, 1.0 mmol) in 3.0 mL anhydrous THF at room temperature. The reaction was stirred at room temperature for 2 hours then diluted with brine and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 232 mg of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (**10**) as a red-orange oil (65%).

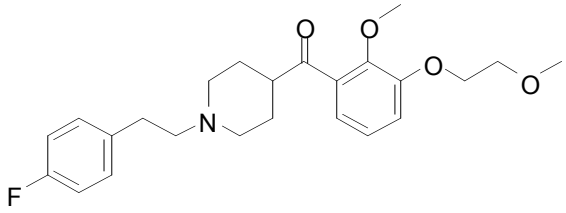
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14-7.11 (m, 2H), 7.06-7.02 (m, 2H), 6.96-6.93 (m, 3H), 3.80 (s, 3H), 3.09 (tt, J= 10.1, 4.0Hz, 1H), 3.00 (d, J=11.4Hz, 2H), 2.77 (dd, J= 8.0, 5.7Hz, 2H), 2.58 (dd, J= 8.0, 5.2,Hz, 2H), 2.16 (dd, J= 10.0, 10Hz, 2H), 1.90 (d, J=12Hz, 2H), 1.88 (qd, J=3.5, 10.9Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.5, 162.5, 160.5, 149.4, 145.3, 132.8, 130.2, 130.1, 125.0, 120.3, 118.9, 115.3, 115.2, 62.9, 60.7, 53.2, 32.8, 28.1; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{21}H_{24}FNO_3$: 358.1818, measured 358.1824.

(3-butoxy-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (**11**)



Butyl 4-methylbenzenesulfonate (232.9 mg, 1.02 mmol) and K_2CO_3 (141 mg, 1.02 mmol) was added to a solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2 methoxyphenyl)methanone (**10**) (181.5 mg, 0.51 mmol) in 8 mL acetone . The reaction mixture was refluxed for 22 hours then cooled to room temperature. The solvent was removed under reduced pressure. Flash chromatography (100% CH_2Cl_2 to 8% MeOH in CH_2Cl_2) isolated 205 mg of (3-butoxy-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone(**11**) as an orange oil (97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16-7.13 (m, 2H), 7.06-6.99 (m, 2H), 6.96-6.92 (m, 3H), 4.01 (t, J = 6.3 Hz, 2H), 3.88 (s, 3H), 3.11-3.08 (m, 1H), 2.97 (d, J = 11.4 Hz, 2H), 2.78-2.74 (m, 2H), 2.56-2.53 (m, 2H), 2.11 (t, J = 9.8 Hz, 2H), 1.91 (d, J = 11.5 Hz, 2H), 1.85-1.82 (m, 2H), 1.80-1.74 (m, 2), 1.53 (sextet, J = 7.4 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 162.3, 160.4, 152.3 147.1, 136.2, 136.2, 134.4, 130.1, 124.2, 120.1, 115.8, 115.2, 115.0, 68.5, 61.6, 60.8, 53.5, 53.4, 48.2, 32.9, 31.4, 28.1, 19.4, 13.9; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{25}H_{32}FNO_3$: 414.2444, measured 414.2438.

(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2methoxyethoxy)phenyl)-methanone (**12**)



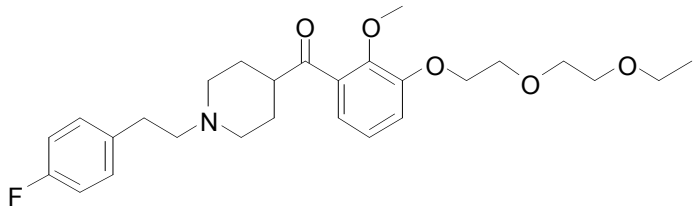
((1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2 methoxyphenyl)methanone (**10**) (85.4 mg, 0.24 mmol), 2-methoxyethyl 4-methylbenzenesulfonate (110 mg, 0.48 mmol), and K_2CO_3 (66 mg, 0.48 mmol) in 5 mL acetone were refluxed for 22 hours then cooled to room temperature. The solvent was removed under reduced pressure and the crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 8% MeOH in CH_2Cl_2) to afford 75.3 mg of (1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2-methoxyethoxy)phenyl)methanone(**12**) as an orange oil (75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.13 (m, 2H), 7.08-7.02 (m, 2H), 7.00-6.93 (m, 3H), 4.17 (dd, J = 6.0, 4.6 Hz, 2H), 3.90 (s, 3H), 3.80 (dd, J = 6.0, 4.6 Hz, 2H), 3.45 (s, 3H), 3.14-3.09 (m, 1H), 3.00-2.98 (m, 2H), 2.81-2.77 (m, 2H), 2.60-2.56 (m, 2H), 2.18 (dd, J = 10.1, 10.1 Hz, 2H), 1.93 (dd, J = 13.7, 3.2 Hz, 2H), 1.81-1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 162.7, 160.2, 152.0, 147.5, 136.0, 134.5, 130.2, 130.1, 124.3, 120.9, 116.7, 115.3, 115.1, 76.8, 71.1, 70.7, 68.5, 61.7, 60.7, 59.3, 53.2, 47.9, 32.8, 27.9; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{24}H_{30}FNO_4$: 416.2237, measured 416.2239.

General procedure for O-alkylation of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (10) with a tosylated alkylating agent.

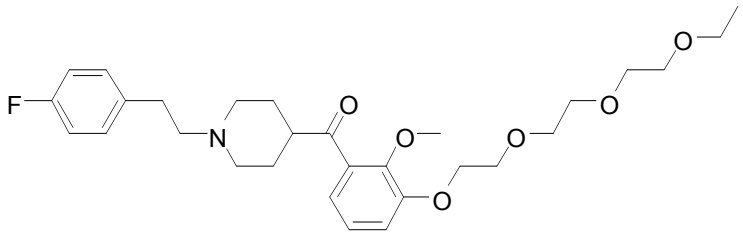
A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (**10**) (105 mg, 0.30 mmol), the appropriate tosylate (0.60 mmol, 190-218 mg), and K_2CO_3 (62 mg, 0.45 mmol) in 8 mL acetone was refluxed for 24 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2).

(3-(2-(2-ethoxyethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (**13**)



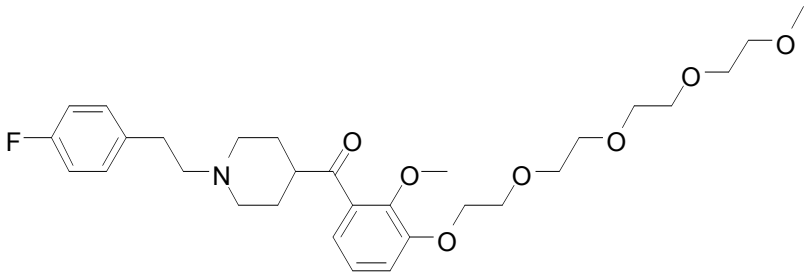
The above procedure with 2-(2-ethoxyethoxy)ethyl 4-methylbenzenesulfonate as the alkylating agent produced 145 mg of (3-(2-(2-ethoxyethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone(**13**) (93%) as a red oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.17-7.13 (m, 2H), 7.07-7.01 (m, 2H), 7.0-6.93 (m, 3), 4.20 (dd, J = 5.1, 4.6 Hz, 2H), 3.91 (dd, J = 6.9, 2.9 Hz, 2H), 3.91 (s, 3H), 3.72 (dd, J = 6.3, 4.6 Hz, 2H), 3.61 (dd, J = 6.3, 4.5 Hz, 2H), 3.52 (q, J = 7.5 Hz, 2H), 3.12 (tt, J = 10.9, 4.0 Hz, 1H), 3.00 (d, J = 11.5 Hz, 2H), 2.78 (dd. J = 8.5, 5.8 Hz, 2H), 2.57 (dd, J = 8.6, 5.8 Hz, 2H), 2.17 (dd, J = 11.5, 9.7 Hz, 2H), 1.93 (d, J = 10.9 Hz, 2H), 1.79 (qd, J = 10.9, 2.9 Hz, 2H). 1.21 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2, 162.1, 160.2, 151.7, 147.1, 134.1, 129.9, 129.8, 124.0, 120.5, 116.3, 115.0, 114.9, 70.7, 69.7, 69.5, 68.2, 66.5, 61.5, 60.4, 53.0, 32.5, 27.7, 15.0; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{27}H_{36}FNO_5$: 496.2475, measured 496.2455.

(3-(2-(2-(2-ethoxyethoxy)ethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (**14**)



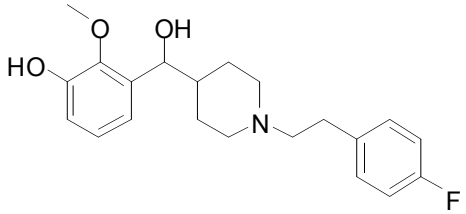
The above procedure with 2-(2-(2-ethoxyethoxy)ethoxy)ethyl 4-methylbenzenesulfonate as the alkylating agent produced 153 mg of (3-(2-(2-(2-ethoxyethoxy)ethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (**14**) (99%) as a red oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.16-7.13 (m, 2H), 7.08-7.02 (m, 2H), 7.00-6.93 (m, 3H), 4.19 (dd, J = 5.1, 4.6 Hz, 2H), 3.90 (dd, J = 5.7, 3.4 Hz, 2H), 3.90 (s, 3H), 3.74 (dd, J = 5.8, 2.9 Hz 2H), 3.68 (dd, J = 5.8, 2.9 Hz, 2H), 3.65 (dd, J = 5.4, 2.9 Hz, 2H), 3.58(dd, J = 5.4, 2.9 Hz, 2H) 3.52 (q, J = 6.9 Hz, 2H), 3.13 (tt, J = 10.9, 4.0 Hz, 1H), 3.01 (d, 11.5 Hz, 2H), 2.78 (dd, J = 8.0, 5.1 Hz, 2H), 2.61 (dd, J = 8.3, 5.2 Hz, 2H), 2.19 (t, J = 10.2 Hz, 2H), 1.93 (d, J = 11.4 Hz, 2H), 1.79 (qd, J = 10.3, 3.4 Hz, 2H), 1.21 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 162.1, 160.2, 151.7, 147.1, 135.6, 134.0, 129.9, 129.8, 124.0, 120.5, 116.4, 115.0, 114.8, 70.6, 70.5, 70.4, 69.6, 69.4, 68.2, 66.4, 61.5, 60.2, 52.8, 47.6, 32.3, 27.5, 15.0; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{29}H_{40}FNO_6$: 518.2918, measured 518.2904.

(3-(2,5,8,11-tetraoxatridecan-13-yloxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)-piperidin-4-yl)methanone (**15**)



The above procedure with 2,5,8,11-tetraoxatridecan-13-yl 4-methylbenzenesulfonate as the alkylating agent produced 164 mg of (3-(2,5,8,11-tetraoxatridecan-13-yloxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (**15**) (100%) as a red oil. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.15 (dd, J = 8.6, 5.1 Hz, 2H), 7.07-7.02 (m, 2H), 7.00-6.93 (m, 3H), 4.18 (dd, J = 5.2, 4.6 Hz, 2H), 3.90 (dd, J = 5.2, 4.6 Hz, 2H), 3.90 (s, 3H), 3.73 (dd, J = 6.3, 4.0 Hz, 2H), 3.69-3.62 (m, 8H), 3.54 (dd, J = 6.3, 4.0 Hz, 2H), 3.37 (s, 3H), 3.11 (tt, J = 10.8, 4.0 Hz, 1.0H), 2.99 (d, J = 11.4 Hz, 2H), 2.77 (dd, J = 8.1, 5.2 Hz, 2H), 2.57 (dd, J = 8.1, 5.7 Hz, 2H), 2.15 (t, J = 10.9 Hz, 2H), 1.92 (d, J = 10.9 Hz, 2H), 1.77 (qd, J = 10.9, 3.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 162.0, 160.0, 151.6, 147.1, 135.6, 134.0, 129.9, 129.8, 123.9, 120.4, 116.2, 114.9, 114.7, 71.6, 70.5, 70.4, 70.3, 70.2, 69.4, 68.1, 62.1, 61.4, 58.8, 47.9, 32.4, 27.6; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{30}H_{42}FNO_7$: 548.3024, measured 548.3030.

3-((1-(4-fluorophenethyl)piperidin-4-yl)(hydroxy)methyl)-2-methoxyphenol (**16**)

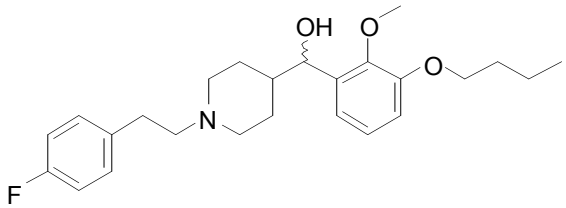


A stirred solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (**10**) (565 mg, 1.58 mmol) in 15 mL anhydrous EtOH was

cooled to 0˚C. $NaBH_4$ (239 mg, 6.32 mmol) was added to this solution portionwise over 5 minutes. The reaction was allowed to warm to room temperature and stirred an additional 2 hours. The EtOH was removed under reduced pressure and the residue was quenched with aqueous NH_4Cl. The aqueous solution was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated to give 403 mg of 3-((1-(4-fluorophenethyl)piperidin-4yl)(hydroxy)methyl)-2-methoxyphenol (**16**) as an orange solid (71%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.12 (dd, J= 8.0, 5.1 Hz, 2H), 7.03 (dd, J= 8.0, 8.0Hz, 1H), 6.95 (dd, J= 8.6, 8.6Hz, 1H), 6.91-6.87 (m, 3H), 4.66 (d, J=8.0Hz, 1H), 3.83 (s, 3H), 3.10 (d, J=10.9Hz, 1H), 2.94 (d, J=10.9Hz, 1H), 2.77 (dd, J= 9.8, 6.9 Hz, 2H), 2.54 (dd, J=8.6, 8.0 Hz, 2H), 2.09 (d, J=13.2Hz, 1H), 2.01 (t, J=10.9Hz, 1H), 1.92 (t, J=9.1Hz, 1H), 1.73-1.69 (m, 1H), 1.50 (qd, J= 12.0, 3.4 Hz, 1H), 1.40-1.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 149.1, 145.3, 136.2, 135.9, 130.1, 130.0, 125.1, 118.9, 115.6, 115.3, 115.1, 73.4, 61.7, 60.9, 53.7, 42.7, 32.8, 28.8, 28.4; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{21}H_{26}FNO_3$: 360.1975, measured 360.1952.

(3-butoxy-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanol (**17**)

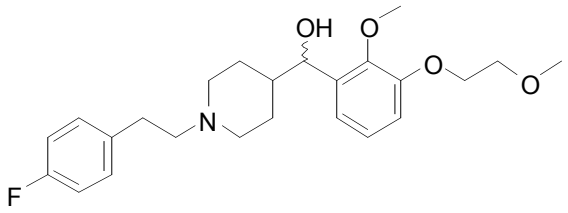


(3-butoxy-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone(**11**) (116.2 mg, 0.28 mmol) in 5 mL anhydrous EtOH was cooled to 0˚ C. $NaBH_4$ was added portionwise with stirring over 5 minutes. The reaction was stirred at 0˚ C an additional 10

minutes and then at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue was taken up in aqueous NH_4Cl and extracted three times with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and concentrated to give 89.1 mg of (3-butoxy-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanol (**17**) as an orange solid (77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.12 (m, 2H), 7.03-6.92 (m, 3H), 6.88 (dd, J = 7.8, 1.3 Hz, 1H), 6.82 (dd, J = 8.2, 1.3 Hz, 1H), 4.66 (d, J = 7.3 Hz, 1H), 3.99 (ddd, J= 6.4, 1.8, 1.8 Hz, 2H), 3.88 (s, 3H), 3.20 (d, J = 11.4 Hz, 1H), 3.85 (d, J = 11.0 Hz, 1H), 2.89-2.85 (m, 2H), 2.68-2.64 (m, 2H), 2.19-2.07 (m, 3H), 1.89-1.79 (m, 2H), 1.77-1.61 (m,2H), 1.60-1.49 (m, 3H), 1.38 (d, J = 12.8 Hz, 1H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.1, 162.8, 160.3, 152.0, 146.5, 136.2, 135.1, 130.2, 130.1, 124.0, 119.5, 115.4, 115.2, 112.4, 74.1, 68.3, 60.9, 60.2, 53.5, 42.3, 32.0, 31.5, 28.1, 27.7, 19.5, 13.9; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{25}H_{34}FNO_3$: 416.2601, measured 416.2587.

(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2-methoxyethoxy)phenyl)-methanol (18)

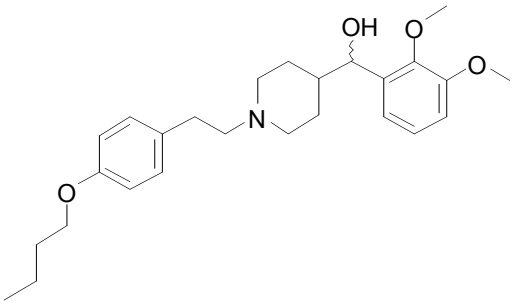


(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2-methoxyethoxy)phenyl)-methanone(**12**) (11.2 mg, 0.028 mmol) in 0.6 mL anhydrous EtOH was cooled to 0˚C. $NaBH_4$ was added with stirring. The reaction was stirred at 0˚C an additional 10

minutes then at room temperature for 1 hour. The solvent was removed under reduced pressure, and the residue was taken up in aqueous NH_4Cl and extracted three times with CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and concentrated to give 6.1 mg of (1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2-methoxyethoxy)phenyl)methanol (**18**) as an orange solid (55%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.12 (dd, J = 8.6, 5.7 Hz, 2H), 7.01 (q, J = 8.0 Hz, 1H), 6.96-6.89 (m, 3H), 6.84 (dd, J = 8.0, 1.7 Hz, 1H), 4.60 (d, J = 8.0 Hz, 1H), 4.14 (dd, J = 5.2, 4.0 Hz, 2H), 3.90 (s, 3H), 3.78 (dd, J = 6.3, 4.0 Hz, 2H), 3.44 (s, 3H), 3.05 (d, J = 11.4 Hz, 1H), 2.91 (d, J = 11.4 Hz, 1H), 2.75 (dd, J = 8.6, 5.8 Hz, 2H), 2.50 (dd, J = 8.6, 8.3 Hz, 2H), 2.05 (d, J = 13.2 Hz, 1H), 1.94 (ddd, J = 12.0, 2.3, 2.3 Hz, 1H), 1.87 (dd, J = 11.4, 2.8 Hz, 1H), 1.66 (qt, J = 11.5, 4.0 Hz, 1H), 1.45 (qd, J = 12.6, 3.5 Hz, 1H), 1.35 (qd, J = 11.8, 3.5 Hz, 1H), 1.27 (d, J = 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 160.4, 151.7, 146.9, 136.6, 136.1, 130.1, 130.0, 123.8, 120.3, 115.2, 115.0, 113.0, 74.6, 71.1, 68.1, 60.9, 59.2, 53.8, 53.5, 42.9, 32.9, 28.8; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{24}H_{32}FNO_4$: 418.2394, measured 418.2379.

(1-(4-butoxyphenethyl)piperidin-4-yl)(2,3-dimethoxyphenyl)methanol (**26**)

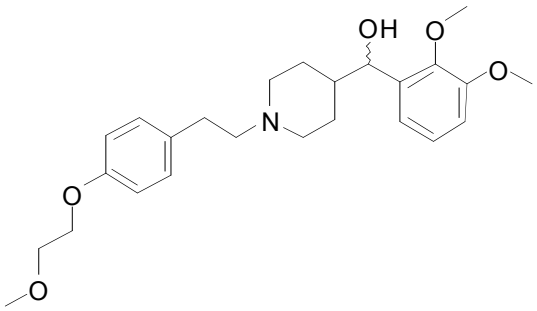


A solution of (2,3-dimethoxyphenyl)(1-(4-hydroxyphenethyl)piperidin-4-yl)methanone (**24**) (172 mg, 0.40 mmol) in 8 mL EtOH was cooled to 0˚C. Then $NaBH_4$ (75 mg, 2.0

mmol) was added portionwise with stirring. The reaction was warmed to room temperature and allowed to stir for 1 hour. After 1 hour the reaction was quenched with aqueous NH_4Cl. The EtOH was removed under reduced pressure. The residue was diluted with H_2O and extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to provide 105 mg of (1-(4-butoxyphenethyl)piperidin-4-yl)(2,3-dimethoxyphenyl)methanol (**26**) as a white solid (62%).

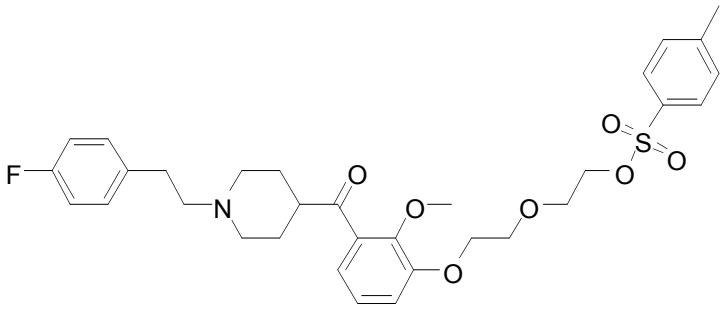
^{1}H NMR (400MHz, $CDCl_3$) δ 7.06 (d, J = 8.2 Hz, 2H), 7.04 (dd, J = 8.3, 8.3 Hz, 1H), 6.90 (dd, J = 7.8, 0.9 Hz, 1H), 6.83 (dd, J = 7.8, 0.9 Hz, 1H), 6.79 (d, J = 8.7 Hz, 2H), 4.63 (d, J = 8.2 Hz, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.85 (s, 6H), 3.07 (d, J = 11.5 Hz, 1H), 2.92 (d, J = 11.4 Hz, 1H), 2.71 (dd, J = 8.7, 7.8 Hz, 2H), 2.49 (dd, 8.7, 7.8 Hz, 2H), 2.07 (d, J = 12.8 Hz, 1H), 1.95 (ddd, J = 11.4, 2.3, 2.3 Hz, 1H), 1.87 (ddd, J = 11.4, 2.3, 2.3 Hz, 1H), 1.74 (quintet, J = 6.4 Hz, 2H), 1.65 (tt, J = 3.6, 11.4 Hz, 1H), 1.47 (sextet, J = 7.8 Hz, 3H), 1.35 (ddd, J = 9.7, 3.2, 3.2 Hz, 1H), 1.27 (d, J = 14.6 Hz, 1H), 0.95 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 152.5, 146.6, 136.6, 132.4, 129.6, 124.1, 119.8, 114.5, 111.4, 74.4, 67.8, 61.3, 61.0, 55.8, 53.8, 43.0, 32.9, 31.4, 28.9, 19.4, 14.0; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{26}H_{37}NO_4$: 428.2801, measured 428.2788.

(2,3-dimethoxyphenyl)(1-(4-(2-methoxyethoxy)phenethyl)piperidin-4-yl)methanol (**27**)



(2,3-dimethoxyphenyl)(1-(4-(2-methoxyethoxy)phenethyl)piperidin-4-yl)methanone, (**25**)(20 mg, 0.05 mmol) in 0.7 mL EtOH was cooled to 0°C. $NaBH_4$ (8.8 mg, 0.25 mmol) was added and the reaction mixture was warmed to room temperature. The reaction was stirred 1 hour and then quenched with aqueous NH_4Cl. The EtOH was removed under reduced pressure. The residue was diluted with H_2O and extracted three times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to provide 13.0 mg of (2,3-dimethoxyphenyl)(1-(4-(2-methoxyethoxy)phenethyl)piperidin-4-yl)methanol (**27**) as a white solid (61%). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.08 (d, J = 9.2 Hz, 2H), 7.04 (dd, J = 7.5, 7.5 Hz, 2H), 6.90 (dd, J = 7.5, 1.2 Hz, 1H), 6.83 (d, J = 6.8 Hz, 3H), 4.64 (d, J = 8.1 Hz, 1H), 4.08 (dd, J = 4.5, 4.5 Hz, 2H), 3.86 (s, 6H), 3.73 (dd, J = 4.5, 4.5 Hz, 2H), 3.44 (s, 3H), 3.12 (d, J = 11.4 Hz, 1H), 2.97 (d, J = 11.4 Hz, 1H), 2.76 (dd, J = 10.3, 6.3 Hz, 2H), 2.55 (dd, J = 8.6, 8.0 Hz, 2H), 2.08 (dd, J = 12.6, 5.8 Hz, 1H), 2.01 (dd, J = 9.4, 9.4 Hz, 1H), 1.95 (t, J = 10.3 Hz, 1H), 1.69 (qdd, J = 12.0, 4.0 Hz, 1H), 1.53 (qd, J = 12.6, 4.1 Hz, 1H), 1.43 (qd, J = 12.6, 4.0 Hz, 1H), 1.31 (d, J = 13.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 152.6, 146.6, 136.5, 132.5, 129.7, 124.1, 119.8, 114.7, 111.5, 74.4, 71.2, 67.4, 61.0, 60.9, 59.3, 55.8, 53.7, 42.8, 32.6, 28.6; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{25}H_{25}NO_5$: 430.2593, measured 430.2578.

2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2methoxyphenoxy)ethoxy)-ethyl 4-methylbenzenesulfonate (28)

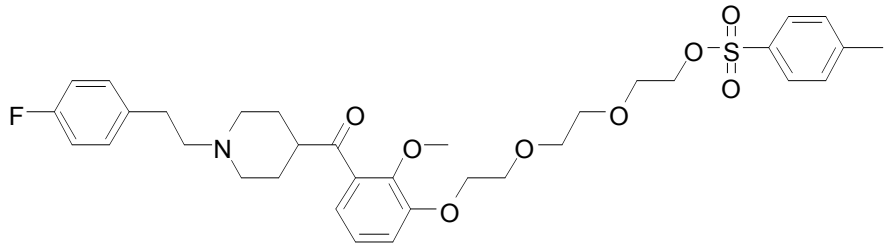


A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (295 mg, 0.82 mmol), 2,2'-oxybis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (1.4 g, 3.3 mmol) and K_2CO_3 (228 mg, 1.65 mmol) in 20 mL acetone was refluxed for 24 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 437 mg of 2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)-ethyl 4-methylbenzenesulfonate (**28**) as a red oil (89%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.1, 2H), 7.15 (dd, J = 8.6, 5.7 Hz, 2H), 7.07-7.01 (m, 1H), 6.95 (tt, J = 8.6, 1.7 Hz, 2H), 4.17 (dd, J = 4.6, 4.5 Hz, 2H), 4.10 (dd, J = 4.6, 4.5 Hz, 2H), 3.87 (s, 3H), 3.82 (dd, J = 4.6, 3.8 Hz, 2H), 3.75 (dd, J = 4.6, 2.9 Hz, 2H), 3.11 (tt, J = 10.9, 4.1 Hz, 1H), 3.00 (d, J = 1.4 Hz, 2H), 2.78 (dd, J = 10.9, 5.1 Hz, 2H), 2.57 (dd, J = 10.8, 5.2 Hz, 2H), 2.41 (s, 3H), 2.15(t, J = 10.3 Hz, 2H), 1.92 (d, J = 11.4 Hz, 2H), 1.76 (qd, J = 11.5, 3.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2,162.2, 160.3, 151.8, 147.3, 144.9, 135.9, 134.2, 132.8, 130.1,

130.0, 129.8, 127.9, 124.1, 120.7, 116.5, 115.1, 114.9, 69.6, 69.3, 68.7, 68.3, 61.6, 60.6, 53.5, 53.2, 47.9, 32.7, 27.9, 21.6; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{32}H_{38}FNO_7S$: 600.2431, measured 600.2437.

2-(2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (**29**)

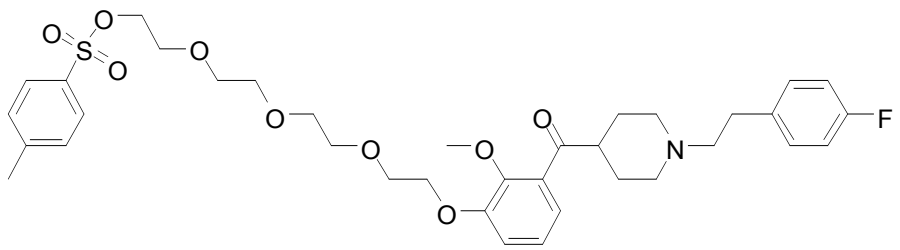


A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (78.3 mg, 0.22 mmol), 2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (215 mg, 0.44 mmol) and K_2CO_3 (61 mg, 0.44 mmol) in 7 mL acetone was refluxed for 24 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 53 mg of 2-(2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (**29**) as an orange oil (38%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.33 (dd, J= 8.0, 5.5 Hz, 2H), 7.14 (dd, J= 8.6, 5.2 Hz, 2H), 7.07-7.01 (m, 2H), 6.99-6.94 (m, 3H), 4.19-4.13 (m, 4H), 3.88 (dd, J= 9.6, 5.6 Hz, 2H), 3.88 (s, 3H), 3.70-3.68 (m, 4H), 3.61 (dd, J = 6.6, 4.0 Hz, 2H), 3.09 (tt, J = 10.8, 3.4 Hz, 1H), 2.98 (d, J = 12.9 Hz, 2H), 2.77 (dd, J = 8.6, 5.1 Hz, 2H), 2.56 (dd, J = 8.6, 5.1 Hz 2H), 2.43 (s, 3H), 2.13 (t, J = 10.9 Hz, 2H), 1.91 (d, J = 11.5 Hz,

2H), 1.75 (qd, J = 11.5, 3.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 162.4, 160.4, 152.0, 147.4, 145.0, 136.1, 134.5, 133.0, 130.2, 130.1, 130.0, 128.0, 124.3, 120.8, 116.6, 115.2, 115.1, 70.9, 70.8, 69.8, 69.3, 68.8, 68.5, 61.7, 60.8, 53.3, 48.1, 32.9, 28.1, 21.7; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{34}H_{42}FNO_8S$: 644.2693, measured 644.2697.

2-(2-(2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (**30**)

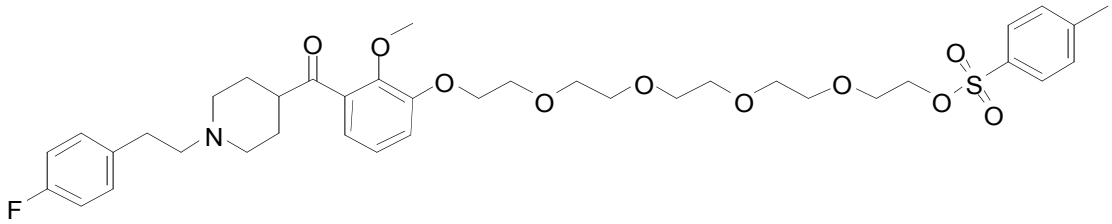


A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (80 mg, 0.22 mmol), 2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis-(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (452 mg, 0.90 mmol) and K_2CO_3 (62 mg, 0.45 mmol) in 7 mL acetone was refluxed for 24 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 143 mg of 2-(2-(2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (**30**) as an orange oil (93%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.78 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.15 (dd, J = 8.6, 5.1 Hz, 2H), 7.07-7.02 (m, 2H), 6.99-6.92 (m, 3H), 4.18 (dd, J = 5.2, 4.5 Hz, 2H), 4.15 (dd, J = 4.6, 4.2 Hz, 2H), 3.90 (dd, J = 5.7, 4.0 Hz, 2H), 3.90 (s, 3H), 3.72 (dd, J = 6.3, 4.0 Hz, 2H), 3.67 (dd, J= 5.2, 4.6 Hz, 2H), 3.64 (dd, J = 6.3, 4.0 Hz, 2H), 3.58

(septet, J = 2.9 Hz,4H), 3.10 (tt, J = 10.9, 4.0 Hz, 1H), 2.98 (d, J= 11.5 Hz, 2H), 2.77 (dd, J= 10.3, 5.7 Hz), 2.56 (dd, J= 10.3, 5.7 Hz, 2H), 2.43 (s, 3H), 2.12 (dd, J= 11.4, 9.8 Hz, 2H), 1.91 (d, J = 11.5 Hz, 2H), 1.75 (qd, J= 10.9, 3.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 162.3, 160.4, 151.9, 147.3, 144.9, 136.1, 134.4, 132.9, 130.1, 130.0, 129.9, 128.0, 124.2, 120.7, 116.5, 115.2, 115.0, 70.8, 70.7, 70.6, 70.5, 69.7, 69.3, 68.7, 68.4; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{36}H_{46}FNO_9S$: 710.2775, measured 710.2780.

14-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12-tetraoxatetradecyl 4-methylbenzenesulfonate (**31**)

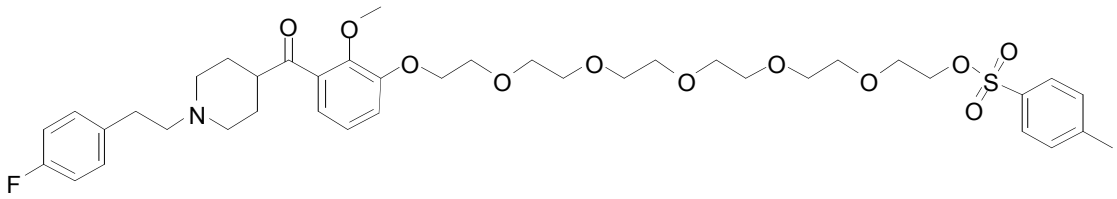


A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (119 mg, 0.34 mmol), 3,6,9,12-tetraoxatetradecane-1,14-diyl bis(4-methylbenzenesulfonate) (738 mg, 1.35 mmol) and K_2CO_3 (94 mg, 0.68 mmol) in 11 mL acetone was refluxed for 24 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 163 mg of 14-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12-tetraoxatetradecyl 4-methylbenzenesulfonate (**31**) as an orange oil (66%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.14 (dd, J = 8.6, 5.8 Hz, 2H), 7.07-7.01 (m, 2H), 6.95 (q, J = 8.6 Hz, 3H), 4.18 (dd, J = 5.2, 4.6

Hz, 2H), 4.15 (dd, J = 5.2, 4.5 Hz, 2H), 3.90 (dd, J = 5.1, 4.5 Hz, 2H), 3.89 (s, 3H), 3.73 (dd, J = 5.1, 4.0 Hz, 2H), 3.69-3.65 (m, 2H), 3.65-3.60 (m, 2H), 3.58 (s, 4H), 3.09 (tt, J = 10.9, 4.0 Hz, 1H), 2.98 (d, J = 11.5 Hz, 2H), 2.77 (dd, J = 8.6, 7.5 Hz, 2H), 2.54 (dd, J = 8.6, 7.5 Hz, 2H), 2.44 (s, 3H), 2.12 (t, J = 10.8 Hz, 2H), 1.90 (d, J = 11.4 Hz, 2H), 1.76 (qd, J = 11.4, 3.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 162.4, 160.5, 152.0, 147.4, 145.0, 136.2, 134.5, 133.1, 130.2, 130.1, 129.9, 128.1, 124.3, 120.8, 116.6, 115.3, 115.1, 70.9, 70.8, 70.7, 70.6, 69.8, 69.4, 68.8, 68.5, 61.8, 60.8, 53.4, 48.2, 33.0, 28.1, 21.8; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{38}H_{50}FNO_{10}S$: 754.3037, measured 754.3030.

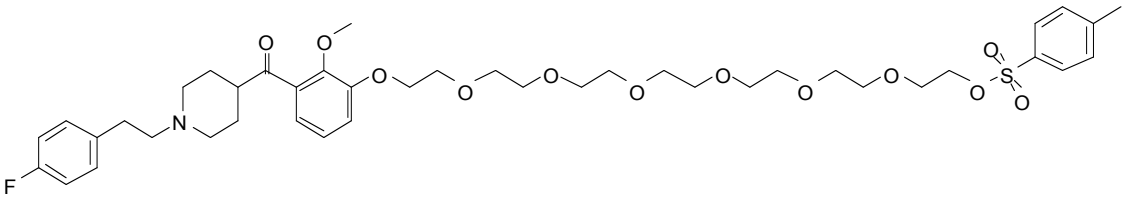
17-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15-pentaoxaheptadecyl 4-methylbenzenesulfonate (**32**)



A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (130 mg, 0.36 mmol), 3,6,9,12,15-pentaoxaheptadecane-1,17-diyl bis(4-methylbenzenesulfonate) (850 mg, 1.44 mmol) and K_2CO_3 (100 mg, 0.72 mmol) in 10 mL acetone was refluxed for 24 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 209 mg of 17-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15-pentaoxaheptadecyl 4-methylbenzenesulfonate (**32**) as an orange-yellow oil (75%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.78 (d, J = 6.9 Hz, 2H), 7.33 (d, J = 6.9 Hz, 2H), 7.14 (dd, J= 6.3, 5.8 Hz, 2H), 7.07-7.03 (m, 2H), 6.98-6.93 (m, 3H), 4.16 (ddd, J= 16.6, 6.3, 3.4 Hz, 4H), 3.90 (s, 3H), 3.90 (dd, J = 4.6, 1.1 Hz, 2H), 3.72 (d, J = 3.4 Hz, 2H), 3.66 (dd, J = 12.6, 12.6 Hz, 14H), 3.56 (dd, J = 4.6, 1.1 Hz, 2H), 3.09 (m, 1H), 2.98 (d, J = 9.7 Hz, 2H), 2.77 (dd, J = 8.6, 6.3 Hz, 2H), 2.55 (dd, J = 9.2, 5.7 Hz, 2H), 2.43 (s, 3H), 2.11 (t, J = 10.9 Hz, 2H), 1.90 (d, J = 12.0 Hz, 2H), 1.75 (dd, J = 10.9, 10.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5,162.3, 160.4, 152.0, 147.4, 144.9, 136.2, 134.4, 133.0, 130.1, 130.0, 129.9, 128.0, 124.2, 120.7, 116.6, 115.2, 115.0, 70.8, 70.7, 70.6, 70.6, 70.5, 69.4, 68.7, 61.7, 60.7, 53.6, 53.3, 48.1, 32.9, 28.1, 21.7; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{40}H_{54}FNO_{11}S$: 798.3299, measured 798.3286.

