Supplemental Information for:

Highly Potent Cell-Permeable and Impermeable NanoLuc Luciferase Inhibitors

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Supplemental figures

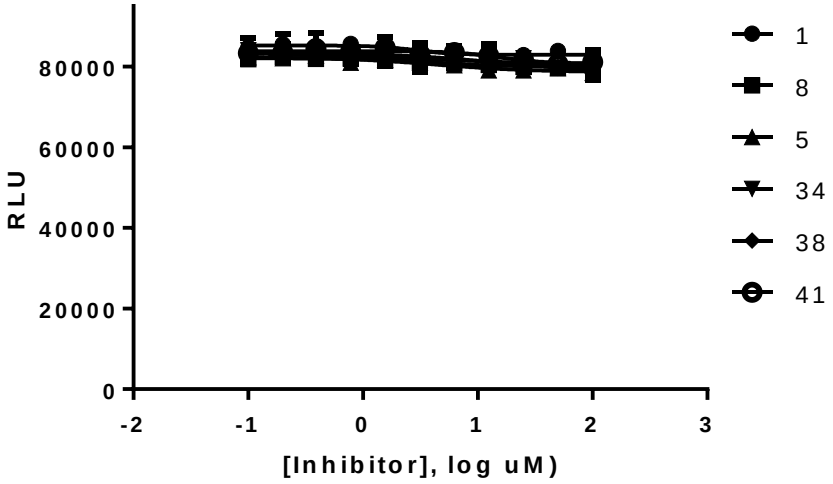


Figure 1. No effect on the luminescence of FLuc with thienopyrrole compounds (**1**, **8**, **5**, **34**, **38**, **41**).

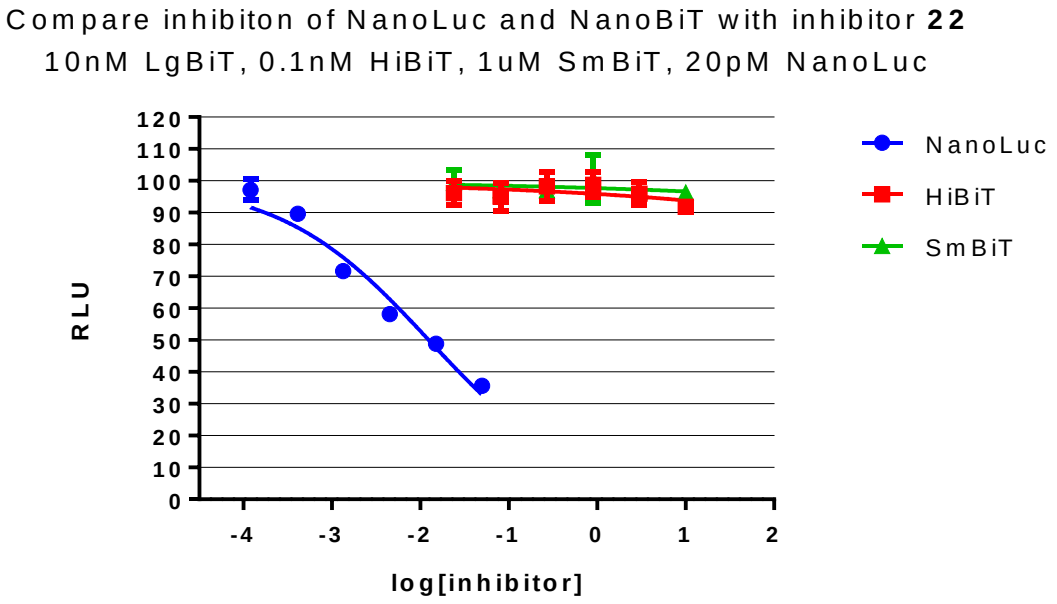
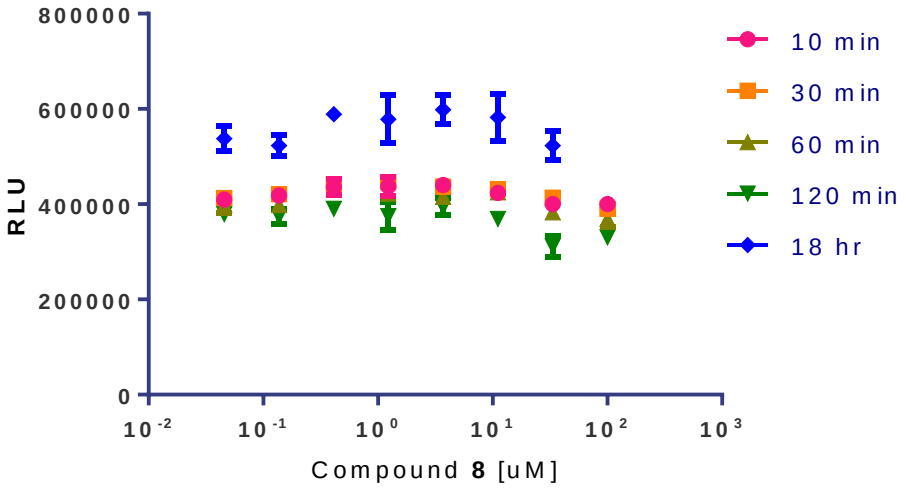
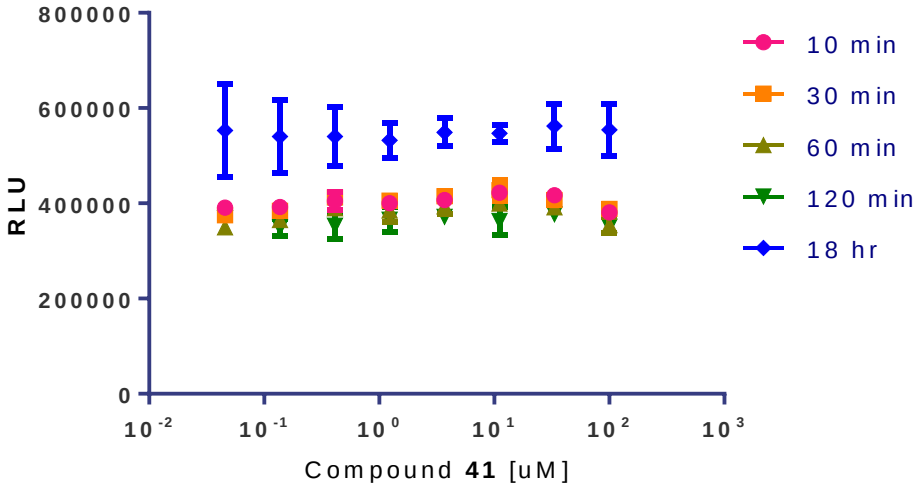


Figure 2. Dose response curves of potent Nluc inhibitor **22** against NanoLuc, LgBit/SmBit, and LgBit/HiBit enzymes. Nluc inhibitors described in this study are not effective against the NanoBit split enzyme system.

(a)


800000
600000
400000
200000
0
RLU
10 -2
10 -1
10 0
10 1
10 2
10 3
Compound 8 [uM]
10 min
30 min
60 min
120 min
18 hr

(b)


800000
600000
400000
200000
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RLU
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10 0
10 1
10 2
10 3
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10 min
30 min
60 min
120 min
18 hr

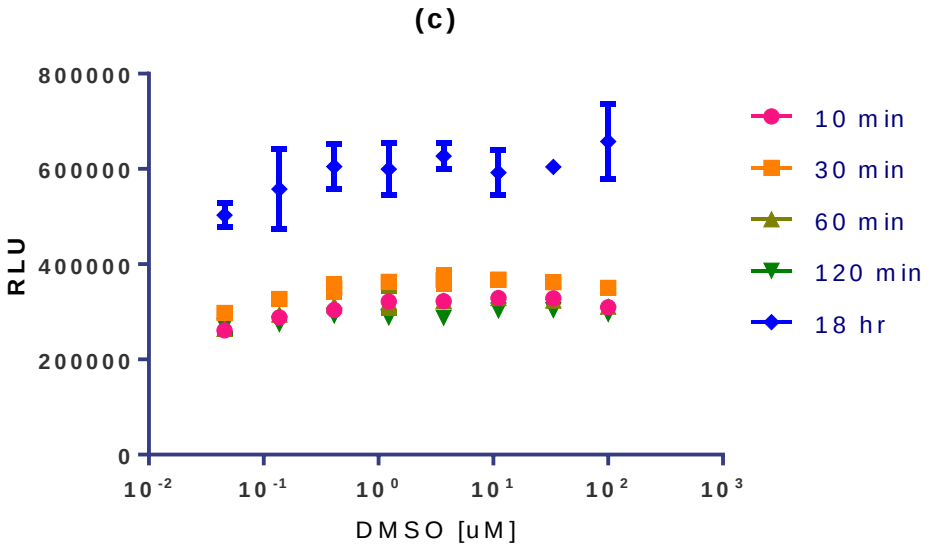


Figure 3. CellTiter Glo® titrations of thienopyrrole compounds **8** (a), **41** (b), and DMSO control (c) with HEK293 cells. Similar results observed with HeLa cells (data not shown).

Table 1. Thermal stability of compound **43** in DMSO and OptiMEM under different temperature

Time days	**DMSO 30 mM** % peak area at 280 nm			**OptiMEM 90μM** % peak area at 280 nm		
	20 ºC	35 ºC	60 ºC	20 ºC	35 ºC	60 ºC
0	99.6	99.6	99.6	99.2	99.2	99.2
1	99.7	99.7	99.6	99.3	99.3	99.3
4	99.6	99.6	98.7	99.2	99.1	98.9
7	99.4	99.4	98.3	99.2	99.1	98.4
14	99.3	99.4	-	94.1	98.6	97.7
28	99.7	99.7	99.0	99.2	99.1	95.1

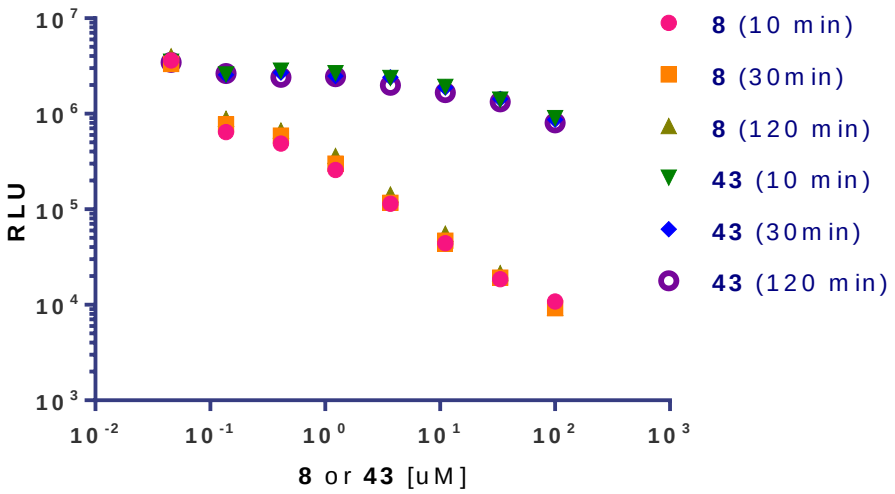
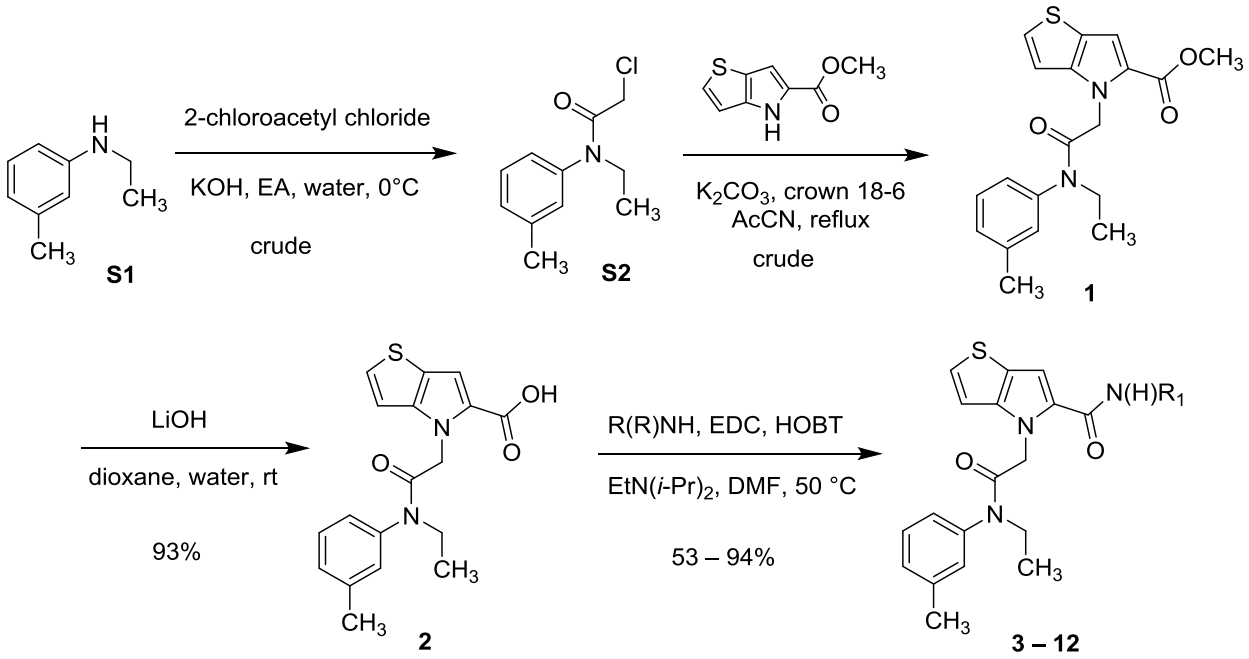


Figure 4. Time courses of cell permeability in HEK293 cells transiently transfected with Nluc with compounds **8** and **43**.

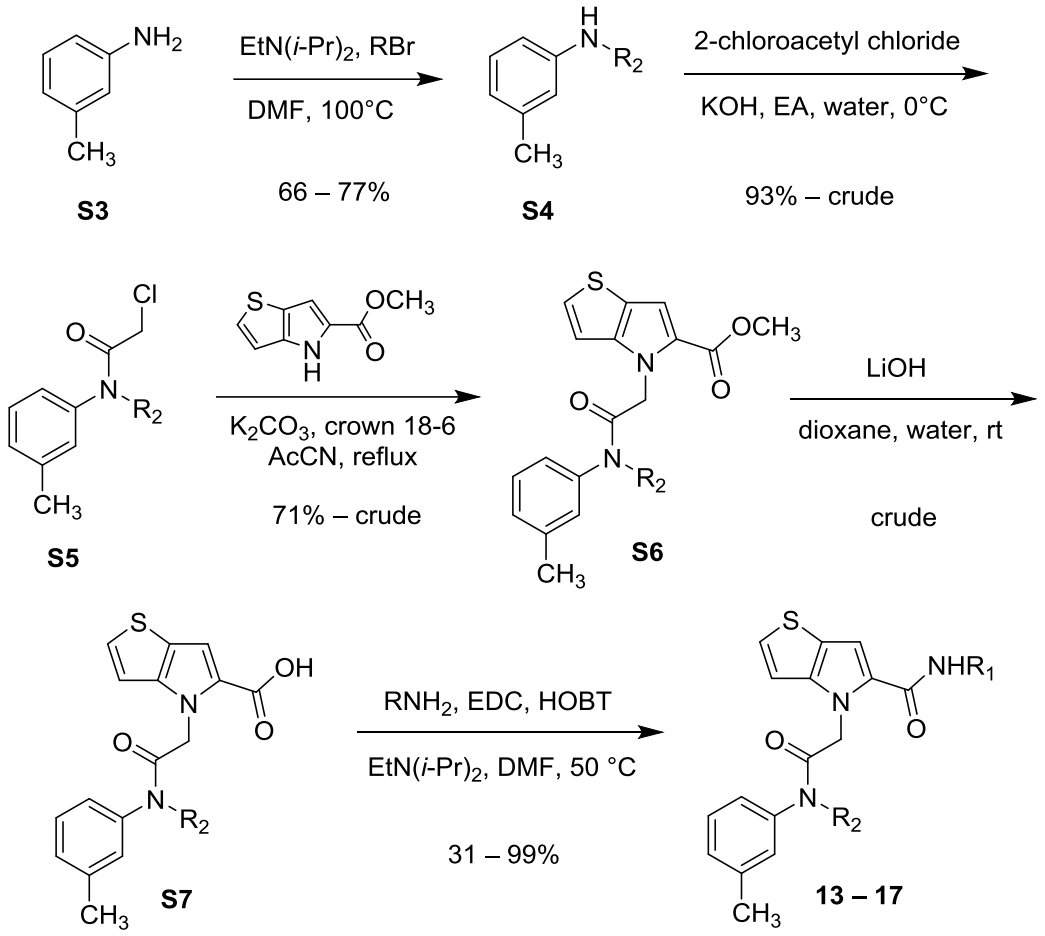
Synthesis and characterization

General Synthesis Procedure A: To a solution of ester intermediate (1eq) in dioxane / water (4:1), lithium hydroxide (5eq) was added. The suspension was heated to 60°C until starting material was consumed (monitored by LCMS or TLC analysis). The reaction mixture was cooled and acidified with HCl (2M) until pH 3. The suspension was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, dichloromethane / methanol) to afford the desired product.

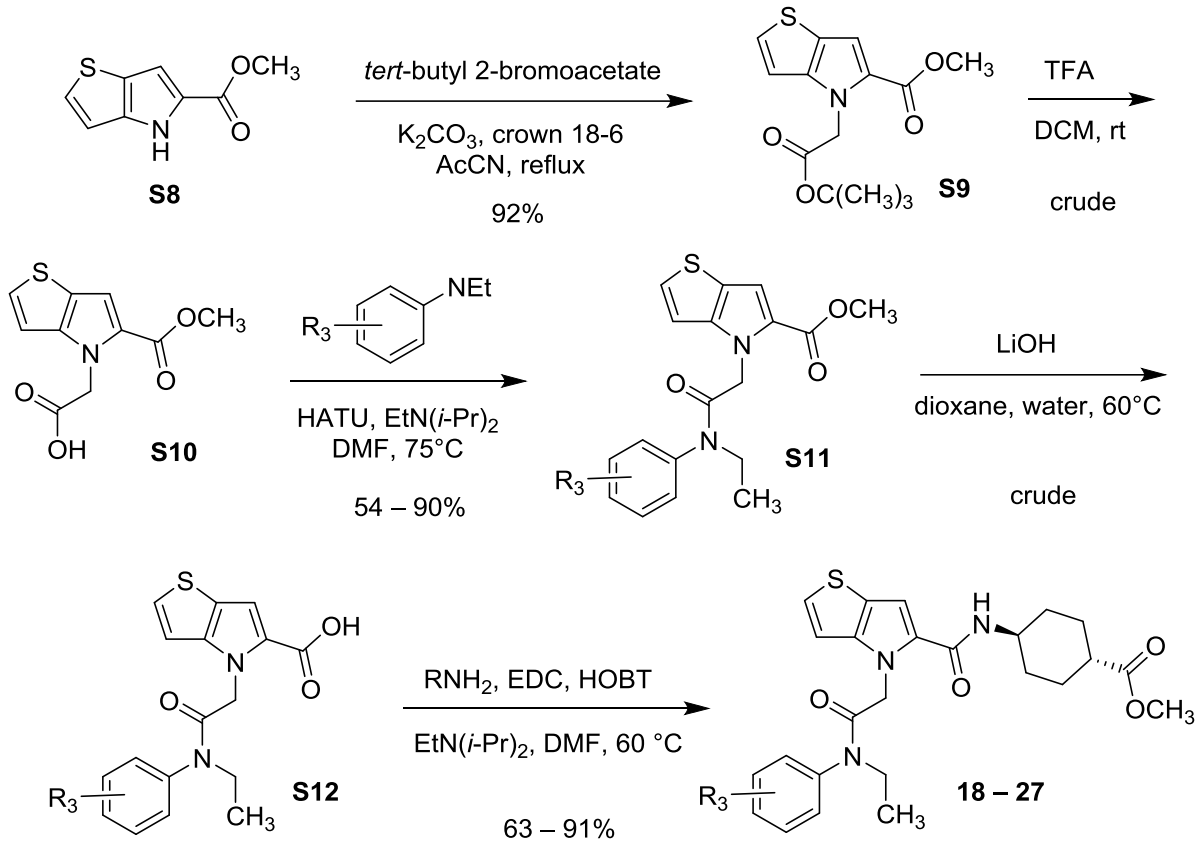
General Synthesis Procedure B: To a solution of carboxylate intermediate (1eq) in dimethylformamide, the requisite amine (or amine hydrochloride), hydroxybenzotriazole (2eq), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2eq) and diisopropylethylamine (3eq) was added. The mixture was heated to 60°C until starting material was consumed (monitored by LCMS or TLC analysis). The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, dichloromethane / methanol or heptane/ethyl acetate) to afford the desired product.



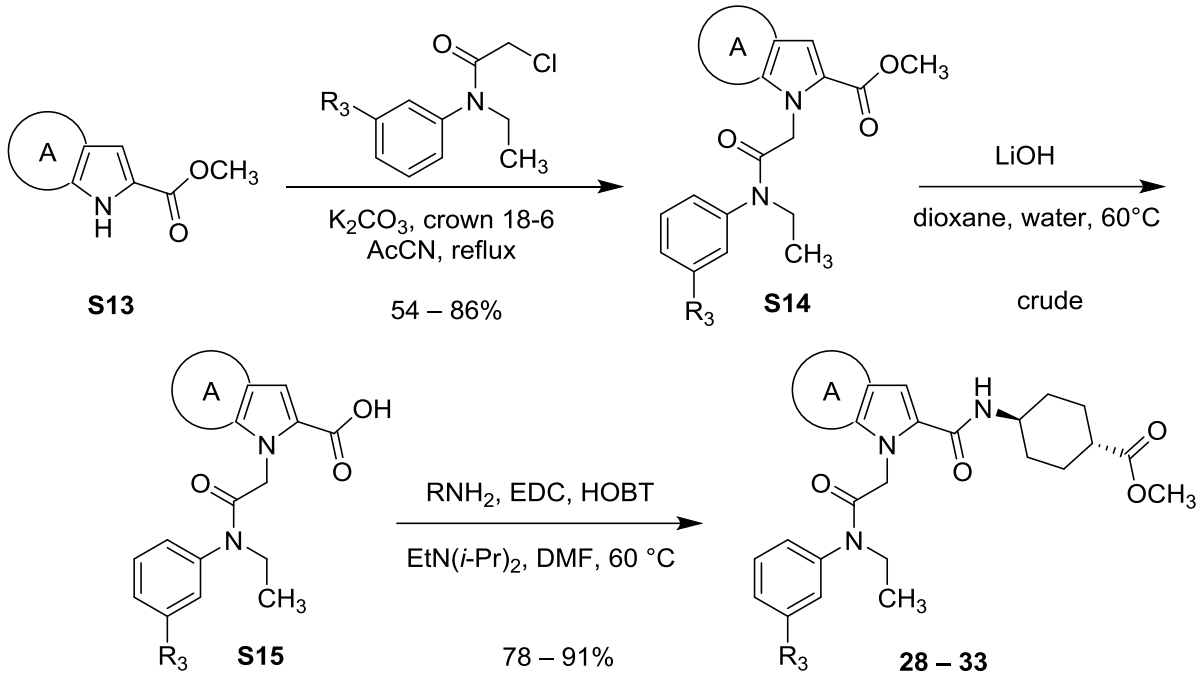
Scheme 1. Synthesis of 2-position thienopyrrole amide analogues (Table 1)



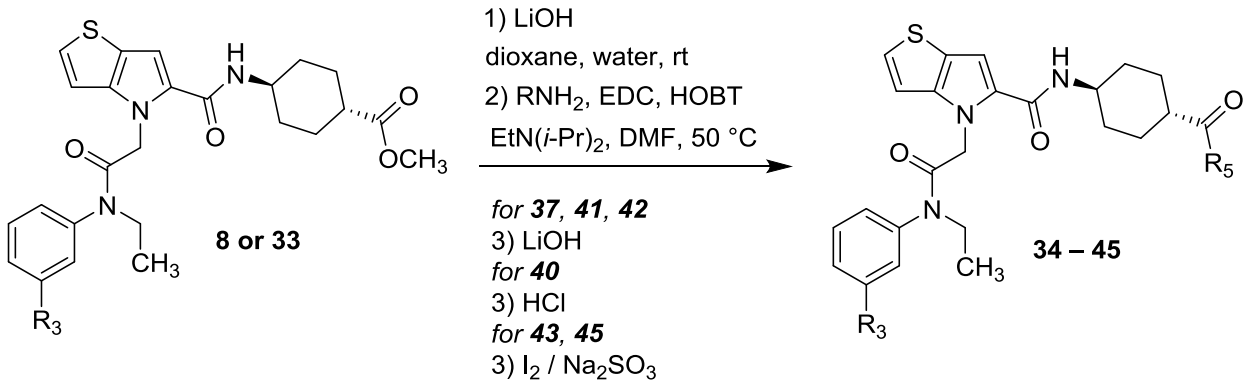
Scheme 2. Synthesis of substituted aniline analogues (Table 2)



Scheme 3. Synthesis of substituted aniline analogues (Table 3)



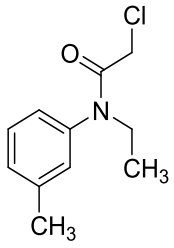
Scheme 4. Synthesis of pyrrolo-analogues (Table 4)



Scheme 5. Synthesis of cyclohexylamide analogues (Table 5)

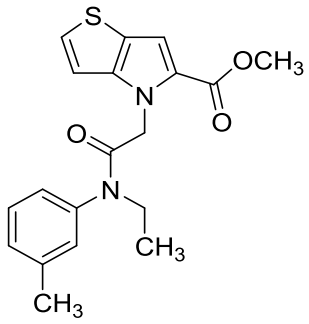
TABLE 1 Compounds

2-chloro-N-ethyl-N-(m-tolyl)acetamide (**S2**)



To a solution of *N*-ethyl-3-methylaniline (2.0g, 14.8mmol) in ethyl acetate (25mL), water (12 mL) was added. The biphasic solution was cooled to 0°C, and potassium hydroxide (2.49g, 44.4mmol) added in one motion. 2-Chloroacetyl chloride (2.5g, 1.8mL, 22.2mmol) was added dropwise over 10min. The mixture was stirred for 1h, diluted with water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated to afford crude product (3.2 g) as a mobile oil. ESI MS m/z 212 [M + H]$^+$.

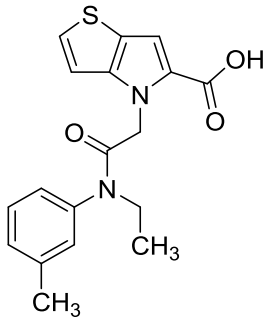
methyl 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**1**)



To a solution of 2-chloro-*N*-ethyl-N-(m-tolyl)acetamide (14.8mmol) in acetonitrile (100mL), methyl 4H-thieno[3,2-b]pyrrole-5-carboxylate (2.28g, 12.6mmol), potassium carbonate (2.09g, 15.1mmol) and 18-crown-6 (166mg, 0.63mmol) was added. The mixture was heated to reflux for 5h, and the reaction was concentrated under vacuum to ~20 mL volume. The suspension was diluted with water, filtered, and washed with water. The solid was dried under vacuum to afford crude product (4.6 g) as a light brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53 (d, J = 5.4,

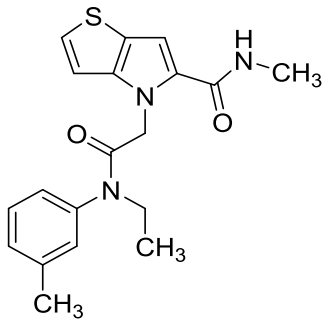
1H), 7.46 - 7.36 (m, 1H), 7.35 - 7.11 (m, 5H), 4.92 (s, 2H), 3.74 (s, 3H), 3.67 - 3.53 (m, 2H), 2.37 (s, 3H), 1.00 (t, *J* = 6.6, 3H); ESI MS m/z 357 $[M + H]^+$.

4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**2**)

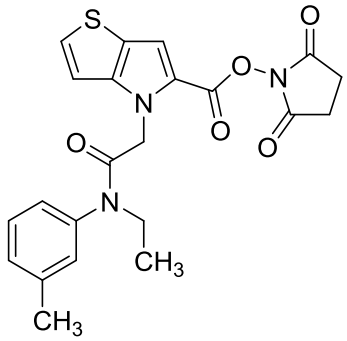


Following general procedure A, methyl 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (2.0g, 5.6mmol) was reacted with lithium hydroxide (671mg 28.0mmol) to afford the desired product (1.8g, 93%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.45 (s, 1H), 7.49 (d, *J* = 5.4, 1H), 7.44 - 7.37 (m, 1H), 7.33 - 7.12 (m, 4H), 7.09 (s, 1H), 4.91 (s, 2H), 3.71 - 3.54 (m, 2H), 2.36 (s, 3H), 1.08 - 0.94 (s, 3H); ESI MS m/z 343 $[M + H]^+$.

4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-methyl-4H-thieno[3,2-b]pyrrole-5-carboxamide (**3**)

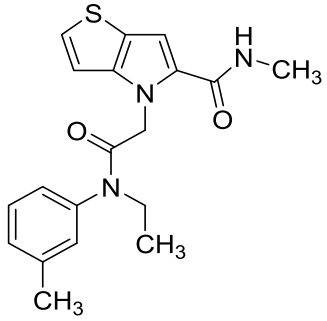


Step 1. 2,5-dioxopyrrolidin-1-yl 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate



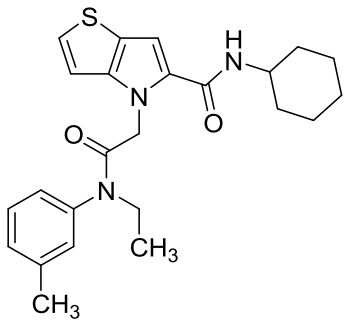
4-(2-(Ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (0.44g, 1.28mmol) and TSTU (1.16g, 3.85mol) was dissolved in 15ml of methylene chloride and 15ml of acetonitrile. DIPEA (0.996g, 7.71mmol) was slowly added at room temperature, and the resultant mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted by 100ml of methylene chloride, washed twice with 30% citric acid and twice with water, and dried over Na_2SO_4. The organic solvent was concentrated to 30ml solution. Without further purification, a portion of the solution was used directly in next step.

Step 2. 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-methyl-4H-thieno[3,2-b]pyrrole-5-carboxamide (**3**)



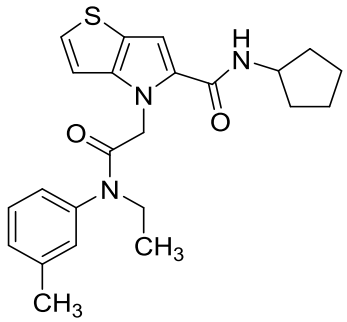
To the above 10ml of crude of 2,5-dioxopyrrolidin-1-yl 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (150mg, 0.34mmol), methyl amine (40%) (0.53g, 6.83mmol) was added, and the resulted mixture was stirred at room temperature for 30 minutes. After removing solvent, the compound was purified by flash column using heptane/ethyl acetate as eluent to give the desired product in a quantitative yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.5 - 6.8 (m, 7H), 4.95 (s, 2H), 3.76 (m, 2H), 2.91 (d, 3H), 2.43 (s, 3H), 1.10 (t, 3H); ESI MS m/z 356 $[M + H]^+$; HPLC 99.6% at 254 nm.

N-cyclohexyl-4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**5**)



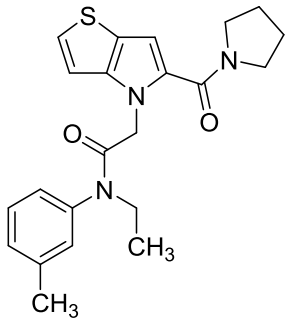
Following general procedure B, 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (75mg, 0.22mmol) was reacted with cyclohexylamine (43mg 0.44mmol) to afford the desired product (50mg, 54%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.83 (d, J = 8.1, 1H), 7.44 - 7.16 (m, 5H), 7.13 - 7.06 (m, 2H), 4.96 (s, 2H), 3.75 - 3.52 (m, 2H), 2.36 (s, 3H), 1.84 - 1.51 (m, 5H), 1.37 - 1.17 (m, 6H), 1.05 - 0.93 (m, 3H); ESI MS m/z 424 $[M + H]^+$; HPLC >99% (AUC), T_R 7.02 min; UV (MeOH) λ_{max} 289 nm, ε 25,200.

N-cyclopentyl-4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**4**)



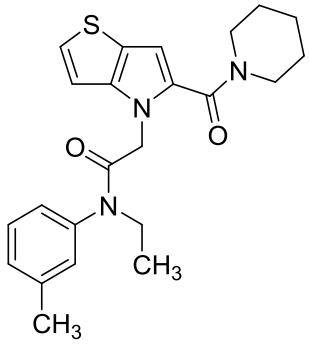
The compound **4** was synthesized by employing the similar method for preparation of 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-methyl-4H-thieno[3,2-b]pyrrole-5-carboxamide (WZ141-84). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.96 (d, 1H), 7.5 - 7.1 (m, 6H), 6.8 (d, 1H), 4.90 (s, 2H), 4.61 (m, 1H), 3.63 (m, 2H), 2.38 (s, br, 3H), 1.9 - 1.4 (m, 8H), 1.00 (t, 3H); ESI MS m/z 410 $[M + H]^+$; HPLC purity 99.1% at 254 nm.

N-ethyl-2-(5-(pyrrolidine-1-carbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)-N-(m-tolyl)acetamide (**6**)



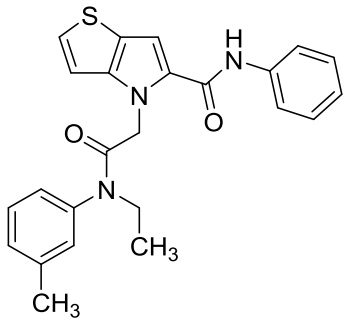
Following general procedure B, 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (75mg, 0.22mmol) was reacted with pyrrolidine (43mg 0.44mmol) to afford the desired product (70mg, 81%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.45 - 7.16 (m, 5H), 7.06 (d, J = 5.2, 1H), 6.83 (s, 1H), 4.83 (s, 2H), 3.77 - 3.32 (m, 6H), 2.36 (s, 3H), 1.91 - 1.75 (m, 4H), 1.06 - 0.92 (m, 3H); ESI MS m/z 396 $[M + H]^+$; HPLC 97.3 % (AUC), T_R 6.24 min; UV (MeOH) λ_{max} 288 nm, ε 21,773.

N-ethyl-2-(5-(piperidine-1-carbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)-N-(m-tolyl)acetamide (**7**)



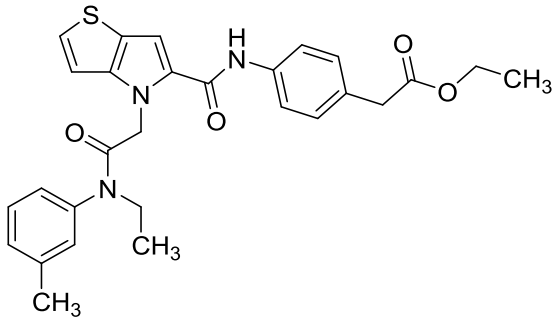
Following general procedure B, 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (80mg, 0.23mmol) was reacted with piperidine (40mg 0.47mmol) to afford the desired product (90mg, 94%) as an orange gum. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52 - 7.13 (m, 5H), 7.05 (d, J = 5.2, 1H), 6.58 (s, 1H), 4.75 (s, 2H), 3.68 - 3.45 (m, 6H), 2.37 (s, 3H), 1.69 - 1.42 (m, 6H), 1.00 (t, J = 6.9, 3H); ESI MS m/z 410 $[M + H]^+$; HPLC 98.8 % (AUC), T_R 5.91 min; UV (MeOH) λ_{max} 284 nm, ε 24,598.

4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-phenyl-4H-thieno[3,2-b]pyrrole-5-carboxamide (**10**)



Following general procedure B, 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (50mg, 0.15mmol) was reacted with aniline (16mg 0.18mmol) to afford the desired product (30mg, 49%) as a foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.74 - 7.68 (m, 2H), 7.49 - 7.19 (m, 9H), 7.16 (d, J = 5.3, 1H), 7.05 (t, J = 7.4, 1H), 4.99 (s, 2H), 3.67 - 3.52 (m, 2H), 2.37 (s, 3H), 1.06 - 0.92 (m, 3H); ESI MS m/z 418 $[M + H]^+$; HPLC 85.4 % (AUC), T_R 6.04 min; UV (EtOH) λ_{max} 306 nm, ε 27,330.

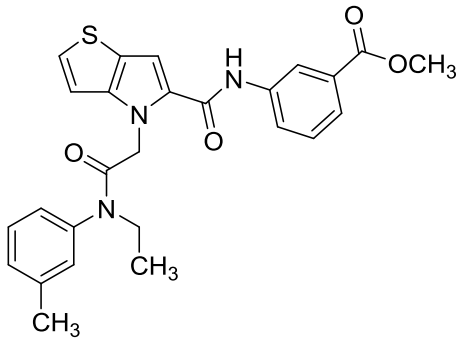
ethyl 2-(4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)phenyl)acetate (**12**)



To a solution of 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (50mg, 0.15mmol) in DMF (3mL), ethyl 2-(4-aminophenyl)acetate (31mg, 0.18mmol), HATU (111mg, 0.29mmol) and diisopropylethylamine (56mg, 0.44mmol) was added. The reaction was heated to 60°C for 18h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (28mg, 38%) as an orange solid. ^{1}H NMR

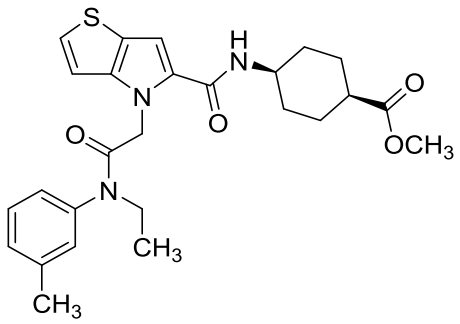
(300 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.64 (d, J = 7.6, 2H), 7.50 - 7.11 (m, 9H), 4.99 (s, 2H), 4.06 (q, J = 6.4 Hz, 2H), 3.60 (s, 4H), 2.37 (s, 3H), 1.17 (t, J = 7.2, 3H), 0.98 (t, J = 6.4, 3H); ESI MS m/z 476 $[M + H]^+$; HPLC 97.2 % (AUC), T_R 7.61 min; UV (EtOH) λ_{max} 308 nm, ε 34,350.

methyl 3-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)benzoate (**11**)



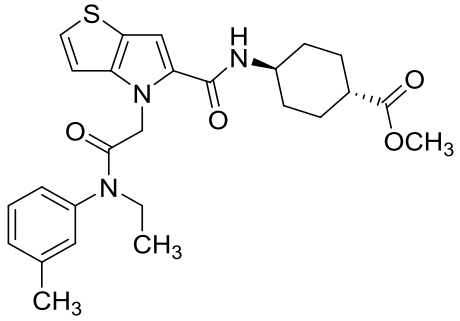
To a solution of 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (50mg, 0.15mmol) in DMF (3mL), methyl 3-aminobenzoate (33mg, 0.22mmol), HATU (111mg, 0.29mmol) and diisopropylethylamine (56mg, 0.44mmol). The reaction was heated to 60°C for 18h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (30mg, 43%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.42 - 8.38 (m, 1H), 8.00 (d, J = 8.2, 1H), 7.67 - 7.63 (m, 1H), 7.56 - 7.10 (m, 8H), 5.00 (s, 2H), 3.86 (s, 3H), 3.67 - 3.55 (m, 2H), 2.38 (s, 3H), 0.99 (t, J = 6.7, 3H); ESI MS m/z 476 $[M + H]^+$; HPLC 98.3 % (AUC), T_R 7.52 min; UV (EtOH) λ_{max} 309 nm, ε 37,302.

methyl-cis-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**9**)



Following general procedure B, 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (150mg, 0.44mmol) was reacted with methyl cis-4-aminocyclohexane-1-carboxylate hydrochloride (127mg, 0.66mmol) to afford the desired product (186mg, 88%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.82 (d, J = 7.8, 1H), 7.45 - 7.33 (m, 2H), 7.32 - 7.16 (m, 3H), 7.12 (s, 1H), 7.08 (d, J = 5.3, 1H), 4.95 (s, 2H), 3.85 - 3.70 (m, 1H), 3.68 - 3.53 (m, 5H), 2.63 - 2.56 (m, 1H), 2.36 (s, 3H), 2.08 - 1.92 (m, 2H), 1.69 - 1.43 (m, 6H), 1.08 - 0.95 (m, 3H); ESI MS m/z 482 $[M + H]^+$; HPLC >99 % (AUC), T_R 7.16 min; UV (MeOH) λ_{max} 288 nm, ε 24,998.

trans-methyl-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**8**)

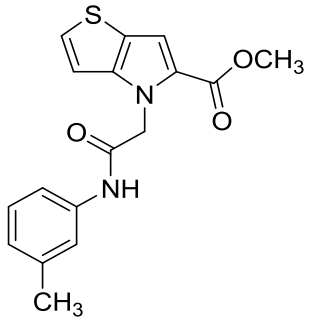


Following general procedure B, 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (100mg, 0.29mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (84mg 0.44mmol) to afford the desired product (103mg, 73%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (d, J = 7.9, 1H), 7.46 - 7.36 (m, 2H), 7.34 - 7.15 (m, 3H), 7.12 - 7.04 (m, 2H), 4.96 (s, 2H), 3.72 - 3.46 (s, 6H), 2.36 (s, 3H), 2.32 -

2.18 (m, 1H), 2.03 - 1.77 (m, 4H), 1.52 - 1.20 (m, 4H), 1.06 - 0.95 (m, 3H); ESI MS m/z 482 [M + H]$^{+}$; HPLC 99.0 % (AUC), T_R 7.75 min; UV (MeOH) λ_{max} 289 nm, ε 26,100.

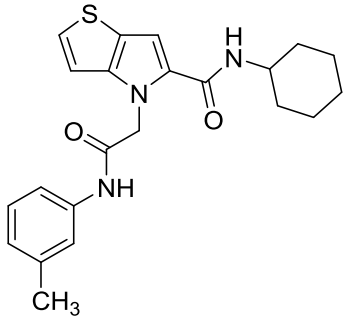
TABLE 2 Compounds

methyl 4-(2-oxo-2-(m-tolylamino)ethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S6**)

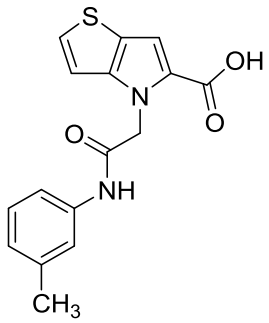


To a solution of 2-chloro-N-(m-tolyl)acetamide (500mg, 2.7mmol) in acetonitrile (20mL), methyl 4H-thieno[3,2-b]pyrrole-5-carboxylate (411mg, 2.3mmol), potassium carbonate (376mg, 2.7mmol) and 18-crown-6 (30mg, 0.11mmol) was added. The reaction was heated to reflux for 1.5h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (530mg, 71%) as a light brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.57 (d, J = 5.4, 1H), 7.42 (s, 1H), 7.37 - 7.30 (m, 1H), 7.27 (d, J = 5.4, 1H), 7.23 (s, 1H), 7.16 (t, J = 7.8, 1H), 6.85 (d, J = 7.8, 1H), 5.31 (s, 2H), 3.73 (s, 3H), 2.24 (s, 3H); ESI MS m/z 329 $[M + H]^+$; HPLC 99.6 % (AUC), T_R 6.32 min; UV (MeOH) λ_{max} 288 nm, ε 29,177.

