Supporting information

Design, Synthesis and Biological Activities of Pyrrole-3-carboxamide Derivatives as EZH2 (Enhancer of Zeste Homologue 2) Inhibitors and Anticancer Agents

Qifan Zhou[a,1], Lina Jia[b,1], Fangyu Du[a], Xiaoyu Dong[b], Wanyu Sun[b], Lihui Wang[b,**], Guoliang Chen[a,*]

[a] Key Laboratory of Structure-Based Drugs Design & Discovery of Ministry of Education, School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, No. 103 Wenhua Road, Shenhe District, Shenyang 110016, P.R. China

[b] Department of Pharmacology, Shenyang Pharmaceutical University, No. 103 Wenhua Road, Shenhe District, Shenyang 110016, P.R. China

E-mail addresses: wlhcw@163.com (L. Wang), spucgl@163.com (G. Chen).

[1] Authors contributed equally to this work

* Corresponding author.

** Corresponding author.

Published in New Journal of Chemistry

Content

In vitro biological activity assay and structure-activity relationships

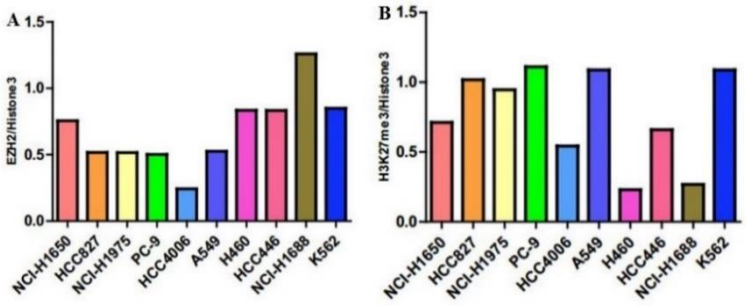


Fig. S1. The expression levels of EZH2 protein and H3K27me3 in NCI-H1650, HCC827, NCI-H1975, PC-9, HCC4006, A549, H460, NCI-H446, NCI-H1688, and K562 cell lines were evaluated by Western Blot analysis.

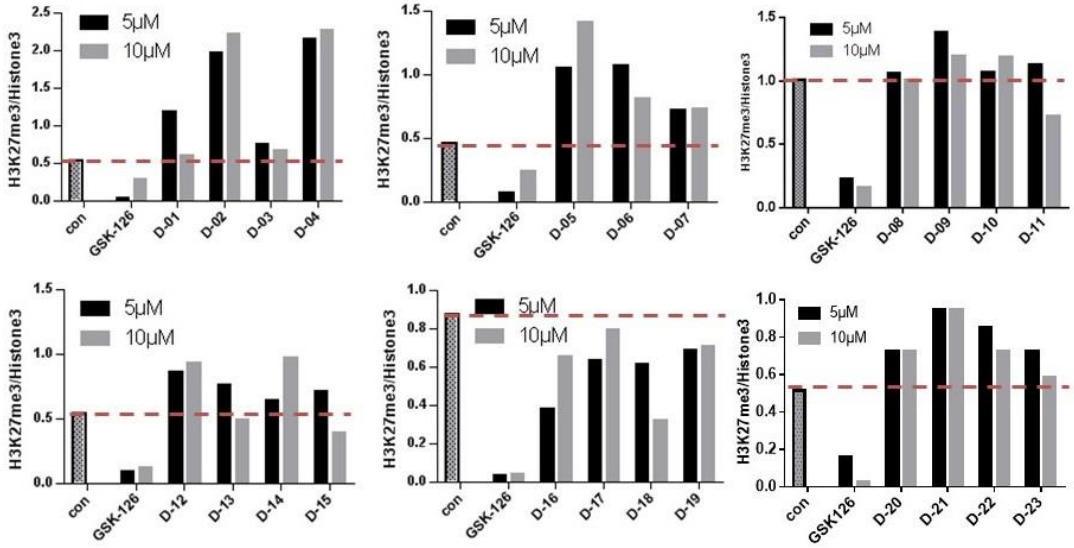


Fig. S2. The analysis results of compounds **D–01**~**D–23**: Western Blot analysis of H3K27me3 and Histone3 from whole cell extracts of K562 cells. Western Blot signal intensities were quantified using Li-Cor Odyssey software.

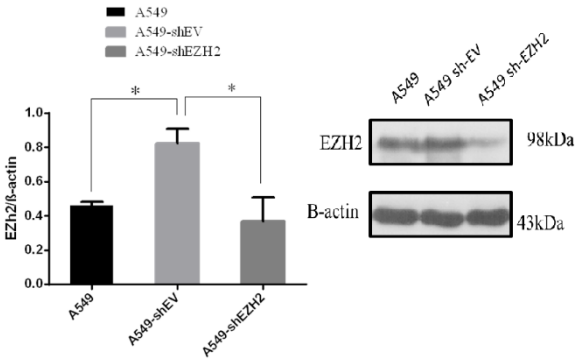


Fig. S3. The expression levels of EZH2 protein in A549, A549 sh-EV and A549 sh-EZH2 cell lines were evaluated by Western Blot analysis.

Table S1. Antiproliferative activities of target **D** compounds

Compd.	IC_{50} (μM)±SEM [a]		cLogP [b]
	A549 sh-EV	A549 sh-EZH2	
D-01	＞100	＞100	2.67
D-02	＞100	-- [c]	2.70
D-03	＞100	＞100	1.95
D-04	＞100	--[c]	2.30
D-05	＞100	70.675±5.68	3.48
D-06	--[c]	＞100	1.01
D-07	＞100	＞100	3.35
D-08	＞100	＞100	3.33
D-09	58.882±2.94	＞100	3.30
D-10	＞100	＞100	2.83
D-11	＞100	＞100	2.81
D-12	＞100	＞100	2.79
D-13	＞100	＞100	3.57
D-14	--[c]	＞100	3.54
D-15	＞100	96.44±15.67	3.96
D-16	--[c]	＞100	2.71
D-17	＞100	＞100	2.73
D-18	＞100	＞100	2.68
D-19	＞100	＞100	2.56
D-20	＞100	＞100	2.72
D-21	nd.[d]	nd.[d]	3.85
D-22	--[c]	--[c]	1.11
D-23	＞100	＞100	0.44

[a] IC_{50}: 50% inhibitory concentration (detemined by standard MTT assay for A549). Each experiment was carried out in triplicate. [b] Octanol-water partition coefficient (LogP) was calculated according to Discovery Studio 3.0. [c] No efficacy. [d] not determined.

