Supporting information

Design, synthesis and biological evaluation of thiourea and nicotinamide-containing sorafenib analogs as antitumor agents

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1. Chemistry: general procedures

All the materials we used were purchased from commercial suppliers and without further purification. Solvents were distilled before using and flash chromatography was performed using silica gel (60 Å, 200–300 mesh). All reactions were monitored by thinlayer chromatography on 0.25 mm silica gel plates (60GF-254) and visualized with UV light. Melting points were determined on an electrothermal melting point apparatus and were uncorrected. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Brucker Avance 400 spectrometer using TMS as an internal standard in DMSO-d_6 solutions. Chemical shifts were reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane. ESI-MS were determined on an API 4000 spectrometer and reported as *m/z* (relative intensity). Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy).

1.1. 6-chloro-N-methylnicotinamide (2)

6-chloronicotinic methyl ester (10.0 g, 58.3 mmol) was dissolved in 10 mL methanol to get a light yellow solution; the methylamine in water solution was added dropwise at the temperature

range of 0-5℃ under stirring. The mixture was stirred at room temperature for 4 h and then concentrated in vacuo. The crude product was recrystallized in EtOAc to get a light yellow crystalline (**2**) 9.4 g, yield: 99.1%, Mp: 140-142℃. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.75 (d, J = 4.5 Hz, 3H), 6.89 (d, J = 8.8 Hz, 1H), 8.16 (dd, J = 8.7, 2.4 Hz, 1H), 8.46 (br d, J = 4.4 Hz, 1H), 8.57 (d, J = 2.3 Hz, 1H). ESI-MS *m/z* 171.1 $[M+H]^+$; Anal. Calcd for ($C_7H_7ClN_2O$ FW: 170.5); C, 49.28; H, 4.14; Cl, 20.78; N, 16.42. Found: C, 49.24; H, 4.16; Cl, 20.79; N, 16.43.

1.2. 6-(3-aminophenoxy)-N-methylnicotinamide (3)

A solution of 3-aminophenol (2.7 g, 25 mmol) in dry N,N-dimethylformamide (DMF, 50 mL) was treated with potassium tert-butoxide (2.8 g, 250 mmol), and the mixture was stirred at room temperature for 1 h under nitrogen atmosphere, then a solution of (**2**) (4.0 g, 23.5 mmol) in DMF (25 mL) and potassium carbonate were added respectively. The mixture was heated to 80–85℃ for 18 h. After cooling to room temperature, the mixture was diluted with water (200 mL) and extracted with EtOAc (3×100 mL). The extract was washed with brine (2×100mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give light-brown solid (**3**) 1.62 g, yield: 42.1%, Mp: 144-146℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.79 (d, J = 4.48 Hz, 3H), 5.33 (s, 2H), 6.95 (m, 1H), 7.11 (d, J = 8.56 Hz, 1H), 7.41 (m, 2H), 7.46 (t, J = 1.84 Hz, 1H), 8.23 (dd, J = 2.4, 8.6 Hz, 1H), 8.52 (q, J = 4.48 Hz, 1H), 8.59 (d, J = 2.28 Hz, 1H); ESI-MS *m/z* 244.2 $[M+H]^+$; Anal. Calcd for ($C_{13}H_{13}N_3O_2$ FW: 243); C, 64.19; H, 5.39; N, 17.27. Found: C, 64.21; H, 5.37; N, 17.28.

1.3. 1-bromo-4-isothiocyanato-2-(trifluoromethyl)benzene (6a)

To a solution of 3-trifluoromethyl-4-bromoaniline (2.06 g, 15.5 mmol) and triethylenediamine (2.08 g, 18.6 mmol) in 40 mL toluene, CS_2 (3.5 g, 46.5 mmol) was added slowly. The resulting mixture was stirred at room temperature for 8 h. After filtration, the filter cake was washed with toluene and dried. Obtained **5a** was suspended in 40 mL DCM. Then, a 25 mL DCM solution of BTC (5.0 g, 17.0 mmol) was added slowly under -5–0℃. The mixture was stirred for 2 h at room temperature, and then was refluxed for 1.5–2 h. After filtration, the filtrate was concentrated in vacuo. The crude product was purified by chromatography (ethyl acetate/petroleum ether = 1:1) on silica gel to give 0.14 g yellow liquid. Yield = 79.8%, Mp: 34-36℃.（B. Xie, G.G. Zhou, *Chemical Industry Times*, 2006, **20**, 71-75.）

1.4. 1-fluoro-4-isothiocyanato-2-(trifluoromethyl)benzene (6b)

The synthesis is analogous to (**6a**) with 3-trifluoromethyl-4-fluoroaniline as the starting material. The product was obtained as a yellow liquid. Yield = 79.8%; Bp: 228-230℃. (B. Xie, G.G. Zhou, *Chemical Industry Times*, 2006, **20**, 71-75.)

1.5. 2-chloro-1-fluoro-4-isothiocyanatobenzene (6c)

The synthesis is analogous to (**6a**) with 3-chloro-4-fluoroaniline as the starting material. The product was obtained as a light yellow liquid. Yield = 79.8%, Bp: 228-230℃. (S.Q. Jiang, Z.Y. Wang, Z.J. Jiang, W.Y. Chen, J.H. Li, *Journal of Sichuan Normal University(Nature Science)*, 2011, **34**, 388-391.)

1.6. 1-isothiocyanato-3-(trifluoromethyl)benzene (6d)

The synthesis is analogous to (**6a**) with 3-trifluoromethylaniline as the starting material. The product was obtained as a light yellow liquid. Yield = 75.2%, Bp: 206-208℃. (S.Q. Jiang, Z.Y. Wang, Z.J. Jiang, W.Y. Chen, J.H. Li, *Journal of Sichuan Normal University(Nature Science)*, 2011, **34**, 388-391.)

1.7. 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (6e)

The synthesis is analogous to (**6a**) with 3,5-bis-trifluoromethylaniline as the starting material. The product was obtained as a light yellow liquid. Yield = 70.2%, Bp: 63℃ (2.5 mmHg). (S.Q. Jiang, Z.Y. Wang, Z.J. Jiang, W.Y. Chen, J.H. Li, *Journal of Sichuan Normal University(Nature Science)*, 2011, 34, 388-391.)

1.8. 1-chloro-4-isothiocyanatobenzene (6f)

The synthesis is analogous to (**6a**) with 4-chloroaniline as the starting material. The product was obtained as a light brown solid. Yield = 86.6%, Mp: 43-45℃. (P. Zhu, J.Y. Feng, *Journal of Nanyang Teachers' College*, 2005, **4**, 57-60.)

1.9. 1,2-difluoro-4-isothiocyanatobenzene (6g)

The synthesis is analogous to (**6a**) with 3,4-difluoroaniline as the starting material. The product was obtained as a light yellow liquid. Yield = 74.5%, Bp: 170℃. (S.Q. Jiang, Z.Y. Wang, Z.J. Jiang, W.Y. Chen, J.H. Li, *Journal of Sichuan Normal University(Nature Science)*, 2011, **34**, 388-391.)

1.10. 1-chloro-4-isothiocyanato-2-(trifluoromethyl)benzene (6h)

The synthesis is analogous to (**6a**) with 3-trifluoromethyl-4-chloroaniline as the starting material. The product was obtained as a light yellow liquid. Yield = 84.7%, Bp: 248-251℃.（B. Xie, G.G.

Zhou, *Chemical Industry Times*, 2006, **20**, 71-75.）

1.11. 1-isothiocyanato-4-(trifluoromethoxy)benzene (6i)

The synthesis is analogous to (**6a**) with 4-trifluoromethoxyaniline as the starting material. The product was obtained as a light yellow liquid. Yield = 78.7%, Bp: 230-231℃.（B. Xie, G.G. Zhou, *Chemical Industry Times*, 2006, **20**, 71-75.）

1.12. 2,4-dichloro-1-isothiocyanatobenzene (6j)

The synthesis is analogous to (**6a**) with 2,4-Dichloroaniline as the starting material. The product was obtained as a white solid. Yield = 60.0%, Mp: 37-42℃. (S.Q. Jiang, Z.Y. Wang, Z.J. Jiang, W.Y. Chen, J.H. Li, *Journal of Sichuan Normal University(Nature Science)*, 2011, **34**, 388-391.)

1.13. 1-isothiocyanato-4-methylbenzene (6k)

The synthesis is analogous to (**6a**) with 4-methylaniline as the starting material. The product was obtained as a white solid. Yield = 68.2%, Mp: 25-26℃. (P. Zhu, J.Y. Feng, *Journal of Nanyang Teachers' College*, 2005, **4**, 57-60.)

1.14. 4-isothiocyanato-1,2-dimethylbenzene (6l)

The synthesis is analogous to (**6a**) with 3,4-dimethylaniline as the starting material. The product was obtained as a white solid. Yield = 74.2%, Mp: 74-76℃.（B. Xie, G.G. Zhou, *Chemical Industry Times*, 2006, **20**, 71-75.）

1.15. 1-fluoro-4-isothiocyanatobenzene (6m)

The synthesis is analogous to (**6a**) with 4-fluoroaniline as the starting material. The product was obtained as a light yellow solid. Yield = 63.9%, Mp: 25-26℃. (P. Zhu, J.Y. Feng, *Journal of Nanyang Teachers' College*, 2005, **4**, 57-60.)

1.16. 1-isothiocyanato-4-methoxybenzene (6n)

The synthesis is analogous to (**6a**) with 4-methoxylaniline as the starting material. The product was obtained as a white solid. Yield = 58.7%, Mp: 18-20℃. (S.Q. Jiang, Z.Y. Wang, Z.J. Jiang, W.Y. Chen, J.H. Li, *Journal of Sichuan Normal University(Nature Science)*, 2011, **34**, 388-391.)

1.17.

6-{3-[3-(4-Bromo-3-trifluoromethyl-phenyl)-thioureido]-phenoxy}-N-methyl-nicotinamide (7a)

To a 10 mL DMF solution of compound **3** (1.00 g, 4.12 mmol), a DMF solution of **6a** (0.99 g, 4.12 mmol) was added slowly at 0–5℃ under nitrogen atmosphere. The mixture was stirred for 0.5 h

in ice bath, and then stirred for another 8 h at room temperature. The mixture was poured in water (100 mL) and extracted with EtOAc (3×50 mL). The extract was washed with brine (2×50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to get the crude product. The crude product was purified by chromatography to get an off white solid. Yield = 62.5%, HPLC: 97.59%, Mp: 147-150℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.80 (d, J = 4.48 Hz, 3H), 6.96-6.99 (m, 1H), 7.10 (d, J = 8.64 Hz, 1H), 7.35 (d, J = 8.68 Hz, 1H), 7.40-7.44 (m, 2H), 7.72 (dd, J = 2.48, 8.68 Hz, 1H), 7.82 (d, J = 8.68 Hz, 1H), 8.09 (d, J = 2.48 Hz, 1H), 8.25 (dd, J = 2.44 Hz, 8.60 Hz, 1H), 8.51 (q, J = 4.48 Hz, 1H), 8.61 (d, J = 2.28 Hz, 1H), 10.16 (s, 1H), 10.20 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.09, 110.79 , 112.90 (q, J = 1.62 Hz), 116.19, 117.49, 119.86, 122.63 (q, J = 5.52 Hz), 122.77 (q, J = 271 Hz), 125.66, 128.04(q, J = 30.30 Hz), 128.46 , 129.62, 135.00 , 139.08, 139.51, 140.31, 146.98, 153.41, 164.29, 164.51, 179.55; ESI-MS *m/z* 526.0 $[M+H]^+$; Anal. Calcd for ($C_{21}H_{16}BrF_3N_4O_2S$ FW: 525): C, 48.01; H, 3.07; Br, 15.21; F, 10.85; N, 10.66; S, 6.10. Found: C, 48.02; H, 3.04; Br, 15.26; F, 10.83; N, 10.65; S, 6.12.

The other compounds of **7** series were synthesized following the general procedure as described above.

1.18.

6-{3-[3-(4-Fluoro-3-trifluoromethyl-phenyl)-thioureido]-phenoxy}-N-methyl-nicotinamide (7b)

Off white solid, Yield = 52.4%, HPLC: 97.80%, Mp: 126-128℃. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.80 (d, J = 4.52 Hz, 3H), 6.96-6.99 (m, 1H), 7.12 (d, J = 8.64 Hz, 1H), 7.35 (d, J = 8.44 Hz, 1H), 7.40-7.44 (m, 2H), 7.49 (t, J = 9.52 Hz, 1H), 7.77-7.81 (m, 1H), 7.94 (dd, J = 2.40, 8.80 Hz, 1H), 8.25 (dd, J = 2.44 Hz, 8.60 Hz, 1H), 8.55 (q, J = 4.48 Hz, 1H), 8.61 (d, J = 2.44 Hz, 1H), 10.05 (s, 1H), 10.17 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.15, 110.83, 116.31, 117.05, 117.26, 117.51, 119.95, 122.64 (q, J = 4.56 Hz), 125.66, 129.68, 130.67 (d, J = 8.38 Hz), 136.26 (d, J = 2.98 Hz), 139.14, 140.43, 147.04, 153.43, 154.28, 156.78, 164.37, 164.56, 180.01; ESI-MS *m/z* 465.1 $[M+H]^+$; Anal. Calcd for ($C_{21}H_{16}F_4N_4O_2S$ FW: 464): C, 54.31; H, 3.47; F, 16.36; N, 12.06; S, 6.90. Found: C, 54.33; H, 3.42; F, 16.31; N, 12.07; S, 6.89.