N-cyclohexyl-4-(2-oxo-2-(m-tolylamino)ethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**13**)

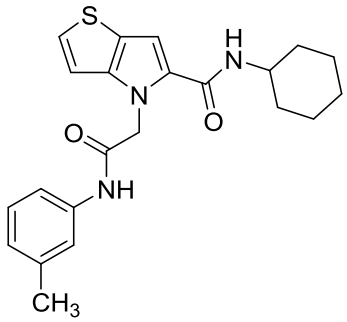


Step 1. 4-(2-oxo-2-(m-tolylamino)ethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S7**)



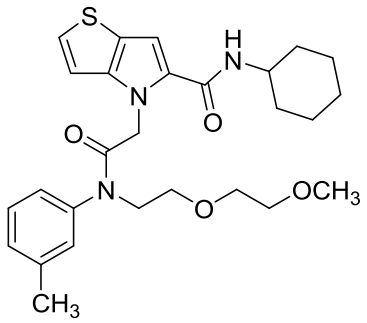
Following general procedure A, methyl 4-(2-oxo-2-(m-tolylamino)ethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (130mg, 0.39mmol) was reacted with lithium hydroxide (47mg 2.0mmol) to afford crude product as a light brown solid.

Step 2. N-cyclohexyl-4-(2-oxo-2-(m-tolylamino)ethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**13**)

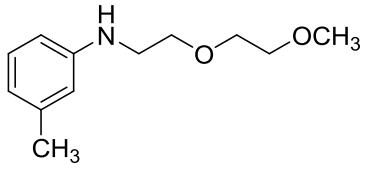


Following general procedure B, 4-(2-oxo-2-(m-tolylamino)ethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (120mg, 0.38mmol) was reacted with cyclohexylamine (56mg, 0.57mmol) to afford the desired product (47mg, 31%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 7.95 (d, J = 8.1, 1H), 7.43 - 7.38 (m, 2H), 7.33 (d, J = 8.1, 1H), 7.23 - 7.10 (m, 3H), 6.84 (d, J = 7.5, 1H), 5.30 (s, 2H), 3.75 - 3.58 (m, 1H), 2.24 (s, 3H), 1.85 - 1.53 (m, 5H), 1.35 - 1.00 (m, 5H); ESI MS m/z 396 $[M + H]^+$; HPLC 94.7 % (AUC), T_R 7.34 min; UV (MeOH) λ_{max} 285 nm, ε 28,066.

N-cyclohexyl-4-(2-((2-(2-methoxyethoxy)ethyl)(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**14**)

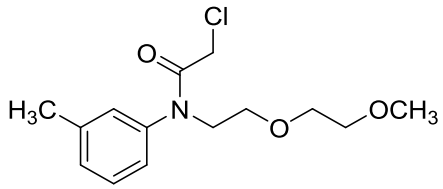


Step 1. N-(2-(2-methoxyethoxy)ethyl)-3-methylaniline (**S4**)



To a solution of m-toluidine (1.0g, 9.3mmol) in DMF (10mL), 1-bromo-2-(2-methoxyethoxy)ethane (0.85g, 4.6mmol) and diisopropylamine (1.2g, 0.93mmol) was added. The mixture was heated to 100°C for 4h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (650mg, 66%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.5, 1H), 6.56 (d, *J* = 7.5, 1H), 6.52 - 6.45 (m, 2H), 3.71 (t, *J* = 5.3, 2H), 3.67 - 3.62 (m, 2H), 3.60 - 3.52 (m, 2H), 3.31 (t, *J* = 5.3, 2H), 2.28 (s, 3H); ESI MS m/z 210 $[M + H]^+$.

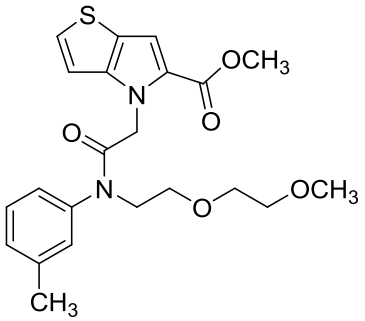
Step 2. 2-chloro-N-(2-(2-methoxyethoxy)ethyl)-N-(m-tolyl)acetamide (**S5**)



To a solution of N-(2-(2-methoxyethoxy)ethyl)-3-methylaniline (650mg, 3.1mmol) in ethyl acetate (15mL), water (5mL) was added. The biphasic solution was cooled to 0°C and potassium hydroxide (522mg, 9.3mmol) was added in one motion. 2-Chloroacetyl chloride (526mg, 4.7mmol) was added dropwise over 10min. The mixture was stirred for 2.5h, diluted with water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated to afford crude product (830mg) as light red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 - 7.25 (m, 1H), 7.18 (d, *J* = 7.7, 1H), 7.15 - 7.03 (m, 2H), 3.89

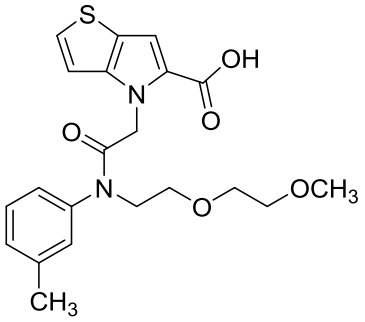
(t, *J* = 5.8, 2H), 3.83 (s, 2H), 3.65 (t, *J* = 5.8, 2H), 3.62 - 3.55 (m, 2H), 3.54 - 3.46 (m, 2H), 2.37 (s, 3H); ESI MS m/z 286 $[M + H]^+$.

Step 3. methyl 4-(2-((2-(2-methoxyethoxy)ethyl)(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S6**)



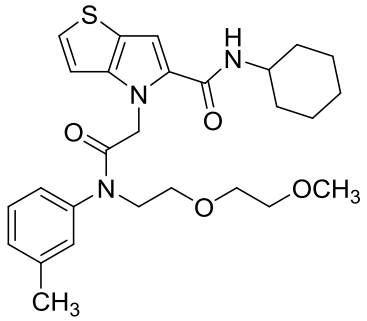
To a solution of 2-chloro-N-(2-(2-methoxyethoxy)ethyl)-N-(m-tolyl)acetamide (830mg, 2.9mmol) in acetonitrile (20mL), methyl 4H-thieno[3,2-b]pyrrole-5-carboxylate (438mg, 2.4mmol), potassium carbonate (400mg, 2.9mmol) and 18-crown-6 (32mg, 0.12mmol) was added. The mixture was heated to reflux for 18h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford crude product (1.3g) as a thick oil. ESI MS m/z 430 $[M + H]^+$.

Step 4. 4-(2-((2-(2-methoxyethoxy)ethyl)(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S7**)



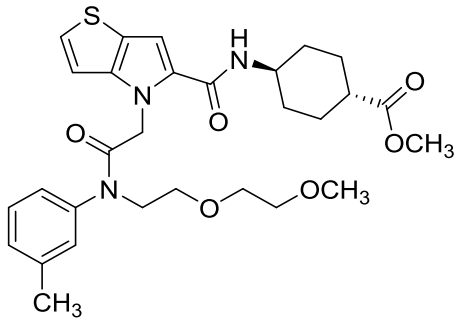
Following general procedure A, methyl 4-(2-((2-(2-methoxyethoxy)ethyl)(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (2.4mmol) was reacted with lithium hydroxide (287mg, 12.0mmol) to afford crude product (1.0g, quant.) as a light yellow solid. ESI MS m/z 417 $[M + H]^+$.

Step 5. N-cyclohexyl-4-(2-((2-(2-methoxyethoxy)ethyl)(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**14**)



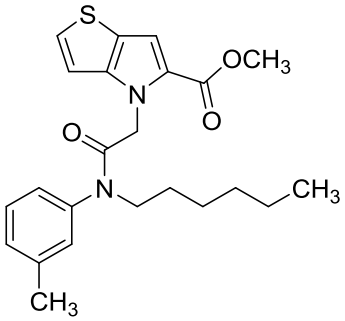
Following general procedure B, 4-(2-((2-(2-methoxyethoxy)ethyl)(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (120mg, 0.28mmol) was reacted with cyclohexylamine (42mg, 0.43mmol) to afford the desired product (120mg, 83%) as a white gum. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.96 - 7.85 (m, 1H), 7.48 - 7.30 (m, 4H), 7.30 - 7.20 (m, 1H), 7.17 - 7.07 (m, 2H), 5.01 (s, 2H), 3.82 - 3.62 (m, 3H), 3.56 - 3.35 (m, 6H), 3.25 (s, 3H), 2.38 (s, 3H), 1.90 - 1.54 (m, 5H), 1.41 - 1.04 (m, 5H); ESI MS m/z 498 $[M + H]^+$; HPLC 96.0 % (AUC), T_R 7.38 min; UV (EtOH) λ_{max} 289 nm, ε 25,434.

Methyl-trans-4-(4-(2-((2-(2-methoxyethoxy)ethyl)(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**15**)

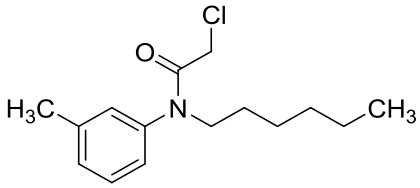


Following general procedure B, 4-(2-((2-(2-methoxyethoxy)ethyl)(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (120mg, 0.28mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (68mg, 0.43mmol) to afford the desired product (140mg, 87%) as a white gum. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J = 7.8, 1H), 7.46 - 7.20 (m, 5H), 7.15 - 7.04 (m, 2H), 5.00 (s, 2H), 3.78 - 3.65 (m, 3H), 3.60 (s, 3H), 3.52 - 3.35 (m, 6H), 3.23 (s, 3H), 2.38 (s, 3H), 2.34 - 2.20 (m, 1H), 2.02 - 1.81 (m, 4H), 1.53 - 1.22 (m, 4H); ESI MS m/z 556 $[M + H]^+$; HPLC 98.7 % (AUC), T_R 6.60 min; UV (MeOH) λ_{max} 289 nm, ε 23,567.

methyl 4-(2-(hexyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S6**)

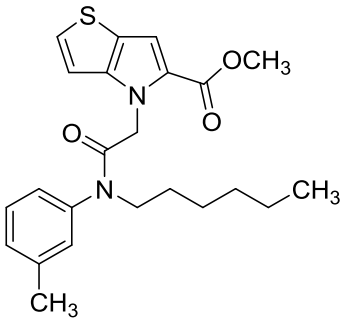


Step 1. 2-chloro-N-hexyl-N-(m-tolyl)acetamide (**S5**)



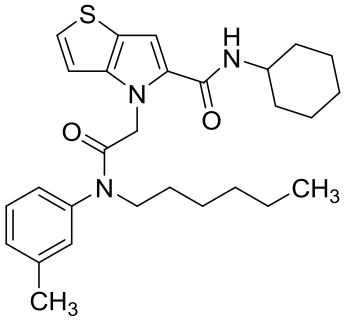
To a solution of N-hexyl-3-methylaniline (500mg, 2.6mmol) in ethyl acetate (15mL), water (5mL) was added. The biphasic solution was cooled to 0°C, and potassium hydroxide (440mg, 7.8mmol) added in one motion. 2-Chloroacetyl chloride (442mg, 3.9mmol) was added dropwise over 10min. The mixture was stirred for 1h, diluted with water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated to afford crude product (730 mg) as light red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, *J* = 8.0, 1H), 7.24 - 7.17 (m, 1H), 7.04 - 6.97 (m, 2H), 3.80 (s, 2H), 3.74 - 3.61 (m, 2H), 2.38 (s, 3H), 1.59 - 1.41 (m, 2H), 1.37 - 1.16 (m, 6H), 0.92 - 0.80 (m, 3H); ESI MS m/z 268 [M + H]$^{+}$.

Step 2. methyl 4-(2-(hexyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S6**)

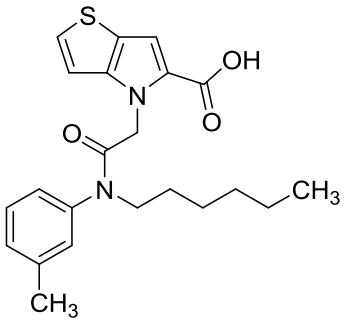


To a solution of 2-chloro-N-hexyl-N-(m-tolyl)acetamide (700mg, 2.6mmol) in acetonitrile (20mL), methyl 4H-thieno[3,2-b]pyrrole-5-carboxylate (394mg, 2.2mmol), potassium carbonate (361mg, 2.6mmol) and 18-crown-6 (29mg, 0.11mmol) was added. The mixture was heated to reflux for 18h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was the concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (780mg, 86%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53 (d, J = 5.4, 1H), 7.41 (t, J = 7.7, 1H), 7.33 - 7.11 (m, 5H), 4.93 (s, 2H), 3.74 (s, 3H), 3.58 (t, J = 6.0 Hz, 2H), 2.37 (s, 3H), 1.48 - 1.30 (m, 2H), 1.28 - 1.15 (m, 6H), 0.81 (t, J = 6.7, 3H); ESI MS m/z 413 $[M + H]^+$; HPLC 97.1 % (AUC), T_R 7.18 min; UV (EtOH) λ_{max} 289 nm, ε 26,840.

N-cyclohexyl-4-(2-(hexyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**16**)

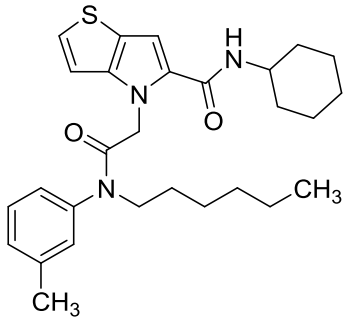


Step 1. 4-(2-(hexyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S7**)



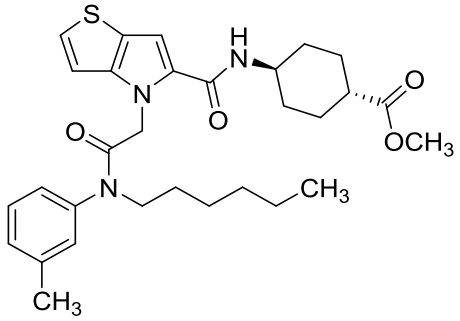
Following general procedure A, methyl 4-(2-(hexyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (300mg, 0.73mmol) was reacted with lithium hydroxide (87mg, 3.6mmol) to afford crude product (300 mg) as a light yellow solid. ESI MS m/z 399 $[M + H]^+$.

Step 2. N-cyclohexyl-4-(2-(hexyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**16**)



Following general procedure B, 4-(2-(hexyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (50mg, 0.12mmol) was reacted with cyclohexylamine (15mg, 0.15mmol) to afford the desired product (60mg, 99%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85 (d, J = 8.2, 1H), 7.46 - 7.16 (m, 5H), 7.12 - 7.06 (m, 2H), 4.96 (s, 2H), 3.75 - 3.60 (m, 1H), 3.56 (t, J = 6.7, 2H), 2.36 (s, 3H), 1.84 - 1.52 (m, 5H), 1.43 - 1.04 (m, 13H), 0.81 (t, J = 6.9, 3H); ESI MS m/z 480 $[M + H]^+$; HPLC 98.1 % (AUC), T_R 8.62 min; UV (EtOH) λ_{max} 288 nm, ε 24,544.

methyl-trans-4-(4-(2-(hexyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**17**)

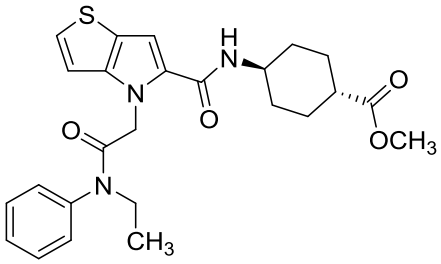


Following general procedure B, 4-(2-(hexyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (50mg, 0.12mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (24mg, 0.15mmol) to afford the desired product (65mg, 96%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 8.0, 1H), 7.44 - 7.33 (m, 2H), 7.33 - 7.17 (m, 3H), 7.12 - 7.06 (m, 2H), 4.96 (s, 2H), 3.75 - 3.47 (m, 6H), 2.36 (s, 3H), 2.31 -

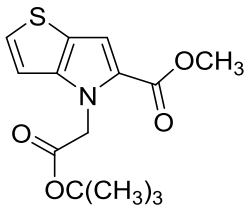
2.20 (m, 1H), 1.99 - 1.78 (m, 4H), 1.51 - 1.10 (m, 12H), 0.81 (t, *J* = 6.9, 3H); ESI MS m/z 538 $[M + H]^+$; HPLC 99.8 % (AUC), T_R 8.17 min; UV (EtOH) λ_{max} 289 nm, ε 26,509.

TABLE 3 Compounds

Methyl trans-4-(4-(2-(ethyl(phenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**18**)

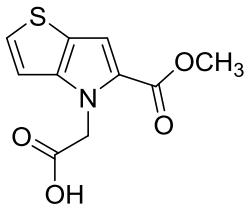


Step 1. methyl 4-(2-(tert-butoxy)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S9**)



To a solution of methyl 4H-thieno[3,2-b]pyrrole-5-carboxylate (1.4 g, 7.73 mmol) in acetonitrile (30 mL), potassium carbonate (1.28 g, 9.28 mmol), 18-crown-6 ether (102 mg, 0.38 mmol), and tert-butyl 2-bromoacetate (1.81 g, 9.28 mmol)was added. The suspension was heated to 75°C for 18h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (2.1 g, 91%) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 5.4, 1H), 7.22 (d, *J* = 0.7, 1H), 6.87 (dd, *J* = 0.7, 5.4, 1H), 5.11 (s, 2H), 3.84 (s, 3H), 1.46 (s, 9H); ESI MS m/z 296 [M + H]+.

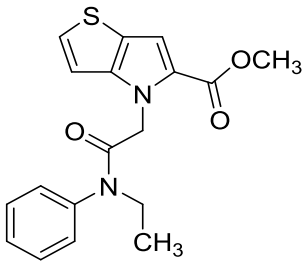
Step 2. 2-(5-(methoxycarbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)acetic acid (**S10**)



To a solution of methyl 4-(2-(tert-butoxy)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (1.92 g, 6.50 mmol) in DCM (20 mL), trifluoroacetic acid (2 mL) was added. The solution stirred at RT for 4h, then the mixture was concentrated. Toluene was added to the residue and

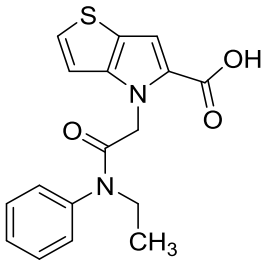
concentrated to obtained crude product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 5.4, 1H), 7.24 (s, 1H), 6.89 (d, *J* = 5.4, 1H), 5.24 (s, 2H), 3.86 (s, 3H); ESI MS m/z 240 [M + H]+.

Step 3. Methyl 4-(2-(ethyl(phenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S11**)



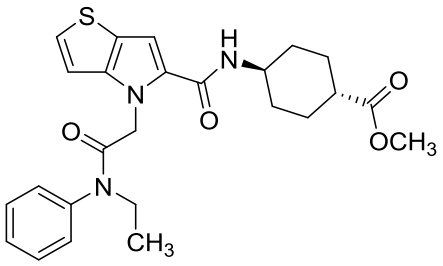
To a solution of 2-(5-(methoxycarbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)acetic acid (100 mg, 0.42 mmol) in DMF (3mL), N-ethylaniline (101 mg, 0.84 mmol), HATU (318 mg, 0.84 mmol), and diisopropylethylamine (108 mg, 0.84 mmol) was added. The reaction was heated to 75°C for 18h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (86 mg, 60%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 - 7.21 (m, 6H), 7.16 (s, 1H), 6.80 (d, *J* = 5.5, 1H), 4.95 (s, 2H), 3.87 - 3.68 (m, 5H), 1.13 (t, *J* = 7.2, 3H); ESI MS m/z 343 $[M + H]^+$.

Step 4. 4-(2-(ethyl(phenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S12**)



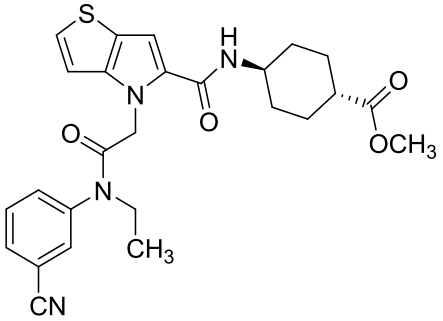
Following general procedure A, methyl 4-(2-(ethyl(phenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (86 mg, 0.25 mmol) was reacted with lithium hydroxide (30 mg, 1.3 mmol) to afford crude product (82 mg) as a light brown solid. ESI MS m/z 329 $[M + H]^+$.

Step 5. Methyl trans-4-(4-(2-(ethyl(phenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**18**)

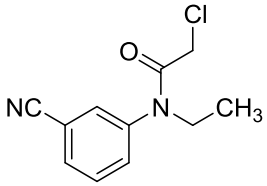


Following general procedure B, 4-(2-(ethyl(phenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (80 mg, 0.24 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (56 mg, 0.29 mmol) to afford the desired product (81 mg, 71%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (d, J = 7.9, 1H), 7.60 - 7.28 (m, 6H), 7.04 - 7.13 (m, 2H), 4.95 (s, 2H), 3.73 - 3.52 (m, 5H), 2.31 - 2.18 (m, 1H), 2.03 - 1.78 (m, 4H), 1.50 - 1.20 (m, 4H), 1.07 - 0.93 (s, 3H); ESI MS m/z 468 $[M + H]^+$; HPLC 97.7 % (AUC), T_R 6.51 min; UV (EtOH) λ_{max} 289 nm, ε 28,274.

Methyl trans-4-(4-(2-((3-cyanophenyl)(ethyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**25**)



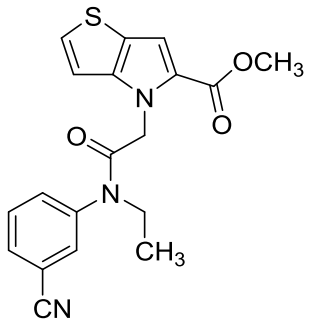
Step 1. 2-chloro-N-(3-cyanophenyl)-N-ethylacetamide (JRW-0313)



To a solution of 3-(ethylamino)benzonitrile (60 mg, 0.41 mmol) in ethyl acetate (7 mL), water (3 mL) was added. The biphasic solution was cooled to 0°C, and potassium hydroxide (69 mg, 1.2 mmol) was added in one motion. 2-Chloroacetyl chloride (69 mg, 0.62 mmol) was added dropwise over 10min. The mixture was stirred for 2h, diluted with water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The

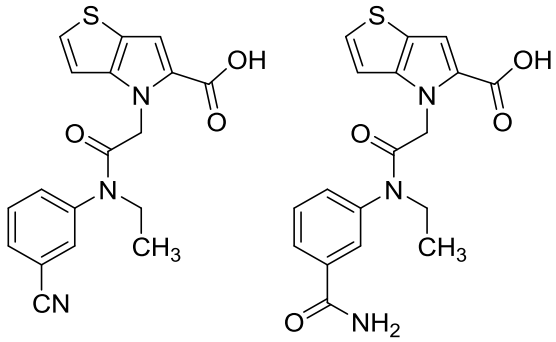
filtrate was then concentrated to afford crude product (98 mg) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 - 7.42 (m, 4H), 3.84 - 3.70 (m, 4H), 1.15 (*t*, J = 7.2, 3H); ESI MS m/z 223 $[M + H]^+$.

Step 2. Methyl 4-(2-((3-cyanophenyl)(ethyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S11**)



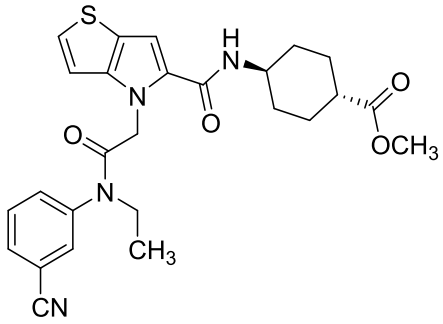
To a solution of methyl 4H-thieno[3,2-b]pyrrole-5-carboxylate (68 mg, 0.37 mmol) in acetonitrile (5 mL), potassium carbonate (62 mg, 0.45 mmol), 18-crown-6 ether (5 mg, 0.019 mmol), and 2-chloro-N-(3-cyanophenyl)-N-ethylacetamide (98 mg, 0.45 mmol) was added. The suspension was heated to 75°C for 18h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (94 mg, 68%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 - 7.62 (m, 1H), 7.61 - 7.49 (m, 3H), 7.33 (d, *J* = 5.4, 1H), 7.12 (s, 1H), 6.82 (d, *J* = 5.4, 1H), 4.98 (s, 2H), 3.87 - 3.70 (m, 5H), 1.14 (t, *J* = 7.1, 3H); ESI MS m/z 368 [M + H]+.

Step 3. 4-(2-((3-cyanophenyl)(ethyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (JRW-0319-1) and 4-(2-((3-carbamoylphenyl)(ethyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S12**)



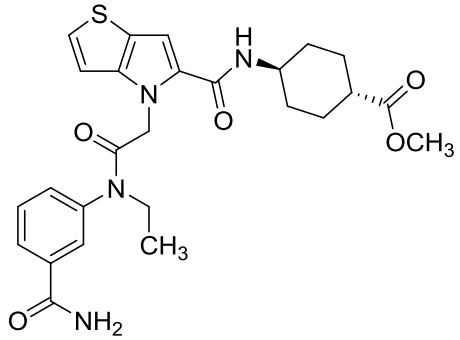
Following general procedure A, methyl 4-(2-((3-cyanophenyl)(ethyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (90 mg, 0.24 mmol) was reacted with lithium hydroxide (12 mg, 0.49 mmol). The two products were separated by column chromatography (silica, dichloromethane/methanol) to afford the nitrile (61 mg) and the amide (31 mg) as white solids. ESI MS m/z 354 $[M + H]^+$ and m/z 372 $[M + H]^+$.

Step 4. Methyl trans-4-(4-(2-((3-cyanophenyl)(ethyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**25**)



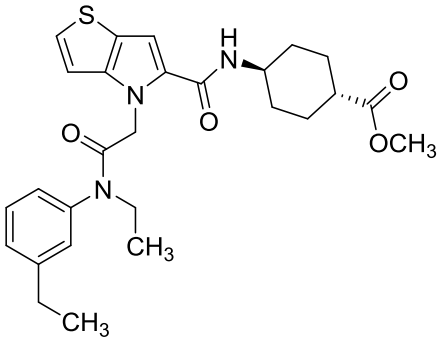
Following general procedure B, 4-(2-((3-cyanophenyl)(ethyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (60 mg, 0.17 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (56 mg, 0.29 mmol) to afford the desired product (68 mg, 81%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 - 7.59 (m, 5H), 7.38 (d, J = 5.3, 1H), 7.17 - 7.03 (m, 2H), 5.02 (s, 2H), 3.77 - 3.55 (m, 6H), 2.32 - 2.18 (m, 1H), 1.99 - 1.79 (m, 4H), 1.54 - 1.20 (m, 4H), 1.10 - 0.95 (m, 3H); ESI MS m/z 493 $[M + H]^+$; HPLC 98.3 % (AUC), T_R 6.12 min; UV (EtOH) λ_{max} 289 nm, ε 26,802.

Methyl trans-4-(4-(2-((3-carbamoylphenyl)(ethyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**27**)

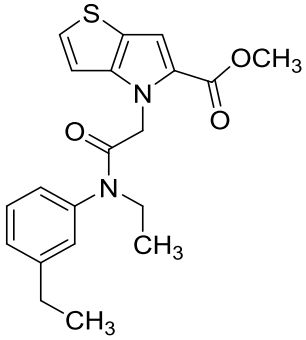


Following general procedure B, 4-(2-((3-carbamoylphenyl)(ethyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (30 mg, 0.08 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (19 mg, 0.10 mmol) to afford the desired product (33 mg, 80%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.97 – 7.83 (m, 3H), 7.72 – 7.43 (m, 3H), 7.37 (d, J = 5.4, 1H), 7.12 – 7.05 (m, 2H), 4.98 (s, 2H), 3.75 – 3.54 (m, 6H), 2.32 – 2.18 (m, 1H), 1.99 - 1.79 (m, 4H), 1.53 – 1.22 (m, 4H), 1.10 - 0.95 (m, 3H); ESI MS m/z 511 $[M + H]^+$; HPLC 98.2 % (AUC), T_R 4.81 min; UV (EtOH) λ_{max} 289 nm, ε 28,223.

Methyl trans-4-(4-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**22**)



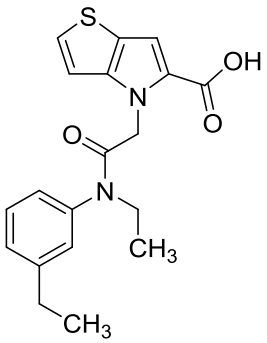
Step 1. Methyl 4-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S11**)



To a solution of 2-(5-(methoxycarbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)acetic acid (100 mg, 0.42 mmol) in DMF (3mL), N,3-diethylaniline (94 mg, 0.63 mmol), HATU (318 mg, 0.84 mmol), and diisopropylethylamine (162 mg, 1.25 mmol) was added. The reaction was heated to 85°C for 18h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl

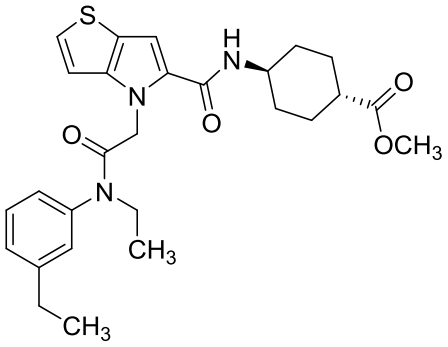
acetate) to afford the desired product (107 mg, 69%) as an orange foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.9, 1H), 7.31 - 7.20 (m, 2H), 7.17 - 7.10 (m, 3H), 6.81 (d, *J* = 5.4, 1H), 4.98 (s, 2H), 3.84 - 3.67 (m, 5H), 2.71 (q, *J* = 7.6, 2H), 1.29 (t, *J* = 7.6, 3H), 1.13 (t, *J* = 7.2, 3H); ESI MS m/z 371 $[M + H]^+$.

Step 2. 4-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S12**)



Following general procedure A, methyl 4-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (100 mg, 0.27 mmol) was reacted with lithium hydroxide (19 mg, 0.81 mmol) to afford crude product (100 mg) as a light yellow solid. ESI MS m/z 357 $[M + H]^+$.

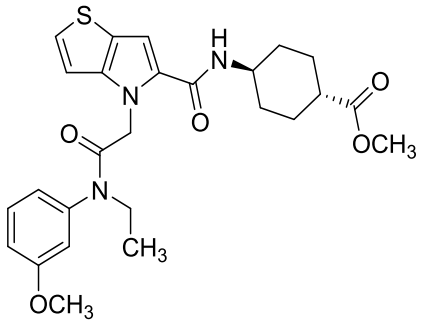
Step 3. Methyl trans-4-(4-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**22**)



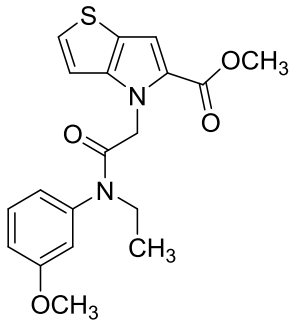
Following general procedure B, 4-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (100 mg, 0.28 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (65 mg, 0.34 mmol) to afford the desired product (105 mg, 75%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, *J* = 7.9, 1H), 7.51 - 7.19 (m, 5H), 7.13 - 7.04 (m, 2H), 4.95 (s, 2H), 3.74 - 3.54 (m, 5H), 2.73 - 2.61 (m, 2H), 2.32 - 2.18 (m,

1H), 2.01 - 1.78 (m, 4H), 1.51 - 1.14 (m, 7H), 1.08 - 0.95 (s, 3H); ESI MS m/z 496 $[M + H]^+$; HPLC 97.6 % (AUC), T_R 7.37 min; UV (MeOH) λ_{max} 288 nm, ε 27,343.

Methyl trans-4-(4-(2-(ethyl(3-methoxyphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**26**)

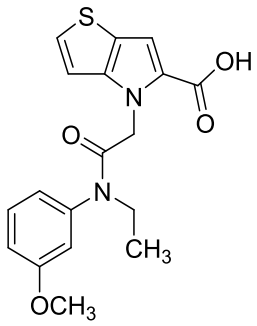


Step 1. Methyl 4-(2-(ethyl(3-methoxyphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S11**)



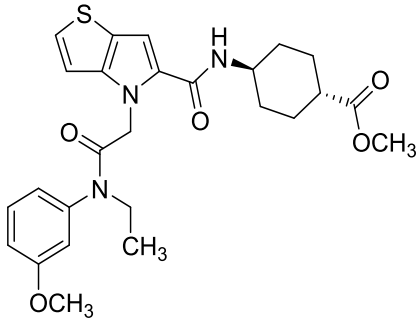
To a solution of 2-(5-(methoxycarbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)acetic acid (100 mg, 0.42 mmol) in DMF (3mL), N-ethyl-3-methoxyaniline (94 mg, 0.63 mmol), HATU (318 mg, 0.84 mmol), and diisopropylethylamine (162 mg, 1.25 mmol) was added. The reaction was heated to 85°C for 18h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (97 mg, 62%) as an orange foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (t, *J* = 8.0, 1H), 7.29 (d, *J* = 5.4, 1H), 7.15 (s, 1H), 6.99 - 6.84 (m, 3H), 6.81 (d, *J* = 5.4, 1H), 5.02 (s, 2H), 3.86 (s, 3H), 3.83 - 3.69 (m, 5H), 1.14 (t, *J* = 7.2, 3H); ESI MS m/z 373 $[M + H]^+$.

Step 2. 4-(2-(ethyl(3-methoxyphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S12**)



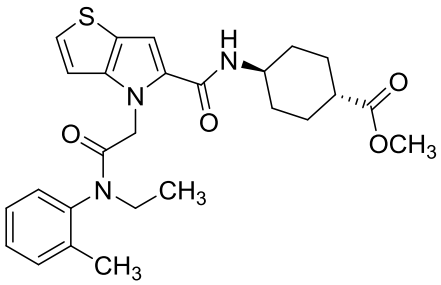
Following general procedure A, methyl 4-(2-(ethyl(3-methoxyphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (95 mg, 0.26 mmol) was reacted with lithium hydroxide (18 mg, 0.77 mmol) to afford crude product (88 mg) as a light yellow solid. ESI MS m/z 359 $[M + H]^+$.

Step 3. Methyl trans-4-(4-(2-(ethyl(3-methoxyphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**26**)

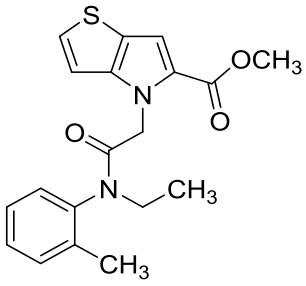


Following general procedure B, 4-(2-(ethyl(3-methoxyphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (88 mg, 0.25 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (48 mg, 0.34 mmol) to afford the desired product (78 mg, 63%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, J = 8.3, 1H), 7.50 - 7.31 (m, 2H), 7.16 - 6.91 (m, 5H), 5.00 (s, 2H), 3.81 (s, 3H), 3.75 - 3.53 (m, 6H), 2.33 - 2.18 (m, 1H), 2.01 - 1.77 (m, 4H), 1.50 - 1.22 (m, 4H), 1.08 - 0.95 (m, 3H); ESI MS m/z 498 $[M + H]^+$; HPLC 96.4 % (AUC), T_R 6.69 min; UV (MeOH) λ_{max} 289 nm, ε 28,671

Methyl trans-4-(4-(2-(ethyl(o-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**19**)

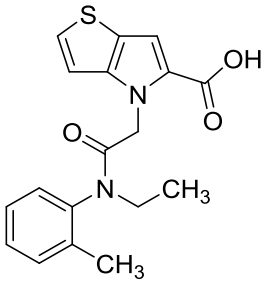


Step 1. Methyl 4-(2-(ethyl(o-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S11**)



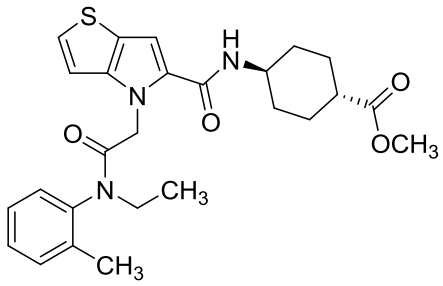
To a solution of 2-(5-(methoxycarbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)acetic acid (100 mg, 0.42 mmol) in DMF (3mL), N-ethyl-2-methylaniline (84 mg, 0.63 mmol), HATU (318 mg, 0.84 mmol), and diisopropylethylamine (162 mg, 1.25 mmol) was added. The reaction was heated to 85°C for 18h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (72 mg, 48%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 - 7.21 (m, 5H), 7.16 (s, 1H), 6.78 (d, *J* = 5.4, 1H), 5.02 (d, *J* = 16.9, 1H), 4.74 (d, *J* = 16.9, 1H), 4.15 (dq, *J* = 7.1, 14.2, 1H), 3.81 (s, 3H), 3.24 (dq, *J* = 7.1, 14.2, 1H), 1.14 (t, *J* = 7.1, 4H); ESI MS m/z 357 $[M + H]^+$.

Step 2. 4-(2-(ethyl(o-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S12**)



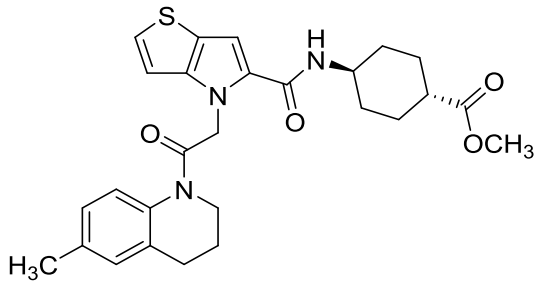
Following general procedure A, methyl 4-(2-(ethyl(o-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (70 mg, 0.20 mmol) was reacted with lithium hydroxide (23 mg, 0.98 mmol) to afford crude product (69 mg) as a light yellow solid. ESI MS m/z 343 $[M + H]^+$.

Step 3. methyl (1r,4r)-4-(4-(2-(ethyl(o-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**19**)

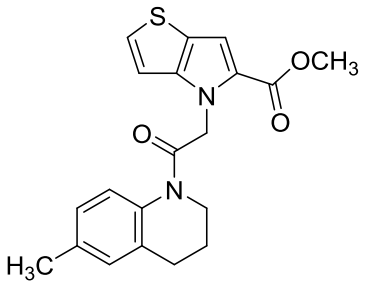


Following general procedure B, 4-(2-(ethyl(o-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (69 mg, 0.25 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (46 mg, 0.24 mmol) to afford the desired product (77 mg, 79%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 7.9, 1H), 7.49 - 7.29 (m, 5H), 7.11 - 6.98 (m, 2H), 4.91 (d, J = 16.7, 1H), 4.79 (d, J = 16.7, 1H), 4.06 - 3.90 (m, 1H), 3.72 - 3.53 (m, 4H), 3.14 - 2.99 (m, 1H), 2.34 (s, 3H), 2.31 - 2.18 (m, 1H), 2.00 - 1.78 (m, 4H), 1.51 - 1.14 (m, 4H), 0.99 (t, J = 7.1, 3H); ESI MS m/z 482 $[M + H]^+$; HPLC 92.3% (AUC), T_R 6.97 min; UV (MeOH) λ_{max} 288 nm, ε 29,468.

Methyl trans-4-(4-(2-(6-methyl-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**21**)

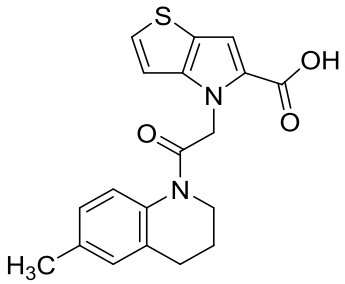


Step 1. Methyl 4-(2-(6-methyl-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S11**)



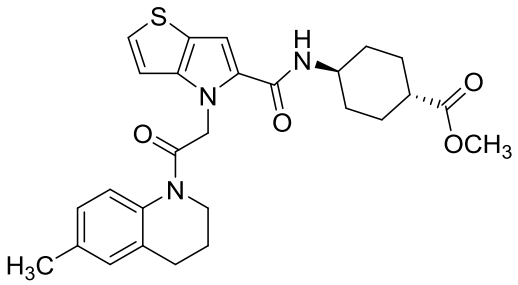
To a solution of 2-(5-(methoxycarbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)acetic acid (100 mg, 0.42 mmol) in DMF (3mL), 6-methyl-1,2,3,4-tetrahydroquinoline (92 mg, 0.63 mmol), HATU (318 mg, 0.84 mmol), and diisopropylethylamine (162 mg, 1.25 mmol) was added. The reaction was heated to 85°C for 18h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (140 mg, 90%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 5.4, 1H), 7.18 (s, 1H), 7.08 - 6.96 (m, 3H), 6.82 (d, *J* = 5.4, 1H), 5.39 (s, 2H), 3.86 - 3.74 (m, 5H), 2.82 - 2.66 (m, 2H), 2.31 (s, 3H), 2.05 - 1.89 (m, 2H); ESI MS m/z 367 $[M + H]^+$.

Step 2. 4-(2-(6-methyl-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S12**)



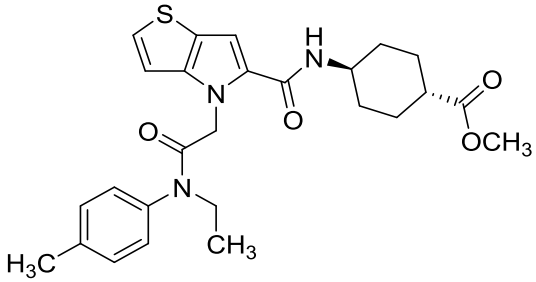
Following general procedure A, methyl 4-(2-(6-methyl-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (130 mg, 0.35 mmol) was reacted with lithium hydroxide (42 mg, 1.76 mmol) to afford crude product (120 mg) as an orange solid. ESI MS m/z 355 $[M + H]^+$.