Table S2. The docking scores of all the tested compounds [a]

Compd.	Dock score [b]	HBond [c]
CPI-1205	-178.347	-5.85427
Tazemetostat	-171.143	-6.17824
D–01	-143.345	-4.32432
D–02	-160.382	-3.5063
D–03	-136.659	-2.86534
D–04	-158.989	-5.6367
D–05	-147.802	-4.21229
D–06	-118.361	-4.82423
D–07	-151.408	-5.36123
D–08	-150.16	-4.39411
D–09	-151.063	-3.76144
D–10	-150.091	-4.82687
D–11	-147.272	-2.15874
D–12	-149.093	-5.11908
D–13	-155.363	-4.49966
D–14	-149.719	-1.22698

D–15	-148.403	-3.3977
D–16	-152.288	-7.89568
D–17	-154.04	-5.45693
D–18	-151.941	-4.81986
D–19	-153.068	-2.19157
D–20	-156.043	-3.96294
D–21	-138.114	-4.13391
D–22	-133.235	-4.48695
D–23	-148.377	-4.08955
DM–01	-170.893	-4.828511
DM–02	-157.206	-4.87884
DM–03	-167.174	-4.87658
DM–04	-166.136	-5.95209
DM–05	-158.779	-4.85084
DM–06	-171.245	-4.73084
DM–07	-156.526	-4.88756
DM–08	-161.45	-6.83564
DM–09	-177.162	-3.34921
DM–10	-168.801	-4.18332
DM–11	-164.937	-4.23492
DM–12	-161.698	-5.38672
DM–13	-166.531	-5.83652
DM–14	-167.418	-4.2586
DM–15	-166.111	-4.50688
DM–16	-169.211	-4.72843
DM–17	-165.457	-0.05118
DM–18	-174.907	-1.90193
DM–19	-159.199	-4.29282
DM–20	-162.987	-3.41619
DM–21	-161.746	-1.94797
DM–22	-160.747	-2.07864
DM–23	-164.24	-0.90063
DM–24	-166.3	-3.76701
DM–25	-159.635	-1.82106
DM–26	-167.104	-1.83783
DM–27	-165.209	-2.06471
DM–28	-170.679	-3.54023

[a] PDB code: 4W2R. [b] Dock score is calculated by Gibbs free energy of the interaction between ligand and receptor. [c] The value of H binding interaction.

Chemistry of experimental section

General

All reagents used were commercially available. All the ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 600 MHz spectrometer in DMSO-d_6. Chemical shifts (δ) were expressed in parts per million using tetramethylsilane as an internal reference. ESI-MS data were obtained using an Agilent 1100 instrument. LC-MS-ESI was recorded by Agilent 1100 Series MSD Trap (SL). Melting points were measured on X-4 digital melting point instrument. Reactions were monitored by thin-layer chromatography (TLC) and visualized by

UV-light. Column chromatography was performed on silica gel (160-200 mesh).

*4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**2**).*

To a solution of potassium carbonate (13.8 g, 0.1 mol) in water (100 ml) was added acetylacetone (11.0 g, 0.1 mol). Then cyanoacetamide (8.4 g, 0.1 mol) was added in portions, maintaining the temperature under 35 ºC. The mixture was stirred at room temperature for 24 h, and large amounts of white solid were precipitated. The mixture was then filtered, and the filter cake was washed with water. The precipitate was recrystallized from absolute methanol (1L) to afford a white crystal (13.0 g, 87.7%). M.p.280-281 ºC. ESI MS: m/z 149.1$[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 6.16 (s, 1H), 2.30 (s, 3H), 2.22 (s, 3H).

*3-(Aminomethyl)-4,6-dimethylpyridin-2(1H)-one hydrochloride (**3**).*

To a solution of **2** (5 g, 0.034 mol) in methanol (250 mL) and aq. ammonia (25%, 25 ml) was added Raney Nickel. The mixture was stirred at 50 ºC under hydrogen pressure (balloon pressure) for 11 h. On completion of reaction, the mixture was filtered off *via* a celite pad, filtrate was concentrated to dryness, and the residue was treated with conc. HCl (6 mL) and EtOH (30 mL). The solution was then cooled to 0 °C, and stirred at 0 °C for 2 h, resulting in a suspension. The precipitate was collected by filtration, and then washed with cold EtOH and ether, and vacuum-dried to give a white solid (5.6g, 87.5%). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 11.84 (brs, 1H), 8.04 (s, 3H), 5.97 (s, 1H), 3.77 (s, 1H), 2.21 (s, 3H), 2.16 (s, 3H).

*Ethyl 2,5-dimethyl-1H-pyrrole-3-carboxylate (**5**).*

Ethyl acetoacetate (10 g, 76.8 mmol) was added dropwise to aq. ammonia (25%, 32 mL, 0.229 mol) under -20 ºC. After the addition was completed, 2-chloroacetone (7.84 g, 76.8 mmol) was added dropwise into the mixture at 0 ºC. Then the mixture was stirred at room temperature. After 3.5 h, the reaction was completed as monitored by TLC. The reaction solution was adjusted to pH 6 with conc. HCl under ice-cooling, and a pale-yellow solid was precipitated (6.25 g, 48.8%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.94 (brs, 1H), 6.20 (d, *J*=2.0 Hz, 2H), 4.25 (q, *J*=7.1 Hz, 14.2 Hz, 2H), 2.48 (s, 3H), 2.19 (s, 3H), 1.32 (t, *J*=7.1 Hz, 3H).

*2,5-Dimethyl-1H-pyrrole-3-carboxylic acid (**8**).*

A mixture of **5** (10 g, 0.06 mol) and KOH (60%, 50 mL) was boiled for 9 h, then cooled, and neutralized to pH5-6 with conc. HCl. The separated brown precipitate was filtered off and dried in air, yield 8.0 g, 95.8%.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-06**).*

EDCI (0.62 g, 3.23 mmol), HOBt (0.44 g, 3.23 mmol) and TEA (1.09 g, 10.8 mmol) were added to a solution of **8** (0.3 g, 2.16 mmol) in anhydrous DCM (10 mL). The mixture was stirred at room temperature for 1 h, and then **3** (0.4 g, 2.16 mmol) was added. The reaction mixture was stirred at room temperature for 5 h and then diluted with water (20 mL), extracted with DCM (2×10 mL). The combined organic phase was successively washed with 10% HCl (3×30 mL), 10% NaOH (3×30 mL), and brine (30 mL). The organic phase was dried over anhydrous Mg_2SO_4 and concentrated under vacuum to give crude product which was purified by silica gel column chromatography using PE/EA as eluent. **D-06** was isolated as a brown solid (0.2 g, 33.9%). ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 11.45 (s, 1H), 10.62 (s, 1H), 7.18 (t, *J*=5.22 Hz, 1H), 5.96 (d, 1H), 5.84 (s, 1H), 4.18 (d, *J*=5.28 Hz, 2H), 2.33 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H).^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm): 165.3, 163.7, 149.1, 142.8, 130.8, 124.8, 123.0, 114.2, 108.0, 104.9, 34.9, 19.3, 18.6, 13.0, 12.8. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{19}H_{21}N_2O_3Na$: 296.1369; found: 296.1379.

