Electronic Supplementary Information

Novel quinoline-piperazine hybrids: The design, synthesis and evaluation of antibacterial and antituberculosis properties

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1. Materials and Methods

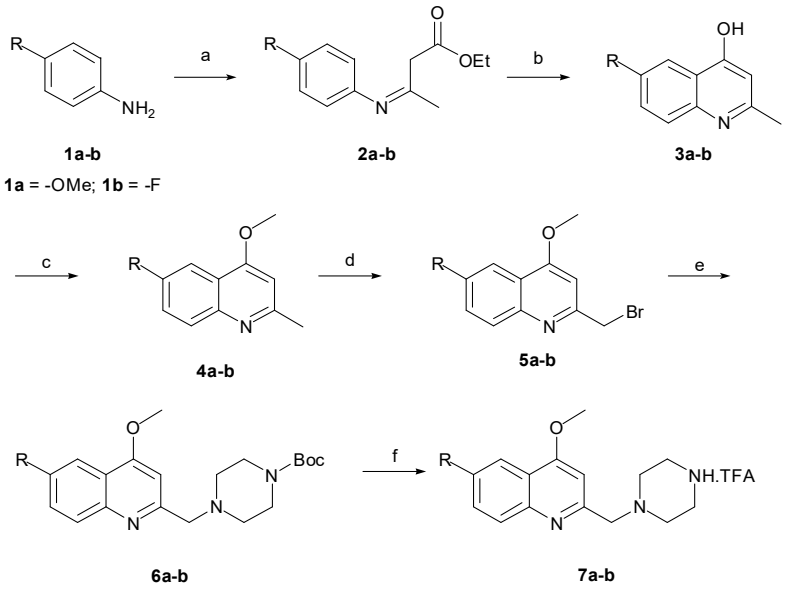
All reagents and solvents were purchased from commercial sources and used without further purification unless otherwise stated. Reactions were performed in round-bottom flasks or jacketed glass reactors or stainless steel/hastelloy pressurised reactors. Small-scale heating reactions were performed using a heating mantle with a thermocouple/temperature probe. Large scale reactions were performed using a jacketed reactor using ethylene glycol-water as the heating media. The temperature listed for each experiment refers to the internal reaction vessel temperature. Stainless steel syringes were used to transfer liquids for in-process check (unless noted otherwise).

Reactions were monitored by TLC [Merk TLC silica plates]. Purification of the crude reaction products, was accomplished on a Grace Reveleris X2 normalphase chromatography system using silica gel cartridges purchased from Grace or Silicycle. Organic solutions were concentrated on a Büchi Rotavapor R-143 at ~120 Torr at 55−60 °C. Yields refer to isolated yields of analytically pure (>95%) material.

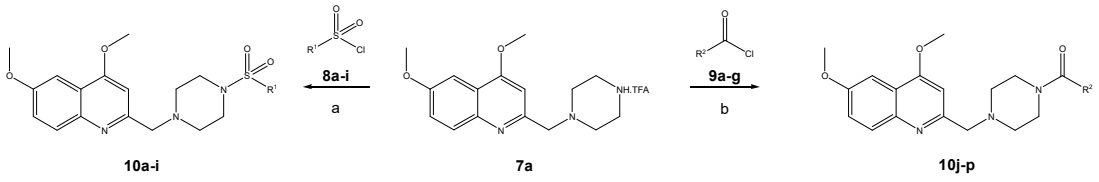
Analytical LC-MS was performed on an Agilent 1100/1200 HPLC system under positive APCI or ESI ionization conditions dependent on the system used. Chemical purity analysed by using HPLC made by Shimadzu with reversed-phase gradient, UV detection at 210 and 220 nm (photodiode array detector) and column Zorbax RX-C8, 250 x 4.6 mm, 5 µm. Acetonitrile and water used as mobile phases, injection volume 5.0 µL, flow rate was 0.8 mL/min and the column temperatue maintained at 45 °C during analysis. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker 300 MHz spectrometer and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the residual protium in the NMR solvent ($CHCl_3$, δ 7.27). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in hertz, integration]. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker 300 MHz spectrometer and are recorded in parts per million from internal tetramethylsilane on the δ scale and are referenced from the carbon resonances in the NMR solvent ($CDCl_3$, δ 77.00). Melting points were determined with a Thomas-Hoover capillary melting point apparatus.

2. Synthesis

2.1 Scheme:



Scheme 1 Synthesis of 6-substituted 4-methoxy-2-[(piperazin-1-yl)methyl] quinoline trifluroacetic acid salt (**7a-b**) Reagents and conditions: (a) Ethyl acetoacetate, *p*-TsOH, toluene, 110 °C, 8 h; (b) PPA, $POCl_3$, 75 °C, 2 h; (c) Me_2SO_4, toluene, 110 °C, 6 h; (d) NBS, AIBN, MeCN, 25 °C, 6 h; (e) Boc-piperazine, K_2CO_3, DMF, 60 °C, 4 h; (f) TFA, DCM, 0 °C to 25 °C, 2 h.



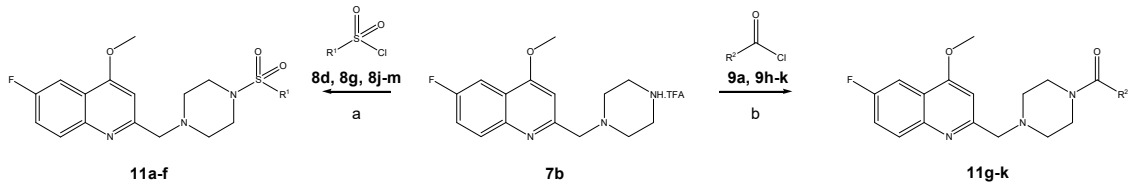
R^1 Sulfonyl chlorides

8a (10a) = (2,4,6-trimethyl)Ph
8b (10b) = Naphthalene
8c (10c) = NHMe
8d (10d) = [4-NH(Ac)]Ph
8e (10e) = Thiophene
8f (10f) = (2-CF_3)Ph
8g (10g) = (2-F)Ph
8h (10h) = (4-F)Ph
8i (10i) = (2,3,4,5,6-penta fluro)Ph

R^2 Benzyol chlorides

9a (10j) = (2-F)Ph
9b (10k) = (2,4-dichloro)Ph
9c (10l) = (2,6-dichloro)Ph
9d (10m) = (3,4-dichloro)Ph
9e (10n) = (2-OMe)Ph
9f (10o) = (3-OMe)Ph
9g (10p) = Cyclobutyl

Scheme 2 Synthesis of 4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazine-1-sulfonamide (**10a-i**) and 4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazine-1-amide (**10j-p**) derivatives. Reagents and conditions: (a) DIPEA, DCM, various sulfonyl chlorides (**8a-i**), 0–10 °C, 8 h; (b) Et_3N, DCM, various acid chlorides (**9a-g**), 0–10 °C, 4 h.



R^1 Sulfonyl chlorides

8j (11a) = (4-Me)Ph
8k (11b) = (2,4,6-triisopropyl)Ph
8l (11c) = (4-OMe)Ph
8d (11d) = [4-NH(Ac)]Ph
8g (11e) = (2-F)Ph
8m (11f) = (2,4-dichloro)Ph

R^2 Benzyol chlorides

9h (11g) = (2-Me)Ph
9i (11h) = (4-OMe)Ph
9a (11i) = (2-F)Ph
9j (11j) = (3-F)Ph
9k (11k) = (3-Cl)Ph

Scheme 3 Synthesis of [4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazine-1-sulfonyl]-amide (**11a-f**) and 4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazine-1-amide (**11g-k**) derivatives. Reagents and conditions: (a) DIPEA, DCM, various sulfonyl chlorides (**8d, 8g, 8j-m**), 0–10 °C, 8 h; (b) DIPEA, DCM, various benzoyl chlorides (**9a, 9h-k**), 0–10 °C, 4 h.

2.2 Synthetic procedures

General procedure for the synthesis of compound 2a-b[1]

In a jacketed reactor equipped with a temperature probe, dissolved 4-methoxy aniline (**1a**) (100 g, 0.812 moles) in toluene (500 mL, 5 vol.) and charged ethyl acetoacetate (110.1 g, 0.852 moles) at ambient temperature. Added catalytic amount of *p*-TsOH (14 g, 0.0812 moles) then refluxed the reaction mass at 110 °C for 8 hours. Reaction was monitored by TLC. Post reaction completion, diluted the reaction mass with water (1 L, 10 volumes) and separated the organic layer then concentrated under reduced pressure for 6 hours at 70 °C to get pale brown oil. The obtained crude was purified by flash column chromatography using Biotage with silica gel cartridges and used ethyl acetate and hexane as an eluent to afford pale yellow liquid (125.3 g, 81.6% yield).[2]

General procedure for the synthesis of compound 3a-b[3]

In a hastelloy pressurised reactors equipped with a temperature probe, compound **2a** (120 g, 0.51 moles) and polyphosphoric acid (PPA) (258.5 g, 0.765 moles) was charged then added catalytic amount of phosphorous oxy-chloride ($POCl_3$) (3.9 g, 0.025 moles) then heated the mixture for 4 hours at 75 °C. Reaction was monitored by TLC. Post reaction completion, quenched the reaction mixture slowly with 10% sodium hydroxide solution and adjusted to pH 7 by maintaining the temperature (0–10 °C). The formed suspension was stirred for an hour at ambient temperature then filtered and dried (86 g). The crude was slurried with methyl tertiary butyl ether (MTBE, 430 mL, 5 volumes) at ambient temperature then filtered and dried under reduced pressure to afford off-white solid (Melting point: 298–299 °C) (81.7 g, 84.7% yield).[2,3]

General procedure for the synthesis of compound 4a-b[4]

In a stainless steel pressurised reactors equipped with a temperature probe, compound **3a** (80 g, 0.393 moles), dimethyl sulphate (258.5 g, 0.765 moles) and toluene (400 mL, 5 volumes) was charged then heated the mixture to 110 °C and stirred for 8 hours. Reaction was monitored by TLC. Post reaction completion, allowed the reaction mixture to 25 °C then diluted with water (400 mL, 5 volumes) and separated the toluene layer. Slowly n-heptane was charged to the toluene layer under stirring at 25 °C to get the precipitation and agitated the suspension for 1 hour, filtered and dried under reduced pressure to afford pale pink solid (Melting point: 93–94 °C) (68.5 g, 79.8% yield).[4,5]

General procedure for the synthesis of compound 5a-b[6]

In a reactor equipped with a temperature probe, dissolved the compound **4a** (68 g, 0.334 moles) in dichloromethane (340 mL, 5 volumes) and acetonitrile (340 mL, 5 volumes) then charged *N*-bromosuccinimide (NBS) (62.5 g, 0.351 moles) followed by an addition of catalytic amount of azobisisobutyronitrile (AIBN) (5.5 g, 0.033 moles). The reaction mixture was slowly heated to 60–65 °C and agitated for 12 hours. Reaction was monitored by TLC. Post reaction completion, allowed the reaction mixture to 10 °C then filtered through celite bed and washed with dichloromethane (3 volumes). Concentrated the filtrate under reduced pressure at 50 °C. The obtained crude was purified by flash column chromatography using Biotage with silica gel cartridges and used ethyl acetate and hexane as an eluent to afford as pale pink solid (71.8 g, 76.1% yield).

General procedure for the synthesis of compound 6a-b

In a reactor equipped with a temperature probe, charged potassium carbonate (K_2CO_3) (41.1 g, 0.297 moles), *N*-boc-piperazine (60.8 g, 0.326 moles) are charged to the solution of compound **5a** (70 g, 0.248 moles) in *N,N*-dimethylformamide (DMF) (420 mL, 6 volumes) and was heated to 60–65 °C for 6 h under agitation. Reaction was monitored by TLC. Post reaction completion, cooled the reaction mass to 25–30 °C then slowly poured to water (12 volumes). Stirred the suspension for 1 hour, filtered and dried (88 g). The obtained crude was purified by slurry operation with isopropyl alcohol (IPA) (10 volumes) at 65 °C for 8 hours under agitation, filtered the suspension at 25 °C and dried the solid under reduced pressure at 75–80 °C to afford as beige solid (83.6 g, 86.9% yield).

Procedure for the synthesis of 4,6-dimethoxy-2-piperazin-1-ylmethyl-quinoline.TFA salt (7a)

In a reactor equipped with a temperature probe, compound **6a** (83 g, 0.214 moles) is dissolved in dichloromethane (DCM) (420 mL, 6 volumes) and cooled to 0–5 °C then slowly trifluro-acetic acid (25.6 g, 0.225 moles) is added over a period of 20–30 minutes. The reaction mass is agitated at 25–30 °C, for 2 hours then concentrated under reduced pressure at 45–50 °C to afford as brown solid (84.8 g).

The obtained crude is purified by slurry operation with ethanol (EtOH) (10 volumes) at 65 °C for 8 hours under agitation, filtered the suspension at 25 °C and dried the solid under reduced pressure at 75–80 °C to afford as pale brown solid **7a** (79.7 g, 96.8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (d, *J* = 4.2 Hz, 4H), 3.53 (s, 2H), 3.65 (s, 2H), 3.75 (s, 2H), 3.93 (s, 3H), 4.07 (s, 3H), 4.76 (bs, 1H), 6.96 (s, 1H), 7.33 (dt, *J* = 9.3 Hz, *J* = 1.5 Hz, 1H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H). LCMS (ESI) calculated m/z for $C_{18}H_{21}F_3N_3O_3$ $[M+H]^+$ 384.3, found 385.4.

Procedure for the synthesis of 6-fluoro-4-methoxy-2-piperazin-1-ylmethyl-quinoline.TFA salt (7b)

In a reactor equipped with a temperature probe, compound 6b (83 g, 0.214 moles) is dissolved in dichloromethane (DCM) (420 mL, 6 volumes) and cooled to 0–5 °C then slowly trifluro-acetic acid (25.6 g, 0.225 moles) is added over a period of 20–30 minutes. The reaction mass is agitated at 25–30 °C, for 2 hours then concentrated under reduced pressure at 45–50 °C to afford as brown solid (84.8 g). The obtained crude is purified by slurry operation with ethanol (EtOH) (10 volumes) at 65 °C for 8 hours under agitation, filtered the suspension at 25 °C and dried the solid under reduced pressure at 75–80 °C to afford as beige solid **7b** (49.2 g, 94.1%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (s, 4H), 3.24 (t, *J* = 4.5 Hz, 4H), 3.76 (s, 2H), 4.08 (s, 3H), 5.15 (bs, 2H), 7.15 (s, 1H), 7.45-7.38 (m, 1H), 7.74 (dd, *J* = 9.3 Hz, *J* = 2.7 Hz, 1H), 7.90-7.95 (m, 1H). LCMS (ESI) calculated m/z for $C_{17}H_{18}F_4N_3O_2$ $[M+H]^+$ 372.3, found 373.2.

General procedure for the synthesis of quinoline conjugated piperazine sulphonamides (10a-i and 11a-f)

In a round bottom flask, compound **7a** or **7b** (0.5 g, 1.3 mmoles) was suspended in dichloromethane (DCM) (5 mL, 10 volumes) under inert atmosphere and cooled to 0–5 °C then slowly added Hunig's base (*N, N*-diisopropylethylamine) (0.42 g, 3.2 mmoles). After 10 minutes, alkyl/aryl sulphonyl chloride (1.4 mmoles) (**8a-i**) or (**9a-f**) was added to the reaction mass and stirred for 8 hours at 0–10 °C. Reaction was monitored by TLC. Post reaction completion, quenched the reaction mass with water (5mL, 10 volumes) then separated the organic layer and concentrated. The obtained crude was purified by flash column chromatography using Biotage with silica cartridges, used methanol and dichloromethane as an eluent to afford respective sulphonamides (**10a-i and 11a-f**).

General procedure for the synthesis of quinoline conjugated piperazine amides (10j-p and 11g-k)

In a round bottom flask, compound **7a** or **7b** (0.5 g, 1.3 mmoles) was suspended in dichloromethane (DCM) (5 mL, 10 volumes) under inert atmosphere and cooled to 0–5 °C then slowly added Hunig's base (*N, N*-diisopropylethylamine) (0.42 g, 3.2 mmoles). After 10 minutes, alkyl/aryl acid chloride (1.4

mmoles) (**8j-p**) or (**9g-k**) was added to the reaction mass and stirred for 8 hours at 0–10 °C. Reaction was monitored by TLC. Post reaction completion, quenched the reaction mass with water (5mL, 10 volumes) then separated the organic layer and concentrated. The obtained crude was purified by flash column chromatography using Biotage with silica cartridges, used methanol and dichloromethane as an eluent to afford respective amides **(10j-p and 11g-k)**.

3. Spectral data of title compounds (10a-p and 11a-f)

4,6-Dimethoxy-2-[4-(2,4,6-trimethyl-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline (10a):
Brown solid (76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.57 (t, *J* = 5.1 Hz, 4H), 2.64 (s, 6H), 3.23 (t, *J* = 5.1 Hz, 4H), 3.76 (s, 2H), 3.94 (s, 3H), 4.06 (s, 3H), 6.97 (d, *J* = 4.8 Hz, 3H), 7.28-7.34 (m, 1H), 7.43 (d, *J* = 3.0 Hz, 1H), 7.88 (d, *J* = 9.3 Hz, 1H). LCMS (ESI) calculated m/z for $C_{25}H_{31}N_3O_4S$ $[M+H]^+$ 469.6, found 470.8.

4,6-Dimethoxy-2-[4-(naphthalene-1-sulfonyl)-piperazin-1-ylmethyl]-quinoline (10b):
Pale brown solid (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.61 (t, *J* = 4.8 Hz, 4H), 3.28 (s, 4H), 3.76 (s, 2H), 3.97 (s, 3H), 4.03 (s, 3H), 6.88 (s, 1H), 7.30-7.34 (m, 1H), 7.38 (d, *J* = 3.0 Hz, 1H), 7.54-7.69 (m, 3H), 7.93 (t, *J* = 8.1 Hz, 2H), 8.09 (d, *J* = 8.1 Hz, 1H), 8.23 (dd, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 8.76 (d, *J* = 8.4 Hz, 1H). LCMS (ESI) calculated m/z for $C_{26}H_{27}N_3O_4S$ $[M+H]^+$ 477.5, found 478.5.

4-(4,6-Dimethoxy-quinolin-2-ylmethyl)-piperazine-1-sulfonic acid methylamide (10c):
Brown solid (73% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (d, *J* = 4.2 Hz, 4H), 3.40 (d, *J* = 1.2 Hz, 3H), 3.53 (s, 2H), 3.66 (s, 2H), 3.75 (s, 2H), 3.93 (s, 3H), 4.07 (s, 3H), 4.76 (bs, 1H), 6.94 (s, 1H), 7.30 (dt, *J* = 9.3 Hz, *J* = 1.5 Hz, 1H), 7.38 (d, *J* = 3.0 Hz, 1H), 8.87 (d, *J* = 9.0 Hz, 1H). LCMS (ESI) calculated m/z for $C_{17}H_{24}N_4O_4S$ $[M+H]^+$ 380.4, found 381.7.

***N*-{4-[4-(4,6-Dimethoxy-quinolin-2-ylmethyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (10d):**
Dark brown solid (67.1% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.65 (d, *J* = 4.5 Hz, 4H), 3.06 (s, 4H), 3.79 (s, 2H), 3.94 (s, 3H), 4.06 (s, 3H), 6.86 (s, 1H), 7.28-7.40 (m, 2H), 7.64 (d, *J* = 9.0 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 9.0 Hz, 1H), 8.16 (s, 1H). LCMS (ESI) calculated m/z for $C_{24}H_{28}N_4O_5S$ $[M+H]^+$ 484.5, found 485.5.

4,6-Dimethoxy-2-[4-(thiophene-2-sulfonyl)-piperazin-1-ylmethyl]-quinoline (10e):
Beige solid (77.6% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (d, *J* = 4.8 Hz, 4H), 3.16 (d, *J* = 4.5 Hz, 4H), 3.76 (s, 2H), 3.94 (s, 3H), 4.03 (s, 3H), 6.82 (s, 1H), 7.15-7.18 (m, 1H), 7.32 (dd, *J* = 9.3 Hz, *J* = 3.0 Hz,

2H), 7.41 (d, *J* = 3.0 Hz, 2H), 7.54-7.56 (m, 1H), 7.63-7.65 (m, 1H), 7.87 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 45.9, 52.2, 55.5, 55.6, 64.9, 99.6, 99.9, 121.2, 122.1, 127.6, 130.0, 132.1, 132.5, 136.0, 144.3, 156.8, 157.3, 161.7. LCMS (ESI) calculated m/z for $C_{20}H_{23}N_3O_4S_2$ $[M+H]^+$ 433.5, found 434.6.

4,6-Dimethoxy-2-[4-(2-trifluoromethyl-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline (10f):
Beige solid (70.8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.61 (d, *J* = 5.1 Hz, 4H), 3.31 (d, *J* = 4.8 Hz, 4H), 3.75 (s, 2H), 3.93 (s, 3H), 4.04 (s, 3H), 6.87 (s, 1H), 7.30 (dd, *J* = 9.3 Hz, *J* = 3.0 Hz, 1H), 7.38 (d, *J* = 2.7 Hz, 1H), 7.70 (dd, *J* = 7.5 Hz, *J* = 7.5 Hz, 2H), 7.86 (d, *J* = 9.3 Hz, 1H), 7.89-7.92 (m, 1H), 8.11-8.14 (m, 1H). LCMS (ESI) calculated m/z for $C_{23}H_{24}F_3N_3O_4S$ $[M+H]^+$ 495.5, found 496.5.