Step 3. Methyl trans-4-(4-(2-(6-methyl-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**21**)

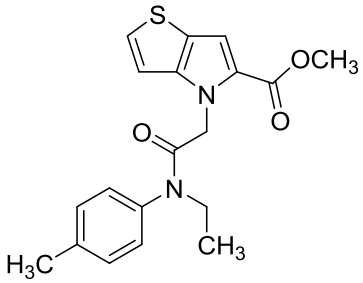


Following general procedure B, 4-(2-(6-methyl-3,4-dihydroquinolin-1(2H)-yl)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (140 mg, 0.40 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (92 mg, 0.47 mmol) to afford the desired product (130 mg, 67%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (d, J = 7.7, 1H), 7.47 (d, J = 7.7, 1H), 7.39 (d, J = 5.3, 1H), 7.19 (d, J = 5.3, 1H), 7.12 (s, 1H), 7.08 - 6.88 (m, 2H), 5.44 (s, 2H), 3.73 - 3.53 (m, 6H), 2.72 (t, J = 6.6, 2H), 2.33 - 2.16 (m, 4H), 2.00 - 1.74 (m, 6H), 1.50 - 1.20 (m, 4H); ESI MS m/z 494 $[M + H]^+$; HPLC 98.9% (AUC), T_R 7.16 min; UV (MeOH) λ_{max} 287 nm, ε 26,027.

Methyl trans-4-(4-(2-(ethyl(p-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**20**)

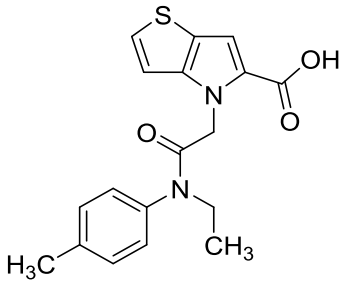


Step 1. Methyl 4-(2-(ethyl(p-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S11**)



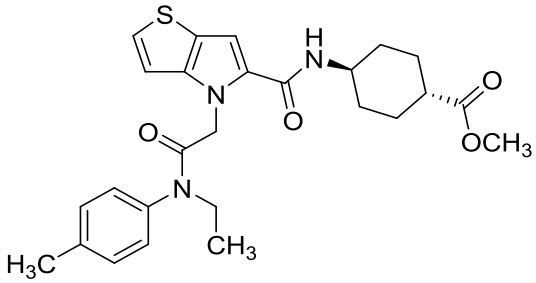
To a solution of 2-(5-(methoxycarbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)acetic acid (100 mg, 0.42 mmol) in DMF (3mL), N-ethyl-4-methylaniline (68 mg, 0.50 mmol), HATU (318 mg, 0.84 mmol), and diisopropylethylamine (162 mg, 1.25 mmol) was added. The reaction was heated to 85°C for 18h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (120 mg, 80%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 - 7.18 (m, 5H), 7.16 (s, 1H), 6.80 (d, *J* = 5.4, 1H), 4.95 (s, 2H), 3.84 (s, 3H), 3.74 (q, *J* = 7.2, 3H), 2.40 (s, 3H), 1.12 (t, *J* = 7.2, 3H); ESI MS m/z 357 $[M + H]^+$.

Step 2. 4-(2-(ethyl(p-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S12**)



Following general procedure A, methyl 4-(2-(ethyl(p-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (120 mg, 0.34 mmol) was reacted with lithium hydroxide (40 mg, 1.68 mmol) to afford crude product (109 mg) as a white solid. ESI MS m/z 343 $[M + H]^+$.

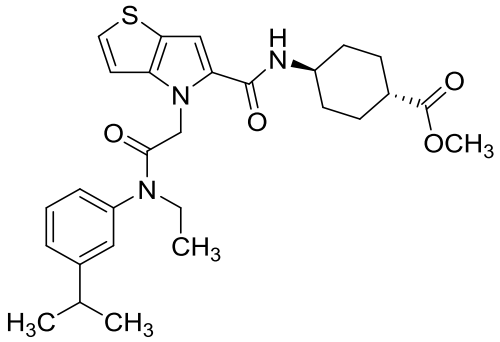
Step 3. methyl trans-4-(4-(2-(ethyl(p-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**20**)



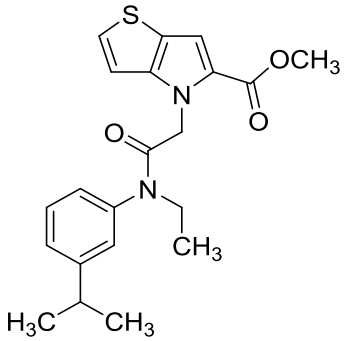
Following general procedure B, 4-(2-(ethyl(p-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (109 mg, 0.32 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (74 mg, 0.38 mmol) to afford the desired product (131 mg, 85%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88 (d, *J* = 7.9, 1H), 7.41 - 7.25 (m, 5H), 7.12 - 7.03 (m, 2H), 4.95 (s, 2H), 3.72 - 3.48 (s, 6H), 2.35 (s, 3H), 2.31 - 2.19 (s, 1H), 2.01 - 1.77 (m, 4H), 1.52 - 1.19

(m, 4H), 1.05 - 0.94 (m, 3H); ESI MS m/z 482 $[M + H]^+$; HPLC 98.0% (AUC), T_R 7.04 min; UV (MeOH) λ_{max} 289 nm, ε 27,490.

methyl trans-4-(4-(2-(ethyl(3-isopropylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**23**)

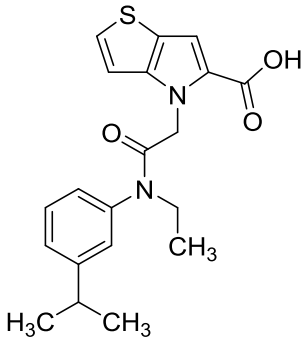


Step 1. methyl 4-(2-(ethyl(3-isopropylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S11**)



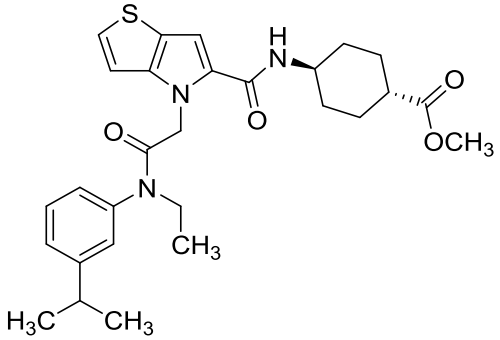
To a solution of 2-(5-(methoxycarbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)acetic acid (110 mg, 0.46 mmol) in DMF (5mL), N-ethyl-3-isopropylaniline (112 mg, 0.69 mmol), HATU (350 mg, 0.92 mmol), and diisopropylethylamine (178 mg, 1.38 mmol) was added. The reaction was heated to 85°C for 1.5h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (147 mg, 83%) as a light orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.34 (m, 1H), 7.31 – 7.23 (m, 2H), 7.20 – 7.11 (m, 3H), 6.80 (d, *J* = 5.4, 1H), 4.96 (s, 2H), 3.83 – 3.71 (m, 5H), 3.05 – 2.87 (m, 1H), 1.35 – 1.25 (m, 6H), 1.18 – 1.09 (m, 3H); ESI MS m/z 385 $[M + H]^+$.

Step 2. 4-(2-(ethyl(3-isopropylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S12**)



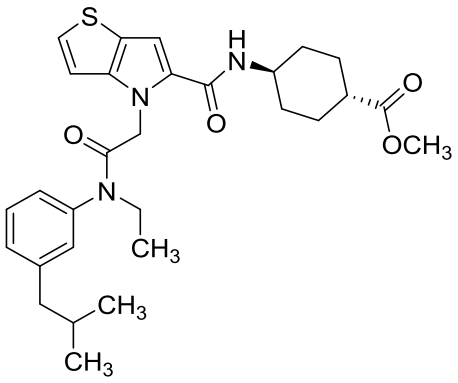
Following general procedure A, methyl 4-(2-(ethyl(3-isopropylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (145 mg, 0.38 mmol) was reacted with lithium hydroxide (45 mg, 1.89 mmol) to afford crude product (134 mg) as a light brown solid. ESI MS m/z 371 $[M + H]^+$.

Step 3. methyl trans-4-(4-(2-(ethyl(3-isopropylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**23**)

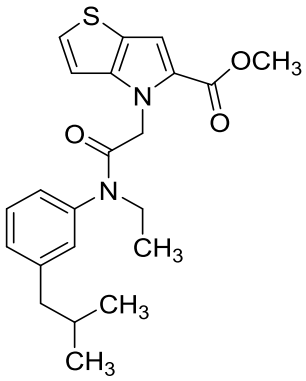


Following general procedure B, 4-(2-(ethyl(3-isopropylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (130 mg, 0.35 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (102 mg, 0..53 mmol) to afford the desired product (135 mg, 75%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 7.9, 1H), 7.48 – 7.33 (m, 3H), 7.32 – 7.19 (m, 2H), 7.12 – 7.03 (m, 2H), 4.93 (s, 2H), 3.73 – 3.52 (m, 6H), 3.04 – 2.87 (m, 1H), 2.33 – 2.18 (m, 1H), 2.00 - 1.78 (m, 4H), 1.51 – 1.18 (m, 10H), 1.08 - 0.95 (m, 3H); ESI MS m/z 510 $[M + H]^+$; HPLC 98.8% (AUC), T_R 7.61 min; UV (MeOH) λ_{max} 289 nm, ε 23,933.

methyl trans-4-(4-(2-(ethyl(3-isobutylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**24**)

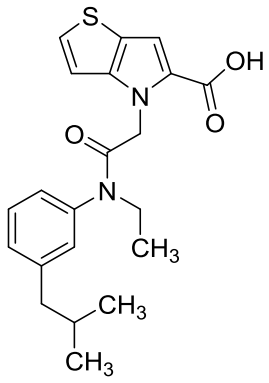


Step 1. methyl 4-(2-(ethyl(3-isobutylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (**S11**)



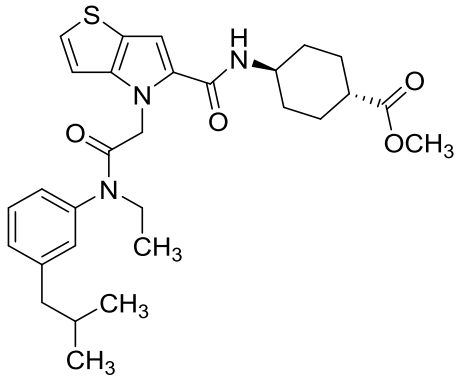
To a solution of 2-(5-(methoxycarbonyl)-4H-thieno[3,2-b]pyrrol-4-yl)acetic acid (100 mg, 0.42 mmol) in DMF (3mL), N-ethyl-3-isobutylaniline (89 mg, 0.50 mmol), HATU (318 mg, 0.84 mmol), and diisopropylethylamine (162 mg, 1.25 mmol) was added. The reaction was heated to 85°C for 4h. The reaction mixture cooled, diluted with ethyl acetate, and washed with water. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (128 mg, 77%) as a thick oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.7, 1H), 7.28 (d, *J* = 5.4, 1H), 7.21 – 7.13 (m, 3H), 7.13 – 7.09 (m, 1H), 6.79 (d, *J* = 4.8, 1H), 4.95 (s, 2H), 3.84 – 3.69 (m, 5H), 2.54 (d, *J* = 7.2, 2H), 1.98 – 1.82 (m, 1H), 1.13 (t, *J* = 7.2, 3H), 0.92 (t, *J* = 6.1, 6H); ESI MS m/z 399 $[M + H]^+$.

Step 2. 4-(2-(ethyl(3-isobutylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (**S12**)



Following general procedure A, methyl 4-(2-(ethyl(3-isobutylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (120 mg, 0.30 mmol) was reacted with lithium hydroxide (36 mg, 1.5 mmol) to afford crude product (125 mg) as a light yellow solid. ESI MS m/z 385 $[M + H]^+$.

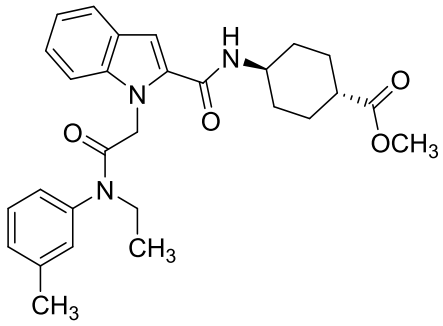
Step 3. methyl trans-4-(4-(2-(ethyl(3-isobutylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**24**)



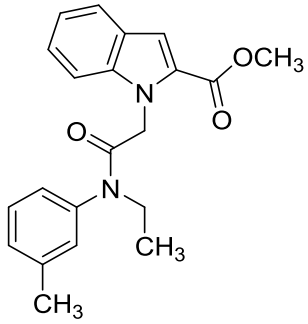
Following general procedure B, 4-(2-(ethyl(3-isobutylphenyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (120 mg, 0.42 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (90 mg, 0.47 mmol) to afford the desired product (130 mg, 80%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, J = 7.9, 1H), 7.47 – 7.13 (m, 5H), 7.12 – 7.04 (m, 2H), 4.93 (s, 2H), 3.72 – 3.52 (m, 6H), 2.57 – 2.46 (m, 2H), 2.32 – 2.19 (m, 1H), 2.00 – 1.79 (m, 5H), 1.50 – 1.20 (m, 4H), 1.06 – 0.94 (m, 3H), 0.86 (d, J = 6.6, 6H); ESI MS m/z 524 $[M + H]^+$; HPLC >99% (AUC), T_R 6.73 min; UV (MeOH) λ_{max} 289 nm, ε 19,115.

TABLE 4 Compounds

Methyl trans-4-(1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-indole-2-carboxamido)cyclohexane-1-carboxylate (**29**)

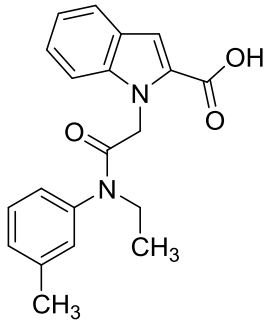


Step 1. Methyl 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-indole-2-carboxylate (**S14**)



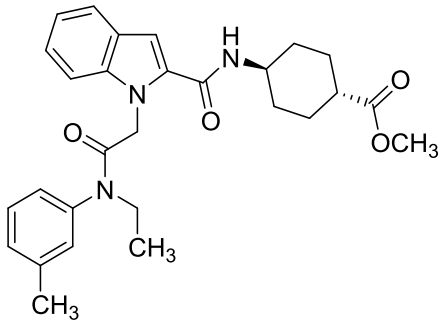
To a solution of methyl 1H-indole-2-carboxylate (100 mg, 0.57 mmol) in acetonitrile (5 mL), potassium carbonate (94 mg, 0.68 mmol), 18-crown-6 ether (7 mg, 0.03 mmol), and 2-chloro-N-ethyl-N-(m-tolyl)acetamide (120 mg, 0.57 mmol) was added. The suspension was heated to 75°C for 18h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (108 mg, 54%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0, 1H), 7.44 - 7.07 (m, 8H), 5.05 (s, 2H), 3.88 (s, 3H), 3.78 - 3.68 (m, 2H), 2.43 (s, 3H), 1.12 (t, J = 7.2, 3H); ESI MS m/z 351 [M + H]+.

Step 2. 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-indole-2-carboxylic acid (**S15**)



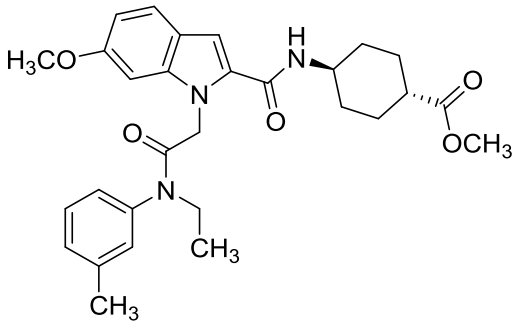
Following general procedure A, methyl 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-indole-2-carboxylate (108 mg, 0.31 mmol) was reacted with lithium hydroxide (37 mg, 1.54 mmol) to afford crude product (103 mg) as a white solid. ESI MS m/z 337 $[M + H]^+$.

Step 3. Methyl trans-4-(1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-indole-2-carboxamido)cyclohexane-1-carboxylate (**29**)

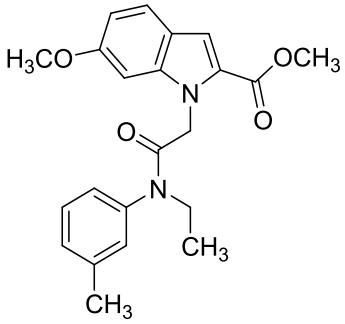


Following general procedure B, 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-indole-2-carboxylic acid (103 mg, 0.31 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (71 mg, 0.37 mmol) to afford the desired product (133 mg, 91%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (d, J = 7.9, 1H), 7.58 (d, J = 7.9, 1H), 7.50 – 7.15 (m, 6H), 7.11 (s, 1H), 7.08 – 7.03 (m, 1H), 5.03 (s, 2H), 3.77 – 3.53 (m, 6H), 2.38 (s, 3H), 2.33 – 2.20 (m, 1H), 2.03 – 1.76 (m, 4H), 1.52 – 1.28 (m, 4H)1.08 – 0.94 (m, 3H); ESI MS m/z 476 $[M + H]^+$; HPLC 99.7 % (AUC), T_R 7.29 min; UV (MeOH) λ_{max} 291 nm, ε 16,809.

Methyl trans-4-(1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6-methoxy-1H-indole-2-carboxamido)cyclohexane-1-carboxylate (**30**)

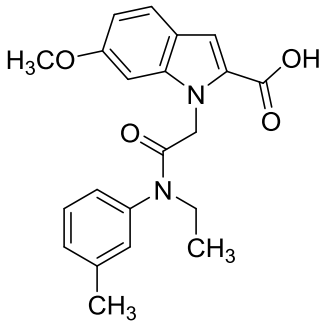


Step 1. Methyl 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6-methoxy-1H-indole-2-carboxylate (**S14**)



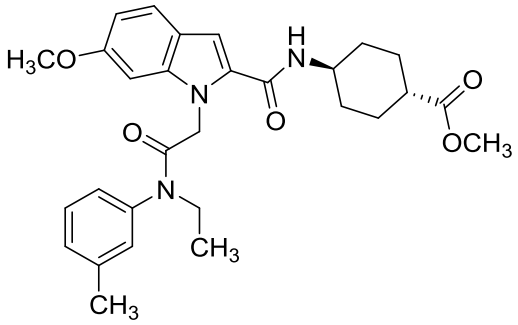
To a solution of methyl 6-methoxy-1H-indole-2-carboxylate (116 mg, 0.57 mmol) in acetonitrile (5 mL), potassium carbonate (94 mg, 0.68 mmol), 18-crown-6 ether (7 mg, 0.03 mmol), and 2-chloro-N-ethyl-N-(m-tolyl)acetamide (120 mg, 0.57 mmol) was added. The suspension was heated to 70°C for 2d. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (155 mg, 72%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.7, 1H), 7.41 - 7.31 (m, 1H), 7.24 - 7.08 (m, 4H), 6.79 (dd, *J* = 2.2, 8.7, 1H), 6.62 - 6.55 (m, 1H), 5.01 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.81 - 3.68 (m, 2H), 2.42 (s, 3H), 1.18 - 1.09 (m, 3H); ESI MS m/z 381 [M + H]+.

Step 2. 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6-methoxy-1H-indole-2-carboxylic acid (**S15**)



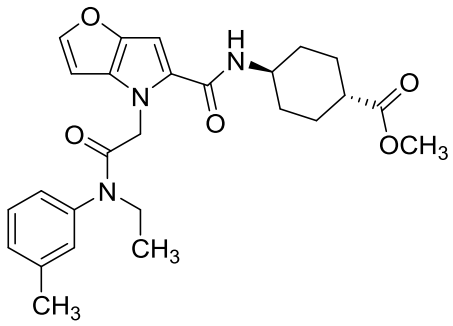
Following general procedure A, methyl 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6-methoxy-1H-indole-2-carboxylate (150 mg, 0.39 mmol) was reacted with lithium hydroxide (47 mg, 1.97 mmol) to afford crude product (150 mg) as a white solid. ESI MS m/z 367 $[M + H]^+$.

Step 3. Methyl trans-4-(1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6-methoxy-1H-indole-2-carboxamido)cyclohexane-1-carboxylate (**30**)

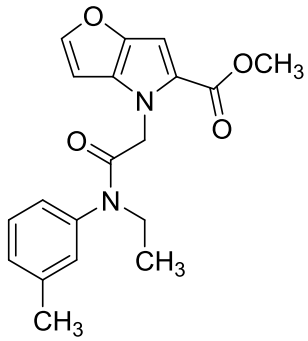


Following general procedure B, 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6-methoxy-1H-indole-2-carboxylic acid (150 mg, 0.41 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (95 mg, 0.49 mmol) to afford the desired product (163 mg, 78%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.09 (d, J = 8.0, 1H), 7.52 – 7.15 (m, 5H), 7.03 (s, 1H), 6.80 (s, 1H), 6.71 (dd, J = 2.2, 8.6, 1H), 4.99 (s, 2H), 3.79 (s, 3H), 3.74 – 3.55 (m, 7H), 2.37 (s, 3H), 2.34 – 2.20 (m, 1H), 2.02 – 1.80 (m, 4H), 1.51 – 1.25 (m, 4H), 1.10 – 0.93 (s, 3H); ESI MS m/z 507 $[M + H]^+$; HPLC 99.5 % (AUC), T_R 7.11 min; UV (MeOH) λ_{max} 311 nm, ε 19,752.

Methyl trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-furo[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**31**)

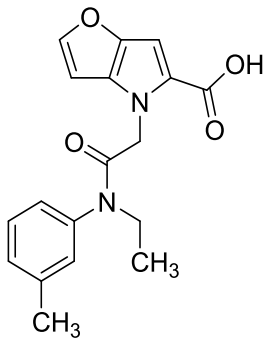


Step 1. Methyl 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-furo[3,2-b]pyrrole-5-carboxylate (**S14**)



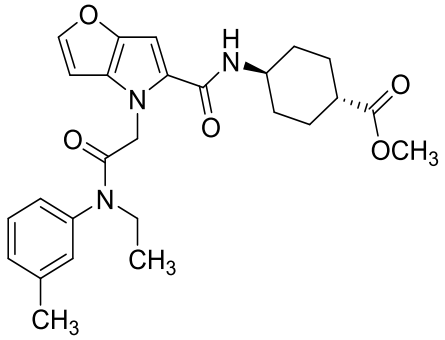
To a solution of methyl 4H-furo[3,2-b]pyrrole-5-carboxylate (94 mg, 0.57 mmol) in acetonitrile (5 mL), potassium carbonate (94 mg, 0.68 mmol), 18-crown-6 ether (7 mg, 0.03 mmol), and 2-chloro-N-ethyl-N-(m-tolyl)acetamide (120 mg, 0.57 mmol) was added. The suspension was heated to 70°C for 2d. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (166 mg, 86%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 2.2, 1H), 7.35 (t, *J* = 7.7, 1H), 7.24 - 7.17 (m, 1H), 7.16 - 7.07 (m, 2H), 6.81 - 6.78 (m, 1H), 6.38 - 6.36 (m, 1H), 4.86 (s, 2H), 3.85 - 3.67 (m, 5H), 2.40 (s, 3H), 1.12 (t, *J* = 7.2, 3H); ESI MS m/z 341 [M + H]+.

Step 2. 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-furo[3,2-b]pyrrole-5-carboxylic acid (**S15**)



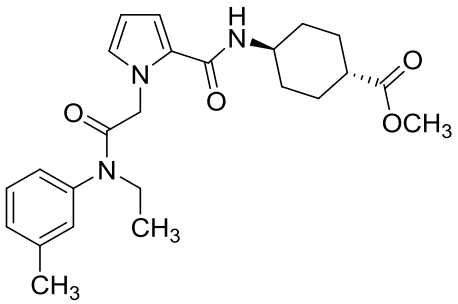
Following general procedure A, methyl 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-furo[3,2-b]pyrrole-5-carboxylate (160 mg, 0.47 mmol) was reacted with lithium hydroxide (56 mg, 2.35 mmol) to afford crude product (150 mg) as a white solid. ESI MS m/z 327 $[M + H]^+$.

Step 3. Methyl trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-furo[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**31**)

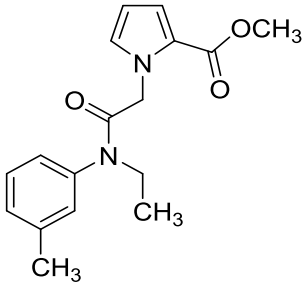


Following general procedure B, 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-furo[3,2-b]pyrrole-5-carboxylic acid (150 mg, 0.46 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (106 mg, 0.55 mmol) to afford the desired product (178 mg, 83%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70 (d, J = 7.9, 1H), 7.62 (d, J = 2.2, 1H), 7.45 – 7.33 (m, 1H), 7.31 – 7.15 (m, 3H), 6.81 (s, 1H), 6.64 (d, J = 2.2, 1H), 4.87 (s, 2H), 3.71 - 3.50 (m, 7H), 2.35 (s, 3H), 2.31 – 2.18 (m, 1H), 1.98 – 1.77 (m, 4H), 1.50 – 1.21 (m, 4H), 1.09 - 0.92 (s, 3H); ESI MS m/z 467 $[M + H]^+$; HPLC 99.6 % (AUC), T_R 6.55 min; UV (MeOH) λ_{max} 294 nm, ε 25,926.

methyl trans-4-(1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-pyrrole-2-carboxamido)cyclohexane-1-carboxylate (**28**)

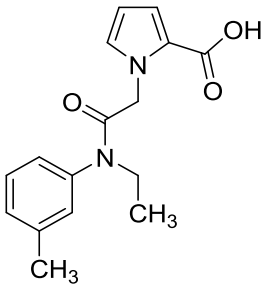


Step 1. methyl 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-pyrrole-2-carboxylate (**S14**)



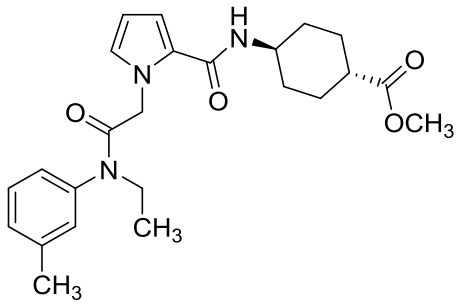
To a solution of methyl 1H-pyrrole-2-carboxylate (295 mg, 2.36 mmol) in acetonitrile (20 mL), potassium carbonate (391 mg, 2.83 mmol), 18-crown-6 ether (31 mg, 0.12 mmol), and 2-chloro-N-ethyl-N-(m-tolyl)acetamide (500 mg, 2.36 mmol) was added. The suspension was heated to 75°C for 18h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (530 mg, 75%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.5, 1H), 7.24 – 7.10 (m, 3H), 6.93 (dd, *J* = 1.8, 3.9, 1H), 6.78 – 6.70 (m, 1H), 6.13 (dd, *J* = 2.6, 3.9, 1H), 4.77 (s, 2H), 3.85 – 3.61 (m, 6H), 2.41 (s, 3H), 1.13 (t, *J* = 7.2, 3H); ESI MS m/z 301 [M + H]+.

Step 2. 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-pyrrole-2-carboxylic acid (**S15**)



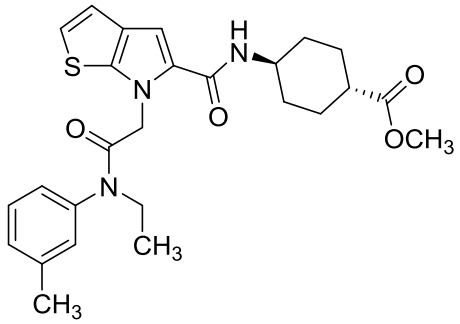
Following general procedure A, methyl 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-pyrrole-2-carboxylate (530 mg, 1.76 mmol) was reacted with lithium hydroxide (211 mg, 8.82 mmol) to afford crude product (475 mg) as a white solid. ESI MS m/z 287 $[M + H]^+$.

Step 3. methyl trans-4-(1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-pyrrole-2-carboxamido)cyclohexane-1-carboxylate (**28**)

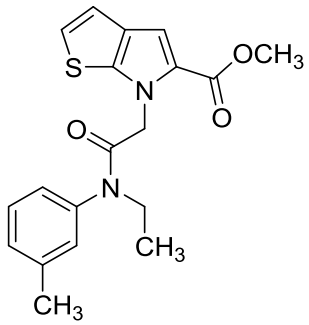


Following general procedure B, 1-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-1H-pyrrole-2-carboxylic acid (475 mg, 1.66 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (482 mg, 2.49 mmol) to afford the desired product (505 mg, 71%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.62 (d, J = 8.0, 1H), 7.41 – 7.30 (m, 1H), 7.26 – 7.12 (m, 3H), 6.82 – 6.67 (m, 2H), 5.94 (dd, J = 2.6, 3.8, 1H), 4.77 (s, 2H), 3.67 – 3.54 (m, 6H), 2.34 (s, 3H), 2.29 – 2.18 (s, 1H), 1.98 – 1.74 (m, 4H), 1.48 – 1.26 (m, 4H), 1.09 – 0.92 (m, 3H); ESI MS m/z 426 $[M + H]^+$; HPLC 97.5 % (AUC), T_R 6.05 min; UV (MeOH) λ_{max} 264 nm, ε 11,978.

methyl trans-4-(6-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6H-thieno[2,3-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**32**)

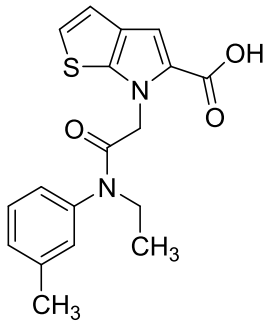


Step1. methyl 6-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6H-thieno[2,3-b]pyrrole-5-carboxylate (**S14**)



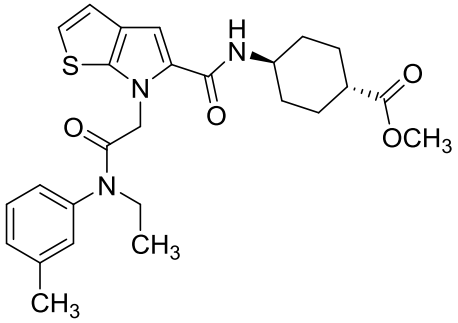
To a solution of methyl 6H-thieno[2,3-b]pyrrole-5-carboxylate (171 mg, 0.94 mmol) in acetonitrile (10 mL), potassium carbonate (157 mg, 1.1 mmol), 18-crown-6 ether (13 mg, 0.047 mmol), and 2-chloro-N-ethyl-N-(m-tolyl)acetamide (200 mg, 0.94 mmol) was added. The suspension was heated to 75°C for 18h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (260 mg, 77%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.6, 1H), 7.25 – 7.09 (m, 4H), 6.99 – 6.95 (m, 1H), 6.91 – 6.85 (m, 1H), 4.93 (s, 2H), 3.92 – 3.64 (m, 5H), 2.43 (s, 3H), 1.14 (t, *J* = 7.2, 4H); ESI MS m/z 357 [M + H]+.

Step 2. 6-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6H-thieno[2,3-b]pyrrole-5-carboxylic acid (**S15**)



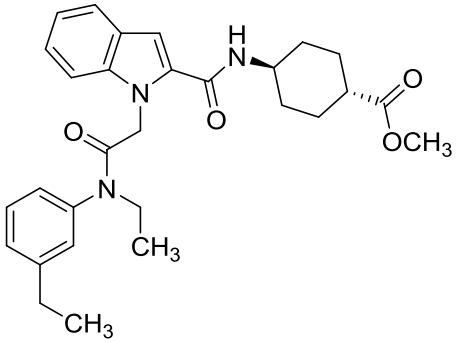
Following general procedure A, methyl 6-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6H-thieno[2,3-b]pyrrole-5-carboxylate (260 mg, 0.73 mmol) was reacted with lithium hydroxide (87 mg, 3.6 mmol) to afford crude product (240 mg) as a white solid. ESI MS m/z 342 $[M + H]^+$.

Step 3. methyl trans-4-(6-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6H-thieno[2,3-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (**32**)

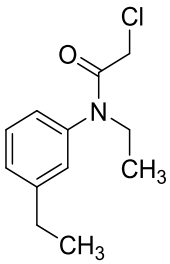


Following general procedure B, 6-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-6H-thieno[2,3-b]pyrrole-5-carboxylic acid (240 mg, 0.70 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (203 mg, 1.05 mmol) to afford the desired product (320 mg, 95%) as a light yellow foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88 (d, J = 8.0, 1H), 7.44 – 7.33 (m, 1H), 7.28 – 7.14 (m, 3H), 7.11 – 6.95 (m, 3H), 4.90 (s, 2H), 3.72 – 3.52 (m, 6H), 2.36 (s, 3H), 2.25 (s, 1H), 2.02 – 1.76 (m, 4H), 1.51 – 1.20 (m, 4H), 1.00 (t, J = 6.9, 3H); ESI MS m/z 482 $[M + H]^+$; HPLC >99 % (AUC), T_R 7.01 min; UV (MeOH) λ_{max} 287 nm, ε 12,894.

methyl trans-4-(1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxamido)cyclohexane-1-carboxylate (**33**)



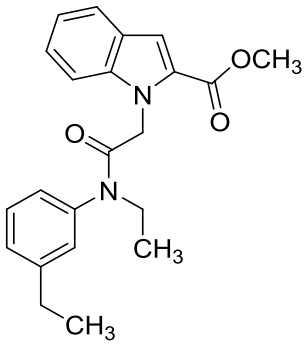
Step 1. 2-chloro-N-ethyl-N-(3-ethylphenyl)acetamide



To a solution of *N*-ethyl-3-ethylaniline (0.97g, 6.50mmol) in ethyl acetate (30mL), water (10 mL) was added. The biphasic solution was cooled to 0°C, and potassium hydroxide (1.09g,

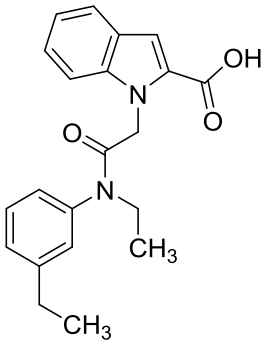
19.5mmol) added in one motion. 2-Chloroacetyl chloride (1.10g, 0.76mL, 9.75mmol) was added dropwise over 10min. The mixture was stirred for 1h, diluted with water, and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated to afford crude product (1.54 g) as a mobile oil. ESI MS m/z 226 $[M + H]^+$.

Step 2. methyl 1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxylate (**S14**)



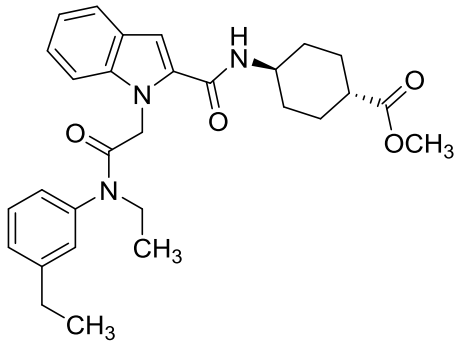
To a solution of methyl 1H-indole-2-carboxylate (582 mg, 3.3 mmol) in acetonitrile (20 mL), potassium carbonate (551 mg, 4.0 mmol), 18-crown-6 ether (44 mg, 0.17 mmol), and 2-chloro-N-ethyl-N-(3-ethylphenyl)acetamide (750 mg, 3.3 mmol) was added. The suspension was heated to 75°C for 18h. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, heptane/ethyl acetate) to afford the desired product (0.74 g, 61%) as a light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1, 1H), 7.50 – 7.07 (m, 8H), 5.06 (s, 2H), 3.87 (s, 3H), 3.82 – 3.69 (m, 4H), 2.78 – 2.63 (m, 2H), 1.35 – 1.24 (m, 3H), 1.18 – 1.06 (m, 3H); ESI MS m/z 365 [M + H]+.

Step 3. 1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxylic acid (**S15**)



Following general procedure A, methyl 1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxylate (740 mg, 2.0 mmol) was reacted with lithium hydroxide (243 mg, 10.1 mmol) to afford crude product (690 mg) as a white solid. ESI MS m/z 350 $[M + H]^+$.

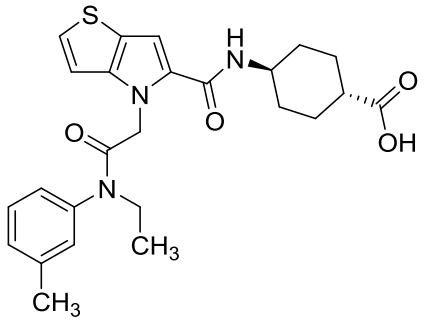
Step 4. methyl trans-4-(1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxamido)cyclohexane-1-carboxylate (**33**)



Following general procedure B, 1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxylic acid (690 mg, 1.97 mmol) was reacted with methyl trans-4-aminocyclohexane-1-carboxylate (457 mg, 2.36 mmol) to afford the desired product (760 mg, 79%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.20 (d, J = 7.9, 1H), 7.58 (d, J = 7.9, 1H), 7.51 – 7.13 (m, 6H), 7.13 – 7.02 (m, 2H), 5.02 (s, 2H), 3.77 – 3.54 (m, 6H), 2.69 (d, J = 7.6, 2H), 2.33 - 2.21 (m, 1H), 2.02 – 1.81 (m, 4H), 1.52 – 1.30 (m, 4H), 1.23 (t, J = 7.6, 3H), 1.08 – 0.95 (m, 3H); ESI MS m/z 490 $[M + H]^+$; HPLC >99 % (AUC), T_R 7.56 min; UV (MeOH) λ_{max} 291 nm, ε 15,737.

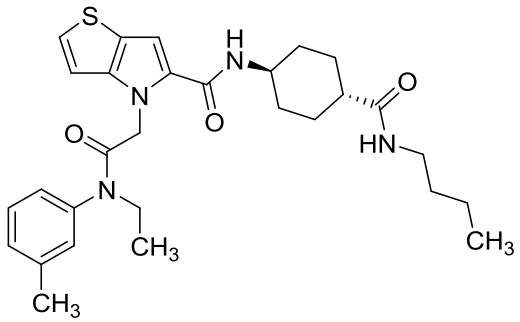
TABLE 5 Compounds

trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (JRW-0034)



Following general procedure A, trans-methyl-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylate (55mg, 0.11mmol) was reacted with lithium hydroxide (14mg, 0.57mmol) to afford the desired product (50mg, 93%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.99 (s, 1H), 7.92 - 7.84 (m, 1H), 7.44 - 7.19 (m, 5H), 7.12 - 7.04 (m, 2H), 4.97 (s, 2H), 3.73 - 3.52 (m, 3H), 2.36 (s, 3H), 2.22 - 2.06 (m, 1H), 1.98 - 1.76 (m, 4H), 1.47 - 1.21 (m, 4H), 1.08 - 0.93 (m, 3H); ESI MS m/z 468 $[M + H]^+$; HPLC 99.4 % (AUC), T_R 5.81 min; UV (MeOH) λ_{max} 290 nm, ε 26,502.

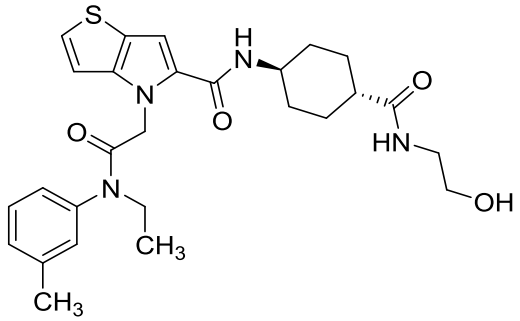
N-(trans-4-(butylcarbamoyl)cyclohexyl)-4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**34**)



Following general procedure B, trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (50mg, 0.11mmol) was reacted with butylamine (9mg, 0.13mmol) to afford the desired product (50mg, 89%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.82 (d, J = 8.1, 1H), 7.65 - 7.57 (m, 1H), 7.46 - 7.11 (m, 5H), 7.06 - 6.98 (m, 2H), 4.91 (s, 2H), 3.66 - 3.45 (m, 3H), 2.96 (q, J = 6.0 Hz, 2H), 2.32 (s, 3H), 2.05

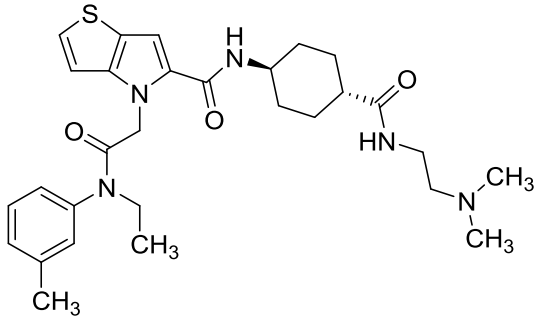
- 1.92 (m, 1H), 1.85 - 1.60 (m, 4H), 1.50 - 1.10 (m, 9H), 1.02 - 0.90 (m, 3H), 0.80 (t, *J* = 7.2, 3H); ESI MS m/z 523 $[M + H]^+$; HPLC 99.6 % (AUC), T_R 6.52 min; UV (MeOH) λ_{max} 288 nm, ε 28,364.

4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-(trans-4-((2-hydroxyethyl)carbamoyl)cyclohexyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**35**)



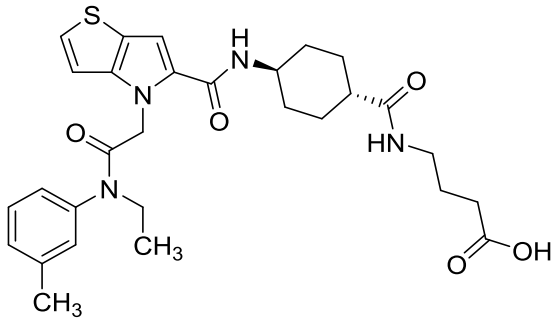
Following general procedure B, trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (50mg, 0.11mmol) was reacted with ethanolamine (7mg, 0.13mmol) to afford the desired product (48mg, 88%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (d, *J* = 7.8, 1H), 7.69 (t, *J* = 5.4, 1H), 7.45 - 7.18 (m, 5H), 7.13 - 7.04 (m, 2H), 4.96 (s, 2H), 4.60 (t, *J* = 5.5, 1H), 3.75 - 3.54 (m, 3H), 3.36 (q, *J* = 5.9, 2H), 3.08 (q, *J* = 5.9, 2H), 2.37 (s, 3H), 2.14 - 2.00 (m, 1H), 1.90 - 1.69 (m, 4H), 1.52 - 1.10 (m, 4H), 1.08 - 0.94 (m, 3H); ESI MS m/z 511 $[M + H]^+$; HPLC 99.7 % (AUC), T_R 6.52 min; UV (MeOH) λ_{max} 289 nm, ε 24,966.