*General procedure for preparation of intermediates **6a-v**.*

To a mixture of sodium hydride (0.28 g, 60% in mineral oil, 0.17g, 7.0 mmol) in DMF (5 mL) stirring at 0 °C, was added **5** (1.0 g, 5.8 mmol) and the solution was stirred at 0 °C for 15 min. Benzyl bromide (0.80 ml, 1.15 g, 6.7 mmol) was then added and the reaction allowed to warm to room temperature. After stirred for 24 h, the reaction was quenched with water, extracted with EA, washed with brine, dried over Na_2SO_4, and concentrated to afford **6a** as brown oil, (1.3 g, 86.7%). This intermediate was taken to the next step without further purification. Intermediates **6b-v** were synthesized according to this method, yield 56.9-86.0%.

*General procedure for preparation of intermediates **7a-v.***

A mixture of **6a** (1.3 g, 5.1 mmol) and KOH (60%, 50 mL) was boiled for 4 h, then cooled, and neutralized to pH1 with conc. HCl. The separated precipitate **7a** was filtered off and dried in air, yield 1.1 g, 96.3%. Intermediates **7b-v** were synthesized according to this method, yield 90.8-97.6%.

*4.1.8. General procedure for preparation of **D** series compounds.* **D-01~D-05** and **D-07~D-23** were prepared from **3** using a procedure analogous to that described for the synthesis of **D-06** but **7a-v** in place of **8**.

Compounds D01-05, D07-23.

*1-Benzyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-01**)*. White solid (0.34 g, 43%). M.p.178-181 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.47 (s, 1H), 7.35 (t, *J*=5.2 Hz, 1H), 7.31 (t, *J*=7.5 Hz, 2H), 7.23 (t, *J*=7.4 Hz, 1H), 6.87 (d, *J*=7.4 Hz, 2H), 6.19 (s, 1H), 5.85 (s, 1H), 5.07 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 2.35 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.2, 163.7, 149.3, 142.9, 138.5, 132.4, 129.1, 127.5, 127.3, 126.1, 122.9, 114.2, 108.1, 105.7, 46.3, 35.0, 19.4, 18.6, 12.4, 11.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{22}H_{25}N_3O_2Na$: 386.1839; found: 386.1847.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(3-methoxybenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-02**)*. White solid (0.15 g, 33%). M.p.89-92 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.45 (brs, 1H), 7.35 (t, *J*=5.1 Hz, 3H), 7.23-7.24 (m, 2H), 6.80-6.82 (dd, *J*=8.2 Hz, 2.2 Hz, 2H), 6.44 (s, 1H), 6.38 (d, *J*=7.6 Hz, 1H), 6.19 (s, 1H), 5.85 (s, 1H), 5.03 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 3.40 (s, 3H), 2.35 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.2, 163.7, 160.0, 149.3, 142.9, 140.2, 132.4, 130.3, 127.3, 122.9, 118.0, 114.2, 112.4, 112.1, 108.0, 55.4, 46.2, 35.1, 19.4, 18.6, 12.4, 11.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{23}H_{27}N_3O_3Na$: 416.1945; found: 416.1955.

*1-(Cyclopropylmethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-03**)*. White solid (0.15 g, 30%). M.p. 108-110 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.51 (s, 1H), 7. 25 (t, *J*=5.2 Hz, 1H), 6.08 (s, 1H), 5.84 (s, 1H), 4.19 (d, *J*=5.3 Hz, 2H), 3.68 (d, *J*=6.5 Hz, 2H), 2.44 (s, 3H), 2.16 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.04-0.99 (m, 1H), 0.48-0.45 (m, 2H), 0.27-0.25 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.2, 162.7, 148.1, 141.8, 130.7, 125.6, 121.9, 112.8, 106.9, 104.3, 45.7, 33.9, 18.3, 17.6, 11.7, 10.9, 10.5, 3.0. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{19}H_{25}N_3O_2Na$: 350.1839; found: 350.1836.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(2,3,4-trimethoxybenzyl)-1H-pyrrole-3-carboxamide (**D-04**)*. White solid (0.10 g, 36%). M.p. 180-182 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.45 (s, 1H), 7.35 (t, *J*=5.2 Hz, 1H), 6.20 (s, 1H), 6.19 (s, 2H), 5.85 (s, 1H), 6.44 (s, 1H), 4.98 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 3.66 (s, 6H), 3.62 (s, 3H), 2.38 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 167.4, 165.2, 163.7, 153.6, 149.3, 142.9, 136.9, 134.2, 132.4, 127.4, 114.2, 108.0, 105.6, 103.4, 60.5, 56.3, 46.4, 35.1, 19.3, 18.6, 12.5, 11.4. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{25}H_{31}N_3O_5Na$: 476.2156; found: 476.2161.

*1-(4-Bromobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-05**)*. White solid (0.33 g, 77%). M.p. 148-151 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.46 (s, 1H), 7.53-7.50 (m, 2H), 7.37 (t, *J*=5.2 Hz, 1H), 6.82 (d, *J*= 8.5 Hz, 2H), 6.21 (s, 1H), 5.85 (s, 1H), 5.05 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm):

165.1, 163.7, 149.3, 142.9, 138.0, 132.3, 132.1, 128.3, 127.2, 122.9, 120.5, 114.4, 108.0, 105.8, 45.8, 35.1, 19.4, 18.6, 12.4, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}BrN_3O_2Na$: 464.0944; found: 466.0937.

*1-(4-Chlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-07**)*. White solid (0.30 g, 67%). M.p. 165-167 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.46 (s, 1H), 7.39-7.36 (m, 3H), 6.88 (d, *J*=8.5 Hz, 2H), 6.21 (d, *J*=0.5 Hz, 1H), 5.85 (s, 1H), 5.07 (s, 2H), 4.20 (d, *J*=5.3 Hz, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.1, 163.7, 149.3, 142.9, 137.6, 132.3, 132.0, 129.1, 128.0, 127.2, 122.9, 114.4, 108.0, 105.8, 45.7, 35.1, 19.4, 18.6, 12.4, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}ClN_3O_2Na$: 420.1449; found: 420.1441.

*1-(3-Chlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-08**)*. White solid (0.30 g, 67%). M.p. 128-130 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.46 (s, 1H), 7.39 (t, *J*=5.2 Hz, 1H), 7.37-7.31 (m, 2H), 6.91 (s, 1H), 6.79 (d, *J*=7.6 Hz, 1H), 6.22 (d, *J*=0.5 Hz, 1H), 5.85 (s, 1H), 5.10 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.1, 163.7, 149.3, 142.9, 141.2, 133.9, 132.3, 131.1, 127.5, 127.3, 125.9, 124.7, 122.9, 114.4, 108.0, 105.9, 45.8, 35.1, 19.4, 18.6, 12.4, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}ClN_3O_2Na$: 420.1449; found: 420.1452.