2-[4-(2-Fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4,6-dimethoxy-quinoline (10g):
Off-white solid 69.8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.51 (s, 2H), 2.65 (s, 2H), 3.38 (s, 2H), 3.77 (s, 2H), 3.86 (s, 2H), 3.93 (s, 3H), 4.07 (s, 3H), 6.95 (s, 1H), 7.07 (t, *J* = 8.7 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.30 (dd, *J* = 9.0 Hz, *J* = 2.7 Hz, 1H), 7.346-7.41 (m, 3H), 7.86 (d, *J* = 9.3 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 41.6, 46.7, 52.9, 53.3, 55.5, 55.6, 65.2, 99.7, 121.2, 122.1, 127.1, 127.7, 129.6, 130.0, 130.1, 130.3, 135.7, 144.3, 157.2, 161.8, 166.8. LCMS (ESI) calculated m/z for $C_{22}H_{24}FN_3O_4S$ $[M+H]^+$ 445.5, found 446.6.

2-[4-(4-Fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4,6-dimethoxy-quinoline (10h):
Beige solid (64.4% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.43-2.46 (m, 1H), 2.56-2.71 (m, 3H), 3.26-3.41 (m, 2H), 3.79 (s, 2H), 3.84-3.91 (m, 2H), 3.93 (s, 3H), 4.06 (s, 3H), 6.97 (s, 1H), 7.29-7.33 (m, 4H), 7.34-7.43 (m, 2H), 7.89 (d, *J* = 9.0 Hz, 1H). LCMS (ESI) calculated m/z for $C_{22}H_{24}FN_3O_4S$ $[M+H]^+$ 445.5, found 446.5.

4,6-Dimethoxy-2-(4-pentafluorobenzenesulfonyl-piperazin-1-ylmethyl)-quinoline (10i):
Pale brown solid (70.6% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.69 (t, *J* = 4.8 Hz, 4H), 3.35 (s, 4H), 3.78 (s, 2H), 3.95 (s, 3H), 4.06 (s, 3H), 6.83 (s, 1H), 7.32 (dd, *J* = 9.0 Hz, *J* = 2.7 Hz, 1H), 7.39 (d, *J* = 3.0 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H). LCMS (ESI) calculated m/z for $C_{22}H_{20}F_5N_3O_4S$ $[M+H]^+$ 517.4, found 518.6.

4[4-(4,6-Dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(2-fluoro-phenyl)-methanone (10j):
Off-white solid (69.8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 22.59 (t, *J* = 7.8 Hz, 4H), 2.04 (s, 1H), 3.47 (s, 2H), 3.79-3.85 (m, 3H), 3.93 (s, 3H), 4.07 (s, 3H), 6.94 (s, 1H), 7.06-7.18 (m, 3H), 7.28-7.33 (m, 1H), 7.36-7.40 (m, 2H), 7.88 (d, *J* = 9.3 Hz, 1H). LCMS (ESI) calculated m/z for $C_{23}H_{24}FN_3O_3$ $[M+H]^+$ 409.4, found 410.5.

(2,4-Dichloro-phenyl)-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (10k):
Pale brown solid (75.6% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.59 (t, *J* = 4.8 Hz, 2H), 2.71 (t, *J* = 9.9 Hz, 2H), 3.31 (t, *J* = 5.4 Hz, 2H), 3.50 (s, 2H), 3.92 (t, *J* = 5.4 Hz, 2H), 3.95 (s, 3H), 4.12 (s, 3H), 7.01 (s, 1H), 7.24 (t, *J* = 6.6 Hz, 1H), 7.32 (s, 2H), 7.35 (t, *J* = 1.8 Hz, 1H), 7.41 (d, *J* = 2.7 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H). LCMS (ESI) calculated m/z for $C_{23}H_{23}Cl_2N_3O_3$ $[M+H]^+$ 460.3, found 461.4.

(2,6-Dichloro-phenyl)-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (10l):
Brown solid (70.7% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 3.42 (t, *J* = 3.6 Hz, 1H), 2.55-2.69 (m, 4H), 3.23-3.31 (m, 3H), 3.75- 3.89 (m, 3H), 3.92 (s, 3H), 4.07 (s, 3H), 6.92 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.28-7.31 (m, 2H), 7.39 (t, *J* = 9.6 Hz, *J* = 2.7 Hz, 1H), 7.85 (d, *J* = 9.3 Hz, 1H). LCMS (ESI) calculated m/z for $C_{23}H_{23}Cl_2N_3O_3$ $[M+H]^+$ 460.3, found 461.4.

(3,4-Dichloro-phenyl)-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (10m):
Brown solid (70.9% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 3.49 (t, *J* = 3.0 Hz, 1H), 2.64-2.79 (m, 3H), 3.29-3.36 (m, 2H), 3.86 (s, 4H), 3.98 (s, 3H), 4.10 (s, 3H), 7.03 (s, 1H), 7.22-7.25 (m, 1H), 7.32-7.35 (m, 2H), 7.36-7.41 (m, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 9.3 Hz, 1H). LCMS (ESI) calculated m/z for $C_{23}H_{23}Cl_2N_3O_3$ $[M+H]^+$ 460.3, found 461.4.

[4-(4,6-Dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(2-methoxy-phenyl)-methanone (10n):
Beige solid (66% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.54-2.65 (m, 4H), 2.91 (s, 2H), 2.48 (s, 2H), 3.79 (s, 2H), 3.82 (s, 3H), 3.93 (s, 3H), 4.07 (s, 3H), 6.90-6.96 (m, 4H), 7.25-7.35 (m, 2H), 7.38 (d, *J* = 2.7 Hz, 1H), 7.89 (d, *J* = 9.3 Hz, 1H). LCMS (ESI) calculated m/z for $C_{24}H_{27}N_3O_4$ $[M+H]^+$ 421.4, found 422.6.

[4-(4,6-Dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(3-methoxy-phenyl)-methanone (10o):
Beige solid (60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.41-2.51 (m, 2H), 2.60-2.68 (m, 2H), 3.29 (t, *J* = 8.4 Hz, 2H), 3.77 (s, 2H), 3.83 (s, 3H), 3.85-3.90 (m, 2H), 3.93 (s, 3H), 4.07 (s, 3H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.95-6.99 (m, 2H), 7.23 (dd, *J* = 7.5 Hz, *J* = 1.8 Hz, 1H), 7.28-7.30 (m, 1H), 7.31-7.35 (m, 1H), 7.38 (d, *J* = 3.0 Hz, 1H), 7.87 (d, *J* = 9.3 Hz, 1H). LCMS (ESI) calculated m/z for $C_{24}H_{27}N_3O_4$ $[M+H]^+$ 421.4, found 422.6.

Cyclobutyl-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (10p):
Beige solid (51.8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.04-2.10 (m, 2H), 2.12-2.16 (m, 2H), 2.28-2.41 (m, 4H), 2.47-2.48 (m, 2H), 2.51-2.55 (m, 2H), 3.16-3.25 (m, 1H), 3.35-3.38 (m, 2H), 3.65-3.66 (m, 2H), 3.73 (s, 2H), 3.93 (s, 3H), 4.06 (s, 3H), 6.95 (s, 1H), 7.30 (dd, *J* = 9.3 Hz, *J* = 2.7 Hz, 1H), 7.38 (d, *J* =

2.1 Hz, 1H), 7.87 (d, *J* = 9.3 Hz, 1H). LCMS (ESI) calculated m/z for $C_{21}H_{27}N_3O_3$ $[M+H]^+$ 369.4, found 370.5.

6-Fluoro-4-methoxy-2-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-quinoline (11a): Off-white solid (78.5% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.63 (d, *J* = 4.8 Hz, 4H), 3.07 (s, 4H), 3.72 (s, 2H), 4.00 (s, 3H), 6.82 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.41 (td, *J* = 8.7 Hz, *J* = 3.0 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.71 (dd, *J* = 9.3 Hz, *J* = 2.7 Hz, 1H), 7.92-7.97 (m, 1H). LCMS (ESI) calculated m/z for $C_{22}H_{24}FN_3O_3S$ $[M+H]^+$ 429.5, found 430.6.

6-Fluoro-4-methoxy-2-[4-(2,4,6-triisopropyl-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline (11b): Beige solid (71.8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25-1.28 (m, 18H), 2.59 (s, 4H), 2.88-2.90 (m, 1H), 3.24 (t, *J* = 4.5 Hz, 4H), 3.76 (s, 2H), 4.08 (s, 3H), 4.16-4.21 (m, 2H), 7.01 (s, 1H), 7.15 (s, 2H), 7.41 (td, *J* = 8.4 Hz, *J* = 3.0 Hz, 1H), 7.74 (dd, *J* = 9.3 Hz, *J* = 2.7 Hz, 1H), 7.90-7.95 (m, 1H). LCMS (ESI) calculated m/z for $C_{30}H_{40}FN_3O_3S$ $[M+H]^+$ 541.7, found 542.7.

6-Fluoro-4-methoxy-2-[4-(4-methoxy-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline (11c): Brown solid (69.3% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63 (t, *J* = 4.5 Hz, 4H), 3.06 (s, 4H), 3.76 (s, 2H), 3.29 (s, 3H), 4.01 (s, 3H), 6.83 (s, 1H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.38-7.45 (m, 1H), 7.68-7.73 (m, 3H), 7.92-7.97 (m, 1H). LCMS (ESI) calculated m/z for $C_{22}H_{24}FN_3O_4S$ $[M+H]^+$ 445.5, found 446.6.

***N*-{4-[4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (11d):** Brown solid (59.1% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84 (s, 3H), 2.29 (s, 4H), 2.62 (s, 3H), 2.69 (s, 4H), 3.40 (s, 2H), 3.70 (s, 3H), 6.56 (s, 1H), 7.08 (td, *J* = 8.7 Hz, *J* = 2.7 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.55 (dd, *J* = 9.6 Hz, *J* = 2.7 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.57-7.62 (m, 1H), 9.67 (s, 1H). LCMS (ESI) calculated m/z for $C_{23}H_{25}FN_4O_4S$ $[M+H]^+$ 472.5, found 473.5.

6-Fluoro-2-[4-(2-fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4-methoxy-quinoline (11e): Beige solid (68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (t, *J* = 4.8 Hz, 4H), 3.08 (s, 4H), 3.75 (s, 2H), 4.08 (s, 3H), 6.83 (s, 1H), 7.20-7.28 (m, 2H), 7.42 (td, *J* = 9.0 Hz, *J* = 2.7 Hz, 1H), 7.72 (dd, *J* = 9.3 Hz, *J* = 2.7 Hz, 1H), 7.76-7.81 (m, 2H), 7.93-7.98 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 41.8, 46.9, 53.0, 53.4, 55.8, 65.1, 99.9, 105.5-105.8, 115.6-115.8, 119.5-119.8, 121.3-121.4, 123.9-124.1, 124.6-124.7, 129.13-129.18, 130.8-130.9, 131.2-131.3, 145.4, 156.4, 158.4, 159.3-159.7, 161.7, 162.3, 162.4, 165.1. LCMS (ESI) calculated m/z for $C_{21}H_{21}F_2N_3O_3S$ $[M+H]^+$ 433.4, found 434.5.

2-[4-(2,4-Dichloro-benzenesulfonyl)-piperazin-1-ylmethyl]-6-fluoro-4-methoxy-quinoline (11f): Off-white solid (77% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 4H), 3.10 (s, 4H), 3.75 (s, 2H), 4.02 (s, 3H), 6.83 (s, 1H), 7.36 (td, *J* = 11.1 Hz, *J* = 2.7 Hz, 1H), 7.56-7.64 (m, 2H), 7.72 (dd, *J* = 9.3 Hz, *J* = 2.4 Hz, 1H), 7.84 (s, 1H), 7.92-7.97 (m, 1H). LCMS (ESI) calculated m/z for $C_{21}H_{20}Cl_2FN_3O_3S$ $[M+H]^+$ 484.4, found 485.4.

[4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-o-tolyl-methanone (11g): Brown solid (56.8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.44 (t, *J* = 4.5 Hz, 2H), 2.65 (t, *J* = 5.1 Hz, 2H), 3.82 (s, 2H), 3.77 (s, 2H), 3.87 (d, *J* = 4.5 Hz, 2H), 4.06 (s, 3H), 6.98 (s, 1H), 7.12-7.28 (m, 4H), 7.42 (td, *J* = 8.7 Hz, *J* = 3.0 Hz, 1H), 7.73 (dd, *J* = 9.6 Hz, *J* = 2.7 Hz, 1H), 7.92-7.97 (m, 1H). LCMS (ESI) calculated m/z for $C_{23}H_{24}FN_3O_2$ $[M+H]^+$ 393.4, found 394.4.

[4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(4-methoxy-phenyl)-methanone (11h): Brown solid (60.8% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41-2.51 (m, 2H), 2.60-2.68 (m, 2H), 3.30 (t, *J* = 7.8 Hz, 2H), 3.77 (s, 2H), 3.83 (s, 3H), 3.86 (s, 2H), 4.06 (s, 3H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.94-7.01 (m, 2H), 7.23 (dd, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.29-7.39 (m, 1H), 7.41-7.45 (m, 1H), 7.73 (dd, *J* = 9.6 Hz, *J* = 3.0 Hz, 1H), 7.93-7.97 (m, 1H). LCMS (ESI) calculated m/z for $C_{23}H_{24}FN_3O_3$ $[M+H]^+$ 409.4, found 410.3.

[4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(2-fluoro-phenyl)-methanone (11i): Beige solid (67.7% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53 (s, 2H), 2.67 (t, *J* = 4.8 Hz, 2H), 3.39 (s, 2H), 3.80 (s, 2H), 3.87 (s, 2H), 4.07 (s, 3H), 7.01 (s, 1H), 7.38 (t, *J* = 9.3 Hz, 1H), 7.17-7.22 (m, 1H), 7.37-7.46 (m, 3H), 7.74 (dd, *J* = 9.3 Hz, *J* = 2.7 Hz, 1H), 7.94-7.99 (m, 1H). LCMS (ESI) calculated m/z for $C_{22}H_{21}F_2N_3O_2$ $[M+H]^+$ 397.4, found 398.4.

[4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(3-fluoro-phenyl)-methanone (11j): Beige solid (68.1% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.53-2.64 (m, 4H), 3.46 (s, 2H), 3.80 (s, 4H), 4.06 (s, 3H), 7.00 (s, 1H), 7.07-7.19 (m, 3H), 7.34-7.46 (m, 2H), 7.75 (dd, *J* = 9.6 Hz, *J* = 3.0 Hz, 1H), 7.95-8.00 (m, 1H). LCMS (ESI) calculated m/z for $C_{22}H_{21}F_2N_3O_2$ $[M+H]^+$ 397.4, found 398.4.

(3-Chloro-phenyl)-[4-(6-fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (11k): Off-white solid (65.3% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44-2.73 (m, 4H), 3.26-3.33 (m, 2H), 3.80 (s, 2H), 3.83-3.90 (m, 2H), 4.06 (s, 3H), 7.00 (s, 1H), 7.28-7.37 (m, 3H), 7.38-7.46 (m, 2H), 7.73 (dd, *J* =

9.3 Hz, *J* = 2.7 Hz, 1H), 7.94-7.99 (m, 1H). LCMS (ESI) calculated m/z for $C_{22}H_{21}ClFN_3O_2$ $[M+H]^+$ 413.8, found 414.9.

4. Antimicrobial evaluation

The standard antibiotic stock solution of Linezolid, Trimethoprim and Ciprofloxacin were prepared in water (4.0 mg/mL) and the test compounds (27 target molecules) were prepared in DMSO with same concentration (4.0 mg/mL). Antimicrobial susceptibility testing (AST) was done as reported[7] by determining minimum inhibitory concentration (MIC) of antimicrobial agents which was done using sub-cultured Soybean Casein Digest Agar medium (SCDA). Bacterial inocula were prepared from mid-log phase grown culture. The culture turbidity was adjusted as per McFarland's standard (~10^8 CFU/mL) which was further diluted to ~10^5 CFU/mL. The concentration used for screening of title compounds and control standards with serial dilution from 64 µg/mL to 0.03 µg/mL. The triplicate assessment results were read after 22–24 h of incubation at 37 °C and the MIC was taken as the lowest concentration of the sample showing no visible growth.

5. Antituberculosis evaluation

The title compounds were evaluated against non-virulent *M. smegmatis* (ATCC 607) using broth micro dilution method as per CLSI standards (Clinical and Laboratory Standards Institute) and adopted the protocol as reported for anti-TB screening.[7-9] The compounds were dissolved in DMSO at 4.0 mg/mL concentration (1 mL DMSO used for dissolution). Middlebrook 7H9 broth with 10% ADC (albumin, dextrose, and catalase) and the test solutions were prepared together at higher concentration of 64 µg/mL followed by serial dilutions up to 0.015 µg/mL. The *M. smegmatis* was inoculated which corresponds to ~10^5 CFU/mL and was verified by 10-fold diluted inoculum on Middlebrook 7H11 agar plates (four weeks incubation at 37 °C). The first line TB drug Rifampin and second line TB drug Levofloxacin served as positive control and drug free broth containing DMSO served as negative control respectively. The bacterial growth inhibition was recorded after 2 days of incubation at 37 °C since it has fast growing ability and the recorded the MICs values. Likewise, title compounds were screened against virulent *M. tuberculosis H37Rv* (ATCC 25618) and multi-drug resistant *M. tuberculosis H37Rv* (MDR-TB) (ATCC 35822) as per above protocol whereas MIC reading was taken after 21 days due to their delayed growth.

6. Cytotoxic evaluation

Cytotoxicity/cell proliferation assay was carried out to analyze the effect of the active title compounds on the growth of HEK293, HepG2 and A549 cells. HEK293 is normal Human Embryonic Kidney cell line, HepG2 is Human Liver cancer cell line and A549 is Human Lung carcinoma cell line. Cells were cultured, seeded in a 96-well plate (Corning, Lowell, MA, USA) and incubated at 37 °C with 5% CO_2 until the cells were adhered (seeding density: 10000 cells/well).[10] Each cells were treated with 10 µL of each test compounds having concentration ranging from 64 to 1 µg/mL (143 to 4.6 µM). The Assay was performed in triplicates. Cells treated with only DMSO was maintained as vehicle control. The plates were incubated for 24 Hours for A549, while HepG2 and HEK293 were incubated for 48 hours at 37 °C with 5% CO_2. 20 µL of Methylthiazolyl diphenyl tetrazolium bromide (MTT; Sigma Aldrich) (1 mg/mL) was added to each well and incubated for 3 hours at 37 °C with 5% CO_2. The absorbance was measured at 570 nm to detect the cell viability or cell death.