N-(trans-4-((2-(dimethylamino)ethyl)carbamoyl)cyclohexyl)-4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**36**)

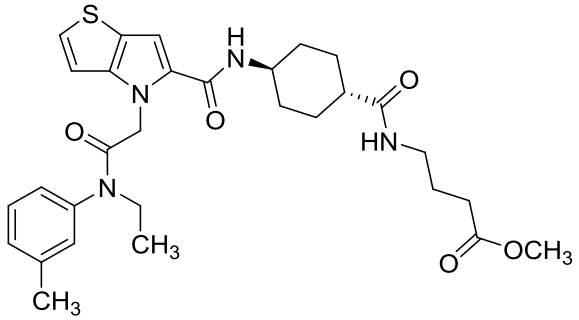


Following general procedure B, trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (50mg, 0.11mmol) was reacted with ethanolamine (18mg, 0.21mmol) to afford the desired product (45mg, 78%) as a light red solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (d, J = 8.1, 1H), 7.62 (t, J = 5.5, 1H), 7.45 - 7.35 (m, 2H), 7.33 - 7.17 (m, 3H), 7.12 - 7.05 (m, 2H), 4.97 (s, 2H), 3.73 - 3.54 (m, 3H), 3.10 (q, J = 6.4, 2H), 2.37 (s, 3H), 2.24 (t, J = 6.4, 2H), 2.15 - 2.00 (m, 7H), 1.88 - 1.691.78 (m, 4H), 1.53 - 1.19 (m, 4H), 1.08 - 0.94 (m, 3H); ESI MS m/z 538 $[M + H]^+$; HPLC 99.4 % (AUC), T_R 4.31 min; UV (MeOH) λ_{max} 289 nm, ε 29,980.

4-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)butanoic acid (**37**)

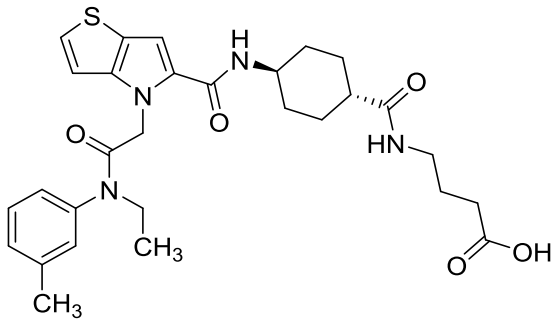


Step 1. methyl 4-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)butanoate



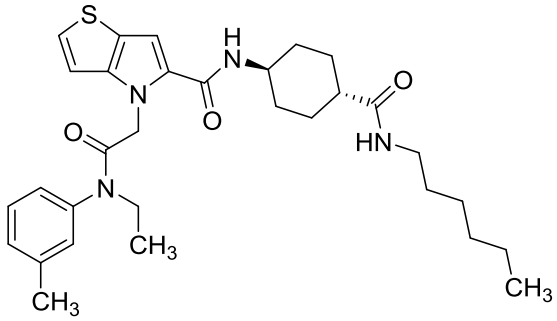
Following general procedure B, trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (50mg, 0.11mmol) was reacted with methyl 4-aminobutanoate (15mg, 0.13mmol) to afford crude product (80mg) as a white glass. ESI MS m/z 567 $[M + H]^+$.

Step 2. 4-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)butanoic acid (**37**)



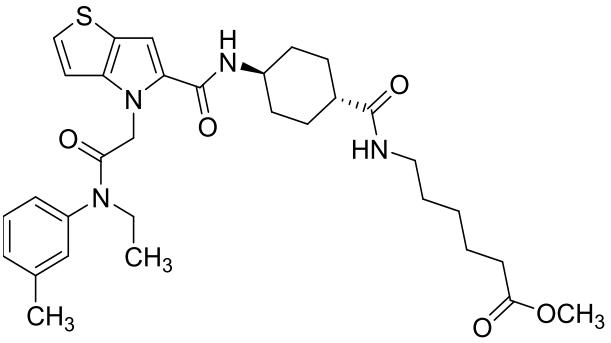
Following general procedure A, methyl 4-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)butanoate (60mg, 0.10mmol) was reacted with lithium hydroxide (13mg, 0.53mmol) to afford the desired product (55mg, 93%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.97 (s, 1H), 7.82 (d, J = 7.7, 1H), 7.66 (t, J = 5.4, 1H), 7.40 - 7.29 (m, 2H), 7.27 - 7.13 (m, 3H), 7.07 - 7.00 (m, 2H), 4.92 (s, 2H), 3.68 - 3.48 (m, 3H), 3.03 - 2.92 (m, 2H), 2.32 (s, 3H), 2.14 (t, J = 7.3, 2H), 2.06 - 1.93 (m, 1H), 1.85 - 1.64 (m, 4H), 1.62 - 1.47 (m, 2H), 1.47 - 1.15 (m, 4H), 1.05 - 0.88 (m, 3H); ESI MS m/z 553 $[M + H]^+$; HPLC >99 % (AUC), T_R 5.17 min; UV (MeOH) λ_{max} 289 nm, ε 24,710.

4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-(trans-4-(hexylcarbamoyl)cyclohexyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**38**)



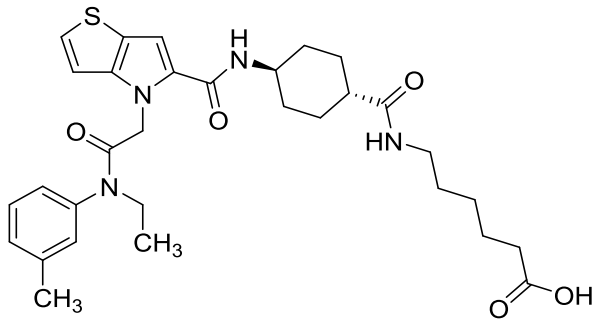
Following general procedure B, trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (50mg, 0.11mmol) was reacted with hexylamine (13mg, 0.13mmol) to afford the desired product (50mg, 85%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88 (d, J = 8.1, 1H), 7.67 (t, J = 5.6, 1H), 7.45 - 7.34 (m, 2H), 7.33 - 7.18 (m, 3H), 7.12 - 7.04 (m, 2H), 4.96 (s, 2H), 3.72 - 3.52 (m, 3H), 2.99 (dd, J = 6.5, 12.6, 2H), 2.36 (s, 3H), 2.10 - 1.96 (m, 1H), 1.88 - 1.68 (m, 4H), 1.52 - 1.16 (m, 12H), 1.08 - 0.92 (m, 3H), 0.88 - 0.78 (m, 3H); ESI MS m/z 551 $[M + H]^+$; HPLC 99.4 % (AUC), T_R 6.54 min; UV (EtOH) λ_{max} 292 nm, ε 29,535.

methyl 6-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)hexanoate



Following general procedure B, trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (50mg, 0.11mmol) was reacted with methyl 6-aminohexanoate (23mg, 0.13mmol) to afford the desired product (60mg, 94%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.88 (d, J = 8.1, 1H), 7.68 (t, J = 5.6, 1H), 7.44 - 7.34 (m, 2H), 7.32 - 7.17 (m, 3H), 7.12 - 7.03 (m, 2H), 4.95 (s, 2H), 3.73 - 3.50 (m, 6H), 2.98 (dd, J = 6.6, 12.5, 2H), 2.36 (s, 3H), 2.26 (t, J = 7.4, 2H), 2.08 - 1.95 (m, 1H), 1.87 - 1.67 (m, 4H), 1.57 - 1.15 (m, 10H), 1.05 - 0.93 (m, 3H); ESI MS m/z 595 $[M + H]^+$; HPLC 99.4 % (AUC), T_R 6.24 min; UV (EtOH) λ_{max} 288 nm, ε 26,555.

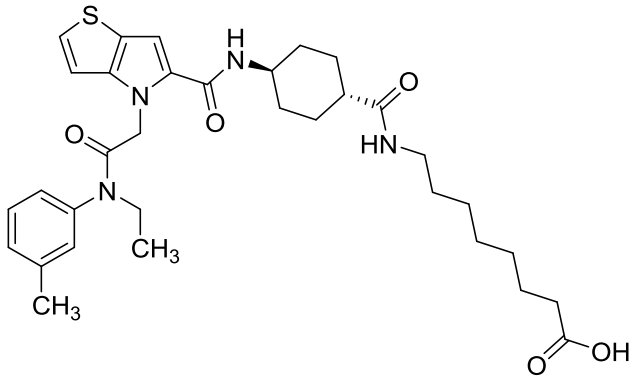
6-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)hexanoic acid (**41**)



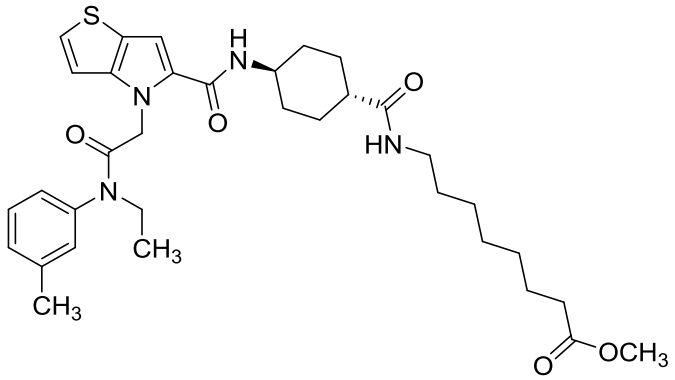
Following general procedure A, methyl 6-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)hexanoate (53mg, 0.089mmol) was reacted with lithium hydroxide (10mg, 0.44mmol) to afford the desired product (50mg, 96%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.98 (s, 1H), 7.88 (d, J = 7.6, 1H), 7.72 - 7.63 (m, 1H), 7.44 - 7.33 (m, 2H), 7.32 - 7.18 (m, 3H), 7.12 - 7.04 (m, 2H), 4.95 (s, 2H),

3.72 - 3.52 (m, 3H), 3.04 - 2.93 (m, 2H), 2.36 (s, 3H), 2.16 (t, *J* = 7.1, 2H), 2.10 - 1.93 (m, 1H), 1.88 - 1.67 (m, 4H), 1.55 - 1.10 (m, 10H), 1.08 - 0.92 (m, 3H); ESI MS m/z 581 $[M + H]^+$; HPLC >99 % (AUC), T_R 5.49 min; UV (EtOH) λ_{max} 288 nm, ε 23,738.

8-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)octanoic acid (**42**)

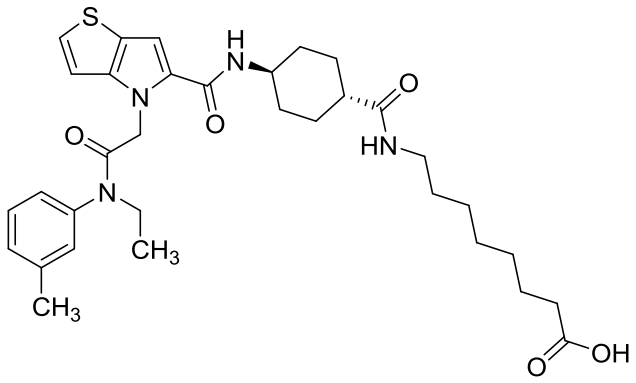


Step 1. methyl 8-((1r,4r)-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)octanoate



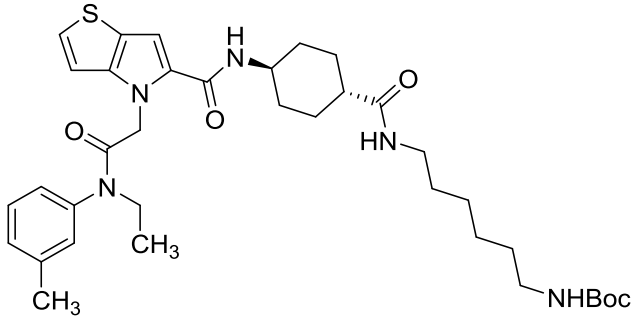
Following general procedure B, trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (50mg, 0.11mmol) was reacted with methyl 8-aminooctanoate (27mg, 0.13mmol) to afford the desired product (55mg, 82%) as an oil. ESI MS m/z 623 $[M + H]^+$.

Step 2. 8-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)octanoic acid (**42**)



Following general procedure A, methyl 8-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)octanoate (50mg, 0.080mmol) was reacted with lithium hydroxide (9mg, 0.40mmol) to afford the desired product (45mg, 92%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 7.87 (d, J = 7.8, 1H), 7.70 - 7.61 (m, 1H), 7.45 - 7.14 (m, 5H), 7.10 - 7.03 (m, 2H), 4.96 (s, 2H), 3.72 - 3.54 (m, 3H), 3.05 - 2.93 (m, 2H), 2.37 (s, 3H), 2.22 - 2.12 (m, 2H), 2.10 - 1.98 (m, 1H), 1.91 - 1.66 (m, 4H), 1.55 - 1.10 (m, 14H), 1.08 - 0.93 (m, 3H); ESI MS m/z 609 $[M + H]^+$; HPLC 96.9 % (AUC), T_R 4.97 min; UV (EtOH) λ_{max} 289 nm, ε 25,824.

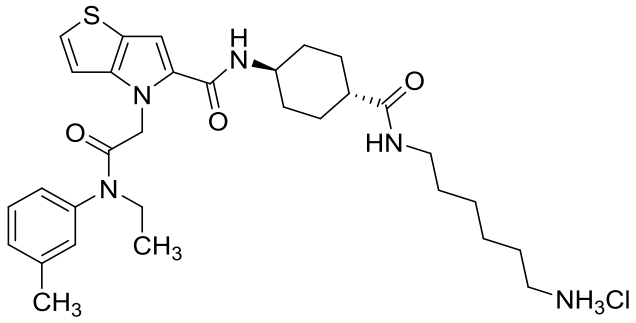
tert-butyl (6-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)hexyl)carbamate



Following general procedure B, trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (115mg, 0.25mmol) was reacted with tert-butyl (6-aminohexyl)carbamate (80mg, 0.37mmol) to afford the desired product (150mg, 91%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (d, J = 8.0, 1H), 7.65 (t, J = 5.1, 1H), 7.45 - 7.33 (m, 2H), 7.32 - 7.17 (m, 3H), 7.12 - 7.06 (m, 2H), 6.77 - 6.68 (m, 1H), 4.96 (s, 2H), 3.72 - 3.53 (m, 3H), 3.03 - 2.93 (m, 2H), 2.87 (dd, J = 6.0, 12.6, 2H), 2.36 (s, 3H), 2.12 -

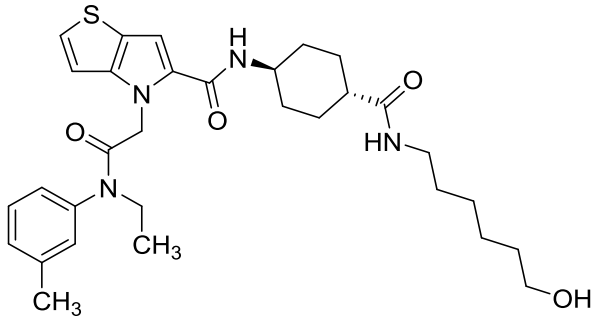
1.96 (m, 1H), 1.88 - 1.68 (m, 4H), 1.51 - 1.16 (m, 21H), 1.06 - 0.93 (m, 3H); ESI MS m/z 666 $[M + H]^+$; HPLC 99.7 % (AUC), T_R 4.11 min; UV (EtOH) λ_{max} 288 nm, ε 21,608.

N-(trans-4-((6-aminohexyl)carbamoyl)cyclohexyl)-4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide hydrochloride (**40**)



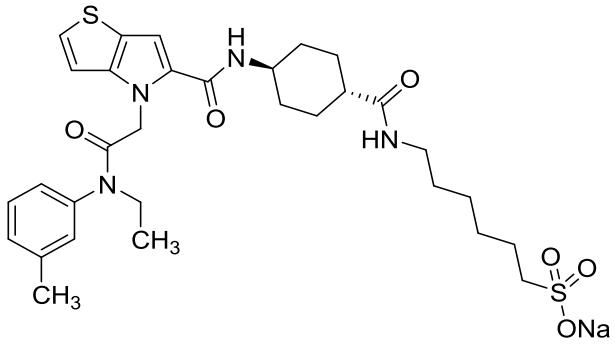
To a solution of tert-butyl (6-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)hexyl)carbamate (100mg, 0.15mmol) in dichloromethane (5mL), trifluoroacetic acid (1mL) was added. The reaction stirred at RT for 1h. The mixture was diluted with toluene and concentrated under vacuum (3X). The residue was dissolved in methanol and HCl (2mL, 1M in ether) was added. The solution was evaporated to afford the desired product (95mg, quant.) of white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 - 7.68 (m, 5H), 7.45 - 7.34 (m, 2H), 7.33 - 7.15 (m, 3H), 7.12 - 7.05 (m, 2H), 4.97 (s, 2H), 3.74 - 3.51 (m, 3H), 3.01 (dd, *J* = 6.5, 12.5, 2H), 2.79 - 2.66 (m, 2H), 2.36 (s, 3H), 2.11 - 1.97 (m, 1H), 1.88 - 1.68 (m, 4H), 1.59 - 1.17 (m, 12H), 1.02 - 0.94 (m, 3H); ESI MS m/z 566 $[M + H]^+$; HPLC 99.0 % (AUC), T_R 4.47 min; UV (MeOH) λ_{max} 289 nm, ε 23,213.

4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-(trans-4-((6-hydroxyhexyl)carbamoyl)cyclohexyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**39**)

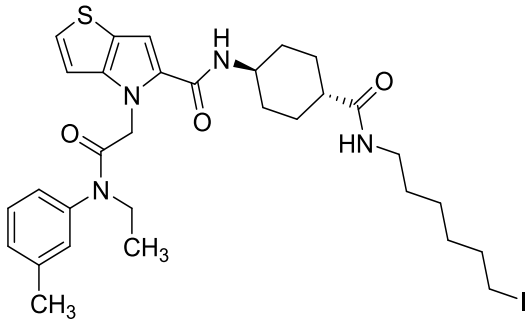


Following general procedure B, trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxylic acid (150mg, 0.32mmol) was reacted with 6-aminohexan-1-ol (56mg, 0.48mmol) to afford the desired product (160mg, 88%) as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (d, J = 7.4, 1H), 7.73 - 7.59 (s, 1H), 7.48 - 7.15 (m, 5H), 7.13 - 7.02 (m, 2H), 4.96 (s, 2H), 4.35 - 4.23 (m, 1H), 3.73 - 3.50 (m, 3H), 3.43 - 3.30 (m, 2H), 3.05 - 2.94 (m, 2H), 2.37 (s, 3H), 2.10 - 1.95 (m, 1H), 1.90 - 1.65 (m, 4H), 1.55 - 1.13 (m, 12H), 1.09 - 0.90 (s, 3H); ESI MS m/z 567 $[M + H]^+$; HPLC >99 % (AUC), T_R 5.48 min; UV (MeOH) λ_{max} 289 nm, ε 26,356.

sodium 6-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)hexane-1-sulfonate (**43**)



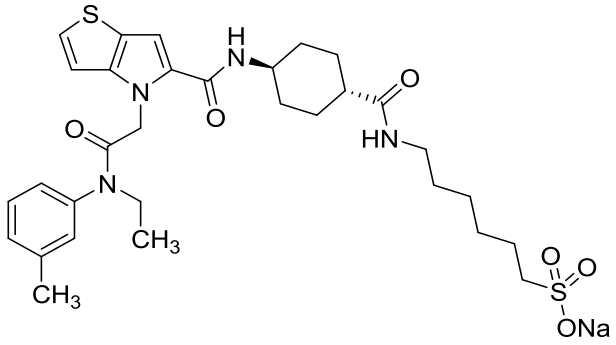
Step 1. 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-(trans-4-((6-iodohexyl)carbamoyl)cyclohexyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide



To a solution of imidazole (36 mg, 0.53 mmol), triphenylphosphine (138 mg, 0.53 mmol), and iodine (134 mg, 0.53 mmol), 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-(trans-4-((6-hydroxyhexyl)carbamoyl)cyclohexyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (100 mg, 0.18 mmol)dissolved in THF (5 mL) was added. The solution stirred for 1h at RT. The reaction was diluted with ethyl acetate and quenched with a 10% $Na_2S_2O_3$ solution. The mixture was diluted

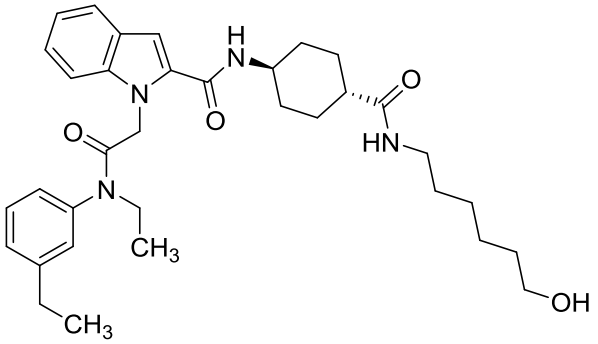
with ethyl acetate and water, and the layers were separated. The organic layer was washed with a 10% $Na_2S_2O_3$ solution and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue was partially purified by column chromatography (silica, dichloromethane / methanol) to afford crude product as a white solid. ESI MS m/z 677 [M + H]+.

Step 2. sodium 6-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexane-1-carboxamido)hexane-1-sulfonate (**43**)

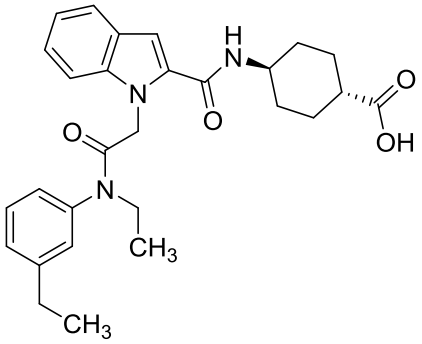


To a solution of 4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-N-(trans-4-((6-iodohexyl)carbamoyl)cyclohexyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (0.18 mmol) in ethanol (5mL), sodium sulfite (66 mg, 0.53 mmol) and water (3 mL)was added. The mixture was heated to 75°C for 2h. The reaction was concentrated, and the residue was purified by column chromatography (silica, dichloromethane / methanol) to afford the desired product (100 mg, 90%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.87 (d, J = 8.0, 1H), 7.67 (t, J = 5.5, 1H), 7.49 - 7.17 (m, 5H), 7.13 - 7.05 (m, 2H), 4.97 (s, 2H), 3.72 - 3.54 (m, 3H), 3.05 - 2.93 (m, 2H), 2.40 - 2.28 (m, 5H), 2.12 - 1.96 (m, 1H), 1.88 - 1.68 (m, 4H), 1.62 - 1.14 (m, 12H), 1.05 - 0.93 (m, 3H); ESI MS m/z 631 $[M + H]^+$; HPLC >99 % (AUC), T_R 4.56 min; UV (MeOH) λ_{max} 288 nm, ε 21,072.

1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-N-(trans-4-((6-hydroxyhexyl)carbamoyl)cyclohexyl)-1H-indole-2-carboxamide (**44**)

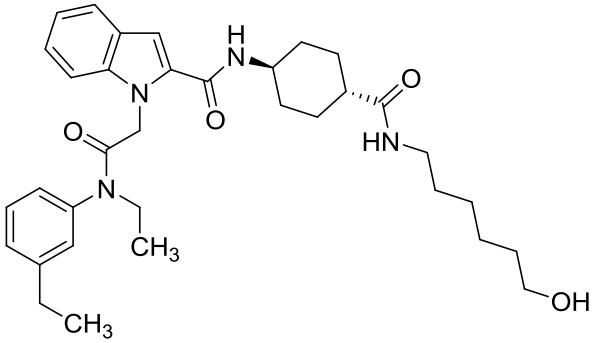


Step 1. trans-4-(1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxamido)cyclohexane-1-carboxylic acid



Following general procedure A, methyl trans-4-(1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxamido)cyclohexane-1-carboxylate (720 mg, 1.47 mmol) was reacted with lithium hydroxide (105 mg, 4.4 mmol) to afford crude product (680 mg) as a white solid. ESI MS m/z 476 $[M + H]^+$.

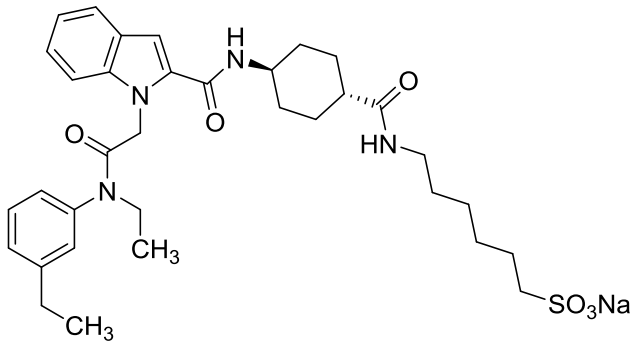
Step 2. 1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-N-(trans-4-((6-hydroxyhexyl)carbamoyl)cyclohexyl)-1H-indole-2-carboxamide (**44**)



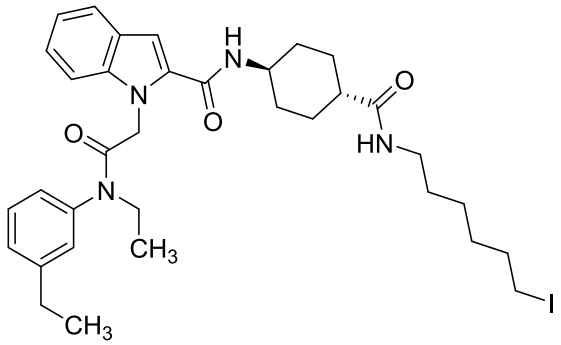
Following general procedure B, trans-4-(1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxamido)cyclohexane-1-carboxylic acid (200 mg, 0.42 mmol) was reacted with 6-

aminohexan-1-ol (74 mg, 0.63 mmol) to afford the desired product (218 mg, 79%) as a light yellow foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (d, J = 8.0, 1H), 7.69 – 7.54 (m, 2H), 7.50 – 7.14 (m, 6H), 7.13 – 7.02 (m, 2H), 5.02 (s, 2H), 4.27 (t, J = 5.2, 1H), 3.77 – 3.52 (s, 3H), 3.36 (dd, J = 6.4, 11.7, 2H), 3.05 – 2.95 (m, 2H), 2.74 – 2.63 (m, 2H), 2.13 – 1.97 (m, 1H), 1.91 – 1.69 (m, 4H), 1.54 – 1.15 (m, 15H), 1.09 - 0.93 (m, 3H) ; ESI MS m/z 575 $[M + H]^+$; HPLC >99 % (AUC), T_R 6.12 min; UV (MeOH) λ_{max} 291 nm, ε 17,243.

sodium 6-(trans-4-(1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxamido)cyclohexane-1-carboxamido)hexane-1-sulfonate (**45**)



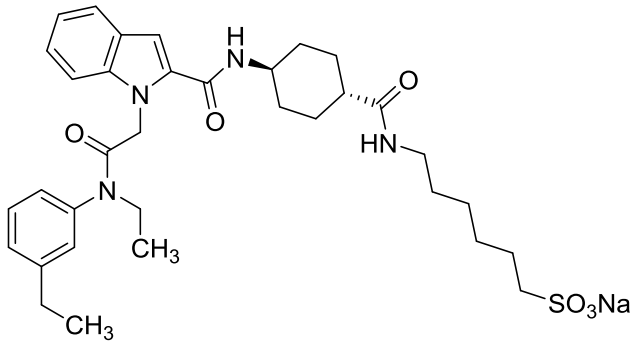
Step 1. 1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-N-(trans-4-((6-iodohexyl)carbamoyl)cyclohexyl)-1H-indole-2-carboxamide



A solution of imidazole (66 mg, 0.97 mmol), triphenylphosphine (254 mg, 0.97 mmol), and iodine (246 mg, 0.97 mmol) in THF (10mL) stirred at RT for 10min. 1-(2-(Ethyl(3-ethylphenyl)amino)-2-oxoethyl)-N-(trans-4-((6-hydroxyhexyl)carbamoyl)cyclohexyl)-1H-indole-2-carboxamide (186 mg, 0.32 mmol) dissolved in THF (5 mL) was added. The solution stirred for 1h at RT. The reaction was diluted with ethyl acetate and quenched with a 10% $Na_2S_2O_3$ solution. The mixture was diluted with ethyl acetate and water, and the layers were separated. The organic layer was washed with a 10% $Na_2S_2O_3$ solution and brine, dried over

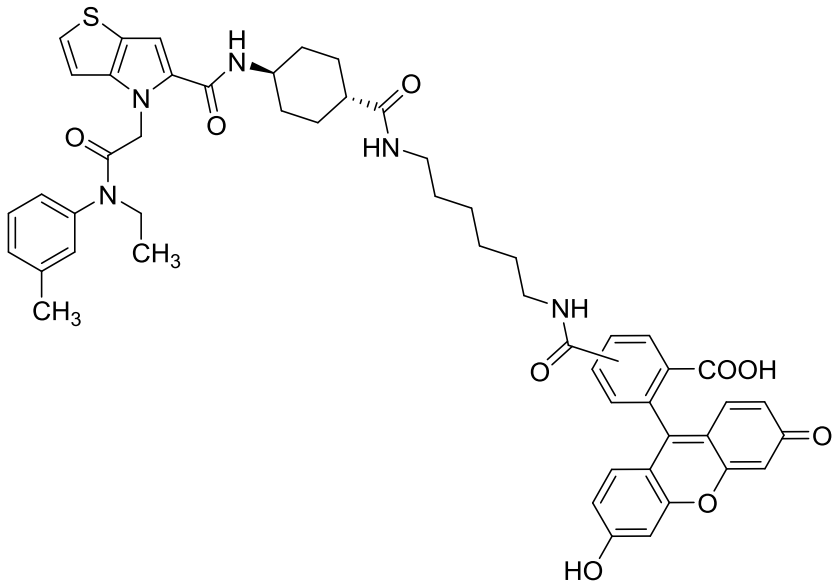
anhydrous sodium sulfate, and filtered. The filtrate was then concentrated. The residue was partially purified by column chromatography (silica, dichloromethane / methanol) to afford crude product as a white solid. ESI MS m/z 685 [M + H]+.

Step 2. sodium 6-(trans-4-(1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-1H-indole-2-carboxamido)cyclohexane-1-carboxamido)hexane-1-sulfonate (**45**)



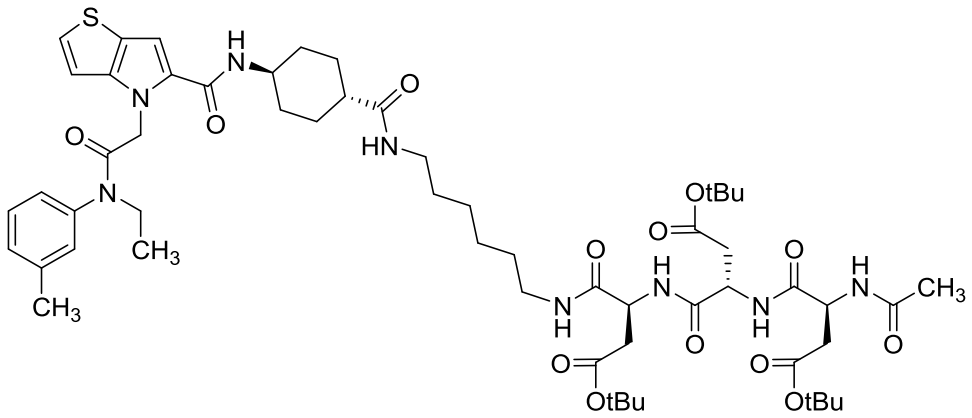
To a solution of 1-(2-(ethyl(3-ethylphenyl)amino)-2-oxoethyl)-N-(trans-4-((6-iodohexyl)carbamoyl)cyclohexyl)-1H-indole-2-carboxamide (0.32 mmol) in ethanol (10mL), sodium sulfite (203 mg, 1.6 mmol) and water (10 mL) was added. The mixture was heated to 75°C for 2h. The reaction was concentrated, and the residue was purified by column chromatography (silica, dichloromethane / methanol) to afford the desired product (190 mg, 89%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.21 (d, J = 8.2, 1H), 7.69 (t, J = 5.6, 1H), 7.58 (d, J = 7.8, 1H), 7.51 – 7.14 (m, 6H), 7.12 – 7.03 (m, 2H), 5.02 (s, 2H), 3.76 - 3.53 (m, 3H), 3.00 (dd, J = 6.6, 12.7, 2H), 2.76 – 2.61 (m, 2H), 2.39 – 2.32 (m, 2H), 2.12 – 1.99 (m, 1H), 1.90 – 1.70 (m, 4H), 1.61 – 1.14 (m, 15H), 1.08 – 0.95 (s, 3H); ESI MS m/z 639 $[M + H]^+$; HPLC >99 % (AUC), T_R 5.07 min; UV (MeOH) λ_{max} 291 nm, ε 15,800.

N-(trans-4-((6-(3',6'-dihydroxy-3-oxo-3H-spiro[isobenzofuran-1,9'-xanthene]-5(6)-carboxamido)hexyl)carbamoyl)cyclohexyl)-4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (**47**)



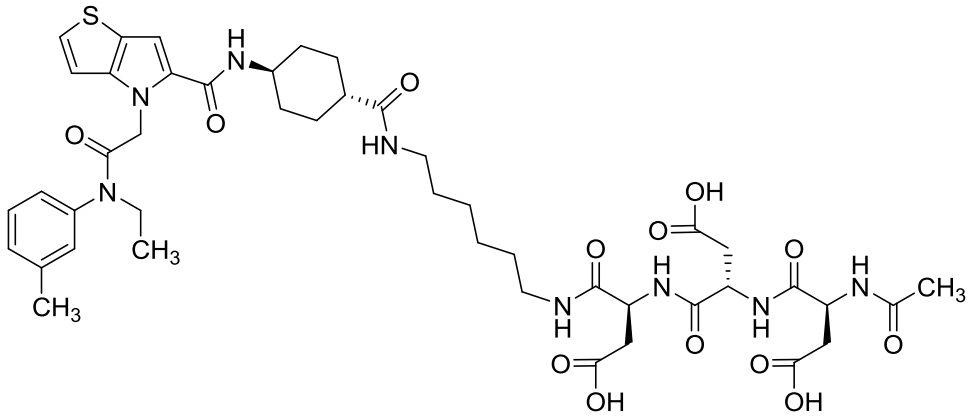
To a solution of N-(trans-4-((6-aminohexyl)carbamoyl)cyclohexyl)-4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide (0.22mmol) in DMF (3mL), 2,5-dioxopyrrolidin-1-yl 3',6'-dihydroxy-3-oxo-3H-spiro[isobenzofuran-1,9'-xanthene]-5(6)-carboxylate [5(6)-FAM-SE] (106mg, 0.22mmol) and diisopropylethylamine (145mg, 1.1mmol) was added. The reaction was stirred at RT for 1h. The reaction mixture was acidified (0.1M HCl), diluted with water, and extracted with 3:1 $CHCl_3$/isopropanol. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was then concentrated. The residue was purified by column chromatography (silica, dichloromethane/methanol) to afford the desired product (145mg, 69%) as an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 2H), 8.78 (t, J = 5.5, 1H, isomer A), 8.64 (t, J = 5.7, 1H, isomer B), 8.44 (s, 1H, isomer A), 8.23 (dd, J = 1.5, 8.1, 1H, isomer A), 8.15 (dd, J = 1.3, 8.1, 1H, isomer B), 8.05 (d, J = 8.1, 1H, isomer B), 7.87 (d, J = 8.0, 1H), 7.72 – 7.60 (m, 1H), 7.44 – 7.32 (m, 3H), 7.32 – 7.17 (m, 3H), 7.12 – 7.04 (m, 2H), 6.70 – 6.65 (m, 2H), 6.61 – 6.49 (m, 4H), 4.96 (s, 2H), 3.70 – 3.52 (m, 3H), 3.32 – 3.23 (m, 2H), 3.22 – 3.12 (m, 1H), 3.08 – 2.91 (m, 2H), 2.36 (s, 3H), 2.11 – 1.95 (m, 1H), 1.89 – 1.65 (m, 4H), 1.61 – 1.16 (m, 11H), 1.06 – 0.92 (m, 3H); ESI MS m/z 925 $[M + H]^+$; HPLC 97.1 % (AUC), T_R 6.16, 6.26 min; UV (MeOH) λ_{max} 284 nm, ε 31,419.

tert-butyl (11S,14S,17S)-17-acetamido-11,14-bis(2-(tert-butoxy)-2-oxoethyl)-1-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexyl)-1,10,13,16-tetraoxo-2,9,12,15-tetraazanonadecan-19-oate



Following general procedure B, (S)-2-((S)-2-((S)-2-acetamido-4-(tert-butoxy)-4-oxobutanamido)-4-(tert-butoxy)-4-oxobutanamido)-4-(tert-butoxy)-4-oxobutanoic acid (81mg, 0.14mmol) was reacted with N-(trans-4-((6-aminohexyl)carbamoyl)cyclohexyl)-4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamide hydrochloride (85mg, 0.14mmol) to afford the desired product (125mg, 78%) as a light yellow solid. ESI MS m/z 1122 $[M + H]^+$.

(11S,14S,17S)-17-acetamido-11,14-bis(carboxymethyl)-1-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-carboxamido)cyclohexyl)-1,10,13,16-tetraoxo-2,9,12,15-tetraazanonadecan-19-oic acid (**46**)

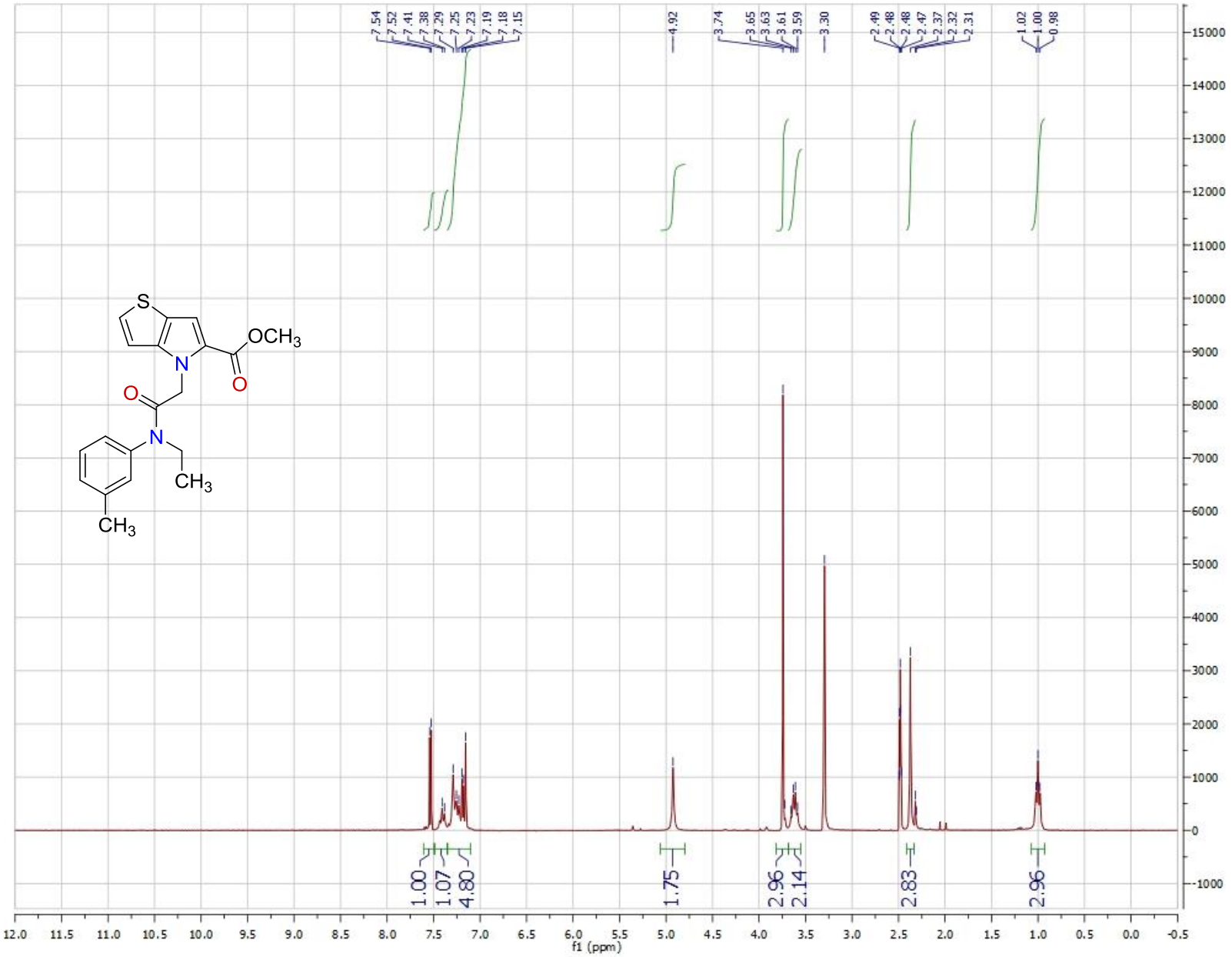


To a solution of tert-butyl (11S,14S,17S)-17-acetamido-11,14-bis(2-(tert-butoxy)-2-oxoethyl)-1-(trans-4-(4-(2-(ethyl(m-tolyl)amino)-2-oxoethyl)-4H-thieno[3,2-b]pyrrole-5-

carboxamido)cyclohexyl)-1,10,13,16-tetraoxo-2,9,12,15-tetraazanonadecan-19-oate (120mg, 0.11mmol) in dichloromethane (10mL), trifluoroacetic acid (1mL) was added. The reaction stirred at RT for 18h. The mixture was diluted with toluene and concentrated under vacuum (3X). The residue was purified by column chromatography (silica, dichloromethane / methanol) to afford the desired product (68mg, 66%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 3H), 8.45 - 8.18 (m, 2H), 7.95 – 7.83 (m, 2H), 7.66 (t, J = 5.5, 1H), 7.52 – 7.17 (m, 6H), 7.11 – 7.04 (m, 2H), 4.96 (s, 2H), 4.55 – 4.35 (m, 3H), 3.71 – 3.52 (m, 2H), 3.06 – 2.90 (m, 4H), 2.75 – 2.60 (m, 3H), 2.60 – 2.42 (m, 4H), 2.36 (s, 3H), 2.09 – 1.96 (m, 1H), 1.89 – 1.66 (m, 7H), 1.53 – 1.13 (m, 12H), 1.06 – 0.93 (m, 3H); ESI MS m/z 953 $[M + H]^+$; HPLC 93.8 % (AUC), T_R 4.74 min; UV (MeOH) λ_{max} 289 nm, ε 24,417.