1.19. 6-{3-[3-(3-Chloro-4-fluoro-phenyl)-thioureido]-phenoxy}-N-methyl-nicotinamide (7c)

Off white solid, Yield = 55.0%, HPLC: 98.66%, Mp: 149-151℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.80 (d, J = 4.48 Hz, 3H), 6.95-6.97 (m, 1H), 7.11 (d, J = 8.64 Hz, 1H), 7.34-7.44 (m, 5H), 7.78

(dd, *J* = 2.48, 8.68 Hz, 1H), 8.25 (dd, *J* = 2.44, 8.60 Hz, 1H), 8.51 (q, *J* = 4.48 Hz, 1H), 8.62 (d, *J* = 2.28 Hz, 1H), 9.93 (s, 1H), 10.04 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.09, 110.76, 116.14, 116.31, 116.53, 117.26, 119.81, 124.70 (d, *J* = 6.91 Hz), 125.64, 125.91, 129.51, 136.53 (d, *J*= 3.12 Hz), 139.06, 140.53, 147.00, 153.35, 155.46, 164.32, 164.52, 179.83; ESI-MS *m/z* 431.0 $[M+H]^+$; Anal. Calcd for ($C_{20}H_{16}ClFN_4O_2S$ FW: 431): C, 55.75; H, 3.74; Cl, 8.23; F, 4.41; N, 13.00; S, 7.44. Found: C, 55.74; H, 3.75; Cl, 8.26; F, 4.41; N, 13.02; S, 7.41.

1.20. 6-{3-[3-(3-trifluoromethyl-phenyl)-thioureido]-phenoxy}-N-Methyl-nicotinamide (7d)

Off white solid, Yield = 50.6%, HPLC: 99.32%, Mp: 146-149℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.79 (d, *J* = 4.52 Hz, 3H), 6.94-6.96 (m, 1H), 7.10 (d, *J* = 8.64 Hz, 1H), 7.33 (d, *J* = 8.16 Hz, 1H), 7.37-7.42 (m, 2H), 7.46 (d, *J* = 7.84 Hz, 1H), 7.56 (t, *J* = 8.16 Hz, 1H), 7.75 (d, *J* = 8.16Hz, 1H), 7.95 (s, 1H) 8.24 (dd, *J* = 2.44 Hz, 8.60 Hz, 1H), 8.51 (q, *J* = 4.48 Hz, 1H), 8.59 (d, *J* = 2.28 Hz, 1H), 10.09 (s, 1H), 10.12 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.13, 110.82, 116.15, 117.39, 119.86, 120.72 (q, *J* = 3.67 Hz), 124.11 (q, *J* = 270 Hz), 125.66 , 127.39, 127.39, 129.03 (q, *J* = 31.77 Hz), 129.53, 129.63, 139.13, 140.34, 140.52, 147.04, 153.40, 164.37, 164.56, 179.68; ESI-MS *m/z* 447.0 $[M+H]^+$; Anal. Calcd for ($C_{21}H_{17}F_3N_4O_2S$ FW: 446): C, 56.50; H, 3.84; F, 12.77; N, 12.55; S, 7.18. Found: C, 56.51; H, 3.86; F, 12.74; N, 12.52; S, 7.19.

1.21. 6-{3-[3-(3,5-Bis-trifluoromethyl-phenyl)-thioureido]-phenoxy}-N-methyl-nicotinamide (7e)

Brown solid, Yield = 70.8%, HPLC: 98.83%, Mp: 153-154℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.79 (d, *J* = 4.52 Hz, 3H), 6.98-7.00 (m, 1H), 7.11 (d, *J* = 8.64 Hz, 1H), 7.32-7.37 (m, 2H), 7.42 (t, *J* = 8.04 Hz, 1H), 7.56 (t, *J* = 8.16 Hz, 1H), 7.80 (s, 1H) 8.23 (dd, *J* = 2.44, 8.60 Hz, 1H), 8.24 (s, 2H), 8.51 (q, *J* = 4.48 Hz, 1H), 8.59 (d, *J* = 2.28 Hz, 1H), 10.29 (s, 1H), 10.37 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.12, 110.83, 116.52, 117.00, 117.87, 120.13, 123.24 (q, *J* = 271 Hz), 123.67, 125.68, 125.54, 129.80, 130.04 (q, *J* = 32.47 Hz), 139.13, 140.08, 141.76, 147.01, 153.51, 164.32, 164.53, 179.79; ESI-MS *m/z* 515.0 $[M+H]^+$; Anal. Calcd for ($C_{22}H_{16}F_6N_4O_2S$ FW: 514): C, 51.36; H, 3.13; F, 22.16; N, 10.89; S, 6.23. Found: C, 51.35; H, 3.14; F, 22.13; N, 10.91; S, 6.25.

1.22. 6-{3-[3-(4-Chloro-phenyl)-thioureido]-phenoxy}-N-methyl-nicotinamide (7f)

Off white solid, Yield = 67.7%, HPLC: 99.50%, Mp: 154-156℃. ^{1}H-NMR (400MHz, DMSO-d_6) δ 2.80 (d, *J* = 4.52 Hz, 3H), 6.91-6.96 (m, 1H), 7.10 (d, *J* = 8.56 Hz, 1H), 7.36-7.41 (m, 4H), 7.49 (s, 1H), 7.55-7.58 (m, 2H), 8.24 (dd, *J* = 2.48, 8.64 Hz, 1H), 8.52 (q, *J* = 4.48 Hz, 1H), 8.62

(d, J = 2.28 Hz, 1H), 10.20 (s, 1H), 10.23 (s, 1H); ^{13}C-NMR (100MHz, DMSO-d_6): δ 26.07 (s, 1C), 110.72 (s, 1C), 115.71 (s, 1C), 116.97 (s, 1C), 119.43 (s, 1C), 125.05 (s, 2C), 125,61 (s, 1C), 128.24 (s, 2C), 129.41 (s, 1C), 138.32 (s, 1C), 139.06 (s, 1C), 140.74 (s, 1C), 147.02 (s, 1C), 147.12 (s, 1C), 153.26 (s, 1C), 164.33 (s, 1C), 164.53 (s, 1C), 179.36 (s, 1C); ESI-MS *m/z* 413.1 $[M+H]^+$; Anal. Calcd for ($C_{20}H_{17}ClN_4O_2S$ FW: 413): C, 58.18; H, 4.15; Cl, 8.59; N, 13.57; S, 7.77. Found: C, 58.16; H, 4.15; Cl, 8.56; N, 13.58; S, 7.78.

1.23. 6-{3-[3-(3,4-Difluoro-phenyl)-thioureido]-phenoxy}-N-methyl-nicotinamide (7g)

Off white solid, Yield = 58.6%, HPLC: 99.87%, Mp: 159-160℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.80 (d, J = 4.52 Hz, 3H), 6.95-6.97 (m, 1H), 7.11 (d, J = 8.64 Hz, 1H), 7.23-7.25 (m, 1H), 7.35 (d, J = 8.80 Hz, 1H), 7.39-7.44 (m, 3H), 7.67-7.73 (m, 1H), 8.25 (dd, J = 2.44 Hz, 8.60 Hz, 1H), 8.53 (q, J = 4.48 Hz, 1H), 8.62 (d, J = 2.28 Hz, 1H), 9.99 (s, 1H), 10.04 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.14, 110.81, 115.14 (dd, J = 20.11, 374 Hz), 116.21, 117.33, 119.87, 120.53 (dd, J = 3.11, 6.08Hz), 125.65， 129.56, 136.32 (dd, J_{FC} = 2.97, 6.59 Hz), 139.12, 140.60, 146.36 (dd, J = 13.66, 222 Hz), 147.05, 148.78 (dd, J = 13.32, 223 Hz), 153.35, 164.38, 164.57, 179.72; ESI-MS *m/z* 415.1 $[M+H]^+$; Anal. Calcd for ($C_{20}H_{16}F_2N_4O_2S$ FW: 414): C, 57.96; H, 3.89; F, 9.17; N, 13.52; S, 7.74. Found: C, 57.94; H, 3.86; F, 9.16; N, 13.54; S, 7.74.

1.24.

6-{3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-thioureido]-phenoxy}-N-methyl-nicotinamide (7h)

Grey solid, Yield = 56.8%, HPLC: 99.83%, Mp: 154-156℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.79 (d, J = 4.52 Hz, 3H), 6.95-6.97 (m, 1H), 7.10 (d, J = 8.64 Hz, 1H), 7.32-7.43 (m, 3H), 7.66 (d, J = 8.80 Hz, 1H), 7.78 (dd, J = 2.40, 8.80 Hz, 1H), 8.07 (d, J = 2.40 Hz, 1H), 8.23 (dd, J = 2.44, 8.60 Hz, 1H), 8.51 (q, J = 4.48 Hz, 1H), 8.59 (d, J = 2.28 Hz, 1H), 10.14 (s, 1H), 10.19 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.13, 110.83, 116.28, 117.57, 119.92, 122.47 (q, J = 5.59 Hz), 122.71 (q, J = 271 Hz), 125.27, 125.66, 126.25 (q, J = 30.65 Hz), 128.56, 129.68, 131.55, 139.09, 139.12, 140.35, 147.03, 153.44, 164.34, 164.55, 179.65; ESI-MS *m/z* 481.0 $[M+H]^+$; Anal. Calcd for ($C_{21}H_{16}ClF_3N_4O_2S$ FW: 481): C, 52.45; H, 3.35; Cl, 7.37; F, 11.85; N, 11.65; S, 6.67. Found: C, 52.51; H, 3.39; Cl, 7.41; F, 11.87; N, 11.69; S, 6.62.

1.25. 6-{3-[3-(4-trifluoromethoxy-phenyl)-thioureido]-phenoxy}-N-Methyl-nicotinamide (7i)

Off white solid, Yield = 47.3%, HPLC: 99.85%, Mp: 160-161℃. ^{1}H-NMR (400 MHz, DMSO-d_6)

δ 2.80 (d, J = 4.48 Hz, 3H), 6.93-6.98 (m, 1H), 7.11 (d, J = 8.64 Hz, 1H), 7.33 (d, J = 8.56 Hz, 2H), 7.38-7.44 (m, 3H), 7.61 (d, J = 8.96 Hz, 2H), 8.25 (dd, J = 2.44Hz, 8.60 Hz, 1H), 8.51 (q, J = 4.48 Hz, 1H), 8.62 (d, J = 2.28 Hz, 1H), 9.98 (s, 1H), 10.02 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.07, 110.76, 115.96, 117.10, 119.66, 120.09 (q, J = 254 Hz), 121.12 , 125.21, 125.64, 129.47, 138.55, 139.06, 140.68, 144.64, 147.00, 153.34, 164.33, 164.53, 179.66; ESI-MS *m/z* 463.0 $[M+H]^+$; Anal. Calcd for ($C_{21}H_{17}F_3N_4O_3S$ FW: 462): C, 54.54; H, 3.71; F, 12.32; N, 12.12; S, 6.93. Found: C, 54.61; H, 3.78; F, 12.37; N, 12.15; S, 6.92.

1.26. 6-{3-[3-(2,4-dichloro-phenyl)-thioureido]-phenoxy}-N-Methyl-nicotinamide (7j)

Off white solid, Yield = 50.0%, HPLC: 98.26%, Mp: 146-149℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.79 (d, J = 4.52 Hz, 3H), 6.94-6.97 (m, 1H), 7.10 (d, J = 8.64 Hz, 1H), 7.36-7.44 (m, 3H), 7.65 (d, J = 8.80 Hz, 1H), 7.74 (dd, J = 2.40, 8.80 Hz, 1H), 8.08 (d, J = 2.40 Hz, 1H), 8.23 (dd, J = 2.44, 8.60 Hz, 1H), 8.51 (q, J = 4.48 Hz, 1H), 8.59 (d, J = 2.28 Hz, 1H), 10.14 (s, 1H), 10.27 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.17, 110.86, 116.12, 117.44, 119.83, 125.66, 127.40, 128.96, 129.64, 131.03, 131.06, 131.31, 135.72, 139.16, 140.50, 147.05, 153.37, 164.38, 164.60, 180.22; ESI-MS *m/z* 448.1 $[M+H]^+$; Anal. Calcd for ($C_{20}H_{16}Cl_2N_4O_2S$ FW: 447): C, 53.70; H, 3.61; Cl, 15.85; N, 12.52; S, 7.17. Found: C, 53.78; H, 3.69; Cl, 15.85; N, 12.55; S, 7.16.

1.27. 6-{3-[3-(4-methyl-phenyl)-thioureido]-phenoxy}-N-Methyl-nicotinamide (7k)

Off white solid, Yield = 59.4%, HPLC: 98.68%, Mp: 158-159℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.28 (s, 3H), 2.79 (d, J = 4.52 Hz, 3H), 6.89-6.92 (m, 1H), 7.09 (d, J = 8.56 Hz, 1H), 7.14 (d, J = 8.28 Hz, 2H), 7.32 (d, J = 8.20 Hz, 2H), 7.31-7.39 (m, 2H), 7.43 (t, J = 1.84 Hz, 1H), 8.23 (dd, J = 2.48, 8.64 Hz, 1H), 8.51 (q, J = 4.48 Hz, 1H), 8.59 (d, J = 2.28 Hz, 1H), 9.79 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 20.54, 26.15, 110.77, 115.88, 116.87, 119.61, 123.93, 125.60, 128.98, 129.41, 133.87, 136.63, 139.10, 141.01, 147.06, 153.26, 164.42, 164.57, 179.42; ESI-MS *m/z* 393.1 $[M+H]^+$; Anal. Calcd for ($C_{21}H_{20}N_4O_2S$ FW: 392): C, 64.27; H, 5.14; N, 14.28; S, 8.17. Found: C, 64.32; H, 5.18; N, 14.32; S, 8.24.