7. References

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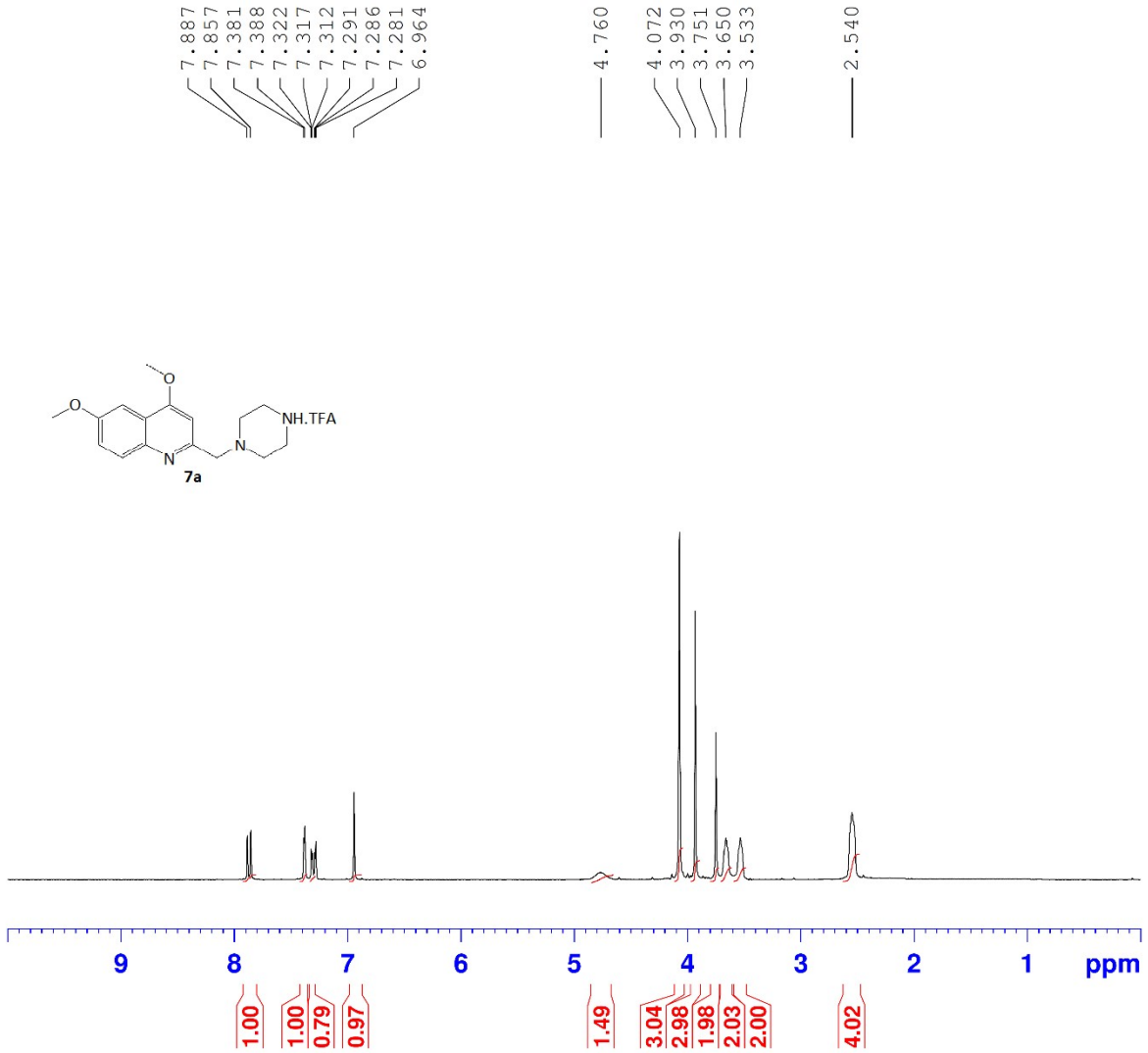
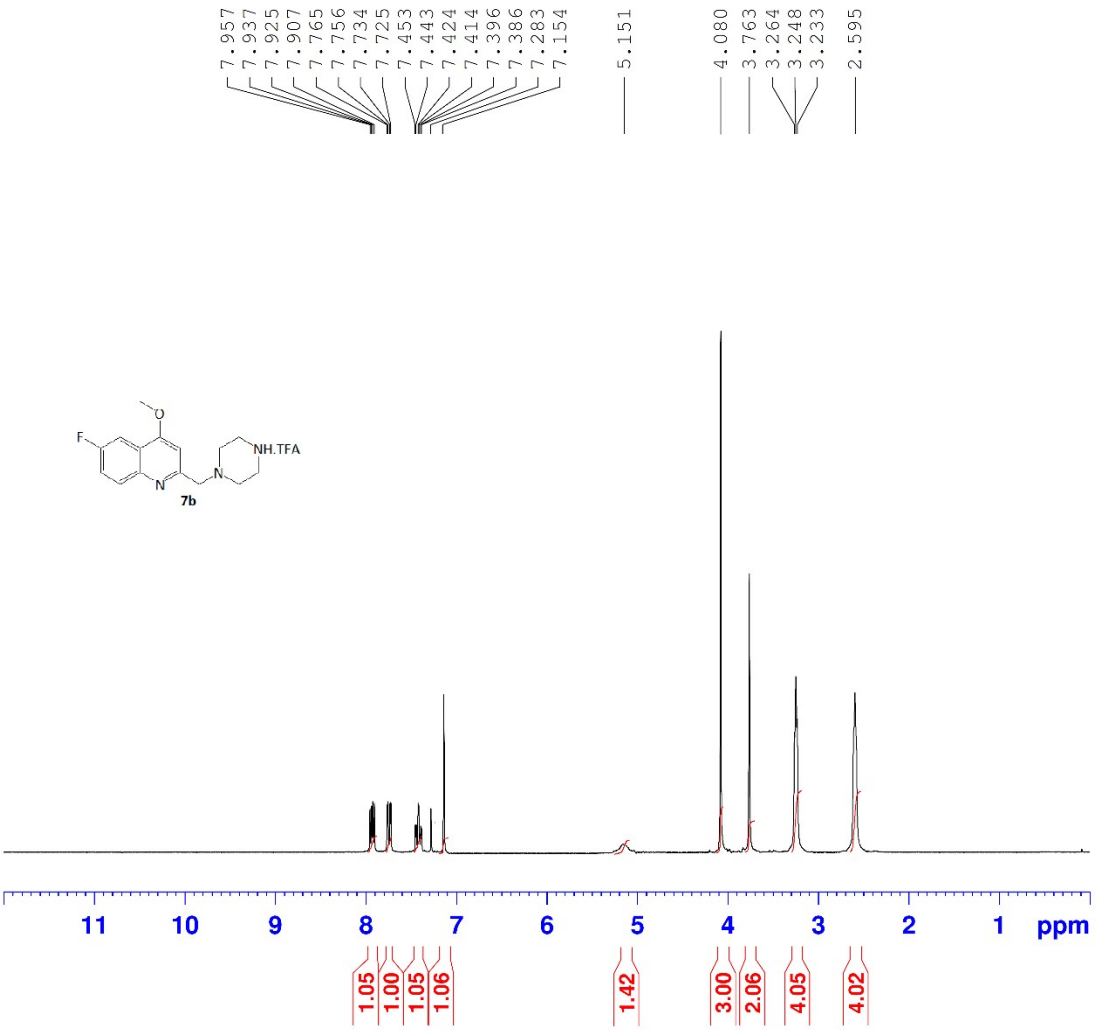
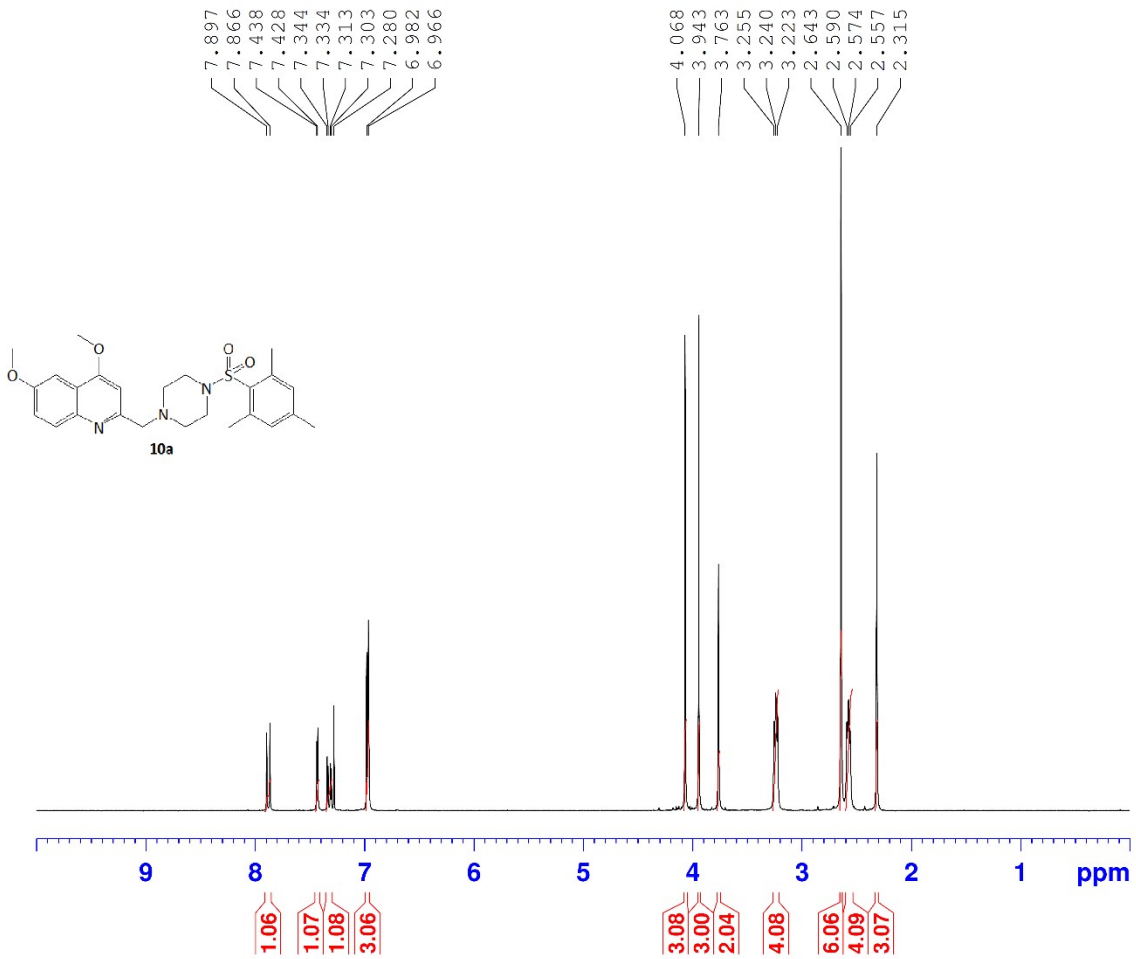
8. Spectra of title compounds (10a-p and 11a-f)



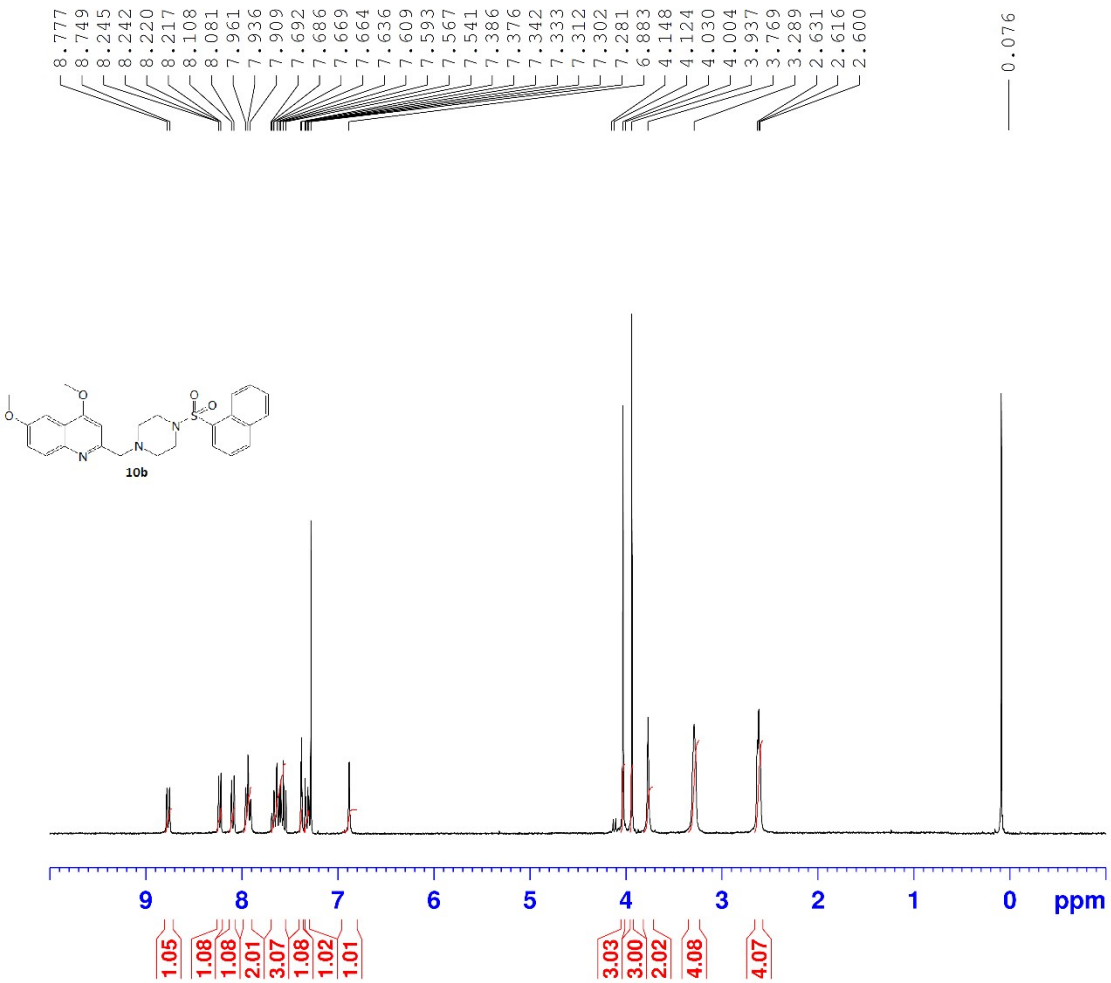
^{1}H NMR of 4,6-dimethoxy-2-piperazin-1-ylmethyl-quinoline TFA salt (**7a**)



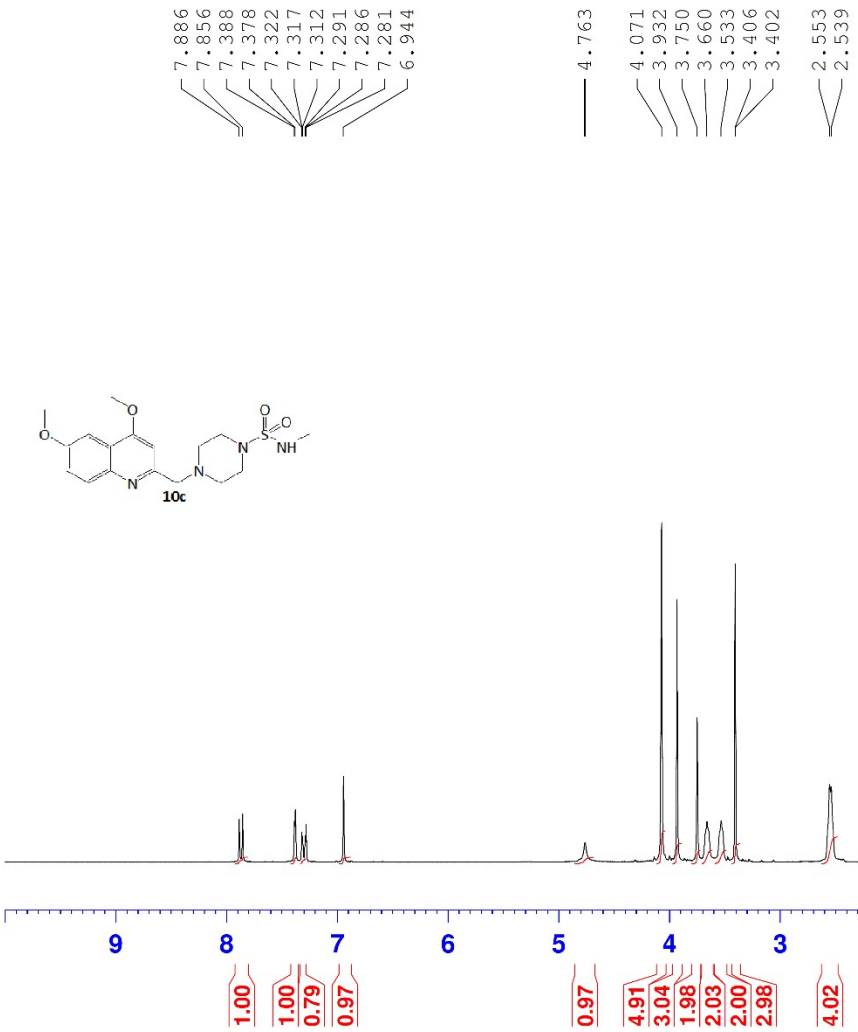
^{1}H NMR of 6-fluoro-4-methoxy-2-piperazin-1-ylmethyl-quinoline (**7b**)



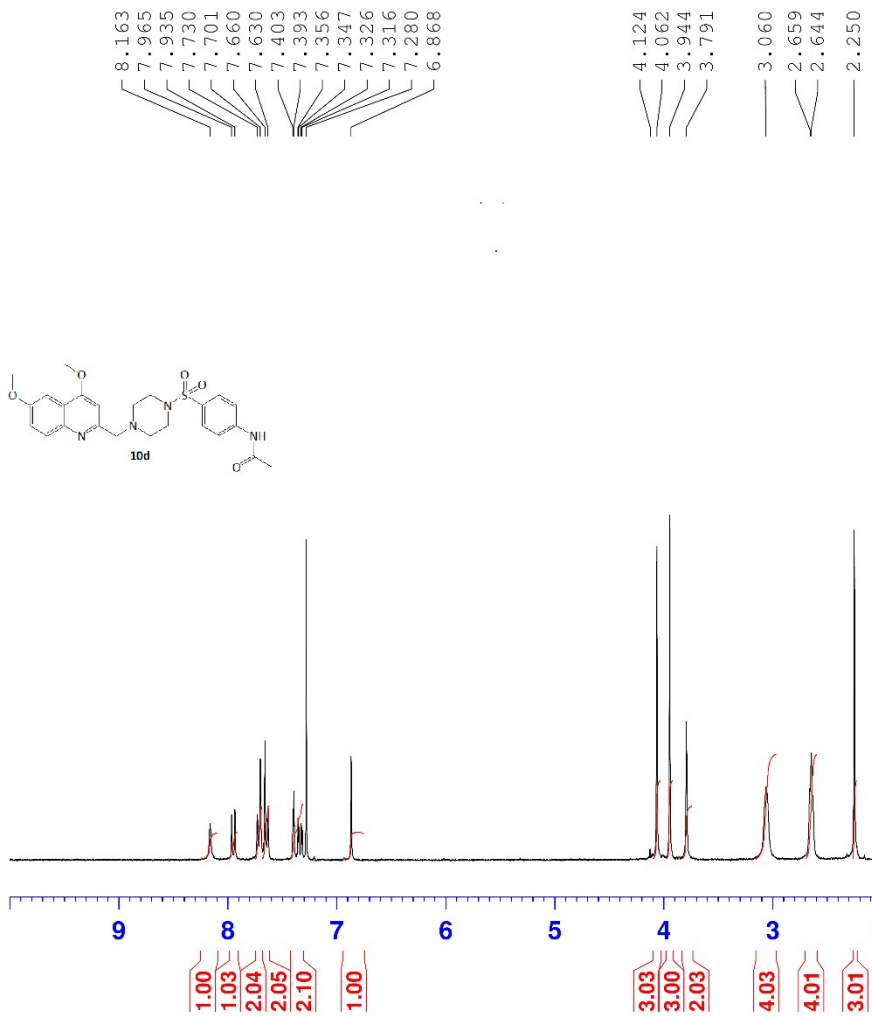
^{1}H NMR of 4,6-dimethoxy-2-[4-(2,4,6-trimethyl-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline (**10a**)



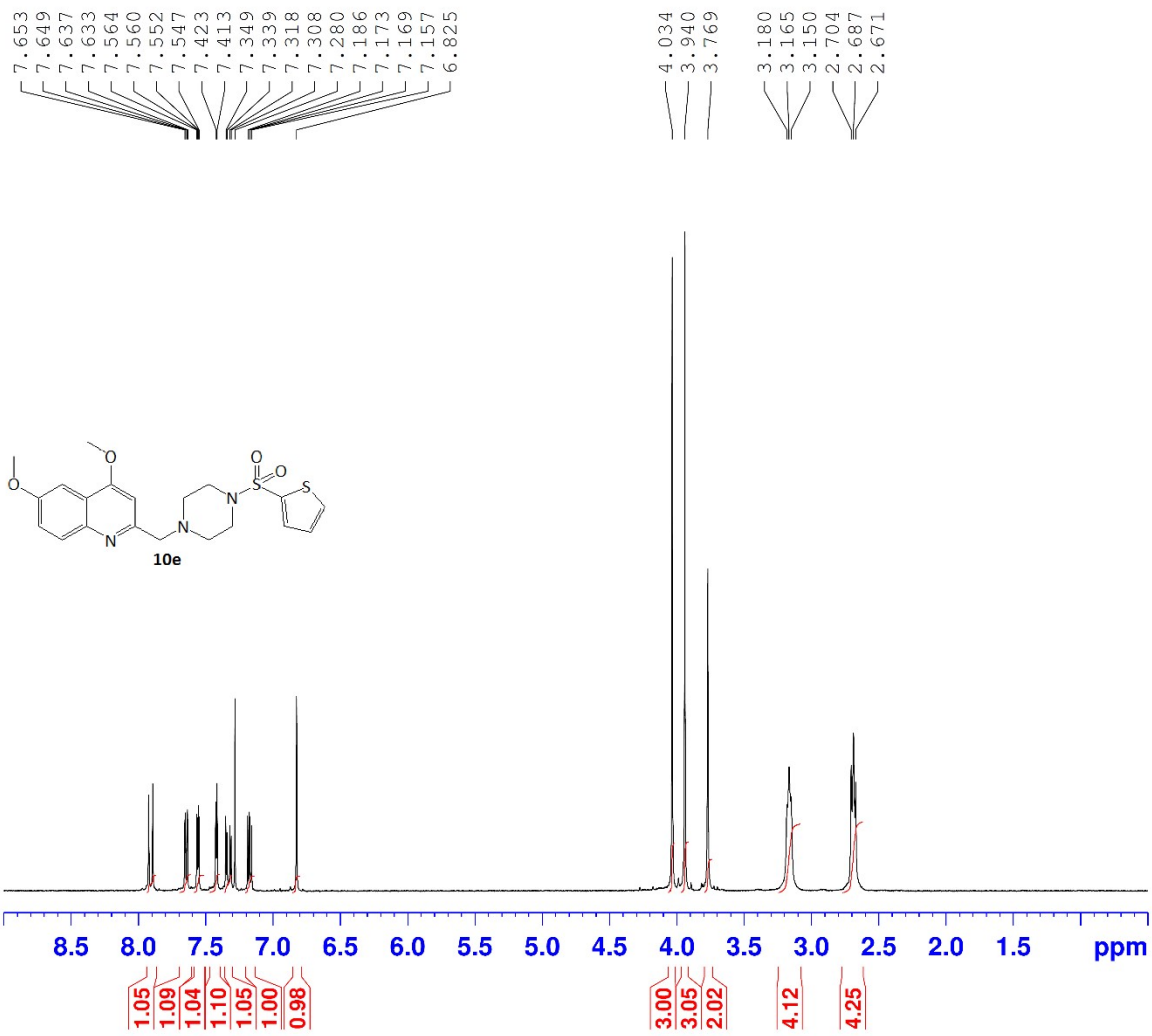
^{1}H NMR of 4,6-dimethoxy-2-[4-(naphthalene-1-sulfonyl)-piperazin-1-ylmethyl]-quinoline (**10b**)



