Supporting Information

Discovery of a *Plasmodium falciparum* glucose-6-phosphate dehydrogenase 6-phosphogluconolactonase inhibitor (*R*,*Z*)-N-((1-ethylpyrrolidin-2-yl)methyl)-2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (ML276) that reduces parasite growth *in vitro*

Janina Preuss[†‡§¶], *Patrick Maloney*[||¶], *Satyamaheshwar Peddibhotla*[||¶], *Michael P. Hedrick*[§¶], *Paul Hershberger*[||¶], *Palak Gosalia*[§], *Monika Milewski*[§], *Yujie Linda Li*[§], *Eliot Sugarman*[||], *Becky Hood*[||], *Eigo Suyama*[||], *Kevin Nguyen*[||], *Stefan Vasile*[||], *Eduard Sergienko*[§], *Arianna Mangravita-Novo*[||], *Michael Vicchiarelli*[||], *Danielle McAnally*[||], *Layton H. Smith*[||], *Gregory P. Roth*[||], *Jena Diwan*[§], *Thomas D.Y. Chung*[§], *Esther Jortzik*[‡], *Stefan Rahlfs*[‡], *Katja Becker*[*‡], *Anthony B. Pinkerton*[*§], *Lars Bode*[*†]

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Experimental Procedures - Chemistry

Methyl 4-fluoro-3-nitrobenzoate (1b)

1a (2 g, 10.8 mmol) was dissolved in methanol (15 mL) and conc. H_2SO_4 (0.5 mL) was added, and the mixture was heated to reflux for 15 h. The solvent was evaporated and the residue was dissolved in dichloromethane (20 mL) and then extracted with 10% NaOH. The organic layer was dried over anhydrous sodium sulfate and evaporated to afford **1b** (2g, 93%) as a pale yellow solid, which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (dd, J = 7.2, 2.1 Hz, 1H), 8.34 (ddd, J = 8.6, 4.2, 2.2 Hz, 1H), 7.40 (dd, J = 9.2, 8.6 Hz, 1H), 4.00 (d, J = 1.3 Hz, 3H).

Ethyl 4-fluoro-3-nitrobenzoate (1c)

1a (5 g, 27.0 mmol) was dissolved in ethanol (20 mL) and conc. H_2SO_4 (0.5 mL) was added, and the mixture was heated to reflux for 15 h. The solvent was evaporated and the residue was dissolved in dichloromethane (20 mL) and then extracted with 10% NaOH. The organic layer was dried over anhydrous sodium sulfate and evaporated to afford **1c** (4.75 g, 83%) as a pale yellow solid, which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (dd, J = 7.2, 2.2 Hz, 1H), 8.34 (ddd, J = 8.6, 4.2, 2.2 Hz, 1H), 7.40 (dd, J = 10.2, 8.7 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H).

Methyl 4-((2-ethoxy-2-oxoethyl)thio)-3-nitrobenzoate (2b)

1b (1.8 g, 9.04 mmol) was dissolved in dry acetonitrile (15 mL). Triethylamine (4.4 mL, 32 mmol) and ethyl mercaptoacetate (1.1 mL, 9.94 mmol) were added. A mild exotherm was observed and allowed to subside. The mixture was then heated at 85 °C for 15 h,

cooled to 23 °C, and then the solvent evaporated. The residue was dissolved in dichloromethane (100 mL) and washed with dil. HCl (50 mL, 3x). The organic layer was then dried over anhydrous sodium sulfate and evaporated to afford a brown residue. The residue was purified by flash chromatography (0-15% ethyl acetate in hexanes) to afford **2b** as an orange yellow solid (2.27 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (d, *J* = 1.9 Hz, 1H), 8.21 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 3H), 3.81 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); LRMS (ESI+ve): calculated for LRMS (ESI+ve): calculated for $C_{12}H_{13}NO_6S$, [M+H] = 300.05, observed [M+H] = 300.05.

Ethyl 4-((2-ethoxy-2-oxoethyl)thio)-3-nitrobenzoate (2c)

Ethyl 4-fluoro-3-nitrobenzoate (**1c**) (2.36 g, 11.1 mmol) was dissolved in dry acetonitrile (15 mL). Triethylamine (5.4 mL, 39.0 mmol) and ethyl mercaptoacetate (1.34 mL, 12.2 mmol) were added. A mild exotherm was observed and allowed to subside. The mixture was then heated at 85 °C for 15 h, cooled to 23 °C, and then the solvent evaporated. The residue was dissolved in dichloromethane (100 mL) and washed with dil. HCl (50 mL, 3x). The organic layer was then dried over anhydrous sodium sulfate and evaporated to afford a brown residue. The residue was purified by flash chromatography (0-15% ethyl acetate in hexanes) to afford **2c** as an orange solid (3.1 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, *J* = 1.9 Hz, 1H), 8.22 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); LRMS (ESI+ve): calculated for LRMS (ESI+ve): calculated for $C_{13}H_{15}NO_6S$, [M+H] = 314.07, observed [M+H] = 314.06.

Methyl 3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (3b)

2b (0.8 g, 2.7 mmol) was dissolved in glacial acetic acid (10 mL) and the solution was cooled to 0 °C in an ice bath. Iron powder (0.6 g, 10.7 mmol) was added in small portions with stirring. After the addition was complete, the reaction mixture was allowed to warm to 23 °C and was then heated to 80 °C in an oil bath for 1 h, at which time the bright yellow solution turned viscous and gray. The reaction mixture was then carefully quenched with ice-cold water and extracted with ethyl acetate (50 mL, 4x). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford a brown residue. Purification by flash chromatography (0-25 % ethyl acetate in hexanes; dichloromethane and 20% MeOH/dichloromethane) afforded **3b** as a yellow solid (0.5 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.70 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.50 (d, *J* = 1.7 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 3.94 (s, 3H), 3.49 (s, 2H); LRMS (ESI+ve): calculated for LRMS (ESI+ve): calculated for $C_{10}H_9NO_3S$, [M+H] = 224.04, observed [M+H] = 224.05.

Ethyl 3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (3c)

2c (2.8 g, 8.9 mmol) was dissolved in glacial acetic acid (20 mL) and the solution was cooled to 0 °C in an ice bath. Iron powder (2.0 g, 36.0 mmol) was added in small portions with stirring. After the addition was complete, the reaction mixture was allowed to warm to 23 °C and was then heated to 80 °C in an oil bath for 1 h, at which time the bright yellow solution turned viscous and gray. The reaction mixture was then carefully quenched with ice cold water (100 mL) and extracted with ethyl acetate (50 mL, 3x). The

organic layer was dried over anhydrous sodium sulfate and evaporated to afford a brown residue. Purification by flash chromatography (0-25% ethyl acetate in hexanes; dichloromethane and 20% MeOH/dichloromethane) afforded **3c** as a yellow solid (1.5 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.70 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.52 (d, *J* = 1.6 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 2H), 1.41 (t, *J* = 7.1 Hz, 3H); LRMS (ESI+ve): calculated for LRMS (ESI+ve): calculated for $C_{11}H_{11}NO_3S$, [M+H] = 238.05, observed [M+H] = 238.06.

_N_-((1-ethylpyrrolidin-2-yl)methyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (3d)

According to the procedure described for **11**, starting from acid **3a** (100 mg, 0.48 mmol), 1-ethylpyrrolidin-2-yl)methanamine (69 μL, 0.48 mmol), triethylamine (200 μL, 1.43 mmol), HOBt (78 mg, 0.57 mmol), and EDCI•HCl (137 mg, 0.72 mmol), **3d** was obtained as a yellow solid (30 mg, 20%) after purification by flash chromatography (0-20% MeOH/chloroform). ^{1}H NMR (500 MHz, methanol-d_4) δ 8.42 (s, 1H), 7.55 – 7.47 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 3.87 – 3.78 (m, 1H), 3.75 – 3.66 (m, 3H), 3.54 (dq, *J* = 12.3, 7.3 Hz, 1H), 3.47 (s, 2H), 3.22 – 3.11 (m, 2H), 2.32 – 2.22 (m, 1H), 2.17 – 2.07 (m, 1H), 2.07 – 1.91 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{16}H_{21}N_3O_2S$, [M+H] = 320.14, observed [M+H] = 320.22; HRMS (ESI+ve): calculated for $C_{16}H_{21}N_3O_2S$, [M+H] = 320.1427, observed [M+H] = 320.1408.

(*Z*)-2-benzylidene-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (4b)

3b (220 mg, 0.99 mmol) was suspended in acetic anhydride (5 mL). Benzaldehyde (199 μL, 1.97 mmol) and triethylamine (412 μL, 2.96 mmol) were added, and the mixture was heated to reflux for 15 h. After cooling to 23 °C, diethyl ether (10 mL) was added, and the mixture was cooled to 0 °C. The precipitate formed was collected by filtration, washed with diethyl ether, and dried to afford (*Z*)-methyl 2-(2-chlorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (80 mg). This material was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.99 (s, 1H), 7.68 (t, *J* = 8.1 Hz, 3H), 7.56 (s, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 3.94 (s, 1H); LRMS (ESI+ve): calculated for $C_{17}H_{13}NO_3S$, [M+H] = 312.07, observed [M+H] = 312.08. The crude product (80 mg, 0.26 mmol) was dissolved in MeOH (5mL) and LiOH solution (62 mg, 2.57 mmol) in water (5 mL), and the mixture was stirred at 23 °C for 15 h. The methanol was evaporated and the mixture diluted with 10 mL water and extracted with ethyl acetate (5 mL, 3x). The aqueous layer was acidified with conc. HCl. The precipitate formed was collected by filtration, washed with water and dried to afford **4b** (55 mg, 19%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.86 (s, 1H), 7.68 – 7.63 (m, 4H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.42 – 7.37 (m, 1H), 7.35 (d, *J* = 8.6 Hz, 1H); LRMS (ESI+ve): calculated for $C_{16}H_{11}NO_3S$, [M+H] = 298.05, observed [M+H] = 298.05.

(*Z*)-2-(2-methylbenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (4c)

3c (200 mg, 0.84 mmol) was suspended in acetic anhydride (5 mL). *o*-Tolualdehyde (195 μL, 1.7 mmol) and triethylamine (352 μL, 2.5 mmol) were added and the mixture was

heated to reflux for 15 h. After cooling to 23 °C, diethyl ether (10 mL) was added, and the mixture was cooled to 0 °C. The precipitate formed was collected by filtration, washed with diethyl ether, and dried to afford (Z)-ethyl 2-(2-methylbenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (80 mg), which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 2H), 7.67 (dt, J = 8.3, 1.4 Hz, 1H), 7.49 (s, 2H), 7.34 – 7.30 (m, 3H), 7.21 (d, J = 8.2 Hz, 1H), 4.43 – 4.35 (m, 2H), 2.37 (s, 3H), 1.43 – 1.39 (m, 3H); LRMS (ESI+ve): calculated for $C_{19}H_{17}NO_3S$, [M+H] = 340.1, observed [M+H] = 340.11. The crude product (80 mg, 0.29 mmol) was dissolved in MeOH (5mL) and LiOH solution (56 mg, 2.4 mmol) in water (5 mL), and the mixture was stirred at 23 °C for 15 h. The methanol was evaporated, and the mixture was diluted with 10 mL water and extracted with ethyl acetate (5 mL, 3x). The aqueous layer was acidified with conc. HCl. The precipitate formed was collected by filtration, washed with water and dried to afford **4c** as a yellow powder (66 mg, 25%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.94 (s, 1H), 7.65 – 7.59 (m, 3H), 7.49 – 7.44 (m, 1H), 7.29 – 7.22 (m, 4H), 2.31 (s, 4H); LRMS (ESI+ve): calculated for $C_{17}H_{14}NO_3S$, [M+H] = 312.07, observed [M+H] = 312.08.

(Z)-2-(2-methoxybenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (4d)

As reported above for **4c**, starting from **3c** (200 mg, 0.85 mmol), *o*-anisaldehyde (203 μL, 1.69 mmol) and triethylamine (352 μL, 2.53 mmol), (Z)-ethyl 2-(2-methoxybenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (130 mg) were obtained and used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s,

1H), 8.18 – 8.15 (m, 1H), 7.66 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.62 (d, 1H), 7.48 (s, 1H), 7.43 – 7.38 (m, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); LRMS (ESI+ve): calculated for $C_{19}H_{17}NO_4S$, [M+H] = 356.1, observed [M+H] = 356.09. As reported above for **4c**, the crude product (130 mg, 0.37 mmol) and LiOH (88 mg, 3.66 mmol) afforded **4d** (95 mg, 34%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.07 (s, 1H), 7.63 (s, 2H), 7.62 – 7.59 (m, 2H), 7.42 – 7.35 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.05 (dd, *J* = 8.0, 3.4 Hz, 2H), 3.87 (s, 3H); LRMS (ESI-ve): calculated for $C_{17}H_{13}NO_4S$, [M+H] = 328.06, observed [M+H] = 328.06.

(*Z*)-2-(3-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (4e)

As described above for **4a**, starting from **3a** (200 mg, 0.96 mmol), 3-fluorobenzaldehyde (203 μL, 1.91 mmol) and triethylamine (400 μL, 2.87 mmol) afforded **4e** as a yellowish brown solid (170 mg, 56%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.0 (broad s, 1H), 11.27 (s, 1H), 7.82 (s, 1H), 7.67 (s, 1H), 7.60 – 7.50 (m, 4H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.28 (t, *J* = 8.8 Hz, 1H); LRMS (ESI-ve): calculated for $C_{16}H_9FNO_3S$, [M-H] = 314.03, observed [M-H] = 314.0.

(Z)-2-(4-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (4f)

As described above for **4a**, starting from **3a** (200 mg, 0.96 mmol), 4-fluorobenzaldehyde (205 μL, 1.91 mmol) and triethylamine (400 μL, 2.87 mmol) afforded **4f** as a yellowish

brown solid (160 mg, 53%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.98 (s, 1H), 11.20 (s, 1H), 7.83 (s, 1H), 7.75 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.66 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.36 (t, *J* = 8.7 Hz, 2H); LRMS (ESI-ve): calculated for $C_{16}H_9FNO_3S$, [M-H] = 314.03, observed [M-H] = 314.0.

(Z)-2-(2,3-difluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (4g)

As described above for **4a**, starting from **3a** (200 mg, 0.96 mmol), 2,3-difluorobenzaldehyde (209 μL, 1.91 mmol) and triethylamine (400 μL, 2.87 mmol) afforded **4g** as a yellowish brown solid (250 mg, 78%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.42 (s, 1H), 7.83 (s, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.65 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.38 (q, *J* = 7.3 Hz, 1H); LRMS (ESI+ve): calculated for $C_{16}H_9F_2NO_3S$, [M+H] = 334.03, observed [M+H] = 334.04.

(Z)-2-(2,6-difluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (4h)

As described above for **4a**, starting from **3a** (200 mg, 0.96 mmol), 2,6-difluorobenzaldehyde (206 μL, 1.91 mmol), and triethylamine (400 μL, 2.87 mmol) afforded **4h** as a yellowish brown solid (200 mg, 63%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.42 (s, 1H), 11.36 (s, 0.3H), 7.73 (s, 1H), 7.69 (s, 0.3 H), 7.66 – 7.54 (m, 4H), 7.54 – 7.48 (m, 1.5 H), 7.41 – 7.30 (m, 1H), 7.29 – 7.22 (m, 3H), 7.04 – 6.96 (m, 0.7H); LRMS (ESI+ve): calculated for $C_{16}H_9F2NO_3S$, [M+H] = 334.03, observed [M+H] = 334.04.

(*Z*)-2-(naphthalen-1-ylmethylene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (4i)

As described above for **4c**, starting from **3c** (200 mg, 0.85 mmol), 1-naphthaldehyde (229 μL, 1.69 mmol) and triethylamine (352 μL, 2.53 mmol), (Z)-ethyl 2-(naphthalen-1-ylmethylene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylate (112 mg) was obtained and used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.16 (s, 1H), 8.04 – 7.99 (m, 1H), 7.94 – 7.90 (m, 2H), 7.67 – 7.62 (m, 2H), 7.60 – 7.54 (m, 3H), 7.52 (s, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.15 – 3.07 (m, 2H), 1.42 (t, *J* = 7.5 Hz, 3H); LRMS (ESI+ve): calculated for $C_{22}H_{17}NO_3S$, [M+H] = 376.1, observed [M+H] = 376.13. As described above for **4c** the crude product (110 mg, 0.29 mmol) and LiOH (70 mg, 2.93 mmol) afforded **4i** (100 mg, 98%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.02 – 7.96 (m, 2H), 7.96 – 7.90 (m, 1H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.66 – 7.55 (m, 4H), 7.49 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H); LRMS (ESI-ve): calculated for $C_{20}H_{13}NO_3S$, [M+H] = 348.06, observed [M+H] = 348.08.

(*Z*)-2-(naphthalen-2-ylmethylene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (4j)

As described above for **4a**, starting from **3a** (200 mg, 0.96 mmol), 2-napthaldehyde (299 mg, 1.91 mmol), and triethylamine (400 μL, 2.87 mmol) afforded **4j** as a yellowish brown solid (170 mg, 51%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.22 (s, 3H), 8.21 (s, 4H), 8.08 – 7.91 (m, 16H), 7.80 (d, *J* = 8.6 Hz, 4H), 7.68 (s, 3H), 7.62 – 7.56 (m, 2H),

7.54 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H); LRMS (ESI+ve): calculated for $C_{16}H_9FNO_3S$, [M+H] = 348.06, observed [M+H] = 348.03.

(*Z*)-*N*-((1-ethylpyrrolidin-2-yl)methyl)-2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5a)

According to the procedure described for **11**, starting from acid **4a** (513 mg, 1.63 mmol), HOBt monohydrate (249 mg, 1.63 mmol), EDCI•HCl (311 mg, 1.63 mmol), triethylamine (0.68 mL, 4.89 mmol), and 2-(aminomethyl)-1-ethylpyrrolidine (210 mg, 1.63 mmol), a crude product (402.7 mg) was recovered. It was purified by flash chromatography (25 mL silica gel, 10% methanol/ethyl acetate, then 5% to 10% methanol / dichloromethane) to return 260 mg of a yellow solid, which was triturated with ethyl acetate to afford **5a** (132 mg 19%) as a yellow solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.98 (s, 1H), 7.83 (t, *J* = 1.6 Hz, 1H), 7.57 – 7.41 (m, 3H), 7.35 (dd, *J* = 13.3, 7.8 Hz, 2H), 7.23 (dd, *J* = 10.5, 8.5 Hz, 1H), 3.66 (d, *J* = 4.4 Hz, 1H), 3.33 (m, 4H), 2.65 (m., 2H), 2.10 (s, 1H), 2.02 – 1.63 (m, 3H), 1.28 (t, *J* = 7.2 Hz, 3H). LRMS (ESI+ve): calculated for $C_{23}H_{25}FN_3O_2S$, [M+H] = 426.17, observed [M+H] = 426.26; HRMS (ESI+ve): calculated for $C_{23}H_{25}FN_3O_2S$, [M+H] = 426.1646, observed [M+H] = 426.1614.