1.28. 6-{3-[3-(3,4-dimethyl-phenyl)-thioureido]-phenoxy}-N-Methyl-nicotinamide (7l)

Off white solid, Yield = 44.6%, HPLC: 98.91%, Mp: 171-173℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.19 (s, 3H), 2.20 (s, 3H), 2.80 (d, J = 4.48 Hz, 3H), 6.91-6.94 (m, 1H), 7.08-7.10 (m, 2H), 7.16-7.20 (m, 2H), 7.34-7.37 (m, 2H), 7.46 (s, 1H), 8.24 (dd, J = 2.44Hz, 8.60 Hz, 1H), 8.50 (q, J = 4.48 Hz, 1H), 8.61 (d, J = 2.28 Hz, 1H), 9.73 (s, 1H), 9.75 (s, 1H); ^{13}C-NMR (100 MHz,

DMSO-d_6): δ 18.80, 19.44, 26.10, 110.72, 115.87, 116.91, 119.60, 121.49, 125.12, 125.59, 129.32, 129.42, 132.73, 136.22, 136.73, 139.05, 141.01, 147.02, 153.23, 164.38, 164.54, 179.38; ESI-MS *m/z* 407.2 $[M+H]^+$; Anal. Calcd for ($C_{22}H_{22}N_4O_2S$ FW: 406): C, 65.00; H, 5.46; N, 13.78; S, 7.89. Found: C, 65.12; H, 5.51; N, 13.83; S, 7.92.

1.29. 6-{3-[3-(4-fluoro-phenyl)-thioureido]-phenoxy}-N-Methyl-nicotinamide (7m)

Off white solid, Yield = 59.4%, HPLC: 98.52%, Mp: 158-159℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.80 (d, *J* = 4.48 Hz, 3H), 6.94-6.95 (m, 1H), 7.11 (d, *J* = 8.60 Hz, 1H), 7.15-7.21 (m, 2H), 7.35-7.49 (m, 5H), 8.24 (dd, *J* = 2.44, 8.60 Hz, 1H), 8.50 (q, *J* = 4.48 Hz, 1H), 8.61 (d, *J* = 2.28 Hz, 1H), 9.84 (s, 1H), 9.90 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.10, 110.76, 115.05 (d, *J* =22.32 Hz), 115.96, 117.00, 119.67, 125.61, 126.26 (d, *J*=8.05 Hz), 129.44, 135.54, 139.07, 140.78, 147.00, 153.29, 159.21 (d, *J* = 240 Hz), 164.35, 164.57, 179.83; ESI-MS *m/z* 397.1 $[M+H]^+$; Anal. Calcd for ($C_{20}H_{17}FN_4O_2S$ FW: 396): C, 60.59; H, 4.32; F, 4.79; N, 14.13; S, 8.09. Found: C, 60.63; H, 4.39; F, 4.83; N, 14.18; S, 8.17.

1.30. 6-{3-[3-(4-methoxy-phenyl)-thioureido]-phenoxy}-N-Methyl-nicotinamide (7n)

Off white solid, Yield = 57.3%, HPLC: 98.14%, Mp: 142-145℃. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.80 (d, *J* = 4.48 Hz, 3H), 3.75 (s, 3H), 6.90-6.93 (m, 3H), 7.10 (d, *J* = 8.60 Hz, 1H), 7.34-7.38 (m, 4H), 7.48 (s, 1H), 8.25 (dd, *J* = 2.44, 8.60 Hz, 1H), 8.52 (q, *J* = 4.48 Hz, 1H), 8.62 (d, *J* = 2.28 Hz, 1H), 9.78 (s, 1H), 9.84 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.10, 55.19, 110.71, 113.68, 115.06, 116.72, 119.49, 125.58, 125.95, 127.28, 131.95, 139.05, 141.04, 147.03, 153.23, 156.61, 164.39, 164.55, 179.65; ESI-MS *m/z* 309.2 $[M+H]^+$. Anal. Calcd for ($C_{21}H_{20}N_4O_3S$ FW: 408): C, 61.75; H, 4.94; N, 13.72; S, 7.85. Found: C, 61.81; H, 4.99; N, 13.77; S, 7.89.

2. Cell inhibition assays

HCT116, MDA-MB-231, PC-3 and HepG2 cell lines were plated on 96-well plates at a density of 5000 per well and incubated overnight. The cells were treated with compounds and sorafenib at final concentrations ranging from 0.5 to 200 μM, while control cells were treated with equal volume DMSO. After 48 hr, 0.5% MTT (Amresco, USA) solution was added to each well, and further incubation for 4 h, then cells were centrifuged at 2,500 rpm for 15 min and removed from the culture medium. And add 150 μL DMSO to dissolve the formazan. After mixing for 5 min,

optical density was detected at 570 nm on a microplate reader (Thermo, USA).

3. *In vitro* HUVEC tuber formation assay

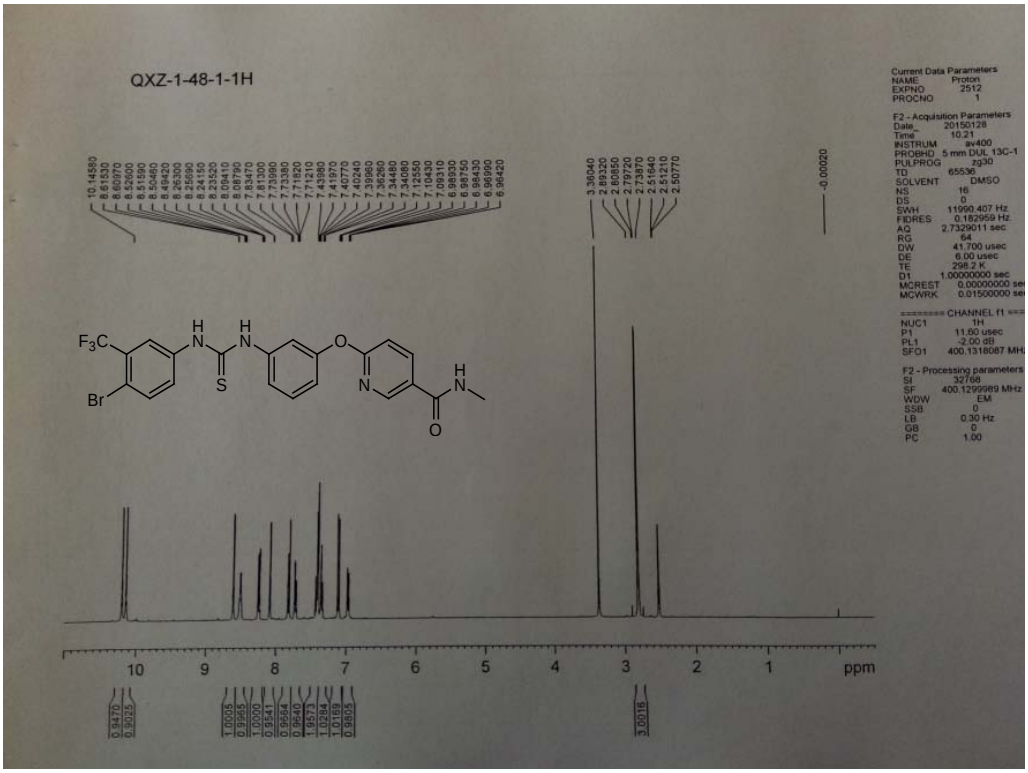
Forty eight-well slide chambers were coated with 100 μL of Matrigel (BD Biosciences, NJ) and allowed to gel at 37℃ and 5% CO_2 for 30 min. HUVECs were then seeded at 40,000 cells/well in M199 (5% FBS) containing either the vehicle (0.5% DMSO), sorafenib or synthesized compounds and incubated at 37℃ and 5% CO_2 for 6 h. The morphological changes of the cells and HUVEC tubes formation were observed under a phase-contrast microscope and photographed at 200× magnification. The corresponding area was measured as the number of pixels using Adobe PhotoShop. The experiments were repeated three times.

4. *Ex vivo* rat thoracic aorta rings (TARs) assay

Forty eight-well tissue culture plates were coated with 100 μL of Matrigel (BD Biosciences, NJ) and allowed to gel for 30 min at℃37and 5% CO $_2$. Thoracic aortas were excised from 8- to 10-week-old male Sprague Dawley rats. After careful removal of fibroadipose tissues, the aortas were cut into 1-mm-long cross-sections, placed on Matrigel-coated wells, and covered with an additional 100 μL of Matrigel. After the second layer of Matrigel set, the rings were incubated for 30 min at 37℃ and 5% CO_2. Aorta rings were treated every other day with either the vehicle (0.5% DMSO), sorafenib, or synthesized compounds for 6 days and photographed on the 7th day at 200× magnification. The experiments were repeated three times using aortas from four different rats. The area of angiogenic sprouting, reported in the number of pixels, was quantified using Adobe PhotoShop. The experiments were repeated three times.