[1]H NMR spectra for Table 1 analogues

1



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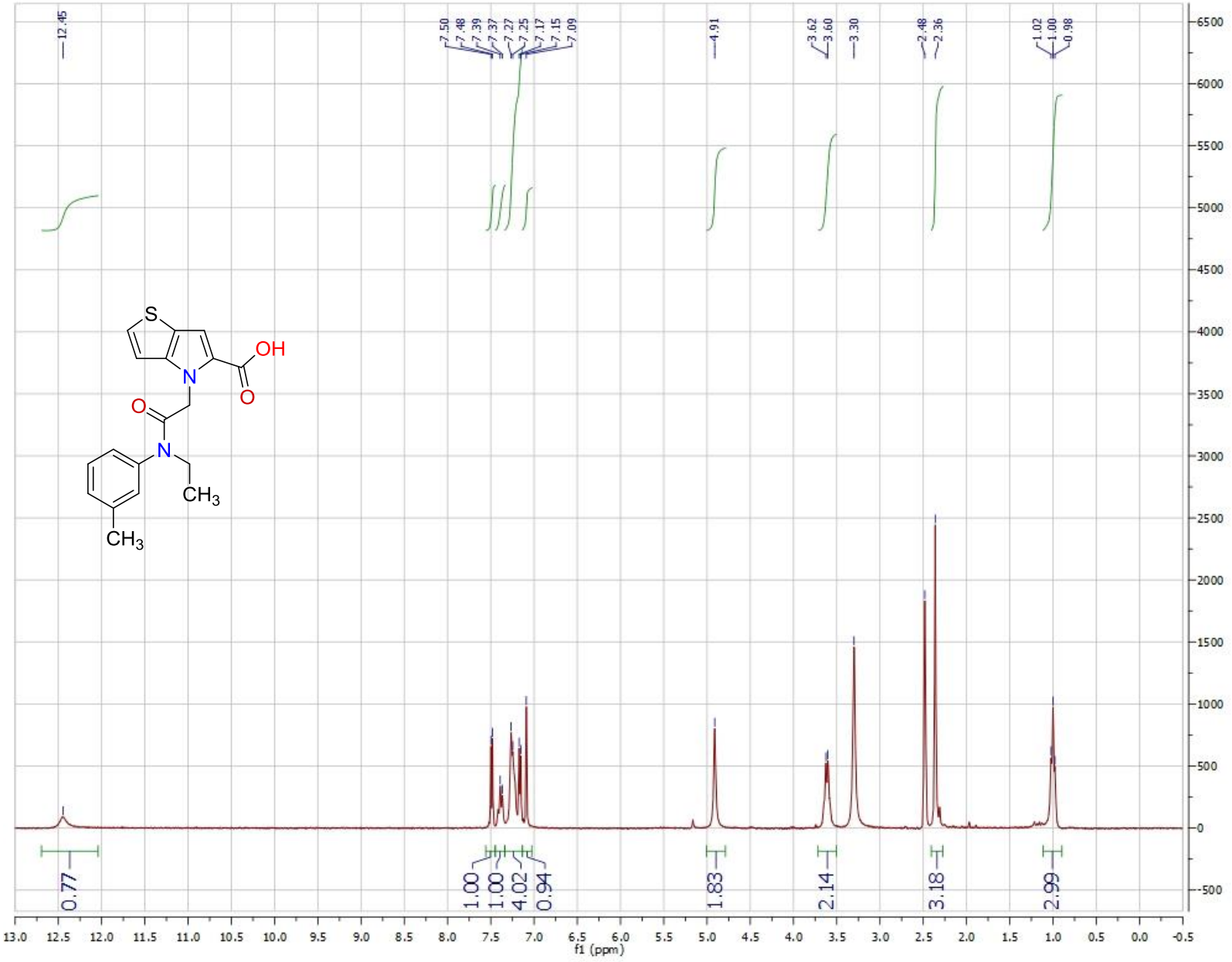
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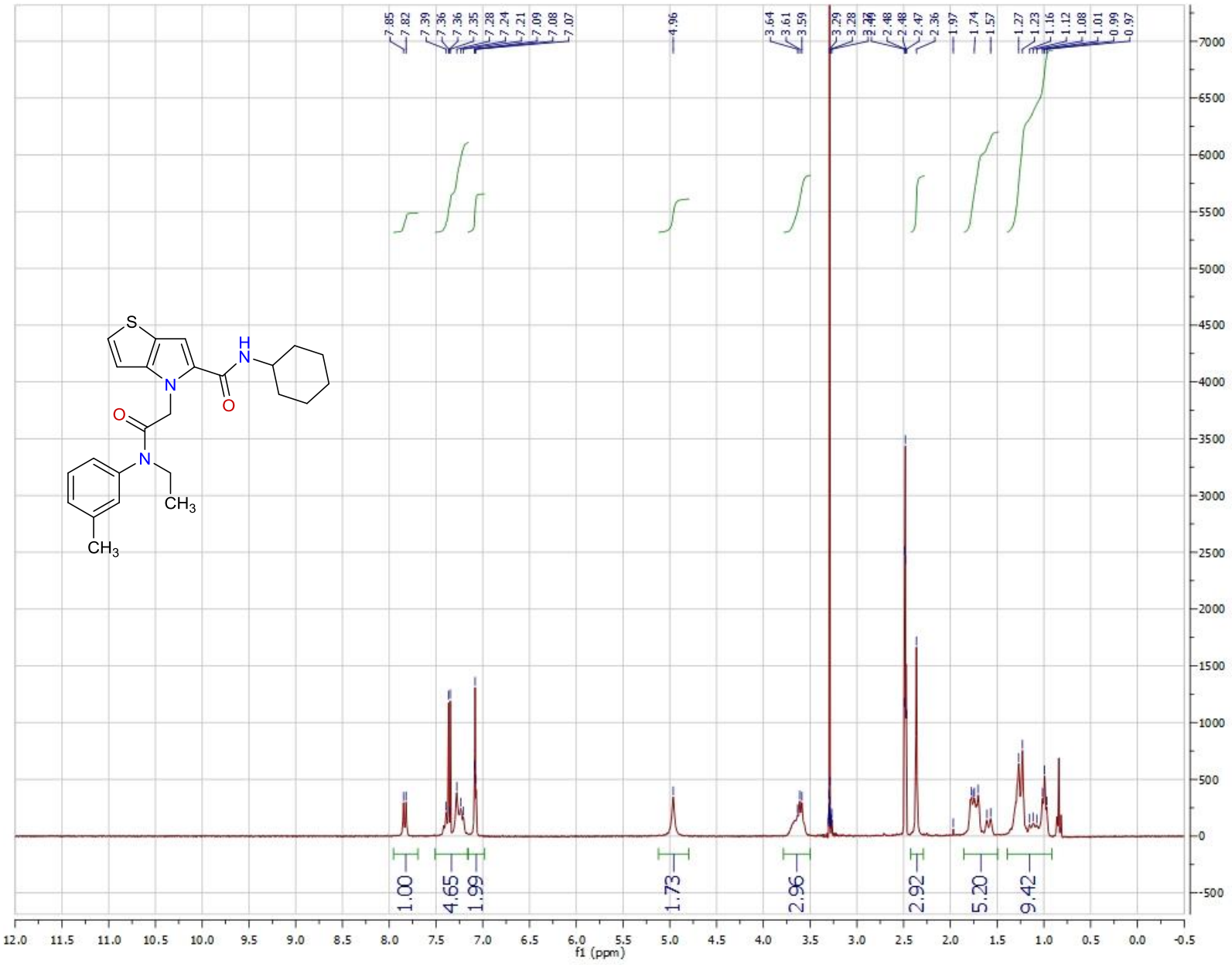
3.30
2.48
2.36
1.02
1.00
0.98
S
OH
N
O
O
N
CH3
CH3
0.77
1.00
1.00
4.02
0.94
1.83
2.14
3.18
2.99
f1 (ppm)

5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7.08
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3.64
3.61
3.59
3.29
3.28
2.48
2.48
2.47
2.36
1.97
1.74
1.57
1.27
1.23
1.16
1.12
1.08
1.01
0.99
0.97
S
N
H
N
O
O
O
N
CH3
CH3
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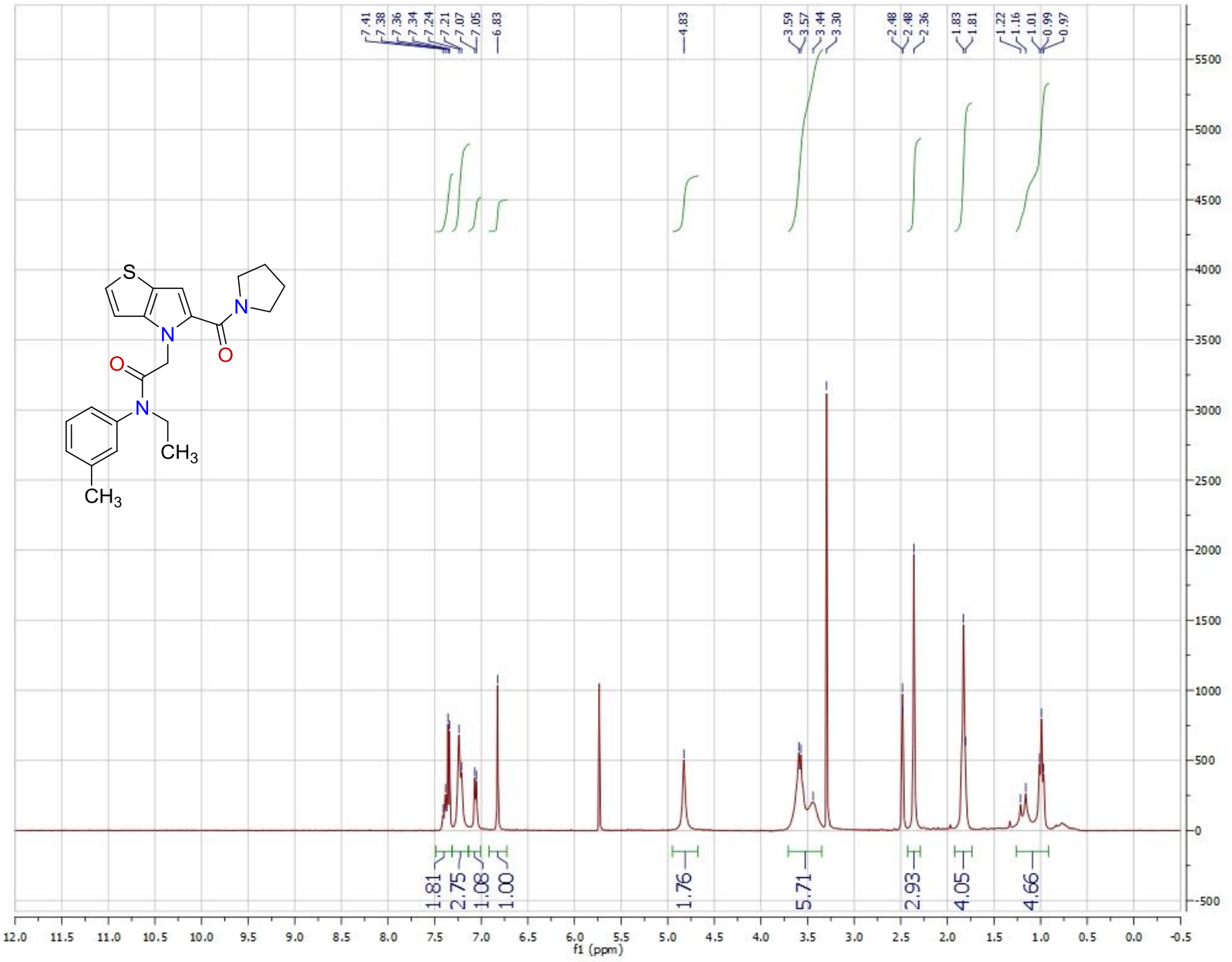
4.65
1.99
1.73
2.96
2.92
5.20
9.42
f1 (ppm)

6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3.44
3.30
2.48
2.48
2.36
1.83
1.81
1.22
1.16
1.01
0.99
0.97
S
N
N
O
O
N
CH3
CH3
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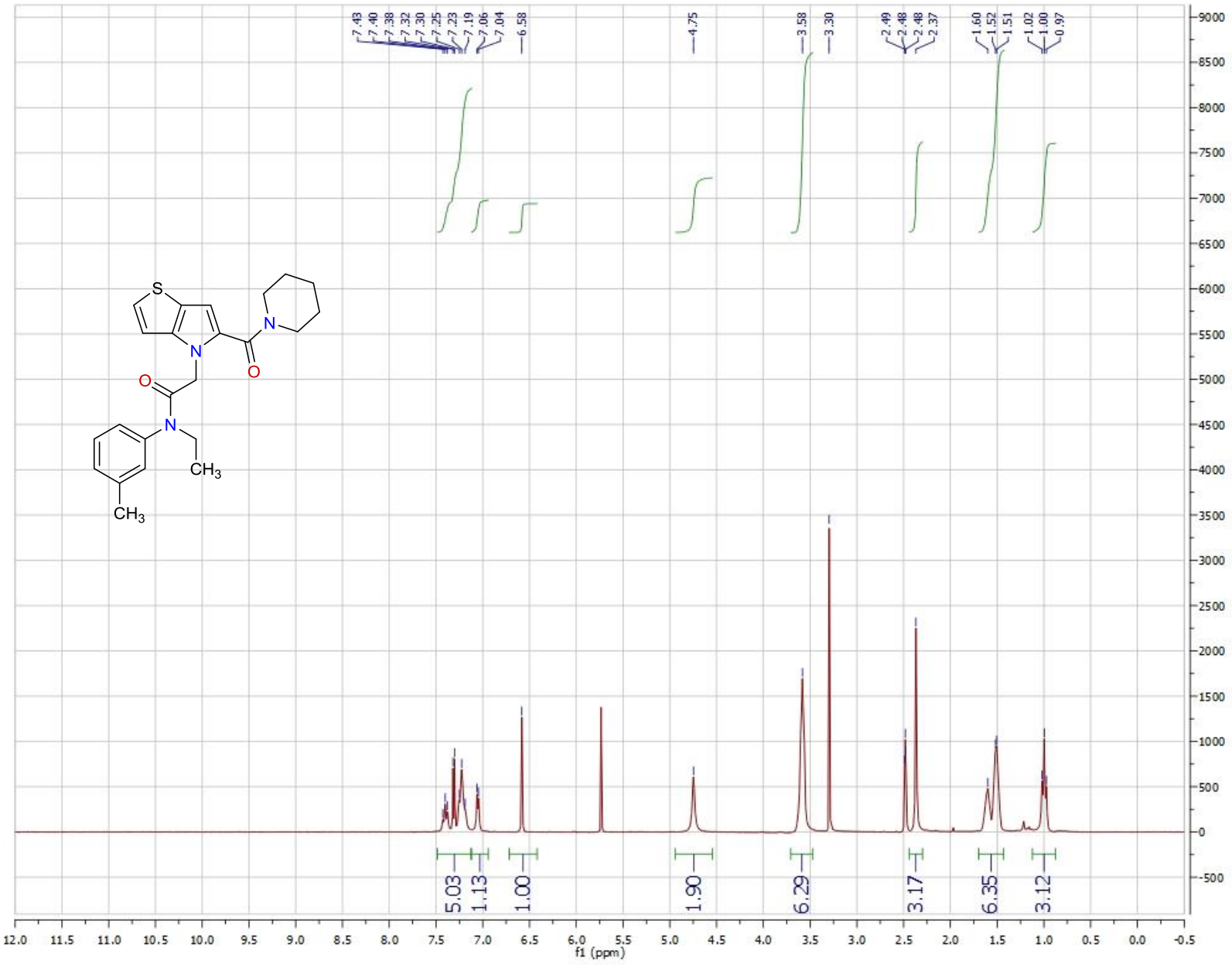
1.08
1.00
1.76
5.71
2.93
4.05
4.66
f1 (ppm)

7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3.30
2.49
2.48
2.48
2.37
1.60
1.52
1.51
1.02
1.00
0.97
S
N
N
O
O
N
CH3
CH3
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1.00
1.90
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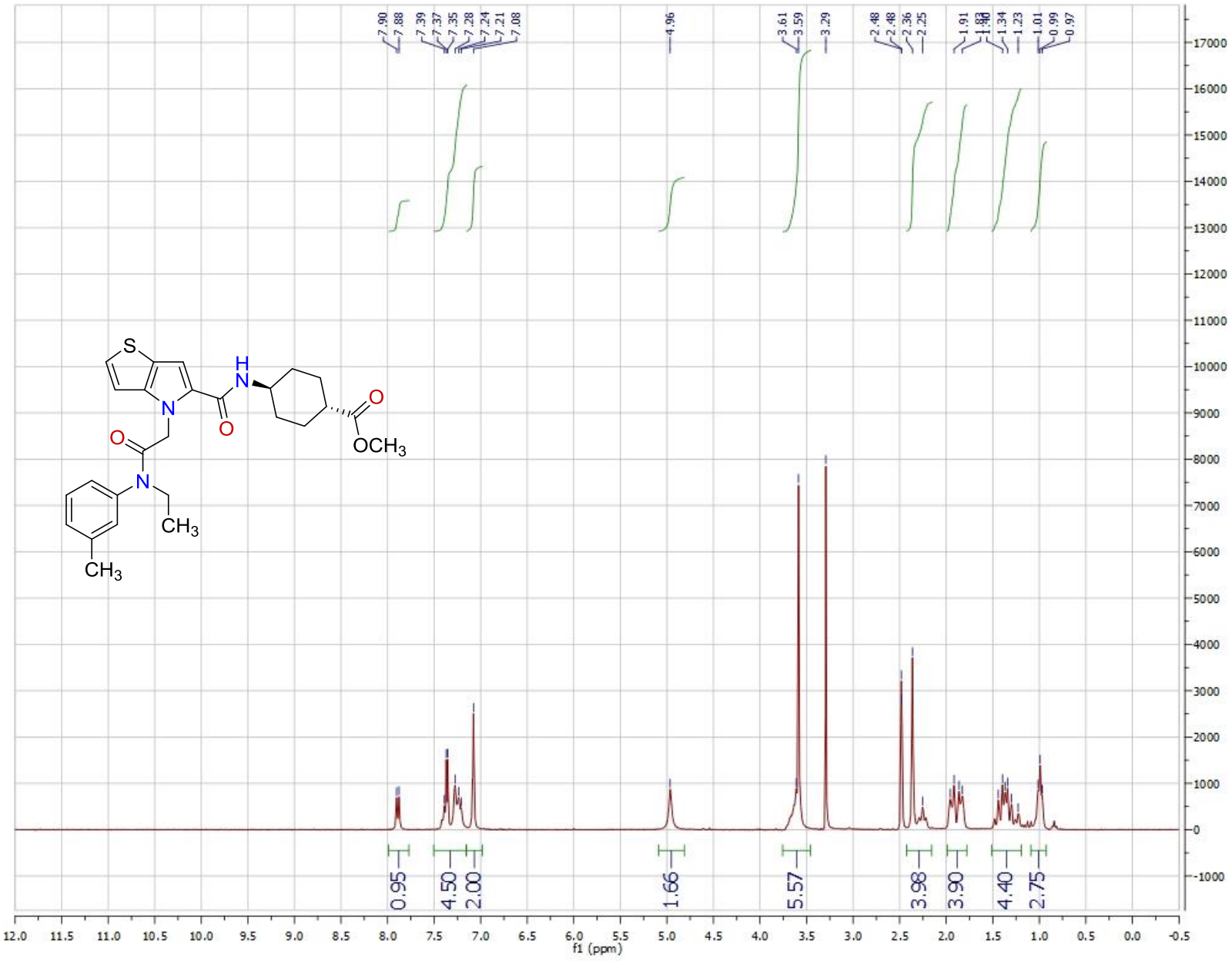
3.17
6.35
3.12
f1 (ppm)

8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4.96
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3.59
3.29
2.48
2.48
2.36
2.25
1.91
1.34
1.23
1.01
0.99
0.97
S
N
H
N
O
O
O
O
OCH3
N
CH3
CH3
0.95
4.50
2.00
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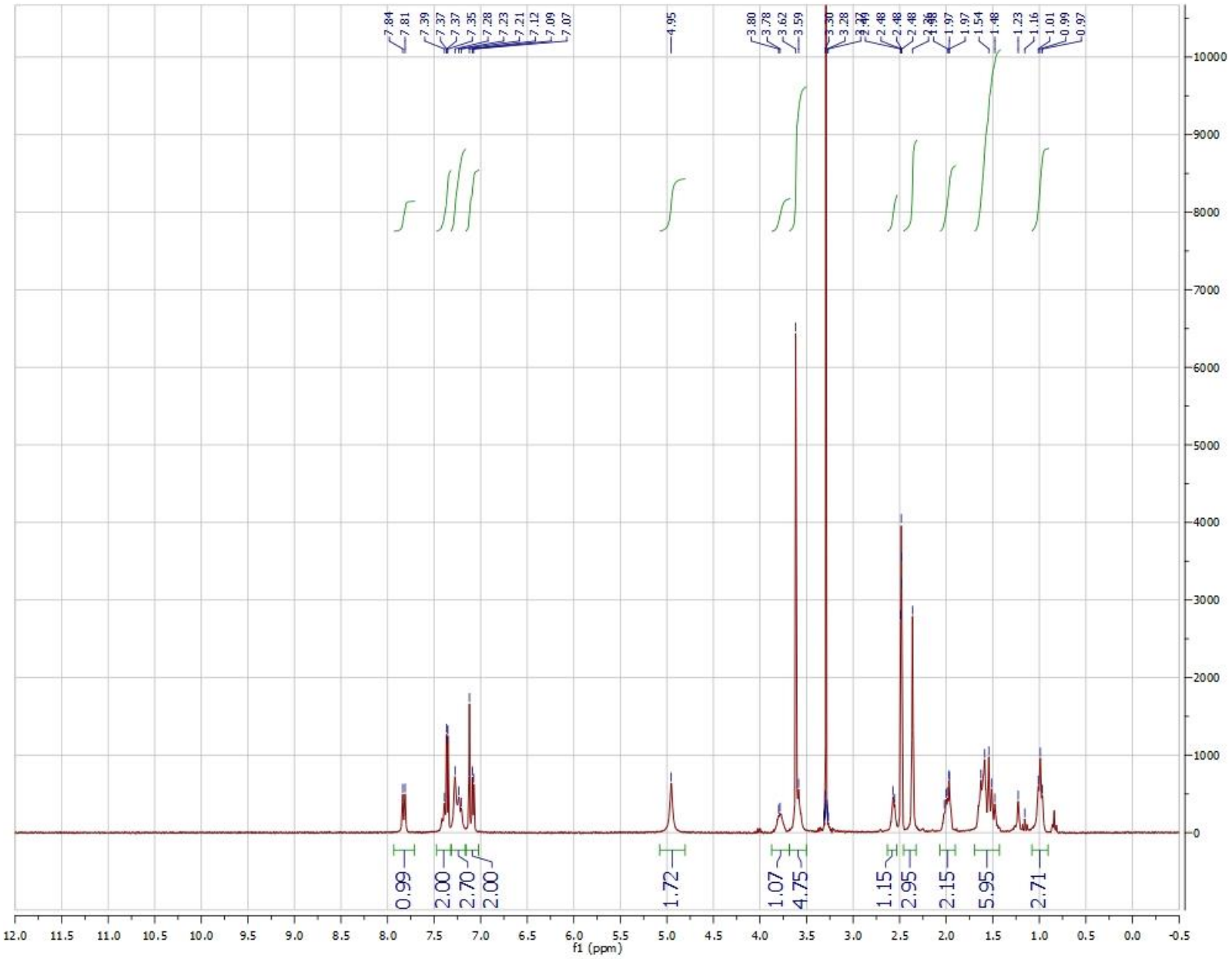
5.57
3.98
3.90
4.40
2.75
f1 (ppm)

9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7.07
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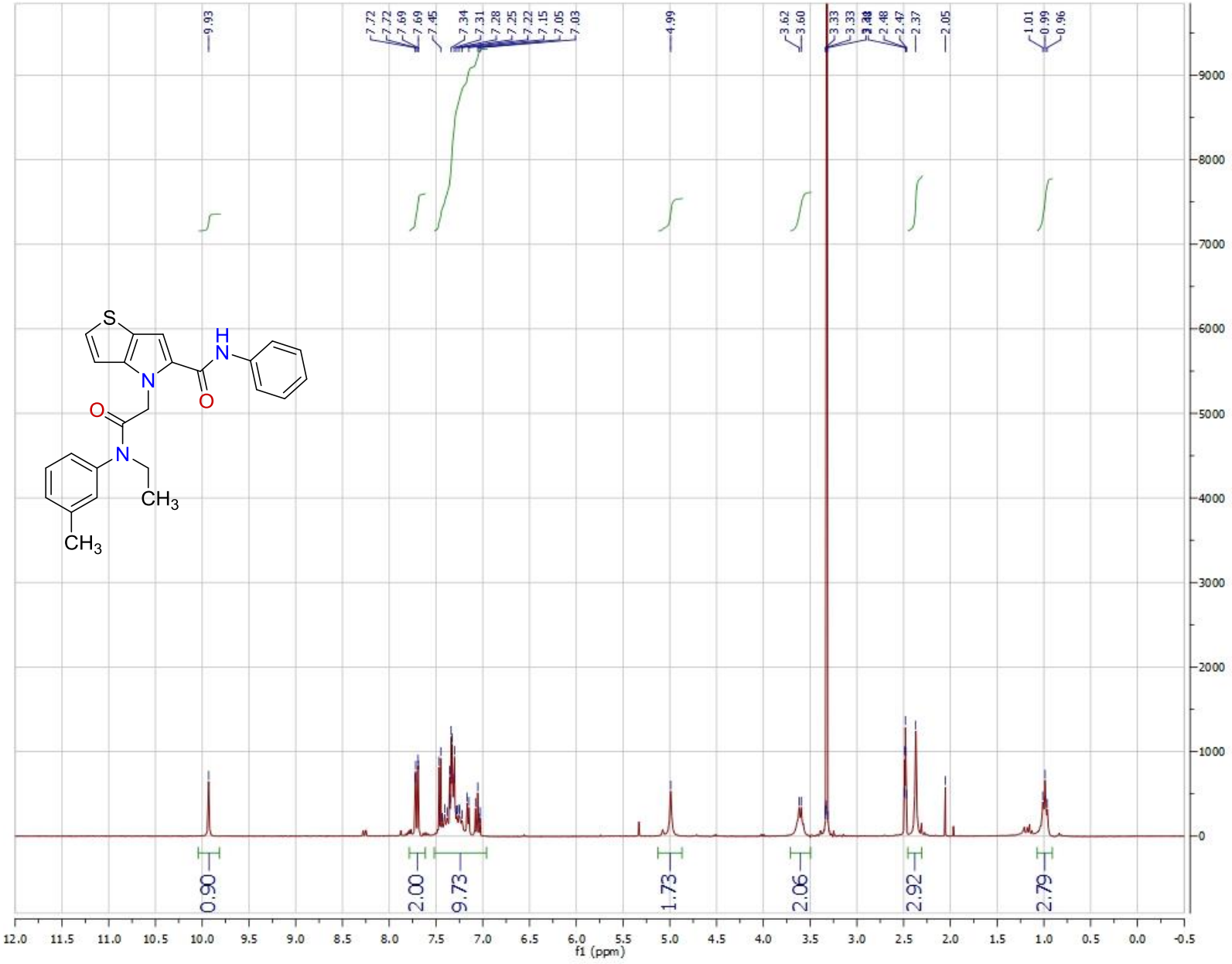
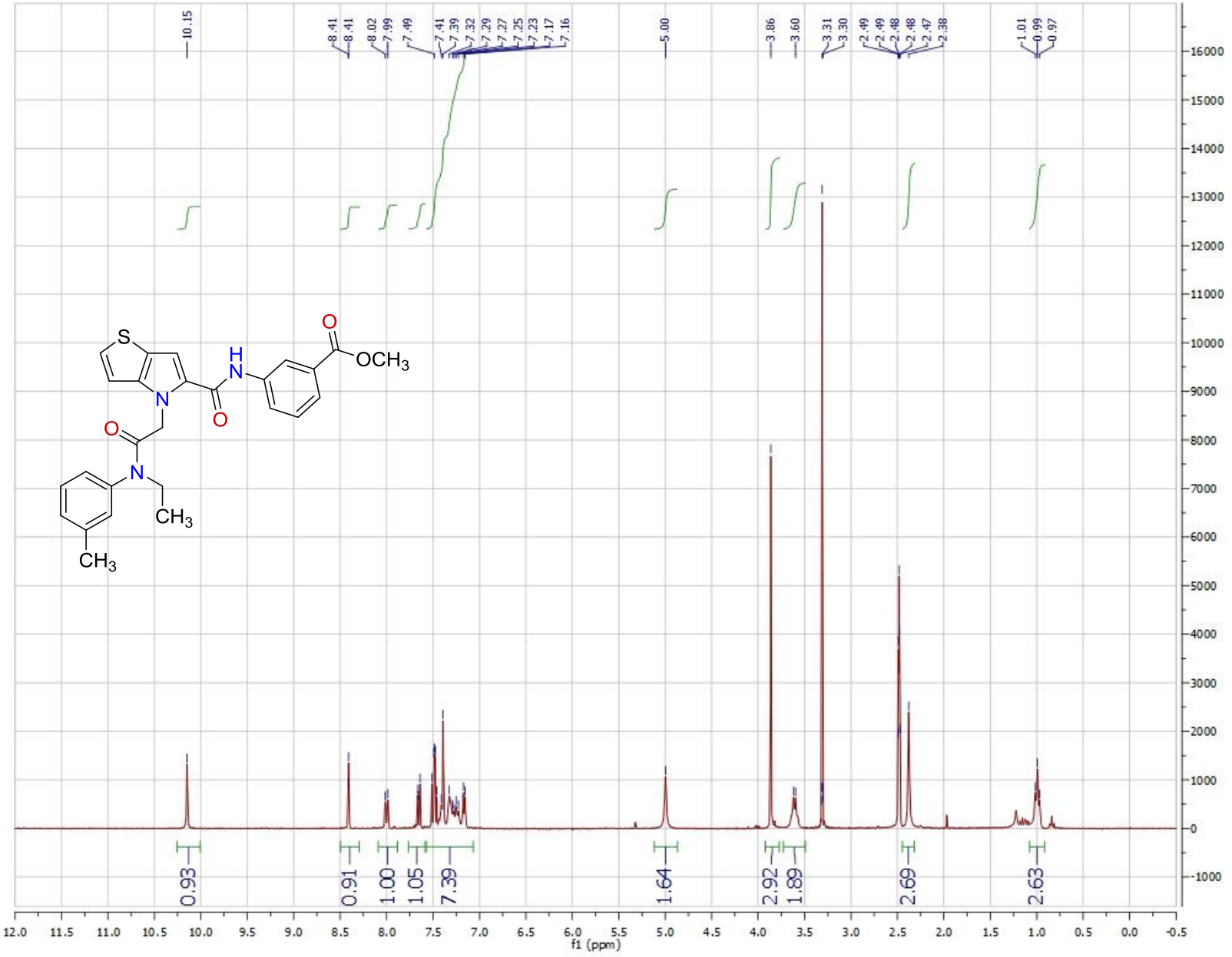
3.80
3.78
3.62
3.59
3.30
3.28
2.48
2.48
2.48
1.97
1.97
1.54
1.48
1.23
1.16
1.01
0.99
0.97
0.99
2.00
2.70
2.00
1.72
1.07
4.75
1.15
2.95
2.15
5.95
2.71
f1 (ppm)

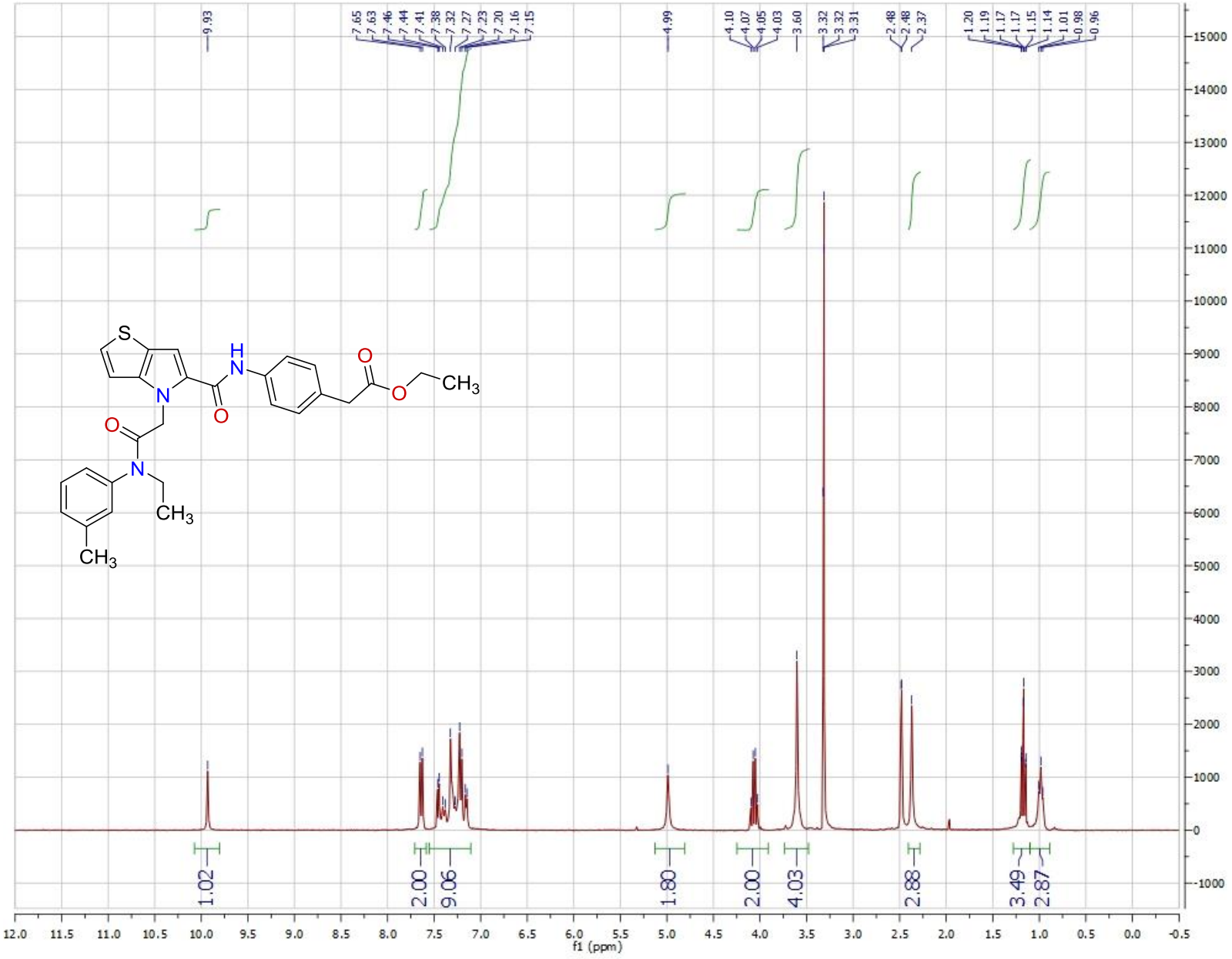
10


9.93
7.72
7.72
7.69
7.69
7.45
7.34
7.31
7.28
7.25
7.22
7.15
7.05
7.03
4.99
3.62
3.60
3.33
3.33
2.48
2.47
2.37
2.05
1.01
0.99
0.96
S
H
N
N
O
O
O
N
CH3
CH3
0.90
2.00
9.73
1.73
2.06
2.92
2.79
f1 (ppm)

11

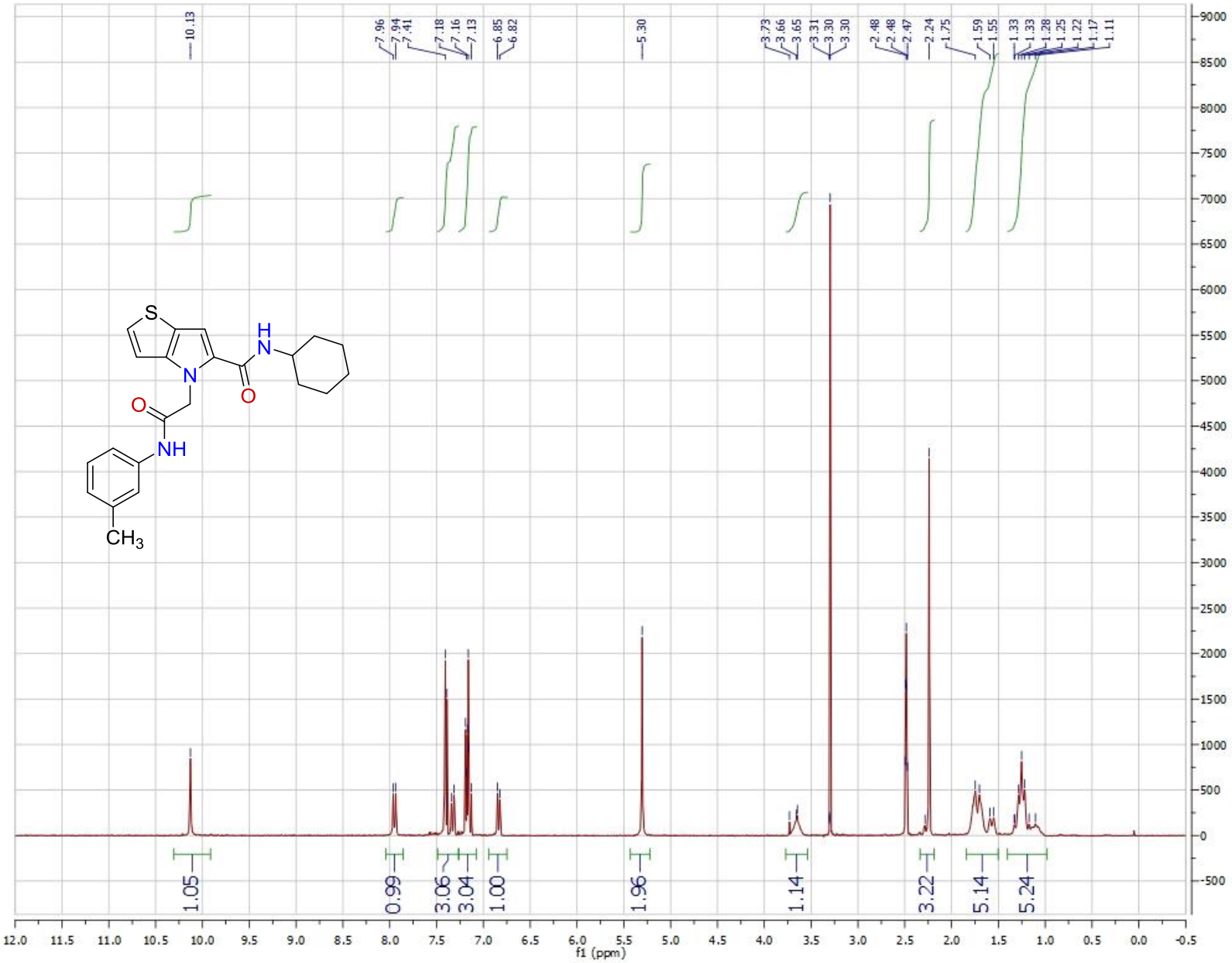

10.15
8.41
8.41
8.02
7.99
7.49
7.41
7.39
7.32
7.29
7.27
7.25
7.23
7.17
7.16
5.00
3.86
3.60
3.31
3.30
2.49
2.49
2.48
2.48
2.47
2.38
1.01
0.99
0.97
S
N
H
N
O
O
O
OCH3
O
N
CH3
CH3
0.93
0.91
1.00
1.05
7.39
1.64
2.92
1.89
2.69
2.63
f1 (ppm)

12

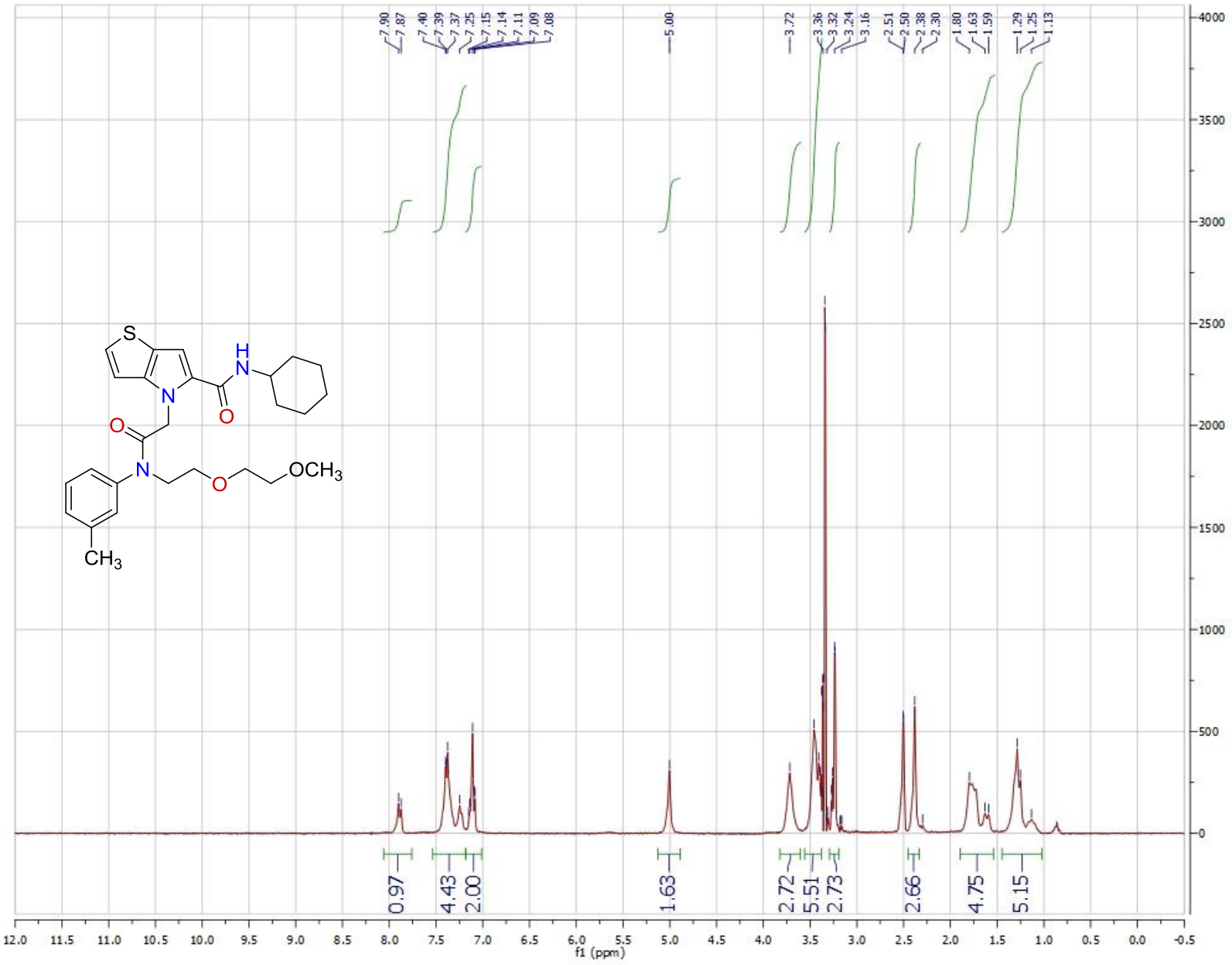

9.93
7.65
7.63
7.46
7.44
7.41
7.38
7.32
7.27
7.23
7.20
7.16
7.15
4.99
4.10
4.07
4.05
4.03
3.60
3.32
3.32
3.31
2.48
2.48
2.37
1.20
1.19
1.17
1.17
1.15
1.14
1.01
0.98
0.96
S
H
N
O
O
O
O
N
CH3
N
CH3
CH3
1.02
2.00
9.06
1.80
2.00
4.03
2.88
3.49
2.87
f1 (ppm)