20-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15,18-hexaoxaicosyl 4-methylbenzenesulfonate (**33**)

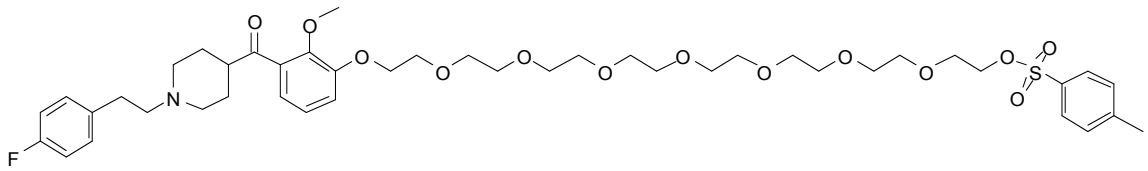


A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (55 mg, 0.15 mmol), 3,6,9,12,15,18-hexaoxaicosane-1,20-diyl bis(4-methylbenzenesulfonate) (198 mg, 0.31 mmol) and K_2CO_3 (43 mg, 0.31 mmol) in 5 mL acetone was refluxed for 24 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 78 mg of 20-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-

3,6,9,12,15,18-hexaoxaicosyl 4-methylbenzenesulfonate (**33**) as an orange-yellow oil (62%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.80 (dd, J = 1.8, 8.2 Hz, 2.0H), 7.34 (dd, J = 7.7, 2.0 Hz, 2H), 7.15 (dd, J = 8.7, 5.5 Hz, 2H), 7.08-7.01 (m, 2H), 6.99-6.93 (m, 3H), 4.19-4.14 (m, 4H), 3.89 (dd, J = 6.8, 2.8Hz, 2H), 3.89 (s, 3H), 3.75-3.57 (m, 22H), 3.09 (tt, J = 11.0, 3.7 Hz, 1H), 2.98 (d, J = 11.9 Hz, 2H), 2.77 (dd, J = 10.7, 7.3 Hz, 2H), 2.56 (dd, J = 11.0, 7.8 Hz, 2H), 2.44 (s, 3H), 2.13 (t, J = 10.9 Hz, 2H), 1.91 (d, J = 11.5 Hz, 2H), 1.75 (qd, J = 11.0, 3.6 Hz, 2H); ^{13}C NMR (400MHz, $CDCl_3$) δ 151.9, 146.4, 144.9, 136.1, 134.5, 133.0, 130.2, 130.1, 129.9, 128.0, 124.3, 120.8, 116.5, 115.3, 115.1, 72.6, 70.9, 70.8, 70.7, 70.6, 70.3, 69.7, 69.3, 68.7, 68.5, 61.7, 60.8, 53.6, 53.3, 48.1, 32.9, 28.1, 21.7; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{42}H_{58}FNO_{12}S$: 842.3561, measured 842.3548.

23-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15,18,21-heptaoxatricosyl 4-methylbenzenesulfonate (**34**)

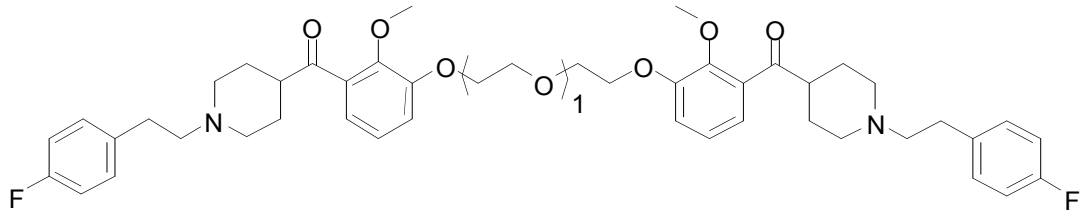


A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (62 mg, 0.17 mmol), 3,6,9,12,15,18,21-heptaoxatricosane-1,23-diyl bis(4-methylbenzenesulfonate) (350 mg, 0.52 mmol) and K_2CO_3 (47 mg, 0.34 mmol) in 10 mL acetone is refluxed for 24 hours. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford

110 mg of 23-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15,18,21-heptaoxatricosyl 4-methylbenzenesulfonate (**34**) as an orange-yellow oil (75%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.79 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.16 (dd, J = 8.6, 5.2 Hz, 2H), 7.07-7.02 (m, 2H), 6.99-6.93 (m, 3H), 4.18 (dd, J = 5.1, 4.6 Hz, 2H), 4.15 (dd, J = 5.2, 4.0 Hz, 2H), 3.90 (dd, J = 5.7, 4.0 Hz, 2H), 3.90 (s, 3H), 3.72 (dd, J = 6.3, 4.0 Hz, 2H), 3.69-3.60 (m, 20H), 3.58 (s, 4H), 3.10 (tt, J = 10.9, 4.0 Hz, 1H), 2.98 (d, J = 11.5 Hz, 2H), 2.77 (dd, J = 8.6, 5.1 Hz, 2H), 2.56 (dd, J = 8.3, 5.7 Hz, 2H), 2.44 (s, 3H), 2.13 (t, J = 10.9 Hz, 2H), 1.91 (d, J = 12 Hz, 2H), 1.75 (qd, J = 11.4, 3.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 162.4, 160.4, 152.0, 147.4, 144.9, 136.1, 134.4, 133.0, 130.2, 130.1, 129.9, 128.0, 124.2, 120.7, 116.5, 115.2, 115.1, 70.9, 70.8, 70.7, 70.7, 70.6, 70.5, 69.7, 69.3, 68.7, 68.5, 61.7, 60.8, 53.6, 53.3, 48.1, 32.9, 28.1, 21.7; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{44}H_{62}FNO_{13}S$: 886.3824, measured 886.3818.

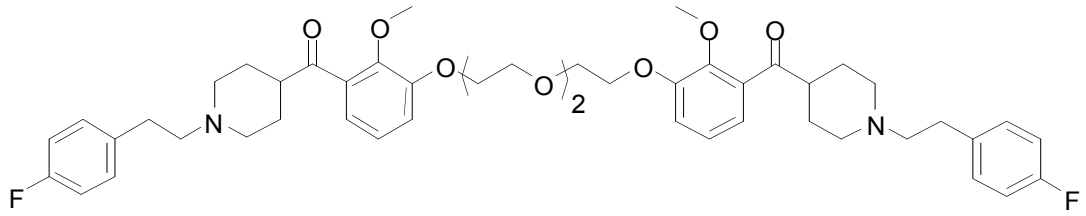
(3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**35**)



A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (68 mg, 0.19 mmol), 2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethyl 4-methylbenzenesulfonate (**28**) (57 mg, 0.096

mmol) and K_2CO_3 (26 mg, 0.19 mmol) in 5 mL acetone was refluxed for 48 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 72 mg of (3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone)(**35**)as an orange oil (96%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.14 (dd, J = 8.7, 5.5 Hz, 4H), 7.08-7.01 (m, 4H), 7.00-6.93 (m, 6H), 4.20 (dd, J = 5.1, 4.6 Hz, 4H), 3.98 (dd, J = 5.1, 4.6 Hz, 4H), 3.88(s, 6H), 3.07 (tt, J = 11.0, 4.2, Hz, 2H), 2.97(d, J = 11.5 Hz, 4H), 2.77 (dd, J = 8.7, 5.5 Hz, 4H), 2.56 (dd, J = 8.3, 5.2 Hz, 4H), 2.12 (t, J = 10.3 Hz, 4H), 1.90 (d, J = 11 Hz, 4H), 1.75 (qd, J = 11.0, 3.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 162.7, 160.3, 152.0, 147.5, 136.1, 134.7, 130.3, 130.2, 124.4, 121.0, 116.7, 115.4, 115.2, 70.1, 69.0, 61.8, 60.9, 53.4, 48.2, 33.0, 28.2; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{46}H_{54}F_2N_2O_7$: 785.3977, measured 785.3966.

(3,3'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy)bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**36**)

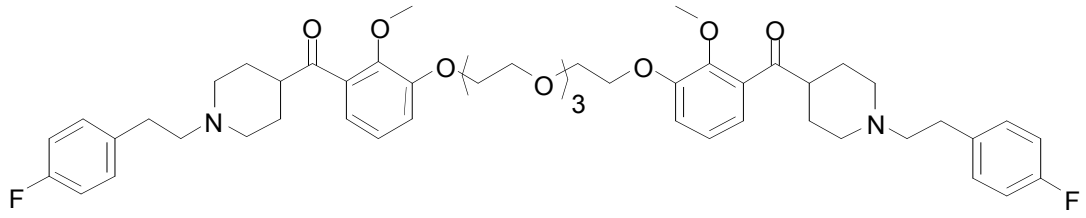


A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (**10**) (59 mg, 0.164 mmol), 2-(2-(2-(3-(1-(4-fluorophenethyl)-piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethoxy)ethyl 4-methylbenzene-sulfonate (**29**) (53 mg, 0.082 mmol) and K_2CO_3 (23 mg, 0.164 mmol) in 5 mL acetone

was refluxed for 48 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 31 mg of (3,3'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy)bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**36**) as an orange oil (44%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, J = 8.3, 5.5 Hz, 4H), 7.07-7.01 (m, 4H), 7.00-6.94 (m, 6H), 4.18(dd, J = 5.0, 4.6 Hz, 4H), 3.90 (dd, J = 5.0, 4.6 Hz, 4H), 3.88 (s, 6H), 3.75 (s, 6H), 3.09 (tt, J = 10.9, 4.0 Hz, 2H), 2.99 (d, J = 11.5 Hz, 4H), 2.79 (dd, J = 11.0, 5.0 Hz, 4H), 2.58 (dd, J = 11.0, 5.5 Hz, 4H), 2.16 (t, J = 10.3 Hz, 4H), 1.92 (d, J = 11 Hz, 4H), 1.76 (qd, J = 11.4, 3.6, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 162.7, 151.9, 147.4, 135.9, 134.5, 130.2, 130.1, 124.3, 120.8, 116.5, 115.3, 115.1, 71.0, 69.8, 68.5, 61.7, 60.6, 53.2, 47.9, 32.7, 27.9; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{48}H_{58}F_2N_2O_8$: 851.4059, measured 851.4045.

(3,3'-(2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(ethane-2,1-diyl))bis(oxy)bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**37**)

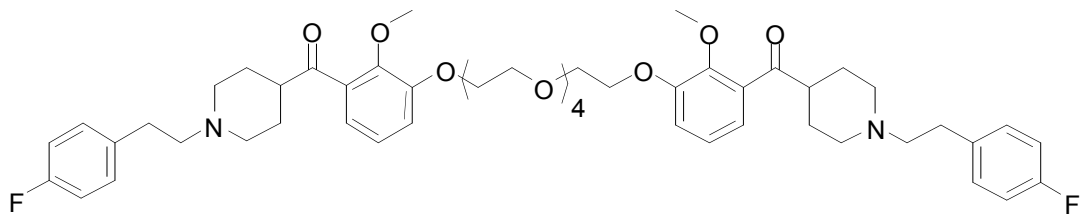


A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (44 mg, 0.12 mmol), 2-(2-(2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate

(**30**) (42 mg, 0.062 mmol) and K_2CO_3 (17 mg, 0.124 mmol) in 5 mL acetone was refluxed for 48 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 28 mg of (3,3'-(2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(ethane-2,1-diyl))bis(oxy)bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**37**) as a red oil (51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16-7.13 (m,4H), 7.07-7.00 (m, 4H), 6.99-6.94 (m, 6H), 4.17 (dd, J = 5.2, 4.6 Hz, 4H), 3.89 (dd, J = 5.2, 4.6 Hz, 4H), 3.89 (s, 6H), 3.73 (dd, J = 3.4, 3.4 Hz, 2H), 3.72 (dd, J = 3.5, 3.5 Hz, 2H), 3.68 (dd, J = 2.3, 2.3 Hz, 2H), 3.67 (dd, J = 3.5, 3.5 Hz, 2H), 3.10 (tt, J = 10.9, 4.0 Hz, 2H), 2.98 (d, J = 11.5 Hz, 4H), 2.79 (dd, J = 8.0, 8.0 Hz, 4H), 2.57 (dd, J = 8.0, 8.0 Hz, 4H), 2.15 (bs, 4H), 1.92 (d, J = 12.0 Hz, 4H), 1.76 (q, J = 10.9 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 162.5, 160.6, 152.1, 147.5, 136.0, 134.6, 130.3, 130.2, 124.4, 120.9, 116.7, 115.4, 115.2, 71.0, 70.9, 69.8, 68.6, 61.8, 60.8, 53.3, 48.0, 32.8, 28.0; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{50}H_{62}F_2N_2O_9$: 895.4321, measured 895.4341.

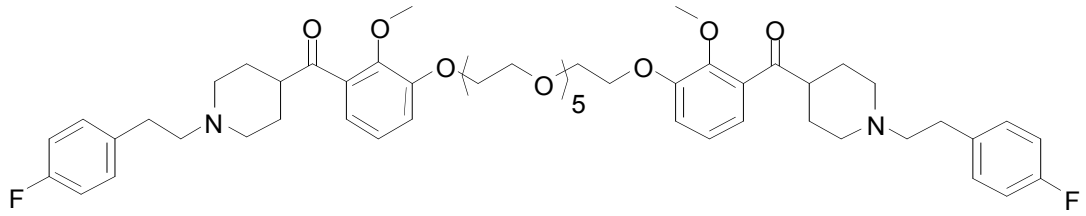
(3,3'-(3,6,9,12-tetraoxatetradecane-1,14-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**38**)



A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (157 mg, 0.44 mmol), 14-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12-tetraoxatetradecyl 4-methylbenzenesulfonate (**31**) (163 mg, 0.22 mmol) and K_2CO_3 (61 mg, 0.44 mmol) in 12 mL acetone was refluxed for 48 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 102 mg of (3,3'-(3,6,9,12-tetraoxatetradecane-1,14-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**38**) as a red-brown oil (51%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.15 (dd, J = 8.0, 5.1 Hz, 4H), 7.069-7.01 (m, 4H), 6.99-6.97 (m, 6H), 4.18 (dd, J = 4.6, 4.6 Hz, 4H), 3.89 (dd, J = 4.6, 4.6 Hz, 4H), 3.89 (s, 6H), 3.73 (dd, J = 6.8, 4.0 Hz, 4H), 3.67 (dd, J = 5.1, 2.9 Hz, 4H), 3.64 (s, 4H) 3.08 (tt, J = 10.9, 4.19 Hz, 2H), 2.98 (d, J = 11.4 Hz, 4H), 2.78 (dd, J = 8.6, 7.4 Hz, 4H), 2.56 (dd, J = 7.4, 5.4 Hz, 4H), 2.13 (t, J = 10.9 Hz, 4H), 1.91 (d, J = 11.4 Hz, 4H), 1.77 (qd, J = 10.8, 2.9 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 162.5, 160.5, 152.0, 147.4, 136.1, 134.6, 130.2, 124.3, 120.8, 116.6,115.3, 115.1, 70.9, 70.8, 70.7, 69.8, 68.5, 61.8, 60.8, 53.4, 48.1, 32.9, 28.1; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{52}H_{66}F_2N_2O_{10}$: 939.4583, measured 939.4551.

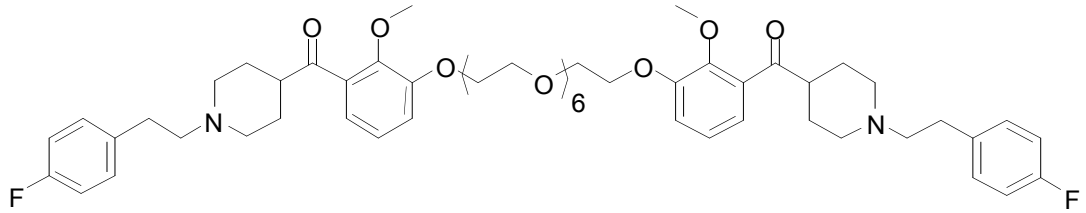
(3,3'-(3,6,9,12,15-pentaoxaheptadecane-1,17-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**39**)



A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (**10**) (193 mg, 0.54 mmol), 17-(3-(1-(4-fluorophenethyl)-piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15-pentaoxaheptadecyl 4-methyl-benzenesulfonate (**32**) (209 mg, 0.27 mmol) and K_2CO_3 (75 mg, 0.54 mmol) in 12 mL acetone was refluxed for 48 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 125 mg of (3,3'-(3,6,9,12,15-pentaoxaheptadecane-1,17-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**39**) as a red-brown oil (48%).

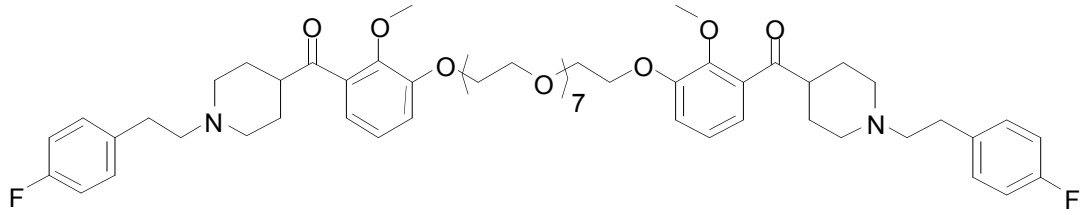
^{1}H NMR (500MHz, $CDCl_3$) δ 7.14 (dd, J = 8.6, 5.2 Hz, 4H), 7.07-7.01 (m, 4H), 6.99-6.94 (m, 6H), 4.18 (dd, J = 5.2, 4.6 Hz, 4H), 3.89 (dd, J = 5.2, 4.6 Hz, 4H), 3.89 (s, 6H), 3.73 (dd, J = 6.3, 4.0 Hz, 4H), 3.66 (dd, J = 6.9, 4.0 Hz, 4H), 3.64 (s, 8H), 3.09 (tt, J = 10.9, 4.0 Hz, 2H), 2.98 (d, J = 11.4 Hz, 4H), 2.78 (dd, J = 8.6, 5.5 Hz, 4H), 2.56 (dd, J = 8.6, 5.2 Hz, 4H), 2.1 (dd, J = 10.9, 10.9 Hz, 4H), 1.91 (d, J = 11.4 Hz, 4H), 1.76 (qd, J = 10.9, 3.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 162.5, 160.5, 152.0, 147.4, 136.1, 134.6, 130.2, 130.1, 124.3, 120.8, 116.6, 115.3, 115.5, 70.9, 70.8, 70.7, 70.7, 69.8, 68.5, 61.8, 60.8, 53.3, 48.1, 32.9, 28.1; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{54}H_{70}F_2N_2O_{11}$: 983.4845, measured 938.4855.

(3,3'-(3,6,9,12,15,18-hexaoxaicosane-1,20-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**40**)



A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)-methanone (**10**) (71 mg, 0.20 mmol), 20-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15,18-hexaoxaicosyl 4-methylbenzenesulfonate (**33**) (84 mg, 0.10 mmol) and K_2CO_3 (28 mg, 0.20 mmol) in 8 mL acetone was refluxed for 48 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 62 mg of (3,3'-(3,6,9,12,15,18-hexaoxaicosane-1,20-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**40**) as a red-brown oil (62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, J = 8.6, 5.1 Hz, 4H), 7.07-7.01 (m, 4H), 6.99-6.94 (m, 6H), 4.18 (dd, J = 4.7, 4.7Hz, 4H), 3.89 (dd, J = 4.7, 4.7 Hz, 4H), 3.89 (s, 6H), 3.73 (dd, J = 6.3, 2.9 Hz, 4H), 3.67 (dd, J = 5.2, 2.9 Hz, 4H), 3.64-3.62 (m, 12H), 3.11-3.06 (tt, J = 10.9, 3.4 Hz, 2H), 2.98 (d, H = 11.5 Hz), 2.77 (dd, J = 8.5, 5.1 Hz, 4H), 2.55 (dd, J = 8.6, 5.7 Hz, 4H), 2.11 (t, J = 9.7 Hz, 4H), 1.90 (d, J = 11.5 Hz, 4H), 1.75 (qd, J = 11.4, 3.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 162.4, 160.5, 152.0, 147.4, 136.1, 134.6, 130.2, 124.3, 120.8, 116.5, 115.3, 115.1, 70.9, 70.7, 70.7, 70.6, 69.7, 68.5, 61.7, 60.8, 53.4, 48.2, 32.9, 28.1; HRMS – ESI: m/z $[M + Na]^+$ calculated for $C_{56}H_{74}F_2N_2O_{12}$: 1027.5108, measured 1027.5078.

(3,3'-(3,6,9,12,15,18,21-heptaoxatricosane-1,23-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**41**)



A solution of (1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (**10**) (91 mg, 0.25 mmol), 23-(3-(1-(4-fluorophenethyl)-piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15,18,21-heptaoxatricosyl 4-methylbenzenesulfonate (**34**) (110 mg, 0.125 mmol) and K_2CO_3 (35 mg, 0.25 mmol) in 8 mL acetone was refluxed for 48 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography (100% CH_2Cl_2 to 10% MeOH in CH_2Cl_2) to afford 69 mg of (3,3'-(3,6,9,12,15,18,21-heptaoxatricosane-1,23-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (**41**) as a red-brown oil (68%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.16 (dd, J = 8.5, 5.7 Hz, 4H), 7.07-7.01 (m, 4H), 6.99-6.93 (m, 6H), 4.18 (dd, J = 5.2, 5.2 Hz, 4H), 3.89 (dd, J = 5.2, .2 Hz, 4H), 3.89 (s, 6H), 3.72 (dd, J = 5.8, 4.0 Hz, 4H), 3.67 (dd, J = 5.1, 4.6 Hz, 4H), 3.65-3.63 (m, 16H), 3.10 (tt, J = 10.9, 4.0 Hz, 2H), 2.98 (d, J = 11.5 Hz, 4H), 2.78 (dd, J = 8.6, 5.1 Hz, 4H), 2.56 (dd, J = 8.5, 5.1 Hz, 4H), 2.13 (t, J = 11.4 Hz, 4H), 1.92 (d, J = 11.5 Hz, 4H), 1.75 (qd, J = 11.4, 3.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 162.4, 160.4, 152.0, 147.4, 136.1, 134.5, 130.2, 130.1, 124.3, 120.8, 116.5, 115.3, 115.1, 70.9, 70.7, 70.7, 70.6, 69.7, 68.5,

61.7, 60.8, 53.6, 53.3, 48.1, 32.9, 28.1; HRMS – ESI: m/z $[M + H]^+$ calculated for $C_{58}H_{78}F_2N_2O_{13}$: 1071.3570, measured 1071.5347.

Cellular Assays

Cell lines and cell culture; Stably transfected CHO cell lines were a generous gift of K. Berg and W. Clarke (University of Texas Health Science Center, San Antonio). The FA4 line is transfected with h5-HT_{2A}R (5-HT_{2A}R-expressing cells) and the 1C19 line with h5-HT_{2C}R (5-HT_{2C}R-expressing cells) with the p198-DHFR-Hygro vector containing a hygromycin resistance gene.[2] Reverse transcription of RNA followed by quantitative real time PCR assay for both transcripts confirmed that FA4 cells express high amounts of 5-HT_{2A}R and no 5-HT_{2C}R mRNA, that 1C19 cells express high amounts of 5-HT_{2C}R and no 5-HT_{2A}R mRNA, and that parental CHO-K1cells do not express detectable amounts of either mRNA (data not shown). Our recent data confirm no 5-HT_{2C}R protein in FA4 cells and no 5-HT_{2A}R protein in 1C19 cells.[1] Protein expression in both the FA4 and 1C19 cells has been assessed at 200 fmol/mg protein[2] which approximates physiological levels in brain. Cells were grown at 37°C, 5% CO_2 and 85% relative humidity in GlutaMaxa-MEM (Invitrogen, Carlsbad CA), 5% fetal bovine serum (Atlanta Biologicals, Atlanta GA), 100 μg/ml hygromycin (FA4 and 1C19, Mediatech, Manassas VA) or penicillin/streptomycin (parental cells, Invitrogen) , and were passaged when they reached 80% confluence.

Intracellular calcium assay Changes in intracellular Ca^{++} levels were determined using the calcium sensitive dye Calcium 4 (FLIPR No-wash kit, Molecular Devices, Sunnyvale CA, part #R8142). Cells were plated in serum-replete medium at 16,000-20,000

cells/well in black-sided, clear bottom 96-well tissue culture plates. Care was taken to ensure even plating of cells. Cells were fed ~24 hrs later with serum-free medium. Following overnight incubation, medium was removed and replaced with 40 µl of serum-free medium plus 40 µl Calcium 4 dye solution supplemented with 2.5 mM water-soluble Probenicid (Invitrogen) to inhibit extracellular transport of the dye. Plates were returned to the 37°C incubator for 60 min then incubated for an additional 60 min at RT in the dark.

Fluorescence was measured with a FlexStation3 (Molecular Devices) using eight measurements per well and high detector sensitivity. A baseline was established for each well during the initial segment of each run. Addition of vehicle [Hank's balanced salt solution (HBSS) without $CaCl_2$ or $MgCl_2$] or test substance (20 µl of 5x concentrated antagonist) occurred at 17 sec..

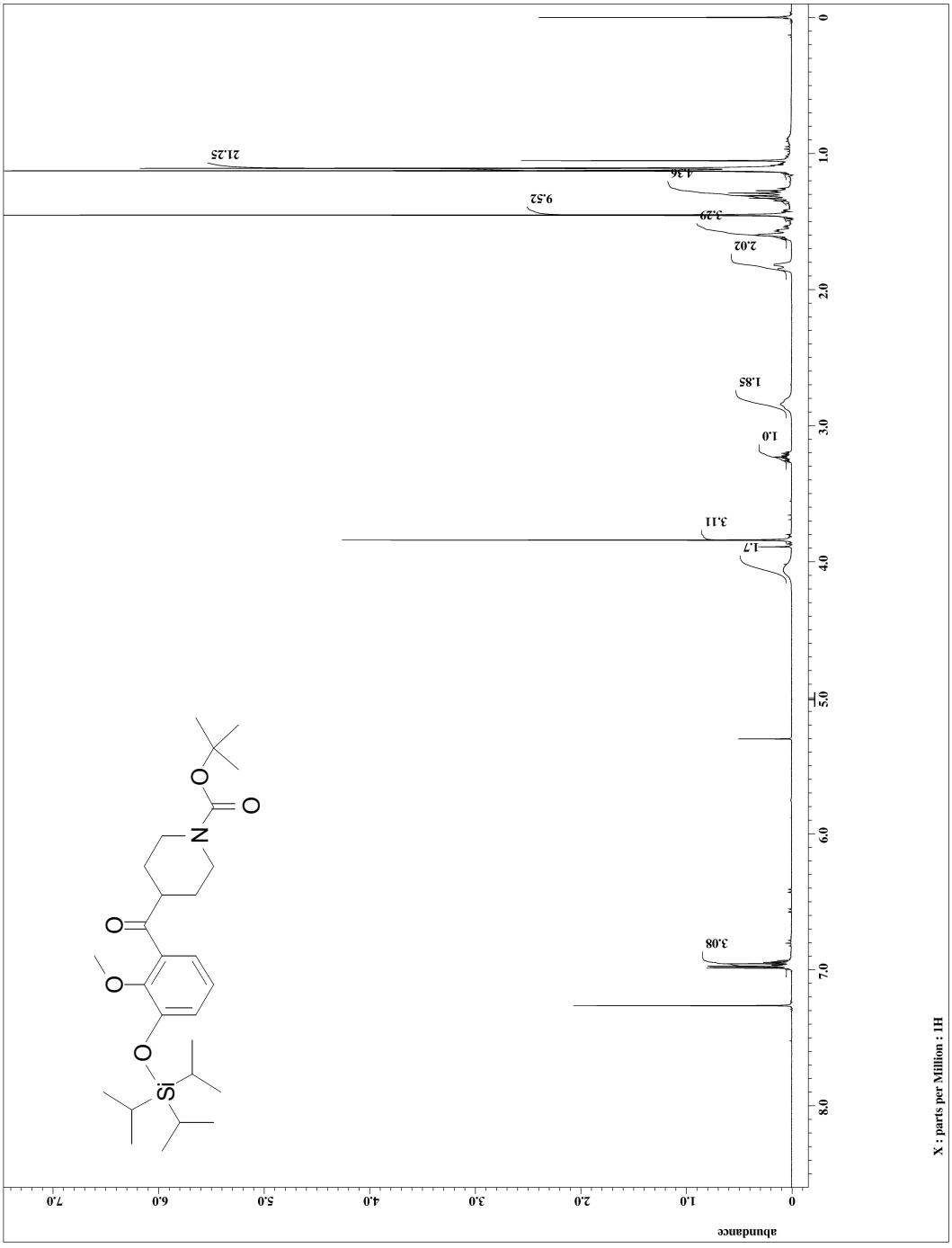
Following addition of test reagent, fluorescence was recorded every 1.7 sec for 60-90 sec. The time required for the first round of 60 sec recordings provided a 15 min antagonist preincubation. Afterward, 25 µl of 5x concentrated agonist (5-HT) was added (following another 17 sec baseline recording) and fluorescence was again measured every 1.7 sec for 60 sec. Maximum peak height was determined by the FlexStation software (SoftMax Pro 5.2) for each respective well.

1. Anastasio, N. C.; Witkin, B. M.; Seitz, P. K.; Watson, C. S.; Cunningham, K. A., Novel medium-throughput 96-well plate assay to immunohistochemicallly detect key brain proteins in the serotonin 5-HT2C receptor-ERK pathway. *Abstract 787.2 Society of Neuroscience Meeting* **2009**.

2. Berg, K. A.; Clarke, W. P.; Sailstad, C.; Saltzman, A.; Maayani, S., Signal transduction differences between 5-hydroxytryptamine type 2A and type 2C receptor systems. *Mol. Pharmacol.* **1994,***46*, 477-484.

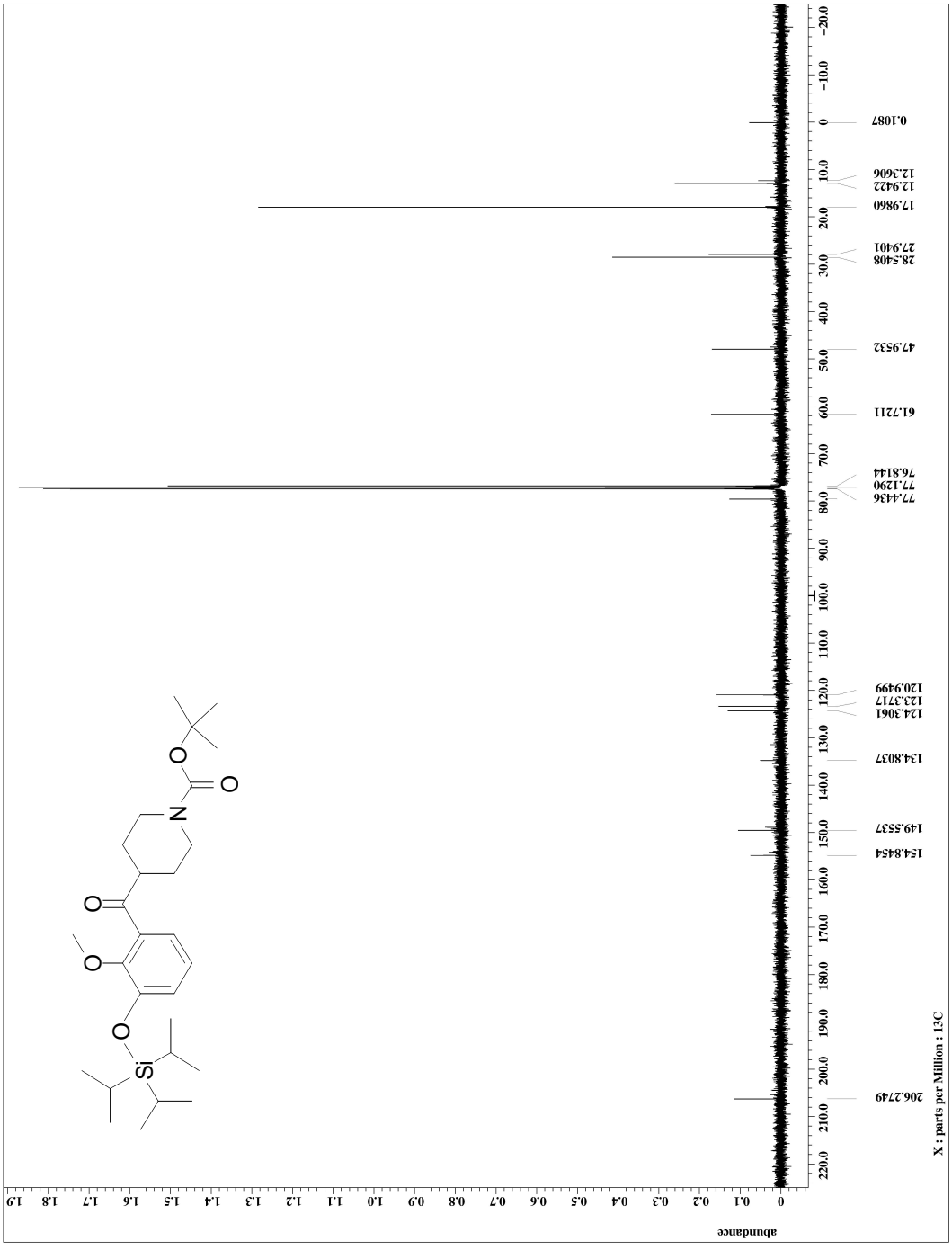
^{1}H-NMR Spectra (500 MHz, $CDCl_3$)

tert-butyl 4-(2-methoxy-3-(triisopropylsilyloxy)benzoyl)piperidine-1-carboxylate (7)



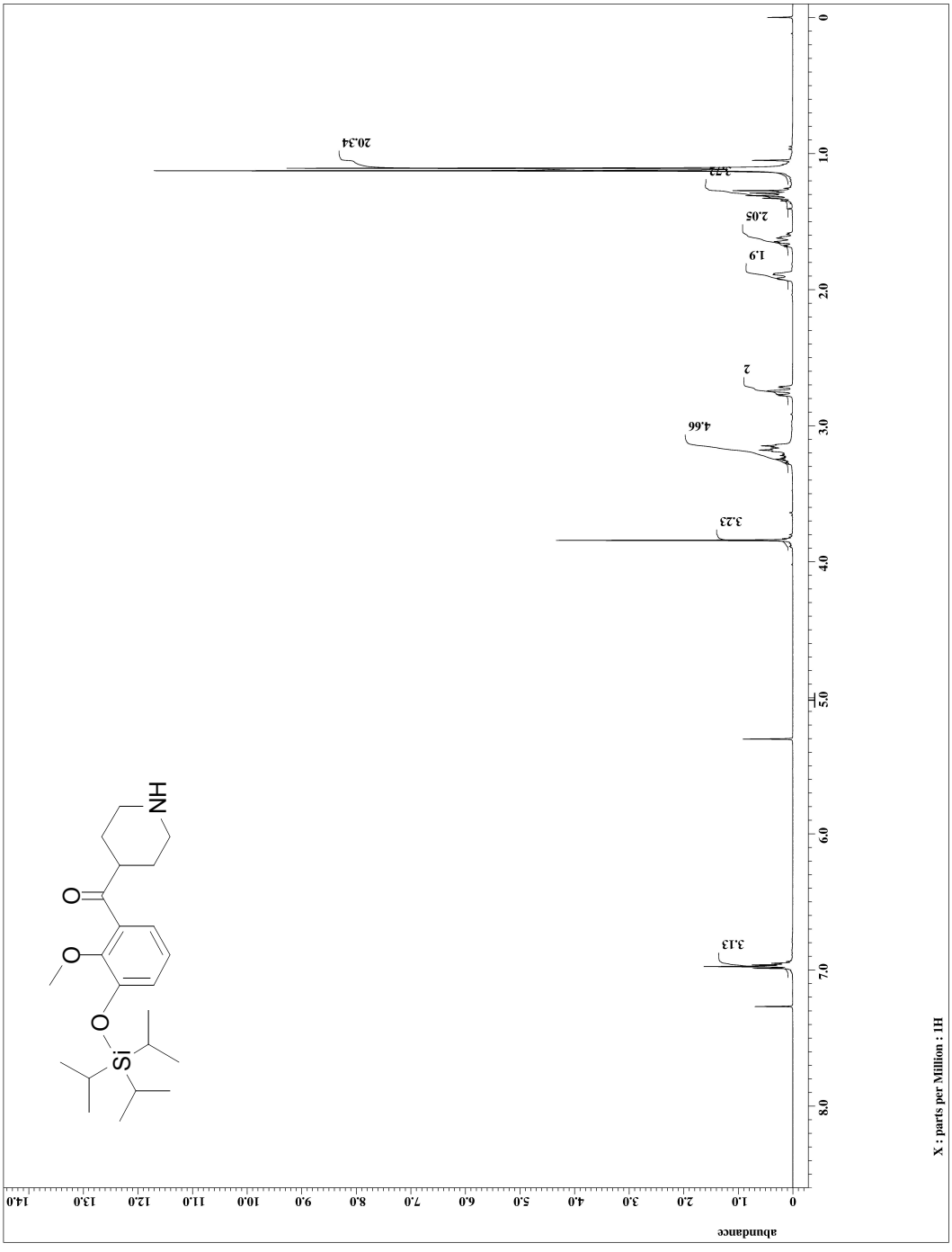
^{1}H-NMR Spectra (500 MHz, $CDCl_3$)

tert-butyl 4-(2-methoxy-3-(triisopropylsilyloxy)benzoyl)piperidine-1-carboxylate (7)