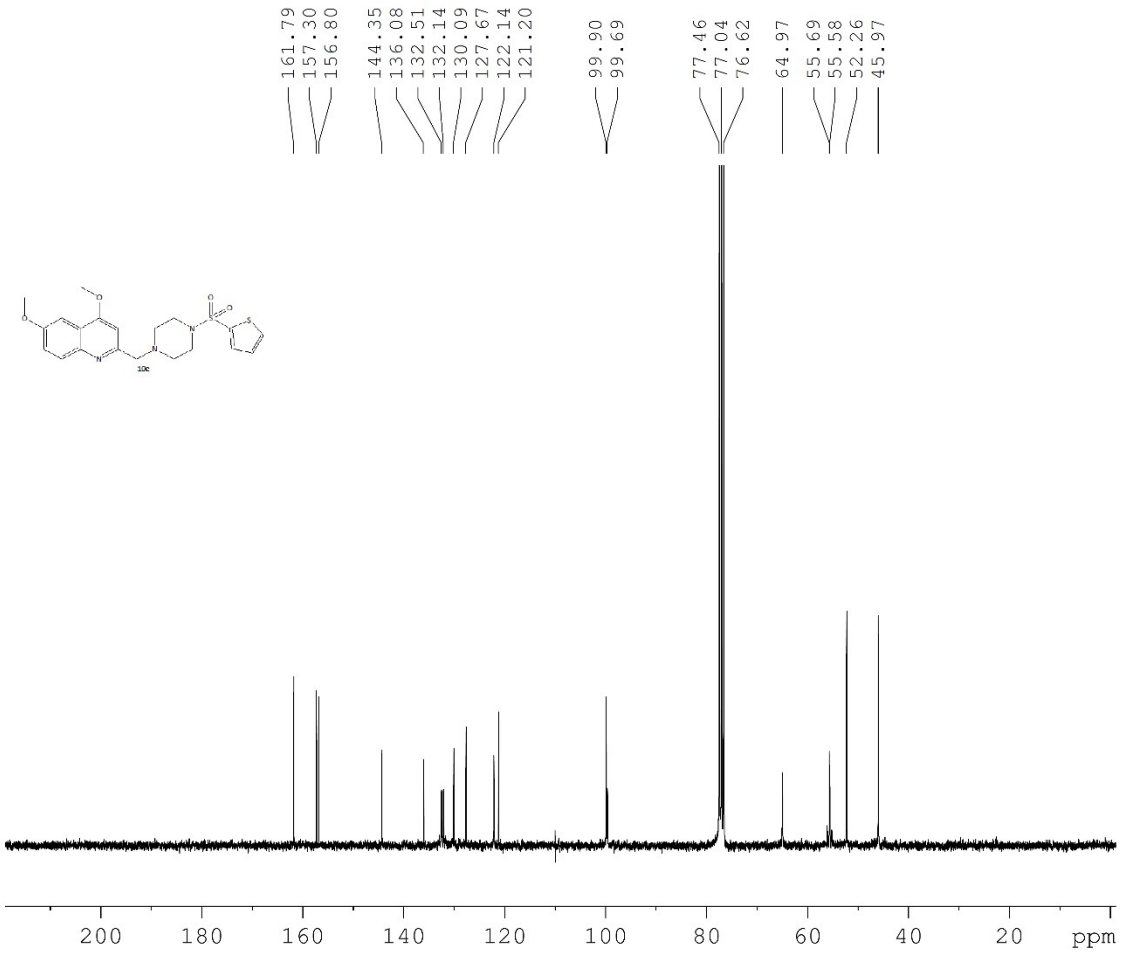
^{1}H NMR of 4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazine-1-sulfonic acid methylamide (**10c**)



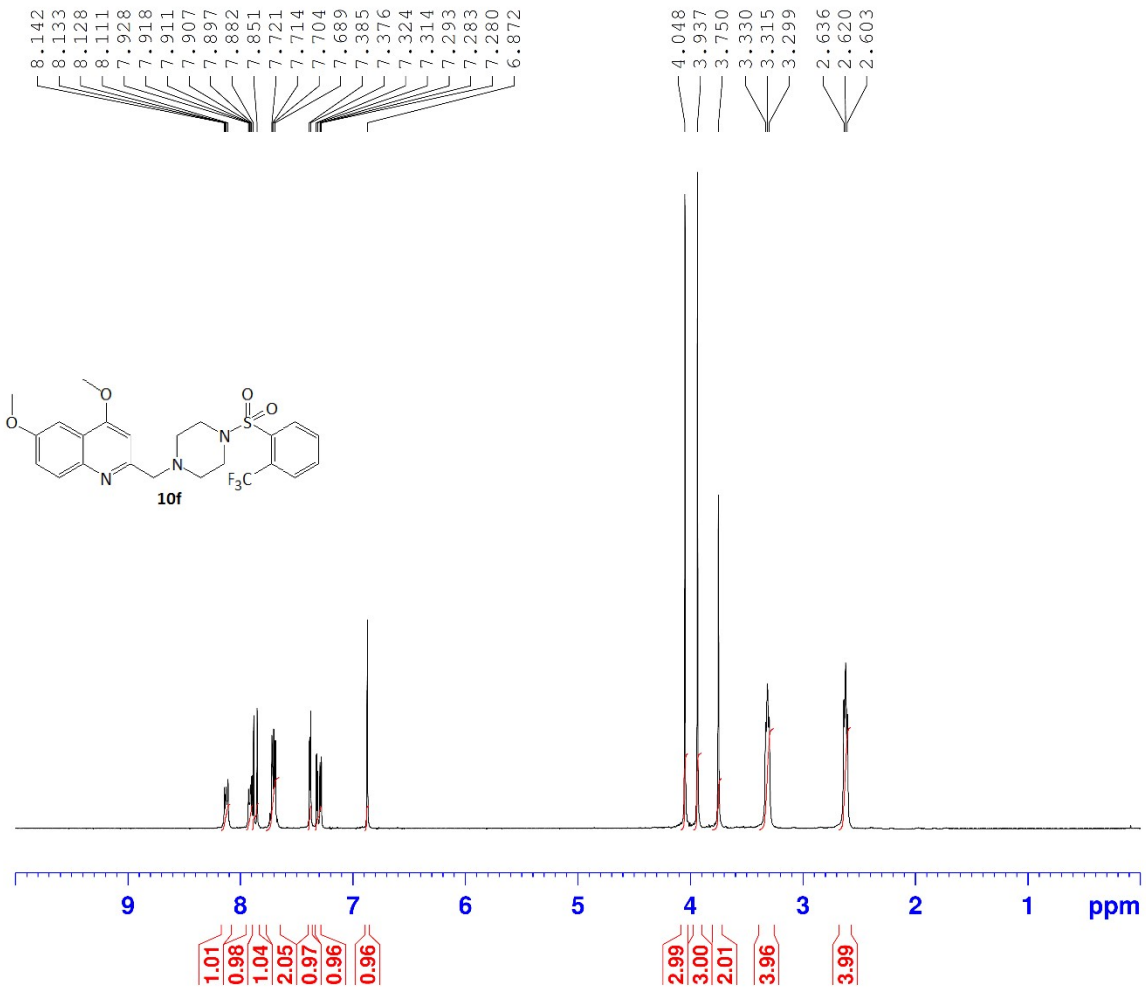
^{1}H NMR of *N*-{4-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**10d**)



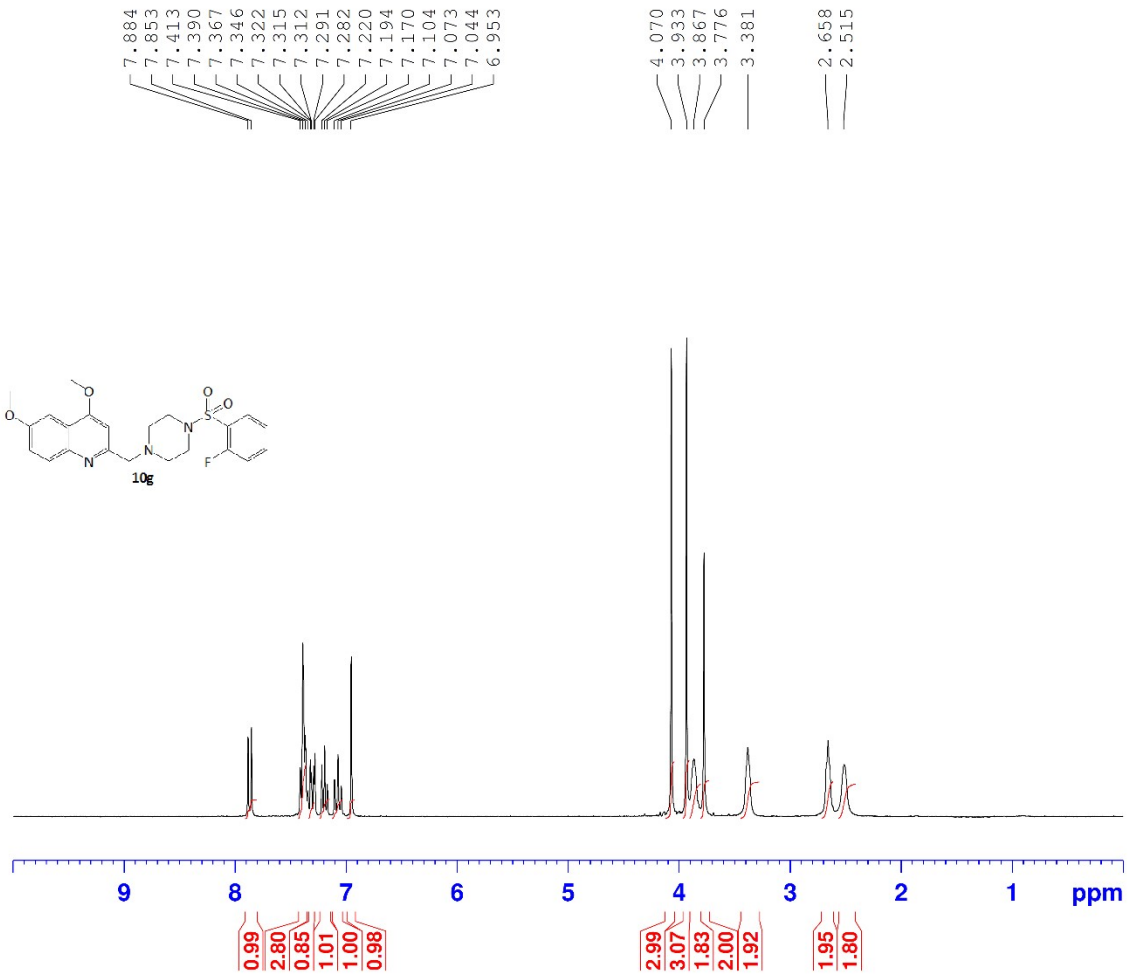
^{1}H NMR of 4,6-dimethoxy-2-[4-(thiophene-2-sulfonyl)-piperazin-1-ylmethyl]-quinoline (**10e**)



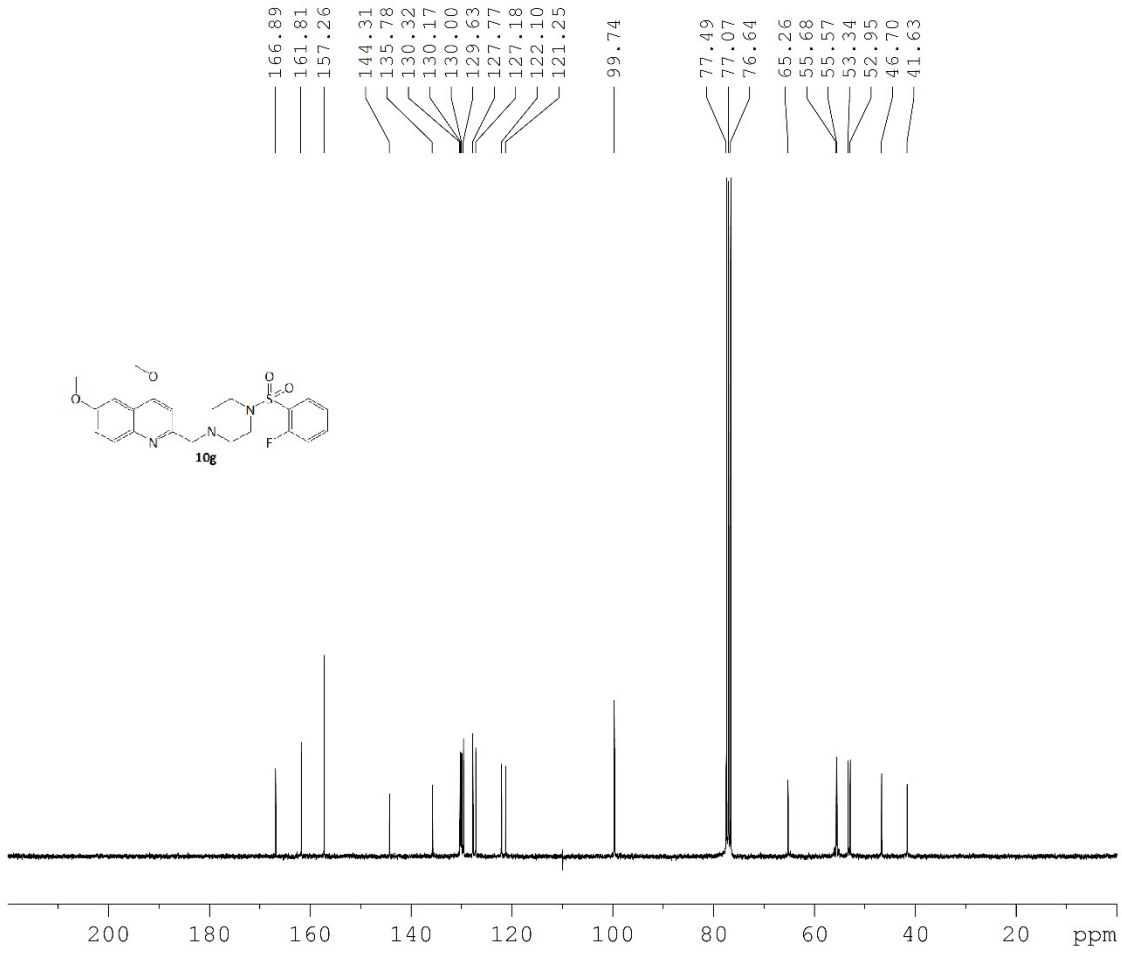
^{13}C NMR of 4,6-dimethoxy-2-[4-(thiophene-2-sulfonyl)-piperazin-1-ylmethyl]-quinoline (**10e**)



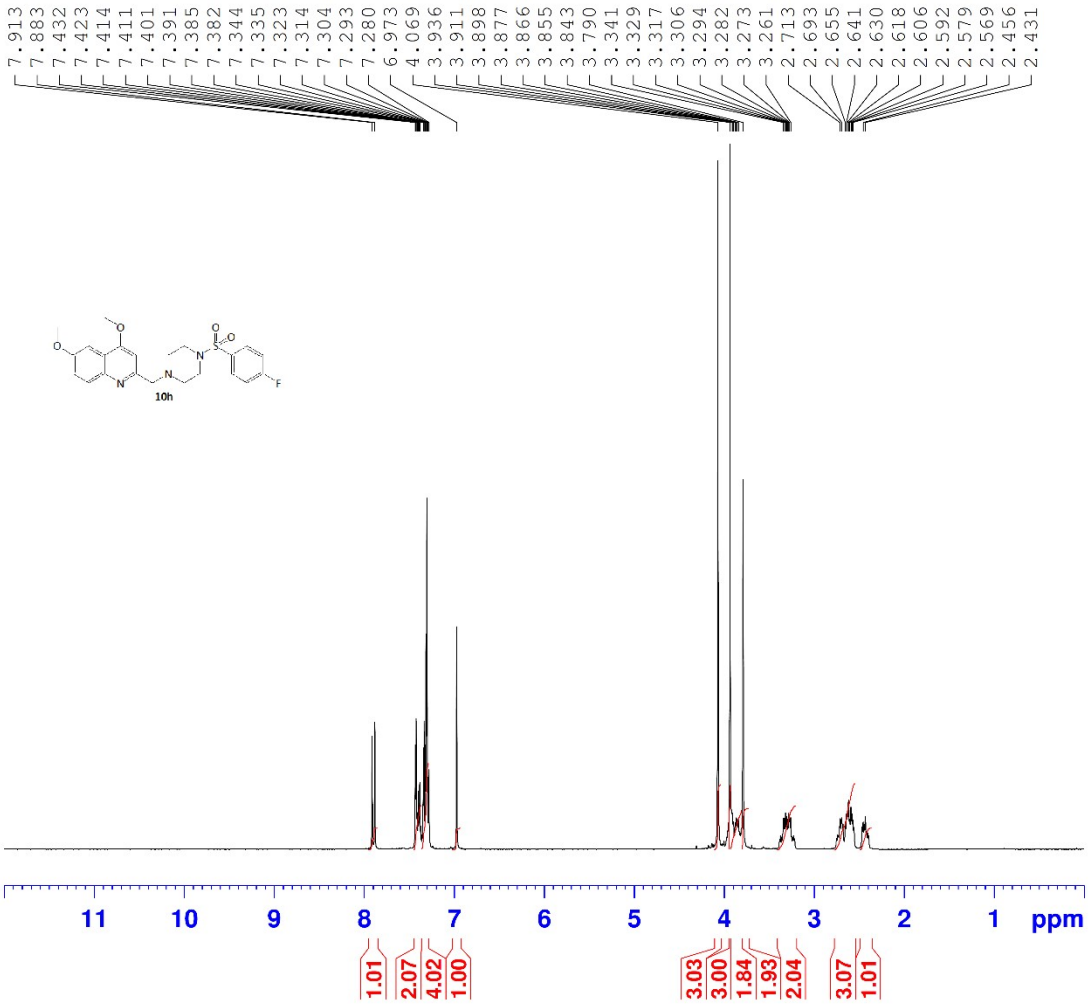
^{1}H NMR of 4,6-Dimethoxy-2-[4-(2-trifluoromethyl-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline (**10f**)



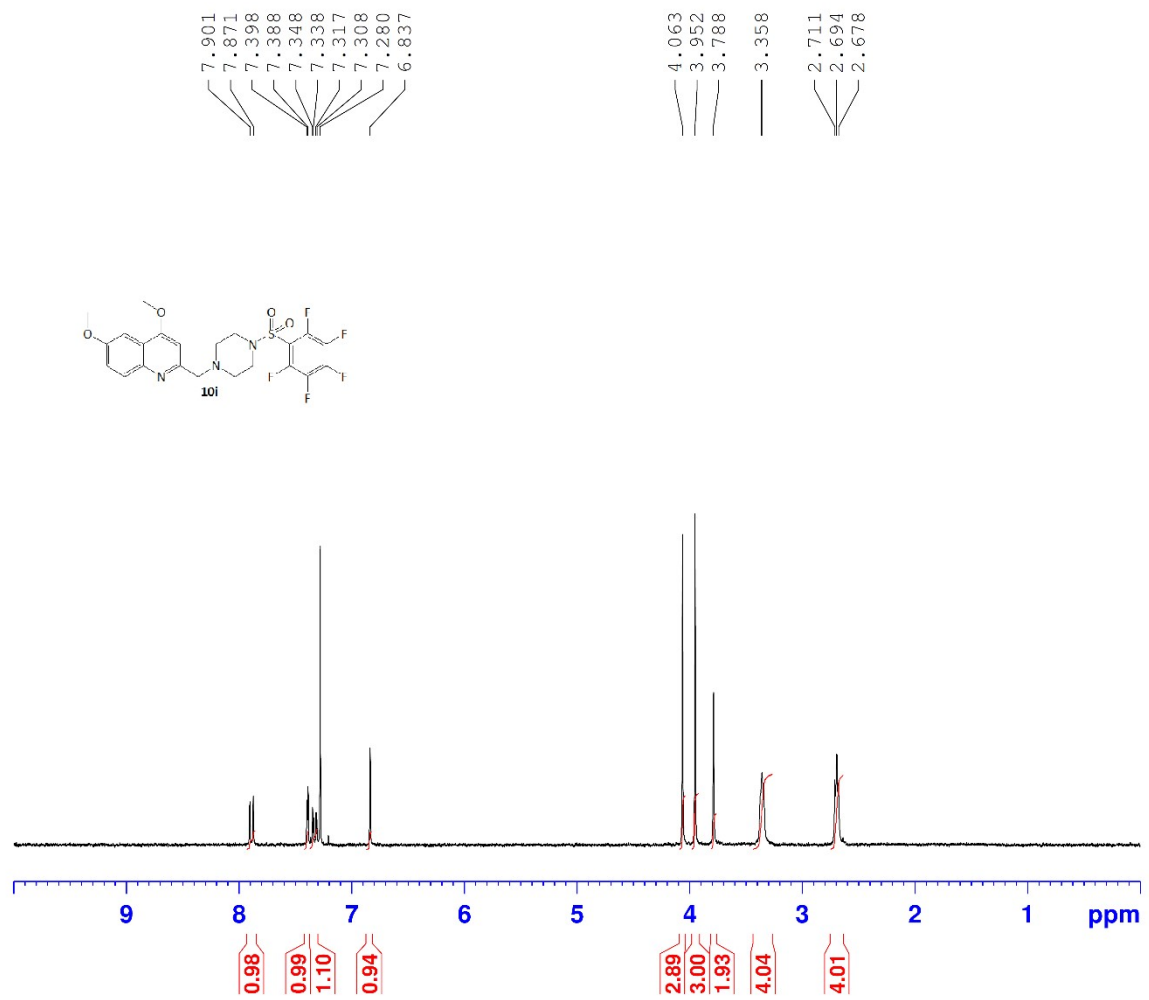
^{1}H NMR of 2-[4-(2-Fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4,6-dimethoxy-quinoline (**10g**)



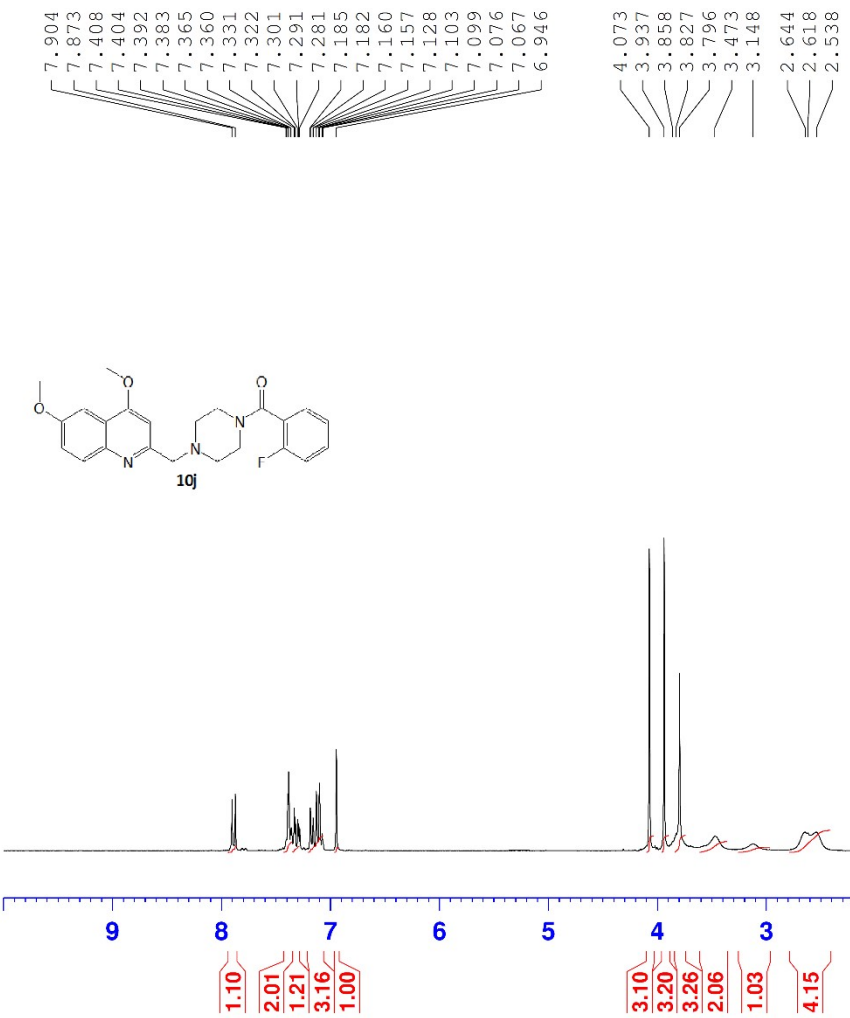
^{13}C NMR of of 2-[4-(2-Fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4,6-dimethoxy-quinoline (**10g**)