*1-(2-Chlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-09**)*. White solid (0.60 g, 67%). M.p. 219-221 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.47 (s, 1H), 7.51 (d, *J*=7.9 Hz, 1H), 7.41 (t, *J*=5.2 Hz, 1H), 7.3Ⅲ-7.24 (m, 2H), 6.27 (s, 1H), 6.16 (d, *J*=7.5 Hz, 1H), 5.86 (s, 1H), 5.09 (s, 2H), 4.21 (d, *J*=5.2 Hz, 2H), 2.32 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.0, 163.7, 149.3, 142.9, 135.6, 132.4, 131.3, 129.8, 129.4, 128.3, 127.3, 126.7, 122.9, 114.6, 108.0, 106.0, 44.4, 35.1, 19.4, 18.6, 12.1, 11.0. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}ClN_3O_2Na$: 420.1449; found: 420.1454.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-10**)*. White solid (0.19 g, 41%). M.p. 219-220 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.46 (s, 1H), 7.39-7.35 (m, 2H), 7.09-7.06 (m, 2H), 6.68-6.66 (m, 2H), 6.22 (d, *J*=0.7 Hz, 1H), 5.85 (s, 1H), 5.10 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.1, 163.7, 162.9 (*J*=242.8 Hz), 149.3, 142.9, 141.6 (*J*=7.3 Hz), 132.3, 131.2 (*J*=8.0 Hz), 127.3, 122.9, 122.1 (*J*=2.0 Hz), 114.4, 114.3 (*J*=23.1 Hz), 112.9 (*J*=22.0 Hz), 108.0, 105.8, 45.9, 35.1, 19.4, 18.6, 12.3, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}FN_3O_2Na$: 404.1745; found: 404.1743.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-11**)*. White solid (0.39 g, 63%). M.p. 222-224 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.46 (s, 1H), 7.39 (t, *J*= 5.2 Hz, 1H), 7.15 (t, *J*=8.8 Hz, 2H), 6.91-6.89 (q, 2H), 6.20 (s, 1H), 5.85 (s, 1H), 5.06 (s, 2H), 4.20 (d, *J*=5.3 Hz, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.1, 163.7, 161.6 (*J*=241.4 Hz), 149.3, 142.9, 134.6 (*J*=2.3 Hz), 132.3, 128.1 (*J*=8.0 Hz), 127.2, 122.9, 115.9 (*J*=21.5 Hz), 114.4, 108.0, 105.8, 45.6, 35.1, 19.4, 18.6, 12.4, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}FN_3O_2Na$: 404.1745; found: 404.1750.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-fluorobenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-12**)*. White solid (0.43 g, 70%). M.p. 176-178 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.46 (s, 1H), 7.38 (t, *J*=5.2 Hz, 1H), 7.34-7.30 (m, 1H), 7.25-7.22 (m, 1H), 7.13-7.10 (m, 1H), 6.37 (t, *J*=7.6 Hz, 1H), 6.23 (d, *J*=0.7 Hz, 1H), 5.85 (s, 1H), 5.11 (s, 2H), 4.20 (d, *J*=5.3 Hz, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.1, 163.7, 159.7 (*J*=242.8 Hz), 149.3, 142.9, 132.5, 129.6 (*J*=8.2 Hz), 127.5 (*J*=18.3 Hz), 127.4, 125.4 (*J*=3.2 Hz), 125.3, 122.9, 115.7 (*J*=20.2 Hz), 114.4, 108.0, 105.8, 40.7 (*J*=4.9 Hz), 35.1, 19.4, 18.6, 12.2, 11.1. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}FN_3O_2Na$: 404.1745; found: 404.1751.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**D-13**)*. White solid (0.54 g, 74%). M.p. 115-116 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.46

(s, 1H), 7.71 (d, *J*=8.2 Hz, 2H), 7.38 (t, *J*=5.2 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 2H), 6.24 (d, *J*=0.5 Hz, 1H), 6.85 (s, 1H), 5.19 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 2.35 (s, 3H), 2.18 (s, 3H), 2.18 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 163.7, 149.3, 143.5, 142.9, 132.3, 128.1 (*J*=31.6 Hz), 127.3, 126.9, 126.1 (*J*=4.0 Hz), 124.7 (*J*=270.4 Hz), 122.9, 114.5, 108.0, 105.9, 46.0, 35.1, 19.4, 18.6, 12.3, 11.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{23}H_{24}F_3N_3O_2Na$: 454.1713; found: 454.1719.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(3-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**D-14**)*. White solid (0.23 g, 52%). M.p. 99-100 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.46 (s, 1H), 7.63 (d, J=7.7 Hz, 1H), 7.56 (t, *J*=7.7 Hz, 1H), 7.40 (t, *J*=5.2 Hz, 1H), 7.31 (s, 1H), 7.05 (d, *J*=7.7 Hz, 1H), 6.24 (s, 1H), 5.85 (s, 1H), 5.20 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.0, 162.6, 148.2, 141.8, 139.1, 131.2, 129.3, 129.0, 128.7 (*J*=31.4 Hz), 126.2, 12.5 (*J*=270.6 Hz), 123.2 (*J*=3.6 Hz), 121.8, 121.6 (*J*=3.9 Hz), 113.4, 106.9, 104.9, 44.8, 34.0, 18.3, 17.6, 11.3, 10.2. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{23}H_{24}F_3N_3O_2Na$: 454.1713; found: 454.1712.

*1-(2,4-Dichlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-15**)*. White solid (0.1 g, 35%). M.p. 251-252 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.47 (s, 1H), 7.69 (d, *J*=2.2 Hz, 1H), 7.42 (t, *J*=5.2 Hz, 1H), 7.37-7.36 (q, *J*=8.4 Hz, 2.1 Hz, 1H), 6.28 (s, 1H), 6.13 (d, *J*=8.4 Hz, 1H), 5.86 (s, 1H), 5.07 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 2.32 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.0, 163.7, 149.3, 142.9, 134.9, 133.0, 132.4, 132.2, 129.3, 128.5, 128.1, 127.3, 122.8, 114.7, 108.0, 106.1, 44.1, 35.1, 19.4, 18.6, 12.1, 11.0. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{22}H_{24}F_3N_3O_2Na$: 454.1060; found: 454.1071.