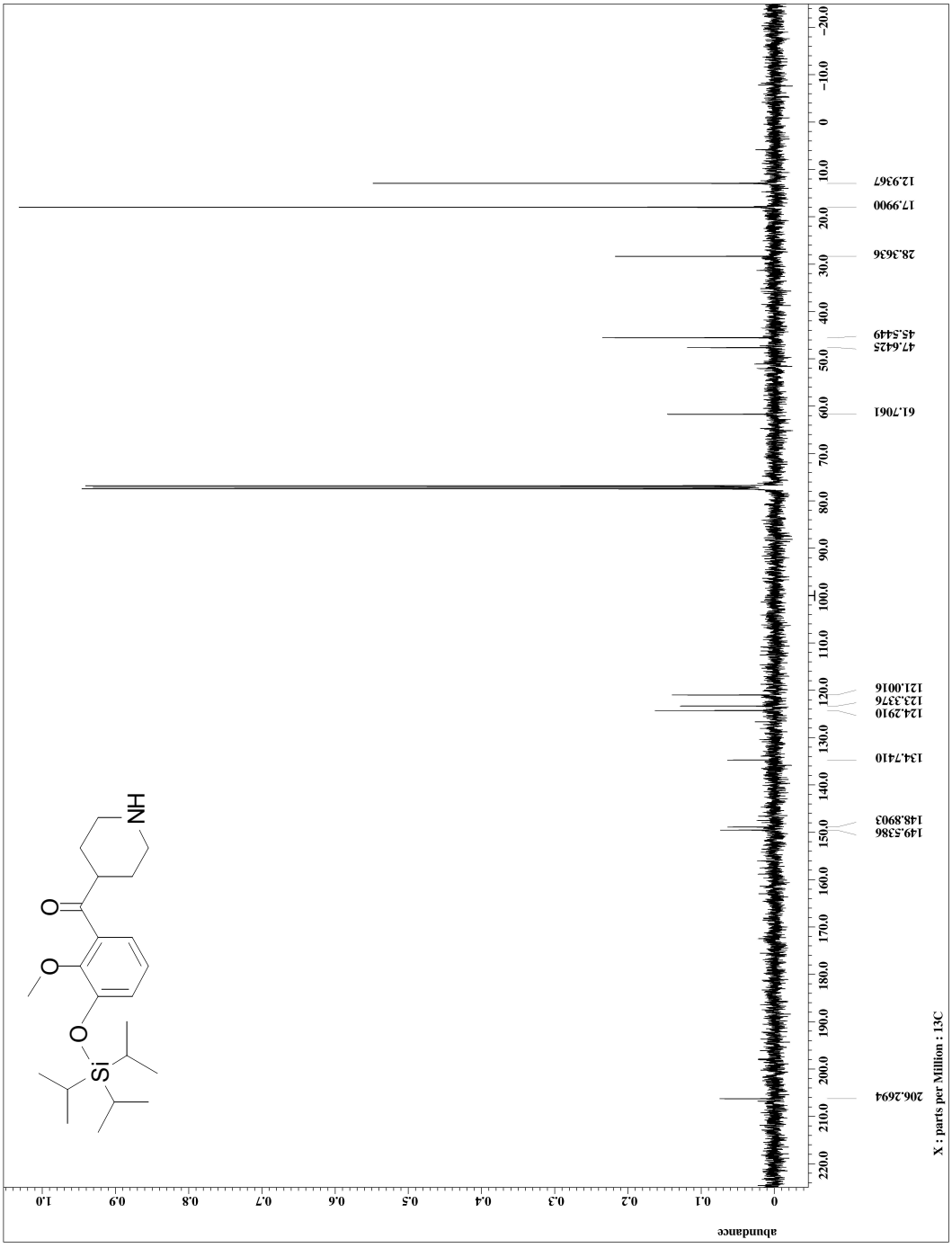
^{1}H-NMR Spectra (500 MHz, $CDCl_3$)

(2-methoxy-3-(triisopropylsilyloxy)phenyl)(piperidin-4-yl)methanone (8)



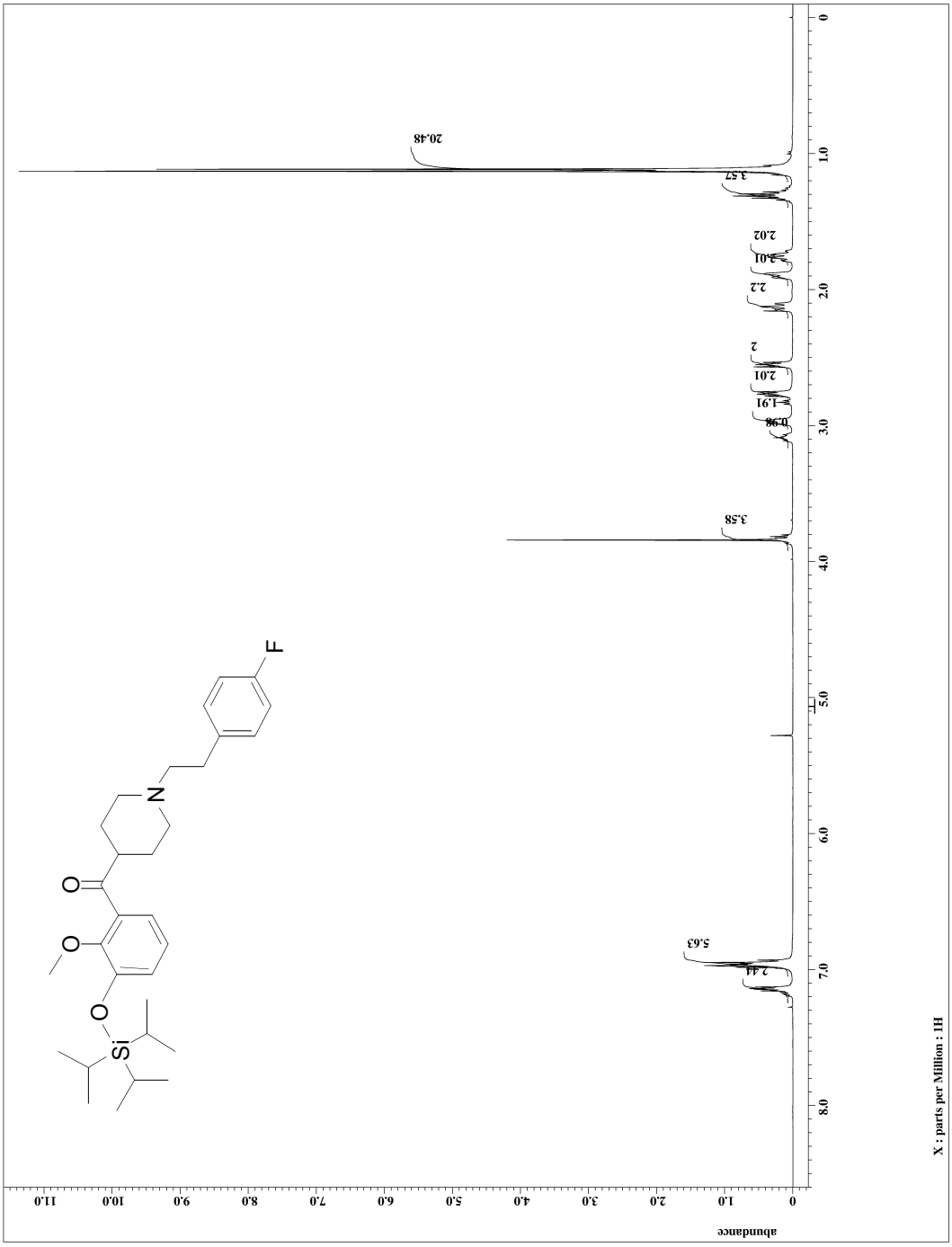
^{13}C-NMR Spectra (500 MHz, $CDCl_3$)

(2-methoxy-3-(triisopropylsilyloxy)phenyl)(piperidin-4-yl)methanone (8)



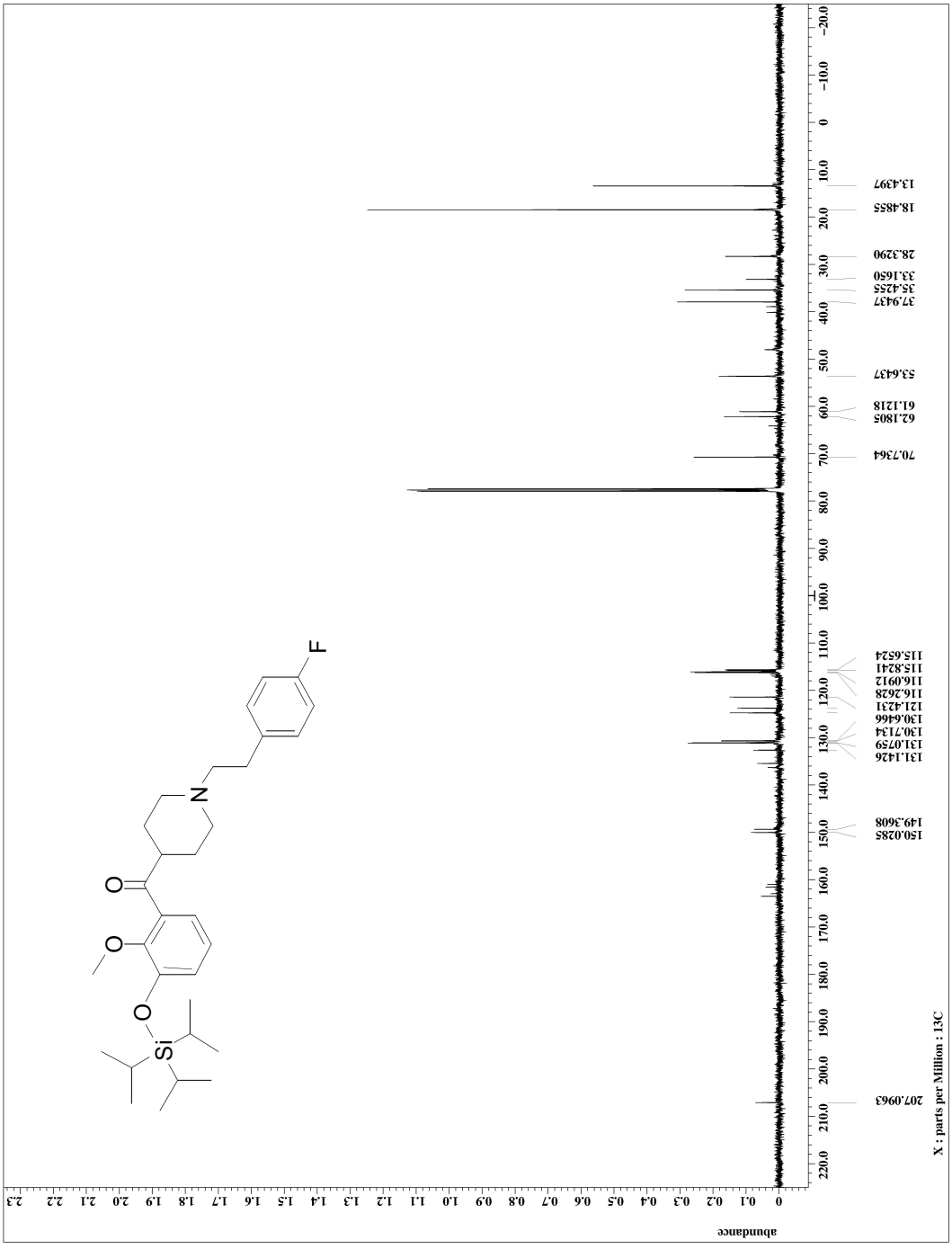
^{1}H-NMR Spectra (500 MHz, $CDCl_3$)

(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(triisopropylsilyloxy)phenyl)methanone (9)

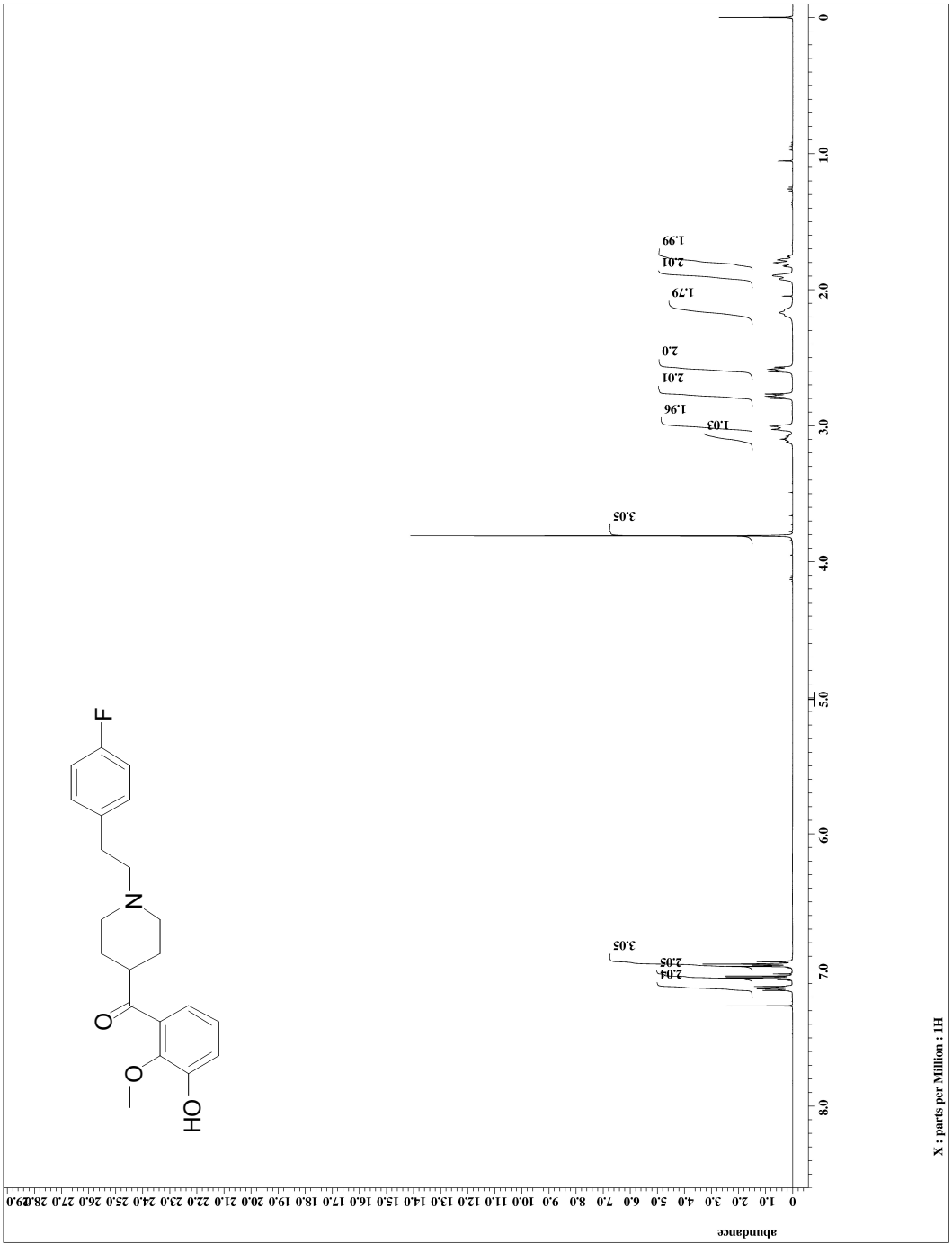


^{1}H-NMR Spectra (500 MHz, $CDCl_3$)

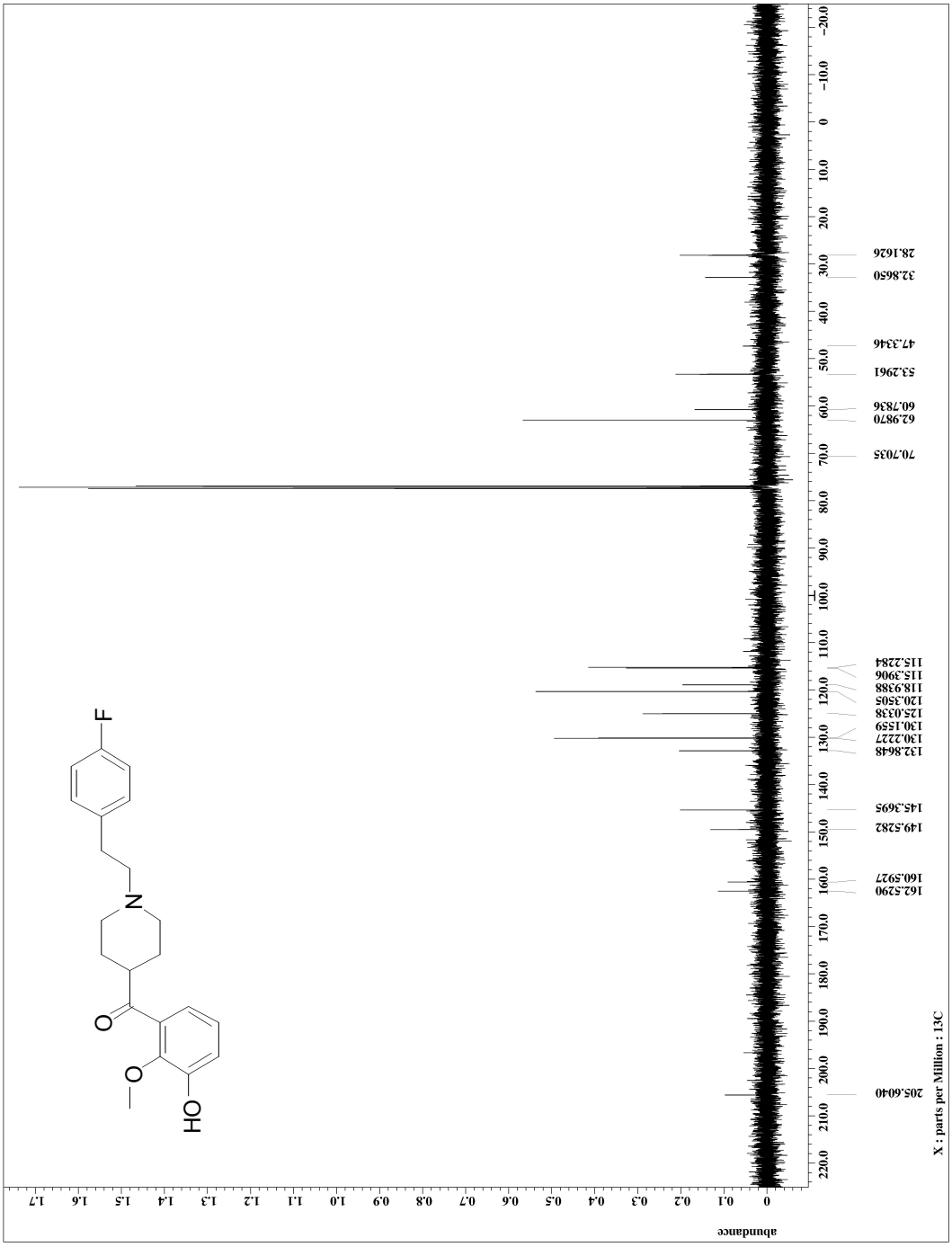
(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(triisopropylsilyloxy)phenyl)methanone (9)



^{1}H-NMR Spectra (500 MHz, $CDCl_3$),
(1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (10)

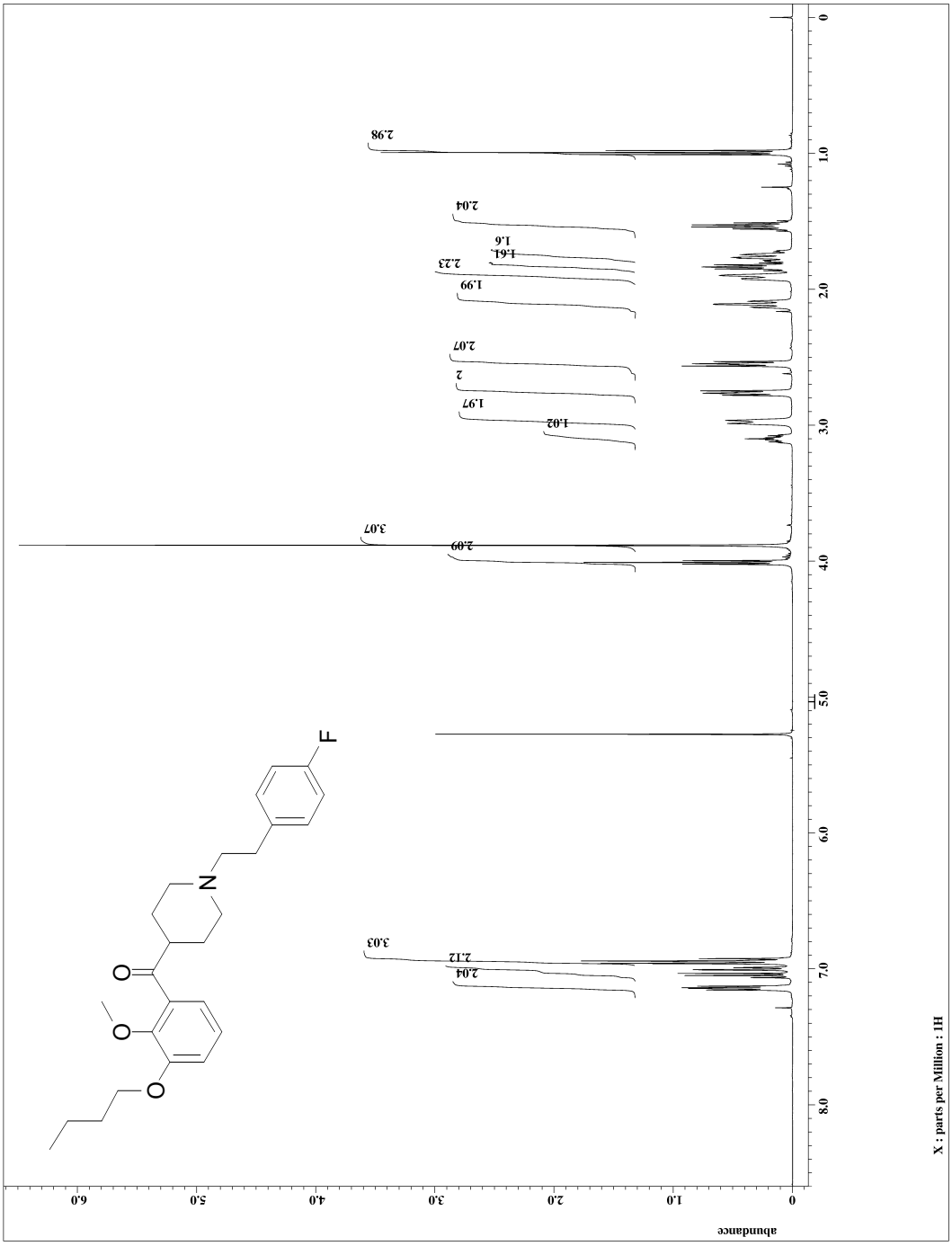


^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
(1-(4-fluorophenethyl)piperidin-4-yl)(3-hydroxy-2-methoxyphenyl)methanone (10)



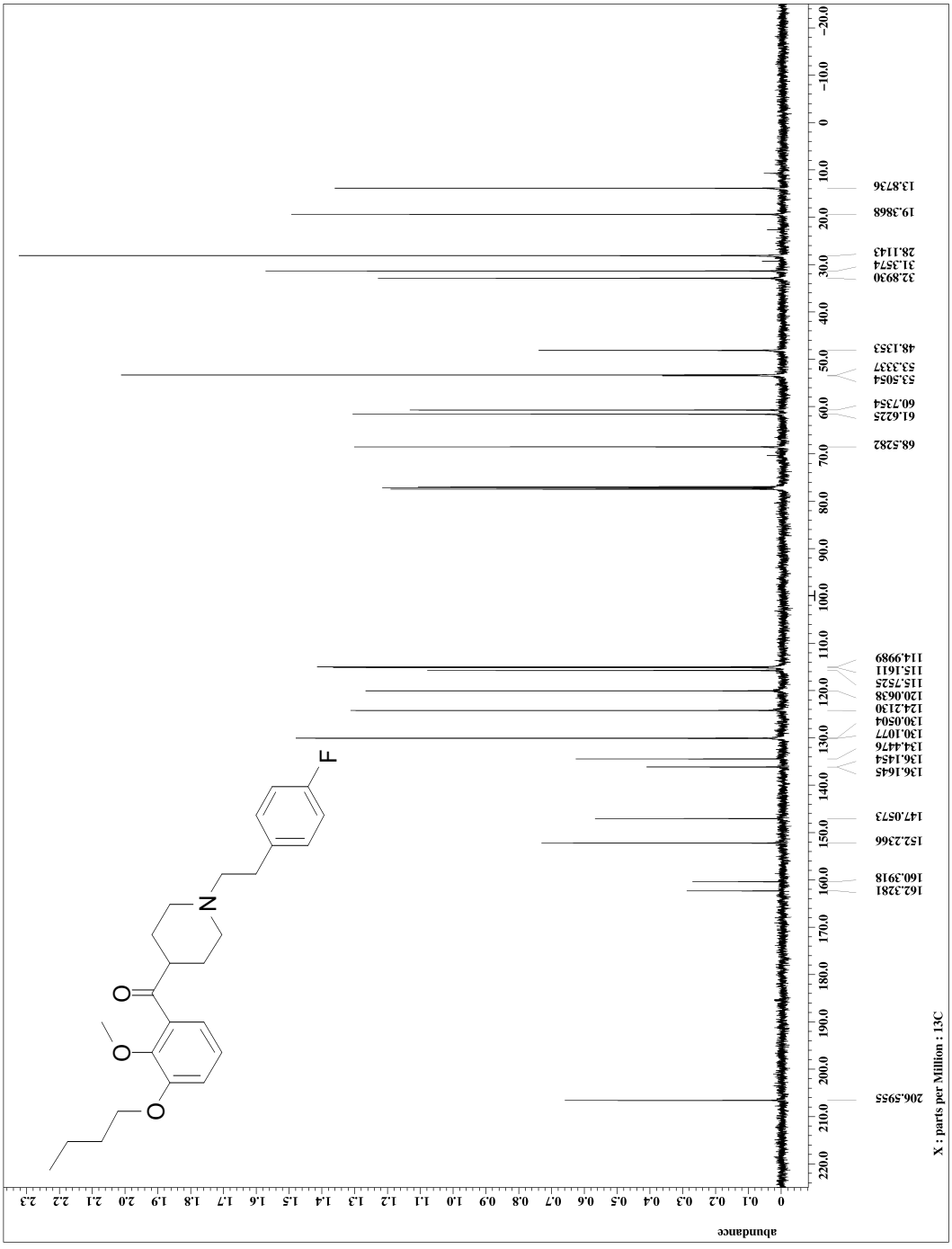
^{1}H-NMR Spectra (500 MHz, $CDCl_3$)

(3-butoxy-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (11)



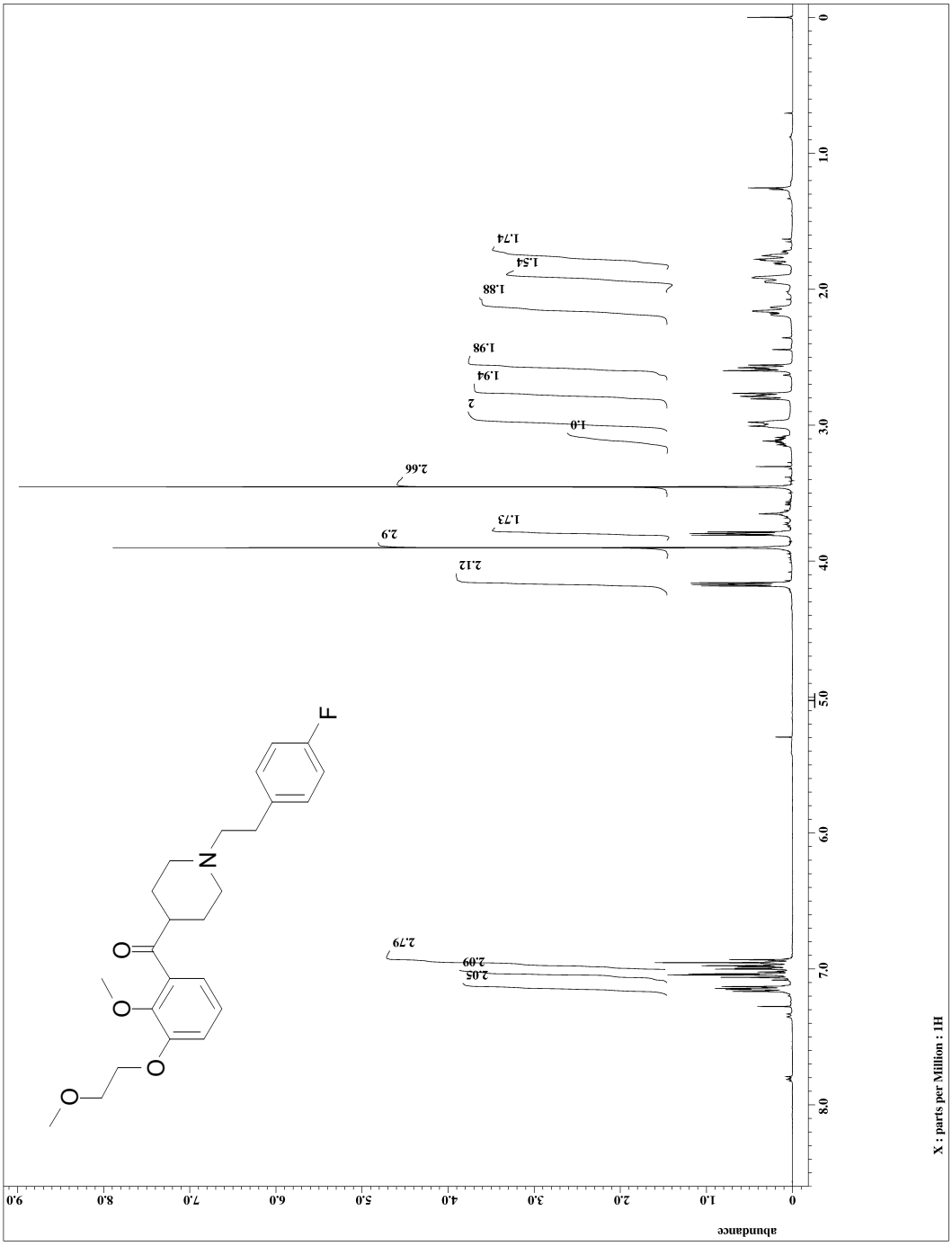
^{13}C-NMR Spectra (500 MHz, $CDCl_3$)

(3-butoxy-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (11)



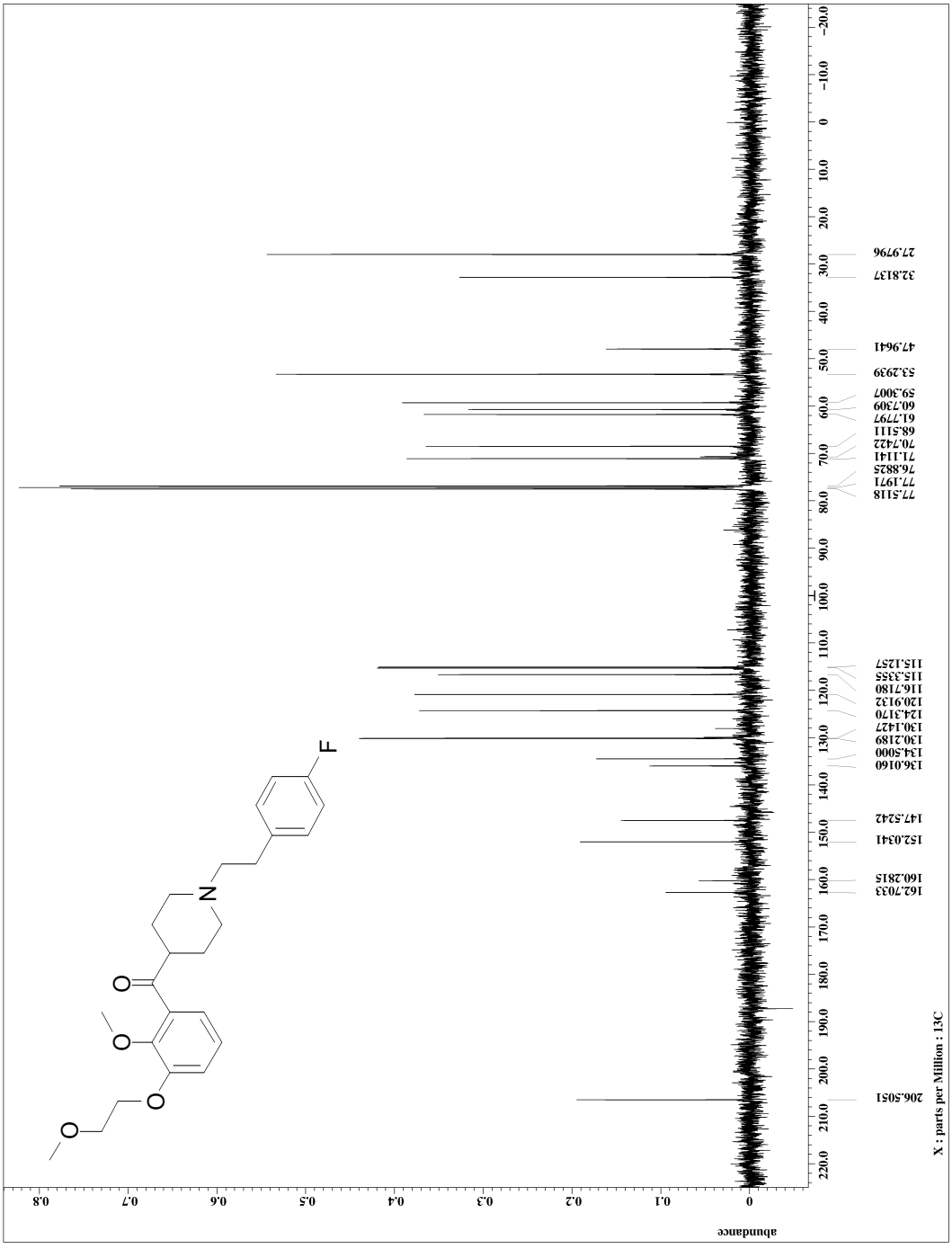
^{1}H-NMR Spectra (400 MHz, $CDCl_3$)

(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2 methoxyethoxy)phenyl)methanone (12)

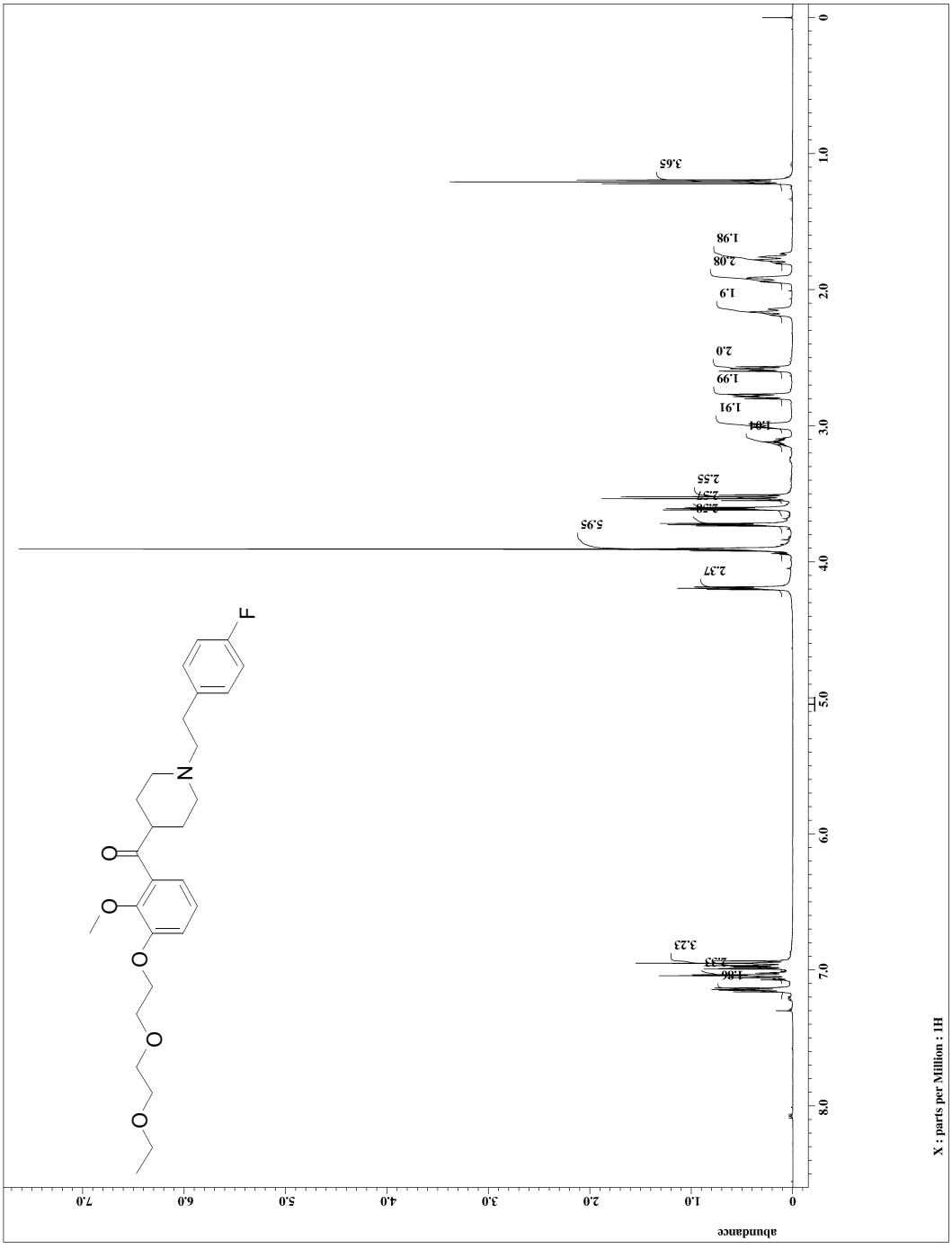


^{13}C-NMR Spectra (400 MHz, $CDCl_3$)