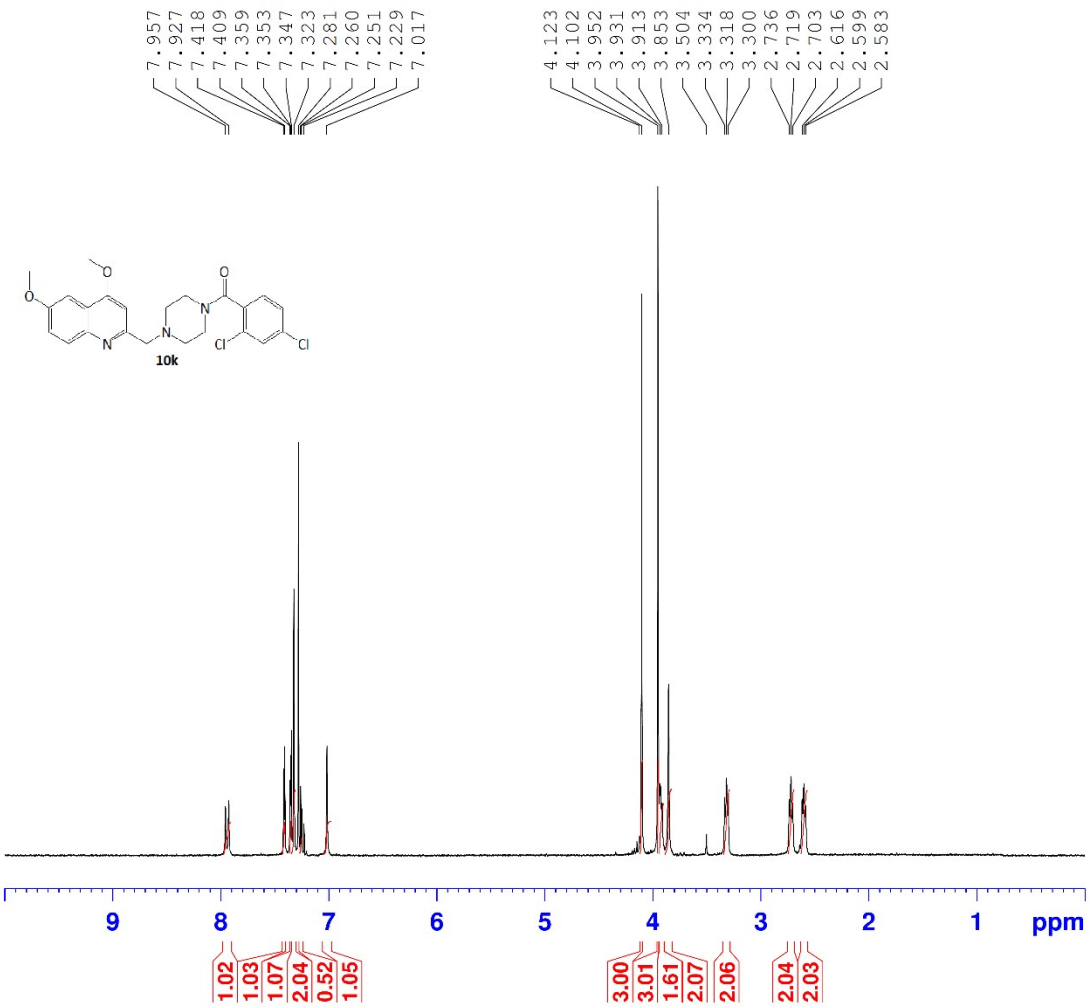
[1]H NMR of 2-[4-(4-Fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4,6-dimethoxy-quinoline (**10h**)



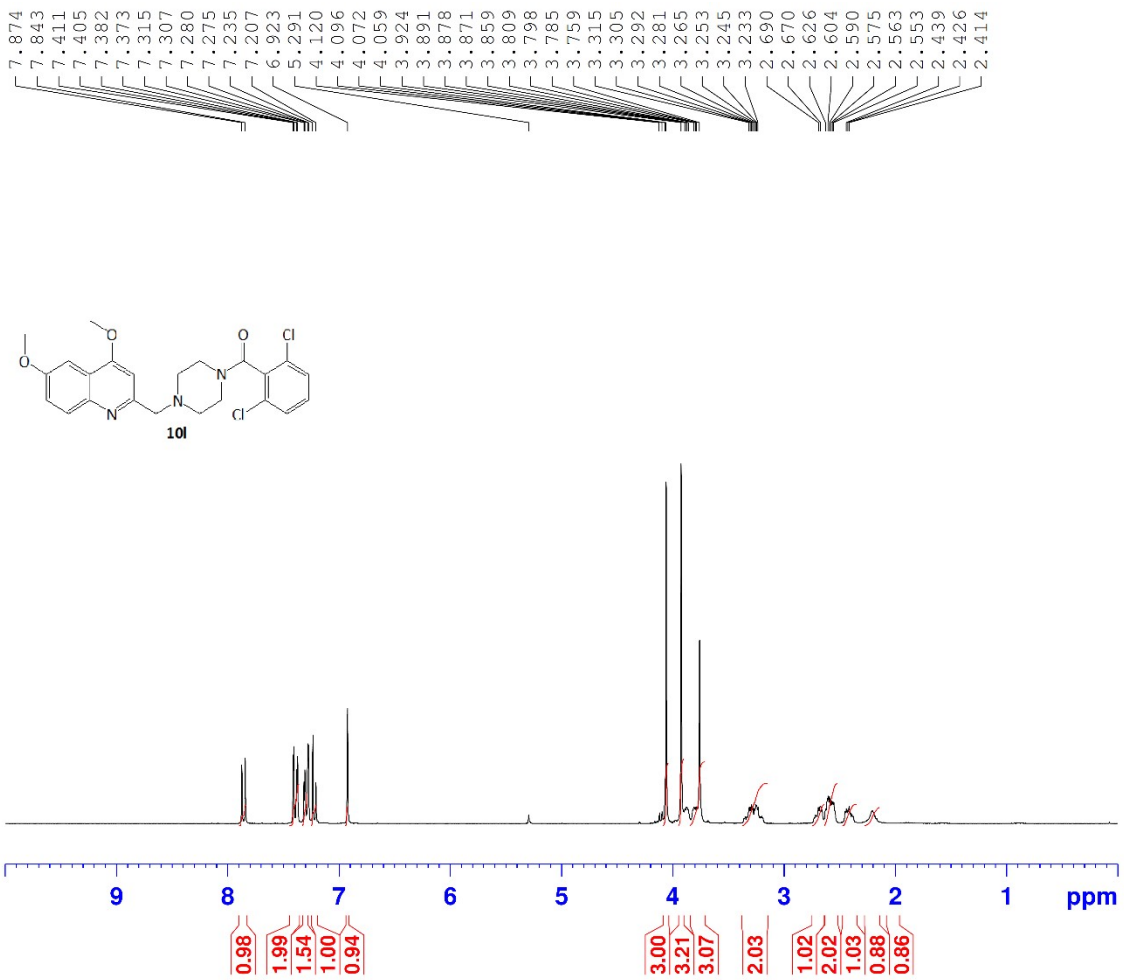
^{1}H NMR of 4,6-Dimethoxy-2-(4-pentafluorobenzenesulfonyl-piperazin-1-ylmethyl)-quinoline (**10i**)



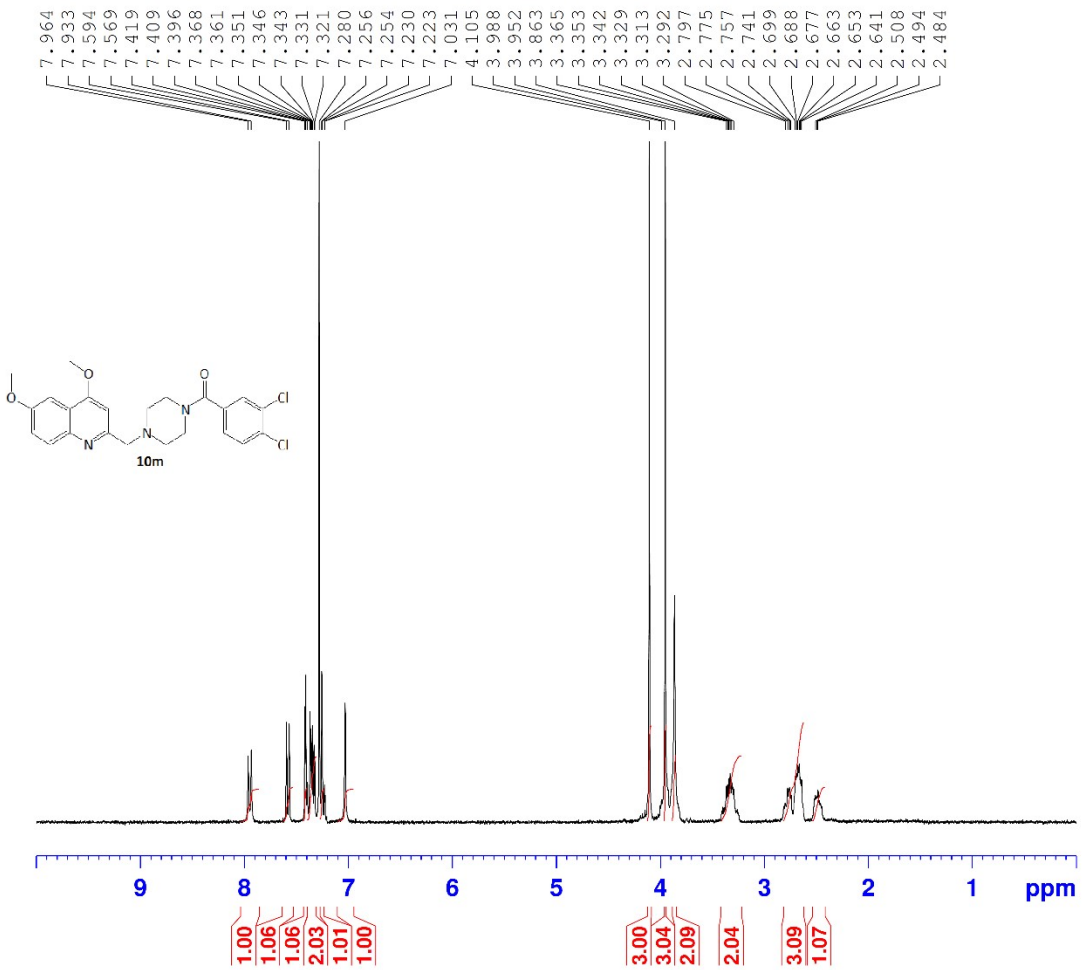
^{1}H NMR of 4[4-(4,6-Dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(2-fluoro-phenyl)-methanone (**10j**)



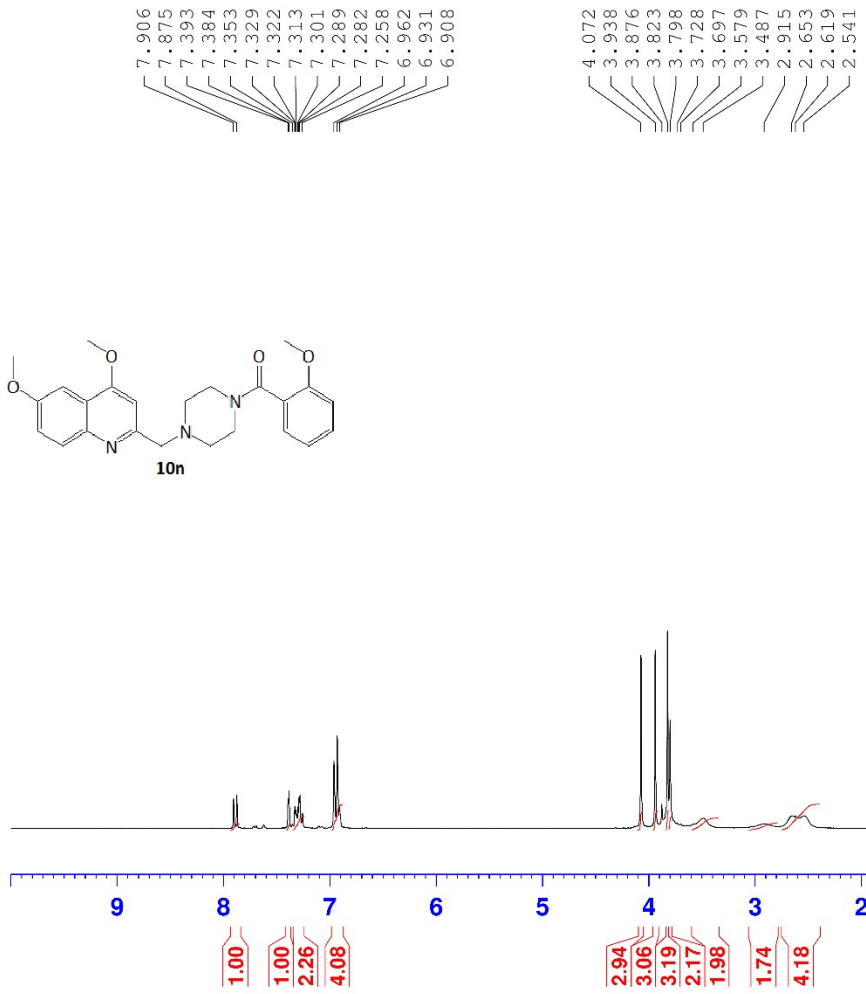
^{1}H NMR of (2,4-Dichloro-phenyl)-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (**10k**)



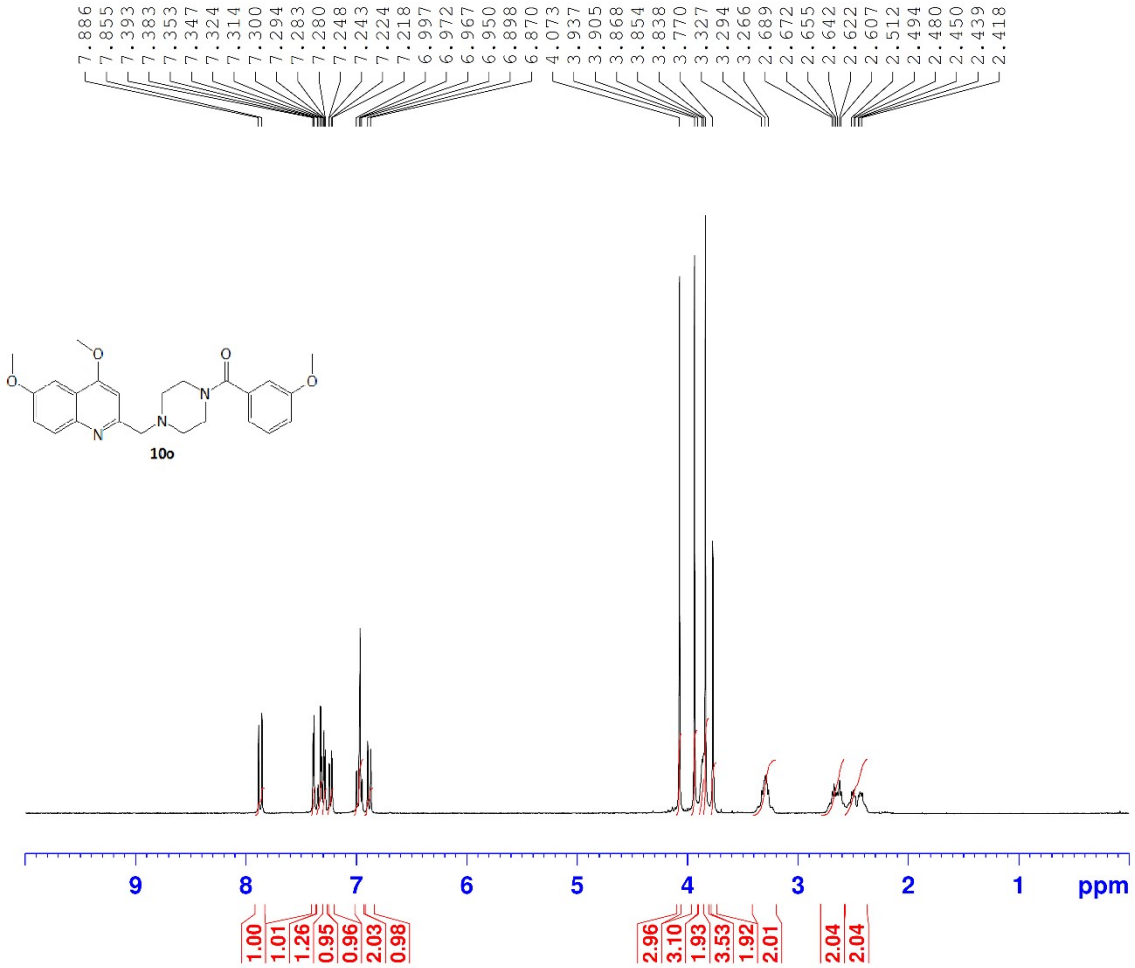
^{1}H NMR of (2,6-Dichloro-phenyl)-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (**10l**)



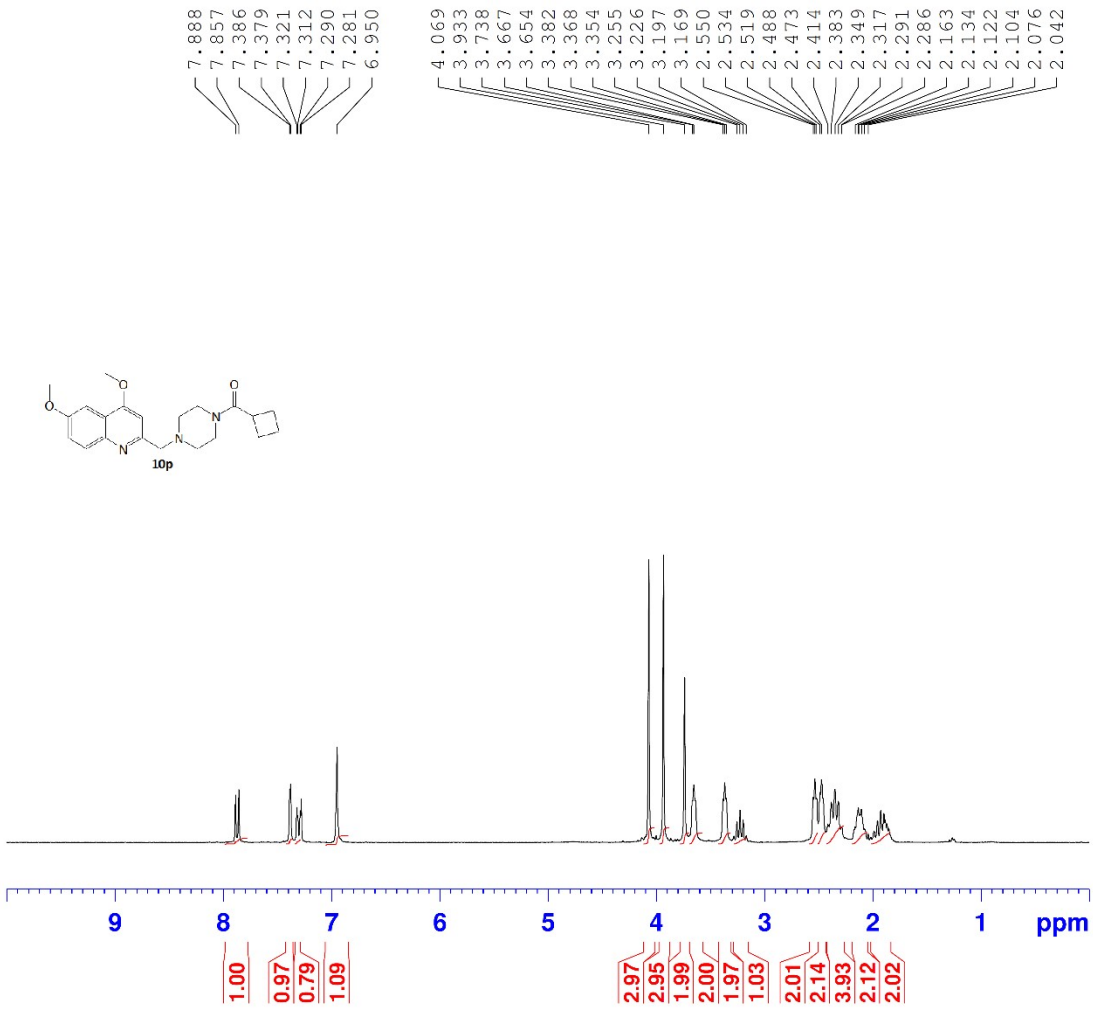
^{1}H NMR of (3,4-Dichloro-phenyl)-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (**10m**)