5. ^{1}H NMR and ^{13}C NMR spectra of compounds

Compound 7a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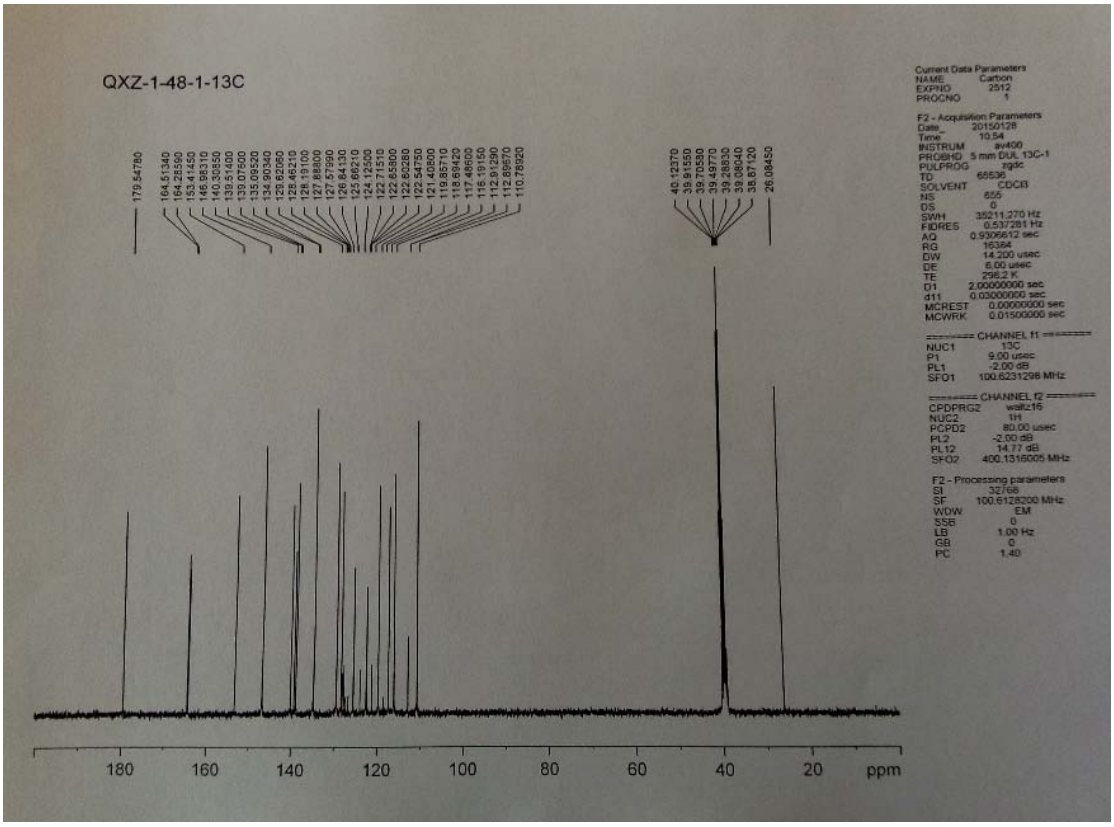
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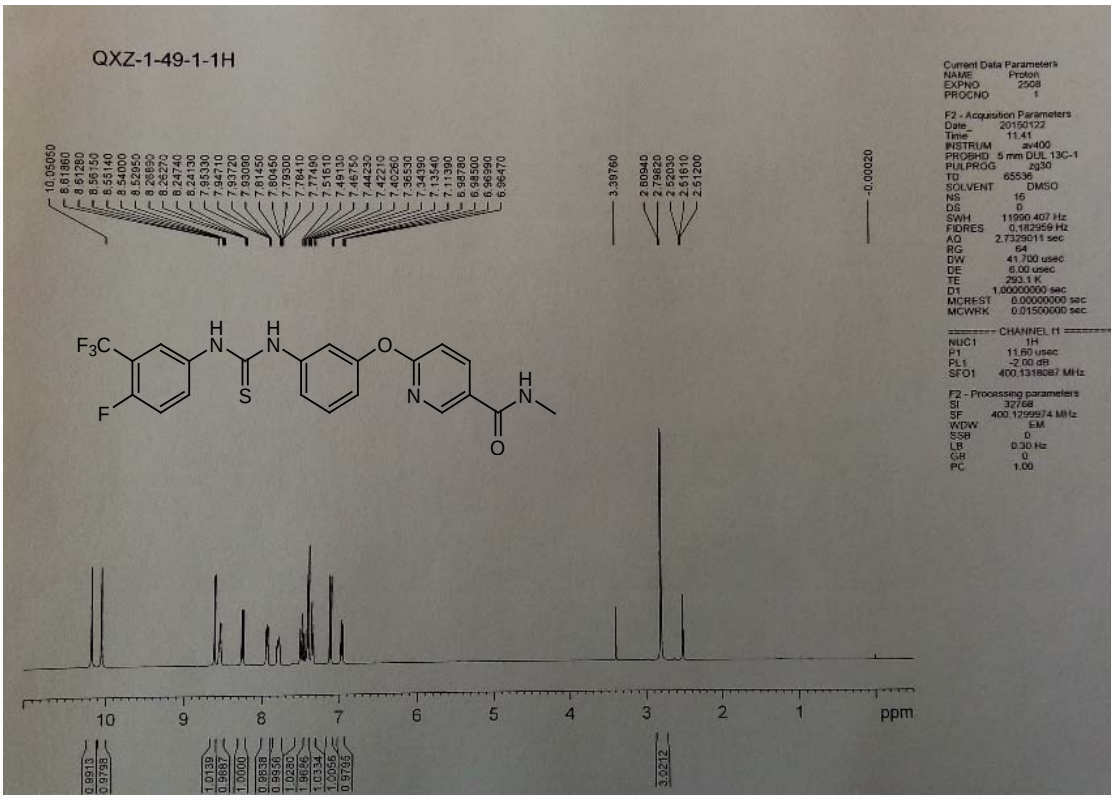
Compound 7b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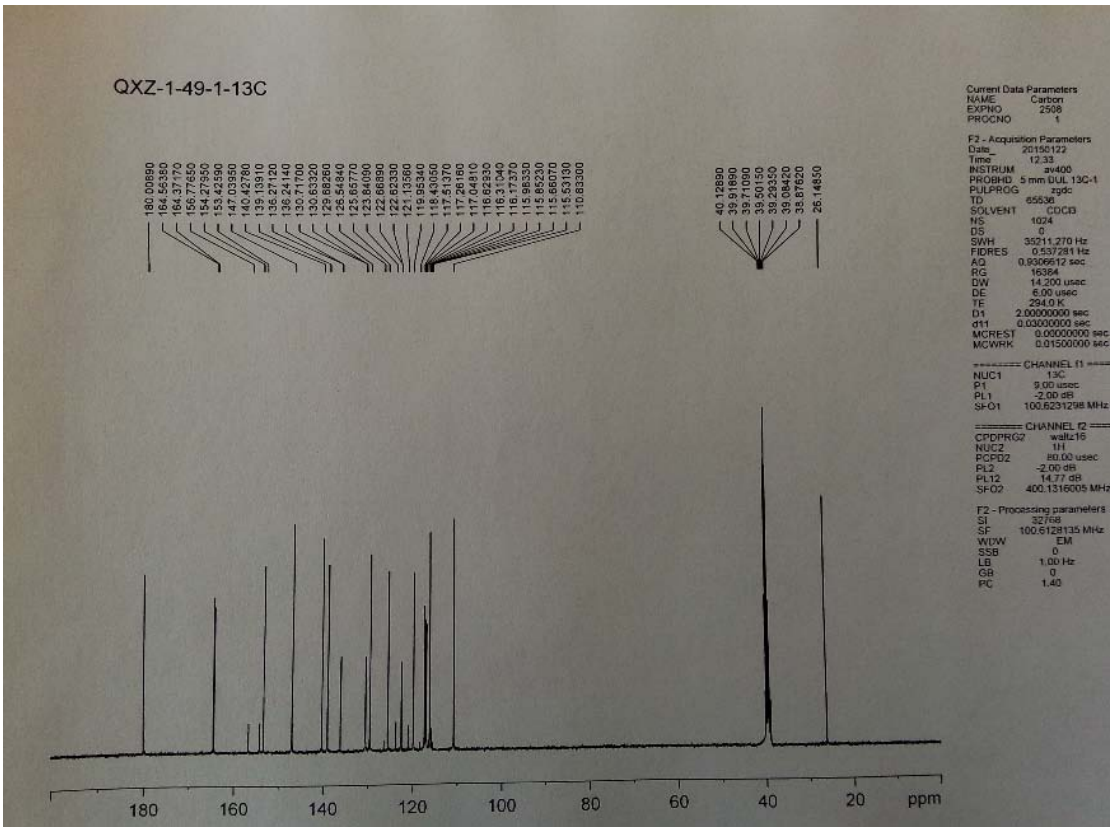
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TE 294.0 K
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MCWRK 0.01500000 sec
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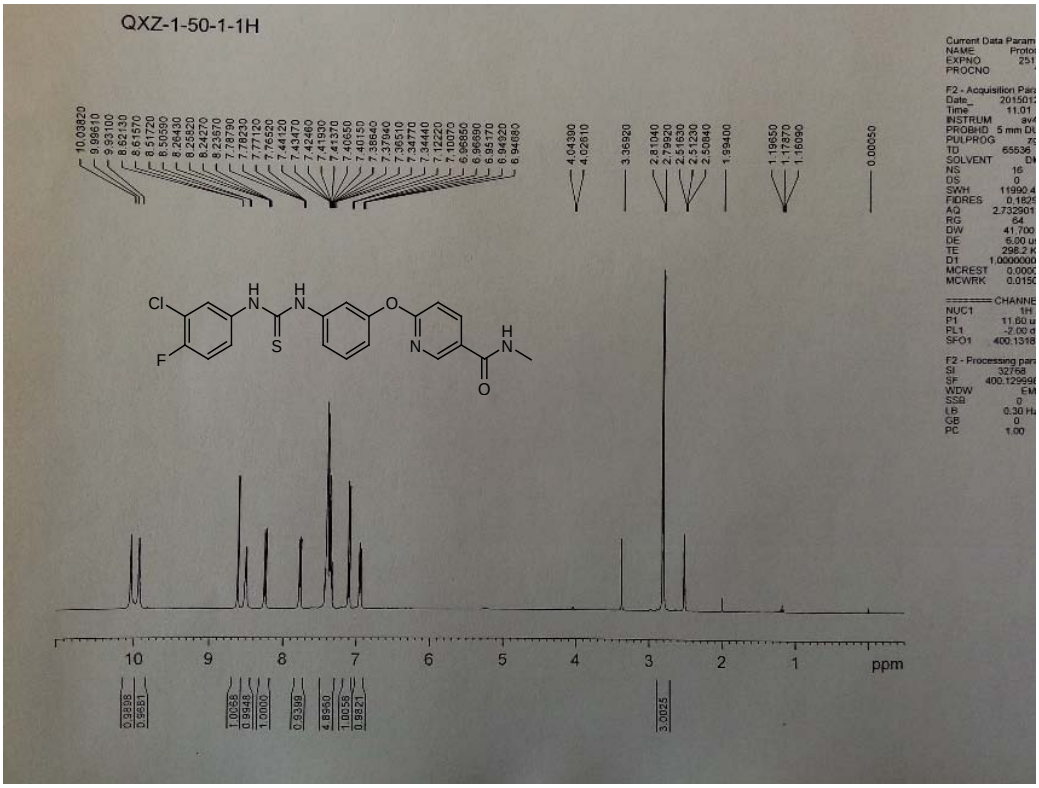
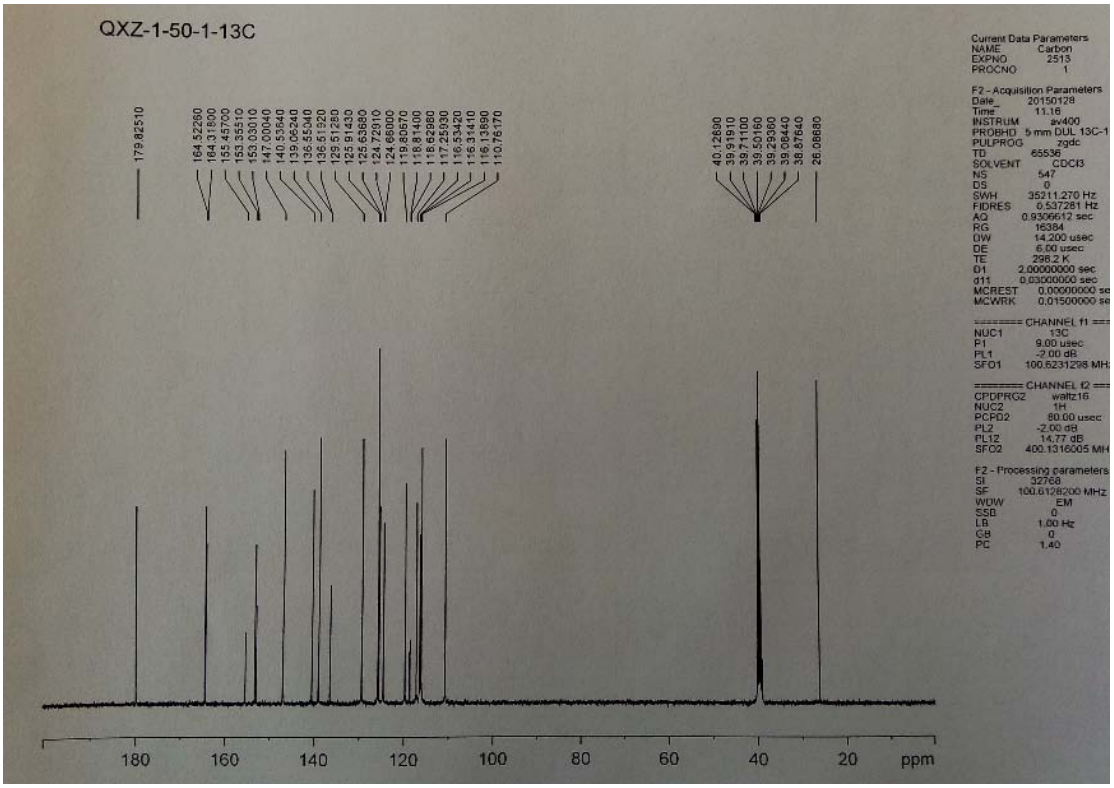
Compound 7c





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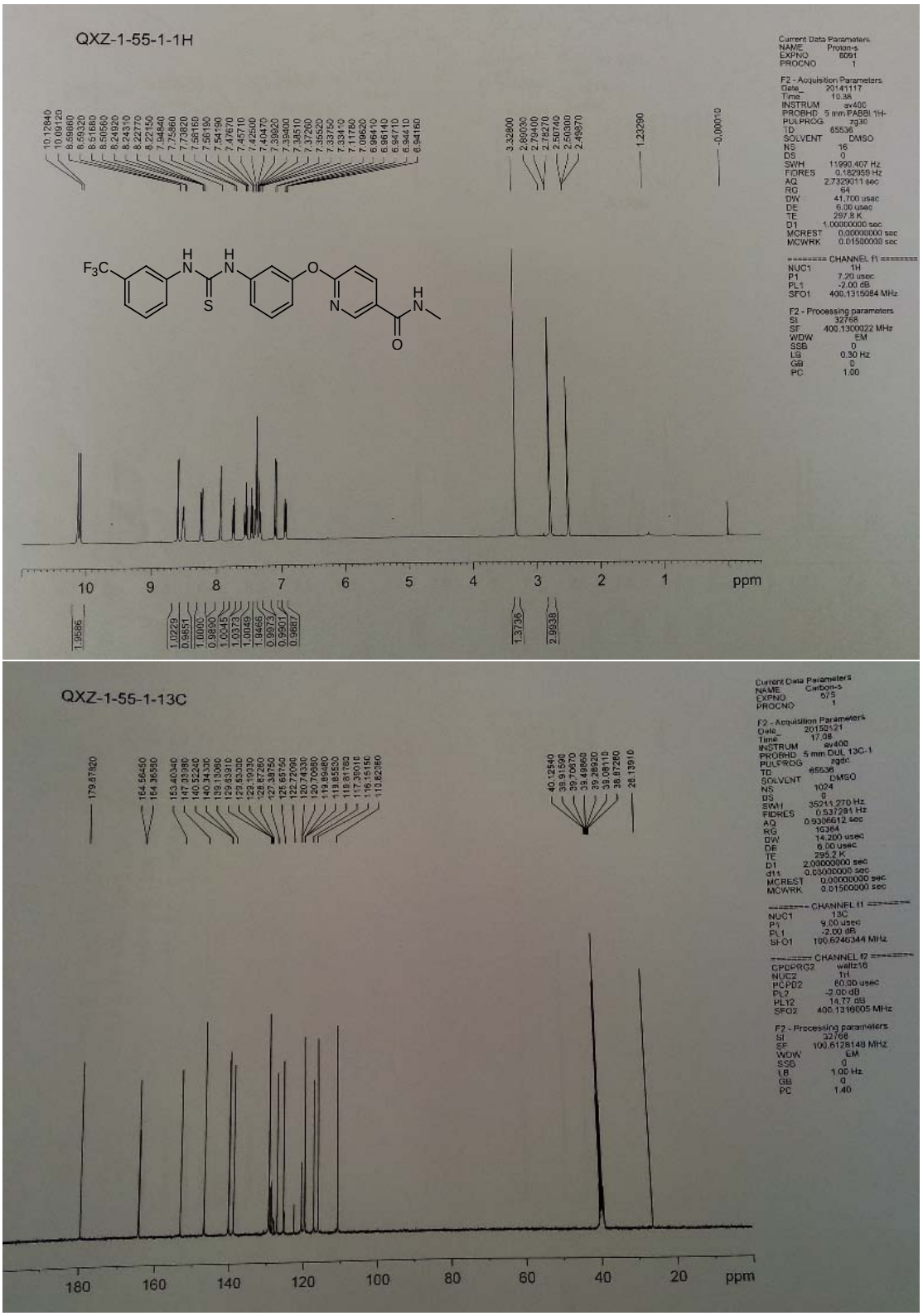