[1]H NMR spectra for Table 2 analogues

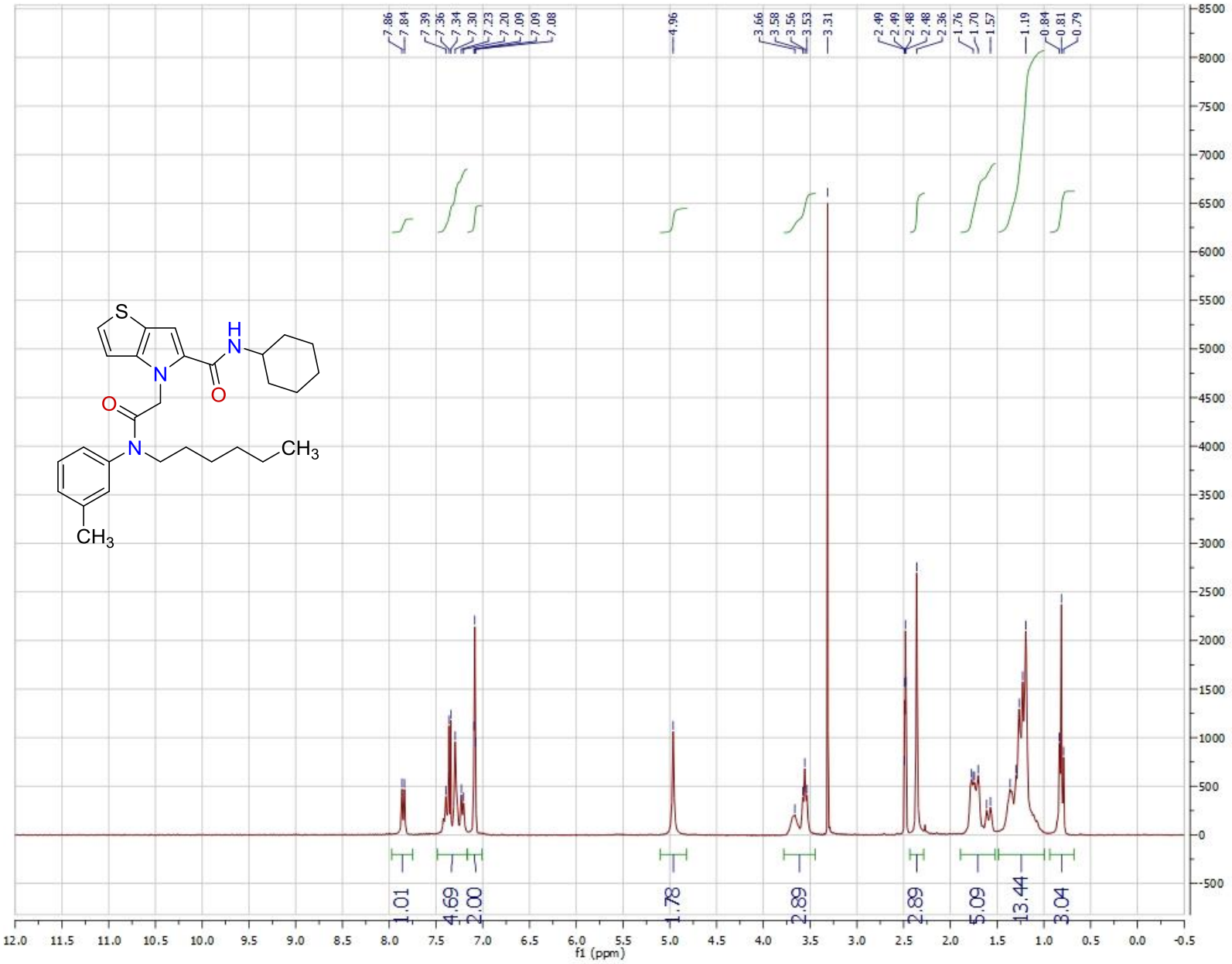
13



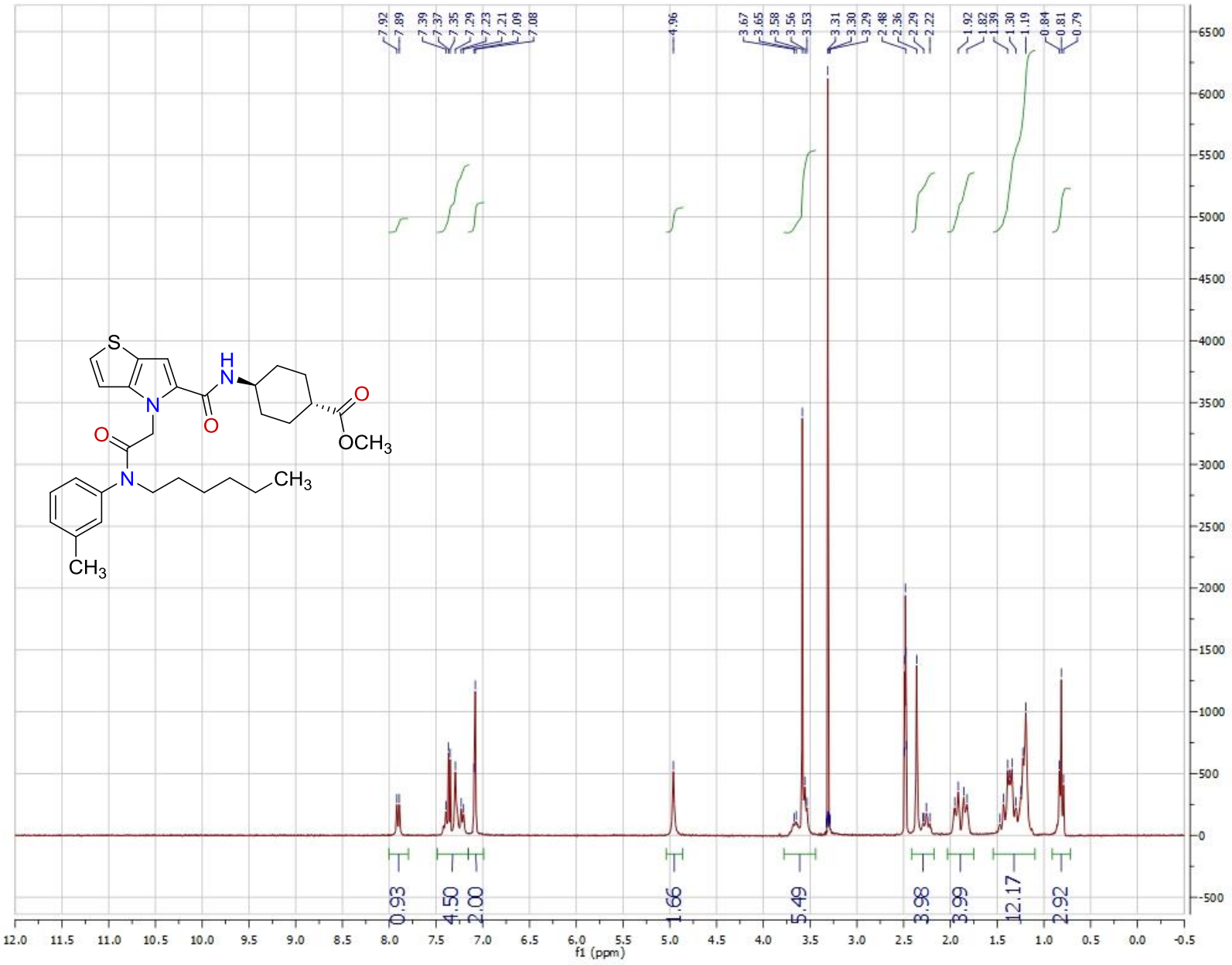
14


7.90
7.87
7.40
7.39
7.37
7.25
7.15
7.14
7.11
7.09
7.08
5.00
3.72
3.36
3.32
3.24
3.16
2.51
2.50
2.38
2.30
1.80
1.63
1.59
1.29
1.25
1.13
S
H
N
N
O
O
O
N
O
OCH3
CH3
0.97
4.43
2.00
1.63
2.72
5.51
2.73
2.66
4.75
5.15
f1 (ppm)

16

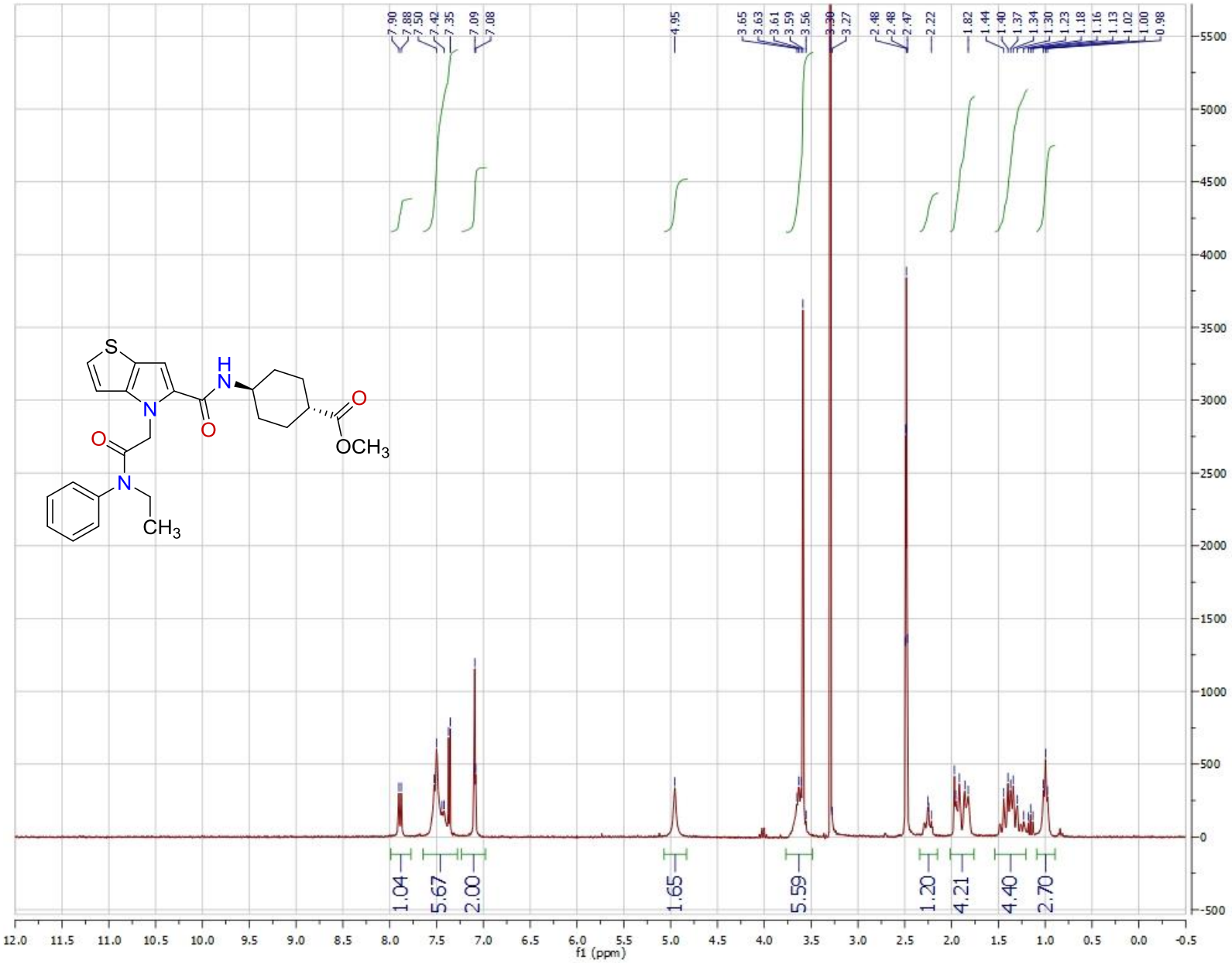

7.86
7.84
7.39
7.36
7.34
7.30
7.23
7.20
7.09
7.09
7.08
4.96
3.66
3.58
3.56
3.53
3.31
2.49
2.49
2.48
2.48
2.36
1.76
1.70
1.57
1.19
0.84
0.81
0.79
S
H
N
N
O
O
O
N
CH3
CH3
1.01
4.69
2.00
1.78
2.89
2.89
5.09
13.44
3.04
f1 (ppm)

17

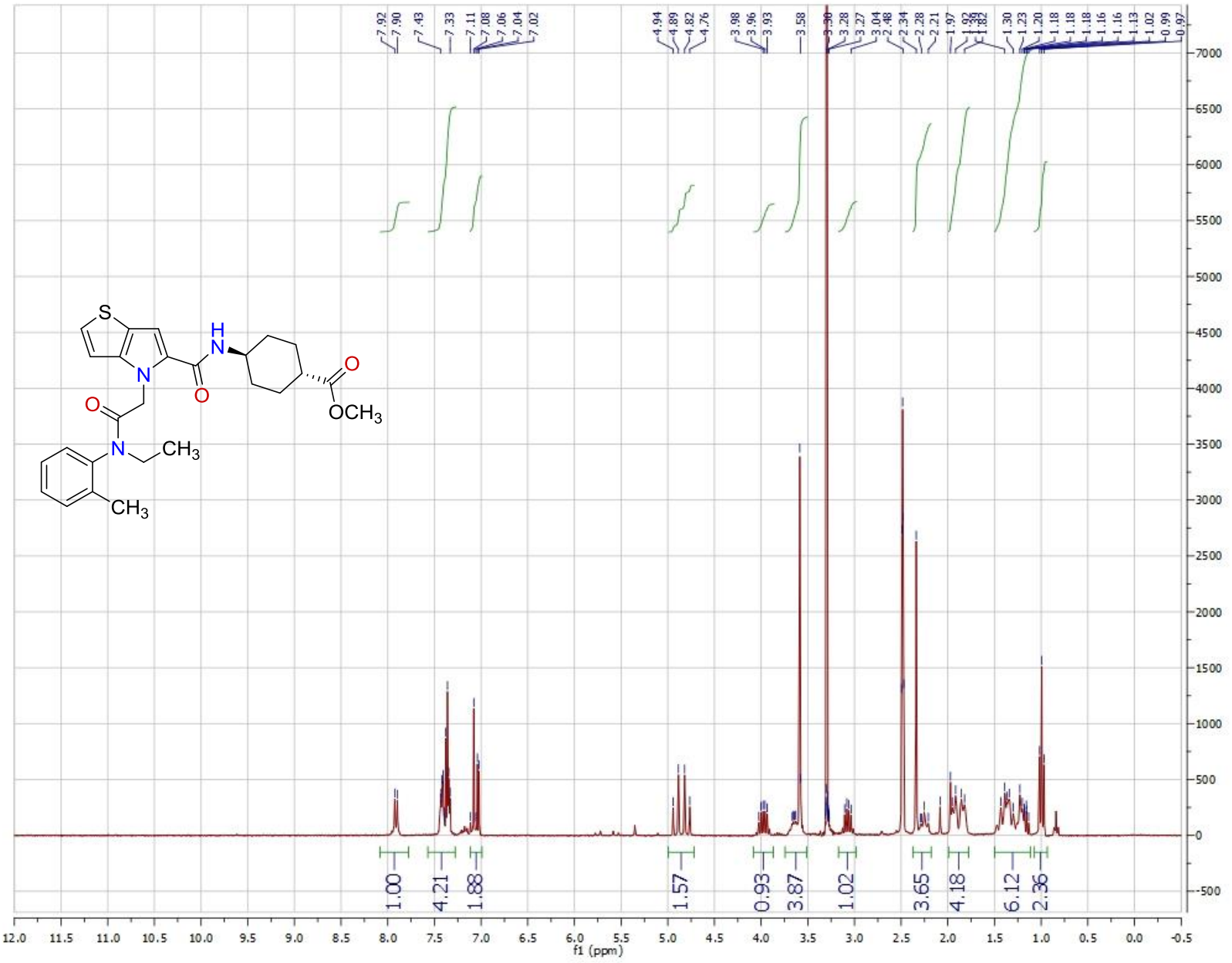

7.92
7.89
7.39
7.37
7.35
7.29
7.23
7.21
7.09
7.08
4.96
3.67
3.65
3.58
3.56
3.53
3.31
3.30
3.29
2.48
2.36
2.29
2.22
1.92
1.82
1.39
1.30
1.19
0.84
0.81
0.79
S
H
N
N
O
O
O
OCH3
N
CH3
CH3
0.93
4.50
2.00
1.66
5.49
3.98
3.99
12.17
2.92
f1 (ppm)

[1]H NMR spectra for Table 3 analogues

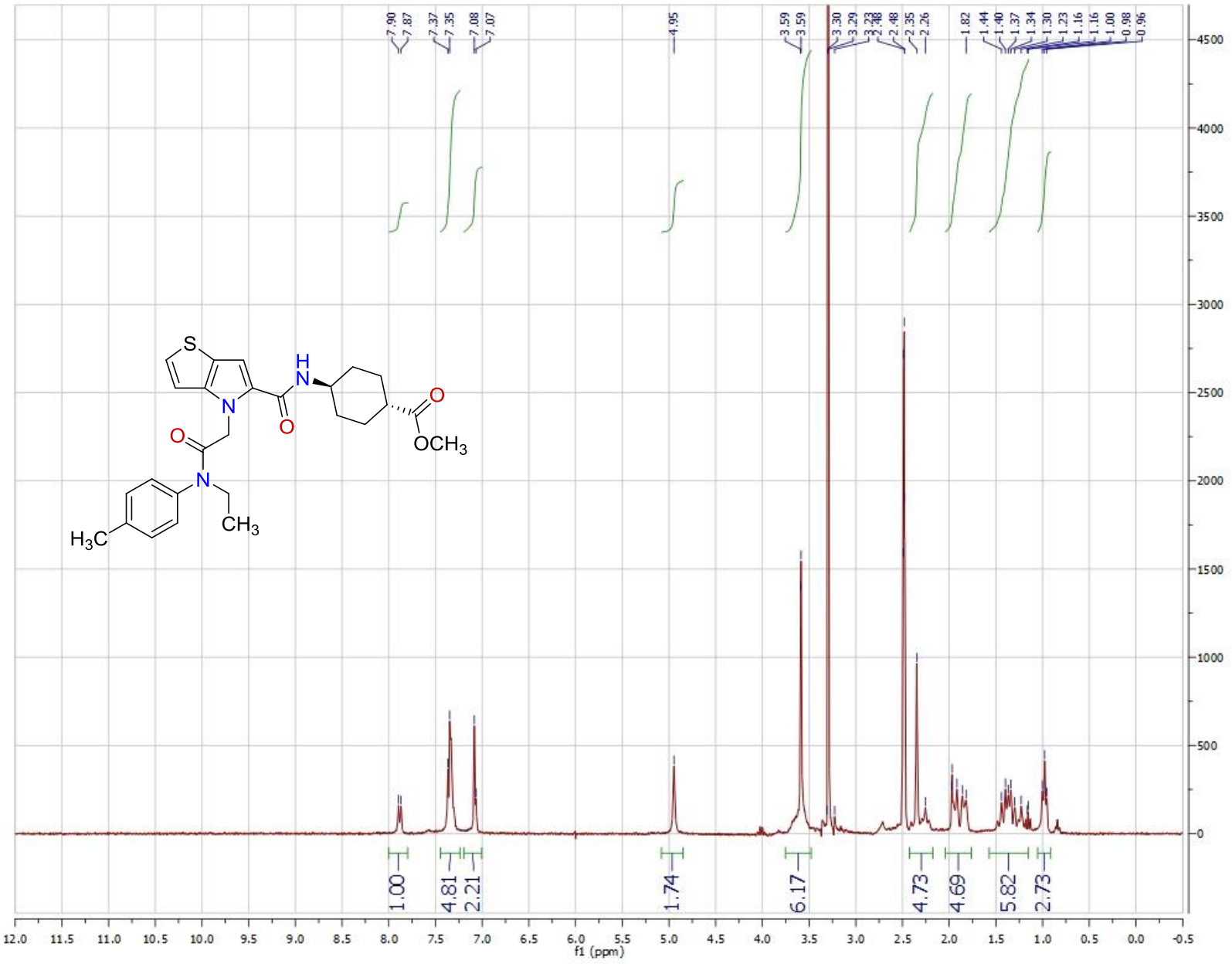
18



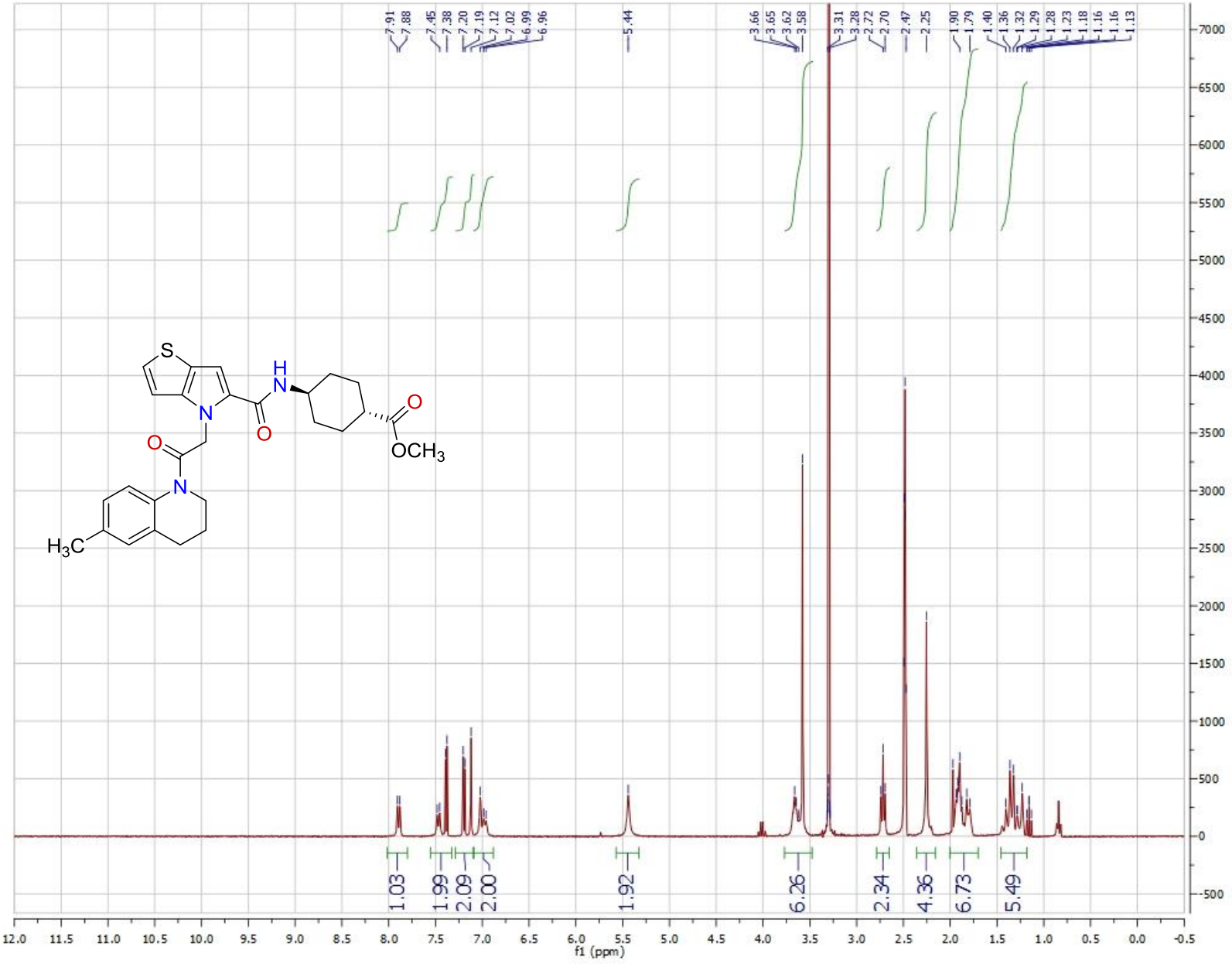
19


7.92
7.90
7.43
7.33
7.11
7.08
7.06
7.04
7.02
4.94
4.89
4.82
4.76
3.98
3.96
3.93
3.58
3.36
3.28
3.27
3.04
2.48
2.34
2.28
2.21
1.97
1.92
1.30
1.23
1.20
1.18
1.18
1.18
1.16
1.13
1.02
0.99
0.97
S
H
N
N
O
O
O
O
OCH3
N
CH3
CH3
1.00
4.21
1.88
1.57
0.93
3.87
1.02
3.65
4.18
6.12
2.36
f1 (ppm)

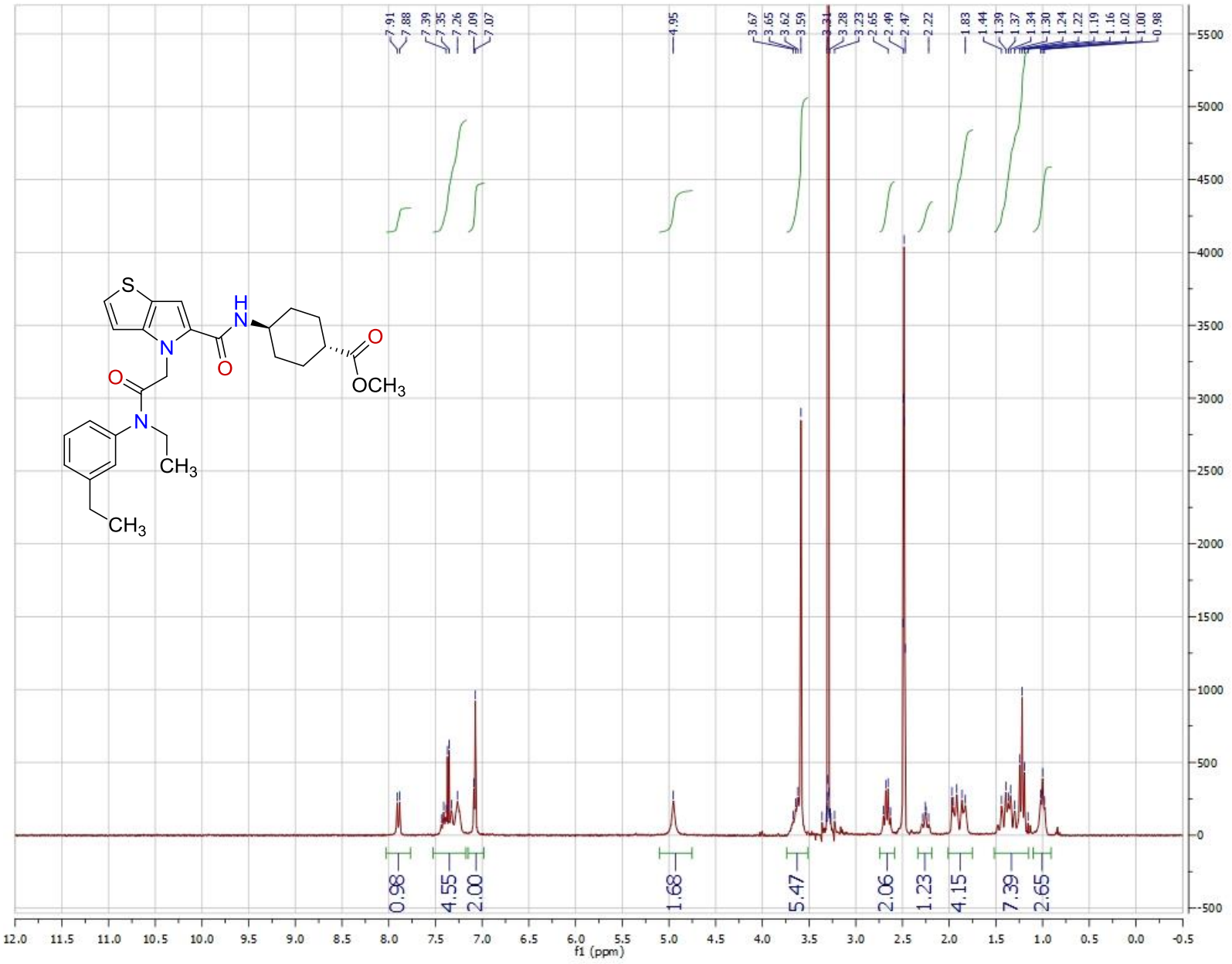
20


7.90
7.87
7.37
7.35
7.08
7.07
4.95
3.59
3.59
3.30
3.29
3.23
2.48
2.35
2.26
1.82
1.44
1.40
1.37
1.34
1.30
1.23
1.16
1.16
1.00
0.98
0.96
S
N
H
N
O
O
O
OCH3
O
N
CH3
H3C
1.00
4.81
2.21
1.74
6.17
4.73
4.69
5.82
2.73
f1 (ppm)

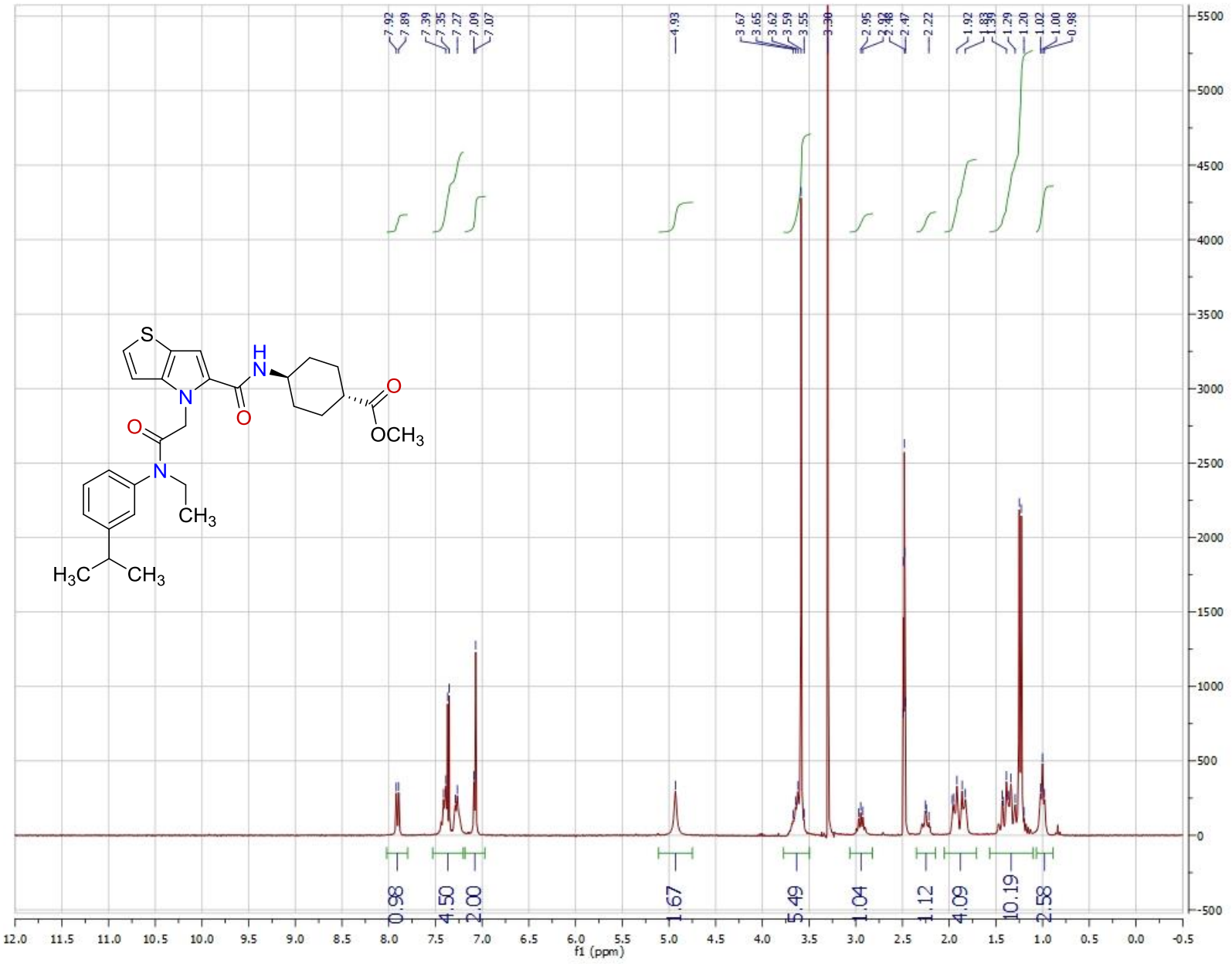
21


7.91
7.88
7.45
7.38
7.20
7.19
7.12
7.02
6.99
6.96
5.44
3.66
3.65
3.62
3.58
3.31
3.28
2.72
2.70
2.47
2.25
1.90
1.79
1.40
1.36
1.32
1.29
1.28
1.23
1.18
1.16
1.16
1.13
S
H
N
N
O
O
O
O
OCH3
N
H3C
1.03
1.99
2.09
2.00
1.92
6.26
2.34
4.36
6.73
5.49
f1 (ppm)

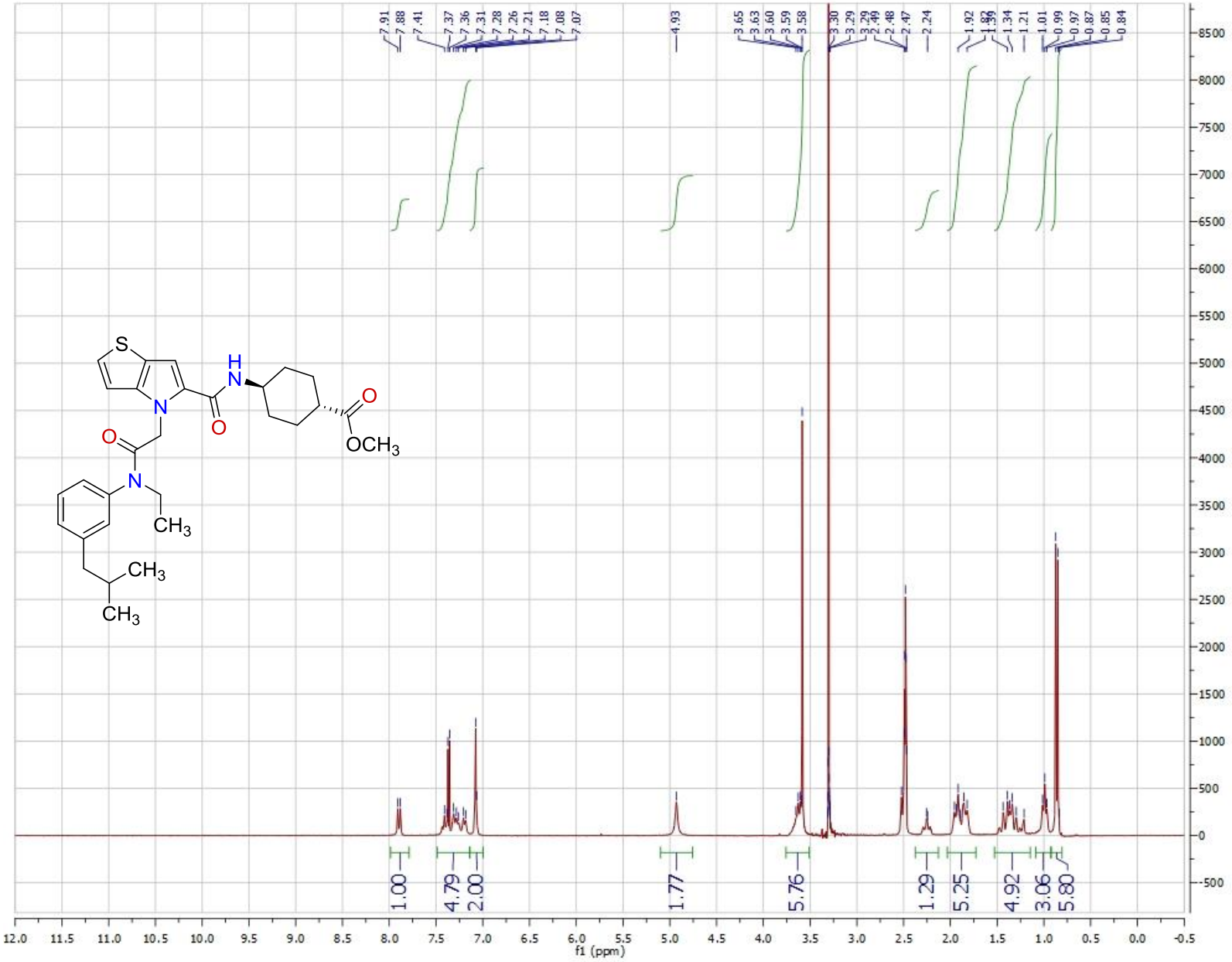
22


7.91
7.88
7.39
7.35
7.26
7.09
7.07
4.95
3.67
3.65
3.62
3.59
3.31
3.28
3.23
2.65
2.49
2.47
2.22
1.83
1.44
1.39
1.37
1.34
1.30
1.24
1.22
1.19
1.16
1.02
1.00
0.98
S
N
H
N
O
O
O
OCH3
N
CH3
CH3
0.98
4.55
2.00
1.68
5.47
2.06
1.23
4.15
7.39
2.65
f1 (ppm)

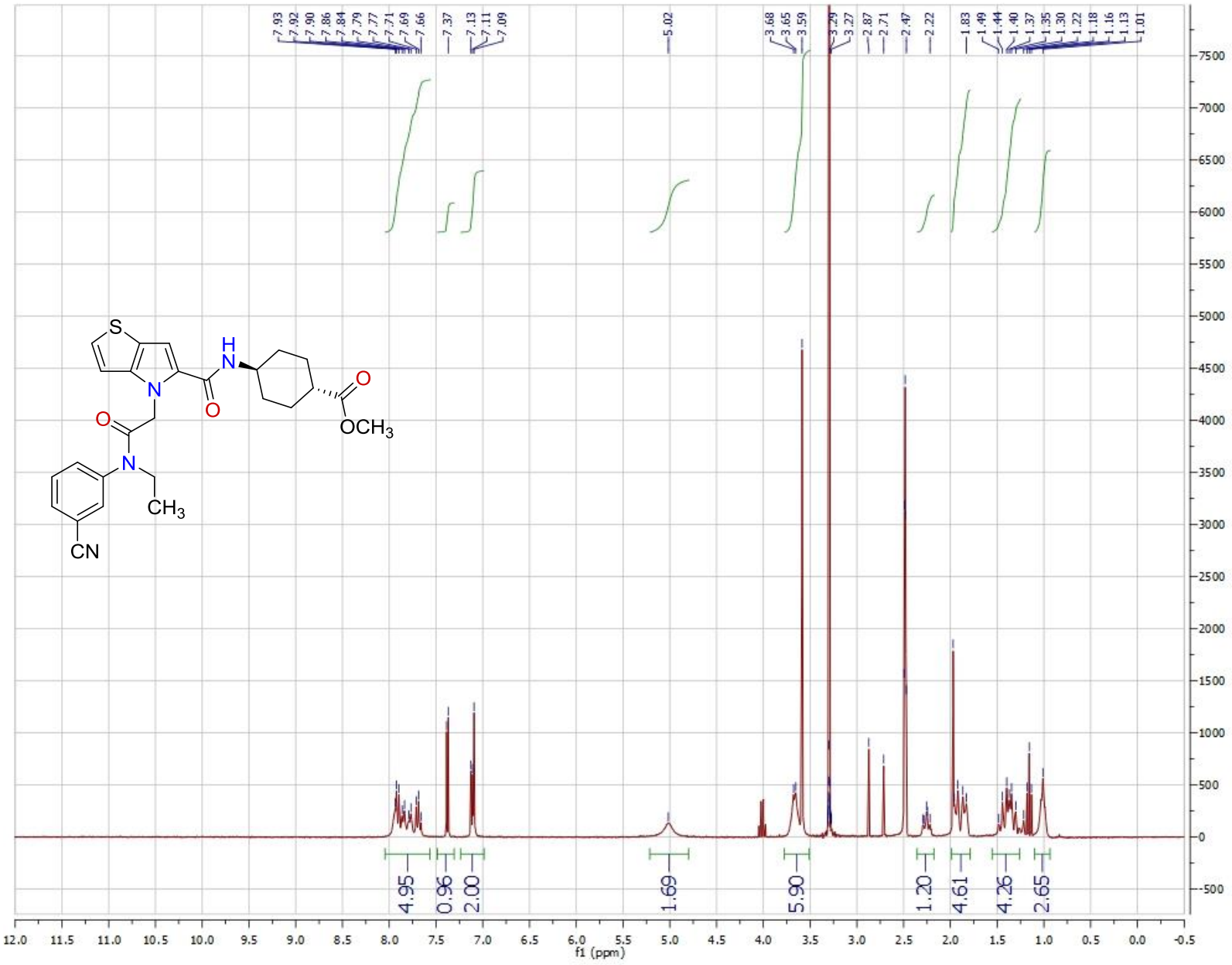
23


7.92
7.89
7.39
7.35
7.27
7.09
7.07
4.93
3.67
3.65
3.62
3.59
3.55
3.30
2.95
2.93
2.48
2.47
2.22
1.92
1.83
1.29
1.20
1.02
1.00
0.98
S
N
H
N
O
O
O
O
OCH3
N
CH3
H3C
CH3
0.98
4.50
2.00
1.67
5.49
1.04
1.12
4.09
10.19
2.58
f1 (ppm)

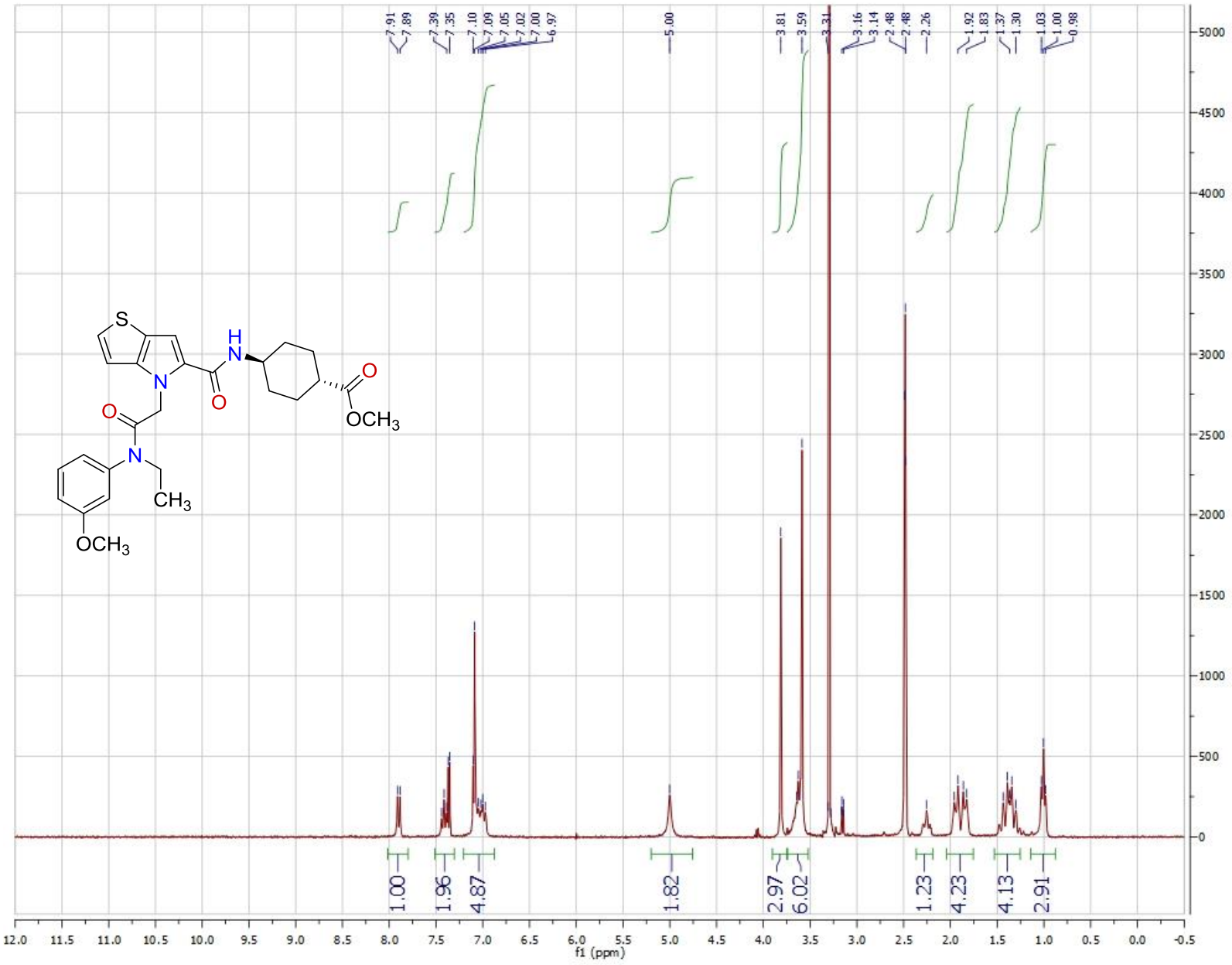
24


7.91
7.88
7.41
7.37
7.36
7.31
7.28
7.26
7.21
7.18
7.08
7.07
4.93
3.65
3.63
3.60
3.59
3.58
3.30
3.29
3.29
2.49
2.48
2.47
2.24
1.92
1.34
1.21
1.01
0.99
0.97
0.87
0.85
0.84
S
H
N
N
O
O
O
O
OCH3
N
CH3
CH3
CH3
1.00
4.79
2.00
1.77
5.76
1.29
5.25
4.92
3.06
5.80
f1 (ppm)