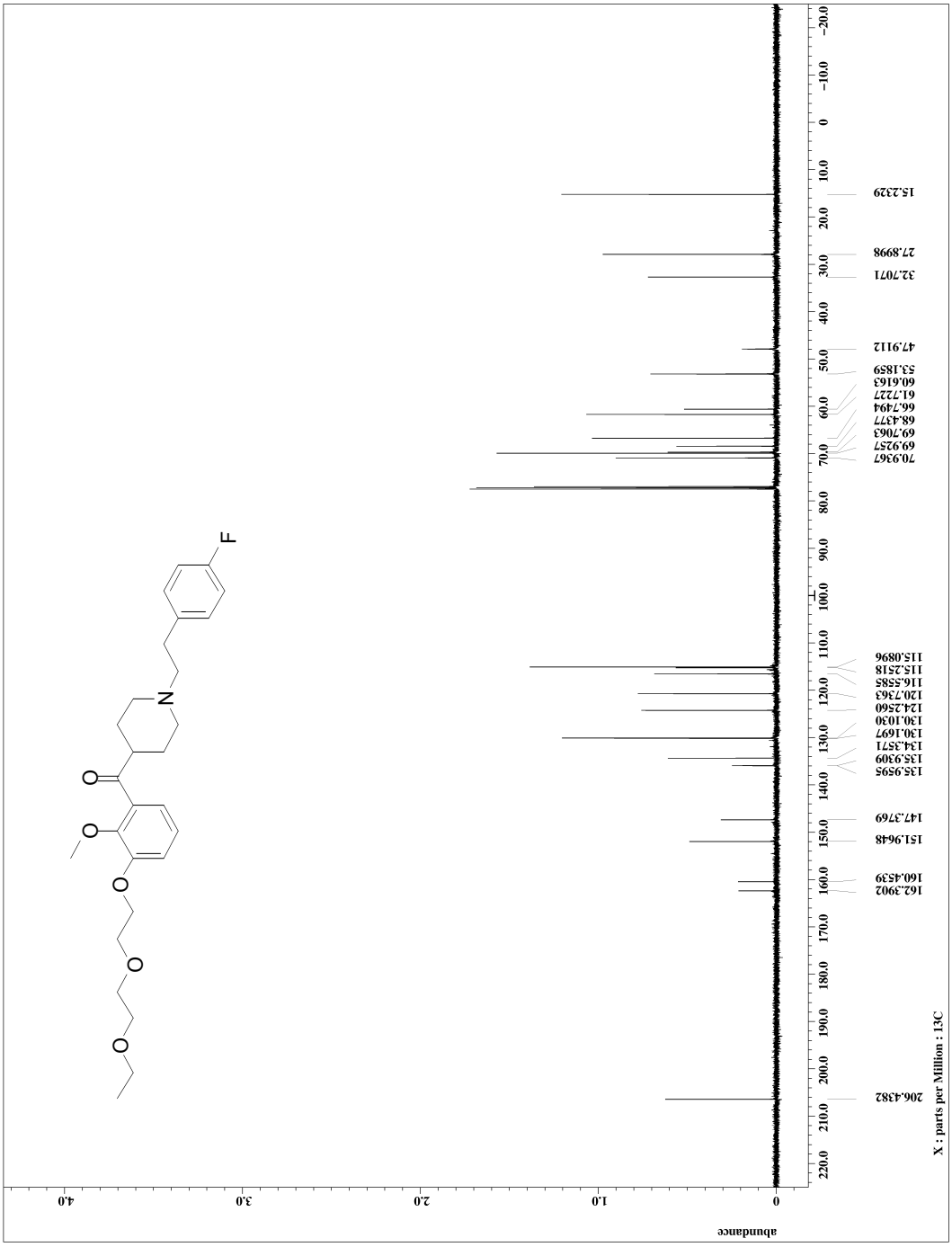
(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2-methoxyethoxy)phenyl)methanone (12)



^{1}H-NMR Spectra (500 MHz, $CDCl_3$),
(3-(2-(2-ethoxyethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (13)

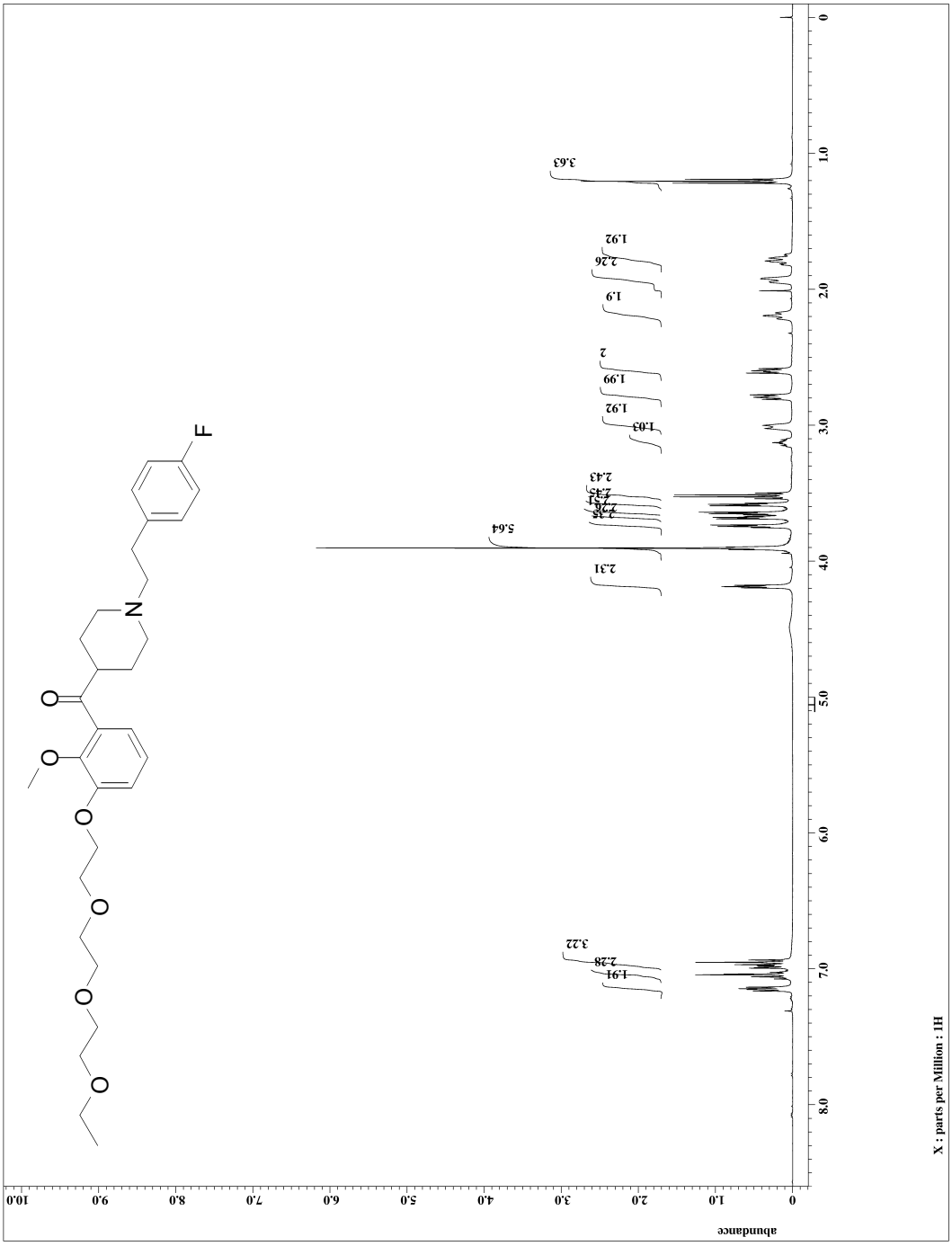


^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
(3-(2-(2-ethoxyethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (13)

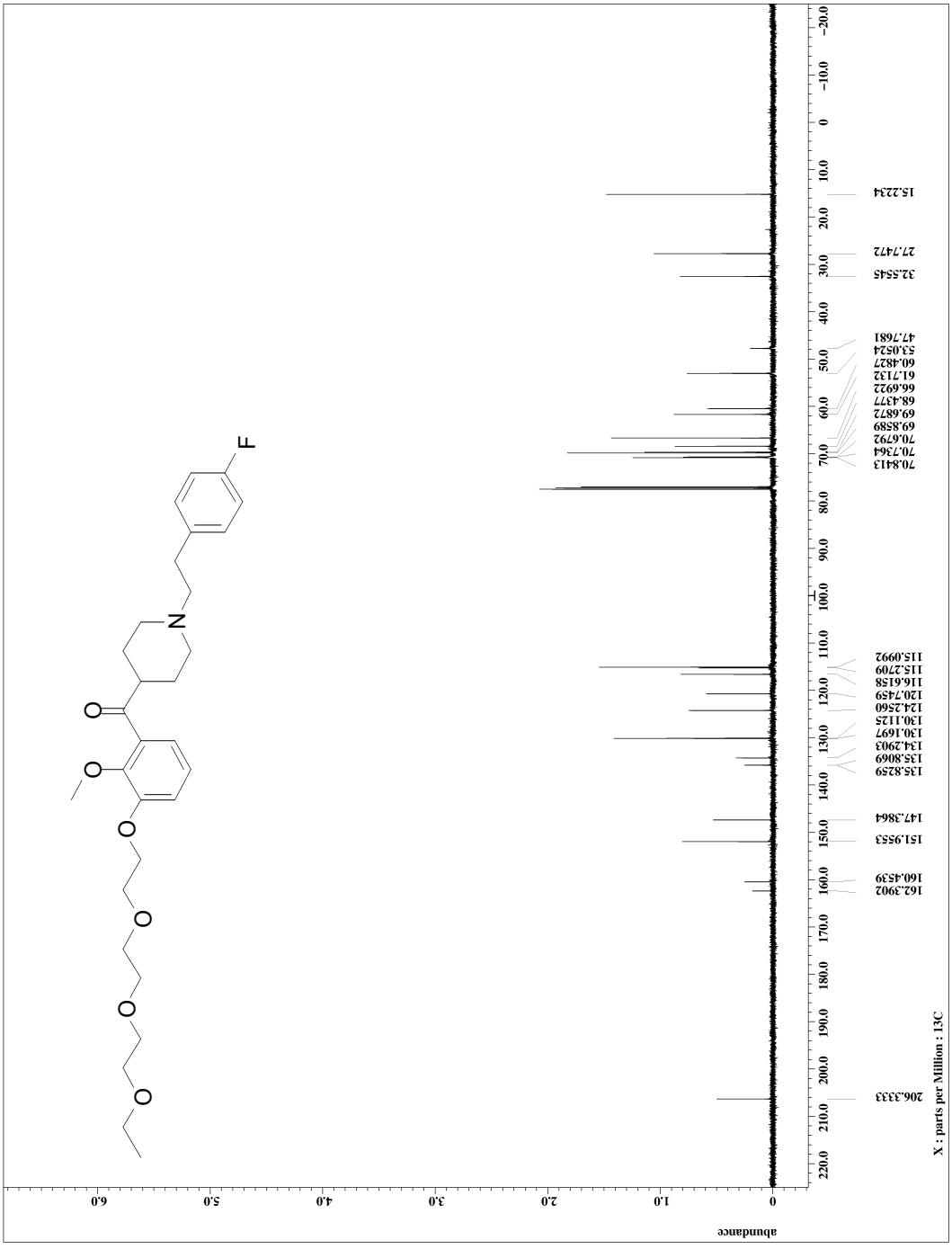


^{1}H-NMR Spectra (500 MHz, $CDCl_3$),

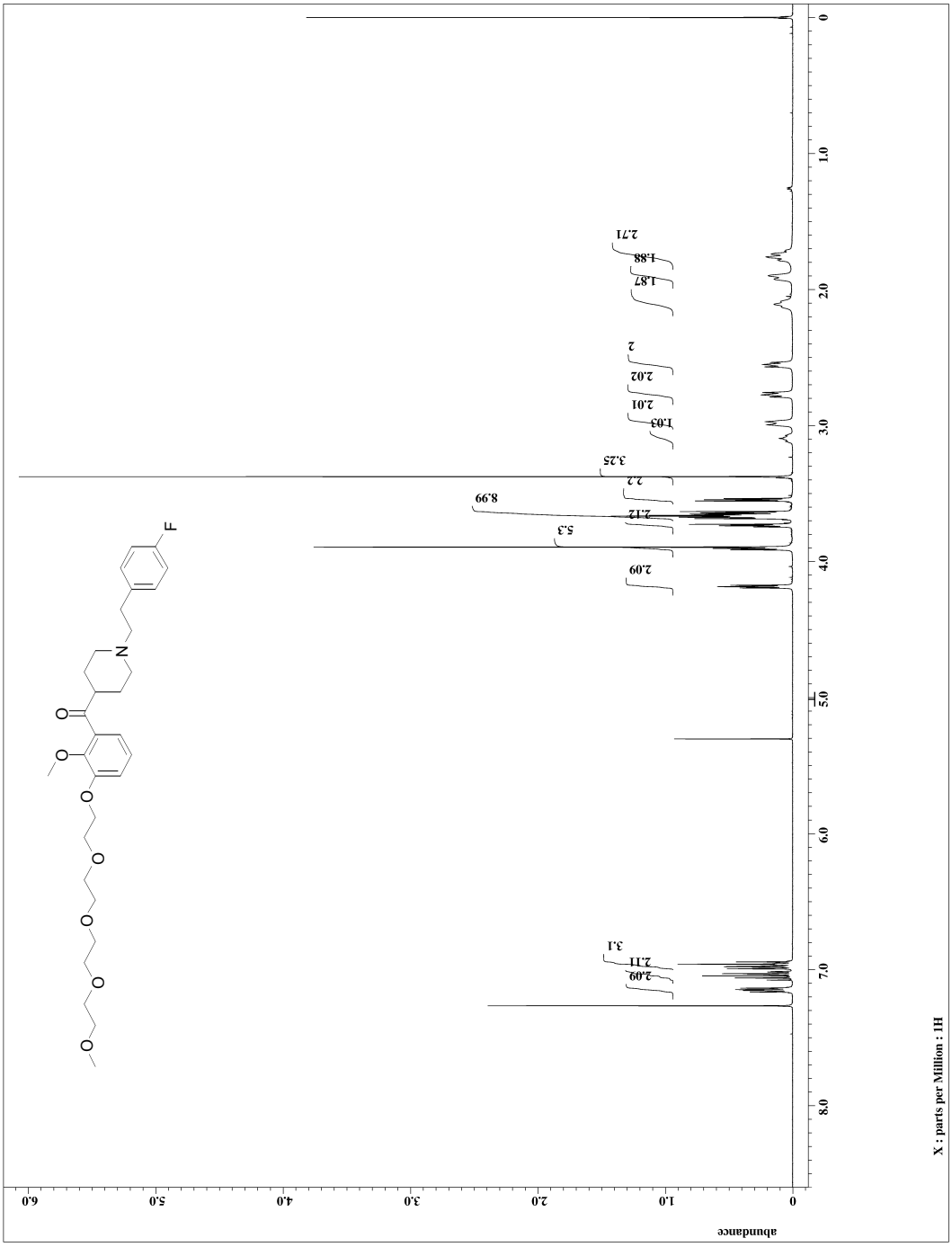
(3-(2-(2-(2-ethoxyethoxy)ethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (14)



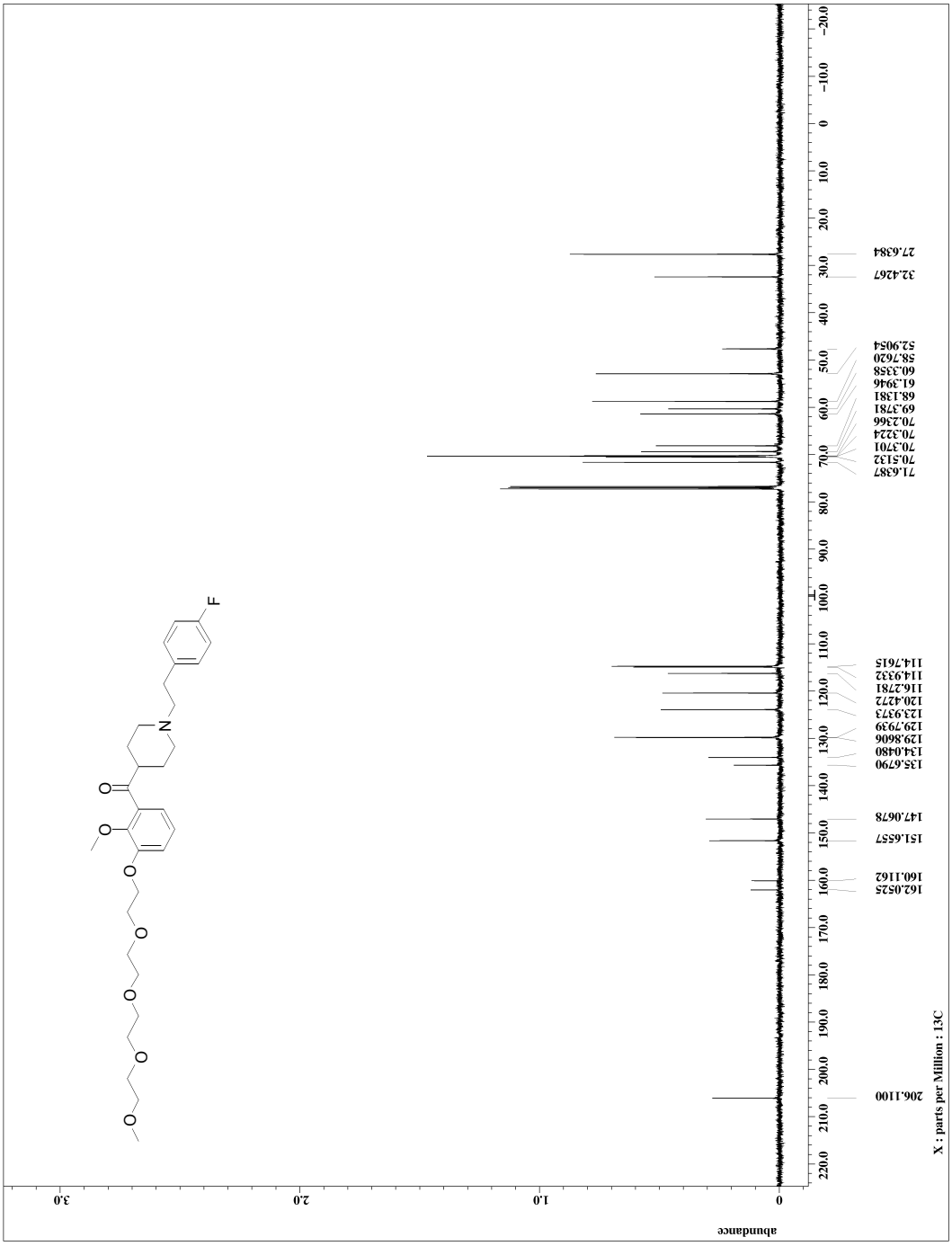
^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
(3-(2-(2-(2-ethoxyethoxy)ethoxy)ethoxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (14)



^{1}H-NMR Spectra (500 MHz, $CDCl_3$),
(3-(2,5,8,11-tetraoxatridecan-13-yloxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (15)

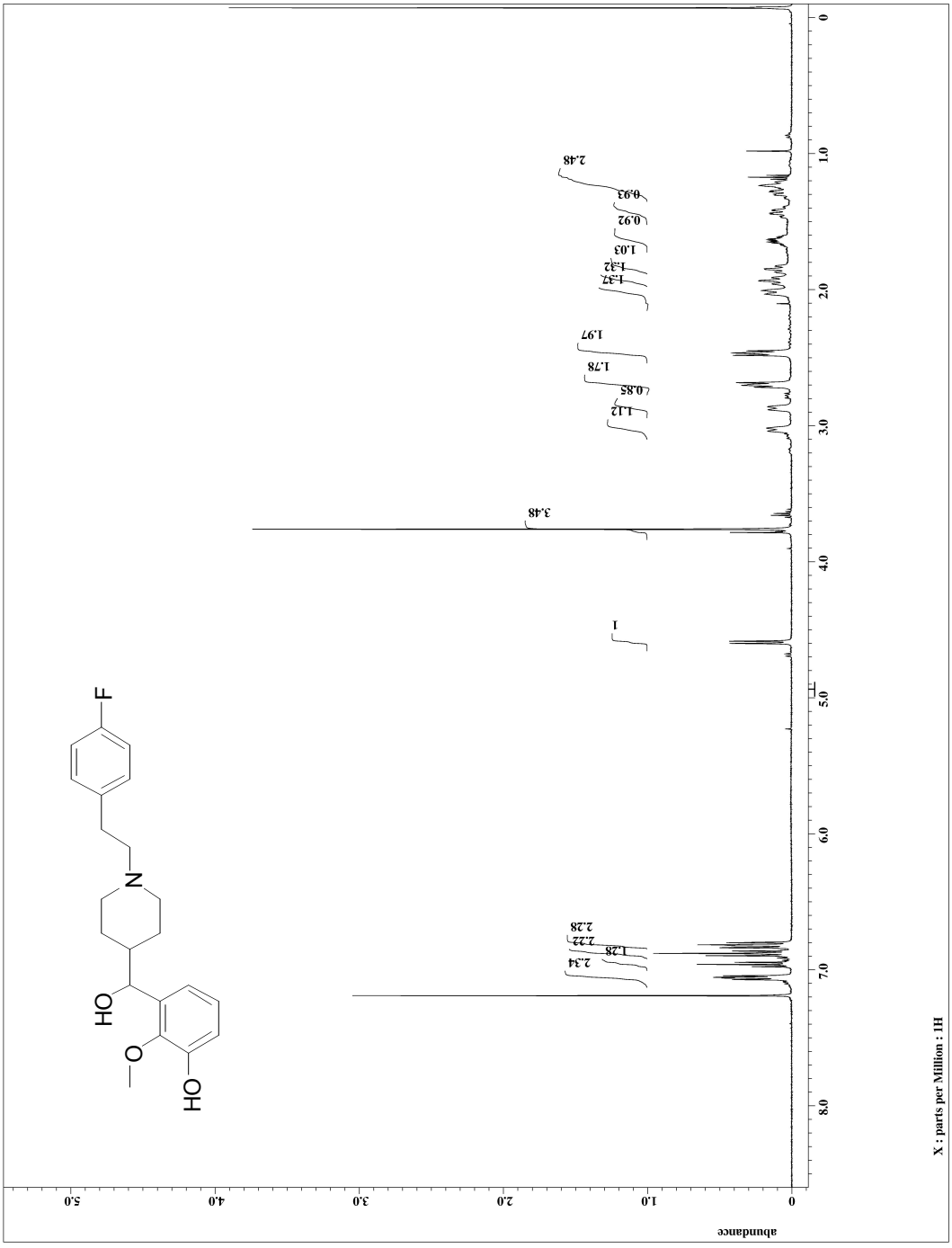


^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
(3-(2,5,8,11-tetraoxatridecan-13-yloxy)-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanone (15)



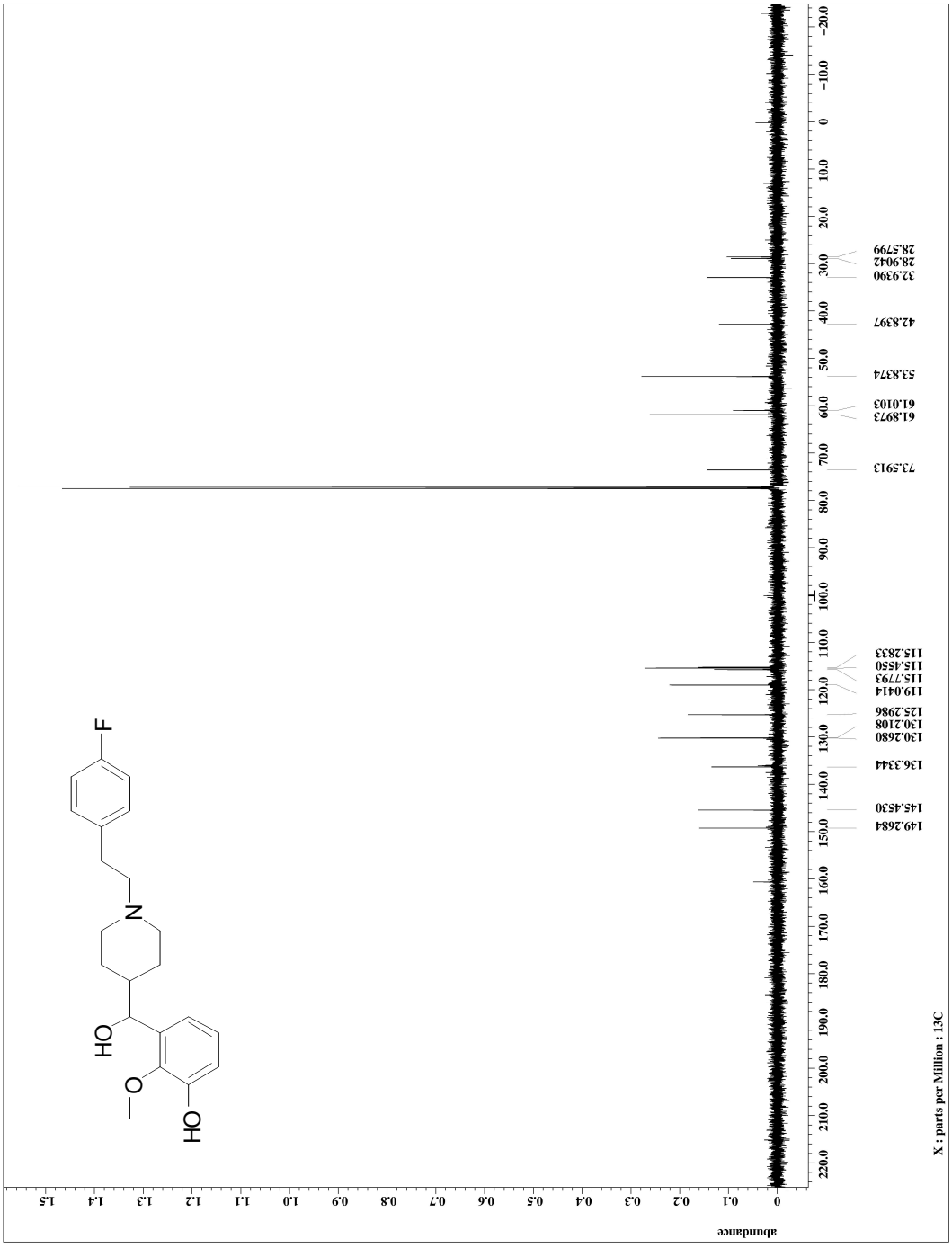
^{1}H-NMR Spectra (500 MHz, $CDCl_3$),

3-((1-(4-fluorophenethyl)piperidin-4-yl)(hydroxy)methyl)-2-methoxyphenol (16)



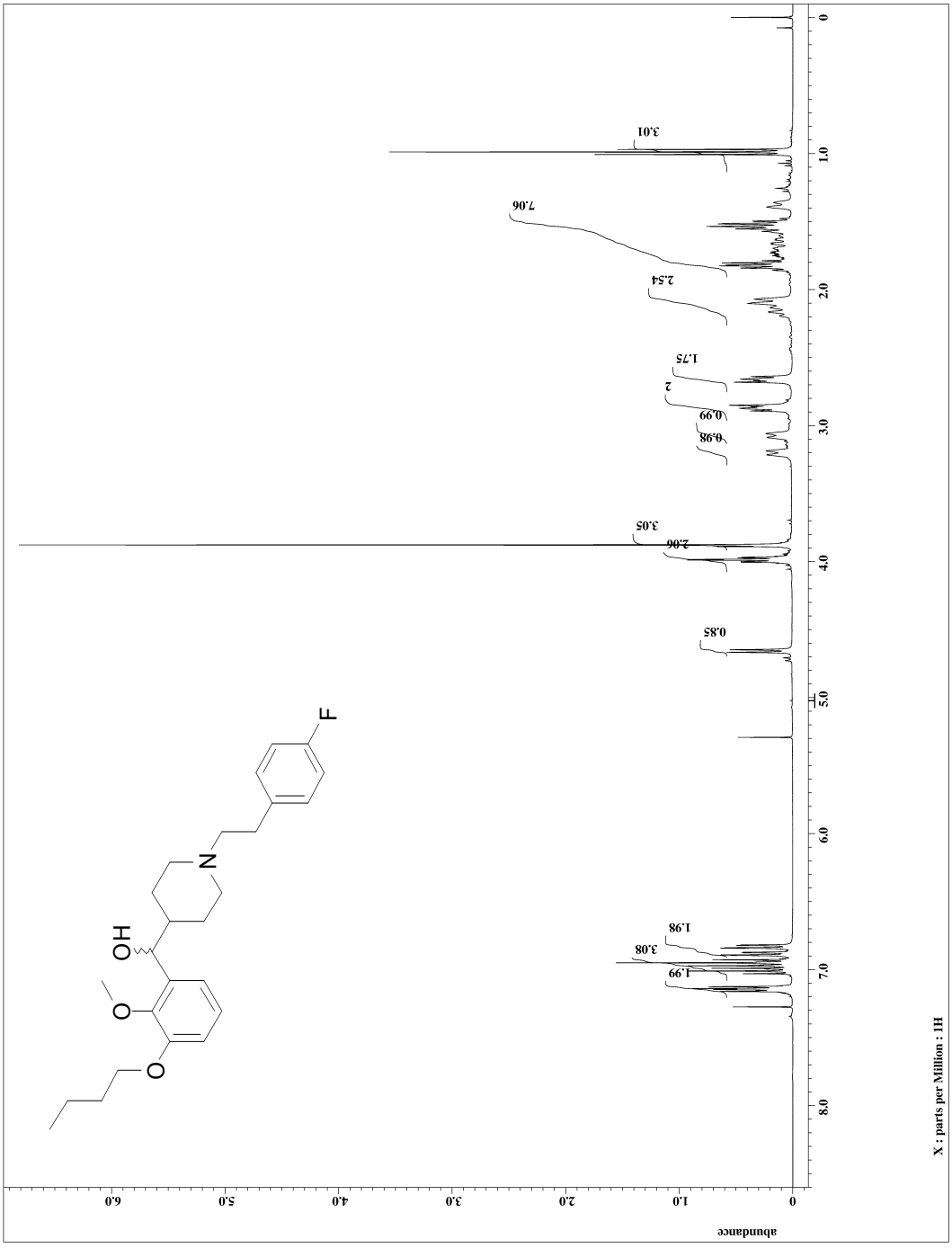
^{13}C-NMR Spectra (500 MHz, $CDCl_3$),

3-((1-(4-fluorophenethyl)piperidin-4-yl)(hydroxy)methyl)-2-methoxyphenol (16)



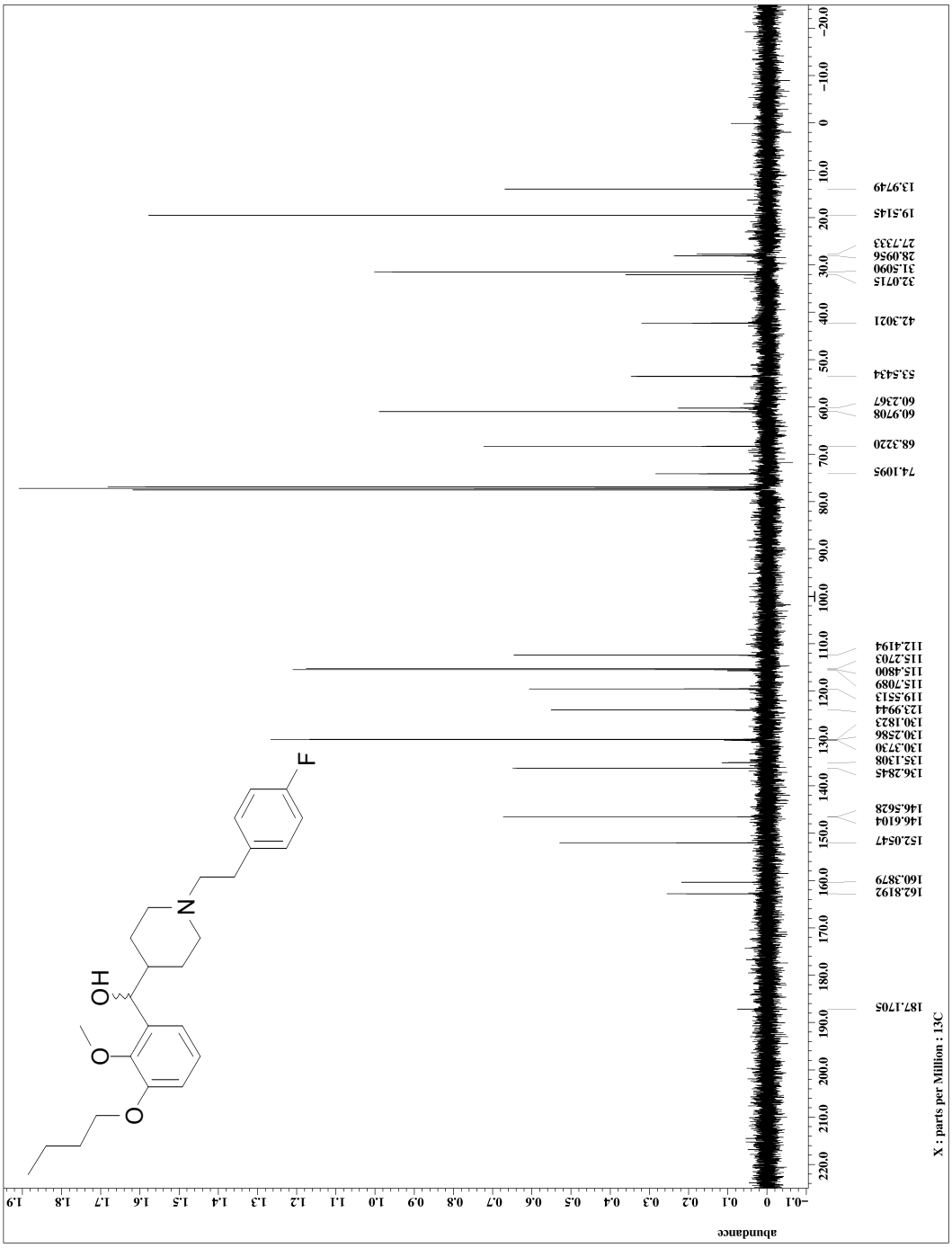
^{1}H-NMR Spectra (400 MHz, $CDCl_3$)

(3-butoxy-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanol (17)