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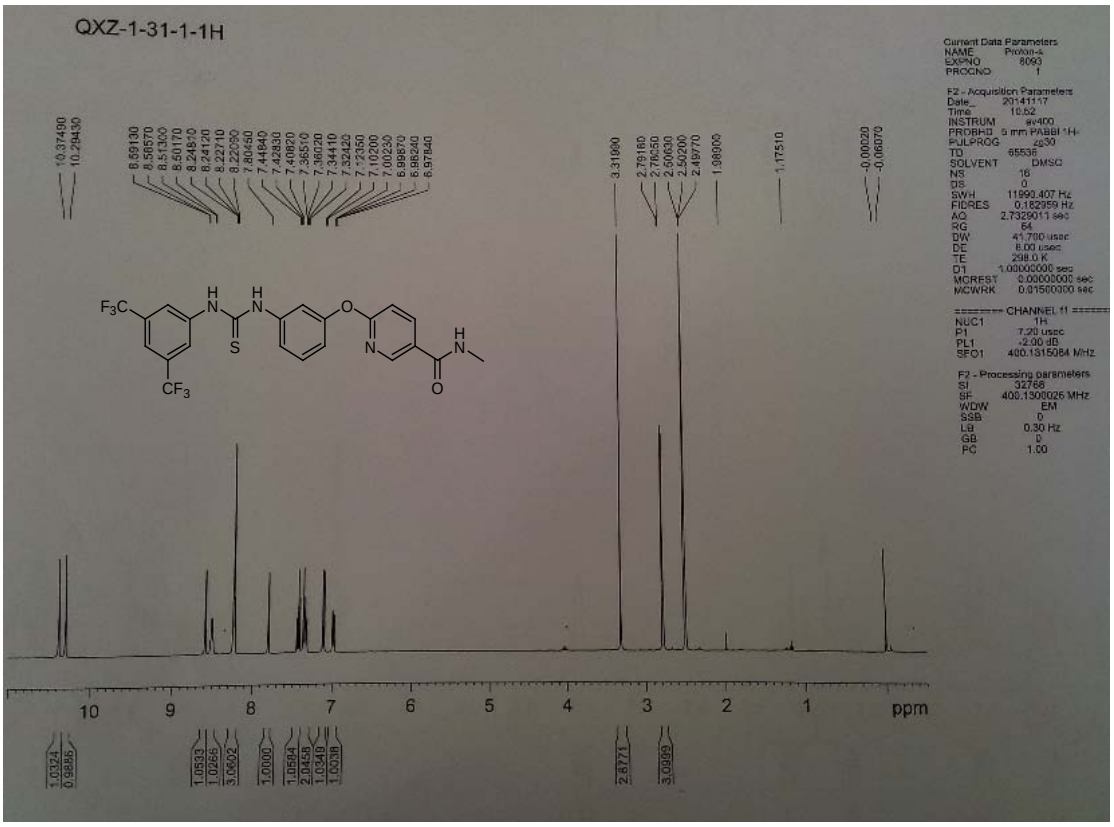
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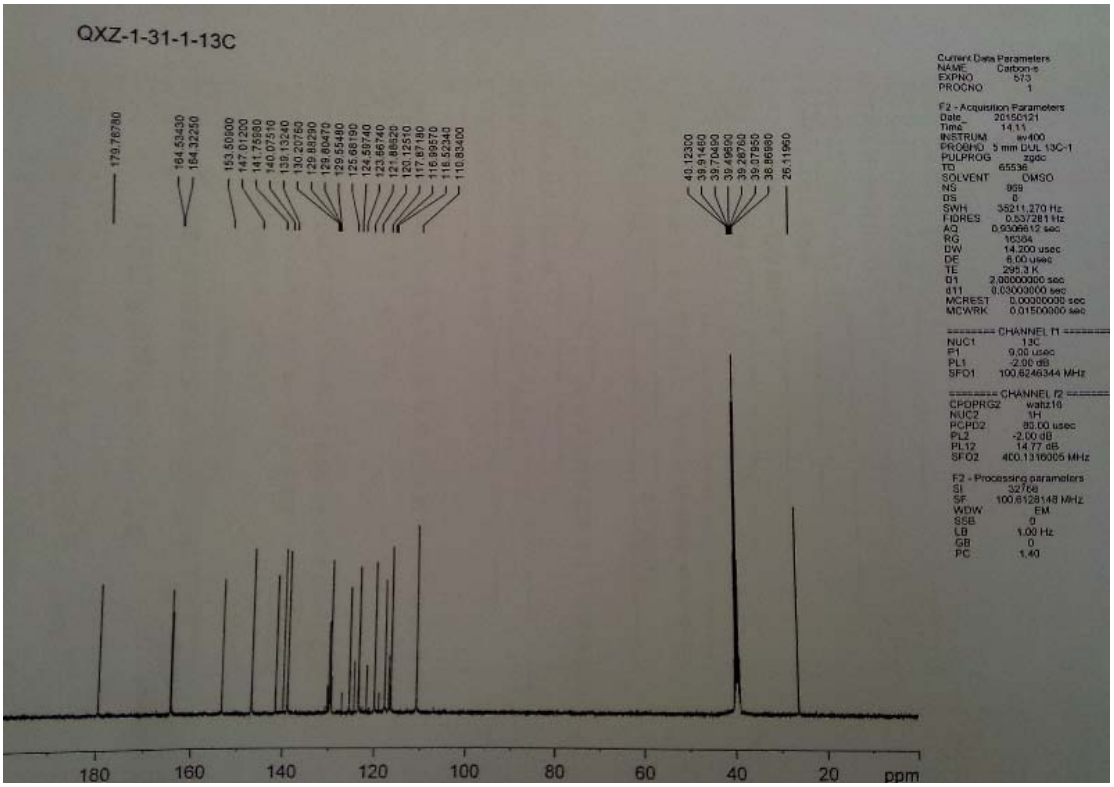
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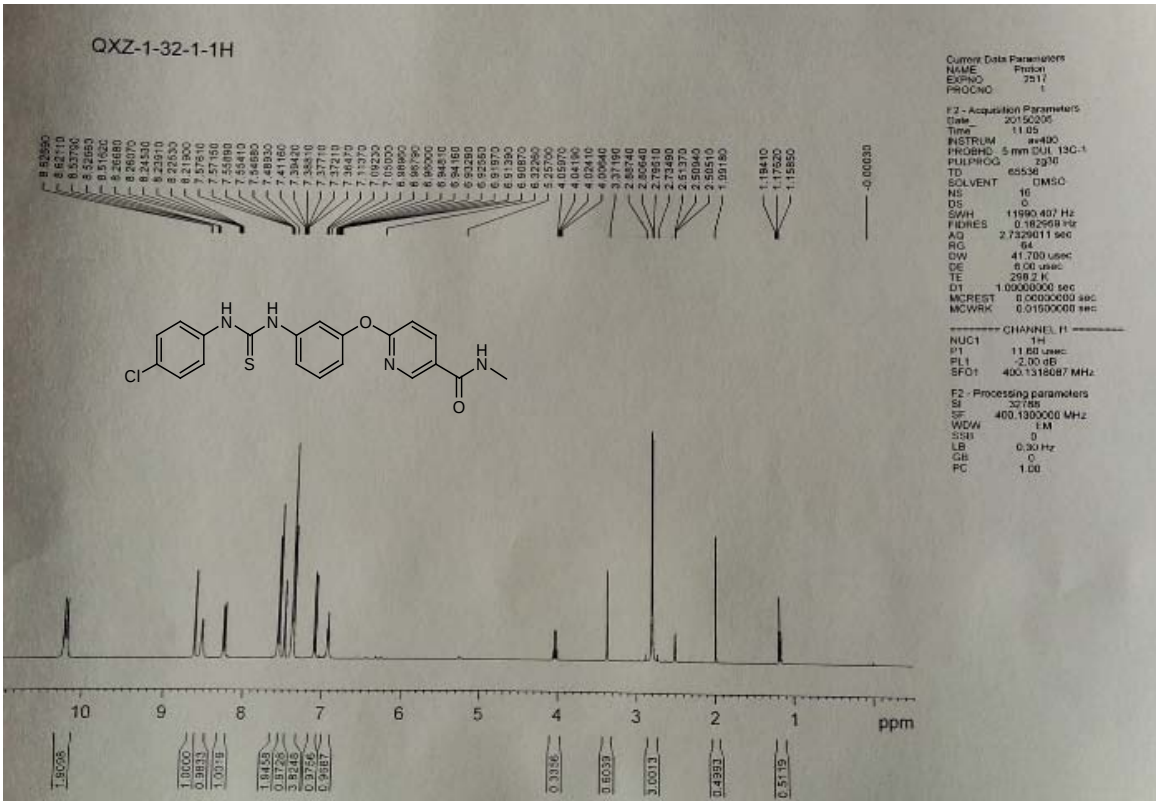
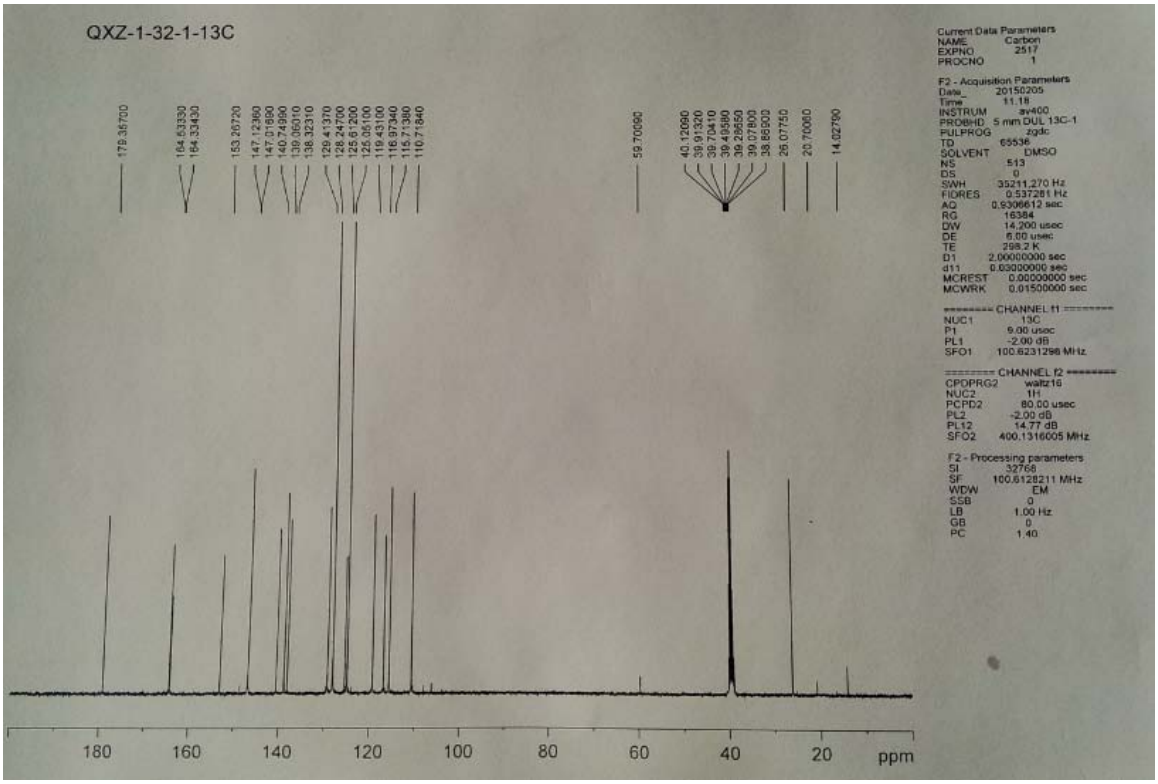
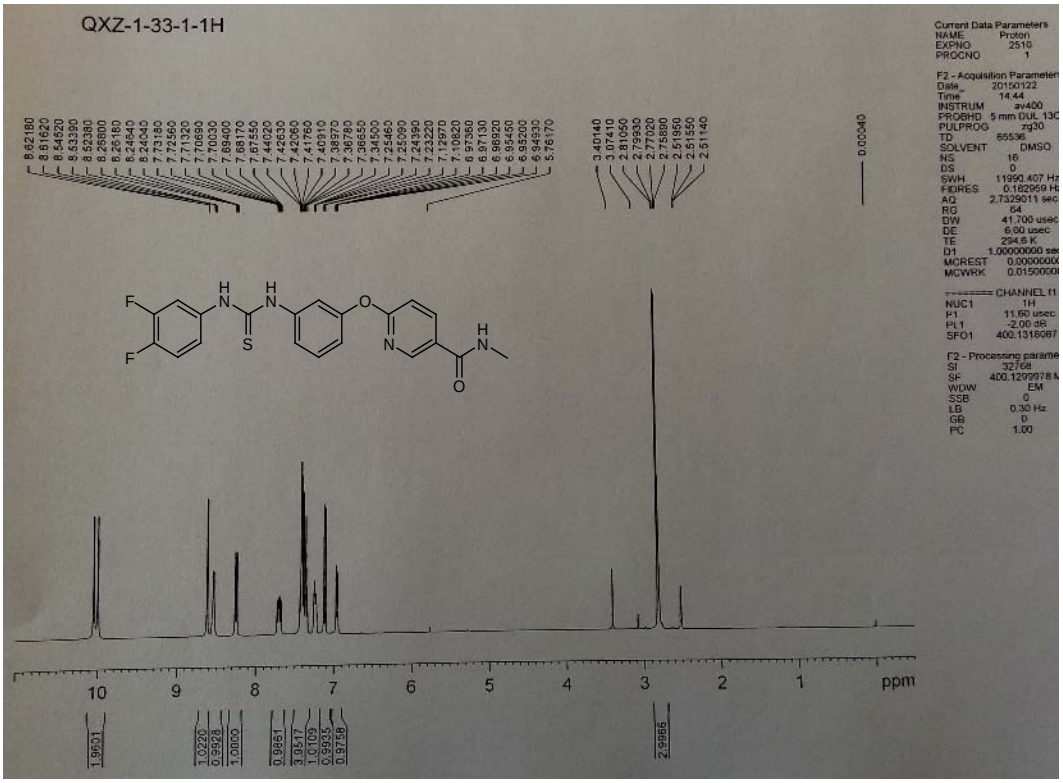
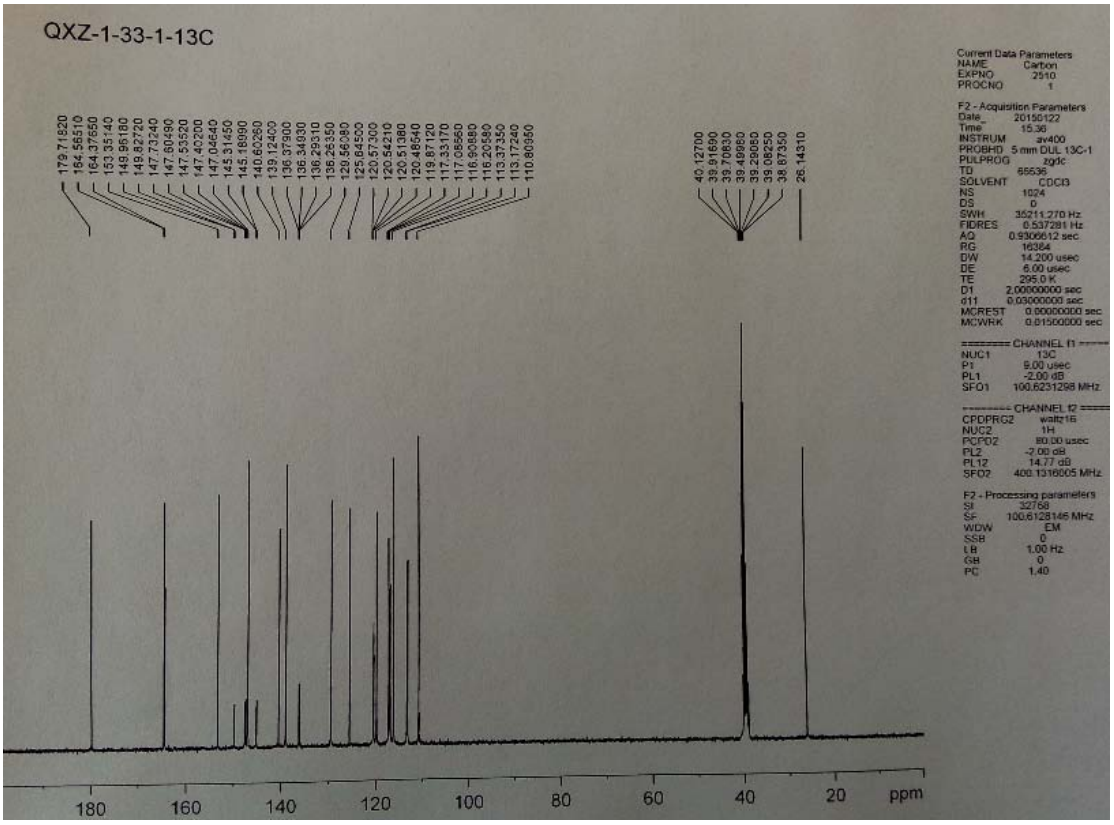
Compound 7f