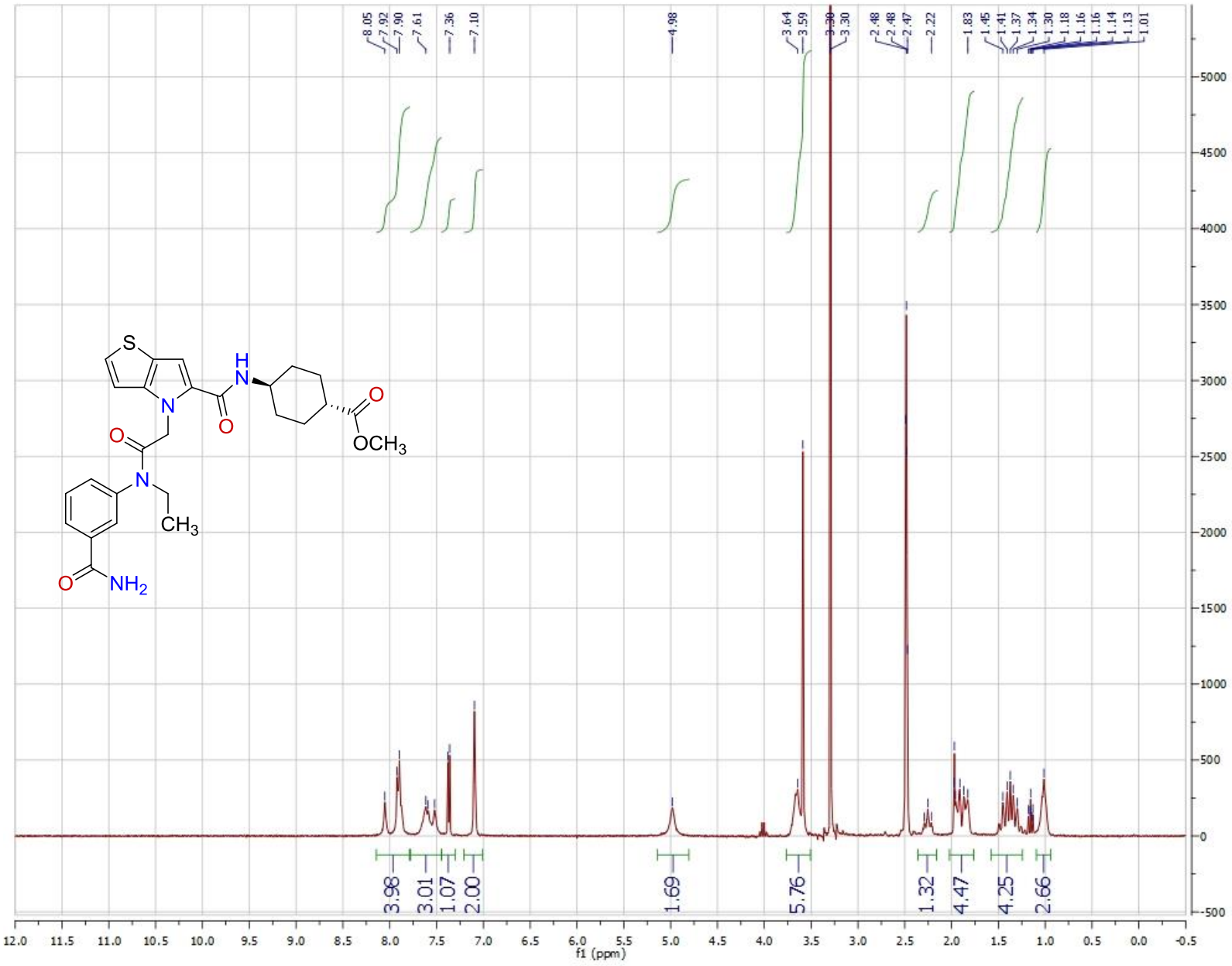
25


7.93
7.92
7.90
7.86
7.84
7.79
7.77
7.71
7.69
7.66
7.37
7.13
7.11
7.09
5.02
3.68
3.65
3.59
3.29
3.27
2.87
2.71
2.47
2.22
1.83
1.49
1.44
1.40
1.37
1.35
1.30
1.22
1.18
1.16
1.13
1.01
4.95
0.96
2.00
1.69
5.90
1.20
4.61
4.26
2.65
f1 (ppm)

26

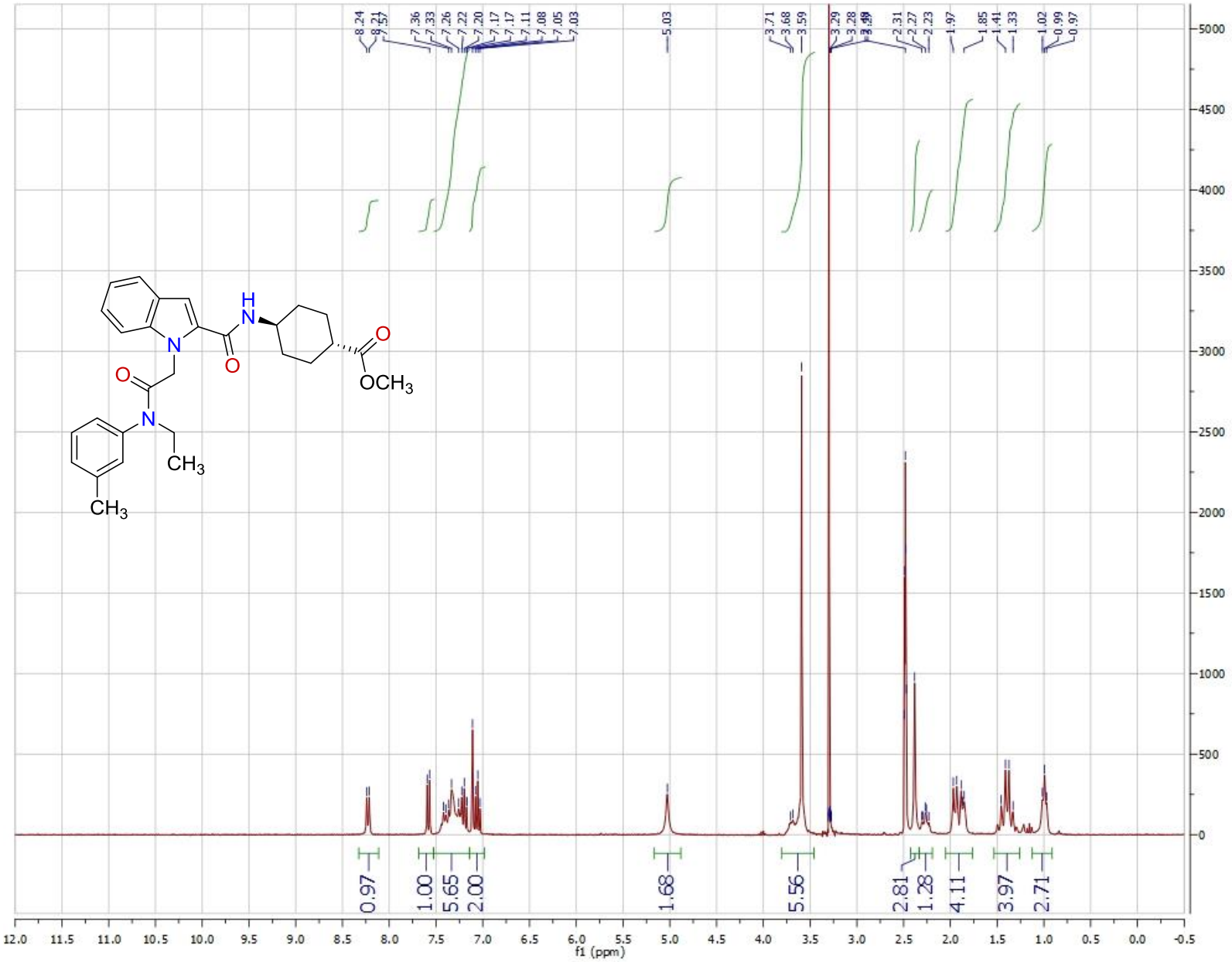

7.91
7.89
7.39
7.35
7.10
7.09
7.05
7.02
7.00
6.97
5.00
3.81
3.59
3.31
3.16
3.14
2.48
2.26
1.92
1.83
1.37
1.30
1.03
1.00
0.98
1.00
1.96
4.87
1.82
2.97
6.02
1.23
4.23
4.13
2.91
f1 (ppm)

27

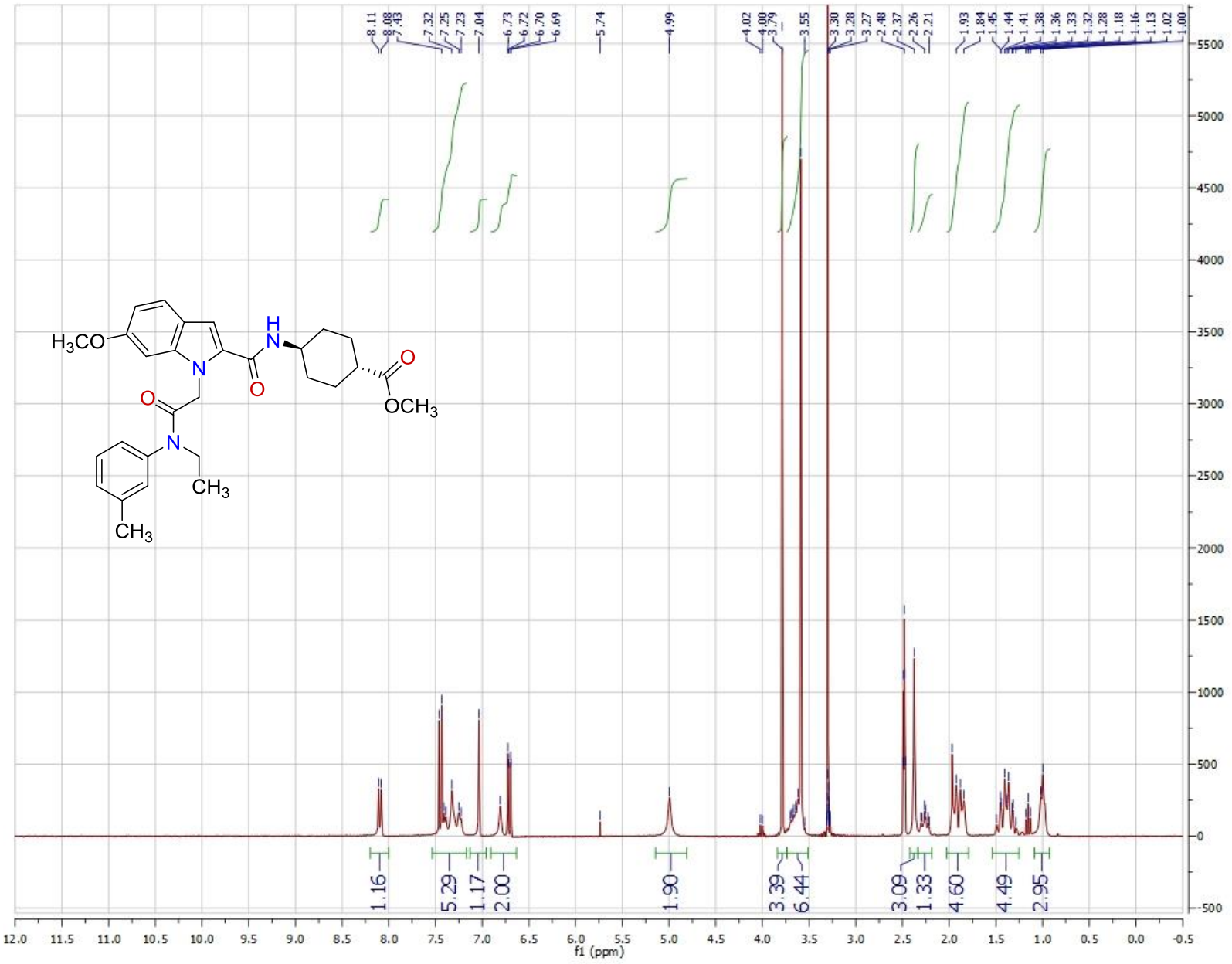

8.05
7.92
7.90
7.61
7.36
7.10
4.98
3.64
3.59
3.30
2.48
2.48
2.47
2.22
1.83
1.45
1.41
1.37
1.34
1.30
1.18
1.16
1.16
1.14
1.13
1.01
S
N
H
N
O
O
O
OCH3
O
N
CH3
O
NH2
3.98
3.01
1.07
2.00
1.69
5.76
1.32
4.47
4.25
2.66
f1 (ppm)

[1]H NMR spectra for Table 4 analogues

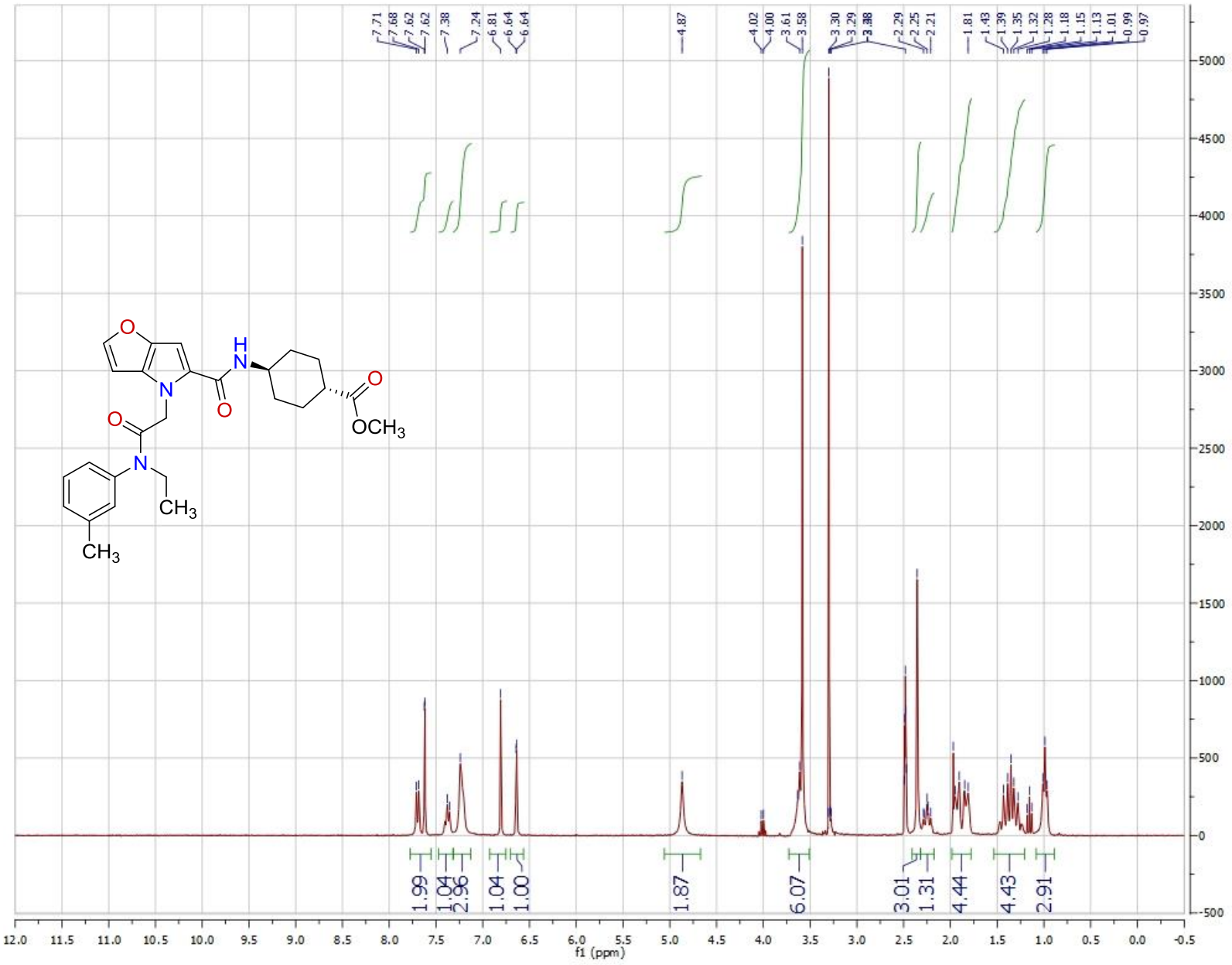
29



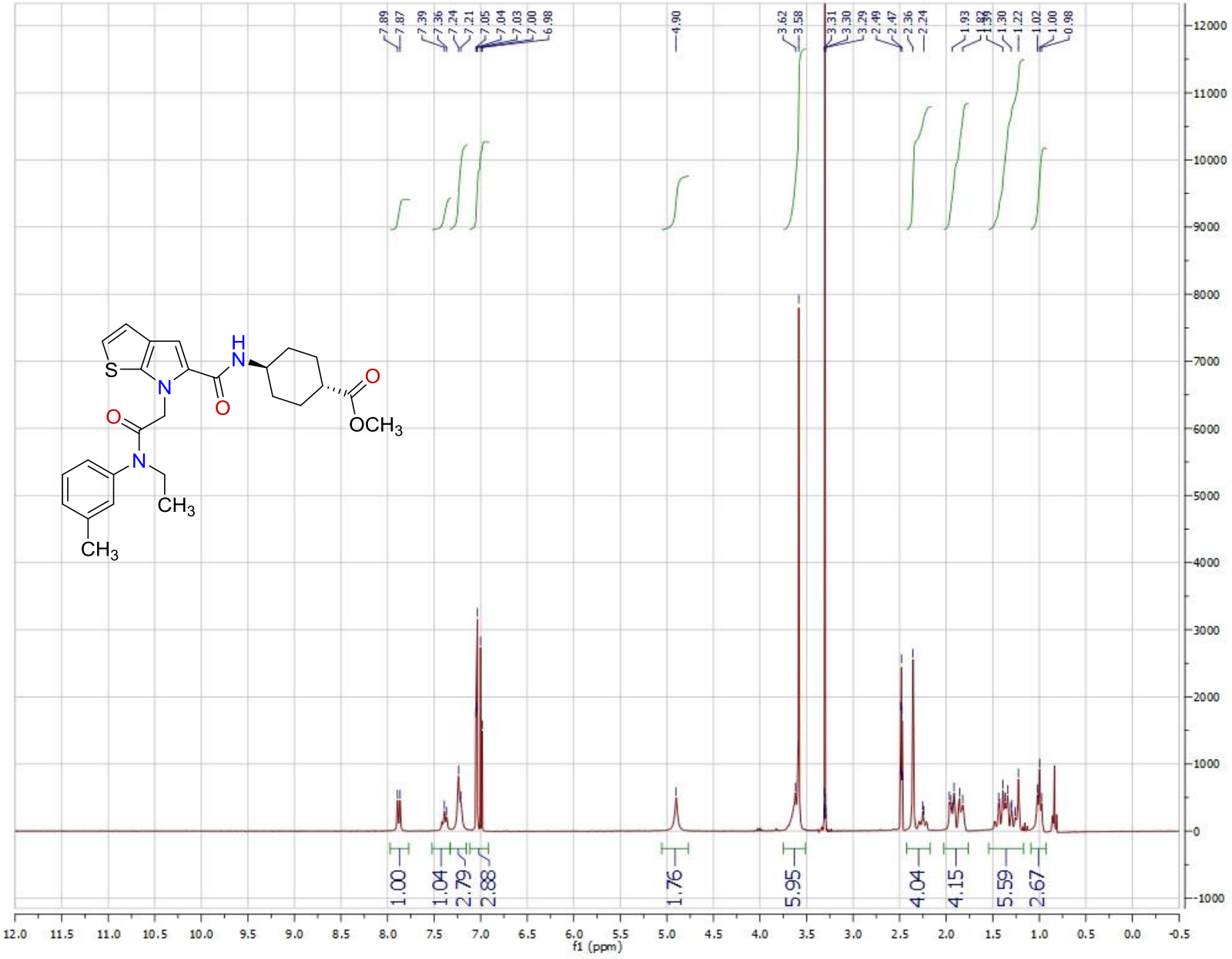
30


8.11
8.08
7.43
7.32
7.25
7.23
7.04
6.73
6.72
6.70
6.69
5.74
4.99
4.02
4.00
3.79
3.55
3.30
3.28
3.27
2.48
2.37
2.26
2.21
1.93
1.84
1.45
1.44
1.41
1.38
1.36
1.33
1.32
1.28
1.18
1.16
1.13
1.02
1.00
H3CO
N
H
O
O
O
OCH3
N
CH3
CH3
1.16
5.29
1.17
2.00
1.90
3.39
6.44
3.09
1.33
4.60
4.49
2.95
f1 (ppm)

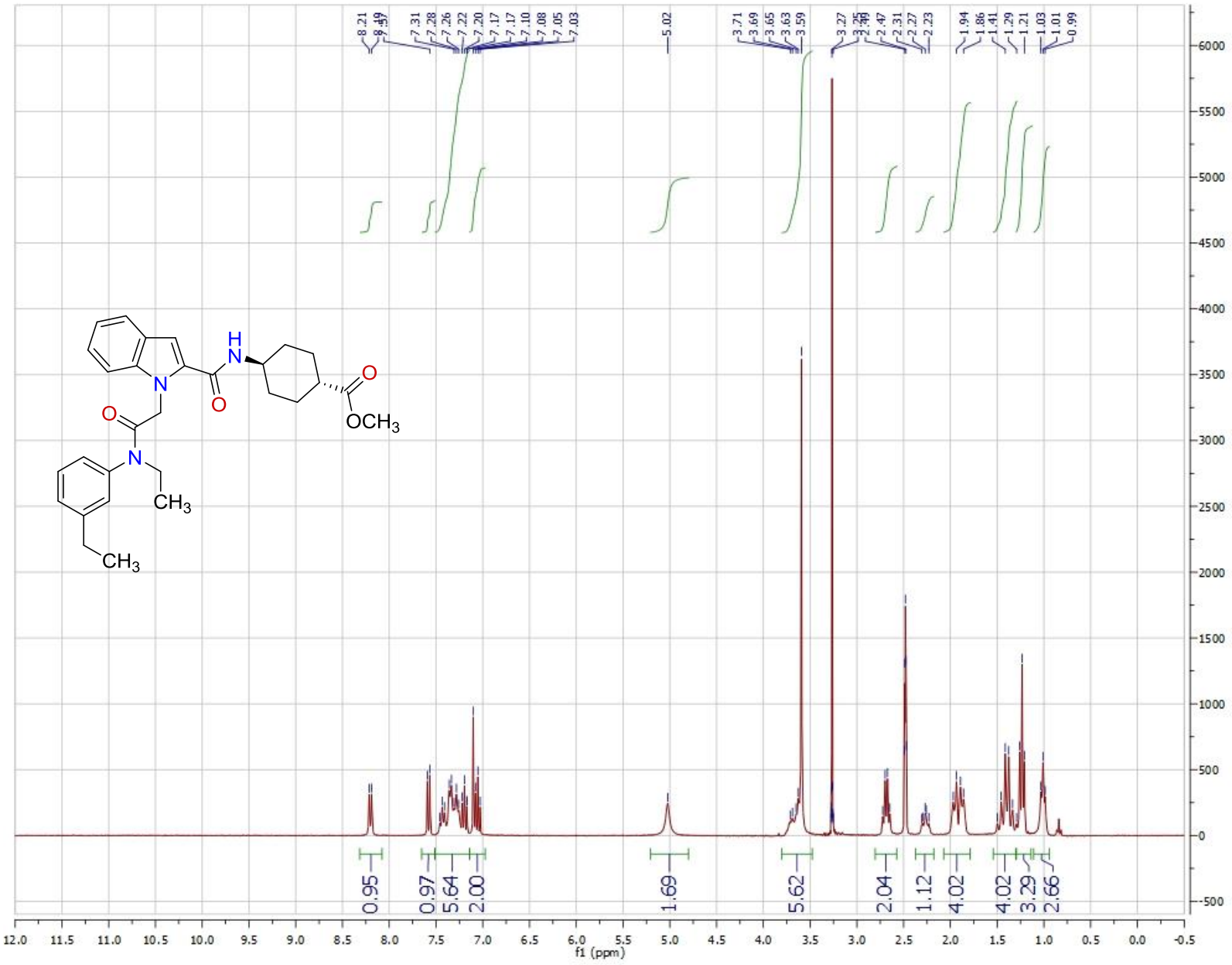
31


7.71
7.68
7.62
7.62
7.38
7.24
6.81
6.64
6.64
4.87
4.02
4.00
3.61
3.58
3.30
3.29
2.29
2.25
2.21
1.81
1.43
1.39
1.35
1.32
1.28
1.18
1.15
1.13
1.01
0.99
0.97
1.99
1.04
2.96
1.04
1.00
1.87
6.07
3.01
1.31
4.44
4.43
2.91
f1 (ppm)

32

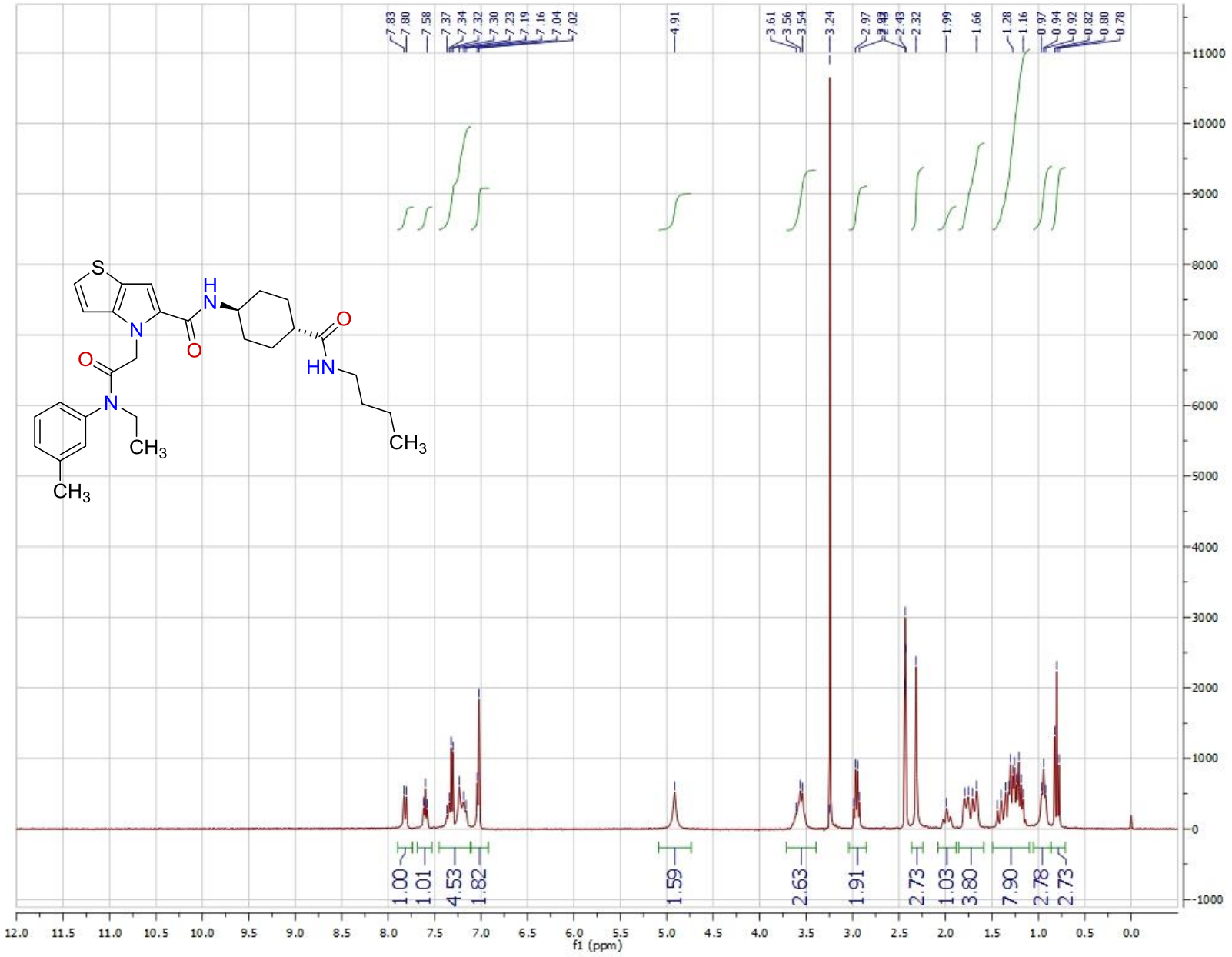

7.89
7.87
7.39
7.36
7.24
7.21
7.05
7.04
7.03
7.00
6.98
4.90
3.62
3.58
3.31
3.30
3.29
2.49
2.47
2.36
2.24
1.93
1.82
1.39
1.30
1.22
1.02
1.00
0.98
1.00
1.04
2.79
2.88
1.76
5.95
4.04
4.15
5.59
2.67
f1 (ppm)

33

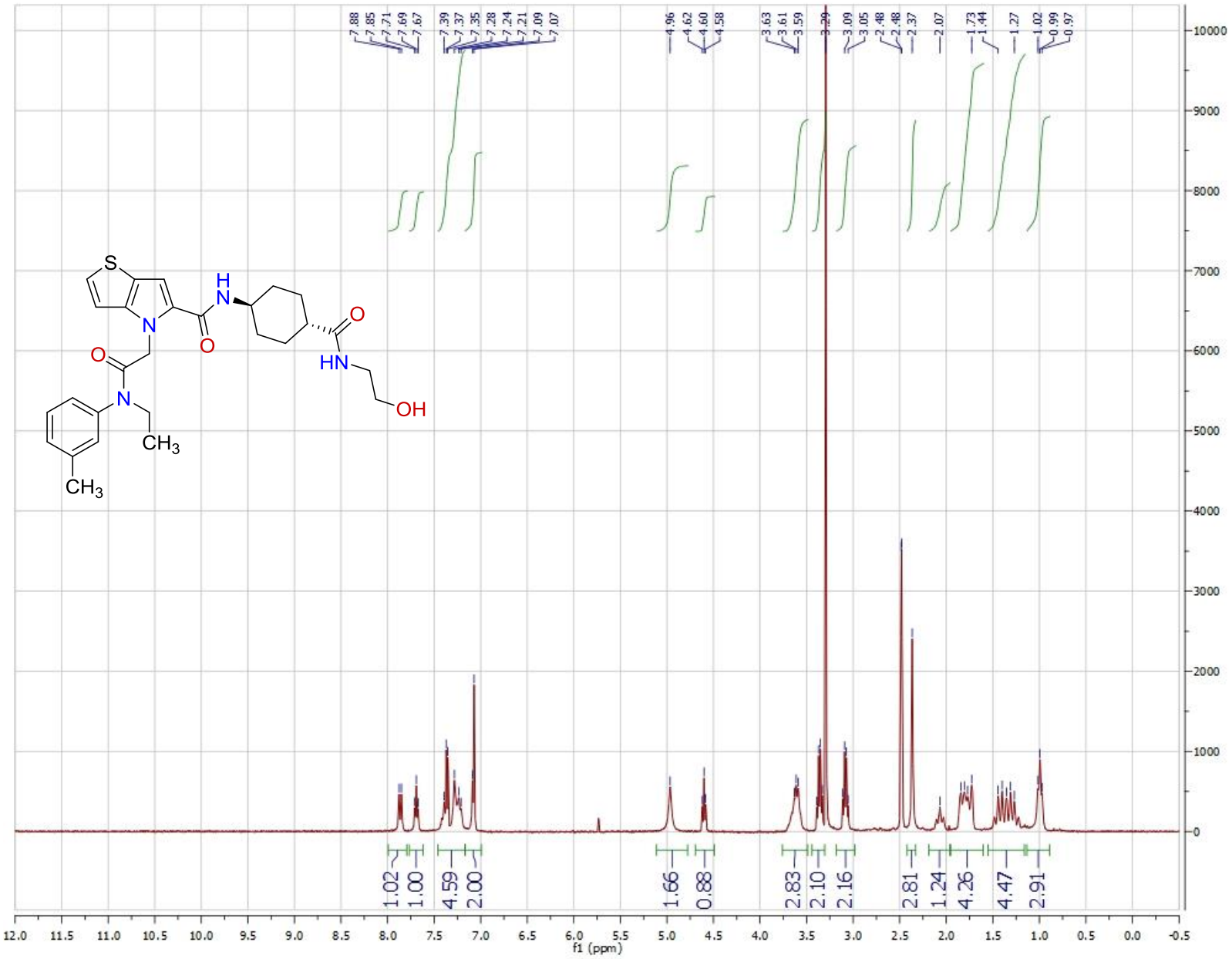

8.21
8.19
7.31
7.28
7.26
7.22
7.20
7.17
7.17
7.10
7.08
7.05
7.03
5.02
3.71
3.69
3.65
3.63
3.59
3.27
2.47
2.31
2.27
2.23
1.94
1.86
1.41
1.29
1.21
1.03
1.01
0.99
H
N
O
O
N
O
O
OCH3
N
CH3
CH3
0.95
0.97
5.64
2.00
1.69
5.62
2.04
1.12
4.02
4.02
3.29
2.66
f1 (ppm)

[1]H NMR spectra for Table 5 analogues

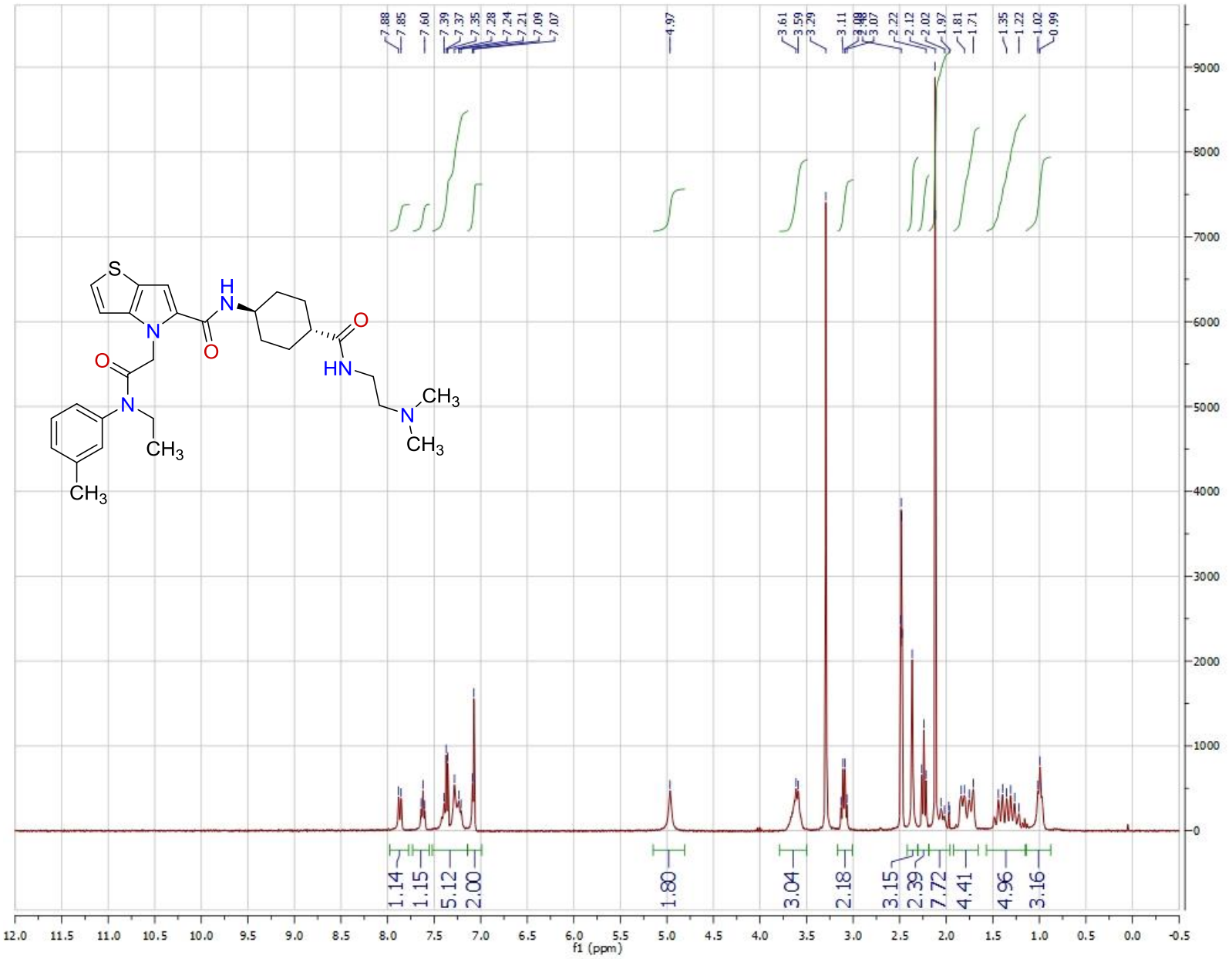
34



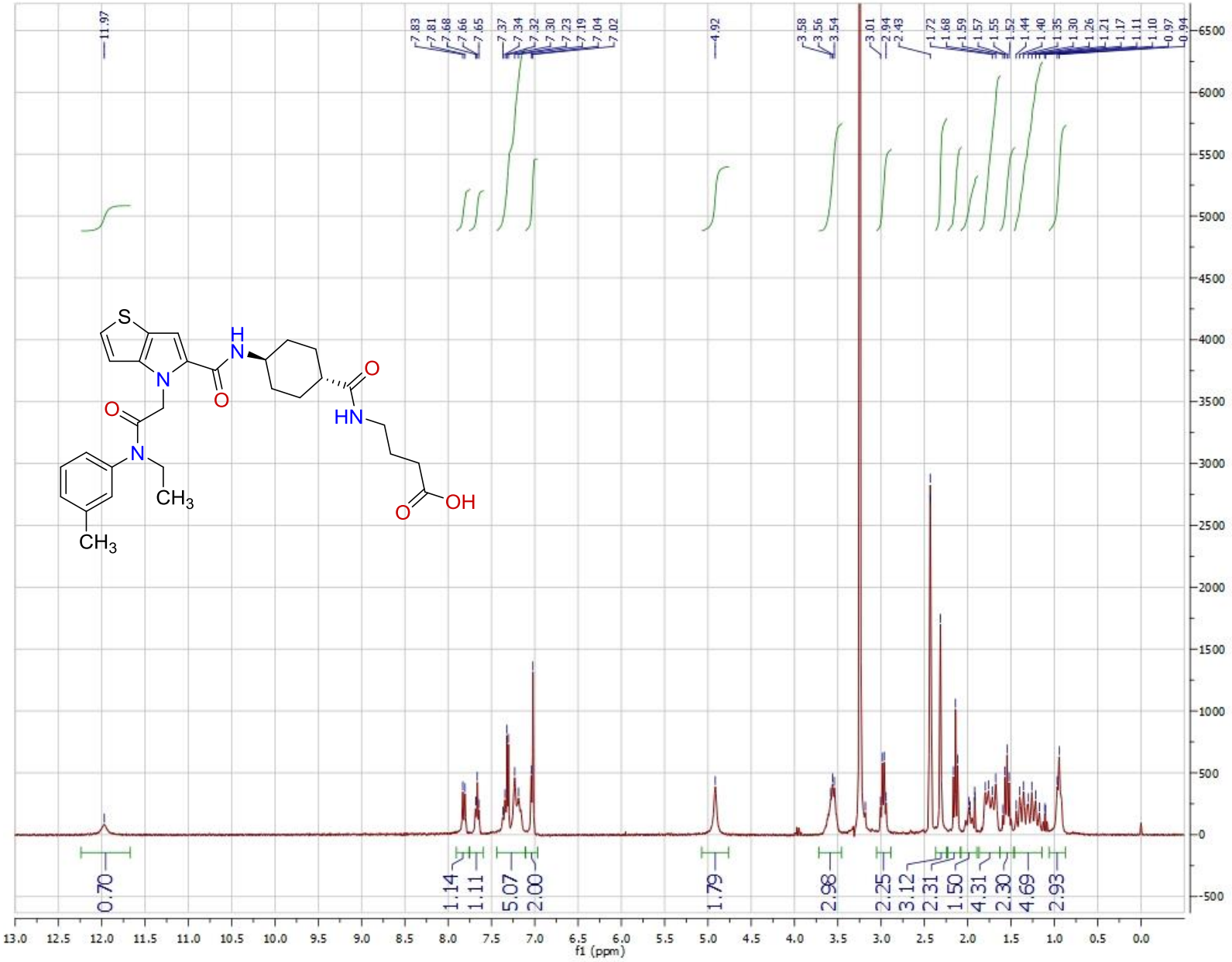
35


7.88
7.85
7.71
7.69
7.67
7.39
7.37
7.35
7.28
7.24
7.21
7.09
7.07
4.96
4.62
4.60
4.58
3.63
3.61
3.59
3.29
3.09
3.05
2.48
2.48
2.37
2.07
1.73
1.44
1.27
1.02
0.99
0.97
S
N
H
N
O
O
O
HN
OH
N
CH3
CH3
1.02
1.00
4.59
2.00
1.66
0.88
2.83
2.10
2.16
2.81
1.24
4.26
4.47
2.91
f1 (ppm)