*1-(3,5-Dimethoxybenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-16**)*. White solid (0.21 g, 48%). M.p. 170-172 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.45 (s, 1H), 7.36 (t, *J*=5.2 Hz, 1H), 6.38 (t, *J*=2.2 Hz, 1H), 6.19 (d, *J*=0.5 Hz, 1H), 5.98 (d, *J*=2.2 Hz, 2H), 5.85 (s, 1H), 4.98 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 3.68 (s, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.1, 163.7, 161.3, 149.3, 142.9, 141.0, 132.4, 127.4, 122.9, 114.2, 108.0, 105.6, 104.2, 98.5, 55.6, 46.3, 35.0, 19.4, 18.6, 12.3, 11.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{24}H_{29}N_3O_4Na$: 446.2050; found: 446.2057.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-methoxybenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-17**)*. White solid (0.10 g, 33%). M.p. 199-200 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.45 (s, 1H), 7.33 (t, *J*=5.2 Hz, 1H), 6.88-6.87 (m, 2H), 6.82 (d, *J*=8.8 Hz, 2H), 6.18 (s, 1H), 5.85 (s, 1H), 4.98 (s, 2H), 4.19 (d, *J*=5.2 Hz, 2H), 2.36 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.1, 162.7, 157.6, 148.2, 141.8, 131.2, 129.2, 126.3, 126.1, 121.8, 113.5, 113.1, 106.9, 104.5, 54.5, 44.7, 34.0, 18.3, 17.6, 11.4, 10.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{23}H_{27}N_3O_3Na$: 416.1945; found: 416.1947.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-methoxybenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-18**)*. White solid (0.14 g, 47%). M.p. 218-220 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.46 (s, 1H), 7.36 (t, *J*=7.7 Hz, 1H), 7.25-7.22 (m, 1H), 7.04 (d, *J*=8.2 Hz, 1H), 6.82 (t, *J*=7.4 Hz, 1H), 6.22 (s, 1H), 6.07 (d, *J*=7.4 Hz, 1H), 5.85 (s, 1H), 4.95 (s, 2H), 4.20 (d, *J*=5.2 Hz, 2H), 3.86 (s, 3H), 2.30 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.2, 163.7, 156.3, 149.3, 142.9, 132.4, 128.7, 127.4, 125.9, 125.6, 122.9, 121.0, 114.2, 110.9, 108.0, 105.6, 55.8, 42.0, 35.1, 19.4, 18.6, 12.2, 11.1. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{23}H_{27}N_3O_3Na$: 416.1945; found: 416.1949.

*1-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydro)Pyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-19**)*. White solid (0.30 g, 67%). M.p. 199-200 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.45 (s, 1H), 7.35 (t, *J*=5.1 Hz, 1H), 6.84 (d, *J*=8.0 Hz, 1H), 6.45 (d, *J*=1.1 Hz, 1H), 6.28 (d, *J*=7.3, 1H), 6.18 (s, 1H), 5.98 (s, 2H), 5.85 (s, 1H), 4.96 (s, 2H), 4.19 (d, *J*=5.2 Hz, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.2, 163.7, 149.3, 148.1, 146.7, 142.9, 132.3, 127.3, 122.9, 119.1, 114.3, 108.9, 108.0, 107.7, 105.7, 101.5, 46.0, 35.1, 19.4, 18.6, 12.4, 11.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{23}H_{25}N_3O_4Na$: 430.1737; found: 430.1744.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(4-methylbenzyl)-1H-pyrrole-3-carboxamide (**D-20**)*. White solid (0.42 g, 60%). M.p. 146-147 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.48 (s, 1H), 7.35 (s, 1H), 7.12 (d, *J*=7.8 Hz, 2H), 6.77 (d, *J*=7.9 Hz, 2H), 6.18 (s, 1H), 5.86 (s, 1H), 5.01 (s, 2H), 4.20 (d, *J*=4.9 Hz, 2H), 2.35 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.2, 163.7, 149.3, 142.9, 136.6, 135.4, 132.3, 129.7, 127.3, 126.0, 122.9, 114.1, 108.0, 105.6, 46.1, 35.1, 21.1, 19.4, 18.6, 12.4, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{23}H_{27}N_3O_2Na$: 400.1995; found: 400.1994.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(naphthalen-2-ylmethyl) -1H-pyrrole-3-carboxamide (**D-21**)*. White solid (0.25 g, 57%). M.p. 148-149 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.47 (s, 1H), 8.19 (d, *J*=8.3 Hz, 1H), 7.99 (d, *J*=8.0 Hz, 1H), 7.83 (d, *J*=8.2 Hz, 1H), 7.66-7.59 (m, 2H), 7.42 (t, *J*=5.0 Hz, 1H), 7.37 (t, *J*=7.6 Hz, 1H), 6.30 (s, 1H), 6.19 (d, *J*=7.0 Hz, 1H), 5.87 (s, 1H), 5.55 (s, 2H), 4.23 (d, *J*=5.1 Hz, 2H), 2.34 (s, 3H), 2.20 (s, 3H), 2.12 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.2, 163.8, 149.3, 142.9, 134.1, 133.5, 132.6, 130.2, 129.1, 127.8, 127.6, 126.9, 126.6, 126.2, 123.4, 122.9, 121.8, 114.4, 108.0, 105.8, 44.4, 35.1, 19.4, 18.7, 12.2, 11.1. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{26}H_{27}N_3O_2Na$: 436.1995; found: 436.2007.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-(dimethylamino)ethyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-22**)*. White solid (0.10 g, 30%). M.p. 114-116 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.44 (s, 1H), 7.25 (t, *J*=5.2 Hz, 1H), 6.06 (d, *J*=0.4 Hz, 1H), 5.84 (s, 1H), 4.18 (d, *J*=5.3 Hz, 2H), 3.81 (t, *J*=7.3 Hz, 2H), 2.44 (s, 3H), 2.34 (t, *J*=7.3 Hz, 2H), 2.17 (s, 6H), 2.15 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.1, 162.6, 148.1, 141.8, 130.9, 125.8, 121.9, 112.8, 106.9, 106.8, 104.2, 58.0, 44.7, 40.3, 33.9, 20.0, 18.3, 18.2, 17.6, 11.3, 10.1. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{19}H_{28}N_4O_2Na$: 367.2104; found: 367.2106.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-hydroxyethyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-23**)*. White solid (0.20 g, 40%). M.p. 188-189 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.44 (s, 1H), 7.22 (t, *J*=5.0 Hz, 1H), 6.06 (s, 1H), 5.84 (s, 1H), 4.89 (t, J_1=5.2 Hz, 1H), 4.18 (d, *J*=5.2 Hz, 2H), 3.80 (t, *J*=6.2 Hz, 2H), 3.51-3.48 (q, *J*=11.7 Hz, 5.9 Hz, 2H), 2.43 (s, 3H), 2.15 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.3, 163.7, 149.2, 142.9, 132.3, 127.2, 123.0, 113.7, 108.0, 105.2, 60.8, 45.7, 35.0, 19.3, 18.6, 12.6, 11.4. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{17}H_{23}N_3O_3Na$: 340.1632; found: 340.1635.

*General procedure for preparation of enones **9a-j***

To a solution of granular metal sodium (3.2 g, 0.14 mol) and anhydrous ether (300 mL) was added dropwise a mixture of acetone (8.0 g, 0.14 mol) and ethyl formate (10.3 g, 0.14 mol) under ice-cooling, maintaining the temperature under 20 °C. After the mixture was stirred for 6 h, large amounts of white solid were precipitated. The precipitate was collected by filtration, and then washed with cold ether, and vacuum-dried to give **9a** as a white solid (10.9 g, 72%). This intermediate was taken to the next step without further purification. Intermediates **9b-j** were synthesized according to this method.