(*Z*)-2-benzylidene-N-((1-ethylpyrrolidin-2-yl)methyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5b)

According to the procedure described for **11**, starting from acid **4b** (50 mg, 0.17 mmol), 1-ethylpyrrolidin-2-yl)methanamine (37 μL, 0.25 mmol), triethylamine (70 μL, 0.5

mmol), HOBt (27 mg, 0.2 mmol), and EDCI•HCl (48 mg, 0.25 mmol), **5b** was obtained as a yellow solid (28 mg, 41%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.84 (s, 1H), 7.65 (dd, J = 7.5, 1.5 Hz, 2H), 7.49 – 7.44 (m, 2H), 7.44 – 7.40 (m, 2H), 7.40 – 7.35 (m, 1H), 7.34 – 7.30 (m, 1H), 3.62 (dd, J = 13.4, 3.9 Hz, 1H), 3.22 (dd, J = 13.4, 7.7 Hz, 1H), 3.16 (dt, J = 9.7, 4.8 Hz, 1H), 2.96 (dq, J = 11.8, 7.3 Hz, 1H), 2.68 (qd, J = 7.4, 3.9 Hz, 1H), 2.34 (dq, J = 11.9, 7.1 Hz, 1H), 2.28 – 2.19 (m, 1H), 1.95 (dq, J = 12.4, 8.1 Hz, 1H), 1.83 – 1.72 (m, 2H), 1.65 (dq, J = 12.3, 6.9 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{23}H_{25}N_3O_2S$, [M+H] = 408.17, observed [M+H] = 408.27; HRMS (ESI+ve): calculated for $C_{23}H_{25}N_3O_2S$, [M+H] = 408.1740, observed [M+H] = 408.1786.

(*Z*)-N-((1-ethylpyrrolidin-2-yl)methyl)-2-(2-methylbenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5c)

According to the procedure described for **11**, starting from acid **4c** (70 mg, 0.23 mmol), 1-ethylpyrrolidin-2-yl)methanamine (49 μL, 0.34 mmol), triethylamine (94 μL, 0.67 mmol), HOBt (36 mg, 0.27 mmol), and EDCI•HCl (65 mg, 0.34 mmol), **5c** was obtained as a yellow solid (50 mg, 52%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.98 (s, 1H), 7.50 (dd, J = 6.5, 2.8 Hz, 1H), 7.45 (d, J = 1.6 Hz, 1H), 7.43 (dd, J = 8.1, 1.8 Hz, 1H), 7.31 (d, J = 2.5 Hz, 3H), 7.27 (d, J = 8.1 Hz, 1H), 3.66 (dd, J = 13.4, 4.1 Hz, 1H), 3.25 (dd, J = 13.4, 7.7 Hz, 1H), 3.22 – 3.17 (m, 1H), 3.00 (dq, J = 11.9, 7.4 Hz, 1H), 2.72 (qd, J = 7.2, 3.7 Hz, 1H), 2.39 (dt, J = 12.1, 7.1 Hz, 1H), 2.35 (s, 3H), 2.31 – 2.24 (m, 1H), 1.99 (dq, J = 12.4, 8.2 Hz, 1H), 1.85 – 1.76 (m, 2H), 1.69 (ddd, J = 14.1, 12.8, 6.9 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{24}H_{27}N_3O_2S$, [M+H] = 422.18, observed

[M+H] = 422.28; HRMS (ESI+ve): calculated for $C_{24}H_{27}N_3O_2S$, [M+H] = 422.1897, observed [M+H] = 422.1878.

(*Z*)-N-((1-ethylpyrrolidin-2-yl)methyl)-2-(2-methoxybenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5d)

According to the procedure described for **11**, starting from acid **4d** (83 mg, 0.25 mmol), 1-ethylpyrrolidin-2-yl)methanamine (55 μL, 0.38 mmol), triethylamine (106 μL, 0.76 mmol), HOBt (41 mg, 0.3 mmol), and EDCI•HCl (73 mg, 0.38 mmol), **5d** was obtained as a tan solid (38 mg, 34%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.05 – 8.03 (m, 1H), 7.59 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.25 (d, *J* = 8.6 Hz, 1H), 7.06 – 6.98 (m, 2H), 3.85 (s, 3H), 3.60 (dd, *J* = 13.4, 4.0 Hz, 1H), 3.20 (dd, *J* = 13.4, 7.7 Hz, 1H), 3.17 – 3.11 (m, 1H), 3.00 – 2.89 (m, 1H), 2.71 – 2.62 (m, 1H), 2.33 (dq, *J* = 11.8, 7.2 Hz, 1H), 2.22 (q, *J* = 8.9 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.81 – 1.70 (m, 2H), 1.68 – 1.60 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{24}H_{27}N_3O_3S$, [M+H] = 438.18, observed [M+H] = 438.28; HRMS (ESI+ve): calculated for $C_{24}H_{27}N_3O_3S$, [M+H] = 438.1846, observed [M+H] = 438.1826.

(*Z*)-N-((1-ethylpyrrolidin-2-yl)methyl)-2-(3-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5e)

According to the procedure described for **11**, starting from acid **4e** (75 mg, 0.24 mmol), 1-ethylpyrrolidin-2-yl)methanamine (52 μL, 0.36 mmol), triethylamine (100 μL, 0.71 mmol), HOBt (48 mg, 0.36 mmol) and EDCI•HCl (68 mg, 0.36 mmol), **5e** was obtained as a yellow solid (24 mg, 24%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.73 (s, 1H), 7.43 –

7.32 (m, 6H), 7.29 – 7.24 (m, 1H), 7.04 (ddt, *J* = 9.6, 8.3, 1.8 Hz, 1H), 3.54 (dd, *J* = 13.4, 4.0 Hz, 1H), 3.20 – 3.12 (m, 2H), 3.12 – 3.04 (m, 1H), 2.89 (dq, *J* = 14.4, 7.4 Hz, 1H), 2.63 (s, 1H), 2.28 (dq, *J* = 13.8, 7.1 Hz, 1H), 2.18 (q, *J* = 9.2 Hz, 1H), 1.88 (dq, *J* = 12.4, 8.2 Hz, 1H), 1.74 – 1.65 (m, 3H), 1.59 (dt, *J* = 12.9, 6.8 Hz, 1H), 1.07 (t, *J* = 7.2 Hz, 4H); LRMS (ESI+ve): calculated for $C_{23}H_{24}FN_3O_2S$, [M+H] = 426.17, observed [M+H] = 426.27; HRMS (ESI+ve): calculated for $C_{23}H_{24}FN_3O_2S$, [M+H] = 426.1646, observed [M+H] = 426.1627.

(*Z*)-N-((1-ethylpyrrolidin-2-yl)methyl)-2-(4-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5f)

According to the procedure described for **11**, starting from acid **4f** (75 mg, 0.24 mmol), 1-ethylpyrrolidin-2-yl)methanamine (52 μL, 0.36 mmol), triethylamine (100 μL, 0.71 mmol), HOBt (48 mg, 0.36 mmol) and EDCI•HCl (68 mg, 0.36 mmol), **5f** was obtained as a yellow solid (23 mg, 23%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.81 (s, 1H), 7.73 – 7.67 (m, 2H), 7.45 – 7.39 (m, 2H), 7.35 – 7.30 (m, 1H), 7.20 (t, *J* = 8.8 Hz, 1H), 3.62 (dd, *J* = 13.4, 4.0 Hz, 1H), 3.22 (dd, *J* = 13.4, 7.7 Hz, 1H), 3.16 (dt, *J* = 9.7, 4.9 Hz, 1H), 2.96 (dq, *J* = 11.9, 7.3 Hz, 1H), 2.68 (qd, *J* = 7.8, 4.0 Hz, 1H), 2.34 (dq, *J* = 12.0, 7.2 Hz, 1H), 2.23 (q, *J* = 8.8 Hz, 1H), 1.95 (dq, *J* = 12.3, 8.0 Hz, 1H), 1.77 (qd, *J* = 7.6, 4.8 Hz, 2H), 1.65 (dq, *J* = 13.7, 7.0 Hz, 1H), 1.15 (t, *J* = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{23}H_{24}FN_3O_2S$, [M+H] = 426.17, observed [M+H] = 426.28; HRMS (ESI+ve): calculated for $C_{23}H_{24}FN_3O_2S$, [M+H] = 426.1646, observed [M+H] = 426.1628.

(*Z*)-2-(2,3-difluorobenzylidene)-N-((1-ethylpyrrolidin-2-yl)methyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5g)

According to the procedure described for **11**, starting from acid **4g** (250 mg, 0.75 mmol), 1-ethylpyrrolidin-2-yl)methanamine (163 μL, 1.13 mmol), triethylamine (313 μL, 2.25 mmol), HOBt (152 mg, 1.13 mmol), and EDCI•HCl (216 mg, 1.13 mmol), **5g** was obtained as a yellow solid (87 mg, 26 %). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.91 – 7.88 (m, 1H), 7.59 (ddt, *J* = 7.9, 6.3, 1.8 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.35 – 7.24 (m, 3H), 3.62 (dd, *J* = 13.4, 4.0 Hz, 1H), 3.22 (dd, *J* = 13.4, 7.7 Hz, 1H), 3.16 (ddd, *J* = 9.7, 6.1, 4.6 Hz, 1H), 2.96 (dq, *J* = 12.0, 7.3 Hz, 1H), 2.73 – 2.63 (m, 1H), 2.34 (dq, *J* = 12.0, 7.1 Hz, 1H), 2.24 (q, *J* = 9.5 Hz, 1H), 1.95 (dq, *J* = 12.5, 8.2 Hz, 1H), 1.82 – 1.71 (m, 2H), 1.65 (dq, *J* = 12.4, 6.9 Hz, 1H), 1.15 (t, *J* = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{23}H_{23}F_2N_3O_2S$, [M+H] = 444.16, observed [M+H] = 444.26; HRMS (ESI+ve): calculated for $C_{23}H_{23}F_2N_3O_2S$, [M+H] = 444.1552, observed [M+H] = 444.1532.

(*Z*)-2-(2,6-difluorobenzylidene)-N-((1-ethylpyrrolidin-2-yl)methyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5h)

According to the procedure described for **11**, starting from acid **4g** (200 mg, 0.6 mmol), 1-ethylpyrrolidin-2-yl)methanamine (131 μL, 0.9 mmol), triethylamine (251 μL, 1.8 mmol), HOBt (122 mg, 0.9 mmol), and EDCI•HCl (173 mg, 0.9 mmol), **5h** was obtained as a yellow solid (66 mg, 25 %). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.59 (s, 1H), 7.50 – 7.43 (m, 2H), 7.41 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.10 – 7.03 (m, 2H), 6.92 – 6.84 (m, 0.4H), 3.62 (dt, *J* = 13.4, 4.3 Hz, 1H), 3.25 – 3.18 (m, 1H), 3.16 (dq, *J* = 8.0, 5.2, 4.6 Hz, 1H), 2.96 (dq, *J* = 11.9, 7.3 Hz, 1H), 2.72 – 2.63 (m, 1H), 2.34 (dq, *J*

= 12.0, 7.1 Hz, 1H), 2.27 – 2.19 (m, 1H), 1.95 (dq, *J* = 12.5, 8.1 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.65 (dq, *J* = 12.4, 6.9 Hz, 1H), 1.15 (t, *J* = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{23}H_{23}F_2N_3O_2S$, [M+H] = 444.16, observed [M+H] = 444.27; HRMS (ESI+ve): calculated for $C_{23}H_{23}F_2N_3O_2S$, [M+H] = 444.1552, observed [M+H] = 444.1531.

(*Z*)-N-((1-ethylpyrrolidin-2-yl)methyl)-2-(naphthalen-1-ylmethylene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5i)

According to the procedure described for **11**, starting from acid **4i** (92 mg, 0.27 mmol), 1-ethylpyrrolidin-2-yl)methanamine (58 μL, 0.4 mmol), triethylamine (111 μL, 0.8 mmol), HOBt (43 mg, 0.32 mmol), and EDCI•HCl (76 mg, 0.4 mmol), **5i** was obtained as a yellow solid (70 mg, 58%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.40 (s, 1H), 7.98 – 7.90 (m, 3H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.59 – 7.51 (m, 3H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 3.62 (dd, *J* = 13.4, 4.1 Hz, 1H), 3.22 (dd, *J* = 13.4, 7.6 Hz, 1H), 3.19 – 3.13 (m, 1H), 3.01 – 2.92 (m, 1H), 2.73 – 2.65 (m, 1H), 2.35 (dq, *J* = 14.1, 7.1 Hz, 1H), 2.25 (q, *J* = 8.9 Hz, 1H), 1.95 (dq, *J* = 12.5, 8.1 Hz, 1H), 1.81 – 1.73 (m, 2H), 1.65 (dq, *J* = 13.8, 6.9 Hz, 1H), 1.15 (t, *J* = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{27}H_{27}N_3O_2S$, [M+H] = 458.19, observed [M+H] = 458.32; HRMS (ESI+ve): calculated for $C_{27}H_{27}N_3O_2S$, [M+H] = 458.1897, observed [M+H] = 458.1878.

(Z)-N-((1-ethylpyrrolidin-2-yl)methyl)-2-(naphthalen-2-ylmethylene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (5j)

According to the procedure described for **11**, starting from acid **4j** (75 mg, 0.22 mmol), 1-ethylpyrrolidin-2-yl) methanamine (47 μL, 0.32 mmol), triethylamine (90 μL, 0.65 mmol), HOBt (44 mg, 0.32 mmol), and EDCI•HCl (62 mg, 0.32 mmol), **5j** was obtained as a yellow solid (21 mg, 21%).^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (d, J = 1.5 Hz, 1H), 7.97 (s, 1H), 7.96 – 7.91 (m, 1H), 7.90 (s, 0.5 H), 7.87 (dd, J = 6.0, 3.4 Hz, 1H), 7.73 (dd, J = 8.6, 1.8 Hz, 1H), 7.53 (dt, J = 6.2, 3.4 Hz, 2H), 7.47 – 7.44 (m, 0.5 H), 7.41 (dd, J = 6.1, 1.9 Hz, 2H), 7.37 – 7.32 (m, 1H), 3.63 (dd, J = 13.4, 3.9 Hz, 1H), 3.22 (dd, J = 13.4, 7.7 Hz, 1H), 3.19 – 3.09 (m, 1H), 2.96 (dq, J = 11.9, 7.3 Hz, 1H), 2.68 (qd, J = 7.7, 3.9 Hz, 1H), 2.34 (dq, J = 12.1, 7.1 Hz, 1H), 2.24 (q, J = 8.8 Hz, 1H), 1.96 (dq, J = 12.1, 8.1 Hz, 1H), 1.77 (qd, J = 7.6, 4.7 Hz, 2H), 1.66 (dq, J = 13.6, 6.9 Hz, 1H), 1.15 (t, J = 7.3 Hz, 3H); LRMS (ESI+ve): calculated for $C_{27}H_{27}N_3O_2S$, [M+H] = 458.19, observed [M+H] = 458.31; HRMS (ESI+ve): calculated for $C_{27}H_{27}N_3O_2S$, [M+H] = 458.1897, observed [M+H] = 458.1856.

N-((1-ethylpyrrolidin-2-yl)methyl)-2-(2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (10)

4a (485 mg, 1.54 mmol) and $CoCl_2$ (300 mg, 2.31 mmol) were weighed into a flame-dried flask under nitrogen atmosphere. Dry THF (20 mL) was added, and the mixture cooled to 0 °C in an ice-bath. Sodium borohydride (349 mg, 9.23 mmol) was transferred into the flask in portions. The reaction mixture was stirred at 0 °C for 10 minutes and then at 23 °C for 24 h. The reaction mixture was then poured into water (100 mL) and extracted with ethyl acetate (25 mL, 3x). The aqueous layer was acidified with conc. HCl to pH = 2.0 and extracted with 5% methanol/ethyl acetate (50 mL, 3x). The organic layer

was dried over anhydrous sodium sulfate and evaporated to afford a the product 2-(2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxylic acid (0.26, 53%) as a brown solid which was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.19 – 7.10 (m, 2H), 2.95 (t, J = 7.7 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H). According to the procedure described for **11**, the crude acid (0.25 mg, 0.79 mmol), 1-ethylpyrrolidin-2-yl)methanamine (171 μL, 1.2 mmol), triethylamine (329 μL, 2.36 mmol), HOBt (160 mg, 1.2 mmol), and EDCI•HCl (227 mg, 1.2 mmol), **10** was obtained as a yellow gel (138 mg, 41%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.95 (t, J = 1.8 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.10 – 7.00 (m, 2H), 3.64 (dd, J = 13.4, 4.0 Hz, 1H), 3.23 (dd, J = 13.4, 7.7 Hz, 1H), 3.17 (dt, J = 9.7, 4.9 Hz, 1H), 3.04 (t, J = 7.7 Hz, 2H), 3.00 – 2.93 (m, 1H), 2.69 (t, J = 7.6 Hz, 2H), 2.36 (dq, J = 12.0, 7.1 Hz, 1H), 2.25 (q, J = 8.9 Hz, 1H), 2.02 – 1.91 (m, 1H), 1.82 – 1.73 (m, 2H), 1.72 – 1.62 (m, 1H), 1.16 (t, J = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{23}H_{26}FN_3O_2S$, [M+H] = 428.18, observed [M+H] = 428.27; HRMS (ESI+ve): calculated for $C_{23}H_{26}FN_3O_2S$, [M+H] = 428.1803, observed [M+H] = 428.1855.