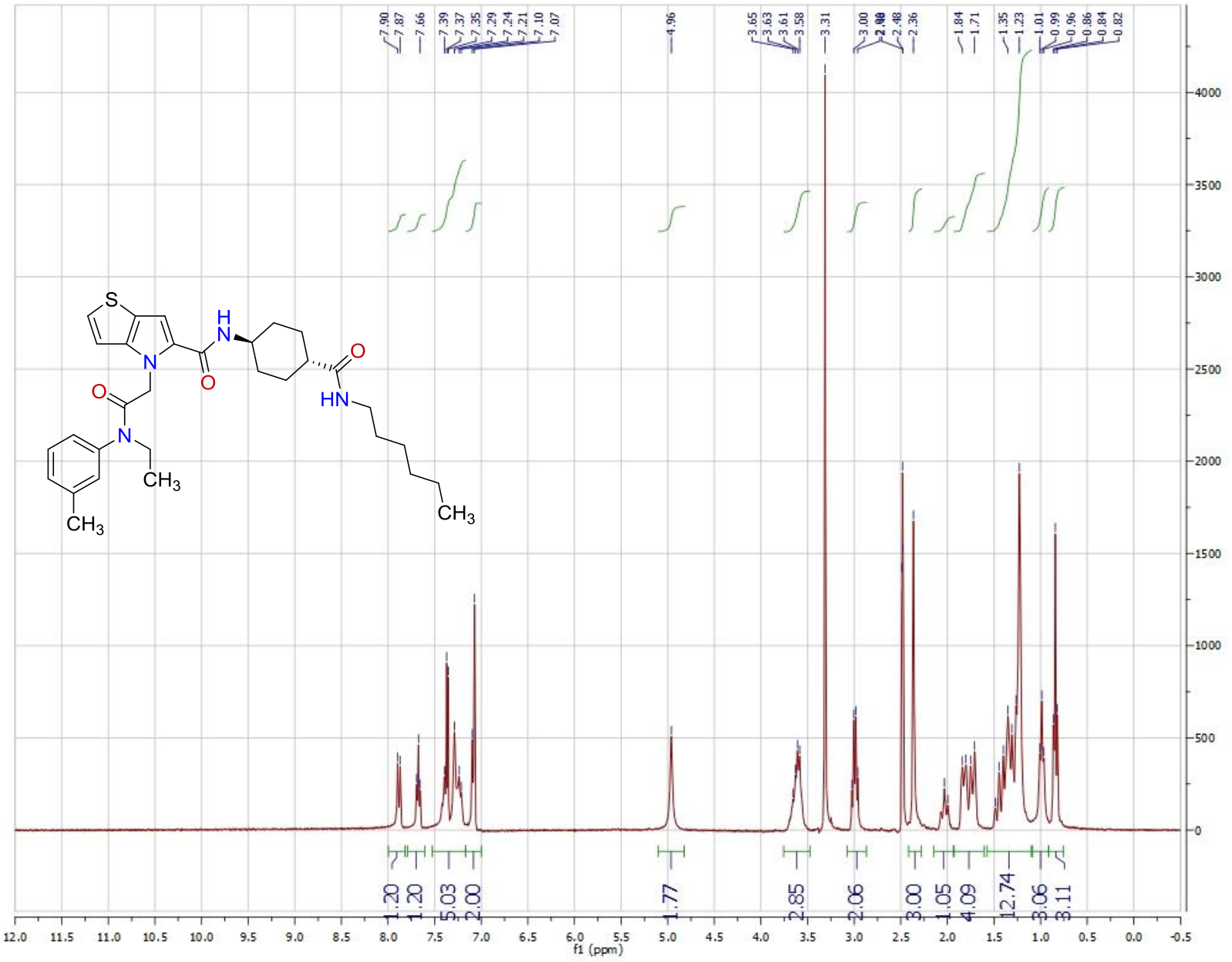
36


7.88
7.85
7.60
7.39
7.37
7.35
7.28
7.24
7.21
7.09
7.07
4.97
3.61
3.59
3.29
3.11
3.07
2.22
2.12
2.02
1.97
1.81
1.71
1.35
1.22
1.02
0.99
S
N
H
N
O
O
O
HN
N
CH3
CH3
N
CH3
CH3
1.14
1.15
5.12
2.00
1.80
3.04
2.18
3.15
2.39
7.72
4.41
4.96
3.16
f1 (ppm)

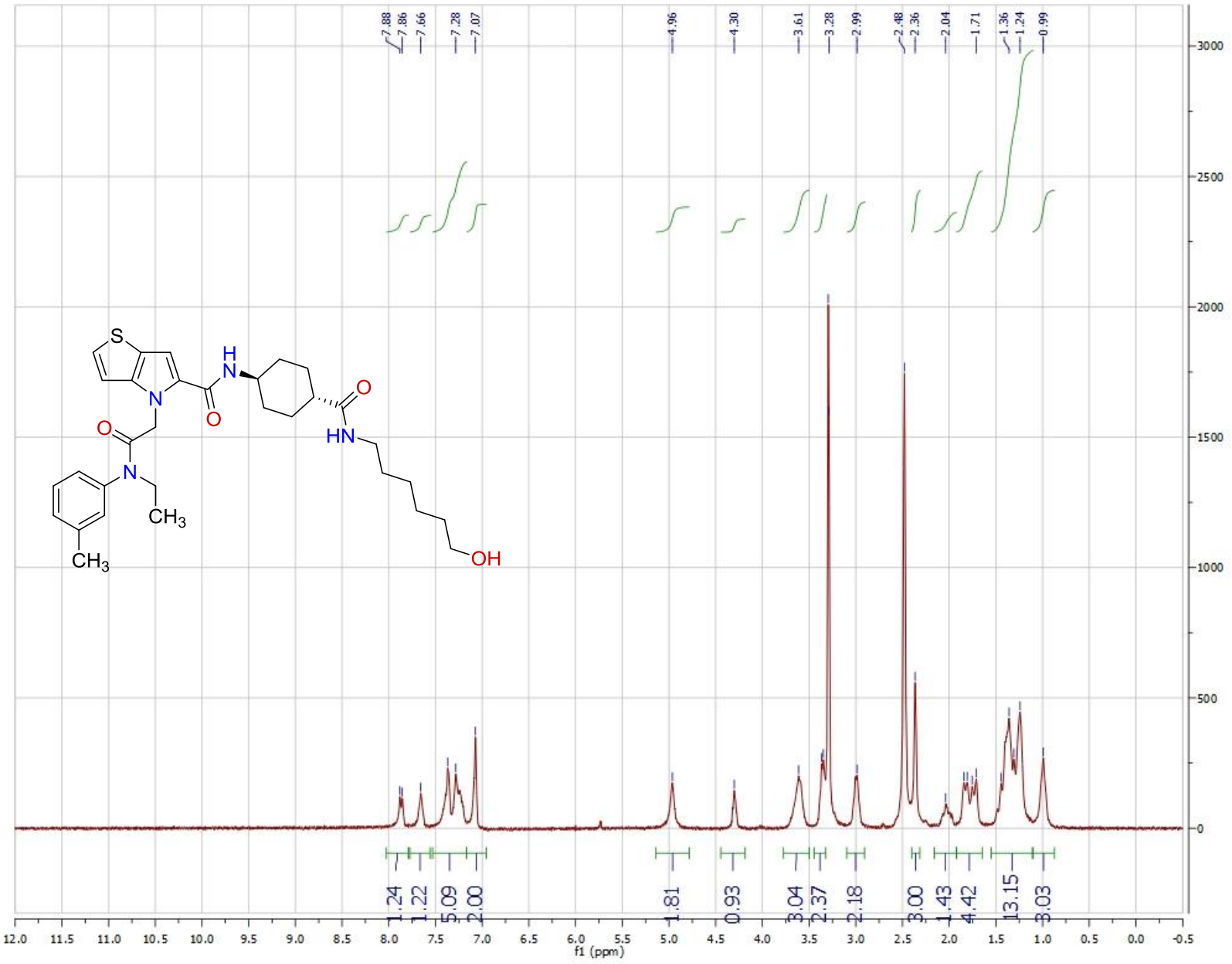
37


11.97
7.83
7.81
7.68
7.66
7.65
7.37
7.34
7.32
7.30
7.23
7.19
7.04
7.02
4.92
3.58
3.56
3.54
3.01
2.94
2.43
1.72
1.68
1.59
1.57
1.55
1.52
1.44
1.40
1.35
1.30
1.26
1.21
1.17
1.11
1.10
0.97
0.94
S
N
H
N
O
O
O
HN
O
OH
N
CH3
CH3
0.70
1.14
1.11
5.07
2.00
1.79
2.98
2.25
3.12
2.31
1.50
4.31
2.30
4.69
2.93
f1 (ppm)

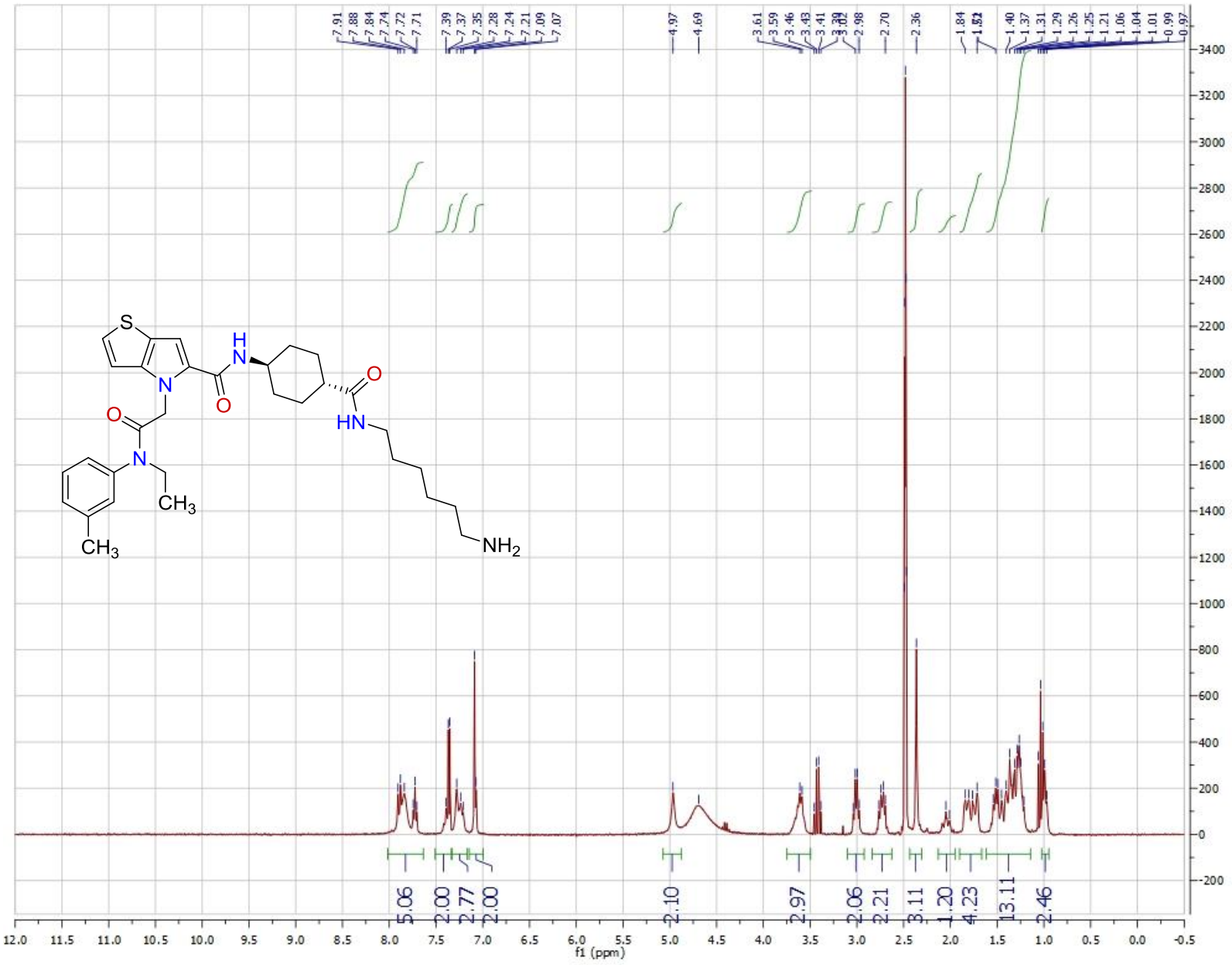
38


7.90
7.87
7.66
7.39
7.37
7.35
7.29
7.24
7.21
7.10
7.07
4.96
3.65
3.63
3.61
3.58
3.31
3.00
2.48
2.36
1.84
1.71
1.35
1.23
1.01
0.99
0.96
0.86
0.84
0.82
S
H
N
N
O
O
O
HN
N
CH3
CH3
CH3
4000
3500
3000
2500
2000
1500
1000
500
0
1.20
1.20
5.03
2.00
1.77
2.85
2.06
3.00
1.05
4.09
12.74
3.06
3.11
12.0
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
-0.5
f1 (ppm)

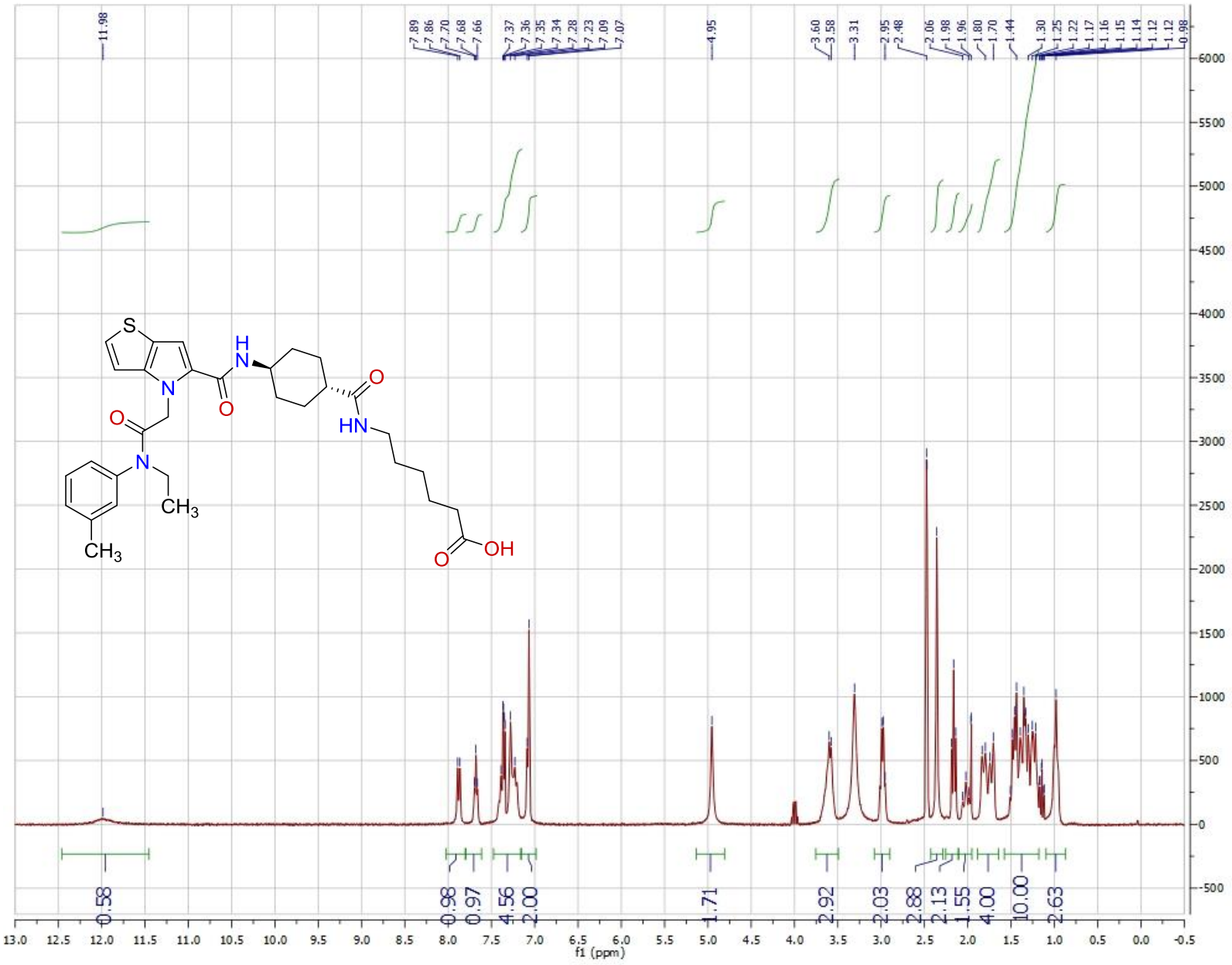
39


7.88
7.86
7.66
7.28
7.07
4.96
4.30
3.61
3.28
2.99
2.48
2.36
2.04
1.71
1.36
1.24
0.99
S
N
H
N
O
O
O
HN
OH
N
CH3
CH3
1.24
1.22
5.09
2.00
1.81
0.93
3.04
2.37
2.18
3.00
1.43
4.42
13.15
3.03
f1 (ppm)

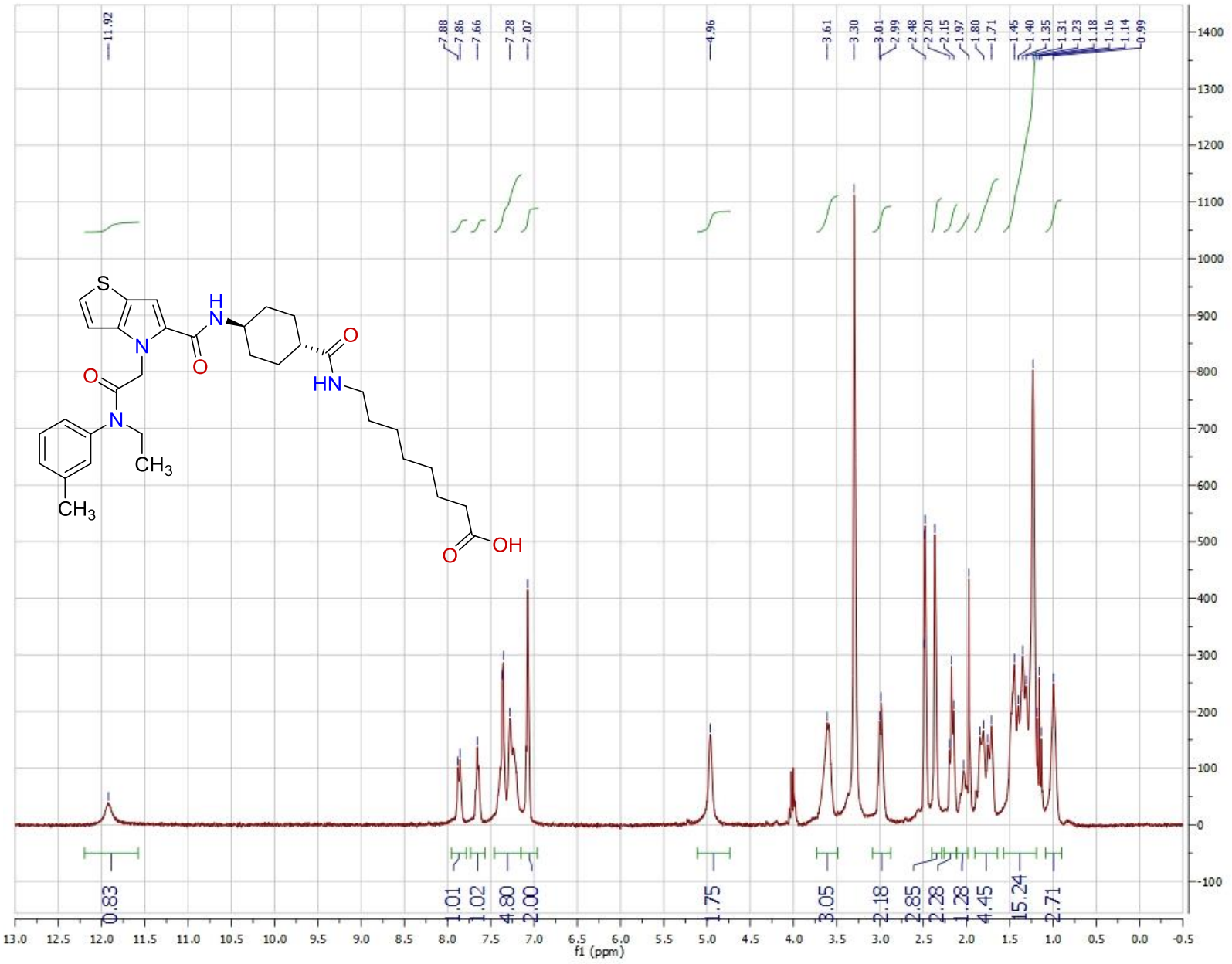
40



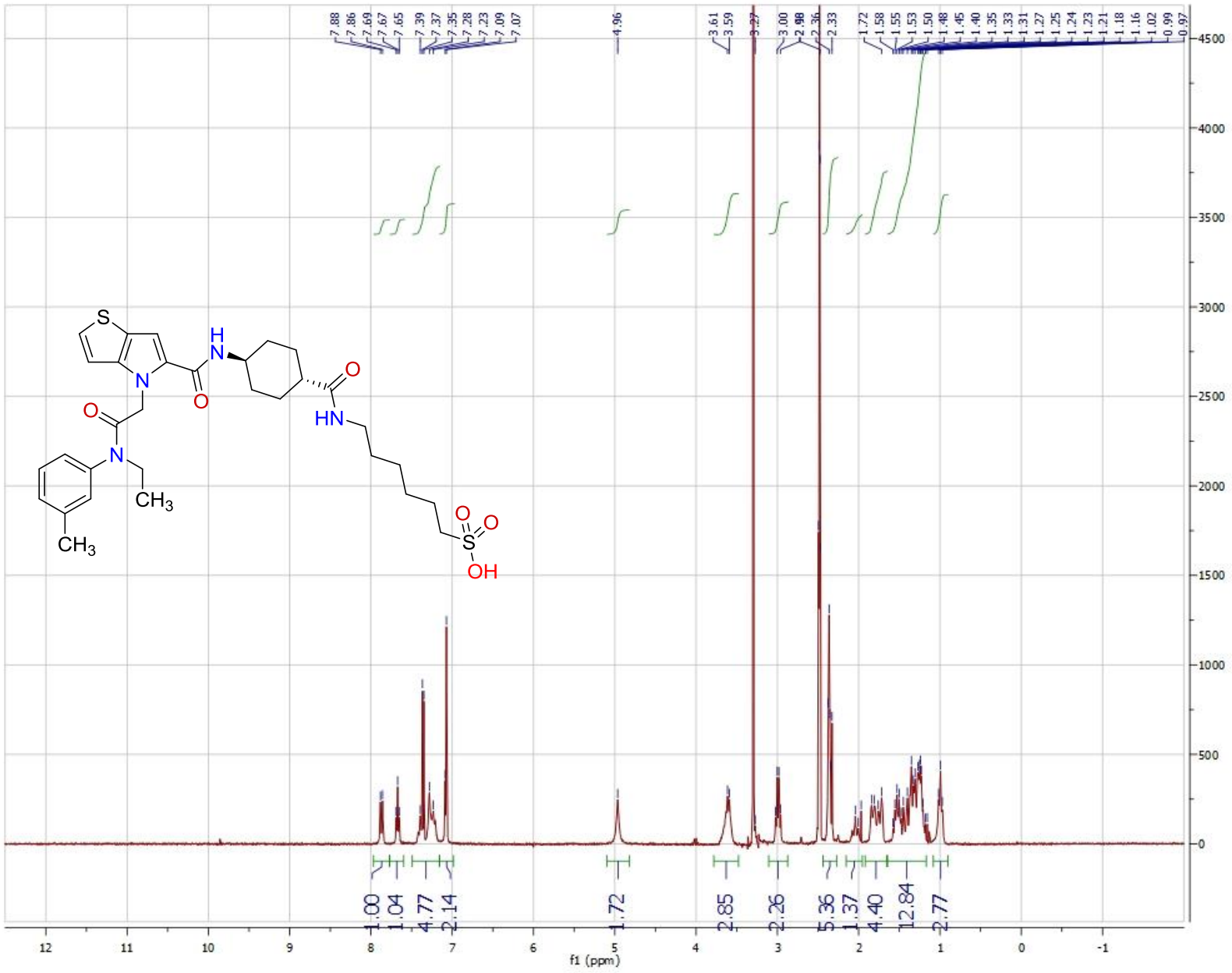
41


11.98
7.89
7.86
7.70
7.68
7.66
7.37
7.36
7.35
7.34
7.28
7.23
7.09
7.07
4.95
3.60
3.58
3.31
2.95
2.48
2.06
1.98
1.96
1.80
1.70
1.44
1.30
1.25
1.22
1.17
1.16
1.15
1.14
1.12
0.98
S
N
H
N
O
O
O
HN
O
N
CH3
CH3
O
OH
0.58
0.98
0.97
4.56
2.00
1.71
2.92
2.03
2.88
2.13
1.55
4.00
10.00
2.63
f1 (ppm)

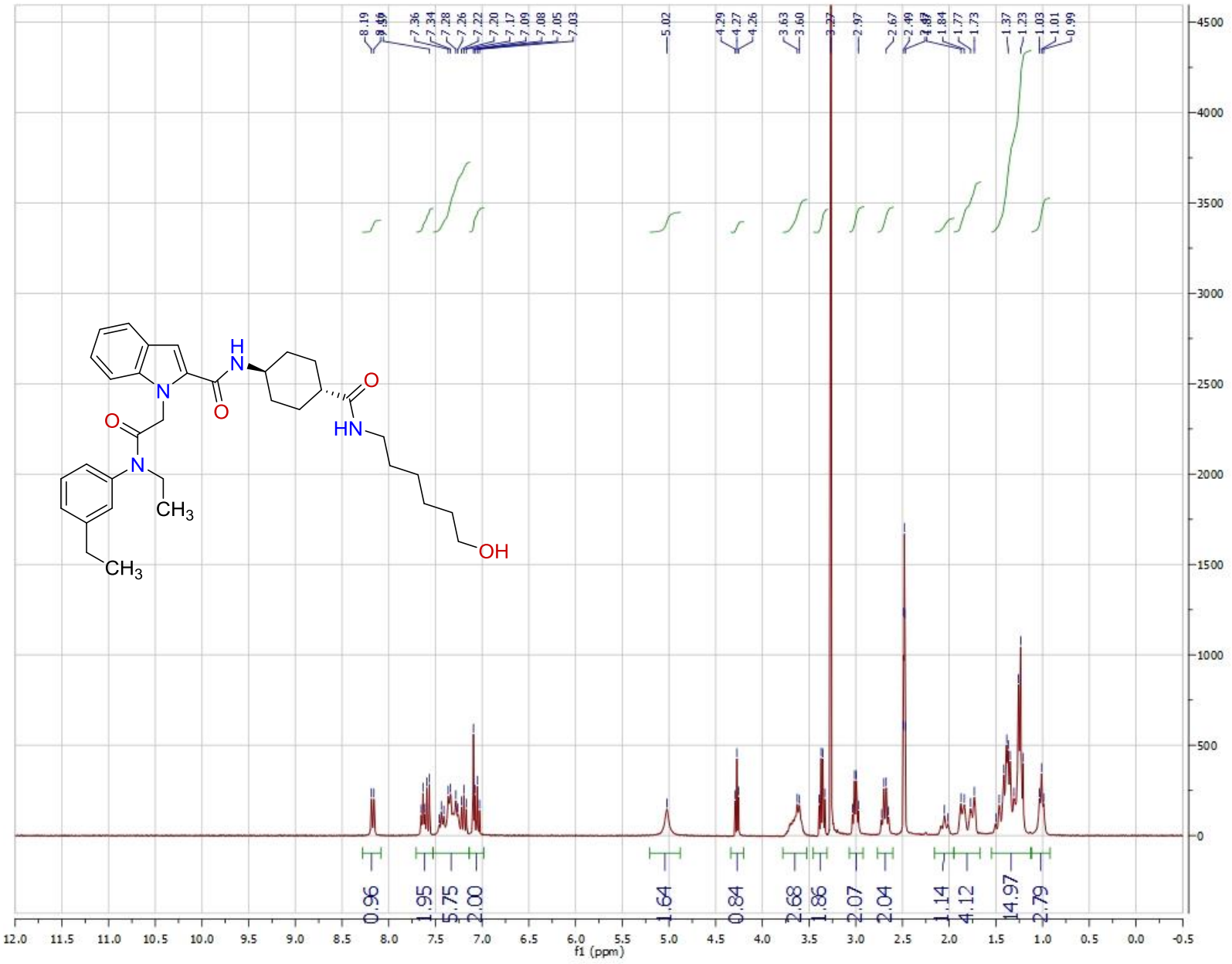
42


11.92
7.88
7.86
7.66
7.28
7.07
4.96
3.61
3.30
3.01
2.99
2.48
2.20
2.15
1.97
1.80
1.71
1.45
1.40
1.35
1.31
1.23
1.18
1.16
1.14
0.99
S
N
H
N
O
O
O
HN
N
CH3
CH3
O
OH
0.83
1.01
1.02
4.80
2.00
1.75
3.05
2.18
2.85
2.28
1.28
4.45
15.24
2.71
f1 (ppm)

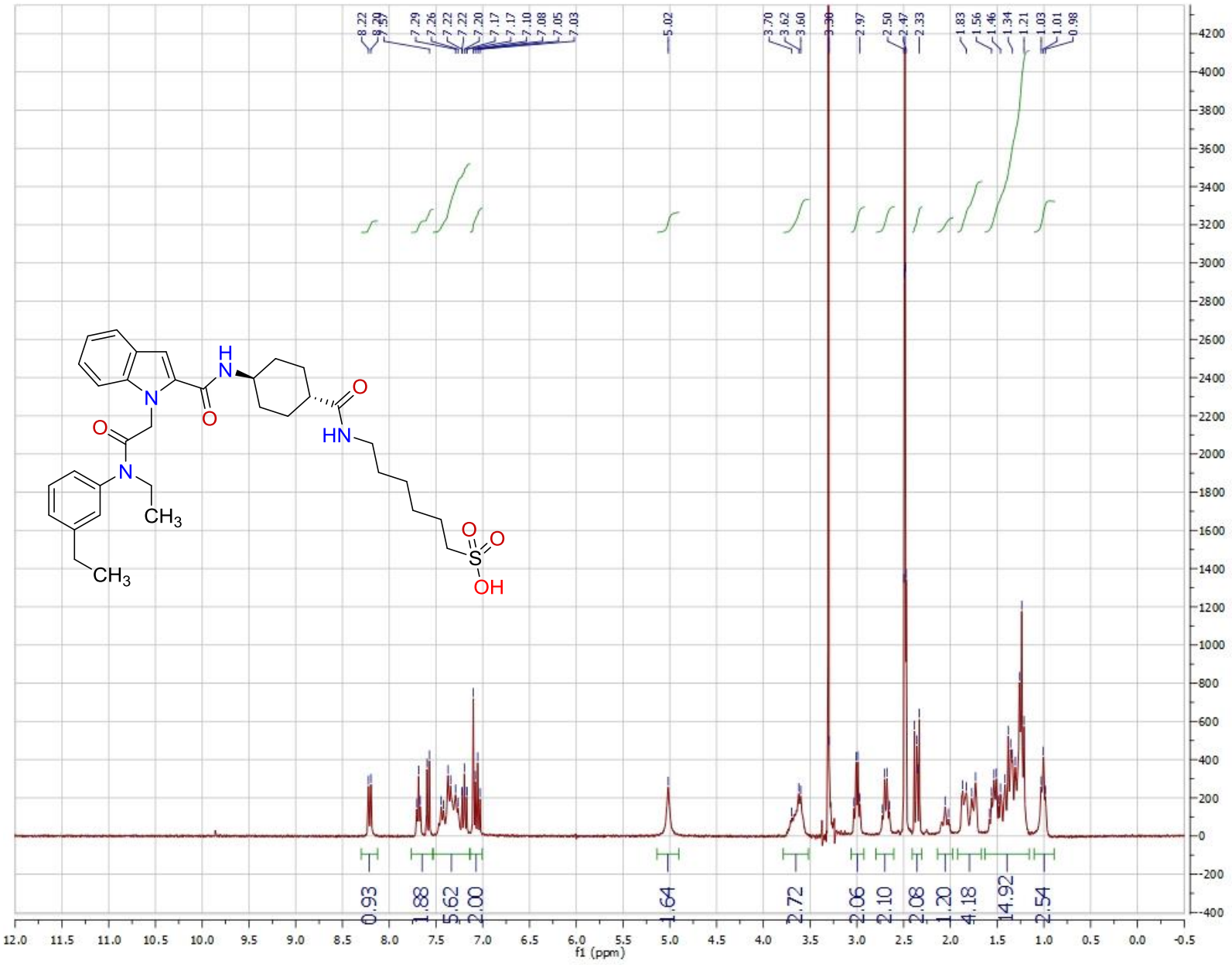
43


7.88
7.86
7.69
7.67
7.65
7.39
7.37
7.35
7.28
7.23
7.09
7.07
4.96
3.61
3.59
3.27
3.00
2.98
2.36
2.33
1.72
1.58
1.55
1.53
1.50
1.48
1.45
1.40
1.35
1.33
1.31
1.27
1.25
1.24
1.23
1.21
1.18
1.16
1.02
0.99
0.97
4500
4000
3500
3000
2500
2000
1500
1000
500
0
S
N
H
N
O
O
O
HN
O
N
CH3
CH3
O
O
S
OH
1.00
1.04
4.77
2.14
1.72
2.85
2.26
5.36
1.37
4.40
12.84
2.77
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

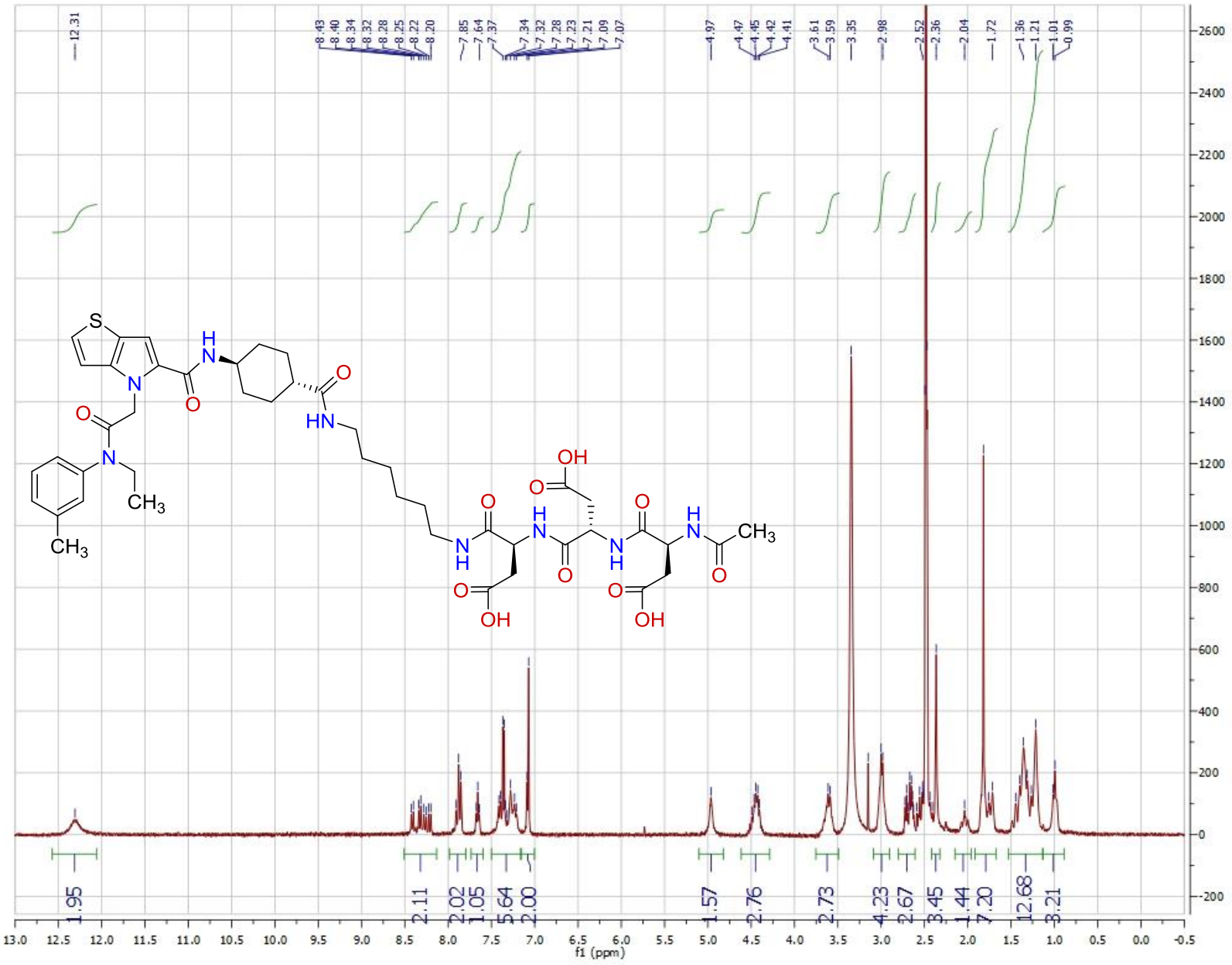
44


8.19
7.36
7.34
7.28
7.26
7.22
7.20
7.17
7.09
7.08
7.05
7.03
5.02
4.29
4.27
4.26
3.63
3.60
3.27
2.97
2.67
2.49
1.84
1.77
1.73
1.37
1.23
1.03
1.01
0.99
0.96
1.95
5.75
2.00
1.64
0.84
2.68
1.86
2.07
2.04
1.14
4.12
14.97
2.79
f1 (ppm)

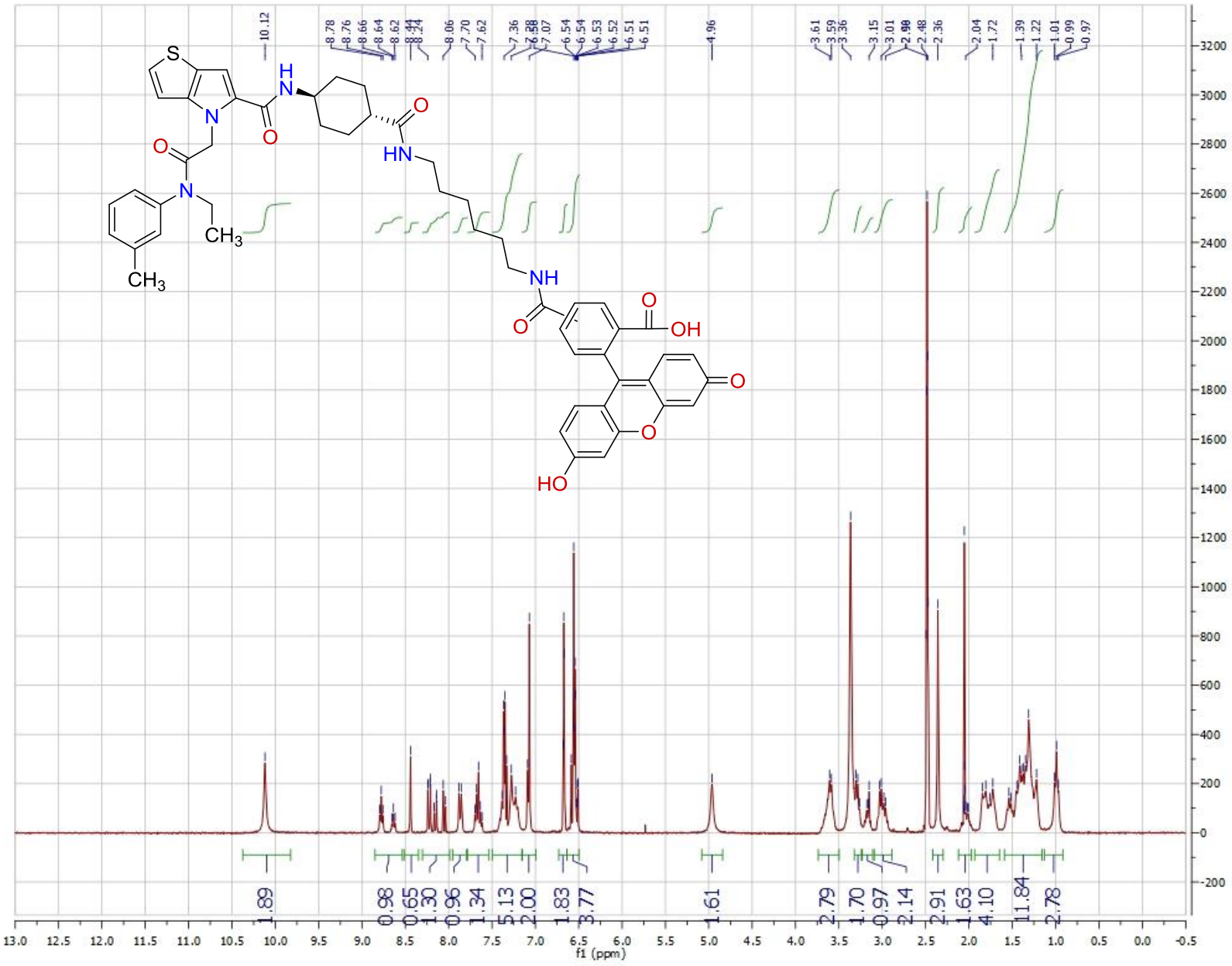
45


8.22
8.20
7.29
7.26
7.22
7.22
7.20
7.17
7.17
7.10
7.08
7.05
7.03
5.02
3.70
3.62
3.60
3.38
2.97
2.50
2.47
2.33
1.83
1.56
1.46
1.34
1.21
1.03
1.01
0.98
0.93
1.88
5.62
2.00
1.64
2.72
2.06
2.10
2.08
1.20
4.18
14.92
2.54
f1 (ppm)

46


12.31
8.43
8.40
8.34
8.32
8.28
8.25
8.22
8.20
7.85
7.64
7.37
7.34
7.32
7.28
7.23
7.21
7.09
7.07
4.97
4.47
4.45
4.42
4.41
3.61
3.59
3.35
2.98
2.52
2.36
2.04
1.72
1.36
1.21
1.01
0.99
1.95
2.11
2.02
1.05
5.64
2.00
1.57
2.76
2.73
4.23
2.67
3.45
1.44
7.20
12.68
3.21
f1 (ppm)

47


S
N
H
N
O
O
O
N
CH3
CH3
HN
O
NH
O
OH
O
O
HO
10.12
8.78
8.76
8.66
8.64
8.62
8.24
8.06
7.70
7.62
7.36
7.07
6.54
6.53
6.52
6.51
4.96
3.61
3.59
3.36
3.15
3.01
2.48
2.36
2.04
1.72
1.39
1.22
1.01
0.99
0.97
1.89
0.98
0.65
1.30
0.96
1.34
5.13
2.00
1.83
3.77
1.61
2.79
1.70
0.97
2.14
2.91
1.63
4.10
11.84
2.78
f1 (ppm)