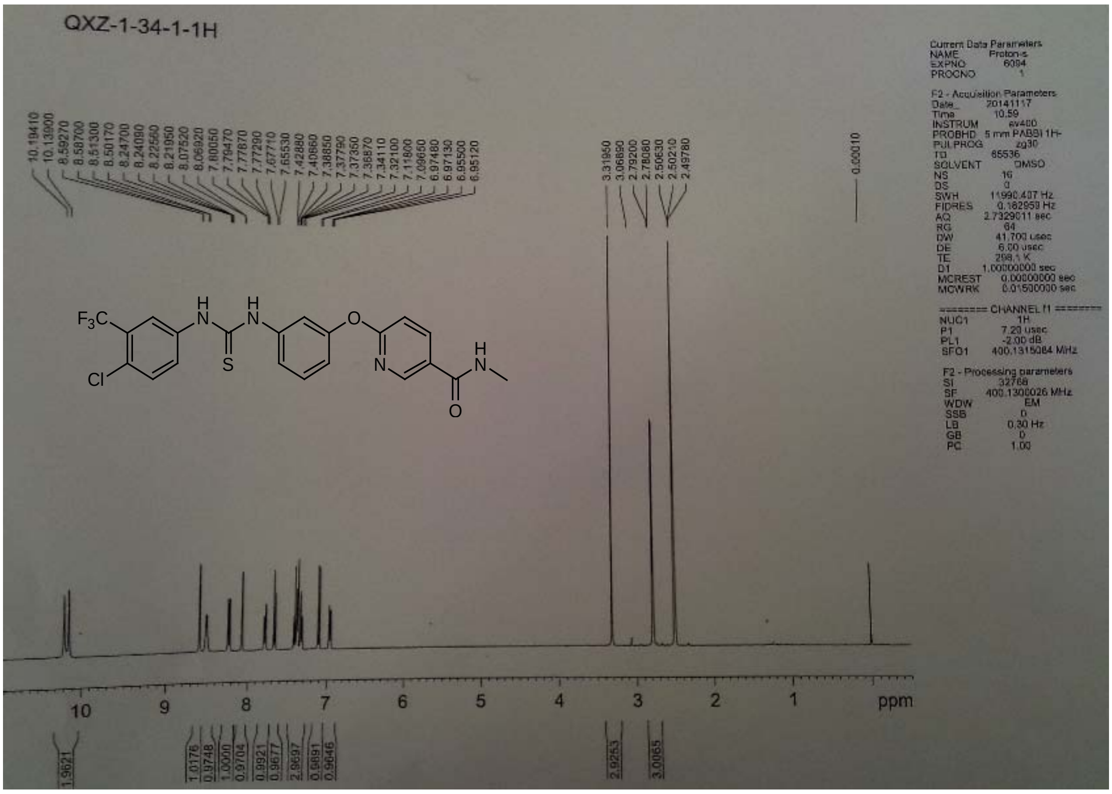


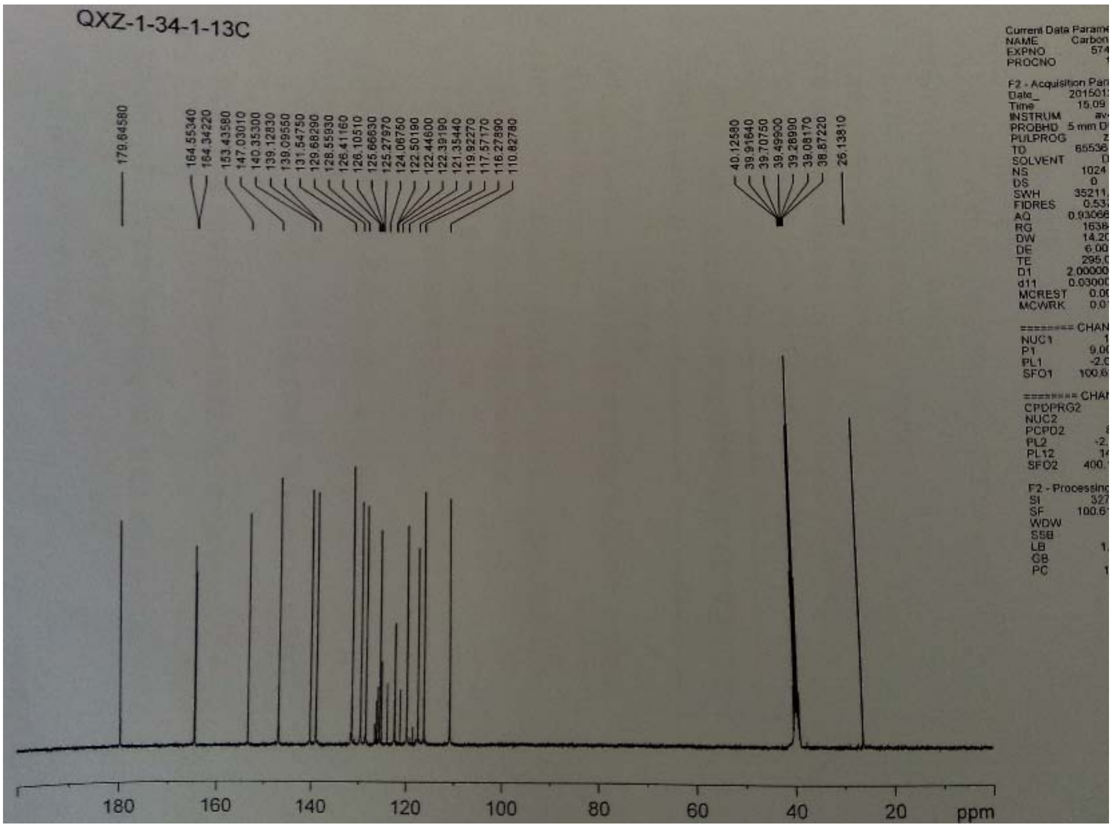
Compound 7g



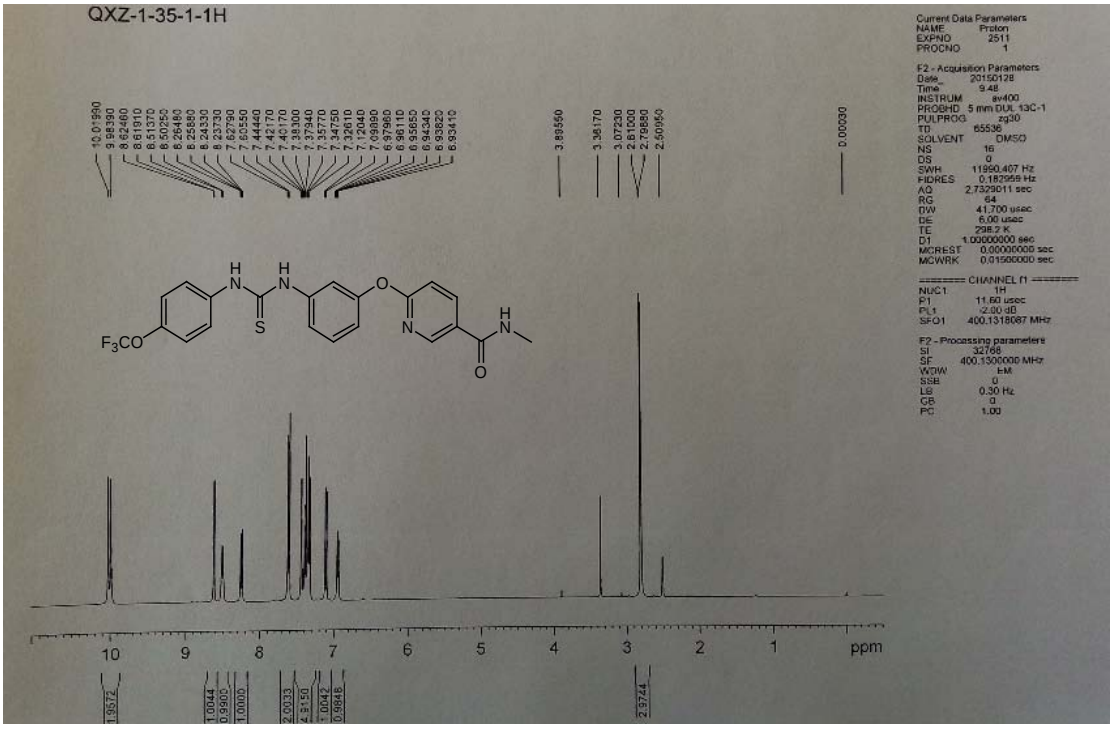


Compound 7h





Compound 7i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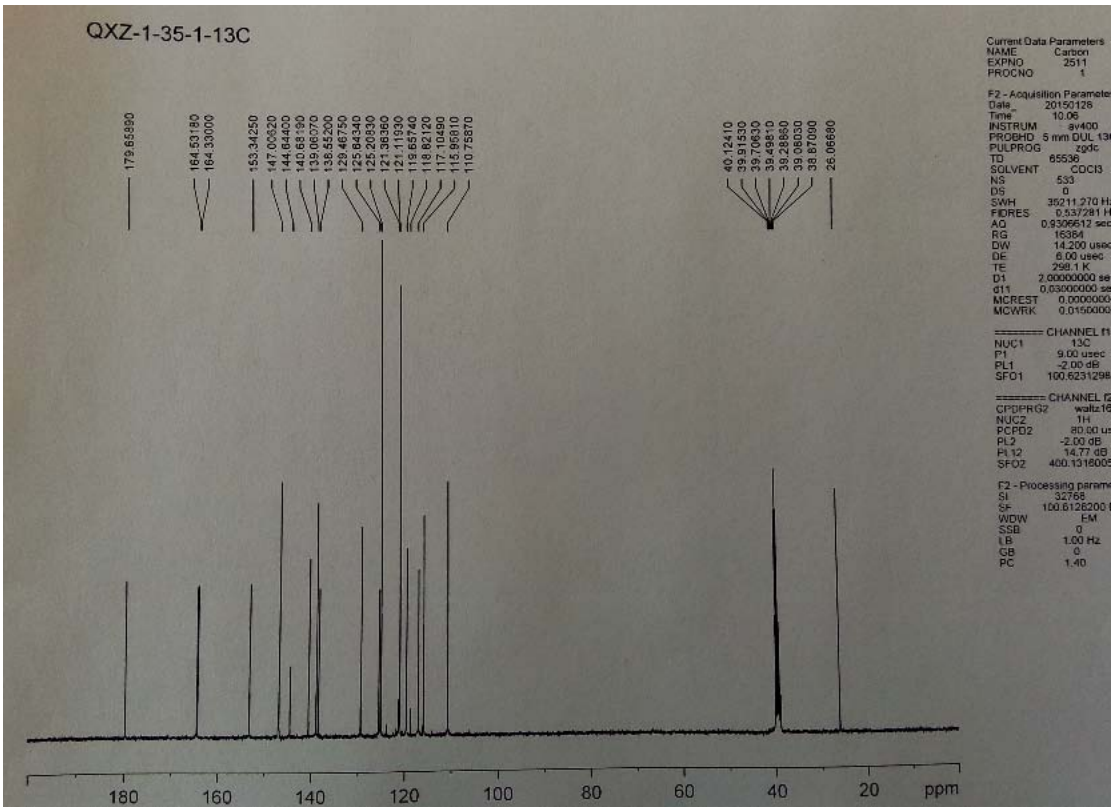
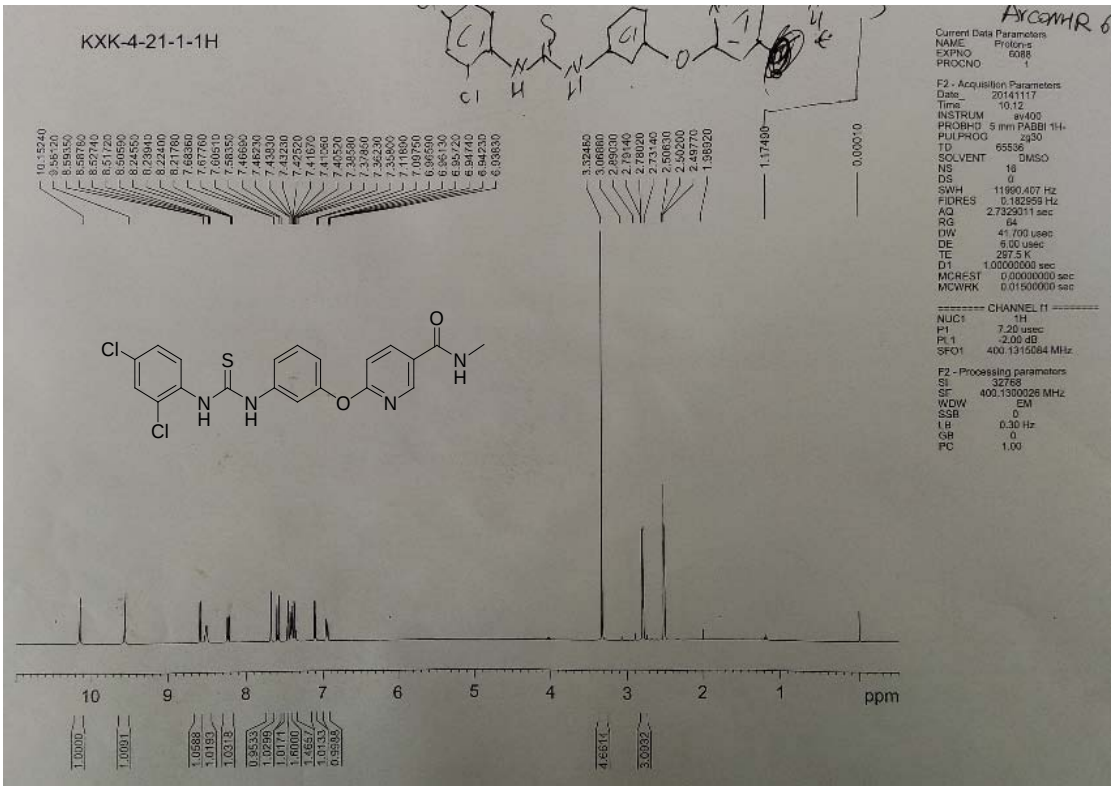
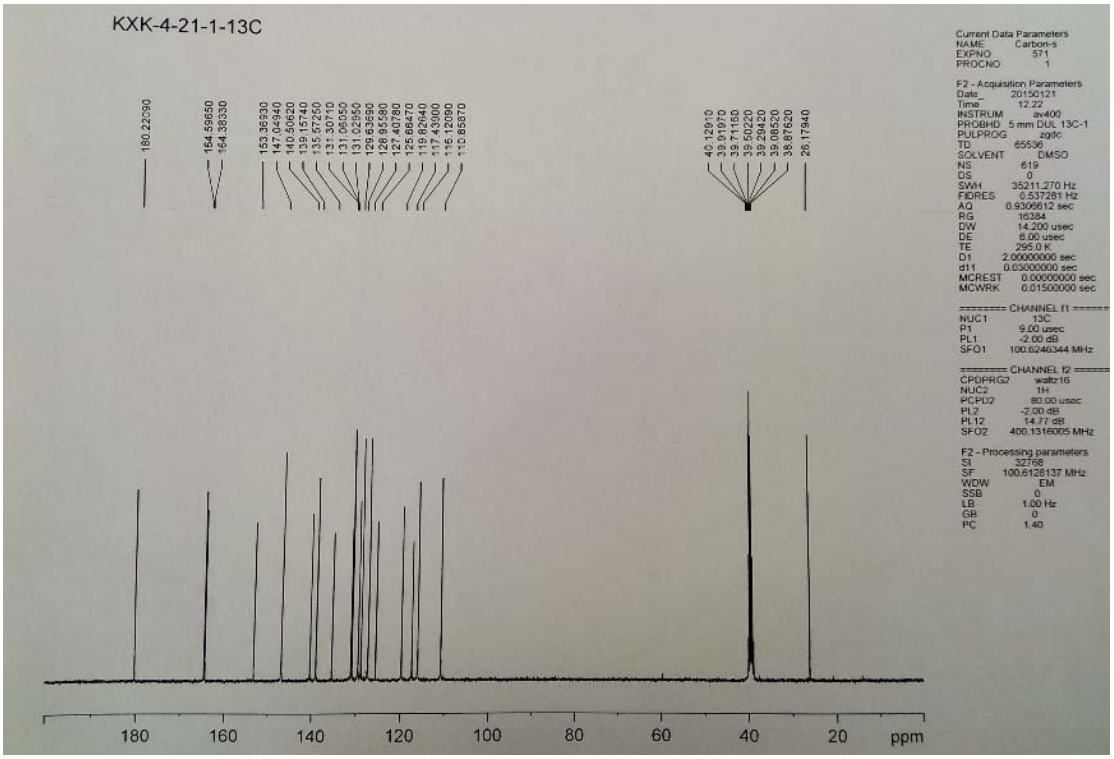