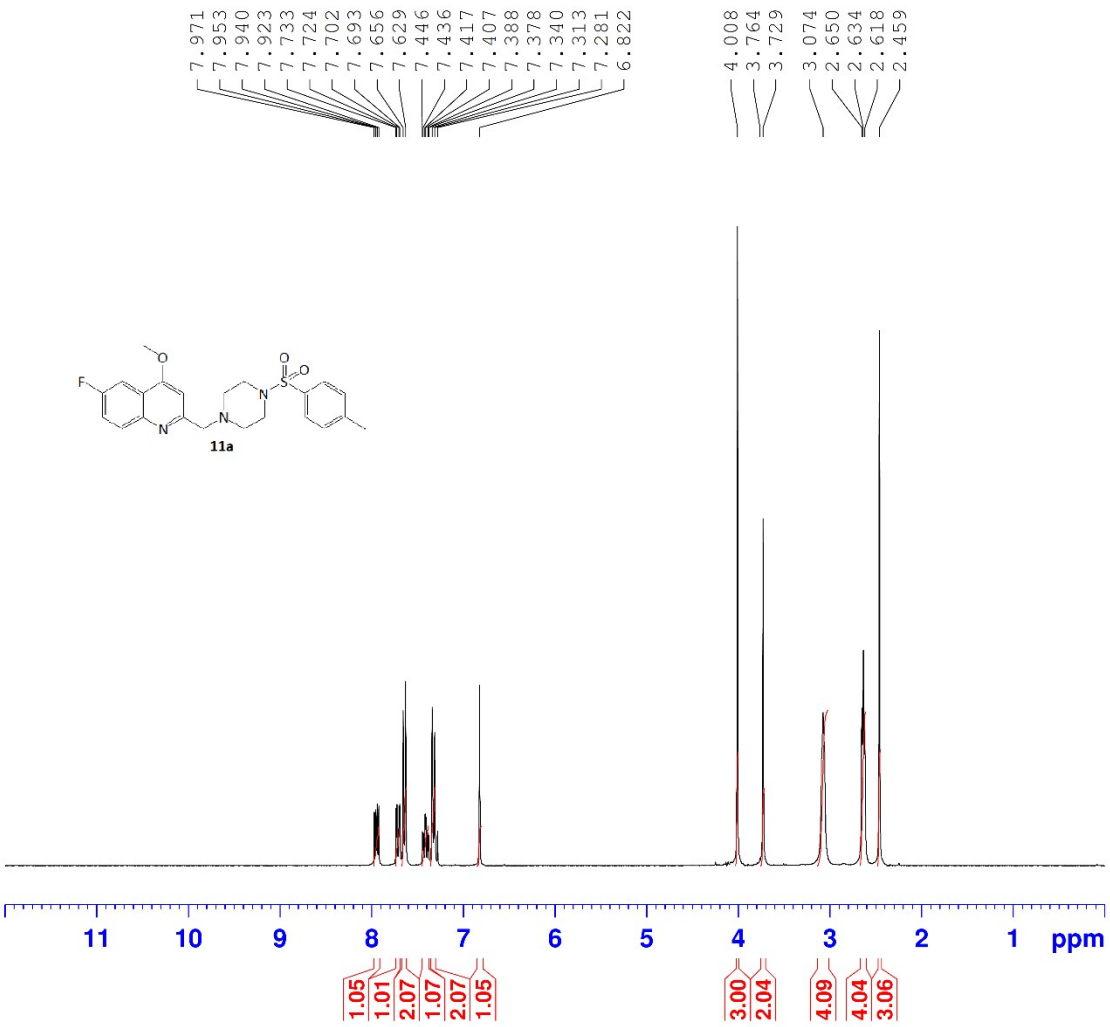
^{1}H NMR of [4-(4,6-Dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(2-methoxy-phenyl)-methanone (**10n**)



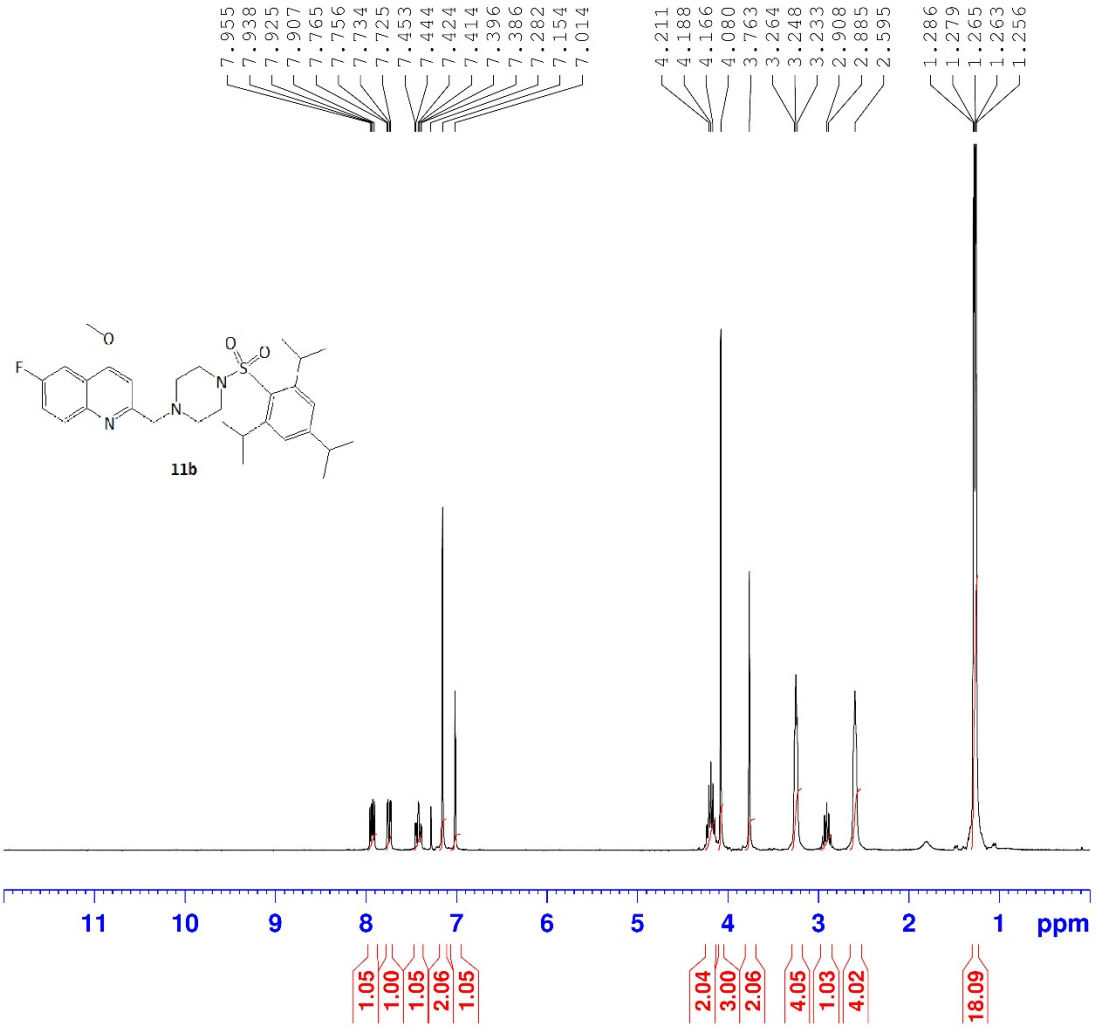
^{1}H NMR of [4-(4,6-Dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(3-methoxy-phenyl)-methanone (**10o**)



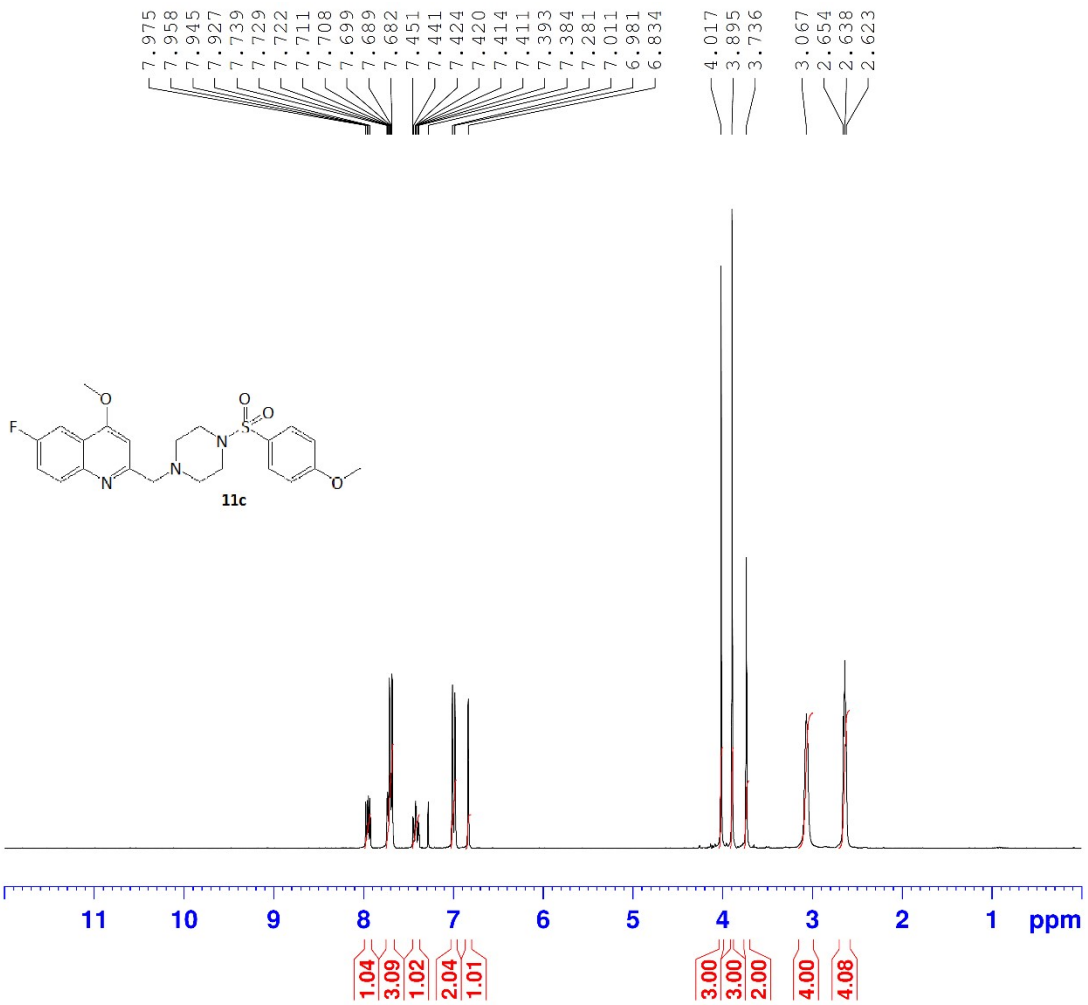
^{1}H NMR of Cyclobutyl-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (**10p**)



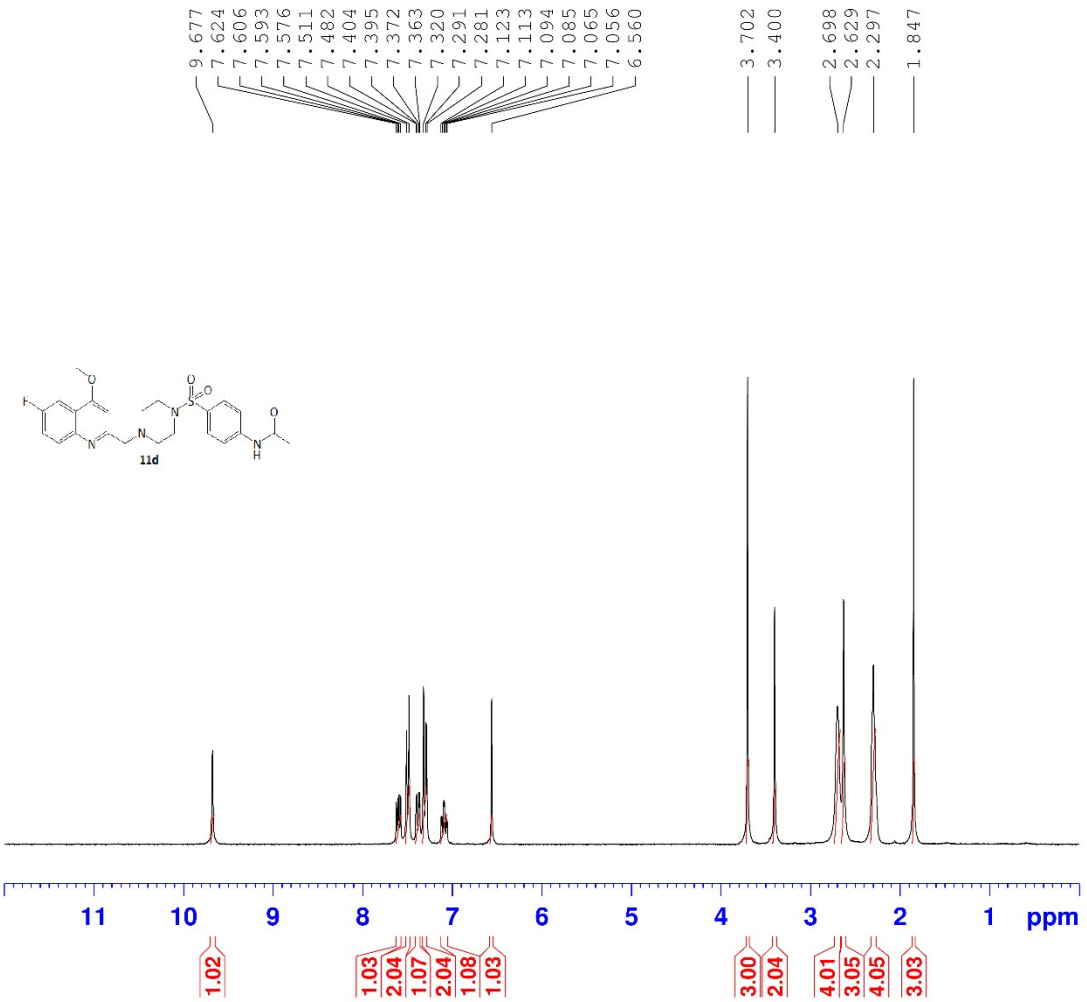
^{1}H NMR of 6-Fluoro-4-methoxy-2-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-quinoline (**11a**)



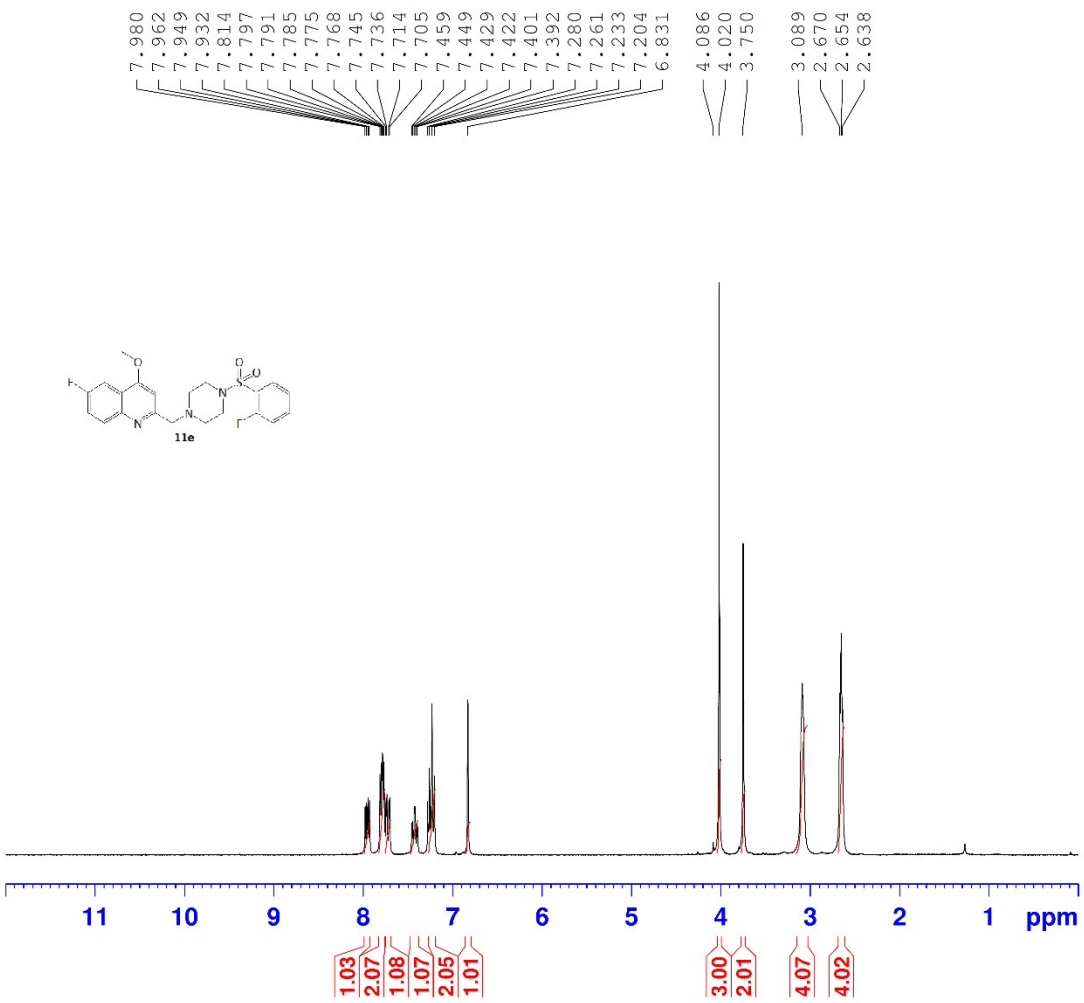
^{1}H NMR of 6-Fluoro-4-methoxy-2-[4-(2,4,6-triisopropyl-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline (**11b**)



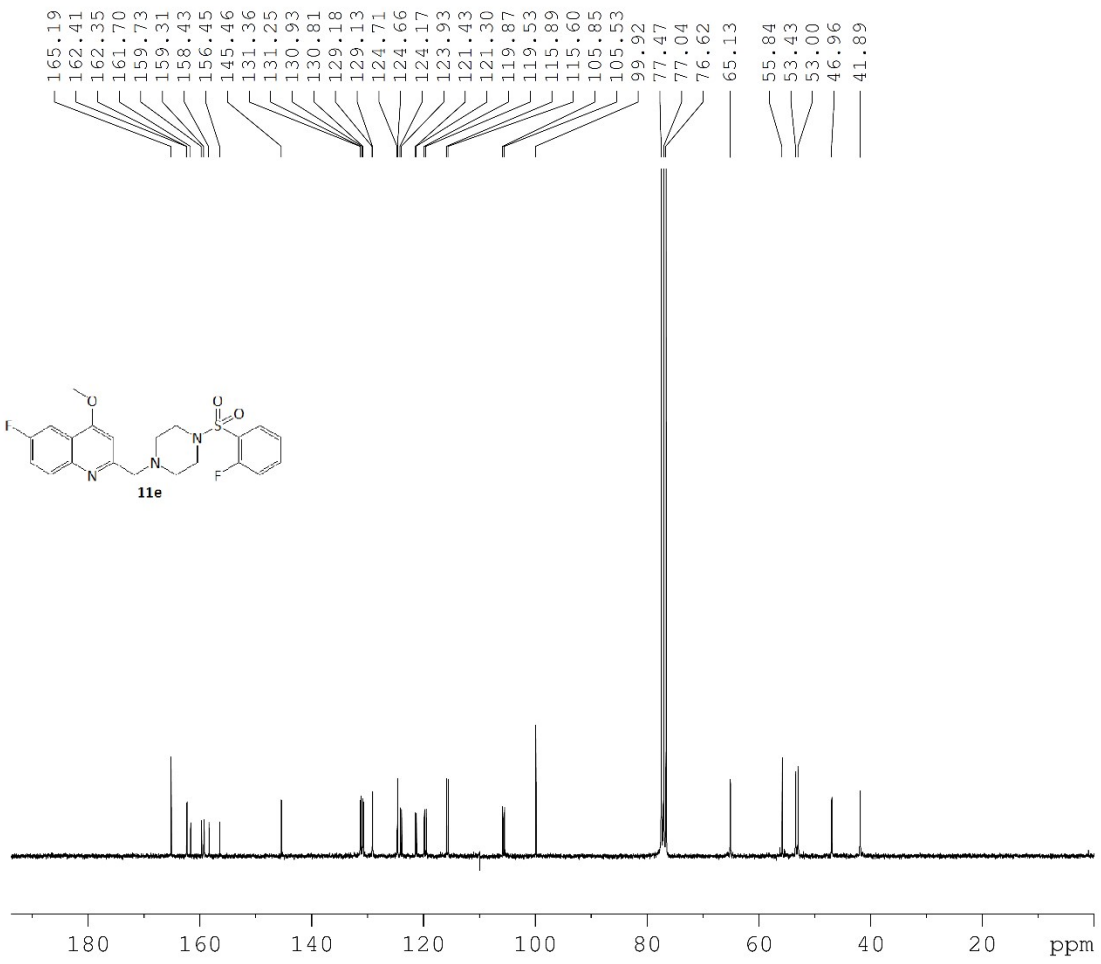
^{1}H NMR of 6-Fluoro-4-methoxy-2-[4-(4-methoxy-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline (**11c**)