*General procedure for preparation of compounds **10a-j**.*

To a solution of **9a** (10 g, 0.09 mol) in water (50 mL) was added cyanoacetamide (8.2 g, 0.097 mol). The mixture was stirred at room temperature for 10 min. Piperidinium acetate (6 mL) was then added and the reaction was heated to 100 °C for another 2 h. The reaction solution was adjusted to pH 4-5 with 10 N HCl under ice-cooling, and a brown solid was precipitated, which was then successively washed with water and ether. The solid was vacuum-dried to give **10a** as a yellow solid (7.0 g, 75%). ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.56 (brs, 1H), 8.01 (d, *J*=6.1 Hz, 1H), 6.21 (d, *J*=5.7 Hz, 1H), 2.27 (s, 3H). Intermediates **10b-j** were synthesized according to this method.

*General procedure for preparation of compounds **11~20***

Compounds **11~20** were prepared from **10b-j** using a procedure analogous to that described for the synthesis of **3**.

*2-Amino-6-methyl-4-oxo-4H-pyran-3-carbonitrile (**23**)*

To a solution of malononitrile (10 g, 0.15 mol) in anhydrous THF (100 mL) was added sodium hydride (60% w/w, 6.0 g, 0.15 mol) at -10°C. The resultant mixture was stirred for 2 hours. Then diketene (12.7 g, 0.15 mol) was added dropwise. The mixture was allowed to warm to room temperature and continued stirring for 1 h. The mixture was neutralized with 4N HCl and then concentrated in vacuo to give crude **23** as yellow oil (22.5 g, 100%), which was used in the next step without further purification.

*2,4-dihydroxy-6-methylnicotinonitrile (**24**)*

A suspension of **23** (22.5 g, 0.15 mol) in 4N HCl (240 mL) was heated to 105 °C for 5 hours. The precipitate was collected by filtration and washed with water, and then recrystallized from methanol to give **24** as yellow solid (9.8 g, 43% yeild).

*2,4-dichloro-6-methylnicotinonitrile (**25**)*

24 (10 g, 66.6 mmol) was dissolved in $POCl_3$ (100 mL) and added by DMF (1 mL). The mixture was heated for 3 h. Then the mixture was concentrated under vacuum. The residue was dissolved in EA (1 L) and neutralized by saturated Na_2CO_3. Then the mixture was filtered through a celite pad to remove the dark flocculating. The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum to give **25** as brown solid (10 g, 79%).

*2,4-dimethoxy-6-methylnicotinonitrile (**26**)*

A mixture of **25** (9.0 g, 48 mmol), sodium methanolate (7 g, 336 mmol) in methanol (60 mL) was heated to reflux. After 4 h, the reaction was completed as monitored by TLC. The mixture was then concentrated and the residue was quenched with water. The solution was neutralized with 6 N HCl. The precipitate was collected by filtration and washed with water and ether successively, and vacuum-dried to give a brown solid (8 g, 95%).

*((2,4-Dimethoxy-6-methylpyridin-3-yl)methyl)carbamic acid tert-butyl ester (**27**)*

A solution of **26** (10.0 g, 56 mmol), Boc_2O (36.8 g, 168 mmol), TEA (29.0 g, 280 mmol) and Raney Ni (10.0 g) in THF (10mL) and MeOH (260 mL) was stirred at 30 °C for 48 h under H_2. It was filtered via a celite pad and the filtrate was concentrated to afford a red-brown oil (13.9 g, 88％).

*3-(Aminomethyl)-4-methoxy-6-methylpyridine-2(1H)-one hydrochloride (**21**)*

A mixture of **27** (13.9 g, 0.05 mol) in 4N HCl (90 mL) was stirred at 100 °C for 5 h. The mixture was concentrated, and the residue was added cool ethanol. The mixture was then stirred and filtered to give a white solid (8.2 g, 82%). ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.74 (brs, 1H), 7.90 (brs, 3H), 6.19 (s, 1H), 3.85 (s, 3H), 3.74-3.71 (q, J=11.3 Hz, 5.6 Hz, 2H), 2.22 (s, 3H).

*2-(tert-butyl) 4-ethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (**29**).*

tert-Butyl 3-oxobutanoate (40.0 g, 0.25 mol) was dissolved in AcOH (80 mL) in a round-bottomed flask, and the mixture was cooled in an ice bath to about 10 °C. $NaNO_2$ (18.8 g, 0.27 mol) was added over 1 h while keeping the temperature under 8-10 °C. The cold bath was removed and the mixture was allowed to stir for 2.5 h. To a stirred mixture of EA (97.6 g, 0.75 mol) and AcOH (100 mL) in an oil bath, zinc dust (32.8 g, 0.5 mol) was added portionwise, maintaining the temperature under 25-30 °C. Then the mixture was heated to 75 °C for 2 h. On

completion of reaction, the reaction mixture was poured into water (40 mL). The precipitate was collected by filtration. The crude product was recrystallized from 95% ethanol (120 mL) to yield **29** as a white solid (32.0, 48%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.90 (brs, 1H), 4.30-4.27 (q, *J*=7.1 Hz, 14.2 Hz, 2H), 2.53 (s, 3H), 2.50 (s, 3H), 1.57 (s, 9H), 1.36 (t, *J*=7.1 Hz, 3H).

*ethyl 2,4-dimethyl-1H-pyrrole-3-carboxylate (**30**).*

To a stirred solution of **29** (10 g, 0.037 mol) in ethanol (50 mL) was added slowly 10 N HCl (8 mL, 75 mmol) and the mixture was stirred at 65 °C for 4 h. After cooling to room temperature, the reaction mixture was poured into ice water (2 L) and extracted into dichloromethane (50 mL×3). The combined organic extracts were washed with water and brine, dried with anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to give **30** as a brown solid (5.4 g, 87%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.03 (br, 1H), 6.35 (s, 1H), 4.30-4.25 (q, *J*=3.4 Hz, 14.3 Hz, 2H), 2.49 (s, 3H), 2.24 (s, 3H), 1.35 (t, *J*=7.1 Hz, 3H).

*General procedure for preparation of intermediates **31a-r** and **32a-r**.*

31a-r were prepared from **30** using a procedure analogous to that described for the synthesis of **6a**. **32a-r** were prepared from **31a-r** using a procedure analogous to that described for the synthesis of **7a**.