(*R*,*Z*)-*N*-((1-ethylpyrrolidin-2-yl)methyl)-2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (11)

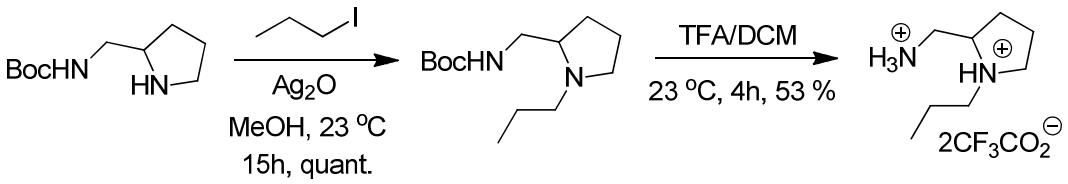
^{1}H NMR (500 MHz, Methanol-d_4) δ 7.85 (s, 1H), 7.71 (td, J = 7.7, 1.6 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.25 – 7.18 (m, 2H), 7.10 (ddd, J = 10.6, 8.2, 1.2 Hz, 1H), 3.54 (dd, J =

13.4, 4.0 Hz, 1H), 3.14 (dd, *J* = 13.4, 7.6 Hz, 1H), 3.08 (ddd, *J* = 9.7, 5.7, 4.0 Hz, 1H), 2.88 (dq, *J* = 12.0, 7.3 Hz, 1H), 2.60 (qd, *J* = 7.6, 3.9 Hz, 1H), 2.26 (dq, *J* = 12.0, 7.1 Hz, 1H), 2.16 (q, *J* = 8.9 Hz, 1H), 1.87 (dq, *J* = 12.5, 8.2 Hz, 1H), 1.74 – 1.63 (m, 2H), 1.57 (dq, *J* = 12.4, 6.9 Hz, 1H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, acetic acid-d_4) δ 170.08, 162.67, 161.76, 160.67, 134.47, 132.48, 132.26, 132.19, 130.77, 126.49, 126.07, 126.02, 125.08, 125.05, 123.85, 123.45, 123.35, 122.51, 122.33, 117.35, 116.69, 116.52, 68.56, 55.00, 51.82, 41.64, 28.39, 23.45, 11.02;

(*S*,*Z*)-N-((1-ethylpyrrolidin-2-yl)methyl)-2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (12)

According to the procedure described for **11**, starting from acid **4a** (200 mg, 0.63 mmol), (*S*)-(1-ethylpyrrolidin-2-yl)methanamine (0.133 mL, 0.95 mmol), triethylamine (0.26 mL, 1.9 mmol), HOBt (129 mg, 0.95 mmol), and EDCI•HCl (182 mg, 0.95 mmol), **12** was obtained as a yellowish brown solid (76 mg, 28%). $[\alpha]_D$ = (-)-16.2 (c = 0.001, MeOH, 23 °C); ^{1}H NMR (500 MHz, Acetic Acid-*d*4) δ 8.05 (s, 1H), 7.82 (td, *J* = 7.6, 1.6 Hz, 1H), 7.60 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.44 (tdd, *J* = 7.4, 5.2, 1.7 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.31 (td, *J* = 7.6, 1.1 Hz, 1H), 7.20 (ddd, *J* = 10.6, 8.3, 1.2 Hz, 1H), 4.01 – 3.74 (m, 4H), 3.53 – 3.42 (m, 1H), 3.24 – 3.08 (m, 2H), 2.30 (dq, *J* = 14.2, 7.3 Hz, 1H), 2.11 – 2.06 (m, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); LRMS (ESI+ve): calculated for $C_{23}H_{24}FN_3O_2S$, [M+H] = 426.17, observed [M+H] = 426.26; HRMS (ESI+ve): calculated for $C_{23}H_{24}FN_3O_2S$, [M+H] = 426.1646, observed [M+H] = 426.1628.

(*Z*)-2-(2-fluorobenzylidene)-3-oxo-N-((1-propylpyrrolidin-2-yl)methyl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide, (13): synthesis of (1-propylpyrrolidin-2-yl)methanamine, bis-trifluoroacetate salt



Silver oxide (231 mg, 0.1 mmol) and *n*-propyl iodide (227 μL, 0.1 mmol) were added to a solution of tert-butyl (pyrrolidin-2-ylmethyl)carbamate (200 mg, 0.1 mmol) in methanol (10 mL). The mixture was stirred for 15 h at 23 °C and then filtered through a celite plug and washed with methanol. The filtrate was evaporated to afford tert-butyl ((1-propylpyrrolidin-2-yl)methyl)carbamate (242 mg, quant.), which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (s, 1H), 3.34 (t, *J* = 10.6 Hz, 1H), 3.26 – 3.13 (m, 1H), 3.09 (s, 1H), 2.66 (t, *J* = 10.0 Hz, 1H), 2.54 (s, 1H), 2.17 (s, 2H), 1.92 – 1.80 (m, 1H), 1.74 (d, *J* = 10.5 Hz, 2H), 1.62 (dt, *J* = 12.1, 7.3 Hz, 1H), 1.57 – 1.51 (m, 1H), 1.46 (s, 9H), 0.92 (t, *J* = 7.4 Hz, 3H); LRMS (ESI+ve): calculated for $C_{13}H_{26}N_2O_2$, [M+H] = 243.21, observed [M+H] = 243.21. TFA (5 mL) was added dropwise to a solution of tert-butyl ((1-propylpyrrolidin-2-yl)methyl)carbamate (0.242 mg, 0.1 mmol) in dichloromethane (5 mL) cooled to 0 °C. The solution was then stirred at 23 °C for 4 h and the solvent evaporated. The residue was dissolved in water (10 mL) and extracted with ethyl acetate (5 mL; 3x). The aqueous solution was freeze dried to afford the product (1-propylpyrrolidin-2-yl)methanamine, bis-trifluoroacetate salt, as an orange yellow oil (0.25 g, 68%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 3.73 (d, *J* = 27.1 Hz, 2H), 3.56 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.42 – 3.32 (m, 1H), 3.28 – 3.23 (m, 1H), 3.07

(td, J = 11.7, 5.3 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.22 – 2.08 (m, 2H), 1.95 (dq, J = 15.6, 8.0 Hz, 1H), 1.85 – 1.70 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); LRMS (ESI+ve): calculated for $C_8H_{18}N_2$, [M+H] = 143.15, observed [M+H] = 143.09.

According to the procedure described for **11**, starting from acid **4a** (100 mg, 0.32 mmol), (1-propylpyrrolidin-2-yl)methanamine, bis-trifluoroacetate salt (0.176 mg, 0.48 mmol), triethylamine (0.132 mL, 0.95 mmol), HOBt (64 mg, 0.48 mmol), and EDCI•HCl (91 mg, 0.48 mmol), **13** was obtained as a tan solid (67 mg, 48%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.92 (s, 1H), 7.80 (td, J = 7.7, 1.6 Hz, 2H), 7.45 – 7.38 (m, 4H), 7.32 – 7.26 (m, 3H), 7.18 (ddd, J = 10.5, 8.2, 1.2 Hz, 1H), 3.62 (dd, J = 13.4, 3.9 Hz, 1H), 3.21 (dd, J = 13.3, 7.7 Hz, 1H), 3.18 – 3.13 (m, 2H), 2.81 (ddd, J = 11.8, 10.1, 6.4 Hz, 1H), 2.72 – 2.63 (m, 1H), 2.31 – 2.19 (m, 3H), 1.94 (dq, J = 12.5, 8.1 Hz, 1H), 1.81 – 1.71 (m, 3H), 1.68 – 1.61 (m, 2H), 1.61 – 1.52 (m, 2H), 0.93 (t, J = 7.4 Hz, 4H); LRMS (ESI+ve): calculated for $C_{24}H_{26}FN_3O_2S$, [M+H] = 440.17, observed [M+H] = 440.29; HRMS (ESI+ve): calculated for $C_{24}H_{26}FN_3O_2S$, [M+H] = 440.1803, observed [M+H] = 440.1784.

(*Z*)-tert-butyl-2-((2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamido)methyl)pyrrolidine-1-carboxylate (14)

According to the procedure described for **11**, starting from acid **4a** (125 mg, 0.32 mmol), tert-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (119 mg, 0.59 mmol), triethylamine (166 μL, 1.19 mmol), HOBt (80 mg, 0.59 mmol), and EDCI•HCl (114 mg, 0.59 mmol), **14** was obtained as a yellow solid (125 mg, 63%) ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.94 (s, 1H), 7.80 (td, J = 7.7, 1.6 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.36 – 7.25 (m, 2H), 7.19

(ddd, *J* = 10.7, 8.2, 1.2 Hz, 1H), 4.06 (s, 1H), 3.54 (s, 1H), 3.49 – 3.42 (m, 1H), 3.37 (t, *J* = 6.8 Hz, 2H), 2.04 – 1.77 (m, 4H), 1.43 (s, 9H).

(*Z*)-2-(2-fluorobenzylidene)-3-oxo-N-(pyrrolidin-2-ylmethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (15)

14 (120 mg, 0.24 mmol) was dissolved in 2 mL of dichloromethane, and TFA (2 mL) was added dropwise; the mixture was then stirred at 23 °C for 2 hours. The solvent was evaporated, and the residue was dissolved in water (10 mL) and extracted with ethyl acetate (2 mL; 3x). The organic layer was discarded. The aqueous layer was basified with solid KOH pellets with cooling to pH = 13.0 and then extracted with ethyl acetate (5mL, 3x). The organic layer was dried over anhydrous sodium sulfate and evaporated to afford **15** as a yellow solid (76 mg, 79%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.94 (s, 1H), 7.80 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 – 7.39 (m, 3H), 7.34 – 7.27 (m, 2H), 7.20 (ddd, *J* = 10.8, 8.3, 1.2 Hz, 1H), 3.44 (dd, *J* = 13.4, 5.6 Hz, 1H), 3.89 - 3.31 (m, 2H), 2.99 - 2.92 (m, 1H), 2.88 – 2.80 (m, 1H), 1.96 – 1.87 (m, 1H), 1.86 – 1.71 (m, 2H), 1.53 – 1.43 (m, 1H); LRMS (ESI+ve): calculated for $C_{21}H_{21}FN_3O_2S$, [M+H] = 398.13, observed [M+H] = 398.23; HRMS (ESI+ve): calculated for $C_{21}H_{21}FN_3O_2S$, [M+H] = 398.1333, observed [M+H] = 398.1318.

(*Z*)-*N*-(2-(dimethylamino)ethyl)-2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (17)

According to the procedure described for **11**, starting from acid **4a** (162 mg, 0.51 mmol), HOBt monohydrate (78 mg, 0.51 mmol), EDCI•HCl (97 mg, 0.51 mmol), triethylamine (0.21 mL, 1.53 mmol), *N,N*-dimethylethylenediamine (45 mg, 0.51 mmol), and 4.5 mL of

N,N-dimethylformamide in place of dichloromethane as solvent, a crude product (226 mg) was recovered and purified by flash chromatography (20 mL silica gel, 5% methanol / ethyl acetate, then 5% to 20% methanol / chloroform) to return a yellow solid, which was triturated with 10% methanol / ethyl acetate to afford **17** as a yellow solid (25.8 mg, 13%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.98 (s, 1H), 7.84 (td, J = 7.9, 1.8 Hz, 1H), 7.58 – 7.41 (m, 3H), 7.41 – 7.29 (m, 2H), 7.29 – 7.02 (m, 1H), 3.56 (t, J = 6.7 Hz, 2H), 2.66 (t, J = 6.7 Hz, 2H), 2.39 (s, 6H). LRMS (ESI+ve): calculated for $C_{20}H_{21}FN_3O_2S$, [M+H] = 386.13, observed [M+H] = 386.22; HRMS (ESI+ve): calculated for $C_{20}H_{21}FN_3O_2S$, [M+H] = 386.1333, observed [M+H] = 386.1243.

(*Z*)-*N*-(2-(diethylamino)ethyl)-2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (22)

According to the procedure described for **11**, starting from acid **4a** (86 mg, 0.27 mmol), HOBt monohydrate (36 mg, 0.23 mmol), EDCI•HCl (78 mg, 0.407 mmol), triethylamine (0.13 mL, 0.93 mmol), and N^1,N^1-diethylethane-1,2-diamine (48 mg, 0.41 mmol), a crude product was recovered and purified by preparative TLC and developed with 8% 2M ammonia in methanol/dichloromethane to afford **22** as a yellow solid after recrystallization from acetonitrile (31 mg, 28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.74 (s, 1H), 7.68 (td, J = 7.7, 1.7 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.19 (m, 1H), 7.12 (d, J = 8.2 Hz, 1H), 7.07 (ddd, J = 9.8, 8.3, 1.2 Hz, 1H), 3.61 (d, J = 5.5 Hz, 2H), 2.84 – 2.73 (m, 2H), 2.66 (d, J = 7.1 Hz, 4H), 1.06 (t, J = 7.1 Hz, 6H). LRMS (ESI+ve): calculated for $C_{22}H_{24}FN_3O_2S$, [M+H] = 414.16, observed [M+H] = 414.19; HRMS

(ESI+ve): calculated for $C_{22}H_{24}FN_3O_2S$, [M+H] = 414.1646, observed [M+H] = 414.1632.

(*Z*)-2-(2-fluorobenzylidene)-3-oxo-*N*-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (29)

According to the procedure described for **11**, starting from acid **4a** (166 mg, 0.526 mmol), HOBt monohydrate (81 mg, 0.526 mmol), EDCI•HCl (101 mg, 0.526 mmol), triethylamine (0.22 mL, 1.58 mmol), 1-(2-aminoethyl)-pyrrolidine (60 mg, 0.526 mmol), and 5 mL of *N,N*-dimethylformamide in place of dichloromethane as solvent, a crude product (195 mg) was recovered and purified by flash chromatography (25 mL silica gel, 10% methanol / ethyl acetate, then 5% to 10% methanol / dichloromethane) to return a yellow solid, which was triturated with ethyl acetate to afford **29** as a yellow solid (38.7 mg, 18%). ^{1}H NMR (500 MHz, Acetic Acid-d_4) δ 7.96 (s, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.72 (s, 1H), 7.60 – 7.55 (m, 1H), 7.5 – 7.4 (m, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.17 (d, J = 8.9 Hz, 1H), 7.09 (m, 1H), 4.06 (m, 2H), 3.94 (m, 2H), 3.63 (m, 2H), 3.17 (m, H), 2.16 (m, 4H). LRMS (ESI+ve): calculated for $C_{22}H_{23}FN_3O_2S$, [M+H] = 412.14, observed [M+H] = 412.26; HRMS (ESI+ve): calculated for $C_{22}H_{23}FN_3O_2S$, [M+H] = 412.1490, observed [M+H] = 412.1485.

(*Z*)-2-(2-fluorobenzylidene)-3-oxo-*N*-(2-(piperidin-1-yl)ethyl)-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (33)

According to the procedure described for **11**, starting from acid **4a** (110 mg, 0.35 mmol), HOBt monohydrate (54 mg, 0.35 mmol), EDCI•HCl (67 mg, 0.35 mmol), triethylamine

(0.15 mL, 1.05 mmol), 1-(2-aminoethyl)-piperidine (41 mg, 0.35 mmol), and 3 mL of *N,N*-dimethylformamide in place of dichloromethane as solvent, a crude product (70 mg) was recovered. Trituration with 50% ethyl acetate / hexane failed to remove all impurities. The partially pure material was purified by flash chromatography (20 mL silica gel, 10% methanol / ethyl acetate, then 5% to 20% methanol / chloroform) to afford **33** as a yellow solid (9.6 mg, 6%). ^{1}H NMR (500 MHz, Acetic Acid-d_4) δ 8.07 (s, 1H), 7.88 – 7.81 (m, 1H), 7.68 (dd, J = 8.1, 1.8 Hz, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.39 – 7.30 (m, 2H), 7.28 – 7.19 (m, 1H), 7.12 – 7.04 (m, 1H), 3.95 (m, 2H), 3.80 (m, 2H), 3.47 (m, 2H), 2.96 (m, 2H), 2.01 – 1.77 (m, 4H), 1.52 (m, 2H). LRMS (ESI+ve): calculated for $C_{23}H_{25}FN_3O_2S$, [M+H] = 426.16, observed [M+H] = 426.27; HRMS (ESI+ve): calculated for $C_{23}H_{25}FN_3O_2S$, [M+H] = 426.1646, observed [M+H] = 426.1662.

(*Z*)-2-(2-fluorobenzylidene)-*N*-(2-morpholinoethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (34)

According to the procedure described for **11**, starting from acid **4a** (120 mg, 0.38 mmol), HOBt monohydrate (58 mg, 0.38 mmol), EDCI•HCl (73 mg, 0.38 mmol), triethylamine (0.16 mL, 1.14 mmol), 1-(2-aminoethyl)-morpholine (46 mg, 0.38 mmol), and 3 mL of *N,N*-dimethylformamide in place of dichloromethane as solvent, a crude product (35.9 mg) was recovered and triturated with 50% ethyl acetate / hexane to afford **34** as a yellow solid (24.1 mg, 15%). ^{1}H NMR (500 MHz, Acetic Acid-d_4) δ 8.40 (m, 1H), 7.85 (s, 1H), 7.79 (t, J = 1.7 Hz, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.51 (m, 1H), 7.48 – 7.40 (m, 2H), 7.40 – 7.31 (m, 2H), 3.58 (t, J = 4.6 Hz, 4H), 3.37 (q, J = 6.6 Hz, 2H), 2.42 (m, 6H). LRMS

(ESI+ve): calculated for $C_{22}H_{23}FN_3O_3S$, [M+H] = 428.14, observed [M+H] = 428.25; HRMS (ESI+ve): calculated for $C_{22}H_{23}FN_3O_3S$, [M+H] = 428.1439, observed [M+H] = 428.1458.