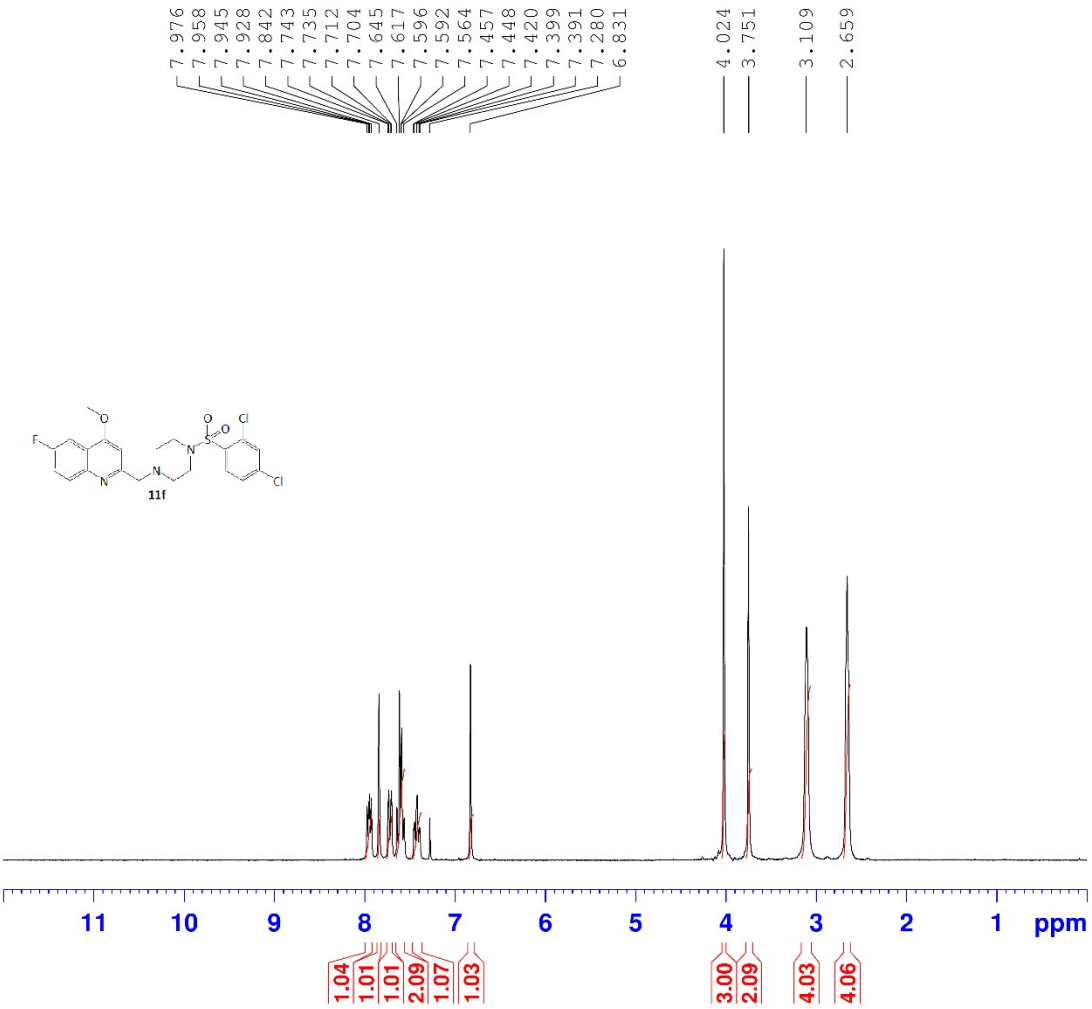
^{1}H NMR of *N*-{4-[4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**11d**)



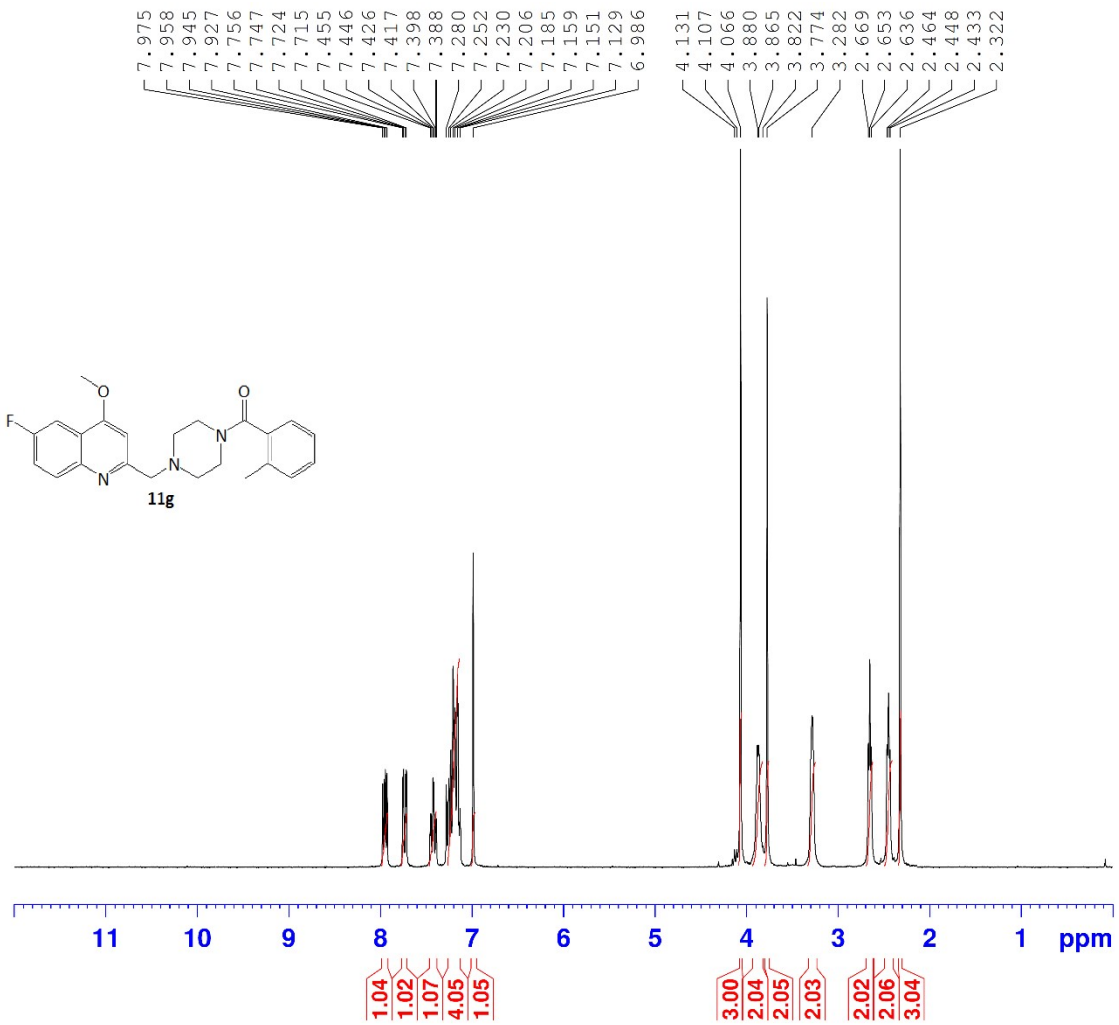
^{1}H NMR of 6-Fluoro-2-[4-(2-fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4-methoxy-quinoline (**11e**)



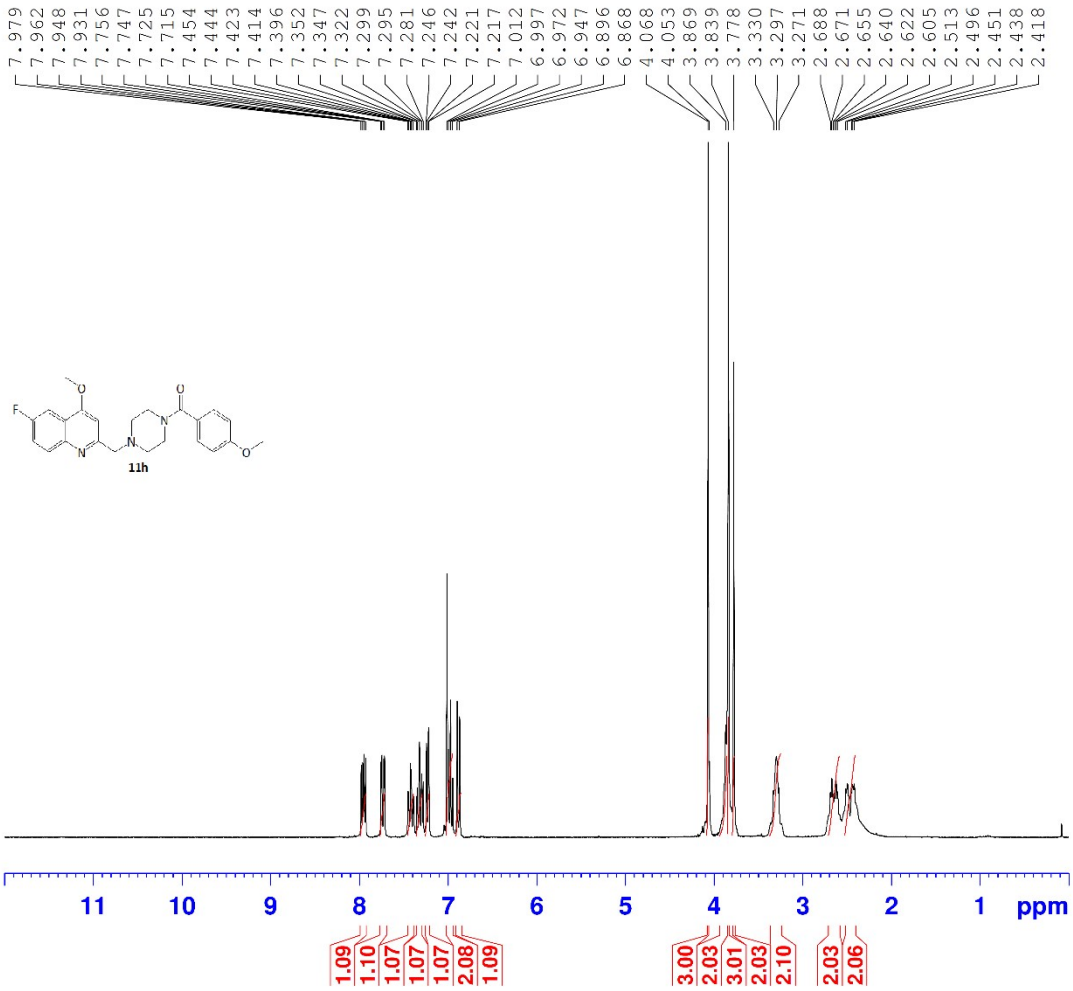
^{13}C NMR of 6-Fluoro-2-[4-(2-fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4-methoxy-quinoline (**11e**)



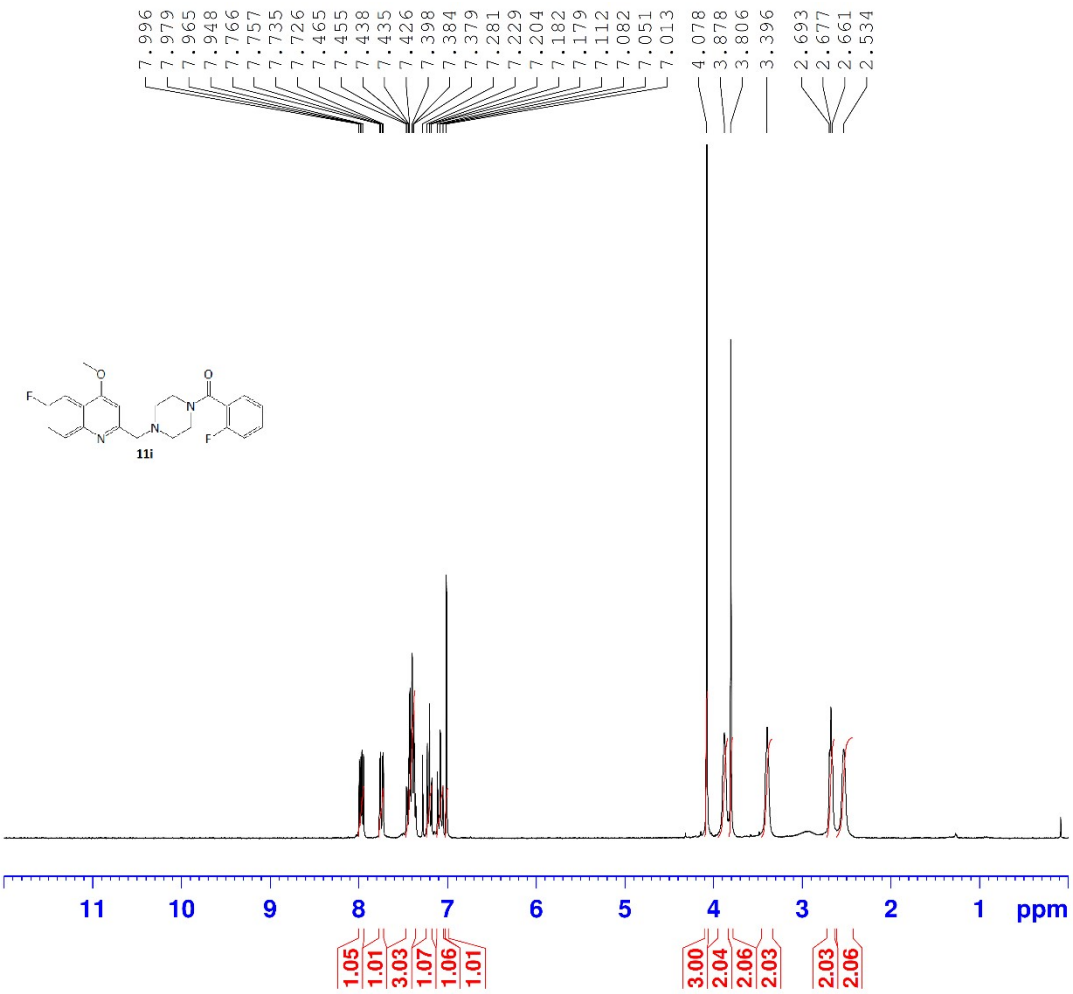
^{1}H NMR of 2-[4-(2,4-Dichloro-benzenesulfonyl)-piperazin-1-ylmethyl]-6-fluoro-4-methoxy-quinoline (**11f**)



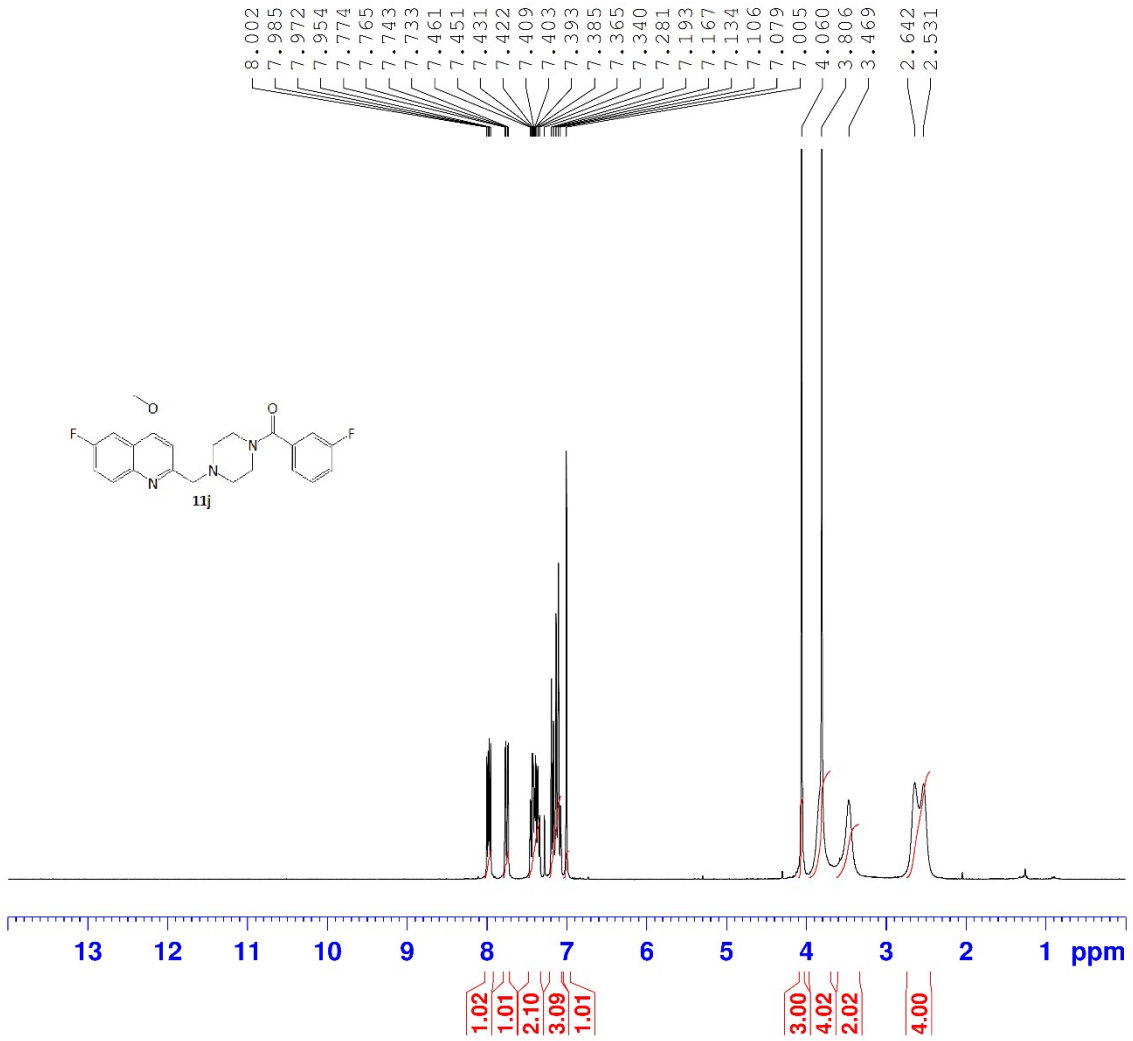
^{1}H NMR of [4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-o-tolyl-methanone (**11g**)



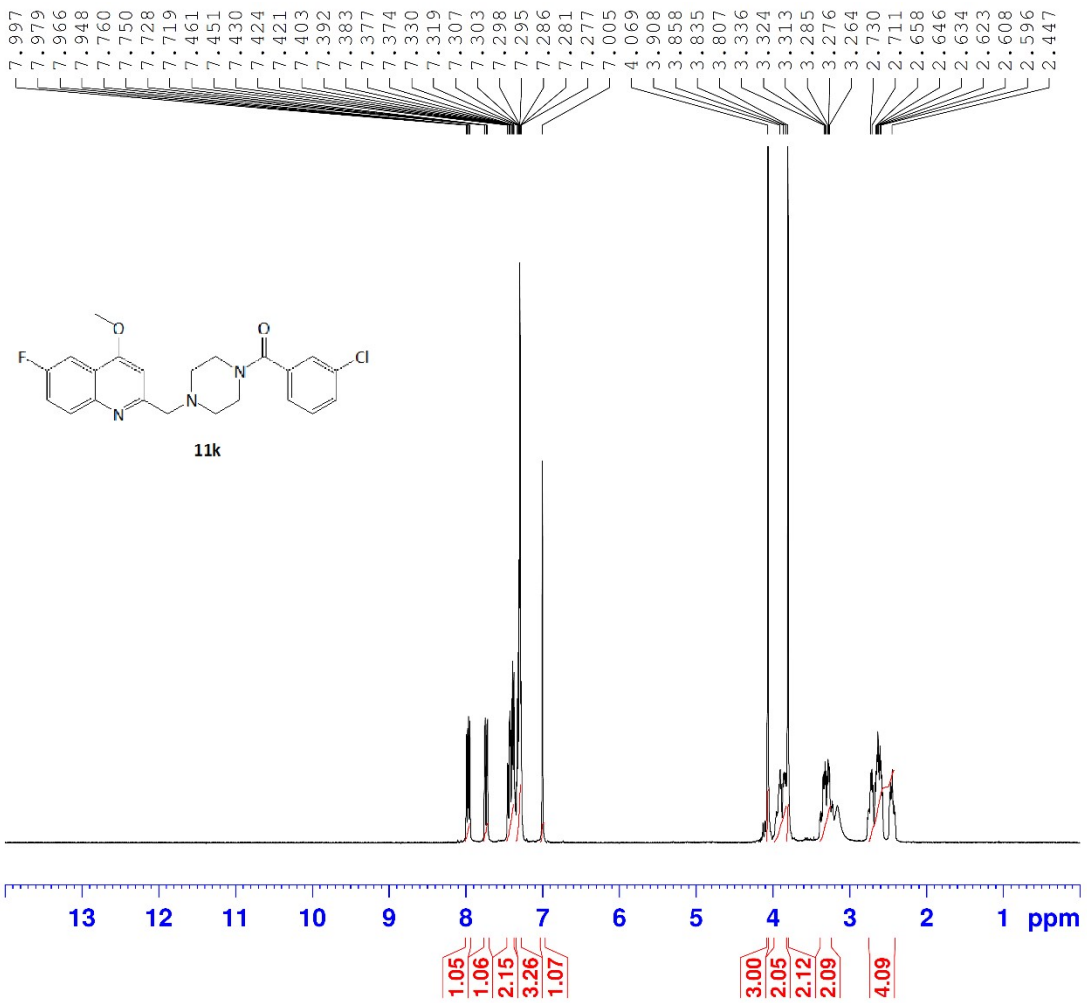
^{1}H NMR of [4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(4-methoxy-phenyl)-methanone (**11h**)



^{1}H NMR of [4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(2-fluoro-phenyl)-methanone (**11i**)