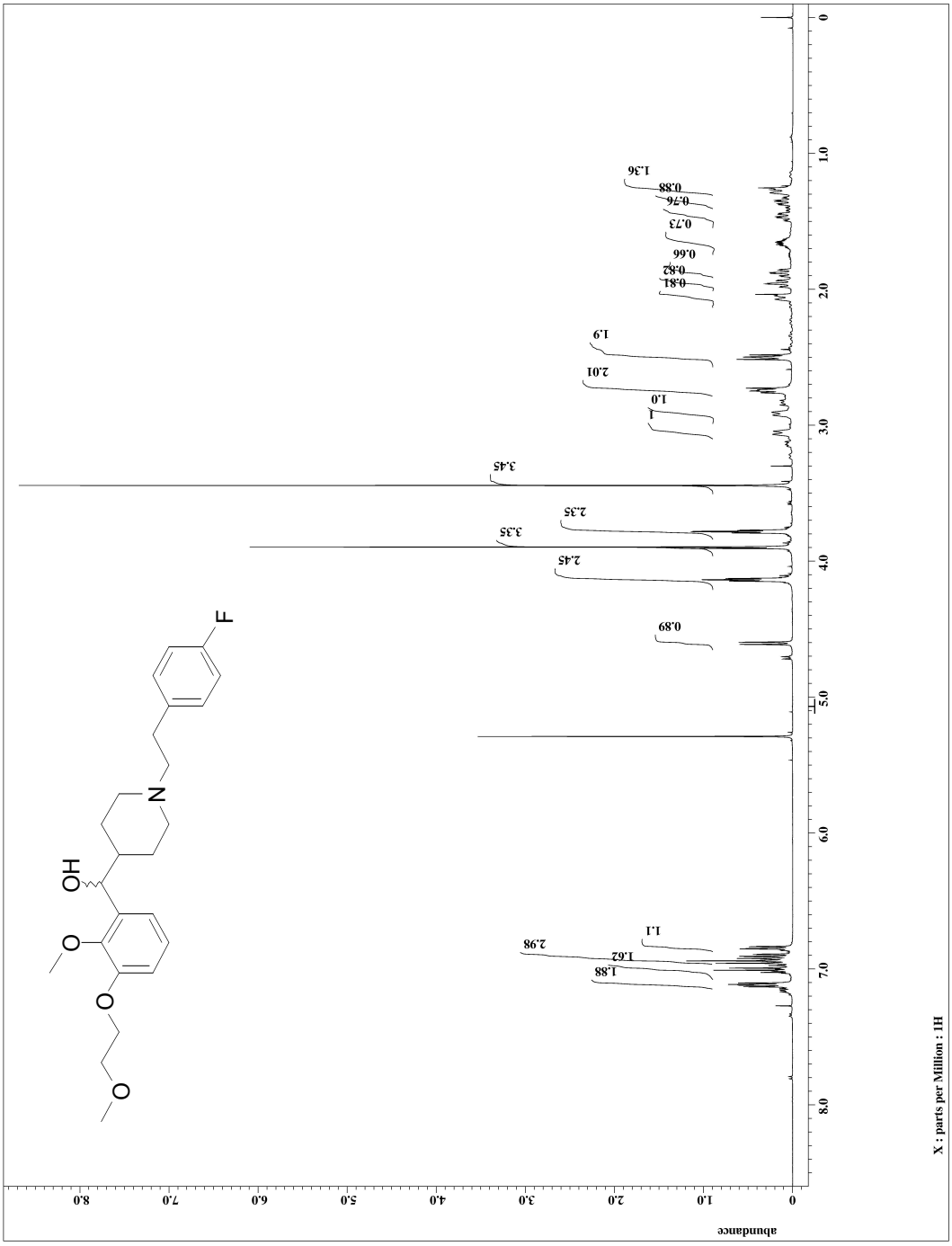


^{13}C-NMR Spectra (400 MHz, $CDCl_3$)

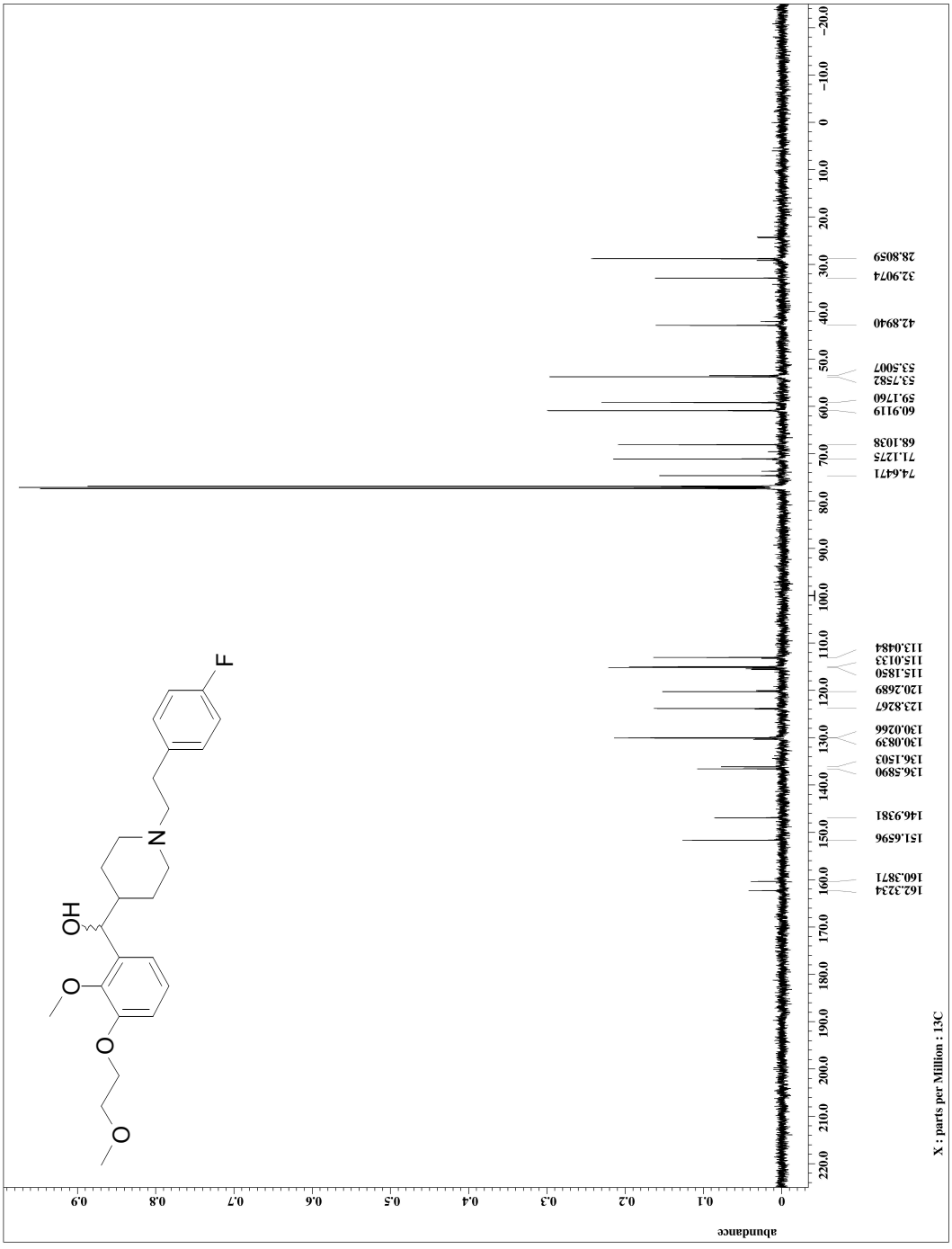
(3-butoxy-2-methoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)methanol (17)



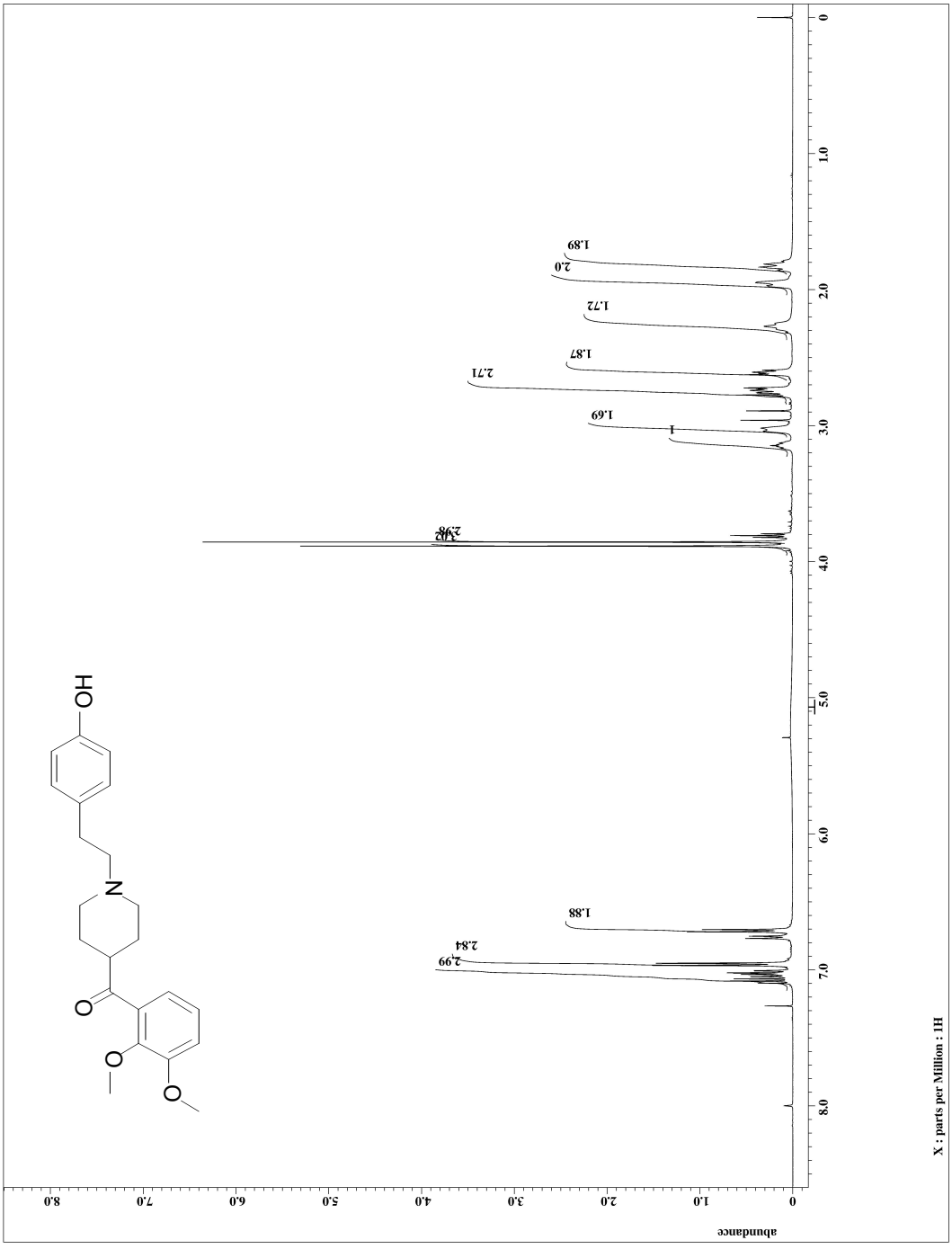
^{1}H-NMR Spectra (500 MHz, $CDCl_3$),
(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2 methoxyethoxy)phenyl)methanol (18)



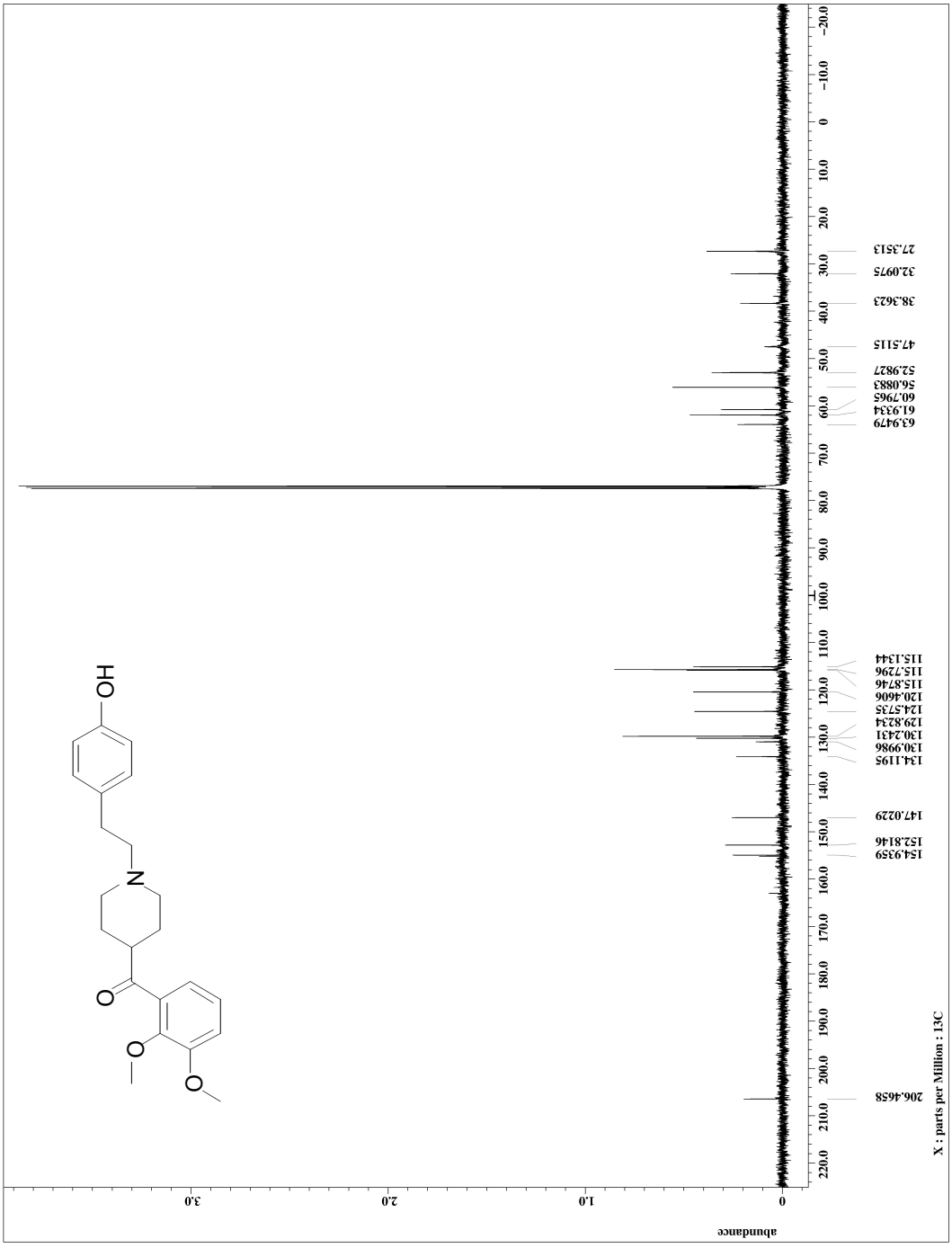
^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
(1-(4-fluorophenethyl)piperidin-4-yl)(2-methoxy-3-(2-methoxyethoxy)phenyl)methanol (18)



^{1}H-NMR Spectra (500 MHz, $CDCl_3$),
(2,3-dimethoxyphenyl)(1-(4-hydroxyphenethyl)piperidin-4-yl)methanone (22)

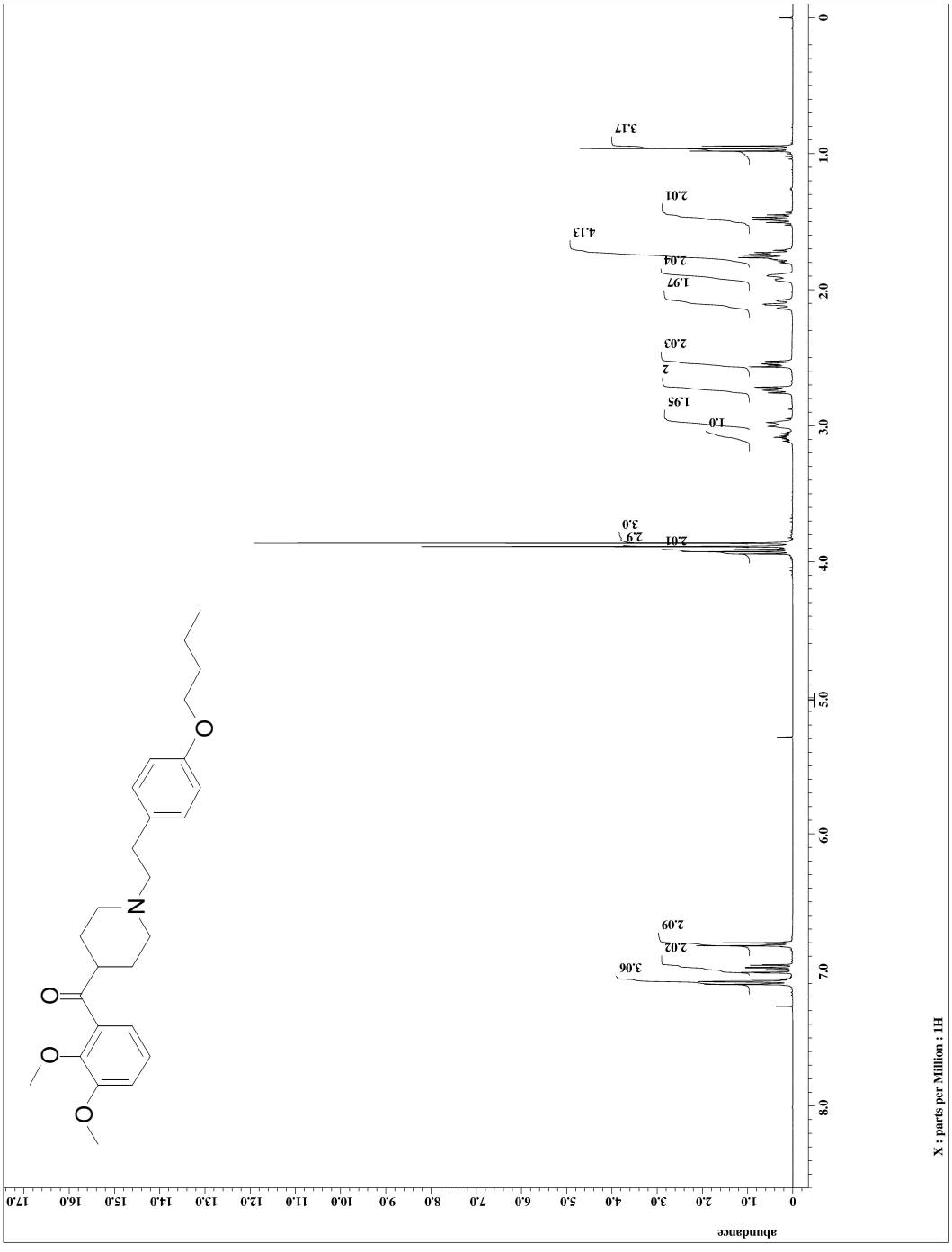


^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
(2,3-dimethoxyphenyl)(1-(4-hydroxyphenethyl)piperidin-4-yl)methanone (22)

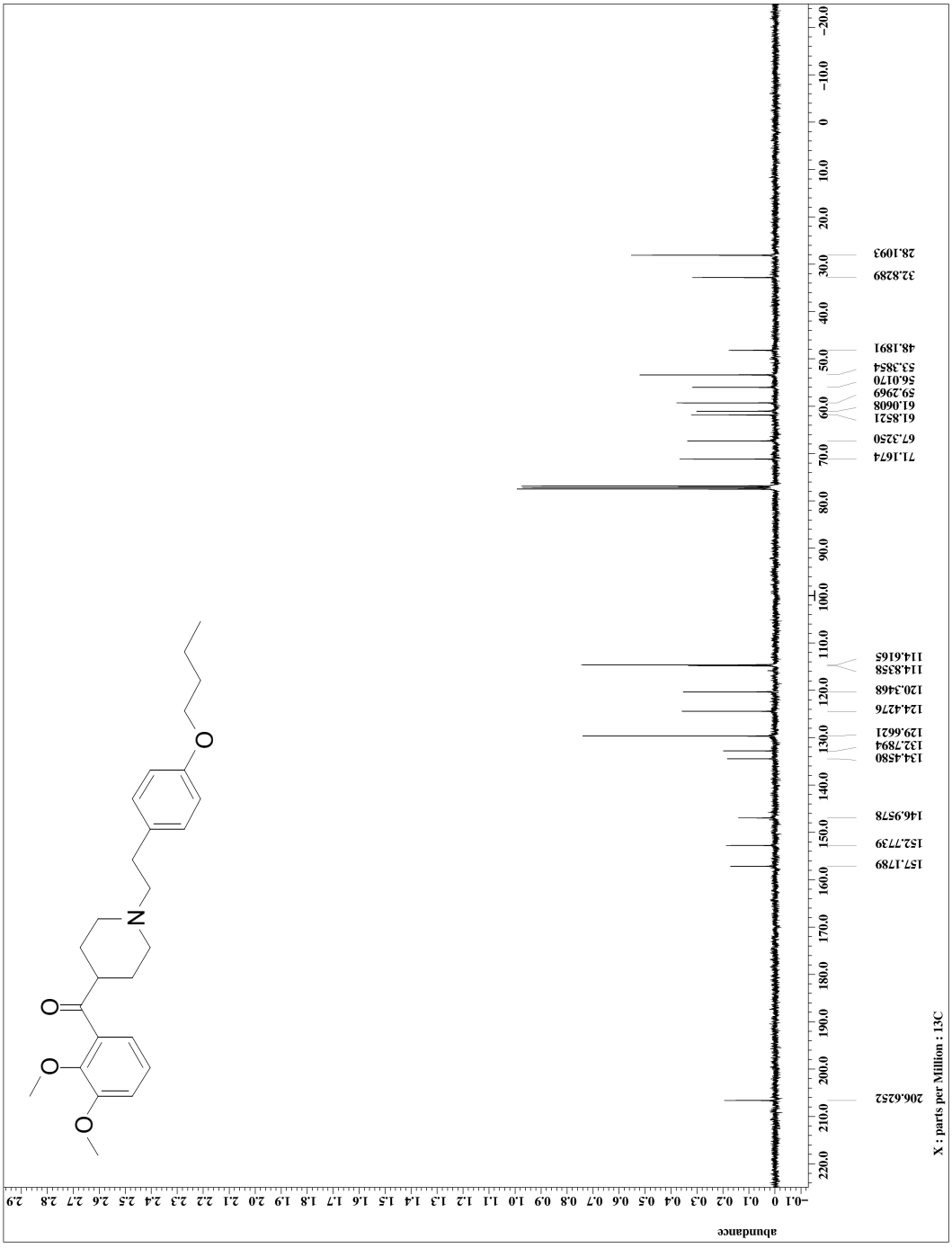


^{1}H-NMR Spectra (400 MHz, $CDCl_3$),

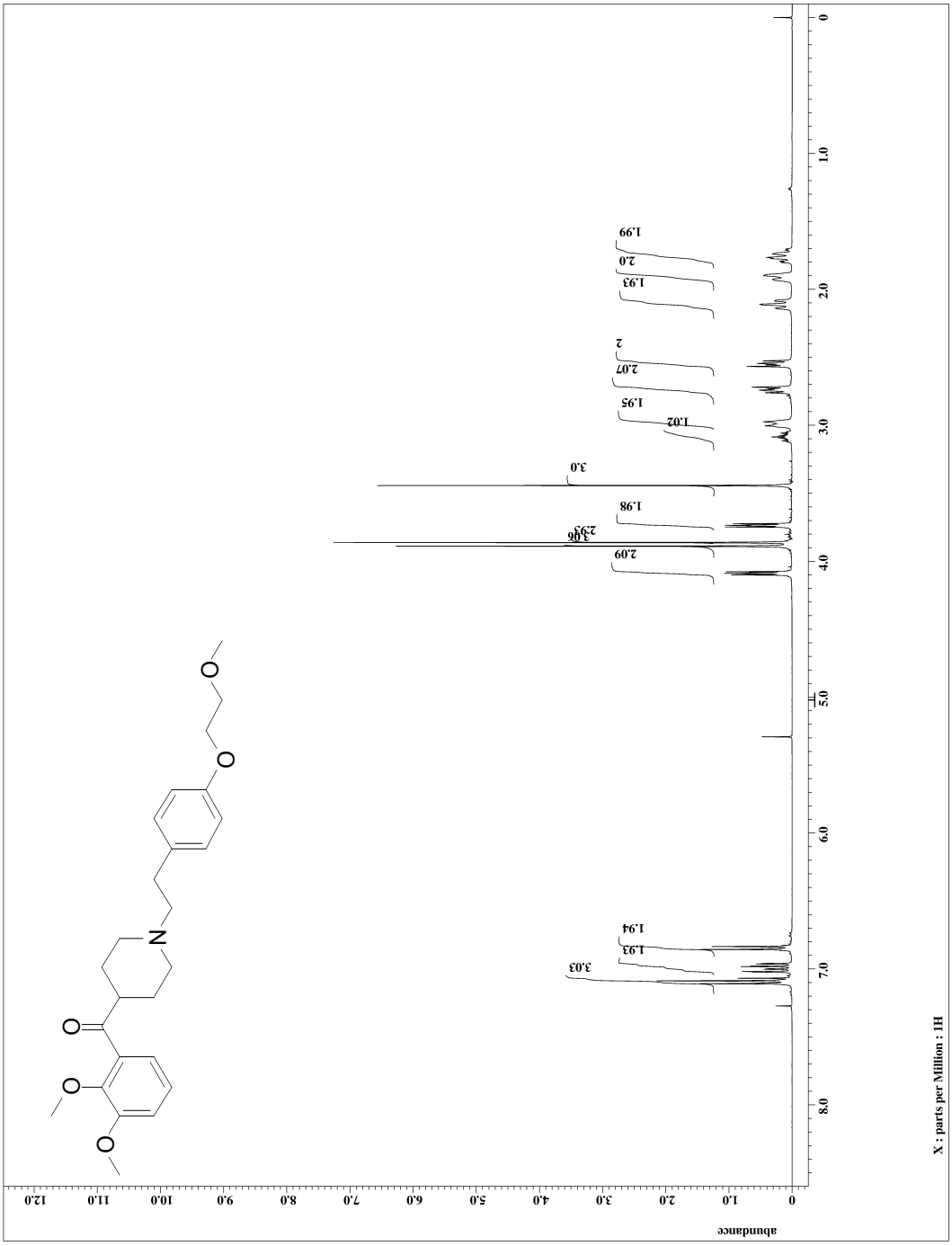
(1-(4-butoxyphenethyl)piperidin-4-yl)(2,3-dimethoxyphenyl)methanone (24)



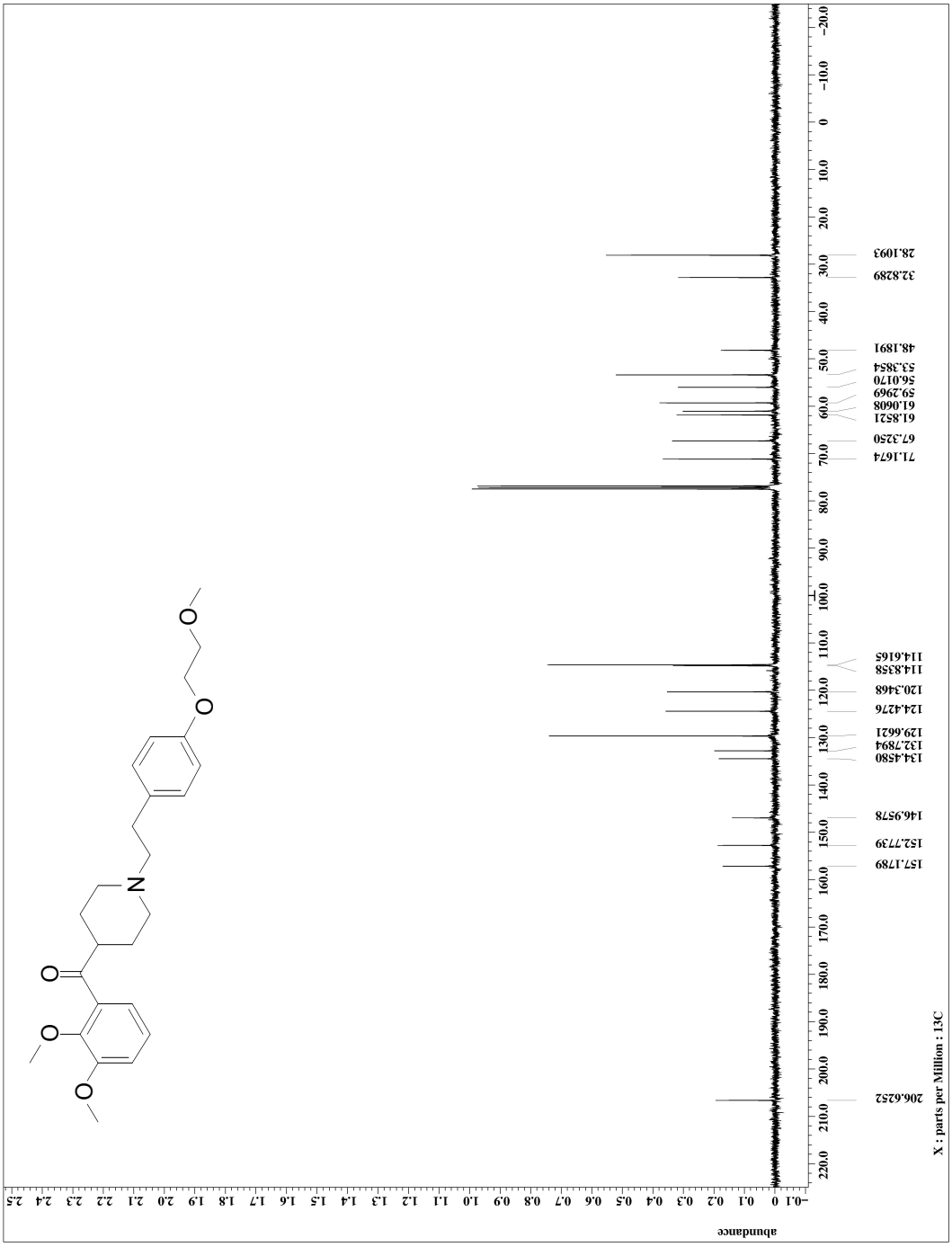
^{13}C-NMR Spectra (400 MHz, $CDCl_3$),
(1-(4-butoxyphenethyl)piperidin-4-yl)(2,3-dimethoxyphenyl)methanone (24)



^{1}H-NMR Spectra (400 MHz, $CDCl_3$),
(2,3-dimethoxyphenyl)(1-(4-(2-methoxyethoxy)phenethyl)piperidin-4-yl)methanone (25)

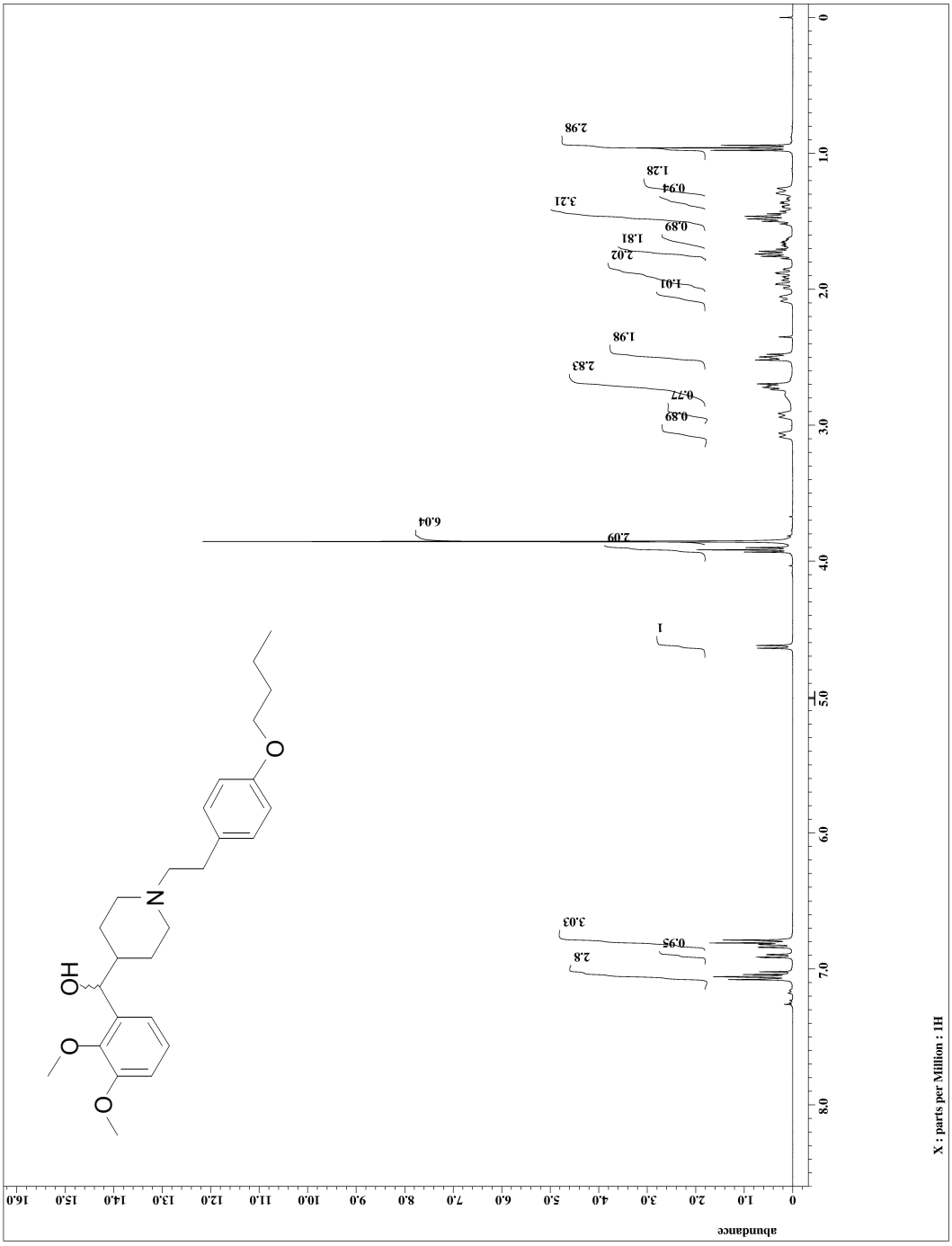


^{13}C-NMR Spectra (400 MHz, $CDCl_3$),
(2,3-dimethoxyphenyl)(1-(4-(2-methoxyethoxy)phenethyl)piperidin-4-yl)methanone (25)



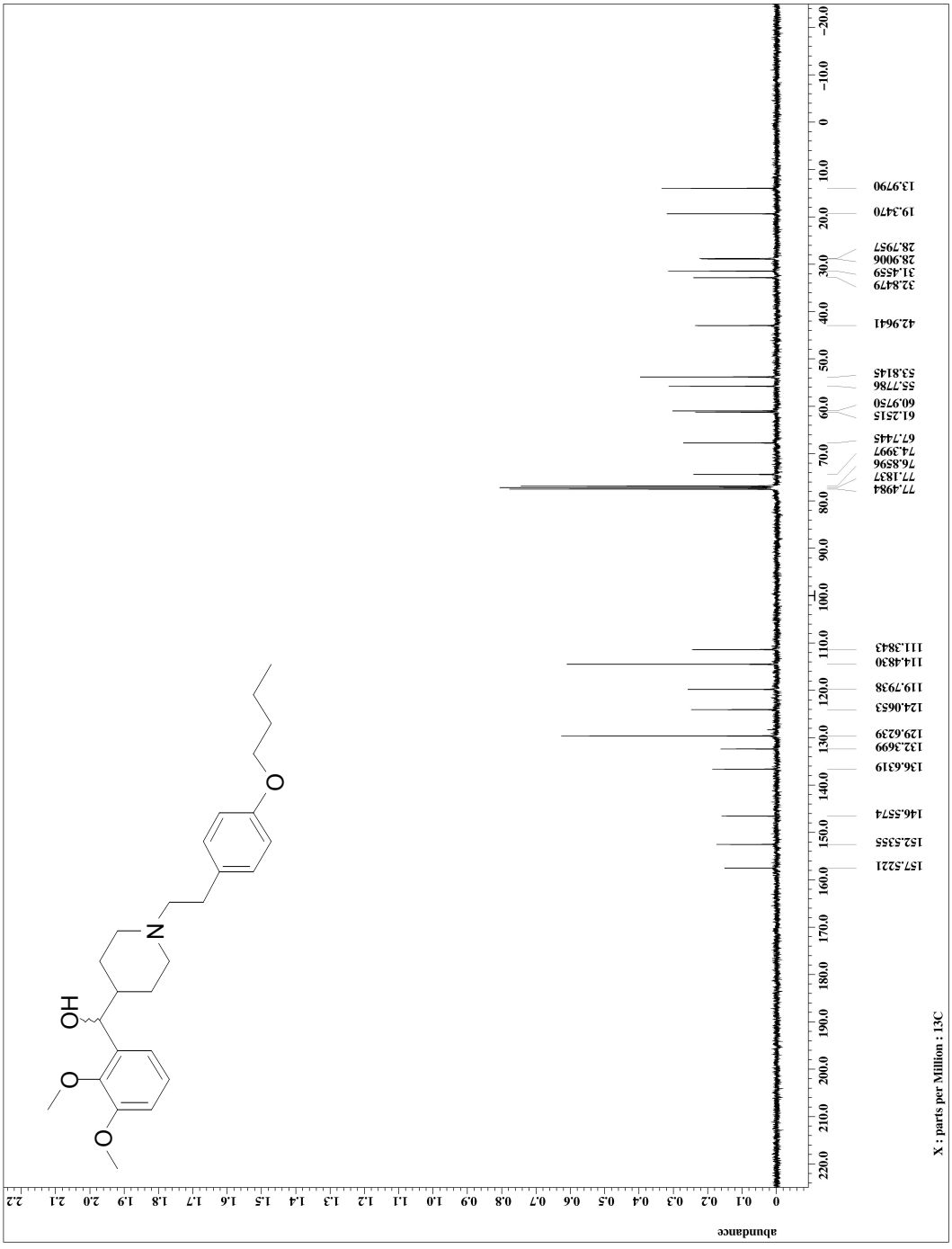
^{1}H-NMR Spectra (400 MHz, $CDCl_3$)