(*Z*)-2-(2-fluorobenzylidene)-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (39)

According to the procedure described for **11**, starting from acid **4a** (127 mg, 0.40 mmol), HOBt monohydrate (62 mg, 0.40 mmol), EDCI•HCl (77 mg, 0.40 mmol), triethylamine (0.17 mL, 1.2 mmol), and 2-(aminoethyl)-1-methylpyrrolidine (50 mg, 0.40 mmol) a crude product (180 mg) was recovered and purified by flash chromatography (20 mL silica gel, neat ethyl acetate, 5% methanol / ethyl acetate, 5% methanol / dichloromethane, 20% methanol / chloroform) to return a yellow solid. Trituration with ethyl acetate afforded **39** as a yellow solid (46.7 mg, 27%). ^{1}H NMR (500 MHz, Acetic Acid-d_4) δ 8.07 (s, 1H), 7.85 (t, J = 7.7 Hz, 1H), 7.63 (dd, J = 8.2, 1.7 Hz, 1H), 7.54 (s, 1H), 7.47 (d, J = 6.7 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.23 (dd, J = 10.4, 8.4 Hz, 1H), 3.87 (m, 1H), 3.78 – 3.63 (m, 1H), 3.57 (m, 1H), 3.41 (m, 1H), 3.10 (m, 1H), 2.97 (s, 3H), 2.56 – 2.32 (m, 2H), 2.07 (m, 4H). LRMS (ESI+ve): calculated for $C_{23}H_{25}FN_3O_2S$, [M+H] = 426.16, observed [M+H] = 426.28; HRMS (ESI+ve): calculated for $C_{23}H_{25}FN_3O_2S$, [M+H] = 426.1646, observed [M+H] = 426.1571.

(*Z*)-6-(3-aminopyrrolidine-1-carbonyl)-2-(2-fluorobenzylidene)-2H-benzo[b][1,4]thiazin-3(4H)-one (40)

According to the procedure described for **11**, starting from acid **4a** (137 mg, 0.43 mmol), HOBt monohydrate (67 mg, 0.43 mmol), EDCI•HCl (83 mg, 0.43 mmol), triethylamine (0.18 mL, 1.3 mmol) and 3-(BOC-amino)-pyrrolidine (81 mg, 0.43 mmol) a yellow solid product (83.3 mg, 40%) precipitated from the reaction mixture and was collected by filtration and used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6, partial data) δ 11.25 (s, 1H), 7.85 (s, 1H), 7.79 (t, J = 7.7 Hz, 1H), 7.50 (m, 1H), 7.37 (m, 3H), 7.29 – 7.08 (m, 3H), 4.06 (s, 0.5H), 3.94 (s, 0.5H), 2.11 – 1.95 (m, 1H), 1.92 – 1.70 (m, 1H), 1.41 (s, 4H), 1.35 (s, 5H). LRMS (ESI+ve): calculated for $C_{25}H_{27}FN_3O_4S$, [M+H] = 484.17, observed [M+H] = 484.28; HRMS (ESI+ve): calculated for $C_{25}H_{27}FN_3O_4S$, [M+H] = 484.1701, observed [M+H] = 484.1688. The BOC-protected intermediate (80.7 mg, 0.167 mmol) was treated with 1 mL of dichloromethane and 1 mL of trifluoroacetic acid. After 30 minutes, the mixture was concentrated and the residue was treated with 5 mL of 1:1 sat. sodium carbonate and water. The resulting slurry was extracted with two 30 mL portions of 10% methanol / dichloromethane. The organics were dried with magnesium sulfate and concentrated to give 48 mg of crude product which was rinsed with ethyl acetate. The sample was dissolved in 10 mL of 50% acetonitrile / water and lyophilized to afford **40** as a pale yellow solid (23 mg, 36%). ^{1}H NMR (500 MHz, Acetic Acid-d_4) δ 8.06 (s, 1H), 7.85 (t, J = 7.7 Hz, 1H), 7.47 (m, 1H), 7.42 – 7.14 (m, 4H), 4.33 – 4.10 (m, 1H), 4.10 – 3.82 (m, 3H), 3.70 (m, 1H), 2.44 (dt, J = 14.1, 7.3 Hz, 1H), 2.35 (m, 1H). LRMS (ESI+ve): calculated for $C_{20}H_{19}FN_3O_2S$, [M+H] = 384.12, observed [M+H] = 384.20; HRMS (ESI+ve): calculated for $C_{20}H_{19}FN_3O_2S$, [M+H] = 384.1177, observed [M+H] = 384.1137.

(Z)-N-benzyl-2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (41)

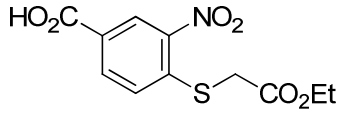
According to the procedure described for **11**, starting from acid **4a** (100 mg, 0.32 mmol), benzylamine (52 μL, 0.48 mmol), triethylamine (133 μL, 0.95 mmol), HOBt (52 mg, 0.38 mmol) and EDCI•HCl (91 mg, 0.48 mmol), 41 was obtained as a yellow solid (46 mg, 36 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.05 (t, J = 6.1 Hz, 0.5H), 7.83 (d, J = 5.8 Hz, 2H), 7.81 – 7.75 (m, 1H), 7.63 (dd, J = 17.6, 1.7 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.43 – 7.37 (m, 2H), 7.37 – 7.32 (m, 3H), 7.32 – 7.25 (m, 3H), 7.25 – 7.20 (m, 0.5H), 4.45 (d, J = 6.0 Hz, 1H), 3.89 (s, 2H); LRMS (ESI+ve): calculated for $C_{23}H_{17}FN_2O_2S$, [M+H] = 405.11, observed [M+H] = 405.19; HRMS (ESI+ve): calculated for $C_{23}H_{17}FN_2O_2S$, [M+H] = 405.1068, observed [M+H] = 405.1058.

(Z)-N-(2-(dimethylamino)benzyl)-2-(2-fluorobenzylidene)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazine-6-carboxamide (42)

According to the procedure described for **11**, the materials **4a** (102.8 mg, 0.33 mmol), HOBt monohydrate (51 mg, 0.33 mmol), EDCI•HCl (63 mg, 0.33 mmol), triethylamine (0.14 mL, 0.99 mmol), and 2-(dimethylamino)-benzylamine (50 mg, 0.33 mmol) were reacted. The mixture was concentrated without workup, and the crude product was stirred for 15 hours with 10 mL of water. The solid was collected and washed with water and diethyl ether to afford **42** (67.8 mg, 46%) as a light beige solid. ^{1}H NMR (500 MHz, Acetic Acid-d_4) δ 8.06 (s, 1H), 7.83 (t, J = 7.8 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.58 (d, J = 7.5 Hz, 1H), 7.54 (m, 1H), 7.47 (m, 1H), 7.40 – 7.30 (m, 2H), 7.23 (t, J = 9.4 Hz, 1H), 4.79 (s, 2H), 3.47 (s, 6H). LRMS

(ESI+ve): calculated for $C_{25}H_{23}FN_3O_2S$, [M+H] = 448.15, observed [M+H] = 448.25; HRMS (ESI+ve): calculated for $C_{25}H_{23}FN_3O_2S$, [M+H] = 448.1490, observed [M+H] = 448.1466.

NMR Spectra



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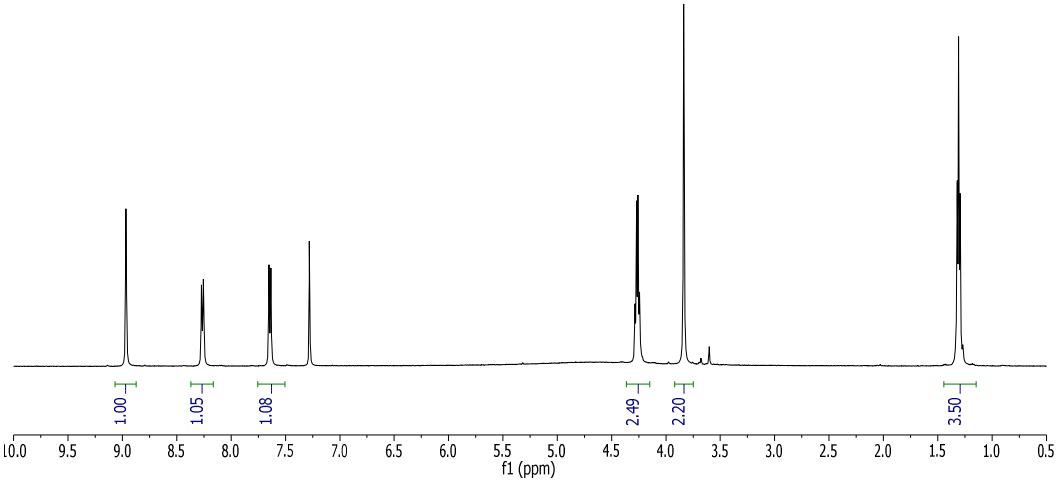

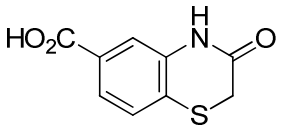
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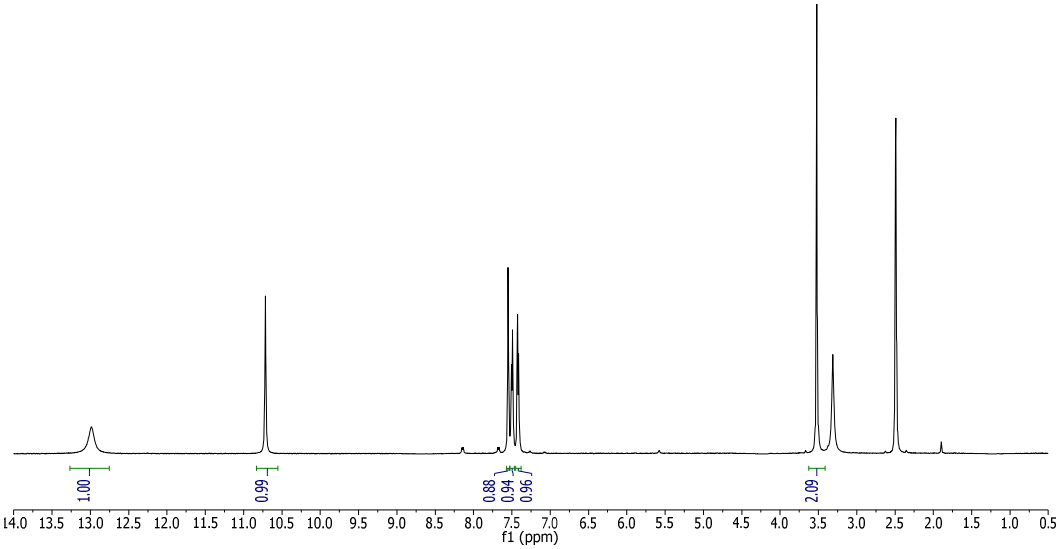
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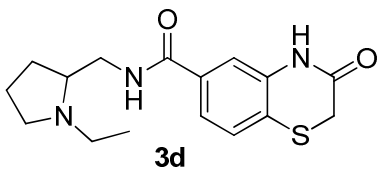
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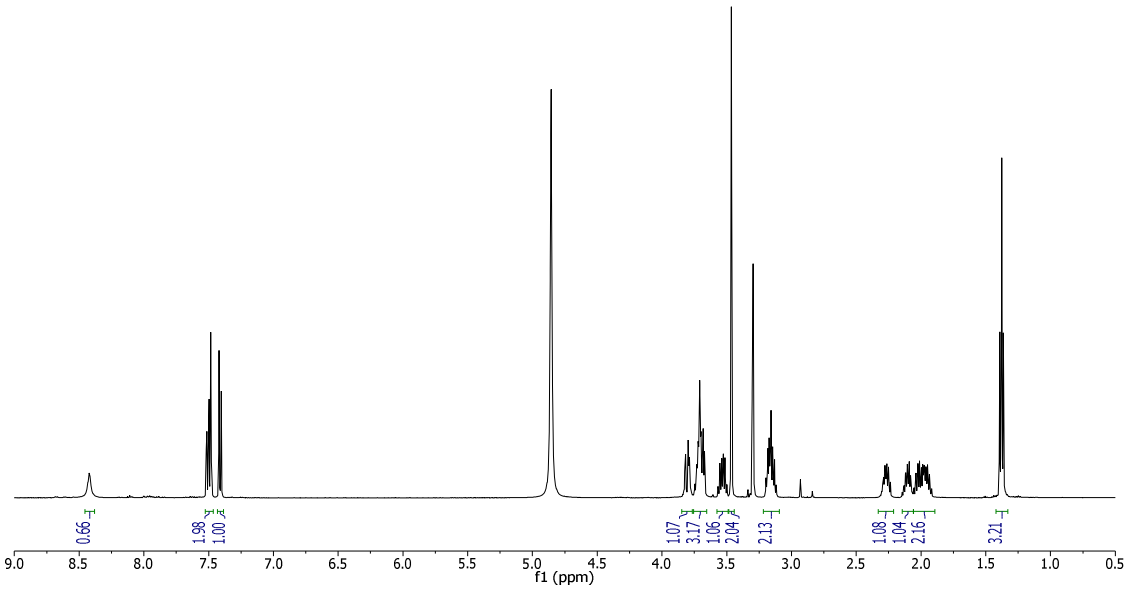
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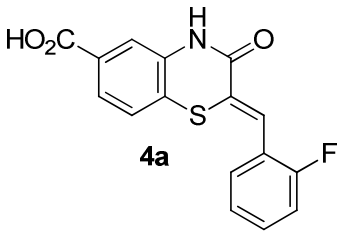
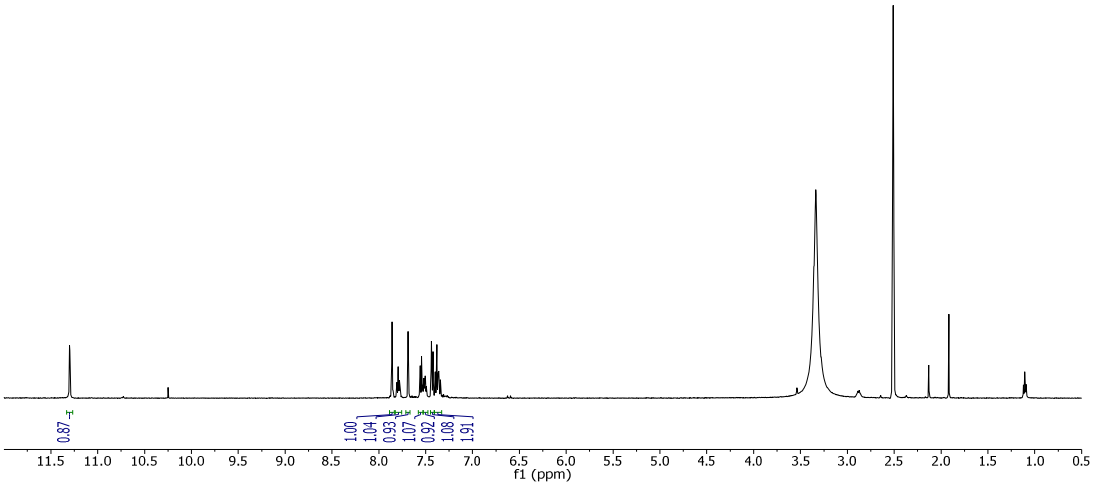
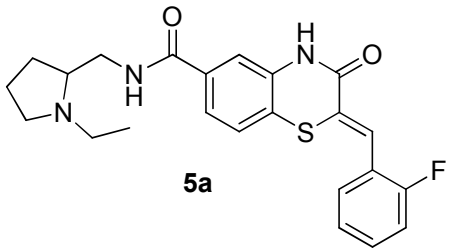
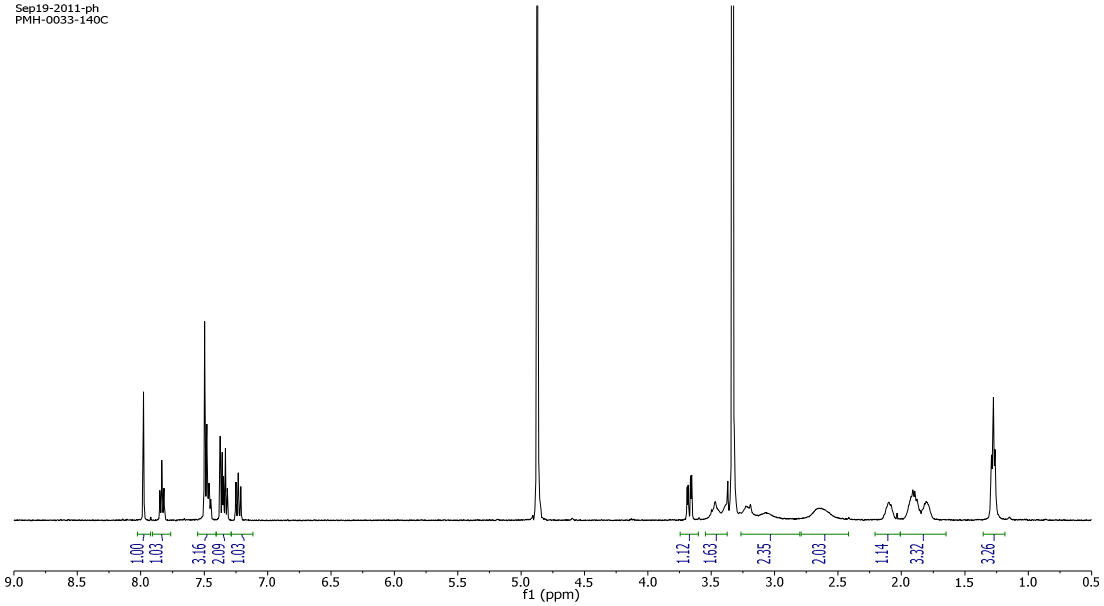

HO2C
H
N
O
S
F

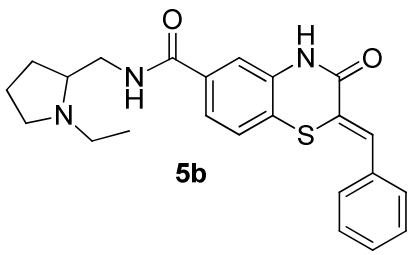
4a


0.87
1.00
1.04
0.93
1.07
0.92
1.08
1.91
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