*4.1.13. General procedure for preparation of compounds **DM-01~DM-28**.*

DM-01~DM-28 were prepared using a procedure analogous to that described for the synthesis of **D-06** but *N*-substituted 2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid in place of 2,5-dimethyl-1*H*-pyrrole-3-carboxylic acid.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-01**).* White solid (0.6 g, 72.5%). M.p.180-182 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 11.52 (brs, 1H), 7.70 (d, *J*=8.22 Hz, 2H), 7.21-7.20 (m, 3H), 6.56 (s, 1H), 5.86 (s, 1H), 5.14 (s, 2H), 4.22 (d, 2H), 2.21 (d, 6H), 2.1 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 164.6, 162.7, 147.8, 142.7, 141.9, 130.3, 127.3, 127.2 (*J*=36.7 Hz), 126.6, 124.9 (*J*=3.5 Hz), 123.6 (*J*=270.3 Hz), 121.9, 118.9, 115.8, 115.2, 106.9, 48.0, 34.2, 18.3, 17.6, 11.2, 10.2. ESI HRMS: m/z $[M+Na]^+$ calcd for $C_{23}H_{24}F_3N_3O_2Na$: 454.1713; found: 454.1704.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-fluorobenzyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-02**).* White solid (0.34 g, 73.9%). M.p. 173-175 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 11.51 (brs, 1H), 7.18 (t, *J*=5.4 Hz, 1H), 7.17-7.13 (m, 2H), 7.09-7.06 (m, 2H), 6.52 (s, 1H), 5.85 (s, 1H), 4.99 (s, 2H), 4,22 (d, *J*=5.4 Hz, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 164.6, 162.7, 160.7 (*J*=241.6 Hz), 147.7, 141.9, 133.9 (*J*=3.0 Hz), 130.2, 128.0 (*J*=8.5 Hz), 121.9, 118.7, 115.3 (*J*=87.1 Hz), 114.7 (*J*=21.0 Hz), 106.9, 47.7, 34.2, 18.3, 17.5, 11.2, 10.3. ESI HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}FN_3O_2Na$: 404.1745; found: 404.1745.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(3-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-03**).* White solid (0.16 g, 36.4%). M.p.174-175 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 11.51 (brs, 1H), 7.64 (d, 1H), 7.56 (t, *J*= 7.7 Hz, 1H), 7.47 (s, 1H), 7.25-7.21 (m, 2H), 6.57 (s, 1H), 5.86 (s, 1H), 5.13 (s, 2H), 4.22 (d, *J*=5.3 Hz, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 165.1, 163.2, 148.2, 142.4, 139.8, 130.7, 130.6, 129.7, 129.1 (*J*=31.2 Hz), 124.0 (*J*=281.1 Hz), 123.9 (*J*=3.8 Hz), 123.1 (*J*=3.9 Hz), 122.4, 119.3, 116.2, 115.7, 107.4, 48.4, 34.7, 18.8, 18.1, 11.7, 10.8. ESI HRMS: m/z $[M+Na]^+$ calcd for $C_{23}H_{24}F_3N_3O_2Na$: 454.1713; found: 454.1730.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(3,4,5-trimethoxybenzyl)-1H-pyrrole-3-carboxamide (**DM-04**).* White solid (0.23 g, 53.5%). M.p.131-132 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 11.50 (brs, 1H), 7.18 (t, *J*=5.2 Hz, 1H), 6.52 (s, 1H), 6.42 (s, 2H), 5.85 (s, 1H), 4.89 (s, 2H), 4.22 (d, *J*=5.4 Hz, 2H), 3.70 (s, 6H), 3.62 (s, 3H), 2.27 (s, 3H), 2.2 (s, 3H), 2.1 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 164.7, 162.7, 152.4, 147.7, 141.9, 136.1, 133.1, 130.3, 121.9, 118.6, 115.4, 114.9, 106.9, 103.9, 59.4, 55.3, 48.6, 34.2, 18.3, 17.6, 11.3, 10.4. ESI HRMS: m/z $[M+Na]^+$ calcd for $C_{25}H_{31}N_3O_5Na$: 476.2156; found: 476.2139.

*1-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-05**).* White solid (0.44 g, 65.2%). M.p.223-225 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 11.50 (brs, 1H), 7.17 (t, *J*=5.3 Hz, 1H), 6.85 (d, *J*=8.0 Hz, 1H), 6.63 (d, *J*=1.4 Hz, 1H), 6.53-6.52 (dd, *J*=1.4 Hz, 7.9 Hz, 1H), 6.50 (s, 1H), 5,97 (s, 2H), 5.85 (s, 1H), 4.88 (s, 2H), 4.22 (d, *J*=5.5 Hz, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 164.6, 162.7, 147.7, 146.9, 145.7, 141.9, 131.4, 130.2, 121.9, 119.4, 118.6, 115.5, 114.8, 107.6, 106.7, 100.4, 48.2, 34.2, 18.3, 17.5, 11.2, 10.3. ESI HRMS: m/z $[M+Na]^+$ calcd for $C_{23}H_{25}N_3O_4Na$: 430.1737; found: 430.1733.

*1-(3,4-Dimethoxybenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-06**).* White solid (0.17 g, 43.9%). M.p.138-140 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 11.51 (brs, 1H), 7.16 (t, *J*=5.3 Hz, 1H), 6.88 (d, *J*=8.3 Hz, 1H), 6.79 (d, *J*=1.7 Hz, 1H), 6.51-6.47 (m, 2H), 5.86 (s, 1H), 4.89 (s, 2H), 4.22 (d, *J*=5.4 Hz, 2H), 3.7 (s, 6H), 2.25 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 165.7, 163.8, 149.2, 148.7, 148.5, 143.0, 131.4, 130.9, 123.0, 119.7, 119.4, 116.4, 115.8, 112.3, 111.4, 108.0, 56.0, 49.3, 35.3, 19.4, 18.6, 12.4, 11.4. ESI HRMS: m/z $[M+Na]^+$ calcd for $C_{24}H_{29}N_3O_4Na$: 446.2050; found: 446.2067.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(3-fluorobenzyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-07**).* White solid (0.32 g, 69.6%). M.p. 230-231 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 11.50 (brs, 1H), 7.38-7.35 (m, 1H), 7.21 (t, *J*=5.3 Hz, 1H), 7.10-7.06 (m, 1H), 6.86-6.82 (m, 2H), 6.54 (s, 1H), 5.86 (s, 1H), 5.04 (s, 2H), 4.22 (d, *J*=5.4 Hz, 2H), 2.20 (s, 6H), 2.10 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 165.7, 163.8, 162.8 (*J*=242.7 Hz), 148.8, 143.0, 141.8 (*J*=6.8 Hz), 131.2 (*J*=32.9 Hz), 131.1, 123.0 (*J*=2.0 Hz), 122.9, 119.9, 116.8, 116.2, 114.5 (*J*=20.8 Hz), 113.7 (*J*=21.9 Hz), 108.0, 48.9, 35.3, 19.4, 18.6, 12.3, 11.3. ESI HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}FN_3O_2Na$: 404.1745; found: 404.1752.