(1-(4-butoxyphenethyl)piperidin-4-yl)(2,3-dimethoxyphenyl)methanol (26)



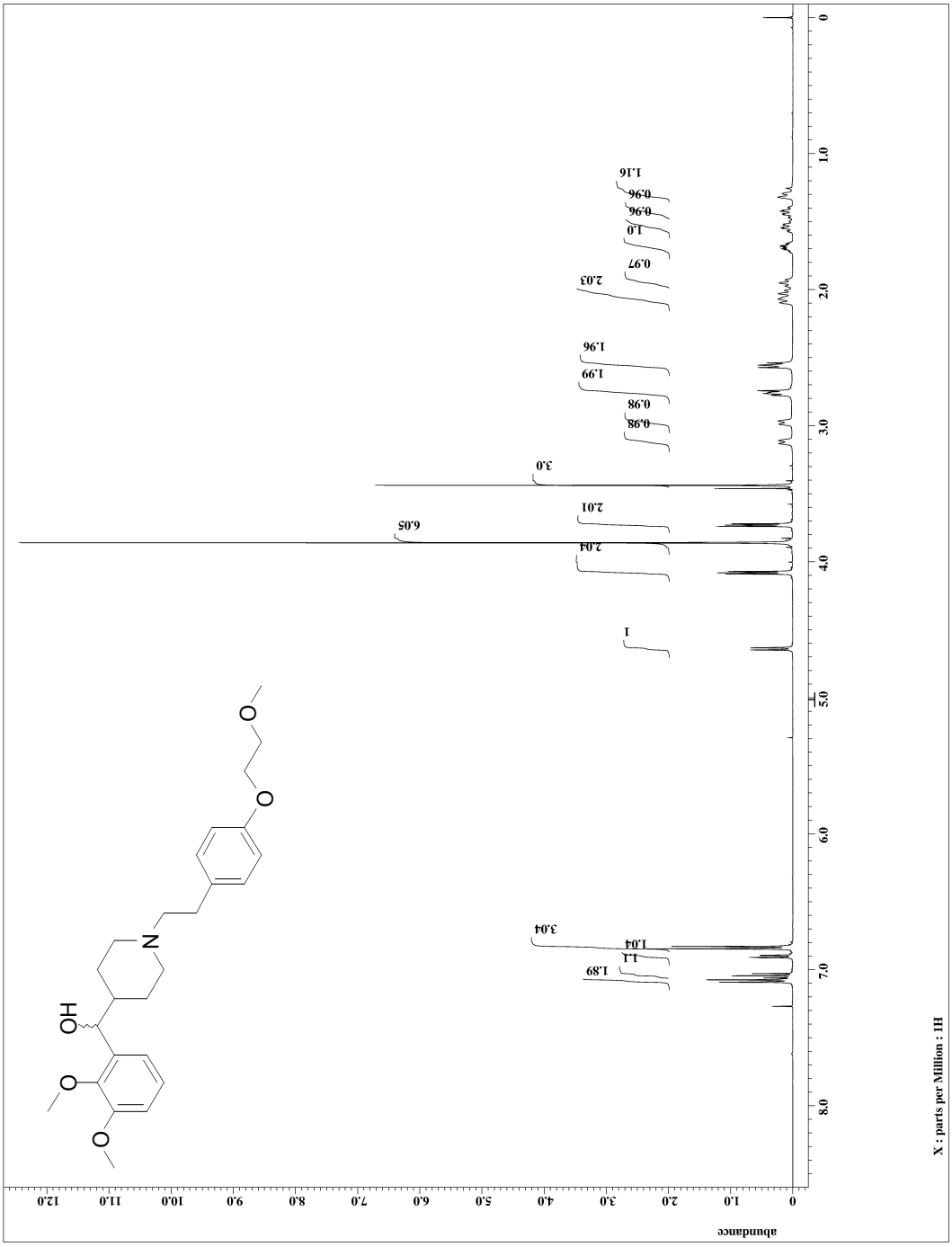
^{13}C-NMR Spectra (400 MHz, $CDCl_3$)

(1-(4-butoxyphenethyl)piperidin-4-yl)(2,3-dimethoxyphenyl)methanol (26)



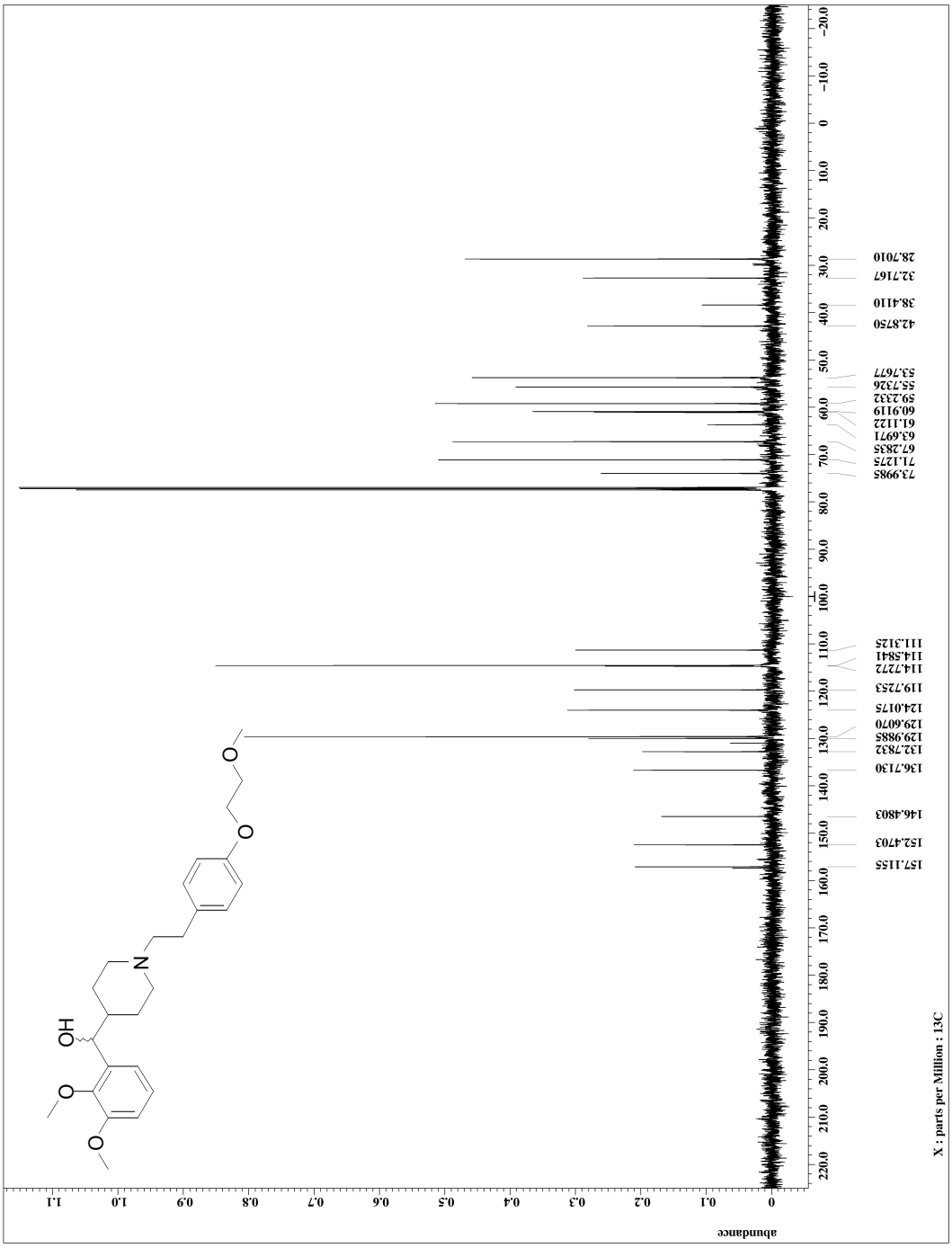
^{1}H-NMR Spectra (500 MHz, $CDCl_3$)

(2,3-dimethoxyphenyl)(1-(4-(2-methoxyethoxy)phenethyl)piperidin-4-yl)methanol (27)



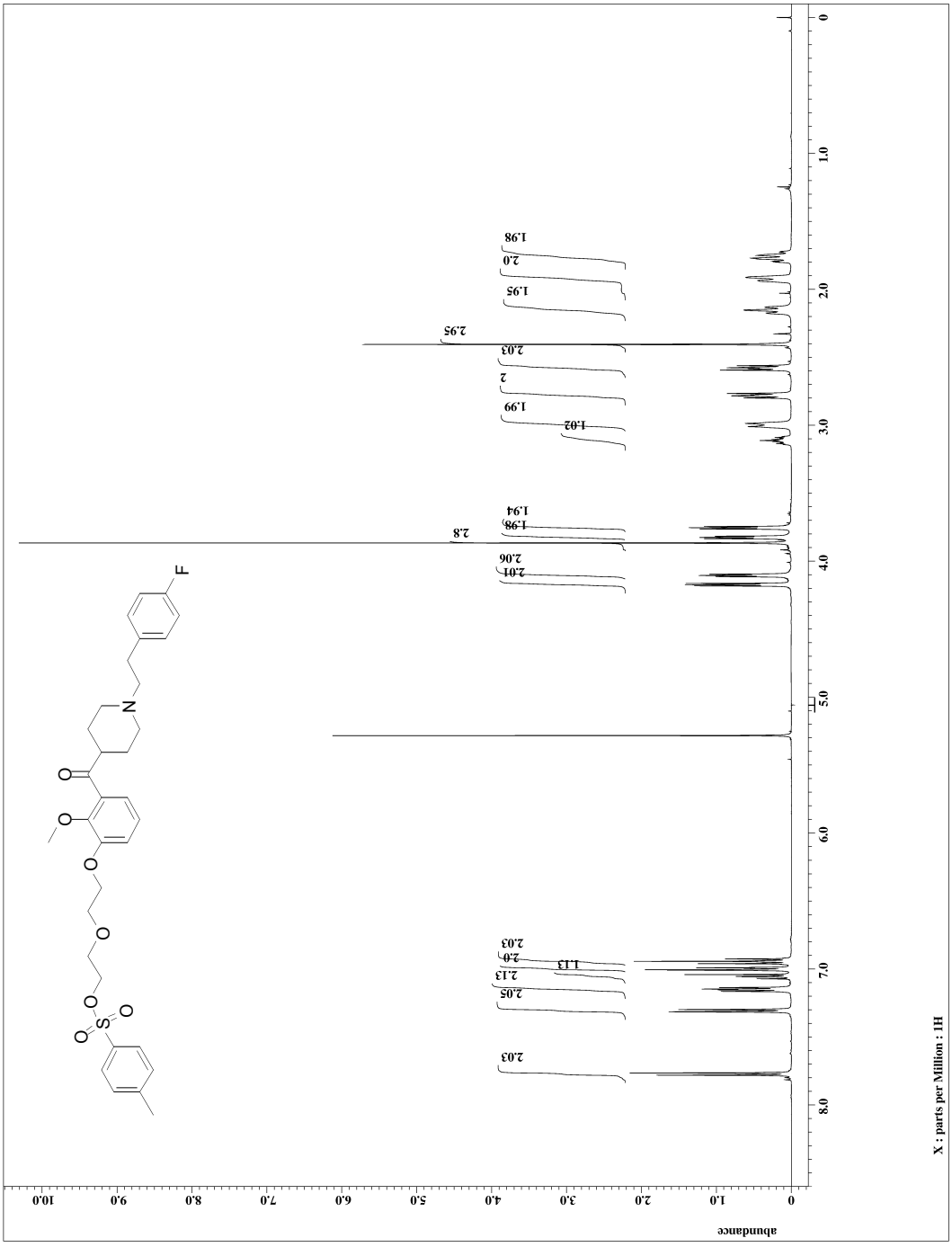
^{1}H-NMR Spectra (500 MHz, $CDCl_3$)

(2,3-dimethoxyphenyl)(1-(4-(2-methoxyethoxy)phenethyl)piperidin-4-yl)methanol (27)

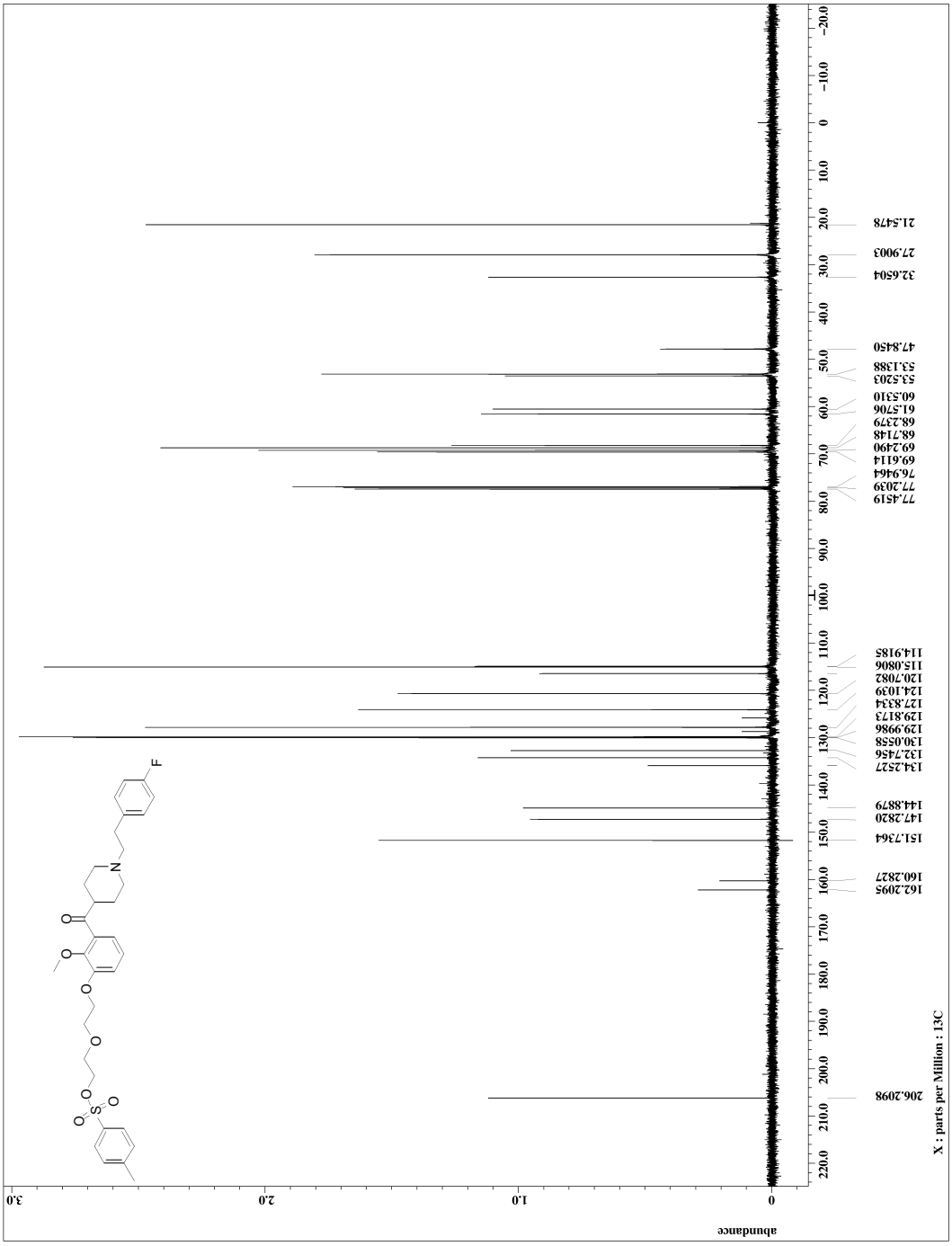


^{1}H-NMR Spectra (500 MHz, $CDCl_3$),

2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethyl 4-methylbenzenesulfonate (28)

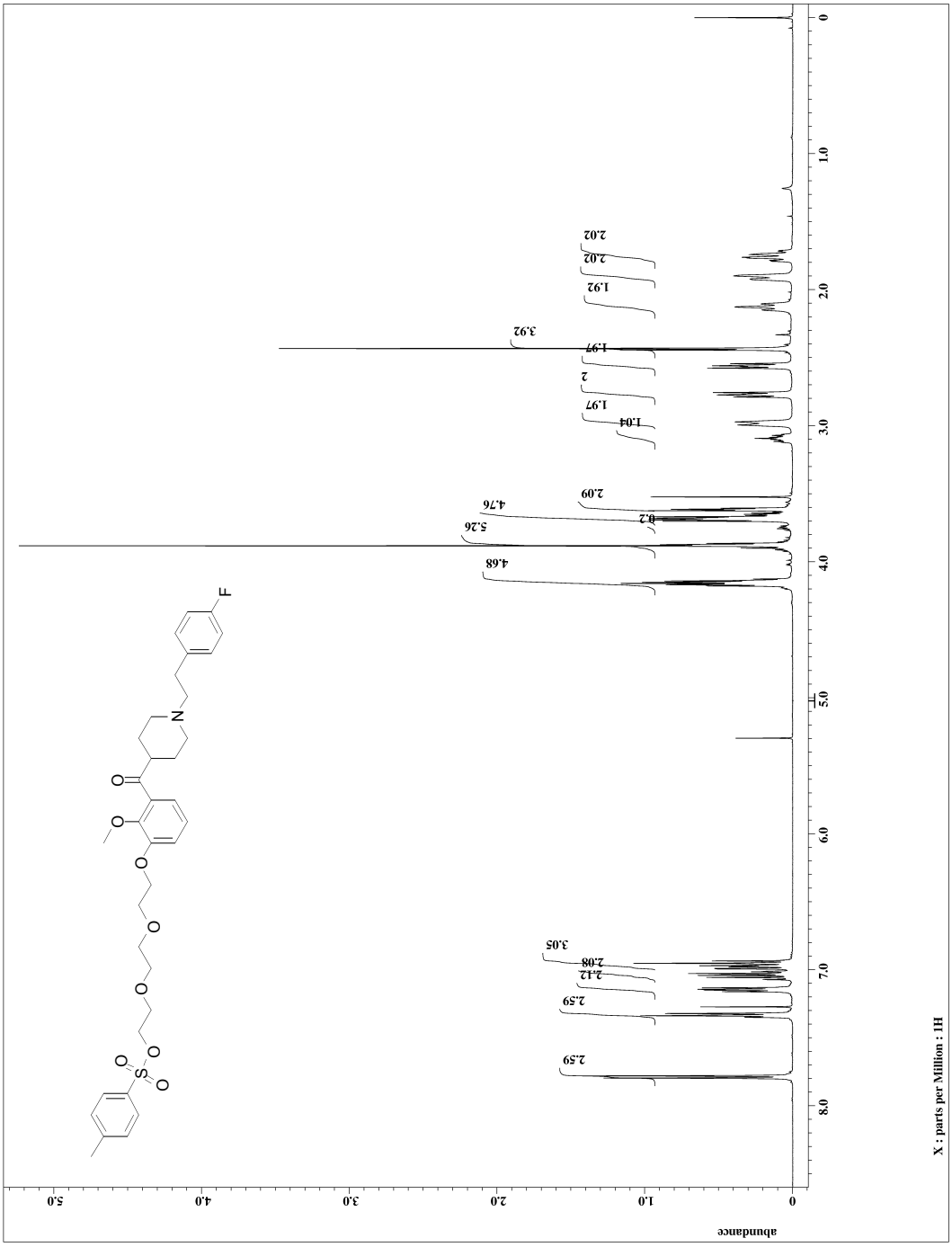


^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethyl 4-methylbenzenesulfonate (28)

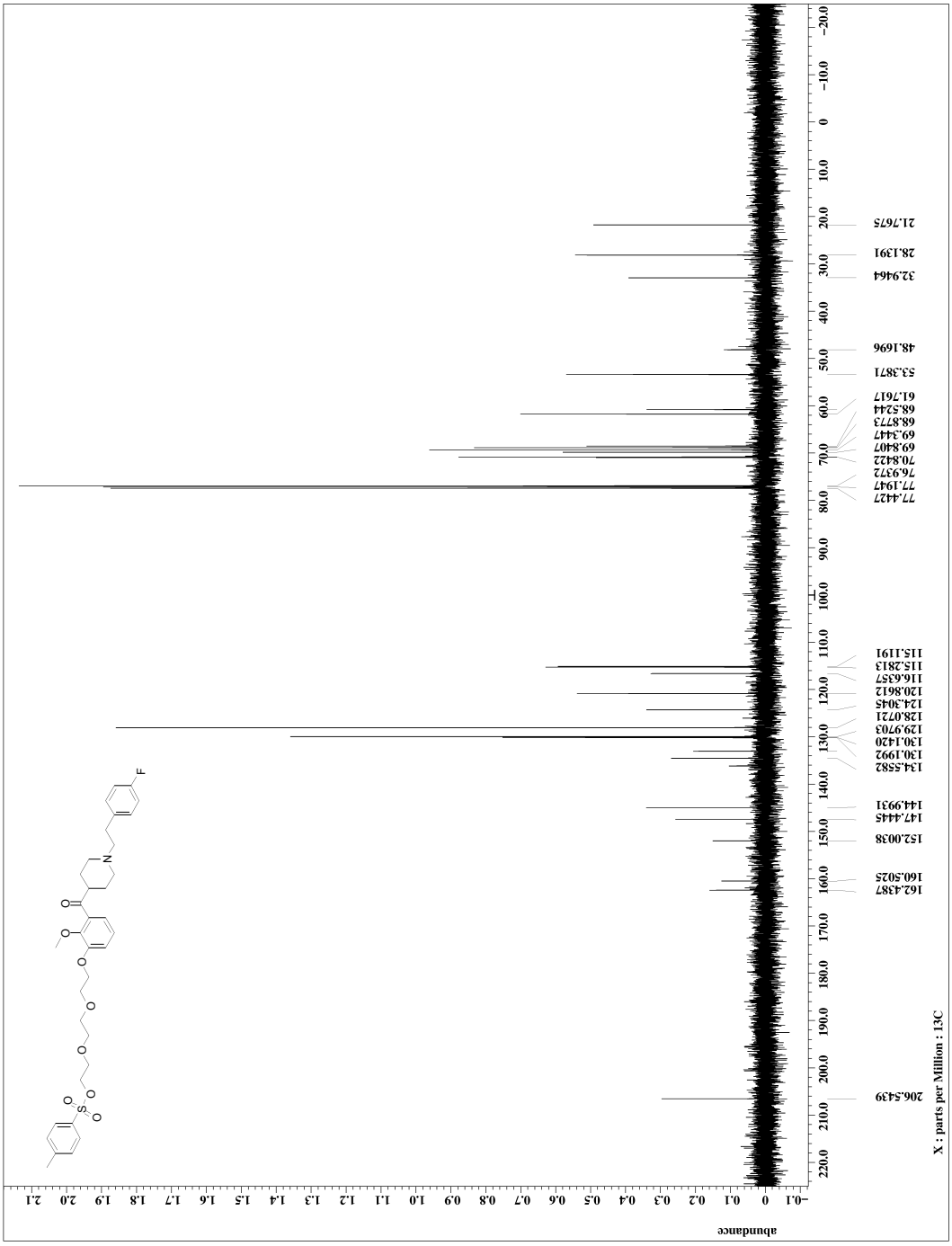


^{1}H-NMR Spectra (500 MHz, $CDCl_3$),

2-(2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (29)

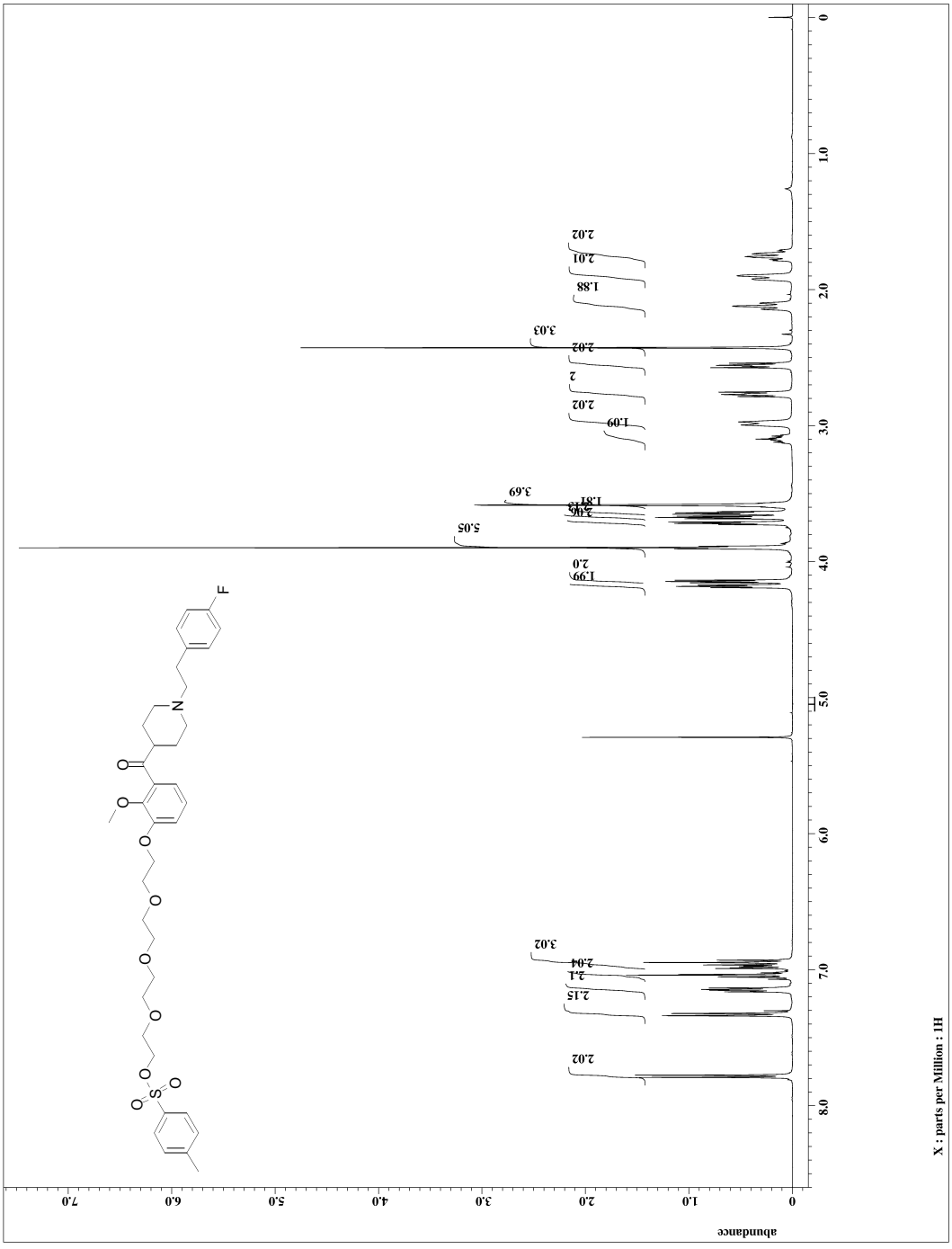


^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
2-(2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (29)

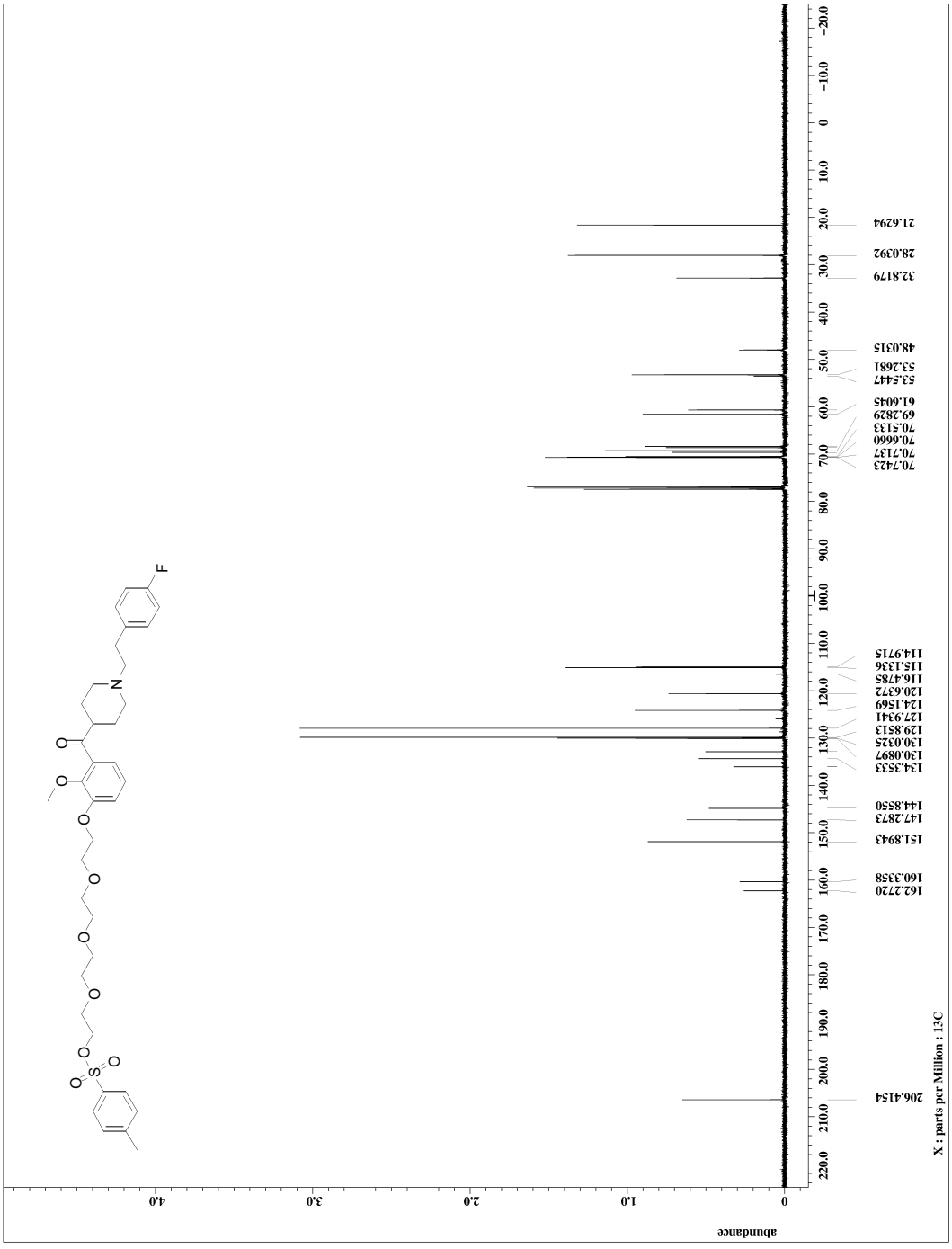


^{1}H-NMR Spectra (500 MHz, $CDCl_3$),

2-(2-(2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (30)

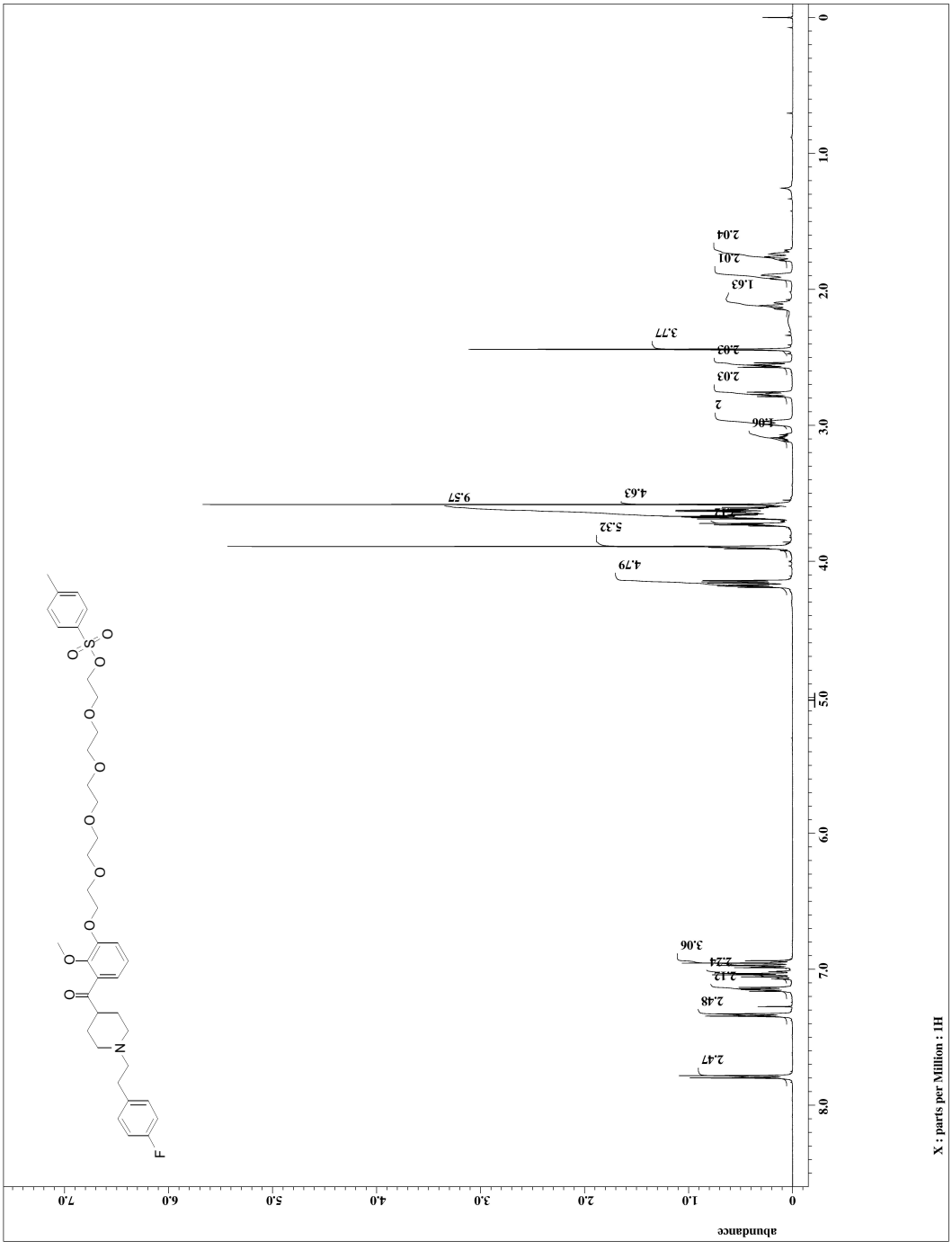


^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
2-(2-(2-(2-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (30)



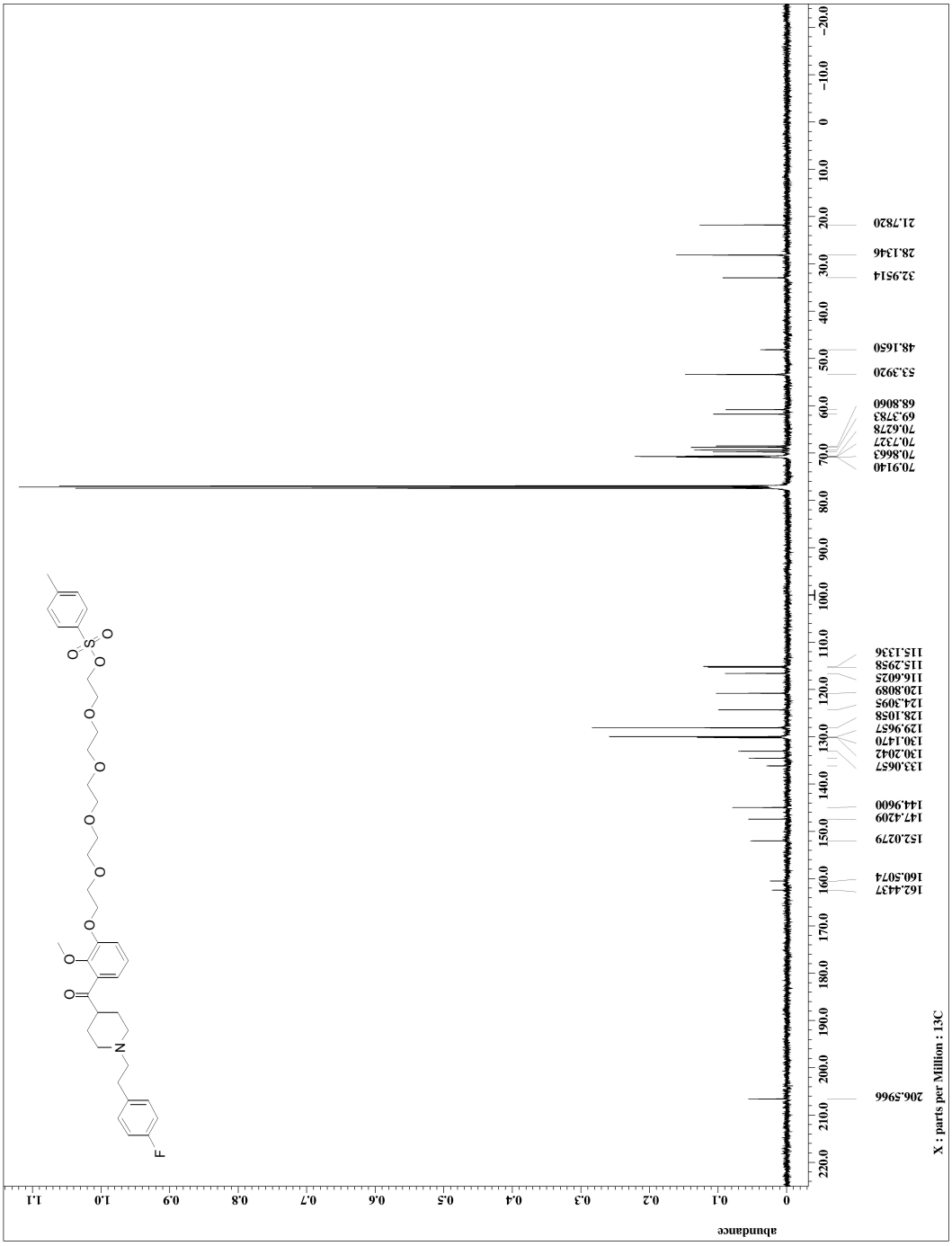
^{1}H-NMR Spectra (500 MHz, $CDCl_3$),

14-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12-tetraoxatetradecyl 4-methylbenzenesulfonate (31)