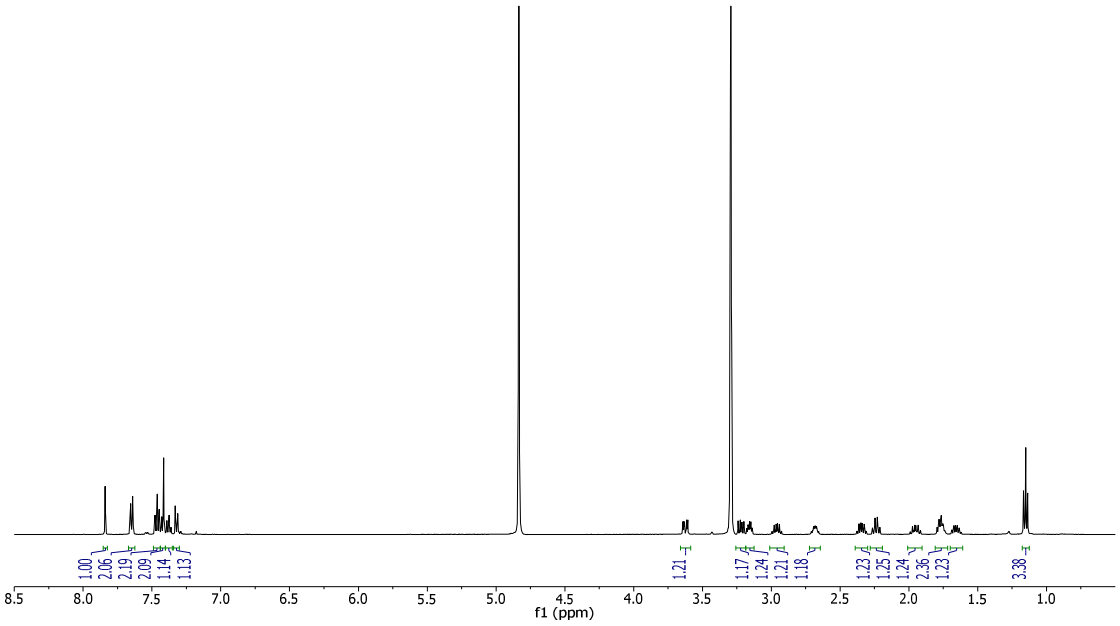

O
H
N
N
H
O
N
S
F

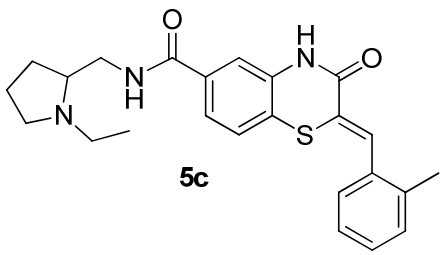
5a


Sep19-2011-ph
PMH-0033-140C
1.00
1.03
3.16
2.09
1.03
1.12
1.63
2.35
2.03
1.14
3.32
3.26
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

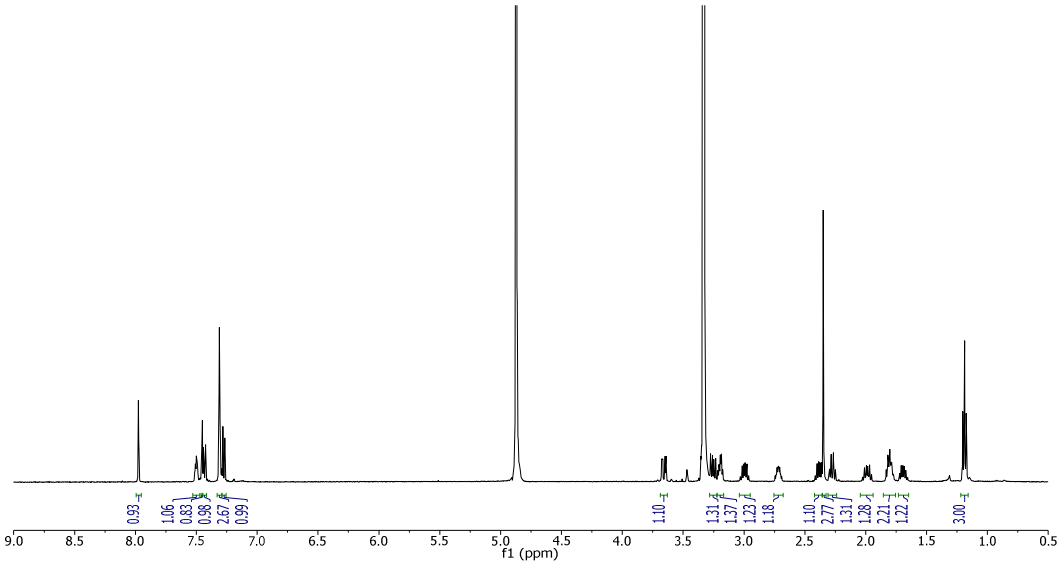

O
H
N
N
H
N
O
S

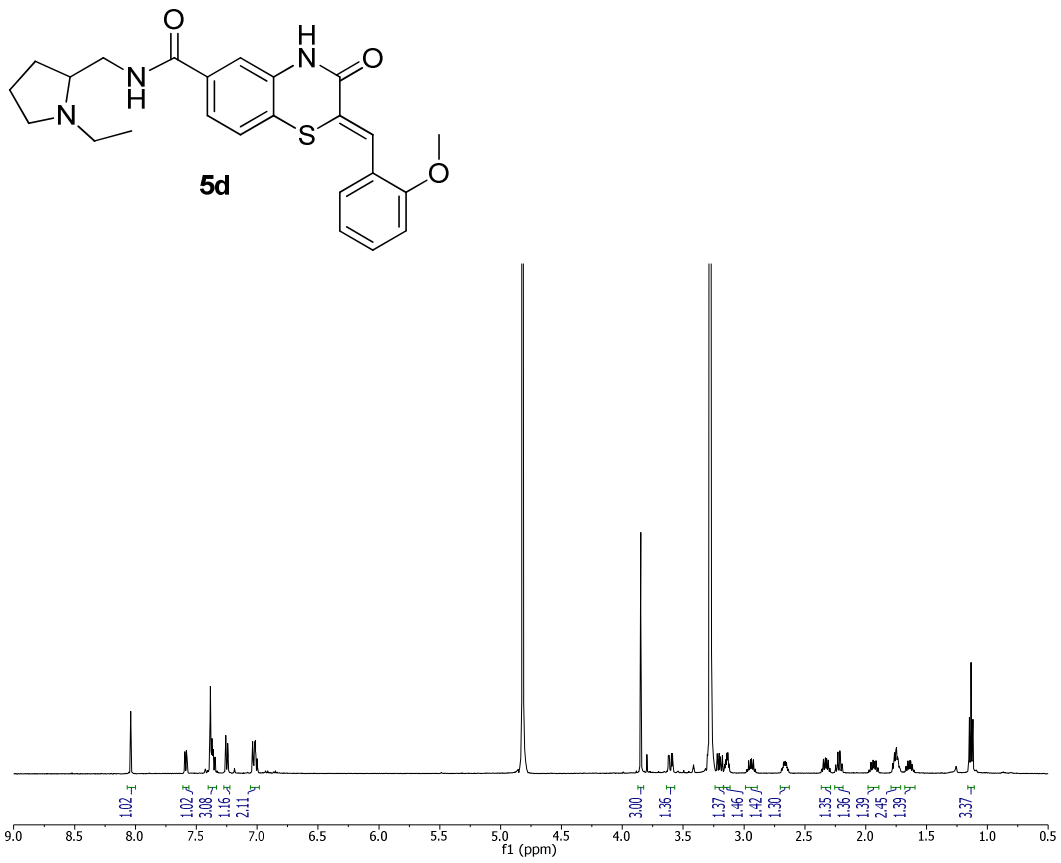
5b

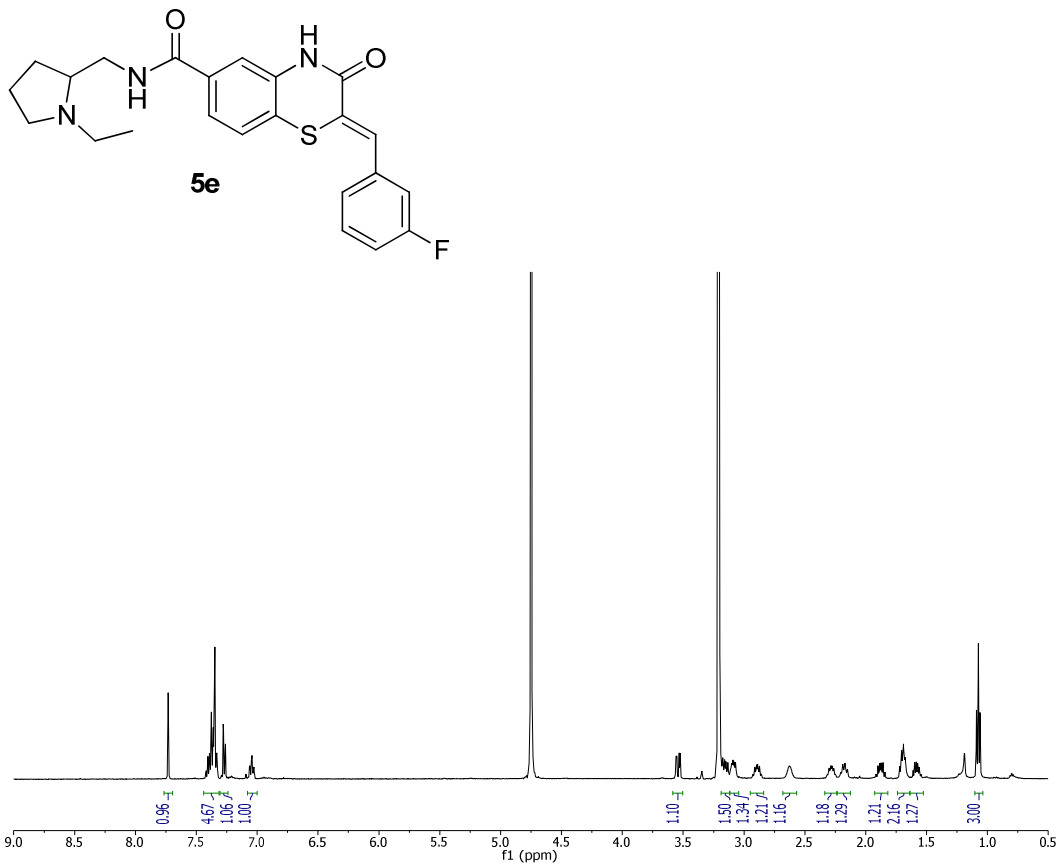

1.00
2.06
2.19
2.09
1.14
1.13
1.21
1.17
1.24
1.21
1.18
1.23
1.25
1.24
2.36
1.23
3.38
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

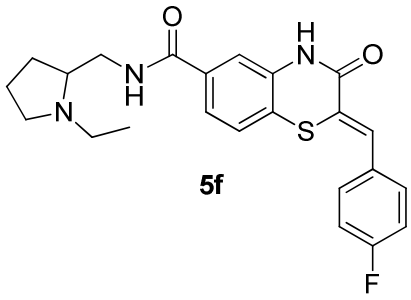


5c

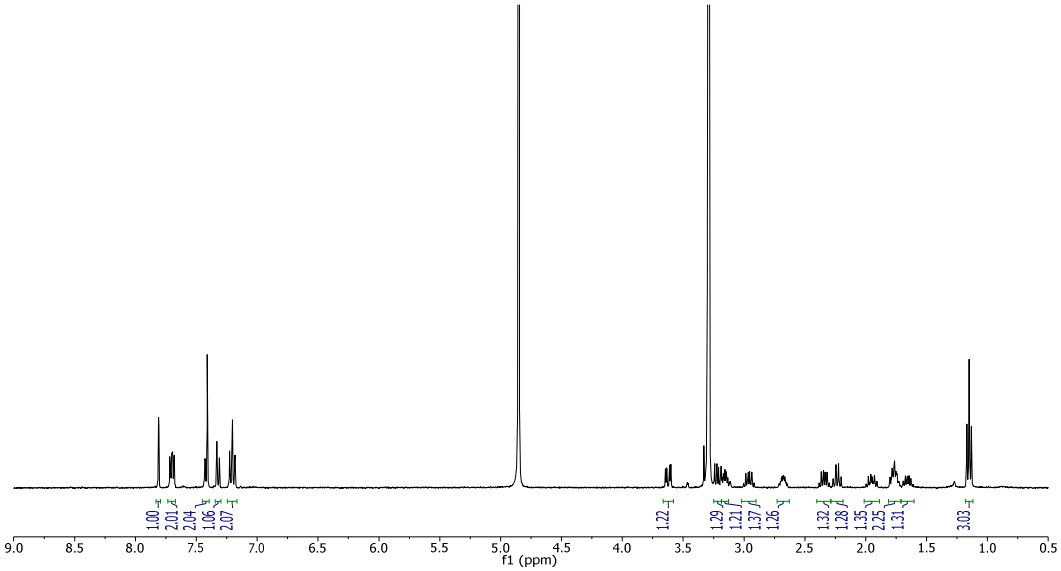

0.93
1.06
0.83
0.98
2.67
0.99
1.10
1.31
1.37
1.23
1.18
1.10
2.77
1.31
1.28
2.21
1.22
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

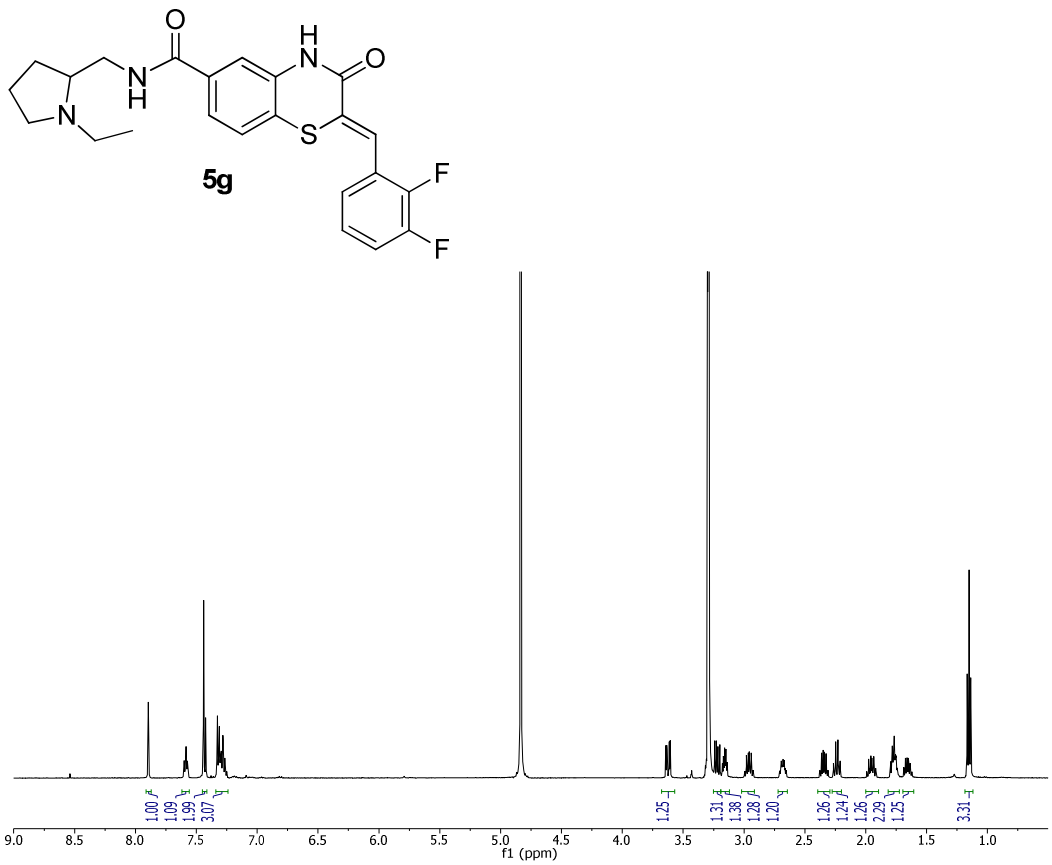

O
H
N
O
N
H
N
S
O
5d
1.02
1.02
3.08
1.16
2.11
3.00
1.36
1.37
1.46
1.42
1.30
1.35
1.36
1.39
2.45
1.39
3.37
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

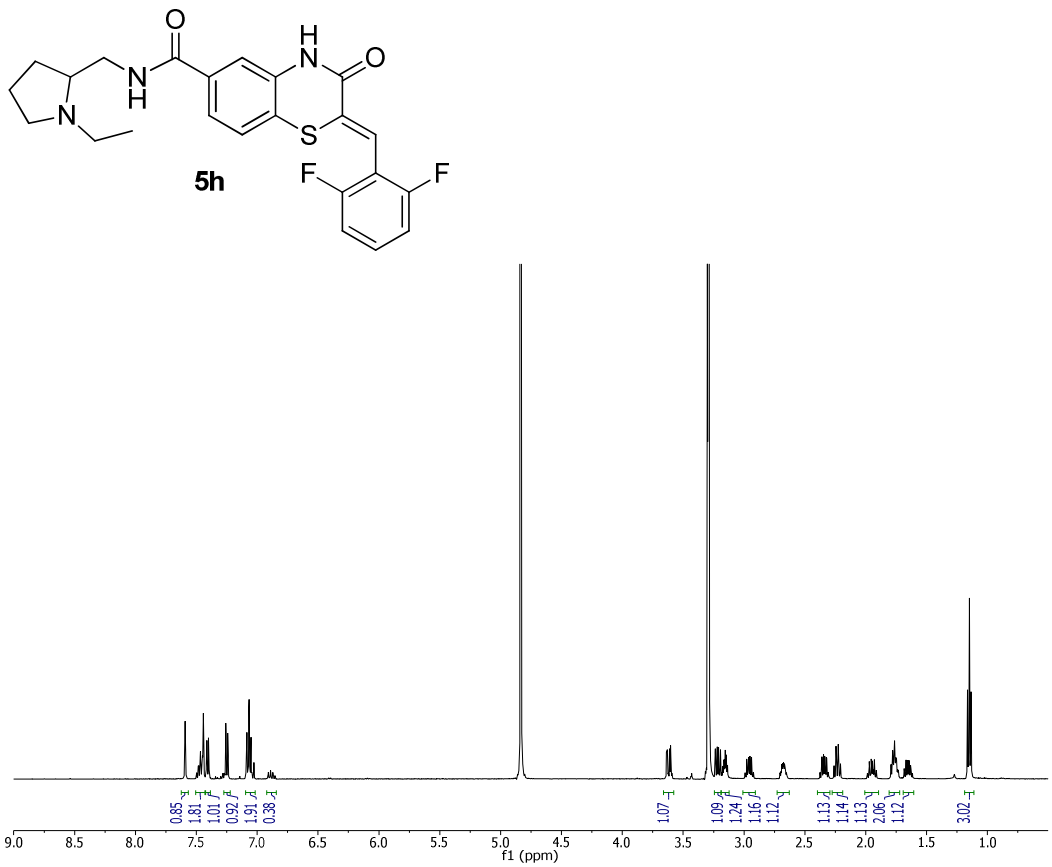

O
H
N
N
H
O
N
S
F
5e
0.96
4.67
1.06
1.00
1.10
1.50
1.34
1.21
1.16
1.18
1.29
1.21
2.16
1.27
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