2.9744

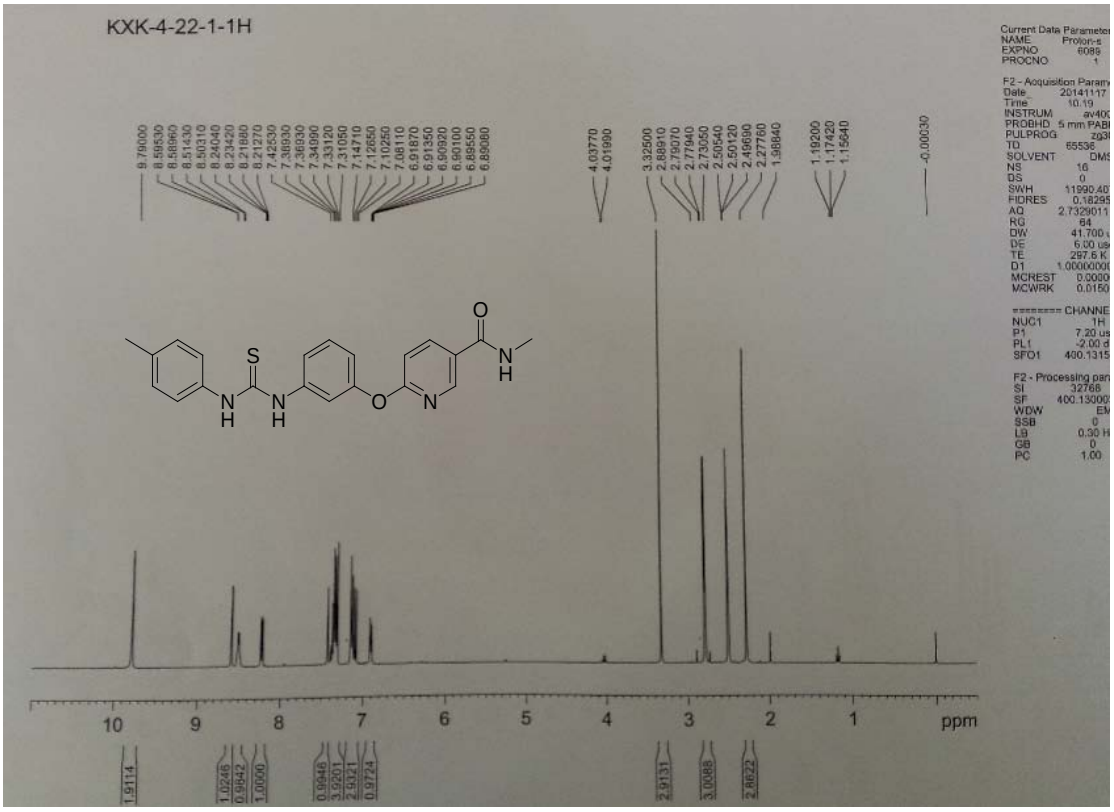

QXZ-1-35-1-13C
179.65990
164.53180
164.33000
153.34250
147.00620
144.64400
140.68190
139.06070
136.85200
129.46750
125.84340
125.20830
121.36360
121.11930
119.65740
118.82120
117.10490
115.95810
110.75870
40.12410
39.91530
39.70630
39.49810
39.28850
39.08030
38.87000
26.06680
ppm