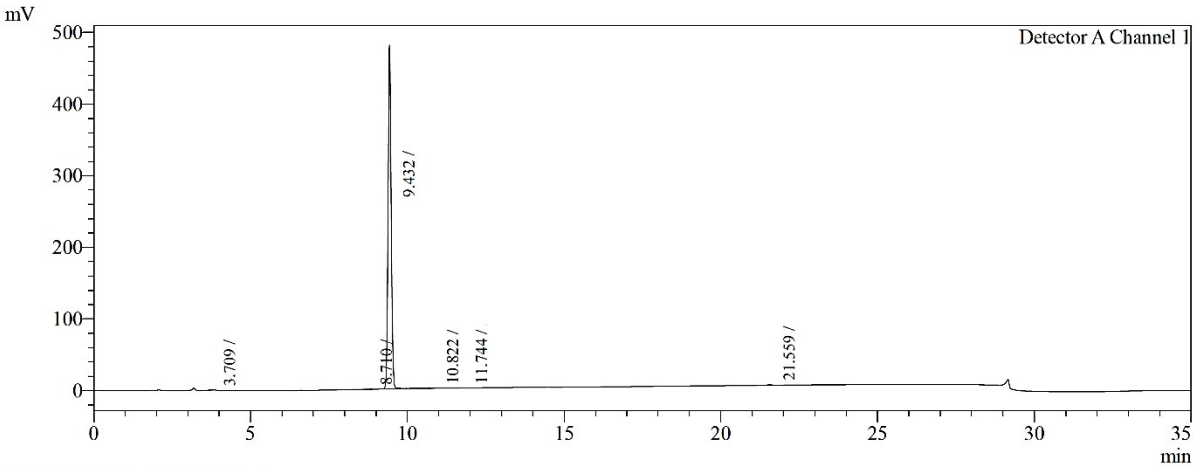


^{1}H NMR of [4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-(3-fluoro-phenyl)-methanone (**11j**)



^{1}H NMR of (3-Chloro-phenyl)-[4-(6-fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone (**11k**)

9. HPLC purity of precursors (7a and 7b) and active test compounds (10f, 10g, 10m, 10p, 11a, 11b, 11d and 11e).



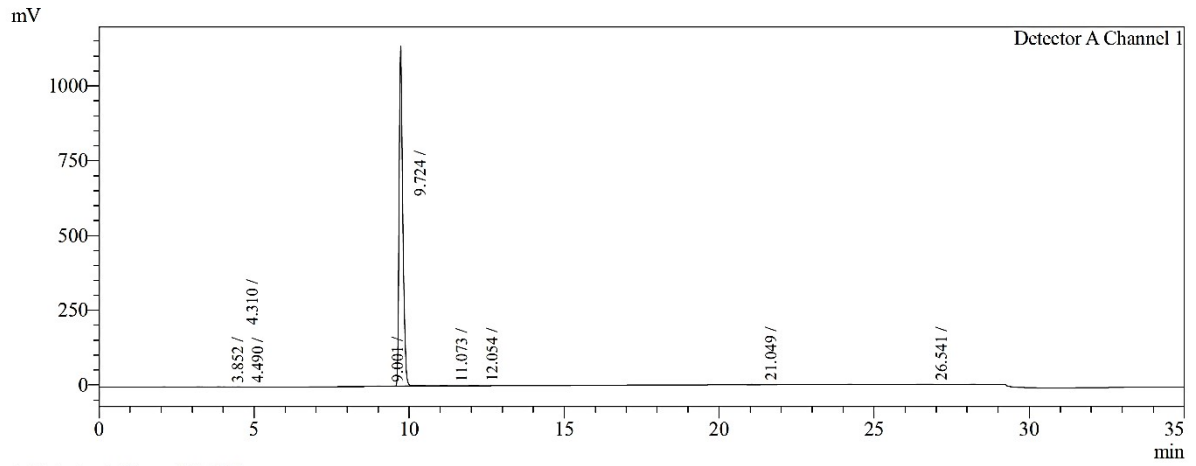
1 Detector A Channel 1 / 210nm

Peak Table

Detector A Channel 1 210nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	3.709	0.393	450	2215	0.067
2	8.710	0.923	323	2327	0.070
3	9.432	1.000	480033	3312474	99.492
4	10.822	1.147	70	432	0.013
5	11.744	1.245	286	2127	0.064
6	21.559	2.286	1244	9804	0.294
Total			482406	3329379	100.000

HPLC purity of 4,6-dimethoxy-2-piperazin-1-ylmethyl-quinoline TFA salt (**7a**)



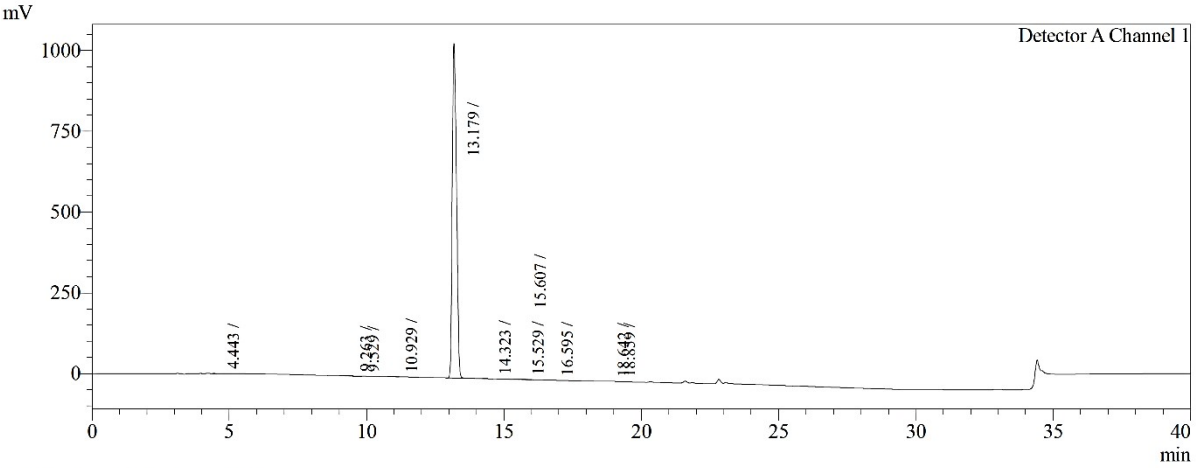
1 Detector A Channel 1 / 210nm

Peak Table

Detector A Channel 1 210nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	3.852	0.396	1101	5889	0.062
2	4.310	0.443	331	2156	0.023
3	4.490	0.462	496	4201	0.044
4	9.001	0.926	927	7114	0.075
5	9.724	1.000	1136365	9487903	99.584
6	11.073	1.139	102	604	0.006
7	12.054	1.240	354	2874	0.030
8	21.049	2.165	1416	11935	0.125
9	26.541	2.729	445	4903	0.051
Total			1141538	9527578	100.000

HPLC purity of 6-fluoro-4-methoxy-2-piperazin-1-ylmethyl-quinoline (**7b**)



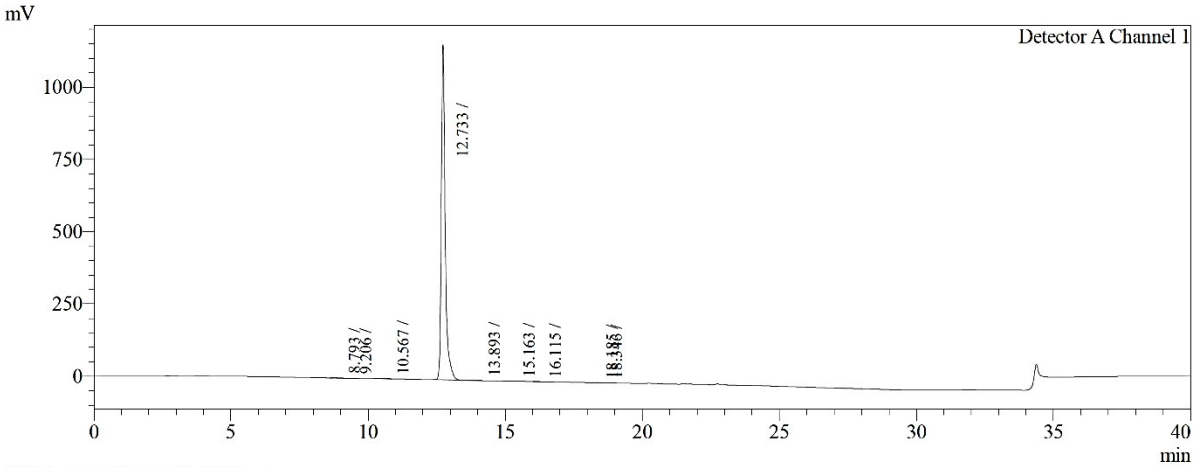
1 Detector A Channel 1 / 220nm

Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	4.443	0.337	484	2261	0.020
2	9.263	0.703	75	794	0.007
3	9.529	0.723	11	1307	0.012
4	10.929	0.829	224	2368	0.021
5	13.179	1.000	1034876	11076472	99.751
6	14.323	1.087	204	2378	0.021
7	15.529	1.178	444	2108	0.019
8	15.607	1.184	863	10657	0.096
9	16.595	1.259	319	3430	0.031
10	18.642	1.414	187	1278	0.012
11	18.859	1.431	185	1014	0.009
Total			1037871	11104068	100.000

HPLC purity of 4,6-Dimethoxy-2-[4-(2-trifluoromethyl-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline (**10f**)



1 Detector A Channel 1 / 220nm

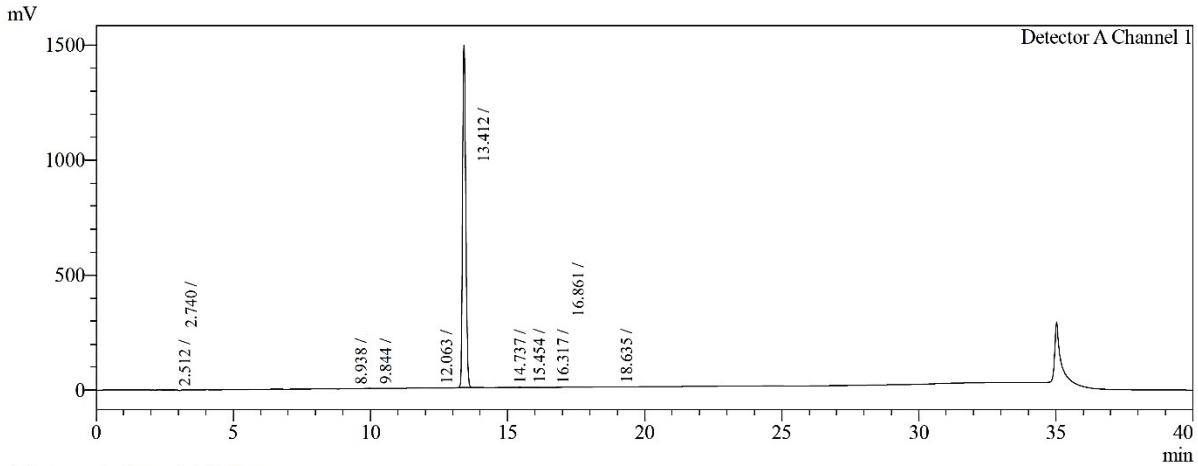
Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	8.793	0.691	792	9697	0.084
2	9.206	0.723	213	1714	0.015
3	10.567	0.830	140	1932	0.017
4	12.733	1.000	1160097	11510471	99.731
5	13.893	1.091	528	4989	0.043
6	15.163	1.191	754	7011	0.061
7	16.115	1.266	155	1393	0.012
8	18.185	1.428	296	2739	0.024
9	18.346	1.441	119	1624	0.014
Total			1163094	11541568	100.000

HPLC purity of 2-[4-(2-Fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4,6-dimethoxy-quinoline **(10g):**

HPLC purity of (3,4-Dichloro-phenyl)-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone **(10m)**



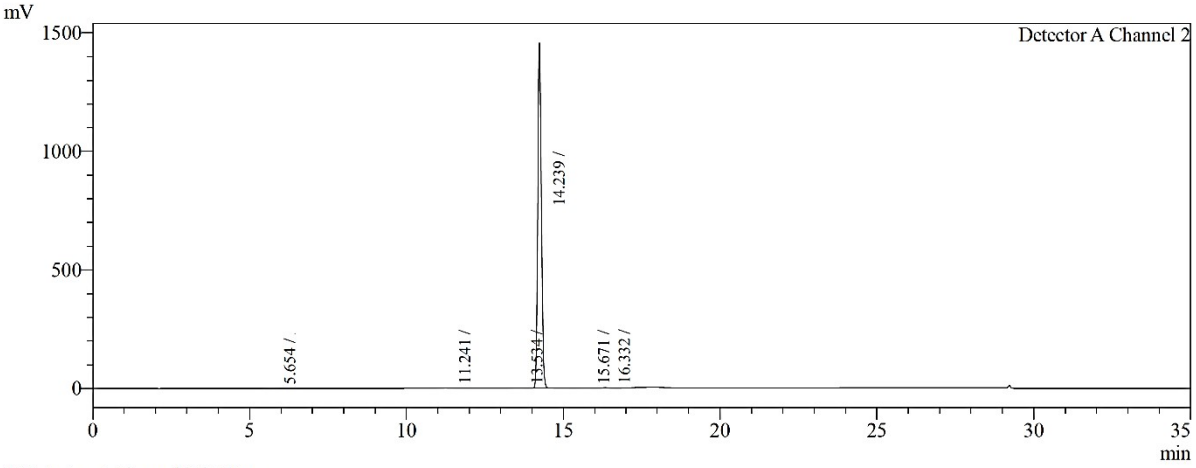
1 Detector A Channel 1 / 220nm

Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	2.512	0.187	205	1426	0.012
2	2.740	0.204	365	1886	0.015
3	8.938	0.666	280	2486	0.020
4	9.844	0.734	589	4471	0.037
5	12.063	0.899	86	692	0.006
6	13.412	1.000	1490274	12177062	99.743
7	14.737	1.099	761	6459	0.053
8	15.454	1.152	1036	8029	0.066
9	16.317	1.217	288	2271	0.019
10	16.861	1.257	308	2523	0.021
11	18.635	1.389	112	1087	0.009
Total			1494304	12208391	100.000

HPLC purity of Cyclobutyl-[4-(4,6-dimethoxy-quinolin-2-ylmethyl)-piperazin-1-yl]-methanone **(10p)**



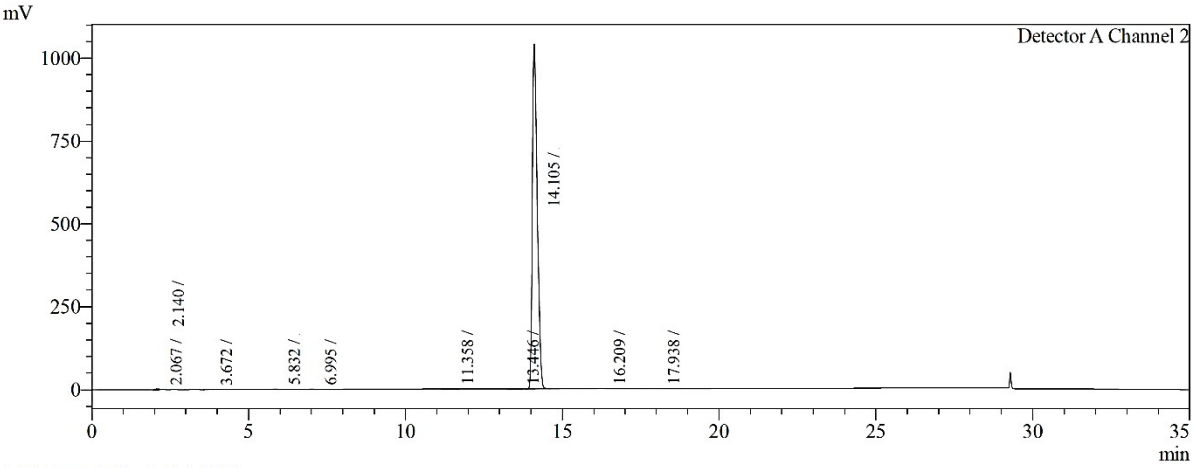
1 Detector A Channel 2 / 220nm

Peak Table

Detector A Channel 2 220nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	5.654	0.397	395	2994	0.026
2	11.241	0.789	1212	8980	0.077
3	13.534	0.950	681	5213	0.045
4	14.239	1.000	1455673	11637244	99.654
5	15.671	1.101	296	2345	0.020
6	16.332	1.147	2580	20859	0.179
Total			1460837	11677635	100.000

HPLC purity of 6-Fluoro-4-methoxy-2-[4-(toluene-4-sulfonyl)-piperazin-1-ylmethyl]-quinoline **(11a)**



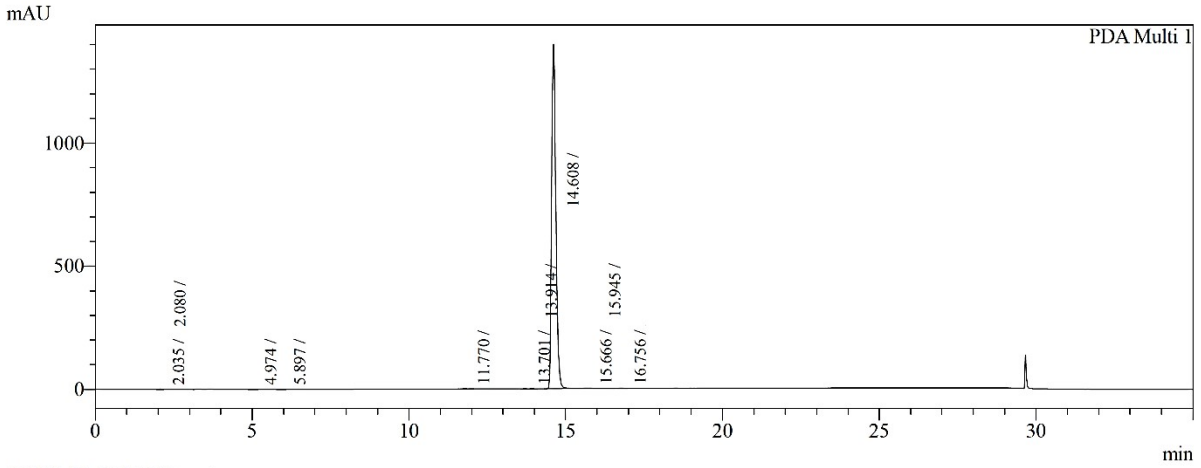
1 Detector A Channel 2 / 220nm

Peak Table

Detector A Channel 2 220nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	2.067	0.147	2375	11546	0.101
2	2.140	0.152	1224	4423	0.039
3	3.672	0.260	761	5147	0.045
4	5.832	0.413	1113	11422	0.100
5	6.995	0.496	483	5659	0.050
6	11.358	0.805	1075	11386	0.100
7	13.446	0.953	583	6520	0.057
8	14.105	1.000	1040277	11337528	99.394
9	16.209	1.149	1108	12410	0.109
10	17.938	1.272	86	607	0.005
Total			1049084	11406648	100.000

HPLC purity of 6-Fluoro-4-methoxy-2-[4-(2,4,6-triisopropyl-benzenesulfonyl)-piperazin-1-ylmethyl]-quinoline **(11b)**



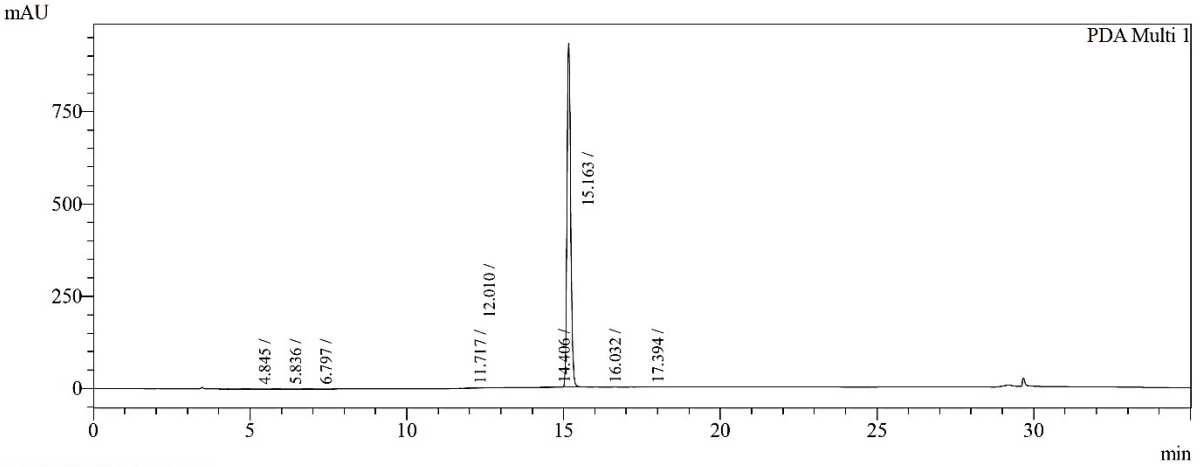
1 PDA Multi 1 / 220nm,4nm

Peak Table

PDA Ch1 220nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	2.035	0.139	1107	4642	0.035
2	2.080	0.142	949	2534	0.019
3	4.974	0.341	474	3544	0.027
4	5.897	0.404	861	7110	0.053
5	11.770	0.806	2101	17833	0.133
6	13.701	0.938	768	6637	0.050
7	13.914	0.952	906	7324	0.055
8	14.608	1.000	1399217	13259760	99.248
9	15.666	1.072	1192	30113	0.225
10	15.945	1.092	658	9944	0.074
11	16.756	1.147	1274	10803	0.081
Total			1409507	13360246	100.000

HPLC purity of *N*-{4-[4-(6-Fluoro-4-methoxy-quinolin-2-ylmethyl)-piperazine-1-sulfonyl]-phenyl}-acetamide (**11d)**



1 PDA Multi 1 / 220nm,4nm

Peak Table

PDA Ch1 220nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	4.845	0.320	403	2326	0.030
2	5.836	0.385	473	3241	0.042
3	6.797	0.448	246	2281	0.030
4	11.717	0.773	11	827	0.011
5	12.010	0.792	1310	10601	0.139
6	14.406	0.950	686	5424	0.071
7	15.163	1.000	930334	7604951	99.587
8	16.032	1.057	182	1192	0.016
9	17.394	1.147	672	5674	0.074
Total			934317	7636518	100.000

HPLC purity of 6-Fluoro-2-[4-(2-fluoro-benzenesulfonyl)-piperazin-1-ylmethyl]-4-methoxy-quinoline **(11e)**