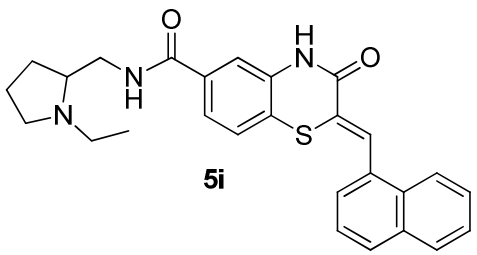

O
H
N
O
N
H
N
S
F

5f

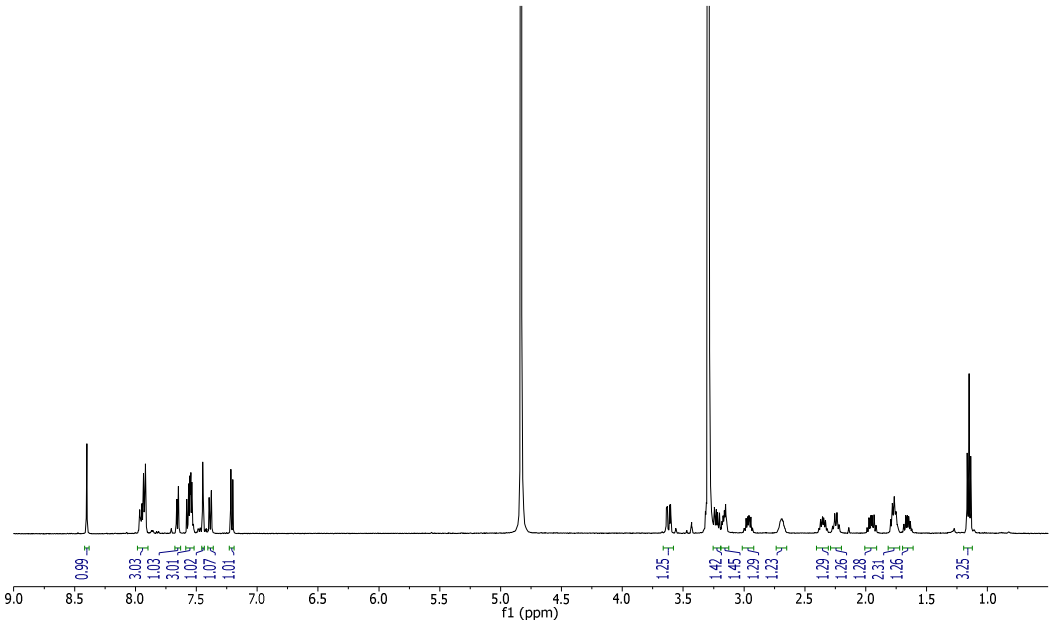

1.00
2.01
2.04
1.06
2.07
1.22
1.29
1.21
1.37
1.26
1.32
1.28
1.35
2.25
1.31
3.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

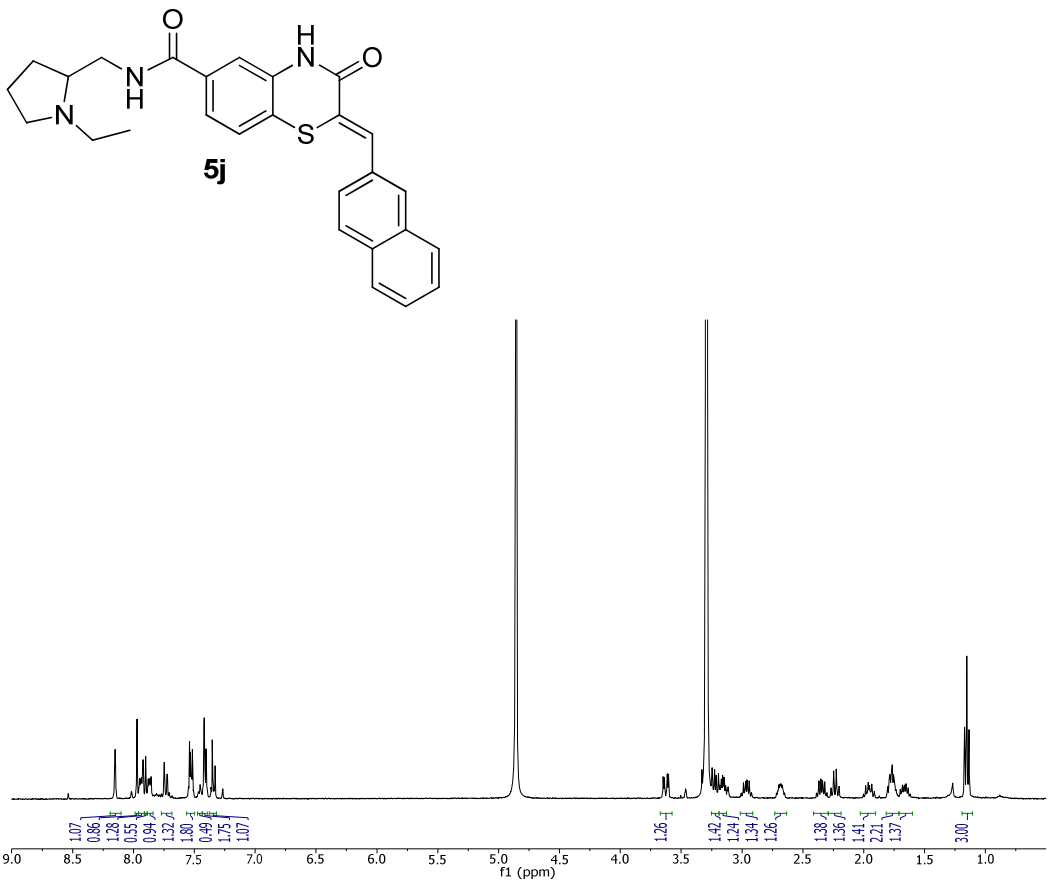

O
H
N
N
H
N
O
S
F
F
5g
1.00
1.09
1.99
3.07
1.25
1.31
1.38
1.28
1.20
1.26
1.24
1.26
2.29
1.25
3.31
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

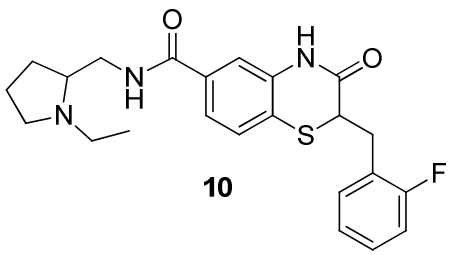

O
H
N
N
H
O
N
S
F
F
5h
0.85
1.81
1.01
0.92
1.91
0.38
1.07
1.09
1.24
1.16
1.12
1.13
1.14
1.13
2.06
1.12
3.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


O
H
N
N
H
O
N
S

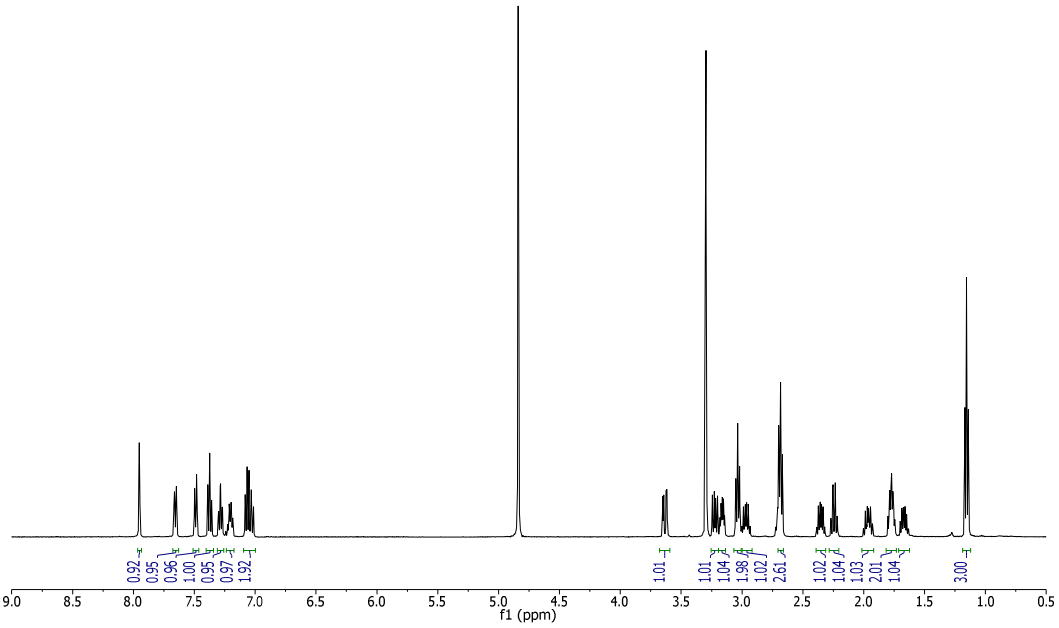
5i

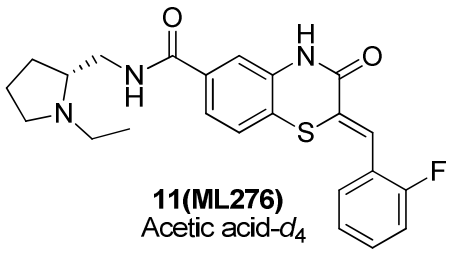

0.99
3.03
1.03
3.01
1.02
1.07
1.01
1.25
1.42
1.45
1.29
1.23
1.29
1.26
1.28
2.31
1.26
3.25
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


O
H
N
O
N
H
N
S
5j
1.07
0.86
1.28
0.55
0.94
1.32
1.80
0.49
1.75
1.07
1.26
1.42
1.24
1.34
1.26
1.38
1.36
1.41
2.21
1.37
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

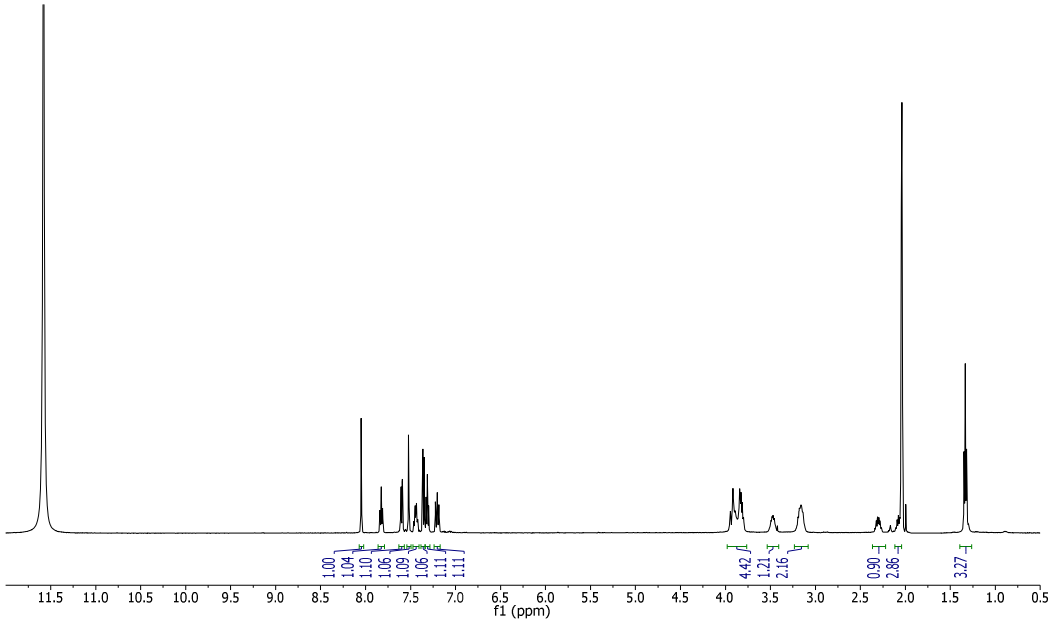

O
H
N
N
H
O
N
S
F

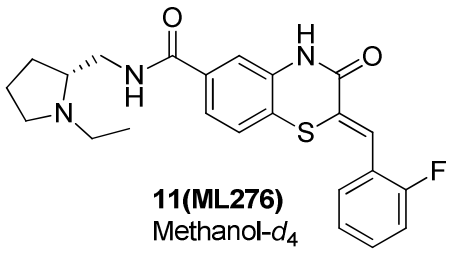
10


0.92
0.95
0.96
1.00
0.95
0.97
1.92
1.01
1.01
1.04
1.98
1.02
2.61
1.02
1.04
1.03
2.01
1.04
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