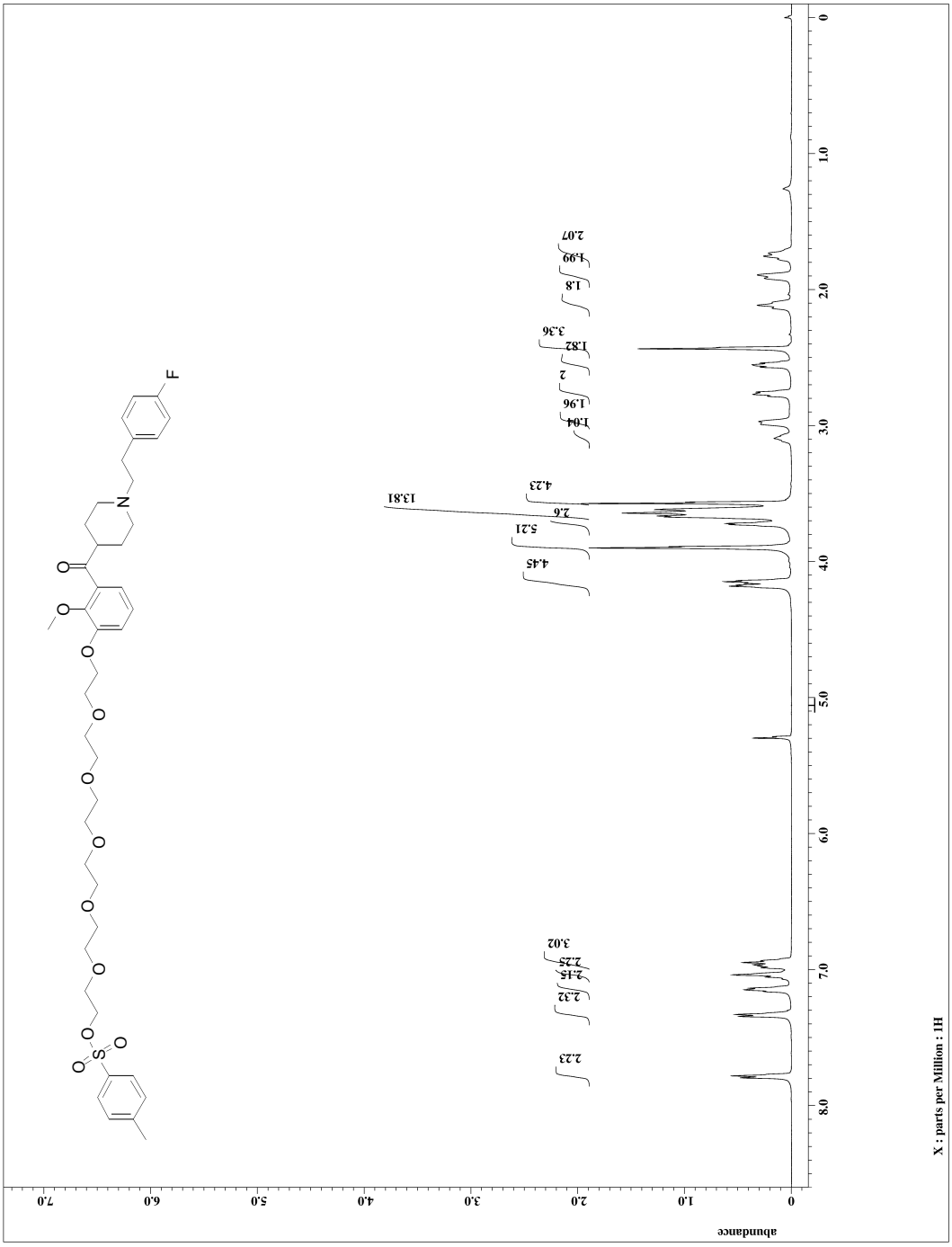
^{13}C-NMR Spectra (500 MHz, $CDCl_3$),

14-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12-tetraoxatetradecyl 4-methylbenzenesulfonate (31)



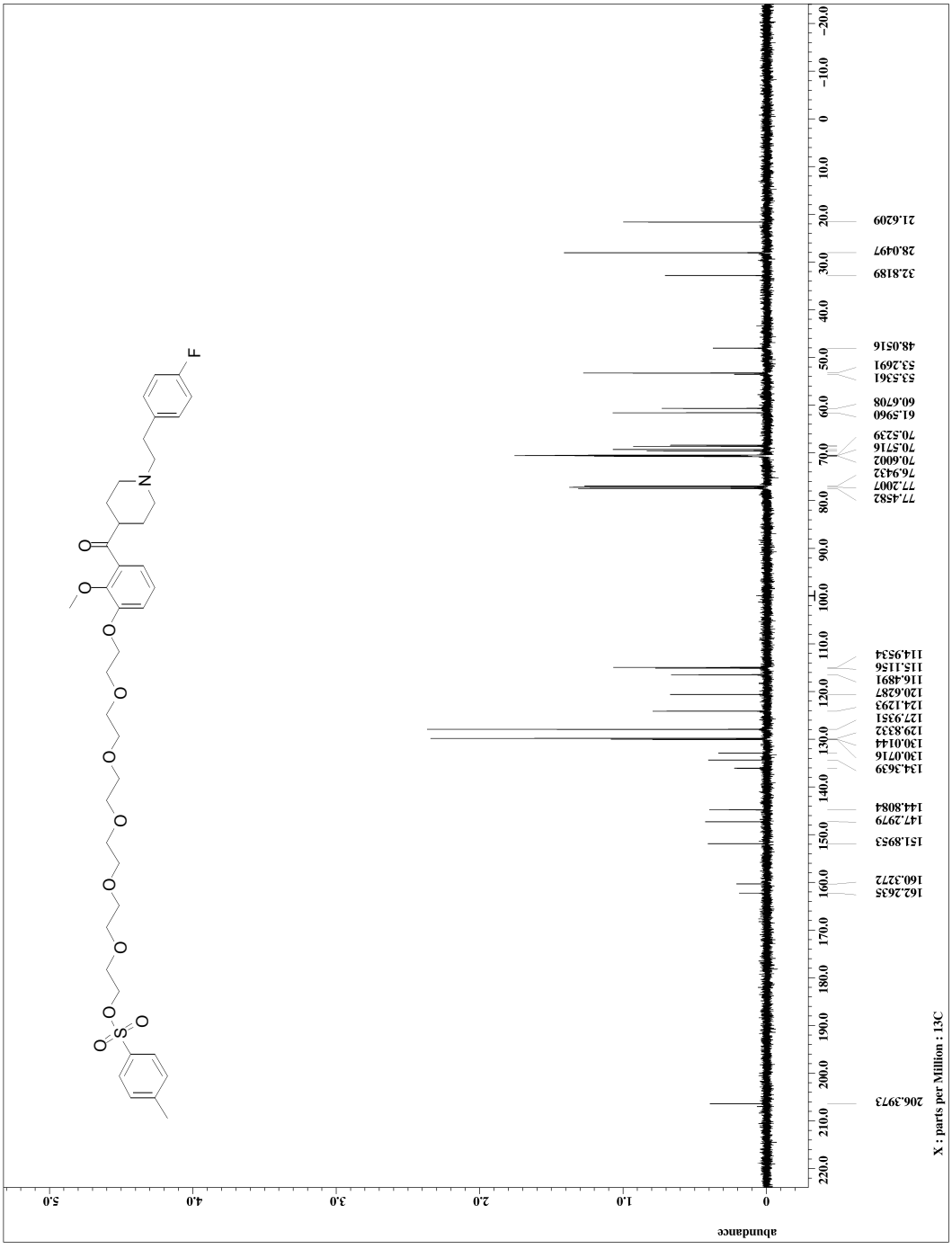
^{1}H-NMR Spectra (500 MHz, $CDCl_3$),

17-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15-pentaoxaheptadecyl 4-methylbenzenesulfonate (32)



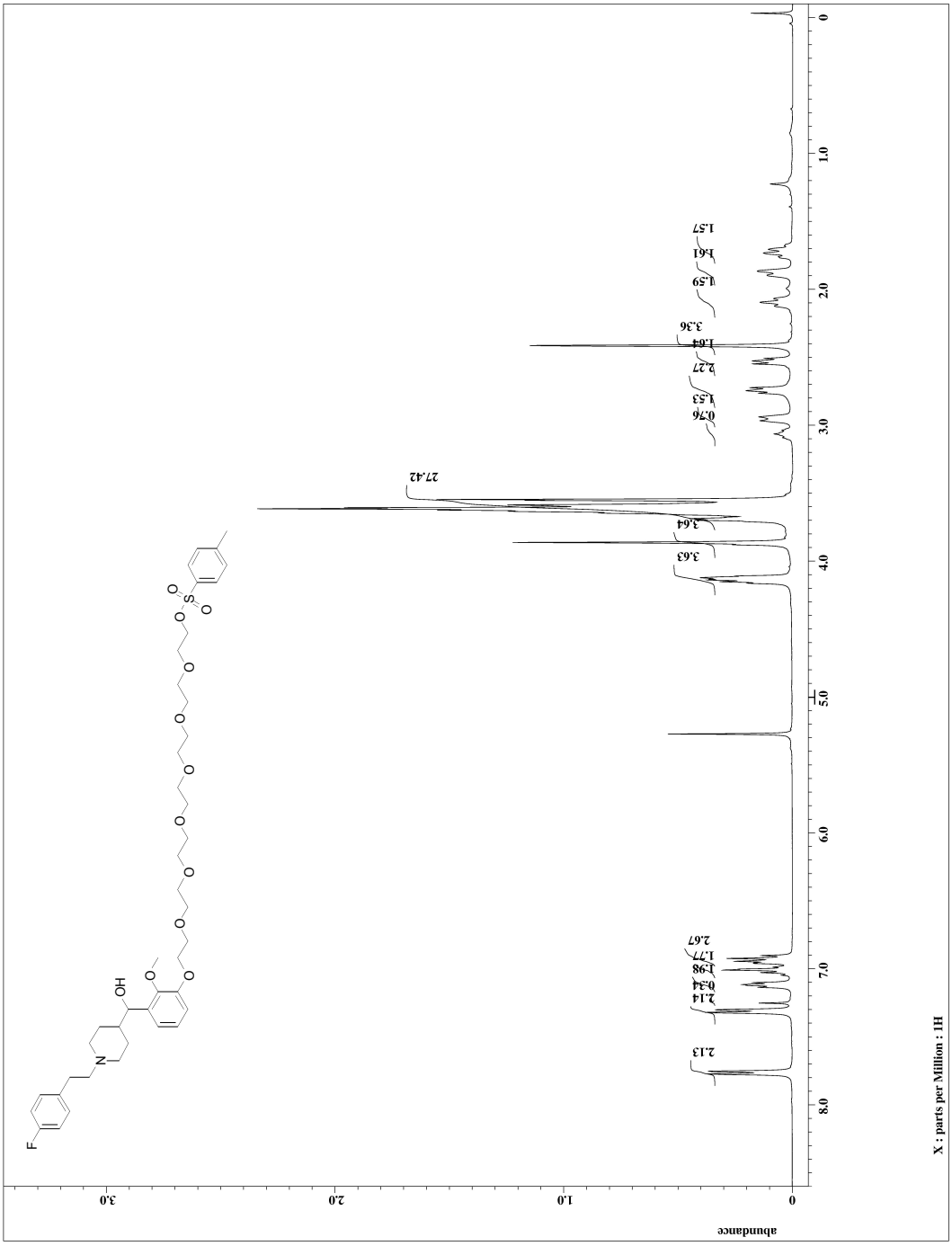
^{13}C-NMR Spectra (500 MHz, $CDCl_3$),

17-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15-pentaoxaheptadecyl 4-methylbenzenesulfonate (32)

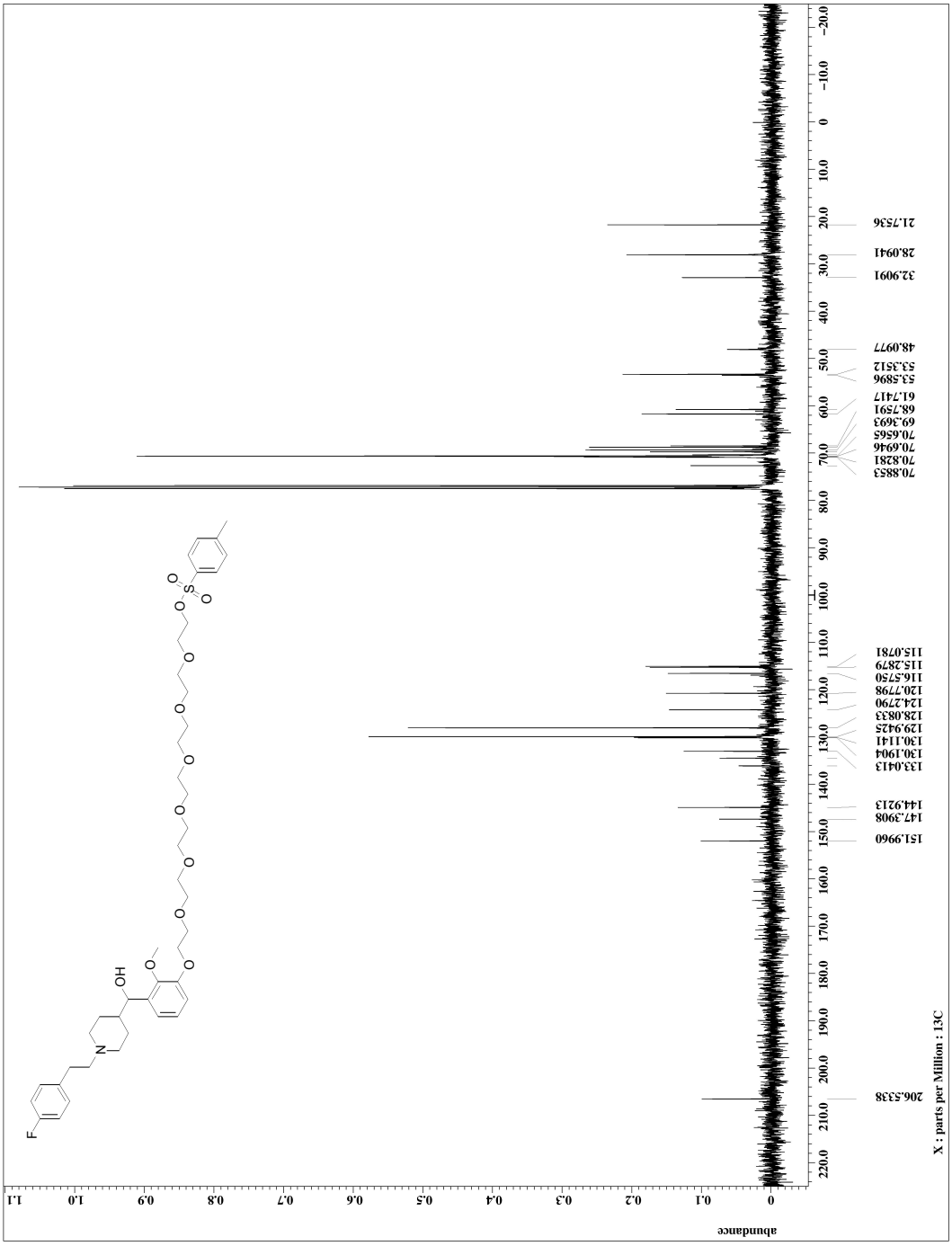


^{1}H-NMR Spectra (400 MHz, $CDCl_3$),

20-(3-((1-(4-fluorophenethyl)piperidin-4-yl)(hydroxy)methyl)-2-methoxyphenoxy)-3,6,9,12,15,18-hexaoxaicosyl 4-methylbenzenesulfonate (33)

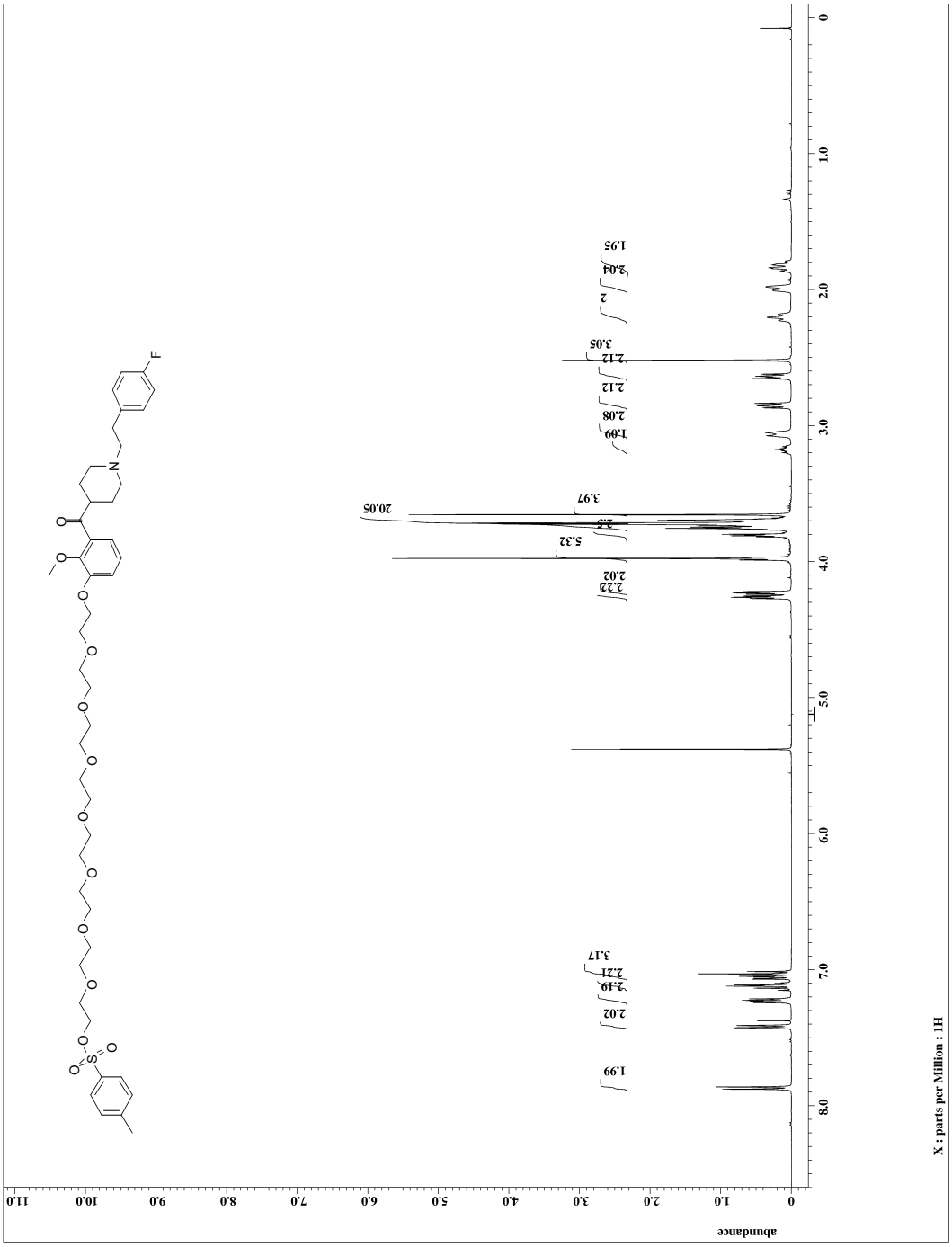


^{13}C-NMR Spectra (400 MHz, $CDCl_3$),
20-(3-((1-(4-fluorophenethyl)piperidin-4-yl)(hydroxy)methyl)-2-methoxyphenoxy)-3,6,9,12,15,18-hexaoxaicosyl 4-methylbenzenesulfonate
(33)



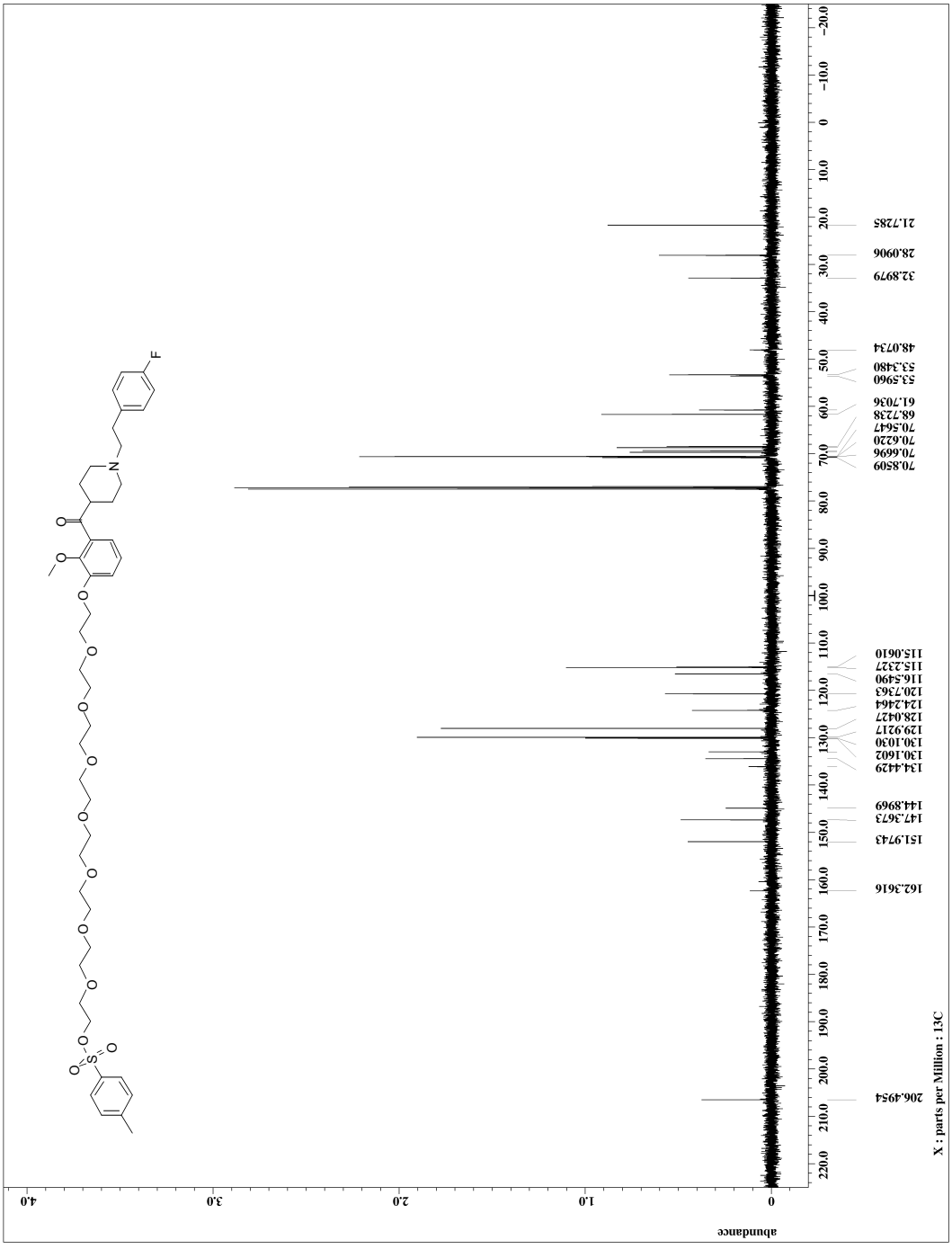
^{1}H-NMR Spectra (500 MHz, $CDCl_3$),

23-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15,18,21-heptaoxatricosyl 4-methylbenzenesulfonate (34)



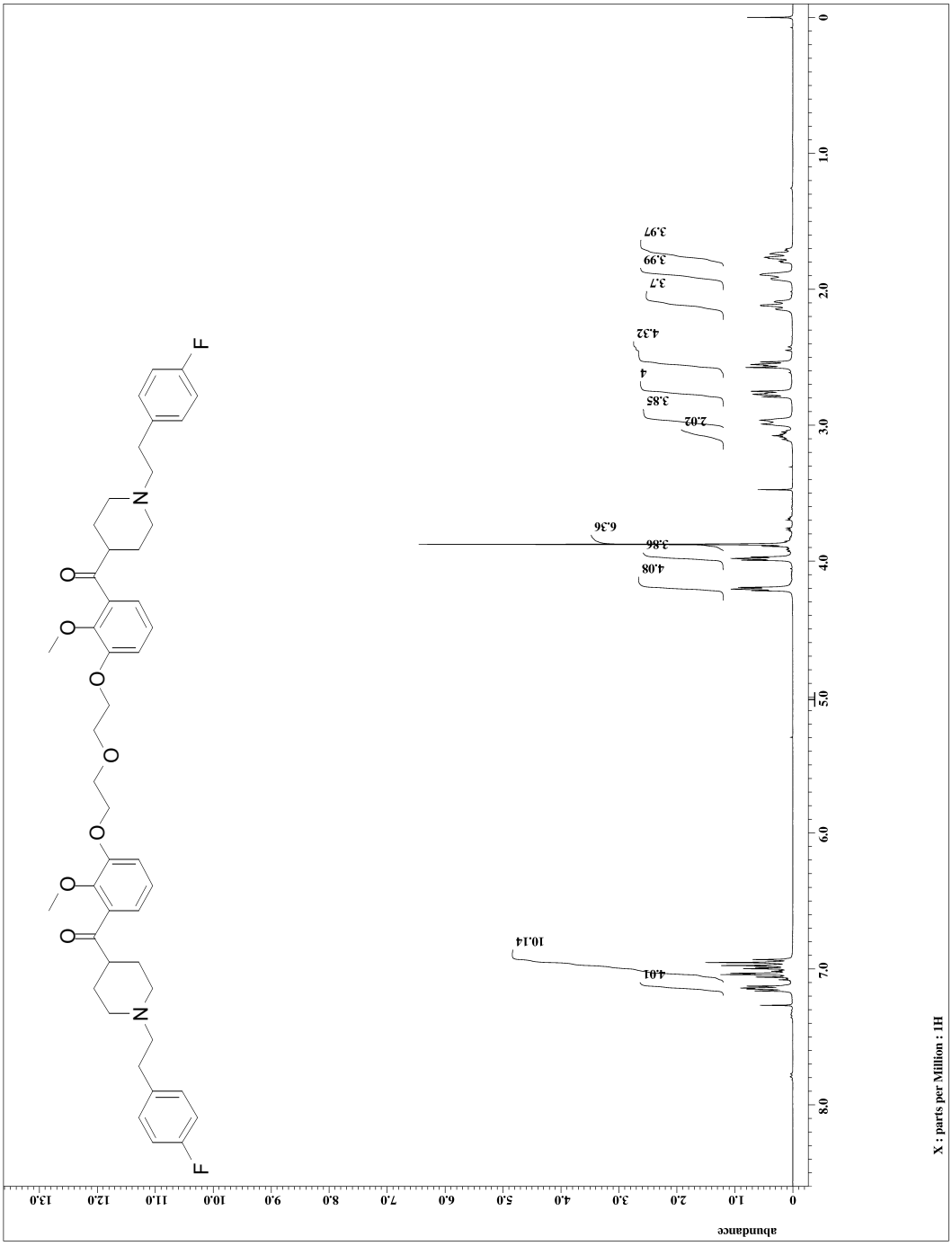
^{13}C-NMR Spectra (500 MHz, $CDCl_3$),

23-(3-(1-(4-fluorophenethyl)piperidine-4-carbonyl)-2-methoxyphenoxy)-3,6,9,12,15,18,21-heptaoxatricosyl 4-methylbenzenesulfonate (34)

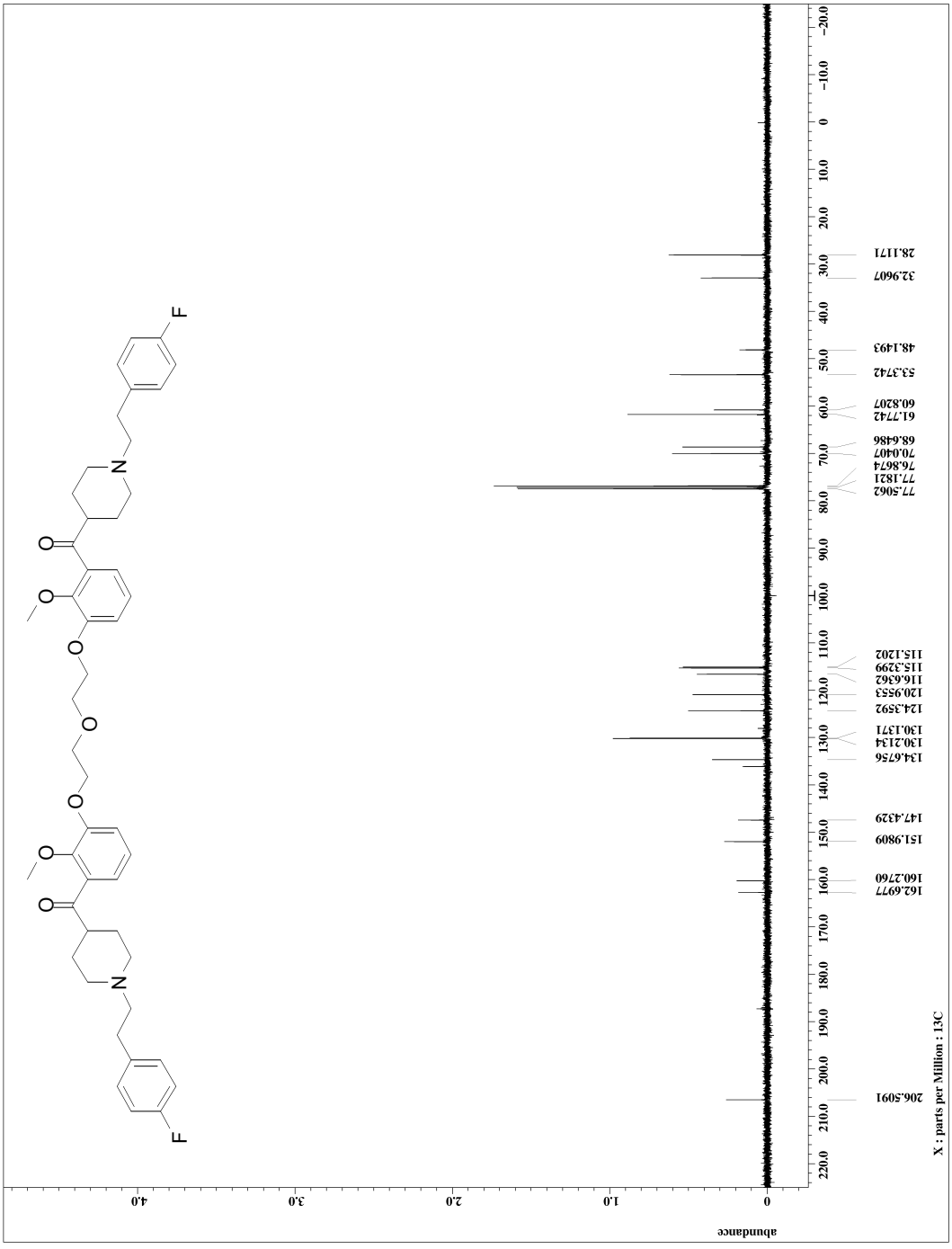


^{1}H-NMR Spectra (400 MHz, $CDCl_3$),

(3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (35)

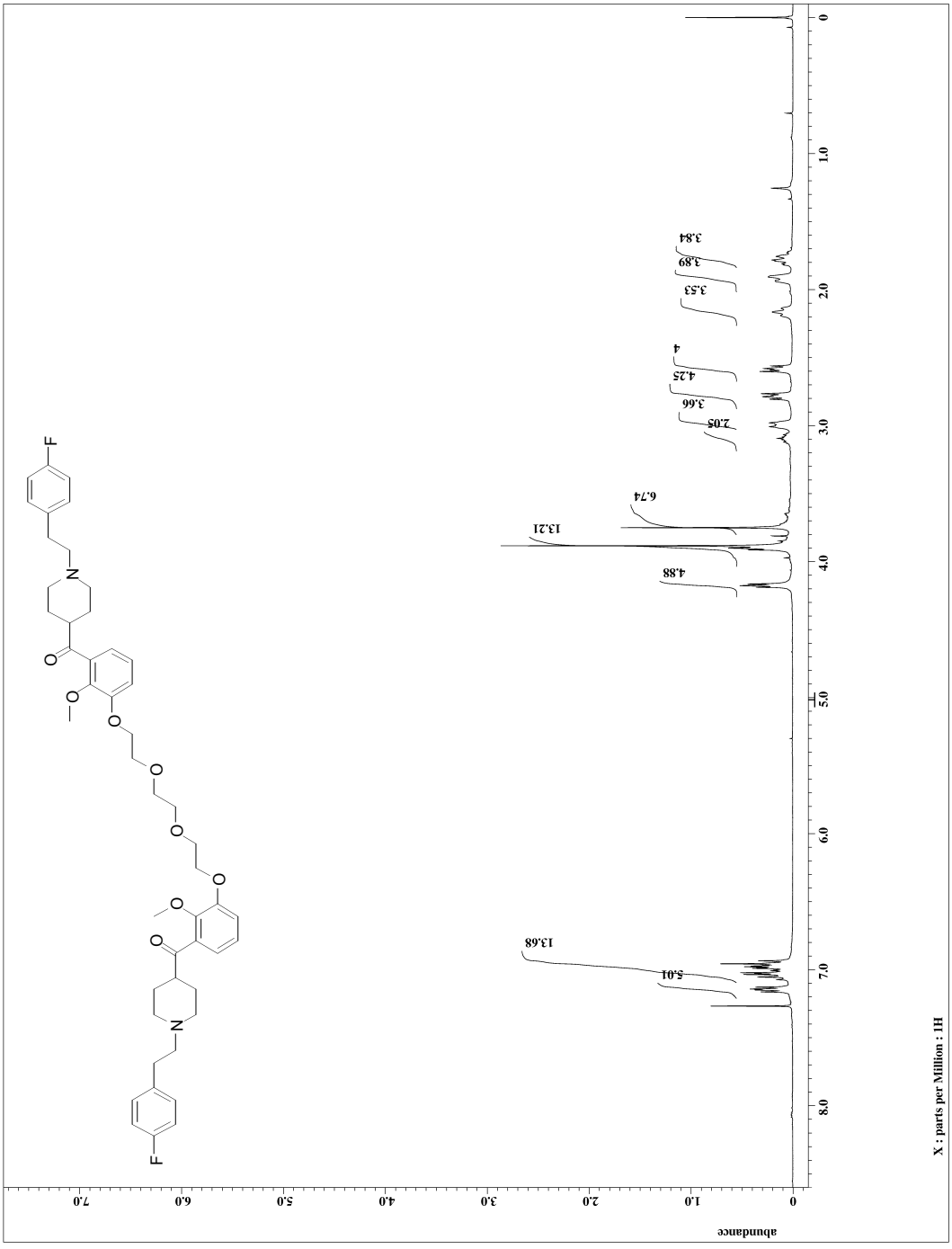


^{13}C-NMR Spectra (400 MHz, $CDCl_3$),
(3,3'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (35)