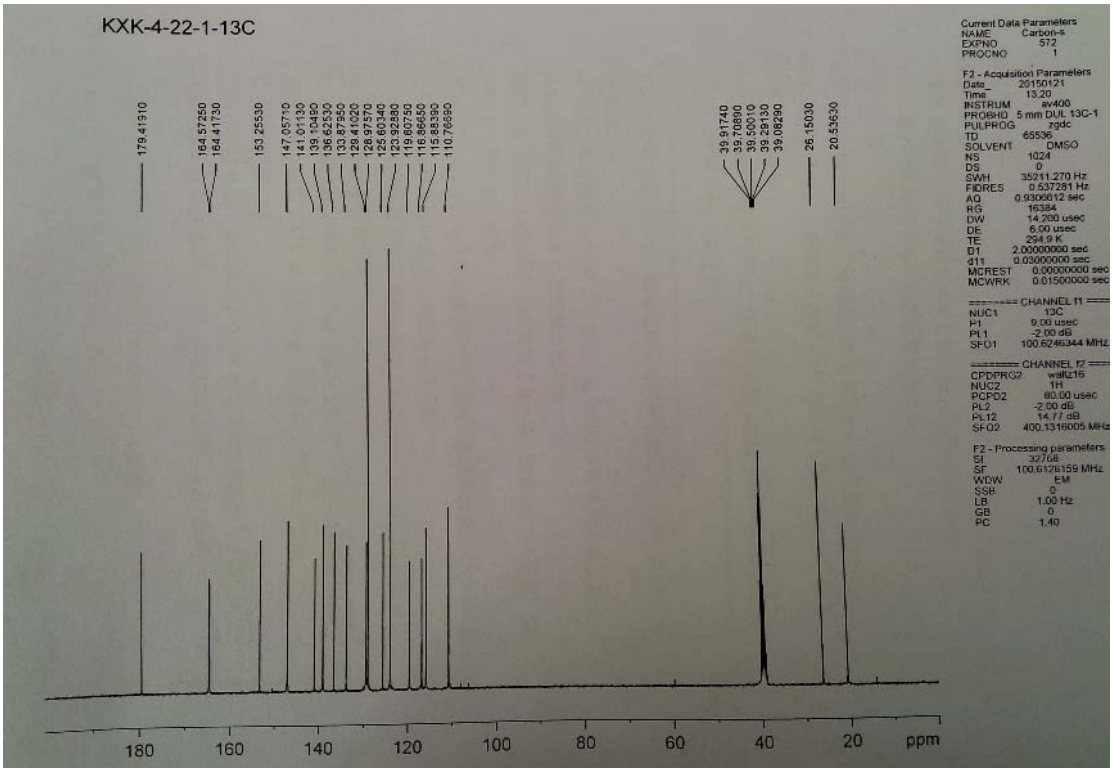
Compound 7j



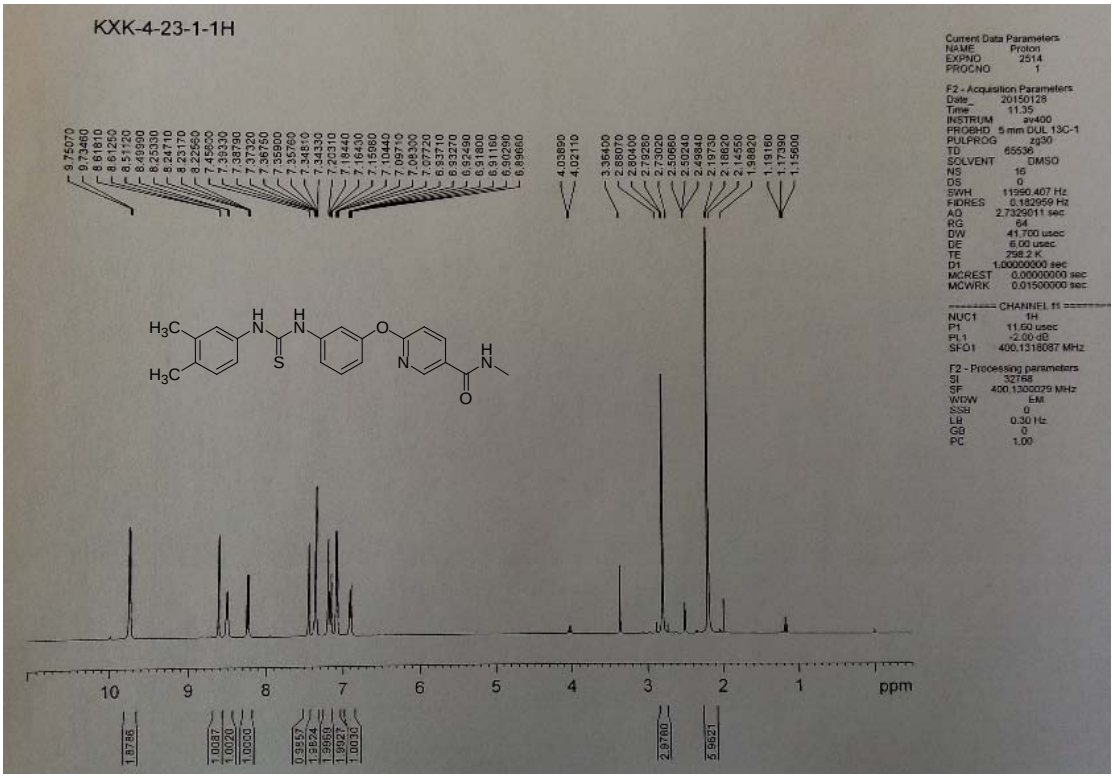


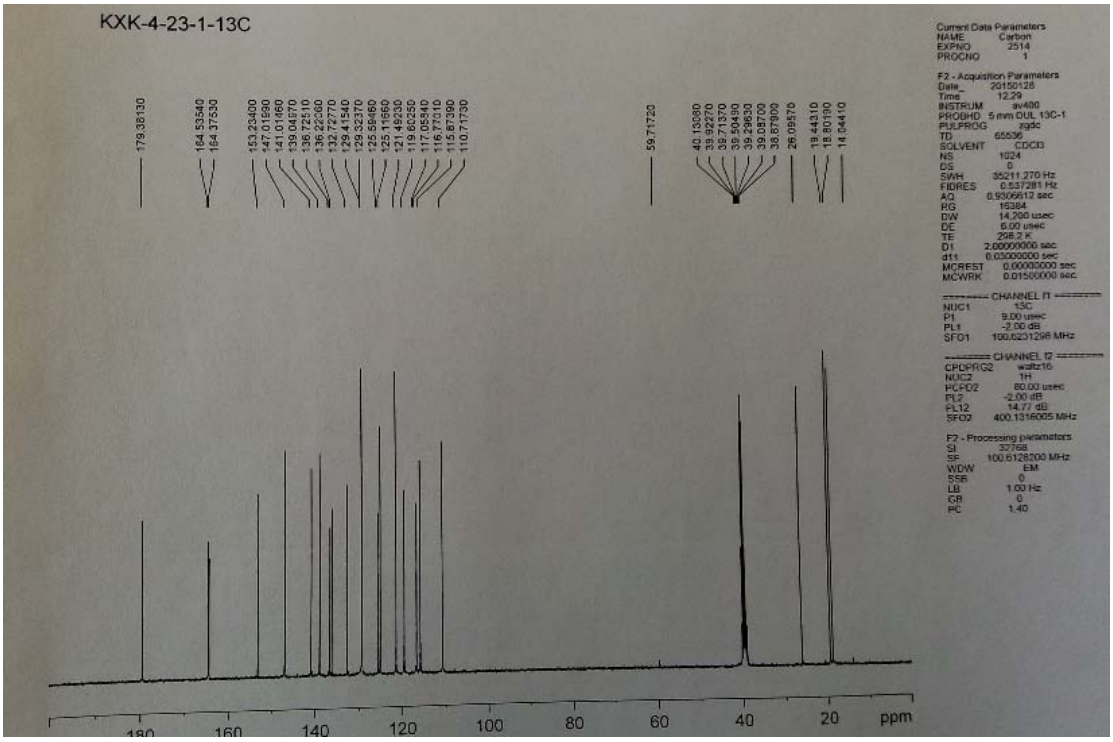
Compound 7k


KXK-4-22-1-1H
9.79000
8.59530
8.58990
8.51430
8.50310
8.24040
8.23420
8.21980
8.21270
7.42630
7.36930
7.36030
7.34990
7.33120
7.31050
7.14710
7.12650
7.10250
7.08110
6.91870
6.91350
6.90920
6.90100
6.89550
6.89060
4.03770
4.01990
3.32500
2.88910
2.79070
2.77940
2.73050
2.50540
2.50120
2.49690
2.27760
1.98840
1.19200
1.17420
1.15640
-0.00030
10
9
8
7
6
5
4
3
2
1
ppm
1.9114
1.0246
0.9942
1.0000
0.9946
3.9201
2.9921
0.9724
2.9131
3.0088
2.8622

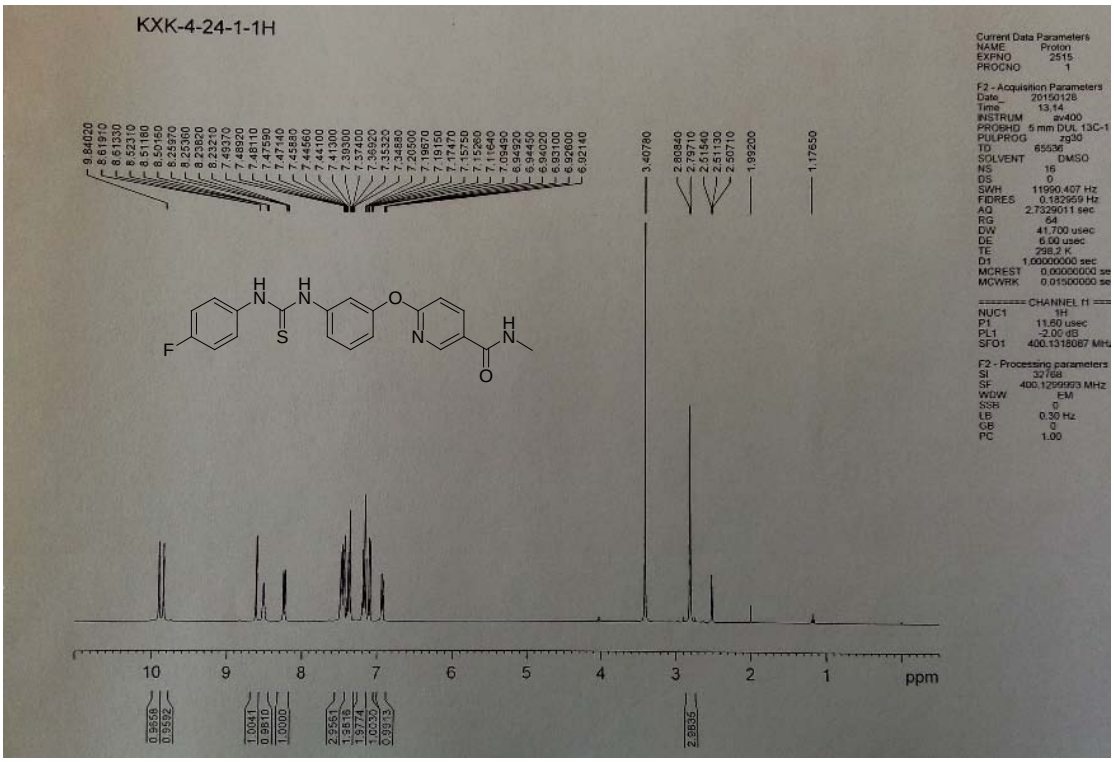

KXK-4-22-1-13C
179.41910
164.57250
164.41730
153.25530
147.05710
141.01130
139.10490
136.62530
130.87950
129.41020
128.97570
125.60340
123.92380
118.87750
118.66650
115.88390
110.76690
39.91740
39.70890
39.50010
39.29130
39.08290
26.15030
20.53630
180
160
140
120
100
80
60
40
20
ppm

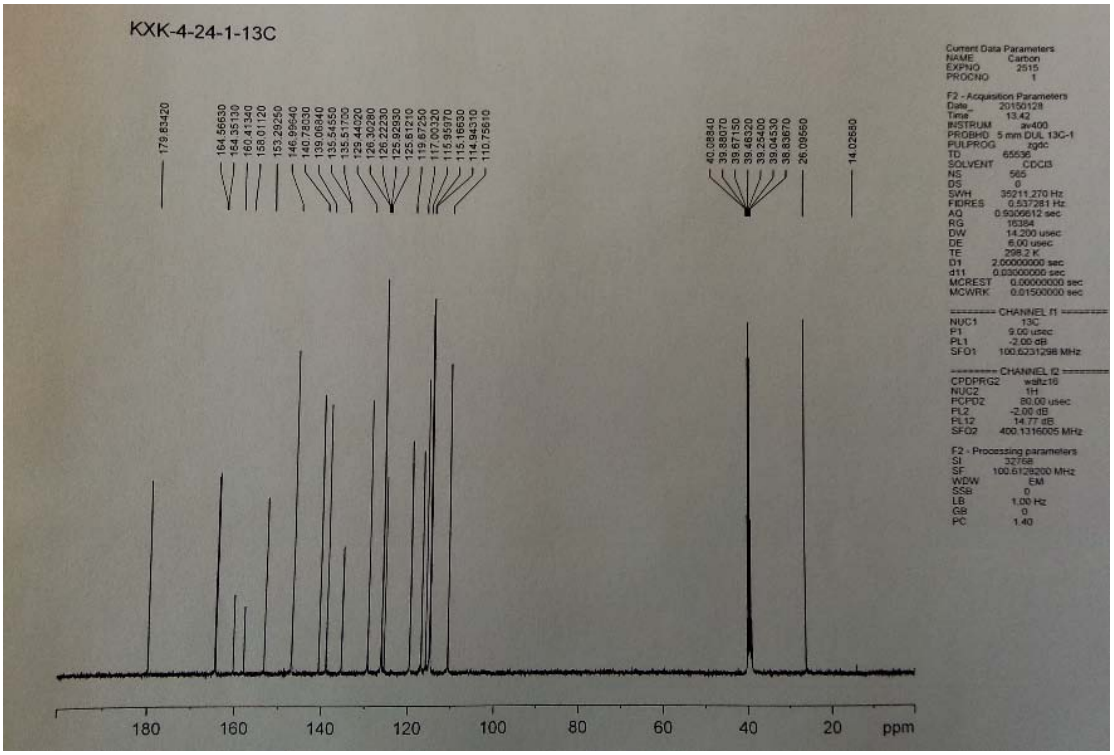
Compound 7l





Compound 7m


KXK-4-24-1-1H
9.84020
8.61910
8.61330
8.52310
8.51180
8.50160
8.25970
8.25360
8.23620
8.23210
7.49370
7.48110
7.47590
7.47140
7.45880
7.44560
7.44100
7.41300
7.39300
7.37400
7.36920
7.35320
7.34680
7.20500
7.19670
7.19150
7.17470
7.15780
7.15260
7.11640
7.09490
6.94920
6.94450
6.94020
6.93100
6.92600
6.92140
3.40780
2.80840
2.79710
2.51540
2.51130
2.50710
1.89200
1.17650
H
N
H
N
O
H
N
F
S
N
O
10
9
8
7
6
5
4
3
2
1
ppm
0.5658
0.5592
1.0041
0.9810
1.0000
2.9561
1.9818
1.9774
1.0030
0.9913
2.8835
Current Data Parameters
NAME Proton
EXPNO 2515
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150128
Time 13.14
INSTRUM av400
PROBHD 5 mm DUL 13C-1
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 0
SWH 11990.407 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 64
DW 41.700 usec
DE 6.00 usec
TE 298.2 K
D1 1.00000000 sec
MCREST 0.00000000 se
MCWRK 0.01500000 se
======== CHANNEL f1 ===
NUC1 1H
P1 11.60 usec
PL1 -2.00 dB
SFO1 400.1318087 MHz
F2 - Processing parameters
SI 32768
SF 400.1299993 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00


KXK-4-24-1-13C
178.83420
164.56630
164.35130
160.41340
158.01120
153.29250
146.99540
140.78030
139.08840
135.54550
135.51700
129.44020
126.30280
126.22230
125.92930
125.81210
119.67550
117.00320
115.95970
115.16630
114.94310
110.75610
40.08840
39.88070
39.67150
39.46320
39.25400
39.04530
38.83670
26.09550
14.02650
180
160
140
120
100
80
60
40
20
ppm
Current Data Parameters
NAME Carbon
EXPNO 2515
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150128
Time 13.42
INSTRUM av400
PROBHD 5 mm DUL 13C-1
PULPROG zgdc
TD 65536
SOLVENT CDCl3
NS 565
DS 0
SWH 35211.270 Hz
FIDRES 0.537281 Hz
AQ 0.9306612 sec
RG 16384
DW 14.200 usec
DE 6.00 usec
TE 298.2 K
D1 2.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 -2.00 dB
SFO1 100.6231298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -2.00 dB
PL12 14.77 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128200 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Compound 7n