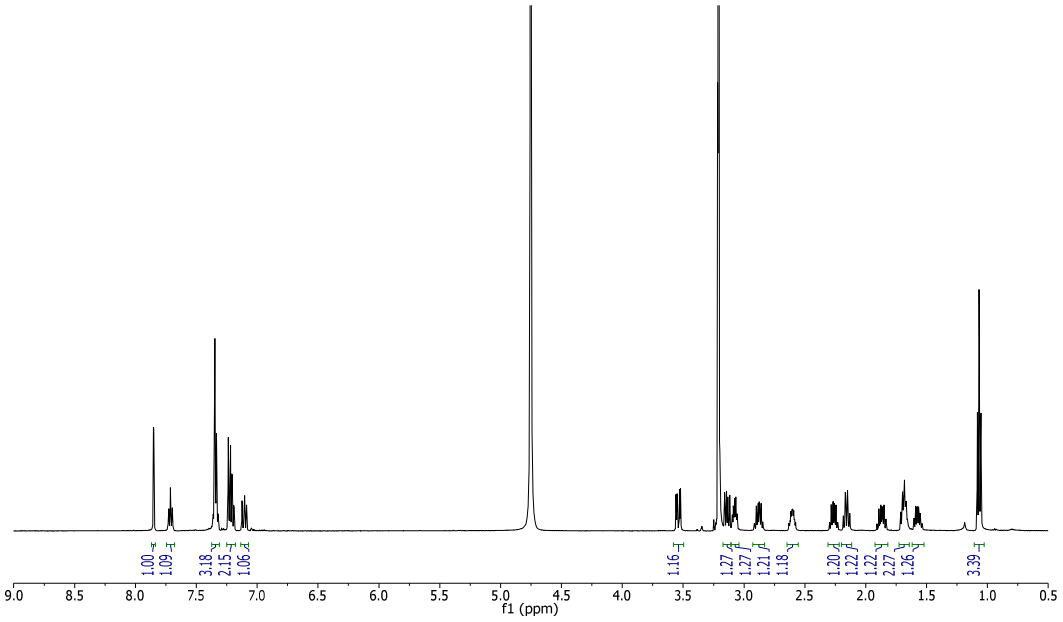


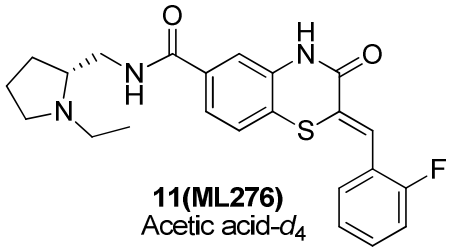
11(ML276)
Acetic acid-d_4



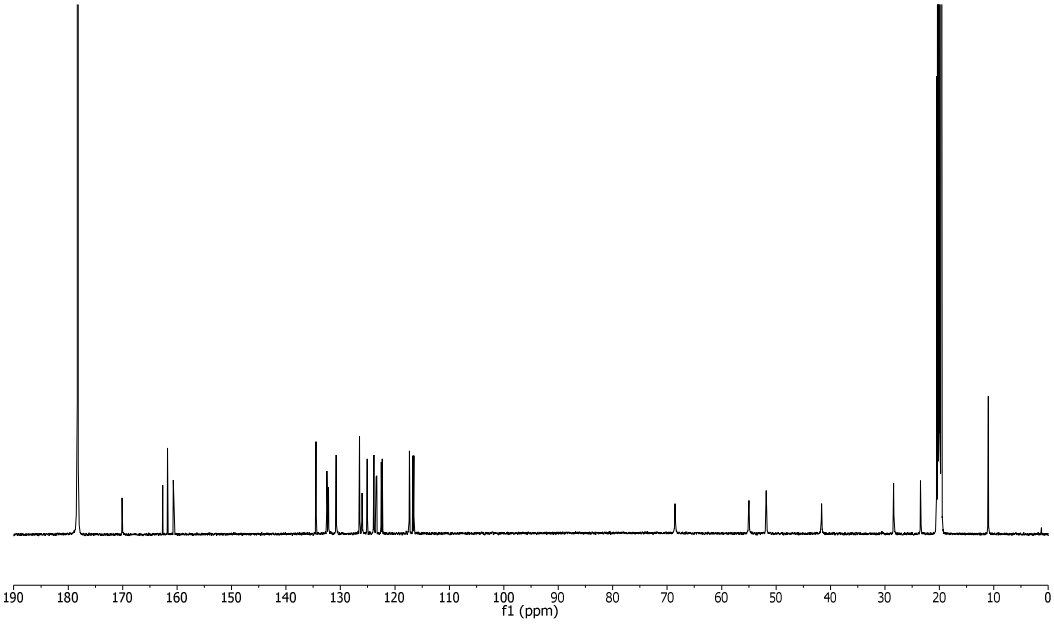


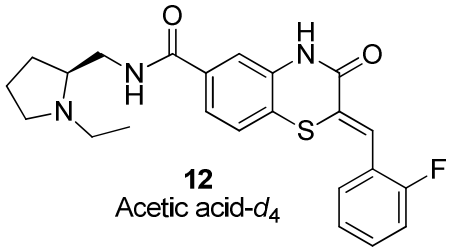
11(ML276)
Methanol-d_4



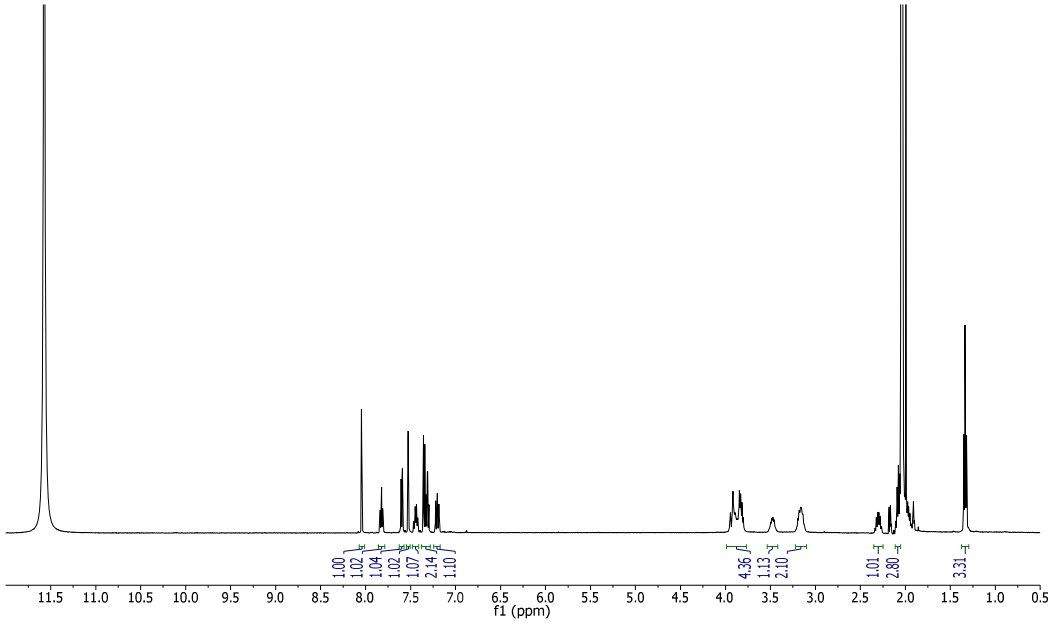


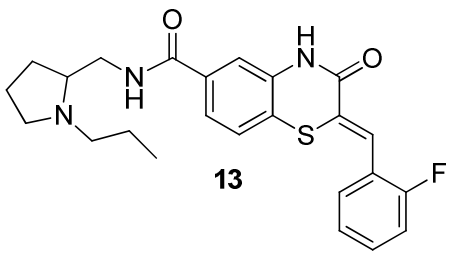
11(ML276)
Acetic acid-d_4



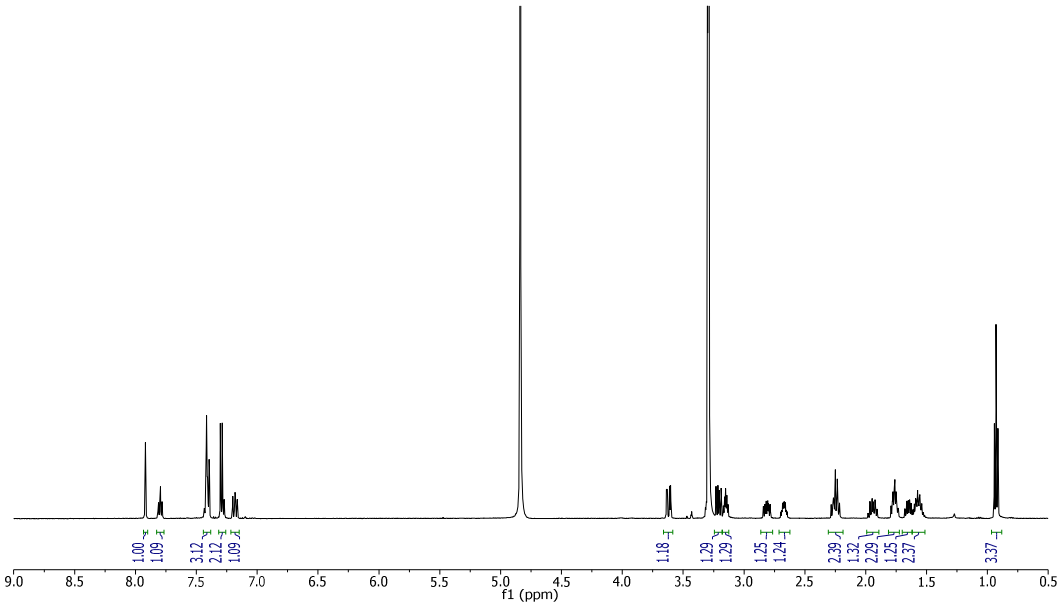


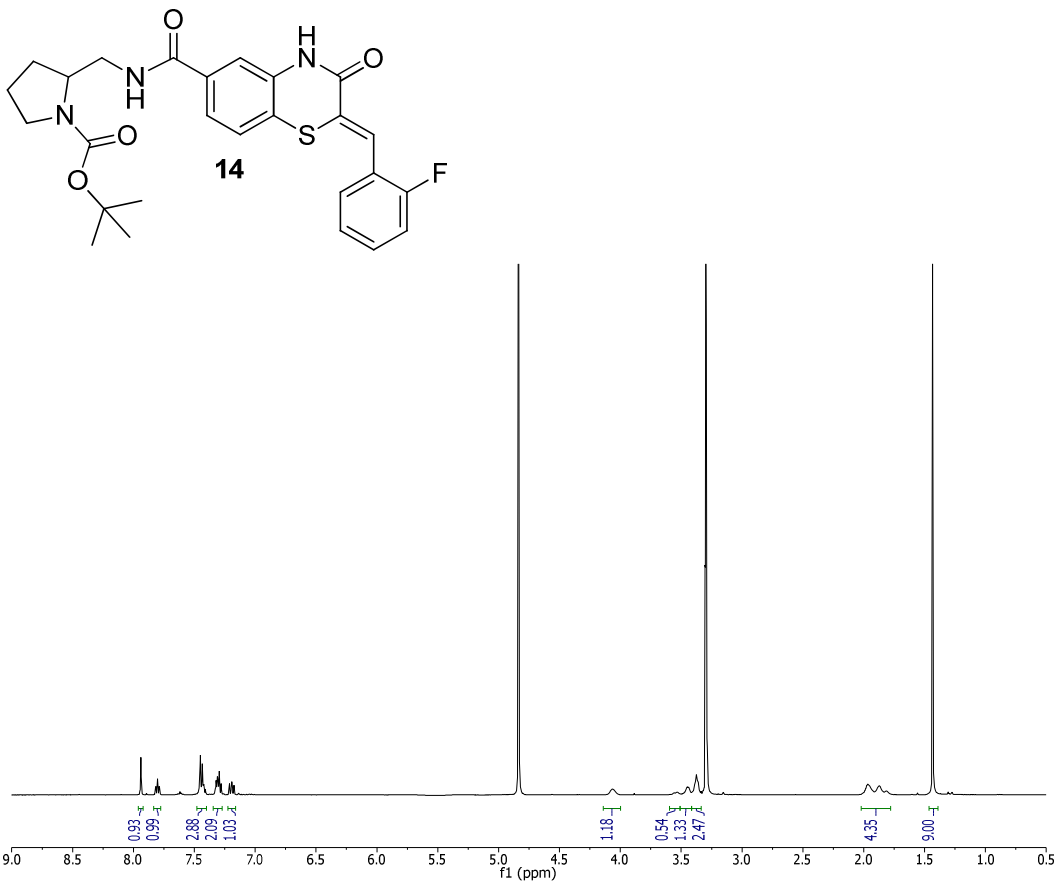
12
Acetic acid-d_4

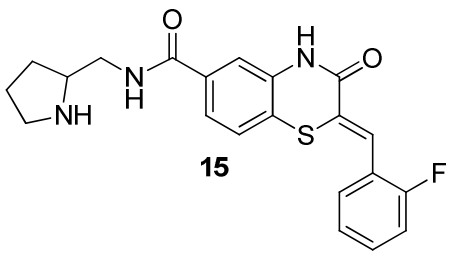



O
H
N
N
H
O
N
S
F

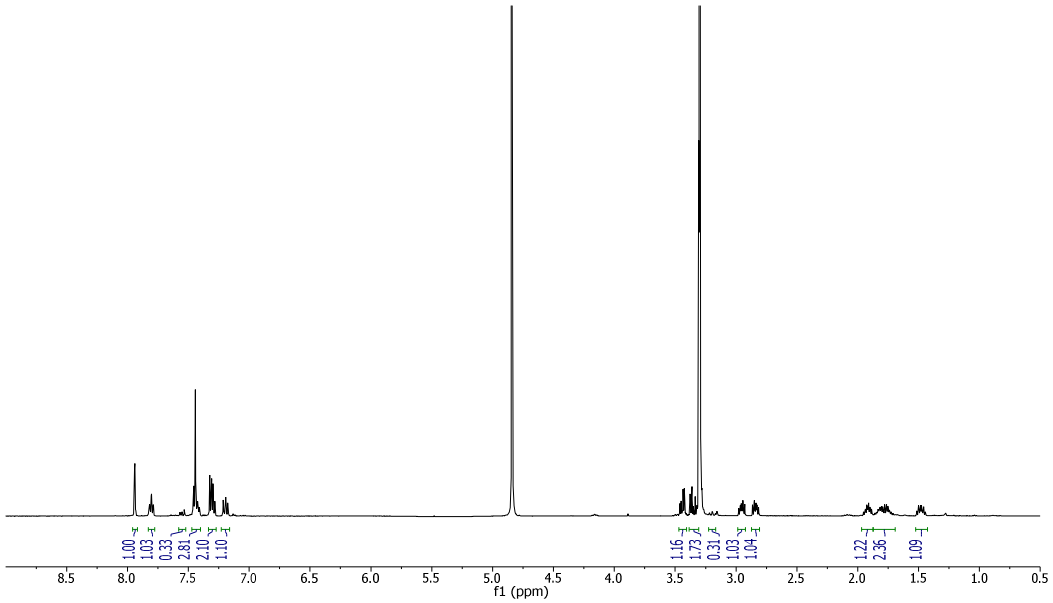
13

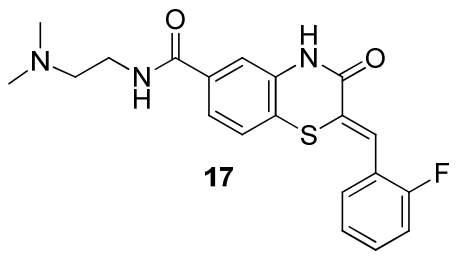

1.00
1.09
3.12
2.12
1.09
1.18
1.29
1.29
1.25
1.24
2.39
1.32
2.29
1.25
2.37
3.37
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


O
H
N
O
N
H
N
O
S
F
O
O
14
0.93
0.99
2.88
2.09
1.03
1.18
0.54
1.33
2.47
4.35
9.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

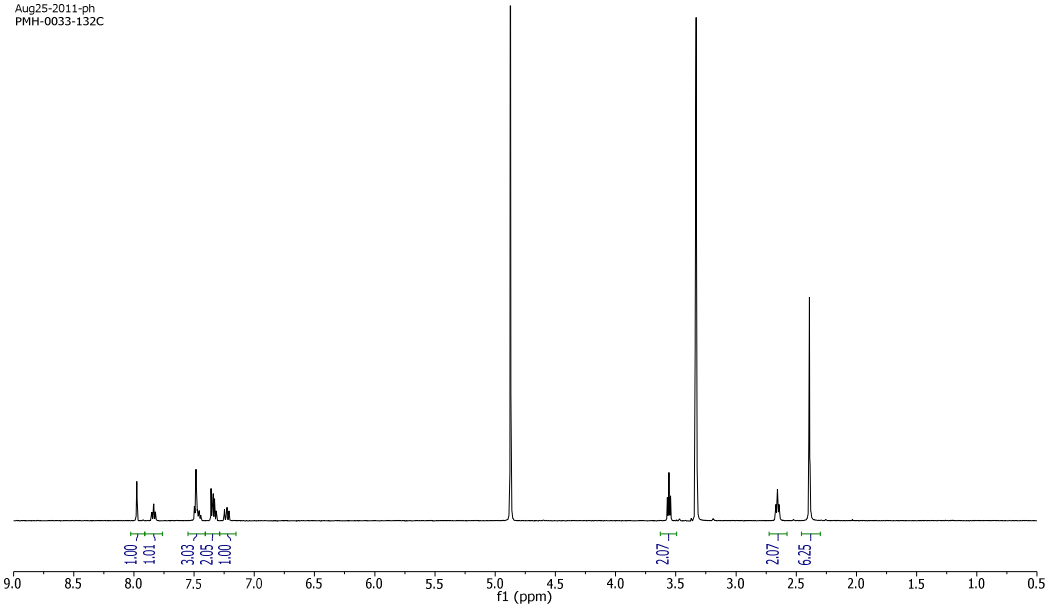

O
H
N
O
N
H
NH
S
F

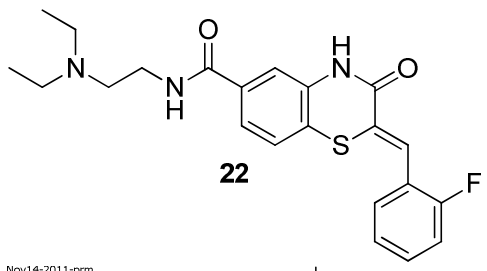
15


1.00
1.03
0.33
2.81
2.10
1.10
1.16
1.73
0.31
1.03
1.04
1.22
2.36
1.09
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

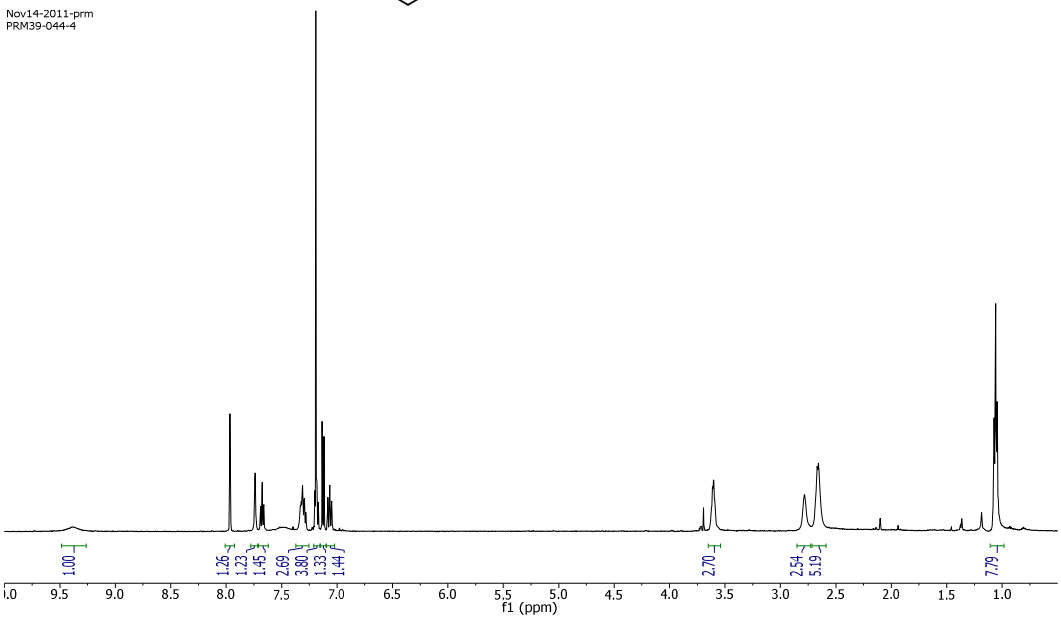

O
H
N
N
H
O
S
F

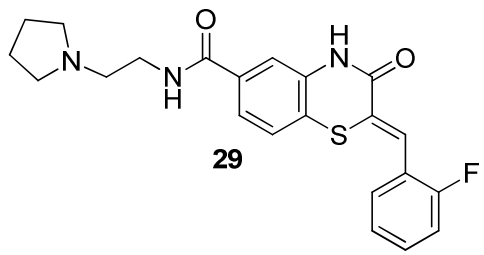
17


Aug25-2011-ph
PMH-0033-132C
1.00
1.01
3.03
2.05
1.00
2.07
2.07
6.25
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

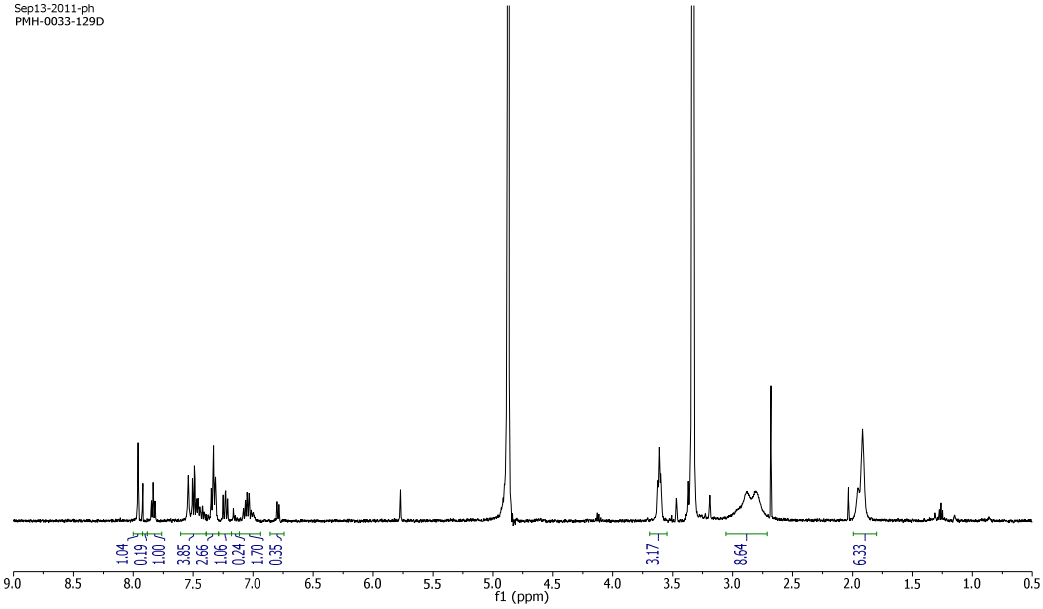

O
H
N
N
H
N
O
S
F

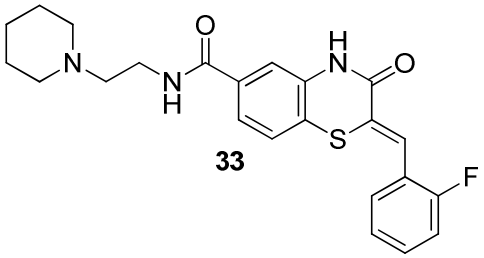
22


Nov14-2011-prm
PRM39-044-4
1.00
1.26
1.23
1.45
2.69
3.80
1.33
1.44
2.70
2.54
5.19
7.79
f1 (ppm)