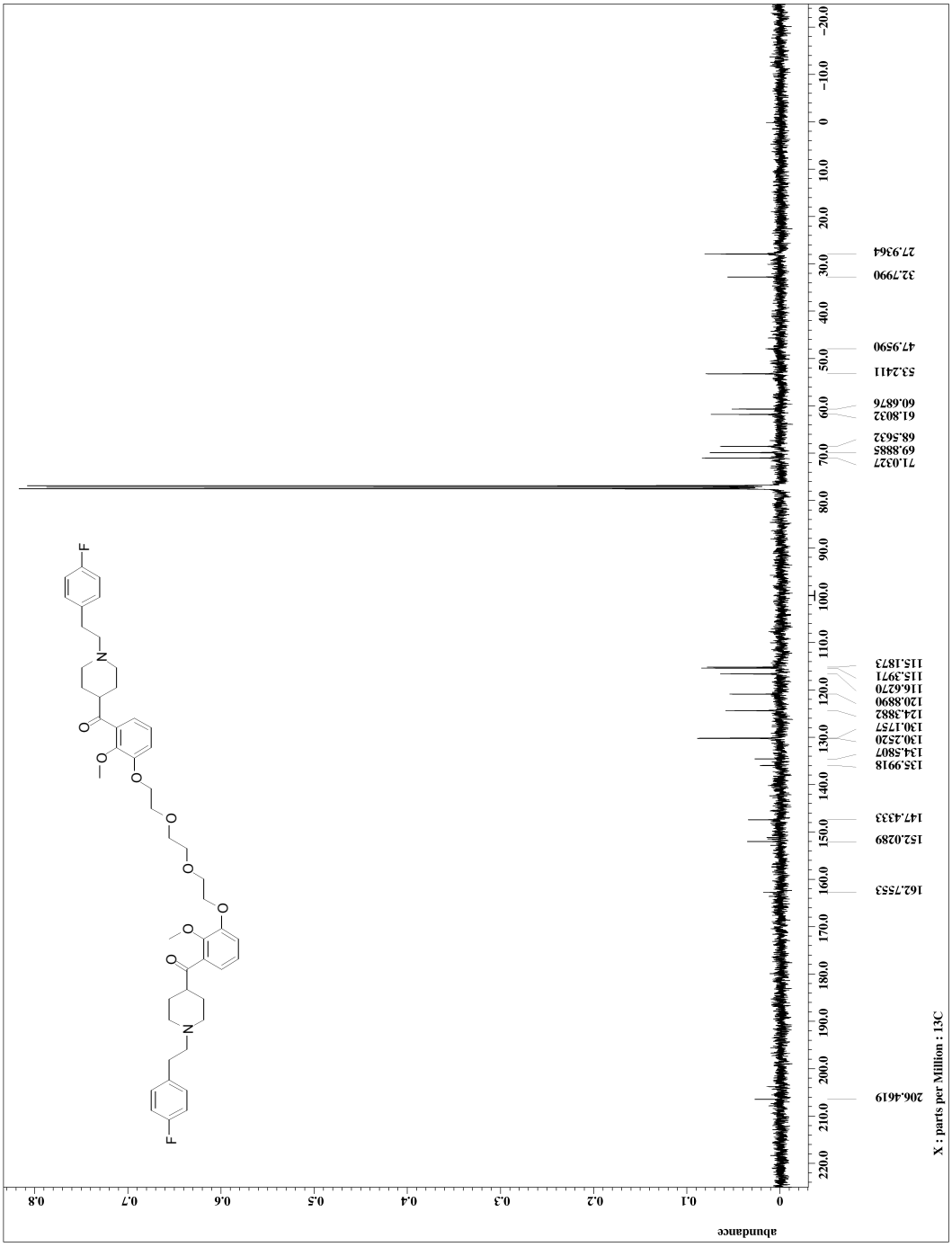


^{1}H-NMR Spectra (400 MHz, $CDCl_3$),

(3,3'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy)bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (36)

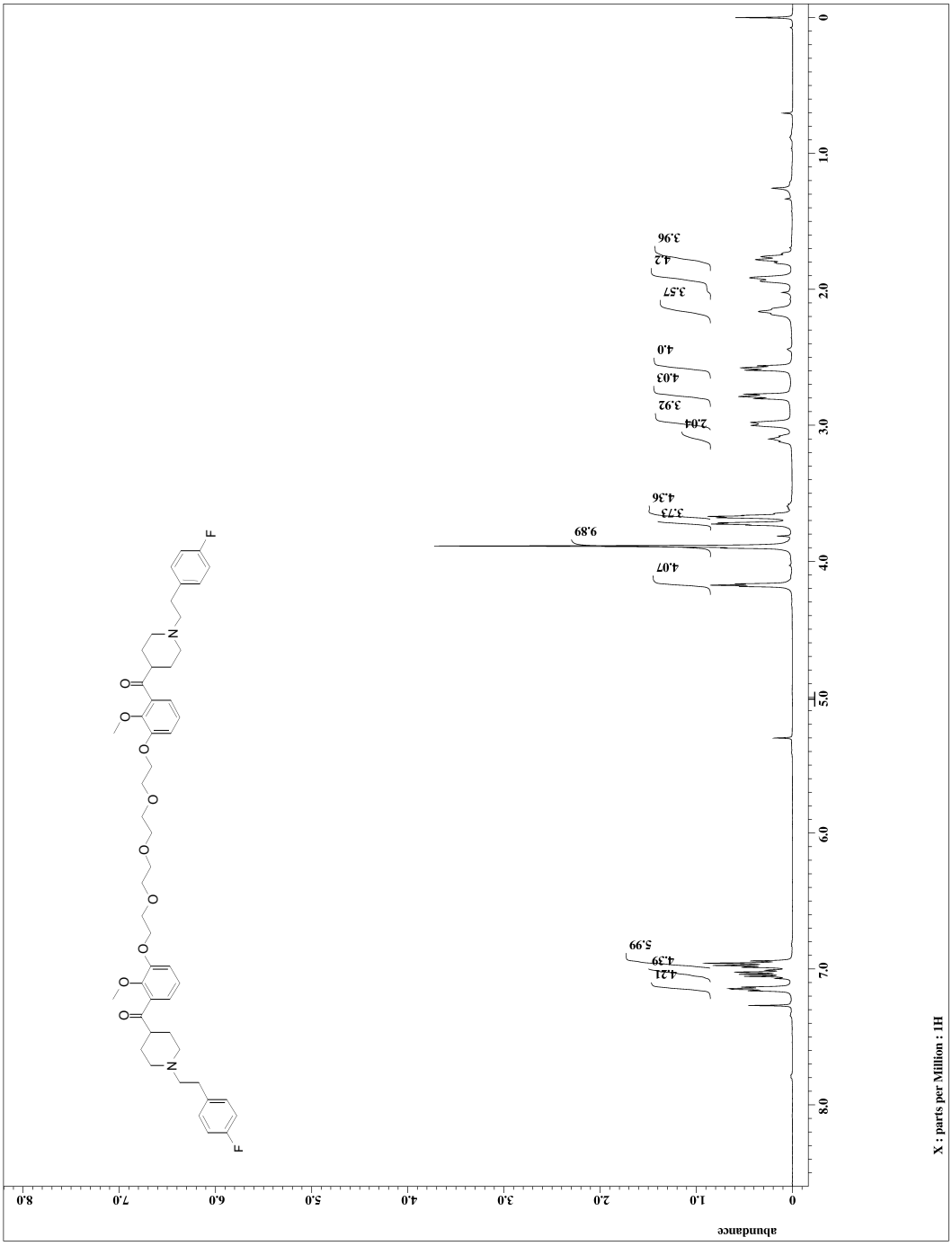


^{13}C-NMR Spectra (400 MHz, $CDCl_3$),
(3,3'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy)bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (36)

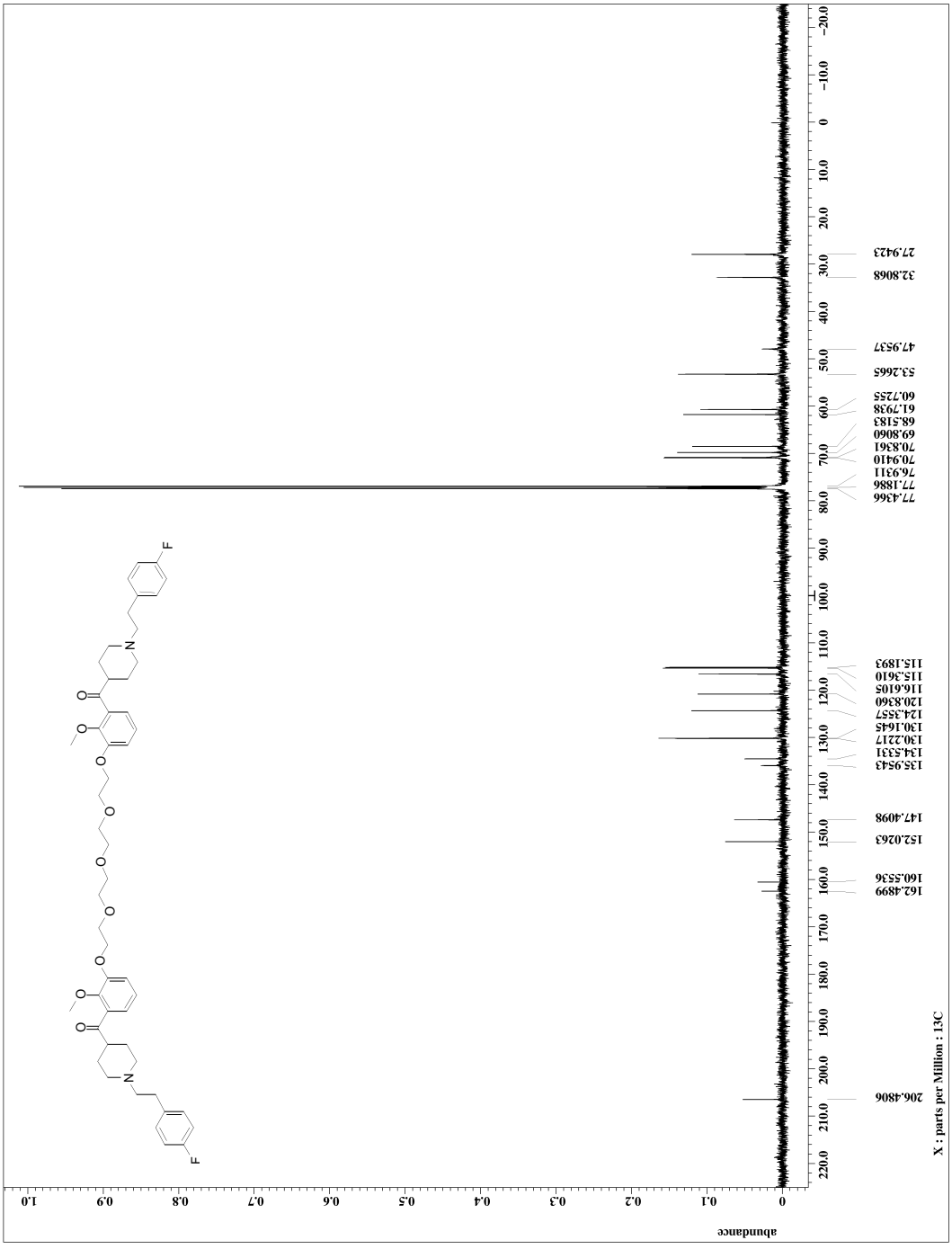


^{1}H-NMR Spectra (500 MHz, $CDCl_3$),

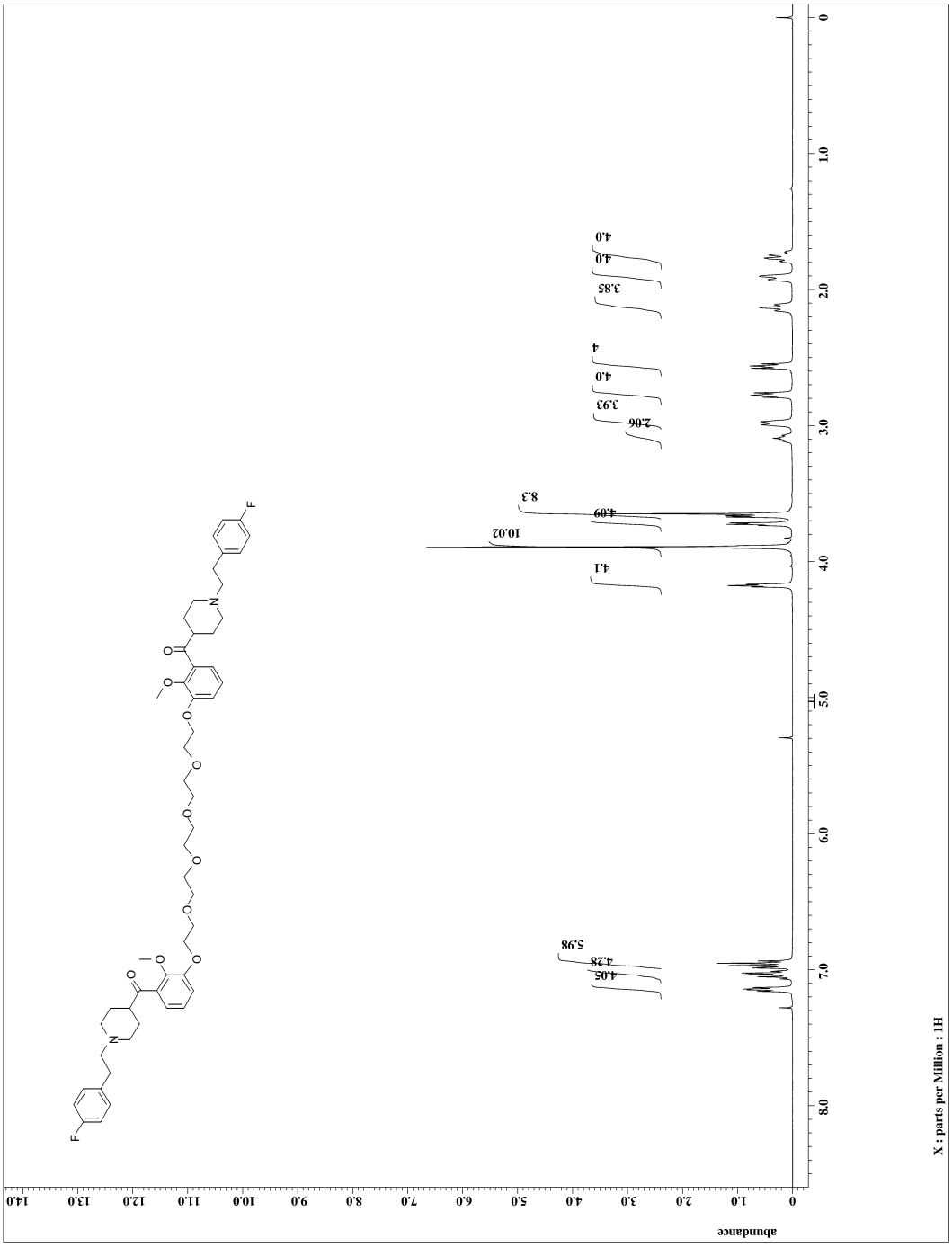
(3,3'-(2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(ethane-2,1-diyl))bis(oxy)bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (37)



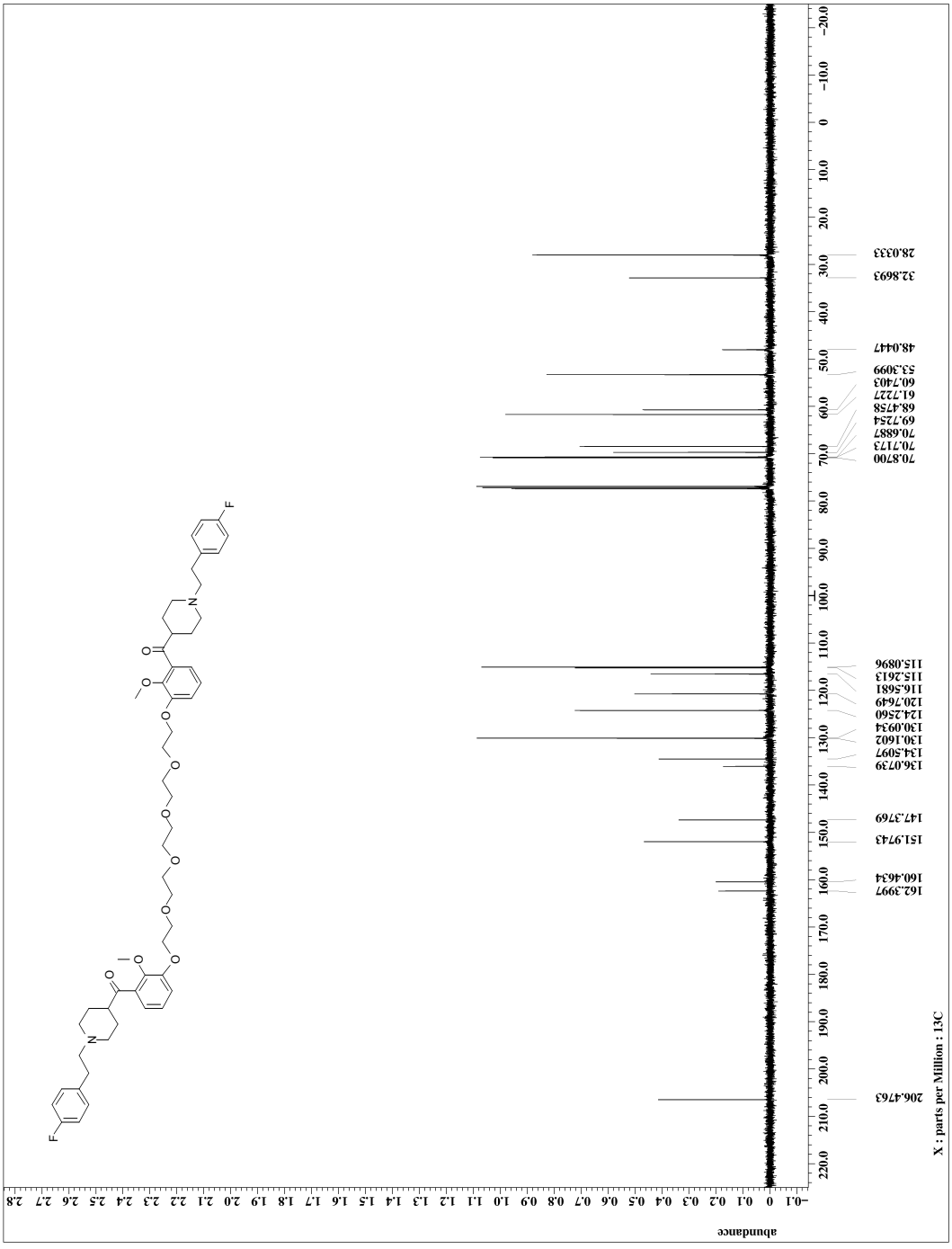
^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
(3,3'-(3,6,9,12-tetraoxatetradecane-1,14-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (37)



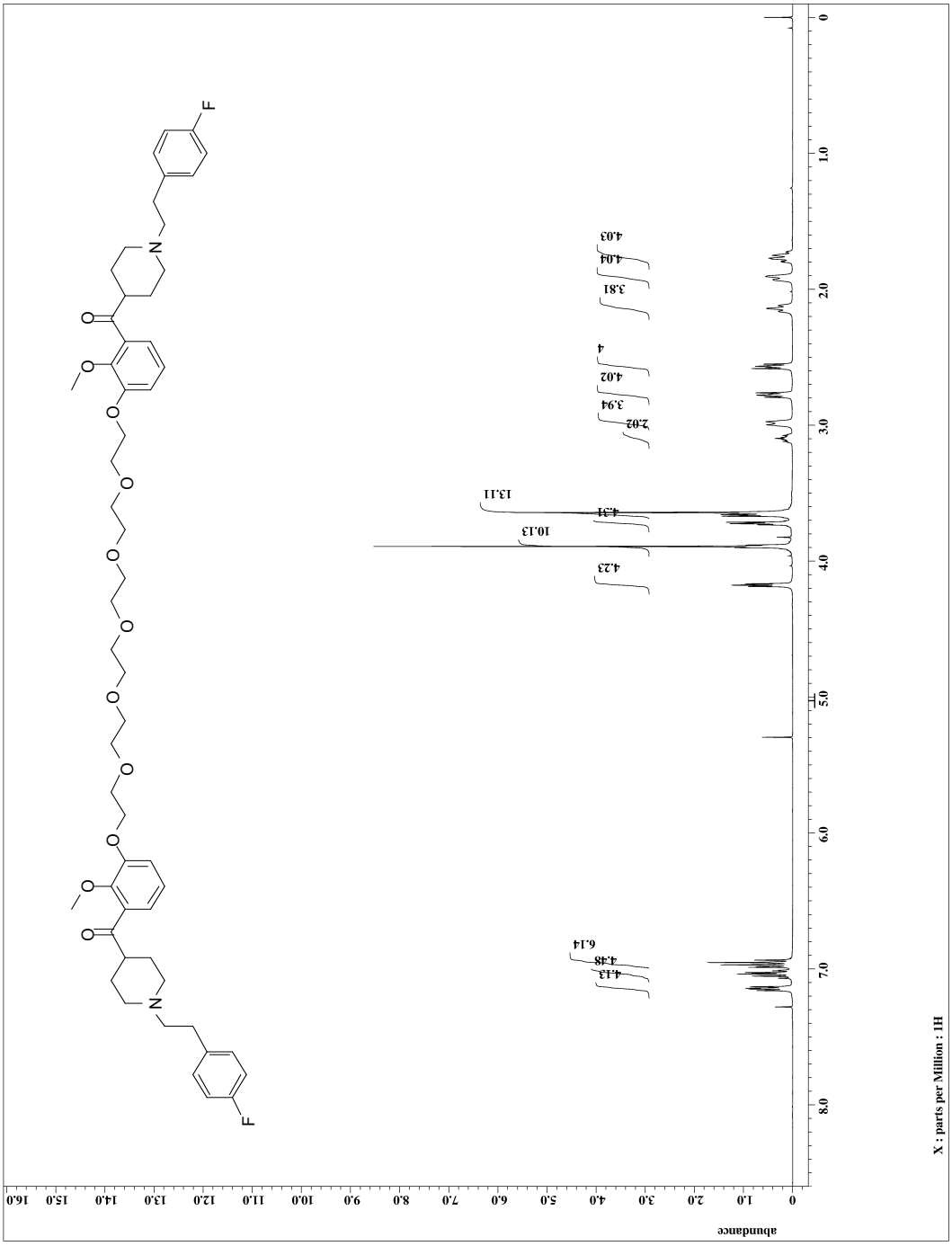
^{1}H-NMR Spectra (500 MHz, $CDCl_3$),
(3,3'-(3,6,9,12-tetraoxatetradecane-1,14-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (38)



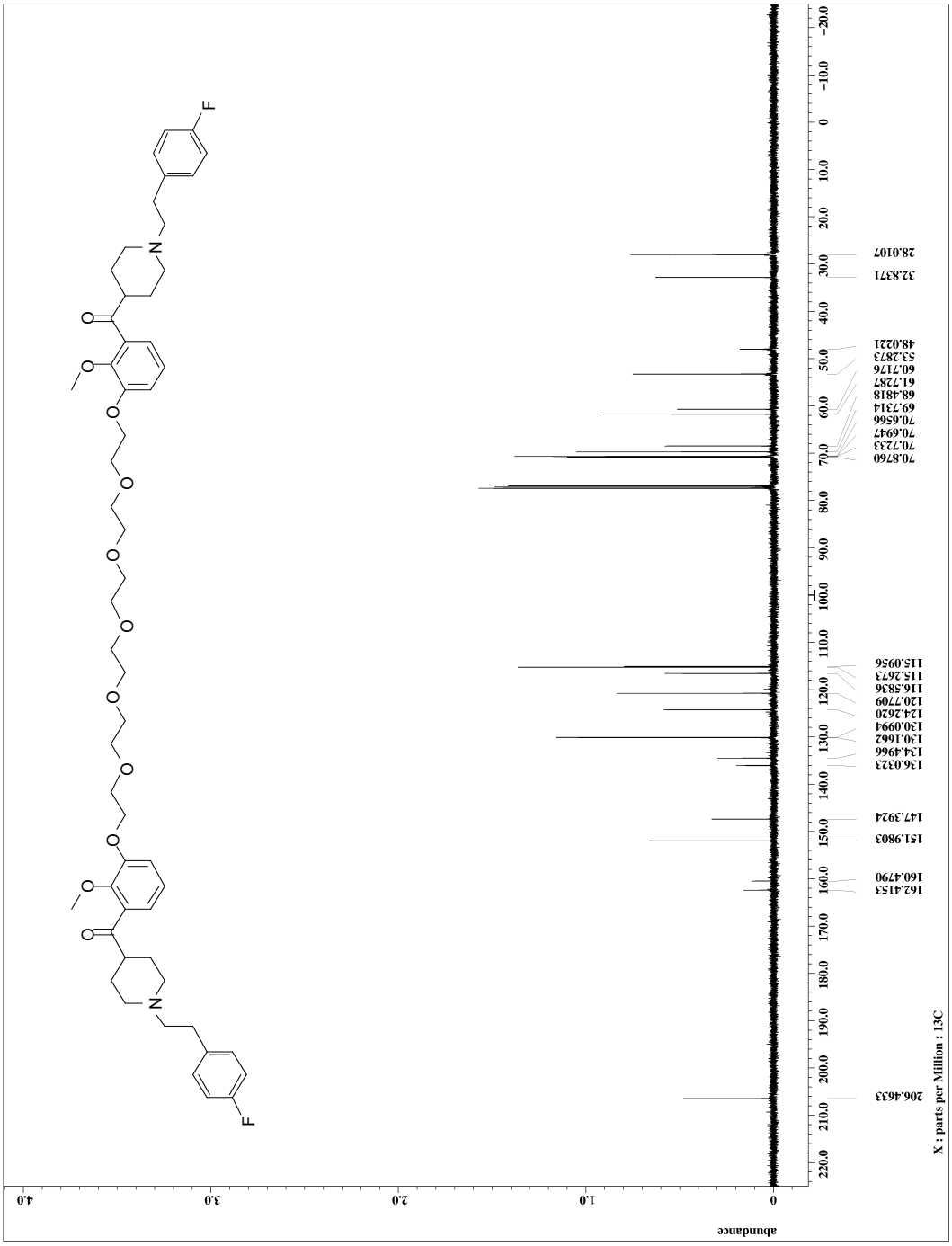
^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
(3,3'-(3,6,9,12-tetraoxatetradecane-1,14-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (38)



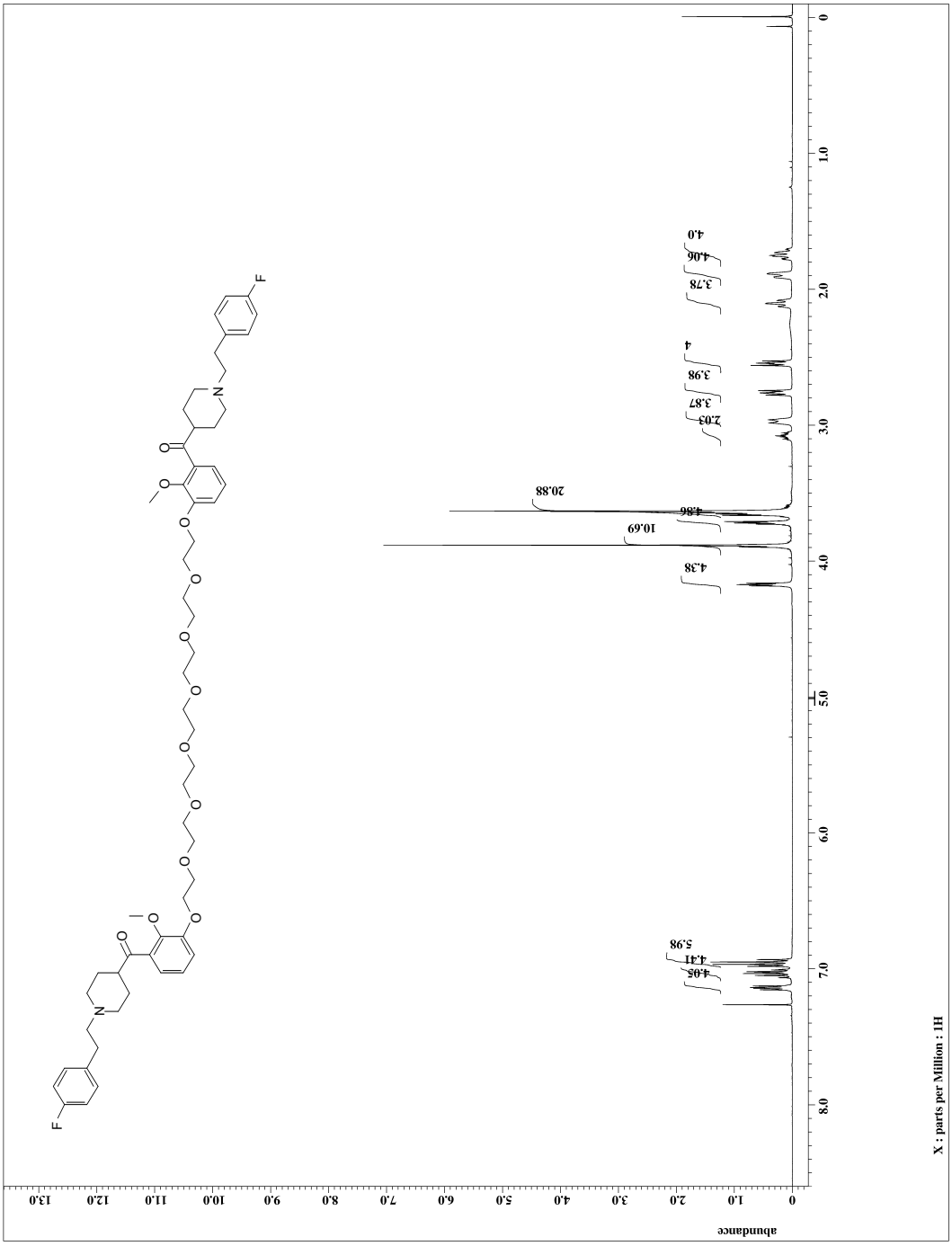
^{1}H-NMR Spectra (500 MHz, $CDCl_3$),
(3,3'-(3,6,9,12,15-pentaoxaheptadecane-1,17-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (39)



^{13}C-NMR Spectra (500 MHz, $CDCl_3$),
(3,3'-(3,6,9,12,15-pentaoxaheptadecane-1,17-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (39)

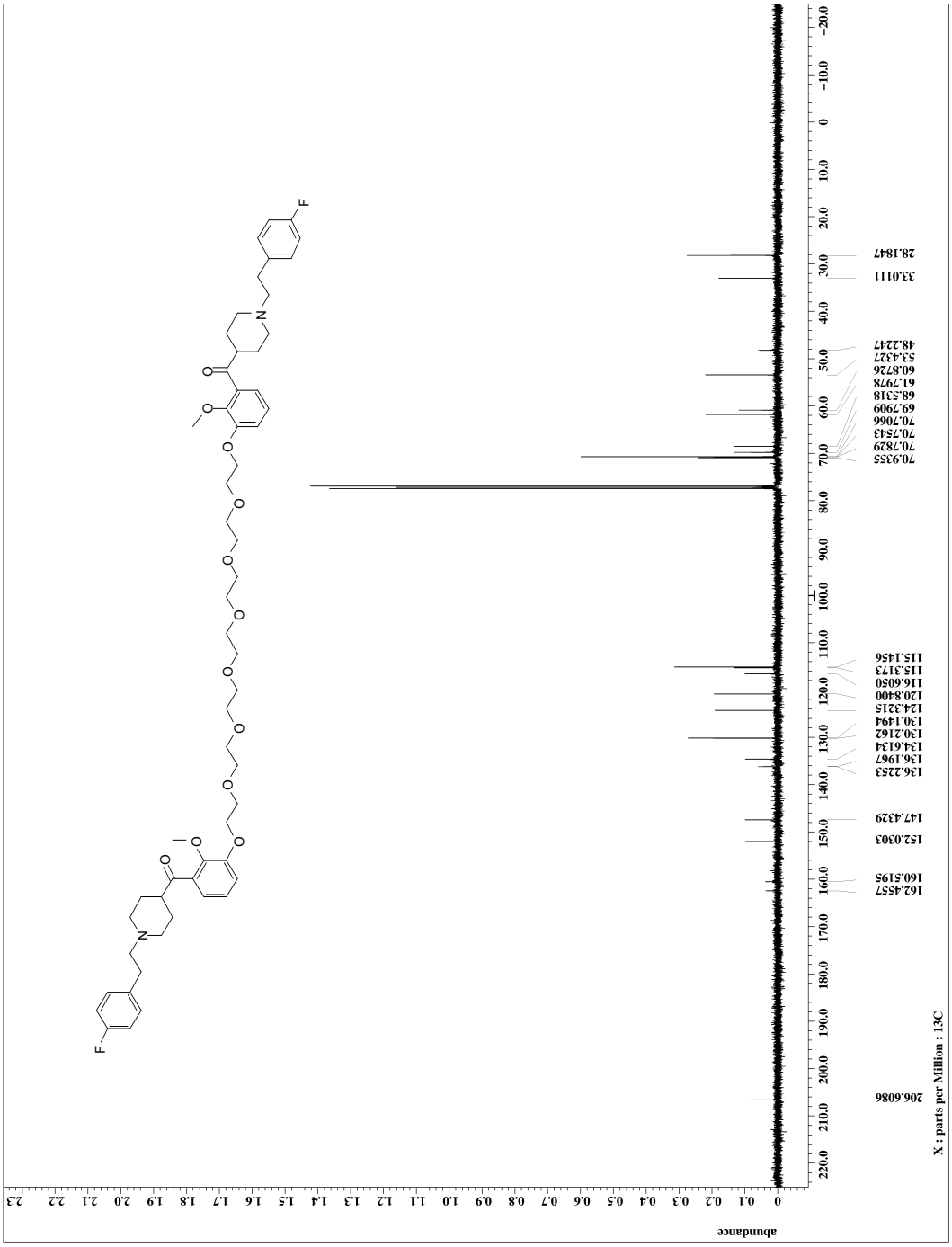


^{1}H-NMR Spectra (500 MHz, $CDCl_3$),
(3,3'-(3,6,9,12,15,18-hexaoxaicosane-1,20-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (40)



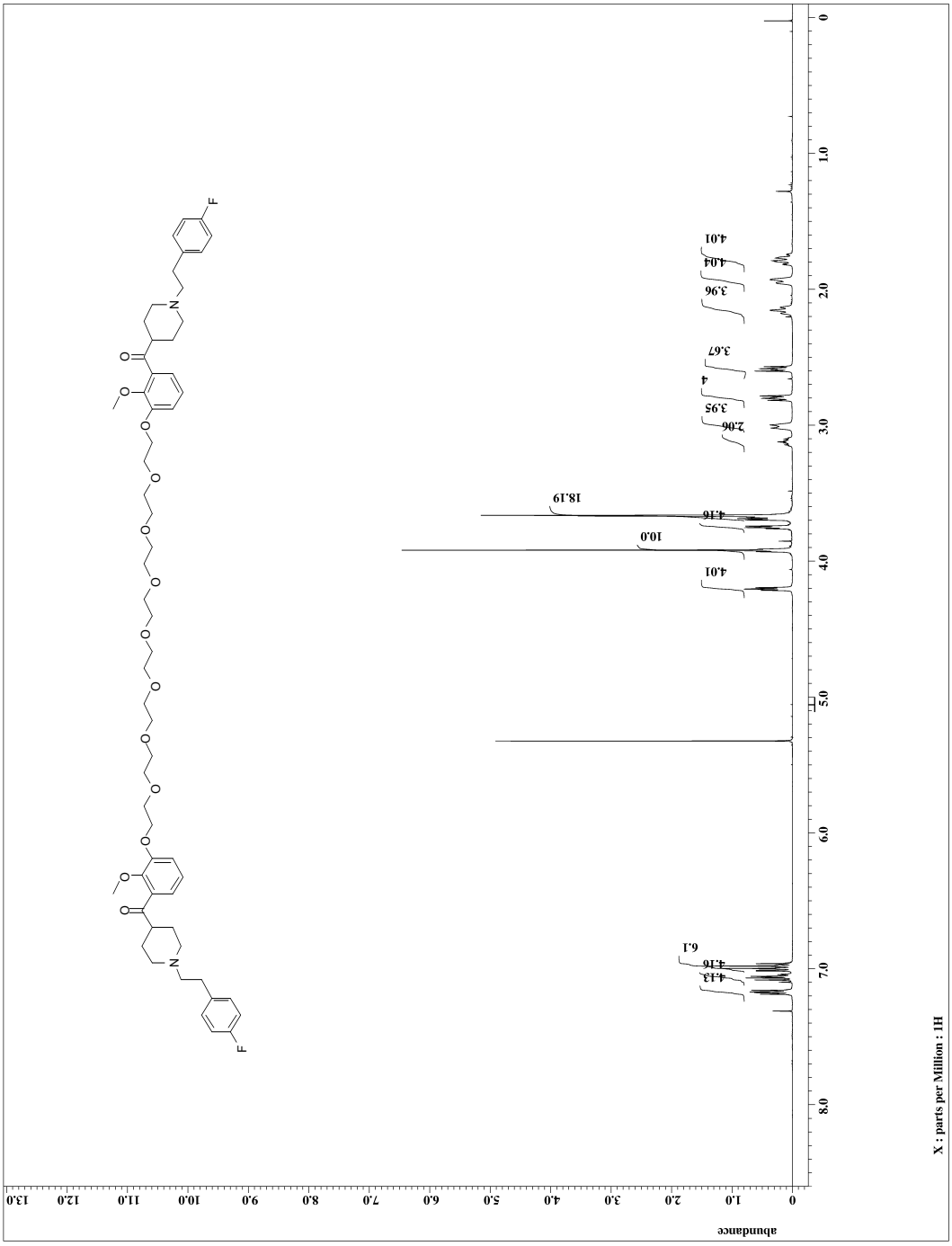
^{13}C-NMR Spectra (500 MHz, $CDCl_3$)

(3,3'-(3,6,9,12,15,18-hexaoxaicosane-1,20-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (40)



^{1}H-NMR Spectra (500 MHz, $CDCl_3$)

(3,3'-(3,6,9,12,15,18,21-heptaoxatricosane-1,23-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (41)



^{13}C-NMR Spectra (500 MHz, $CDCl_3$)

(3,3'-(3,6,9,12,15,18,21-heptaoxatricosane-1,23-diylbis(oxy))bis(2-methoxy-3,1-phenylene))bis((1-(4-fluorophenethyl)piperidin-4-yl)methanone) (41)