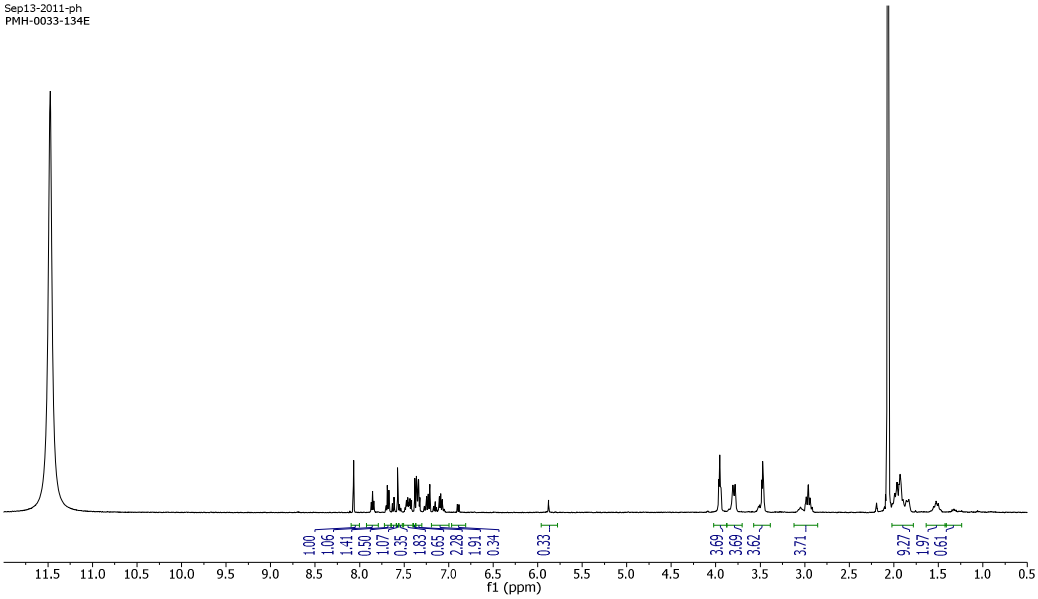

O
H
N
N
H
N
O
S
F

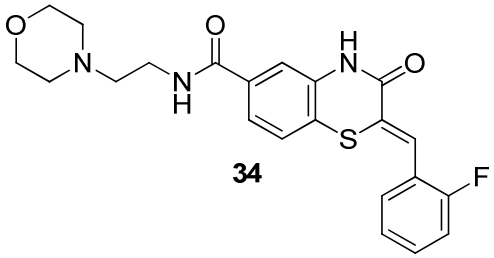
29


Sep13-2011-ph
PMH-0033-129D
1.04
0.19
1.00
3.85
2.66
1.06
0.24
1.70
0.35
3.17
8.64
6.33
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

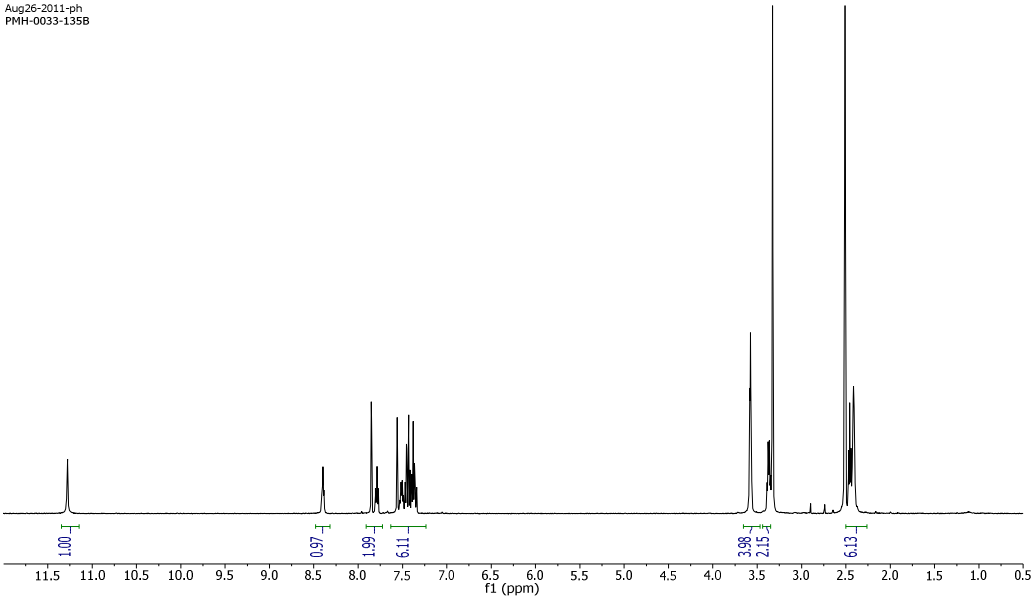

O
H
N
N
H
N
O
S
F

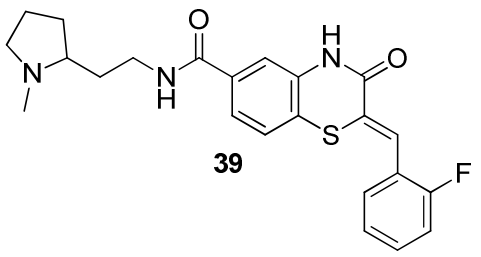
33


Sep13-2011-ph
PMH-0033-134E
1.00
1.06
1.41
0.50
1.07
0.35
1.83
0.65
2.28
1.91
0.34
0.33
3.69
3.69
3.62
3.71
9.27
1.97
0.61
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

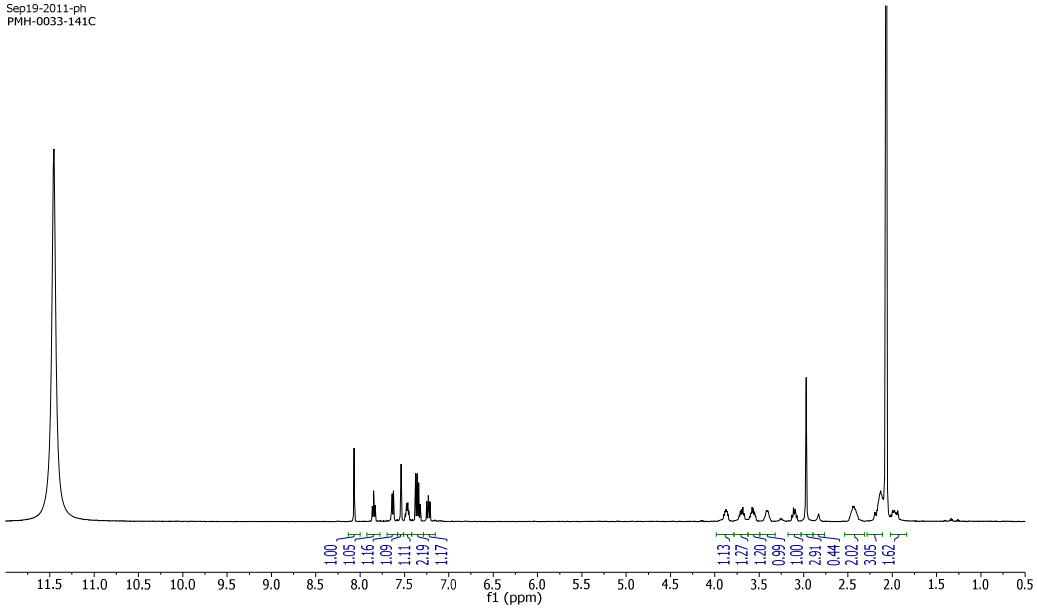

O
N
O
N
H
H
N
O
S
F

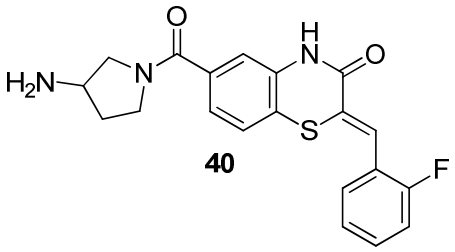
34


Aug26-2011-ph
PMH-0033-135B
1.00
0.97
1.99
6.11
3.98
2.15
6.13
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

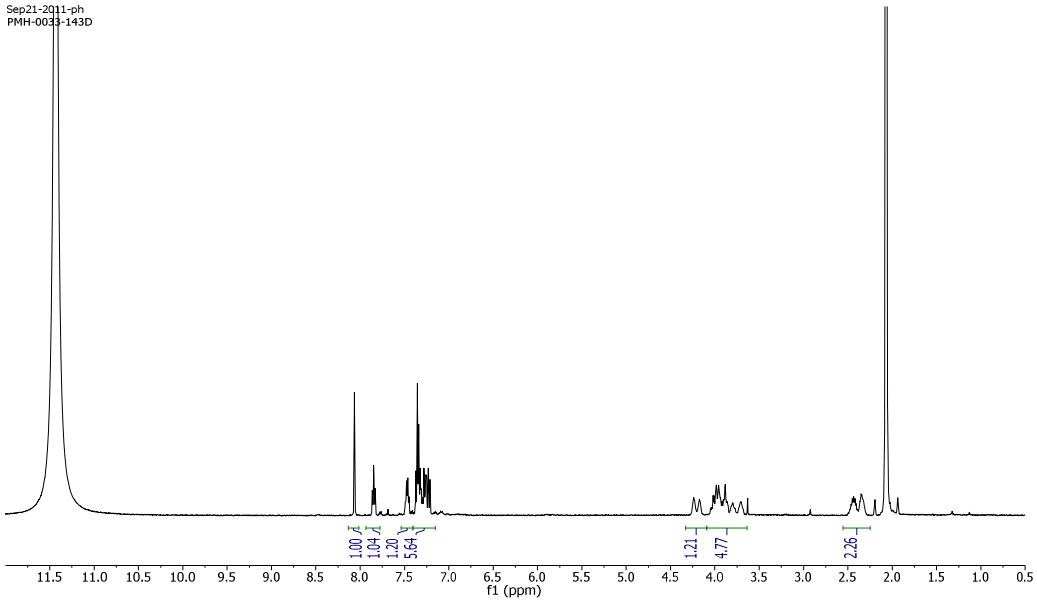

O
H
N
O
N
N
H
S
F

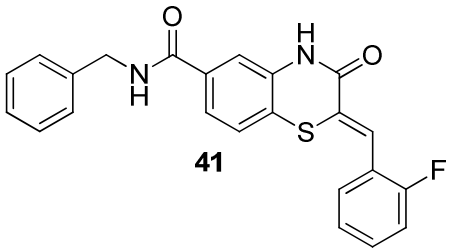
39


Sep19-2011-ph
PMH-0033-141C
1.00
1.05
1.16
1.09
1.11
2.19
1.17
1.13
1.27
1.20
0.99
1.00
2.91
0.44
2.02
3.05
1.62
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

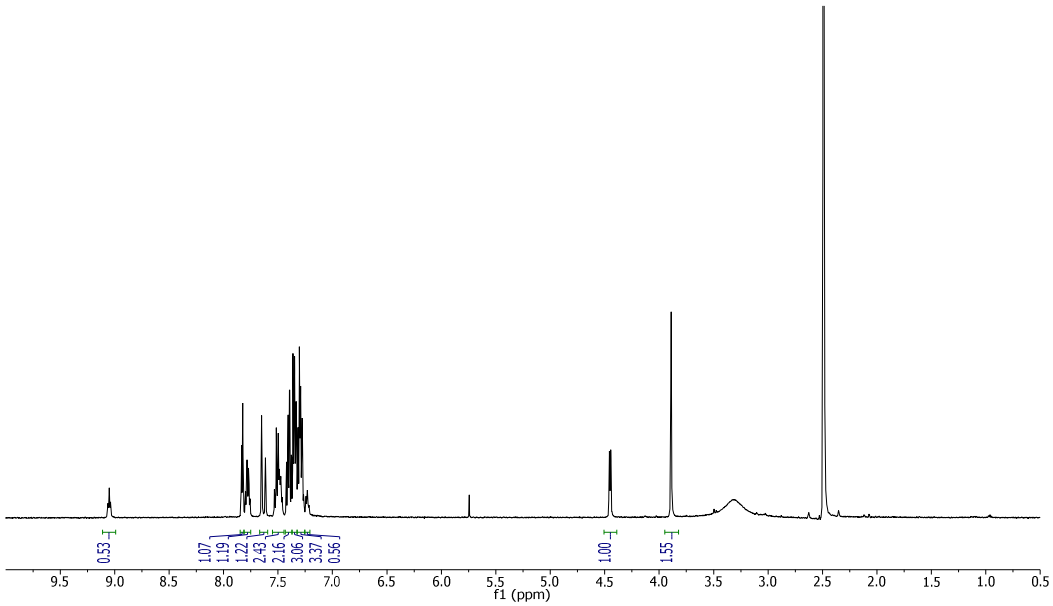

O
H
N
O
H_2N
N
S
F

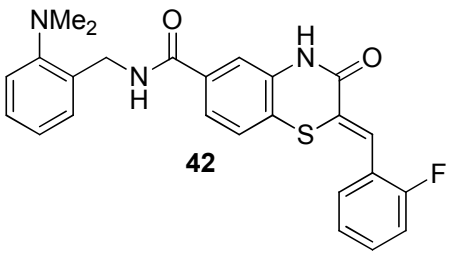
40


Sep21-2011-ph
PMH-0033-143D
1.00
1.04
1.20
5.64
1.21
4.77
2.26
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

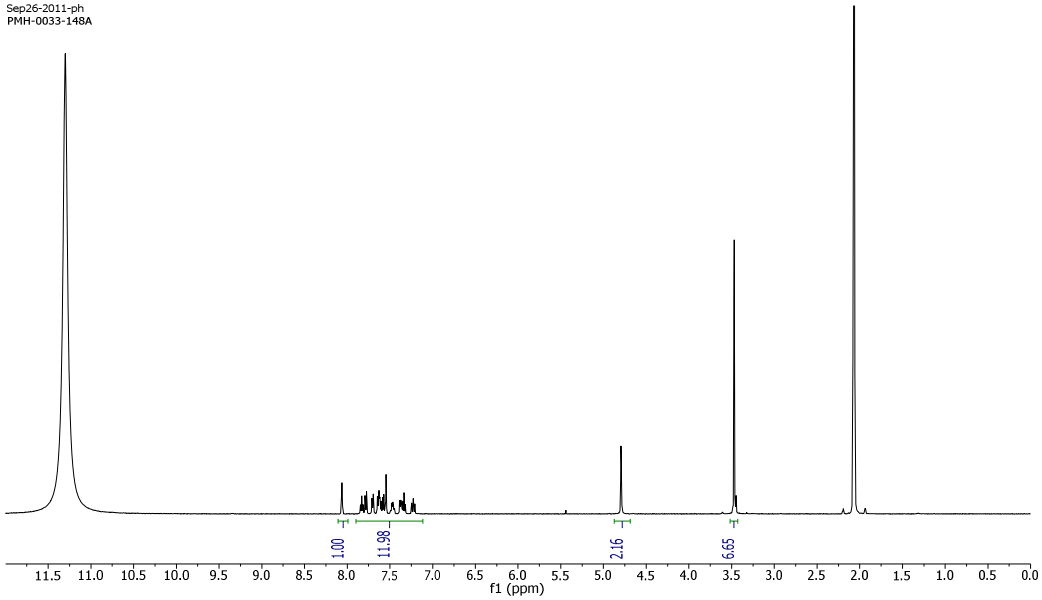

O
H
N
N
H
O
S
F

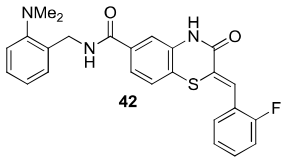
41


0.53
1.07
1.19
1.22
2.43
2.16
3.06
3.37
0.56
1.00
1.55
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

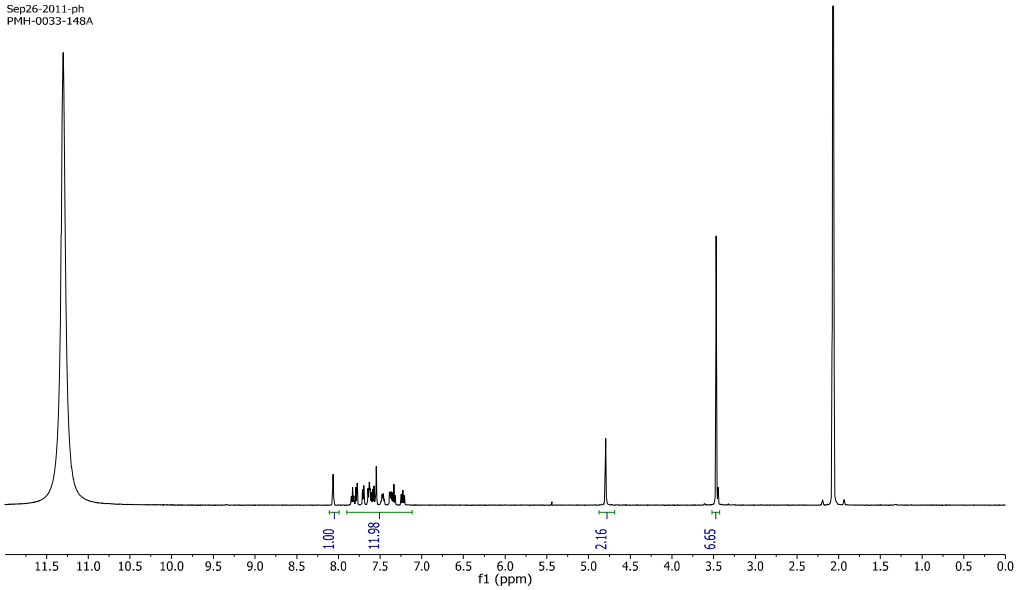

NMe2
O
N
H
H
N
O
S
F

42


Sep26-2011-ph
PMH-0033-148A
1.00
11.98
2.16
6.65
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


NMe2
O
N
H
H
N
O
S
F

42


Sep26-2011-ph
PMH-0033-148A
1.00
11.98
2.16
6.65
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)