*1-(3-Chlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-08**)*. White solid (0.38 g, 84%). M.p. 220-222 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.51 (brs, 1H), 7.37-7.31 (m, 2H), 7.21 (t, *J*=5.3 Hz, 1H), 7.09 (s, 1H), 6.97 (d, *J*=7.4 Hz, 1H), 6.54 (s, 1H), 5.86 (s, 1H), 5.03 (s, 2H), 4.22 (d, *J*=5.5 Hz, 2H), 2.20 (s, 6H), 2.10 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.6, 162.7, 147.8, 141.9, 140.4, 132.7, 130.2, 130.0, 126.6, 125.8, 124.6, 121.9, 118.8, 115.7, 115.1, 107.0, 47.8, 34.2, 18.3, 17.6, 11.2, 10.2. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}ClN_3O_2Na$: 420.1449; found: 420.1454.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(3-fluorobenzyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-09**)*. White solid (0.32 g, 70%). M.p. 230-231 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.50 (brs, 1H), 7.38-7.35 (m, 1H), 7.21 (t, *J*=5.3 Hz, 1H), 7.10-7.06 (m, 1H), 6.86-6.82 (m, 2H), 6.54 (s, 1H), 5.86 (s, 1H), 5.04 (s, 2H), 4.22 (d, *J*=5.4 Hz, 2H), 2.20 (s, 6H), 2.10 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.7, 163.8, 162.8 (*J*=242.7 Hz), 148.8, 143.0, 141.8 (*J*=6.8 Hz), 131.2 (*J*=32.9 Hz), 131.1, 123.0 (*J*=2.0 Hz), 122.9, 119.9, 116.8, 116.2, 114.5 (*J*=20.8 Hz), 113.7 (*J*=21.9 Hz), 108.0, 48.9, 35.3, 19.4, 18.6, 12.3, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}FN_3O_2Na$: 404.1745; found: 404.1752.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-methoxybenzyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-10**)*. White solid (0.28 g, 62%). M.p. 176-177 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.51 (brs, 1H), 7.25 (m, 1H), 7.19 (t, *J*=5.3 Hz, 1H), 7.00 (d, *J*=8.1 Hz, 1H), 6.86 (t, *J*=7.4 Hz, 1H), 6.51 (d, *J*=7.1 Hz, 1H), 6.45 (s, 1H), 5.86 (s, 1H), 4.91 (s, 2H), 4.23 (d, *J*=5.4 Hz, 2H), 3.83 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.7, 163.8, 156.5, 148.8, 143.0, 131.6, 129.1, 127.5, 126.4, 123.0, 120.9, 119.9, 116.3, 115.9, 111.0, 108.0, 55.8, 44.8, 35.3, 19.4, 18.6, 12.4, 11.1. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{23}H_{27}N_3O_3Na$: 416.1945; found: 416.1954.

*1-(2,4-Dichlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-11**)*. White solid (0.28 g, 62%). M.p. 239-240 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.52 (brs, 1H), 7.66 (d, *J*=2.1 Hz, 1H), 7.39-7.37 (dd, *J*=8.4 Hz, 2.1Hz, 1H), 7.25 (t, *J*=5.3 Hz, 1H), 6.50-6.46 (m, 2H), 5.86 (s,1H), 5.06 (s, 2H), 4.23 (d, *J*=5.5 Hz, 2H), 2.21 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H). ^{13}C NMR

(150 MHz, DMSO-d_6) δ (ppm): 164.5, 162.7, 147.7, 141.9, 134.3, 132.0, 131.4, 130.4, 128.4, 128.1, 127.3, 121.8, 118.8, 115.9, 115.4, 106.9, 45.9, 34.2, 18.3, 17.6, 11.2, 10.0. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}Cl_2N_3O_2Na$: 454.1060; found: 454.1065.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(3-methoxybenzyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-12**)*. White solid (0.30 g, 67%). M.p. 192-194 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.51 (brs, 1H), 7.23 (t, *J*=7.9 Hz, 1H), 7.19 (t, *J*=5.3, 1H), 6.83-6.81 (m, 1H), 6.61 (s, 1H), 6.57 (d, *J*=7.6 Hz, 1H), 6.51 (s, 1H), 5.85 (s, 1H), 4.97 (s, 2H), 4.22 (d, *J*=5.3 Hz, 2H), 3.71 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 2.10 (s,3H), 2.06 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.7, 163.8, 159.9, 148.8, 143.0, 140.0, 131.4, 130.2, 123.0, 119.9, 119.1, 116.5, 115.9, 113.1, 112.6, 108.0, 55.5, 49.4, 35.3, 19.4, 18.6, 12.3, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{24}ClN_3O_2Na$: 416.1945; found: 416.1941.

*1-(3,5-Dimethoxybenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-13**)*. White solid (0.29 g, 66%). M.p. 216-217 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.50 (brs, 1H), 7.19 (t, *J*=5.3, 1H), 6.50 (s, 1H), 6.38 (t, *J*=2.1 Hz, 1H), 6.16 (d, *J*=2.1 Hz, 2H), 5.85 (s, 1H), 4.91 (s, 2H), 4.22 (d, *J*=5.4 Hz, 2H), 3.69 (s, 6H), 2.21 (s, 3H), 2.20 (s, 3H), 2.10 (s,3H), 2.06 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.6, 162.7, 160.1, 147.7, 141.9, 140.1, 130.4, 121.9, 118.9, 115.4, 114.8, 106.9, 104.2, 97.7, 54.5, 48.4, 34.2, 18.3, 17.6, 11.2, 10.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{24}H_{29}N_3O_4Na$: 446.2050; found: 446.2065.

*1-(Cyclopropylmethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-14**)*. White solid (0.29 g, 68%). M.p. 192-193 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.51 (s, 1H), 7.12 (t, *J*=5.2 Hz, 1H), 6.46 (s, 1H), 5.86 (s, 1H), 4.23 (d, *J*=5.4 Hz, 2H), 3.58 (d, *J*=6.9 Hz, 2H), 2.30 (s, 3H), 2.21 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.08-1.01 (m, 1H), 0.48-0.45 (m, 2H), 0.29-0.27 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.8, 162.7, 147.6, 141.9, 129.8, 122.0, 118.0, 114.9, 114.3, 106.9, 49.0, 34.2, 18.3, 17.6, 11.3, 11.1, 10.2, 2.9. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{19}H_{25}N_3O_2Na$: 350.1839; found: 350.1845.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(naphthalene-2-yl-methyl)-1H-pyrrole-3-carboxamide (**DM-15**)*. White solid (0.25 g, 57%). M.p. 229-230 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.53 (s, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.98 (d, *J*=7.7 Hz, 1H), 7.85 (d, *J*=8.2 Hz, 1H), 7.61-7.56 (m, 2H), 7.41 (t, *J*=7.5 Hz, 1H), 7.25 (t, *J*=5.2 Hz, 1H), 6.58 (d, *J*=7.0 Hz, 1H), 6.47 (s, 1H), 5.87 (s, 1H), 5.51 (s, 2H), 4.25 (d, J=5.3 Hz, 2H), 2.24 (s, 3H), 2.22 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.7, 162.7, 147.7, 141.9, 133.3, 132.5, 130.8, 129.4, 127.9, 127.0, 125.8, 125.4, 125.0, 122.6, 122.4, 121.9, 118.9, 115.5, 115.0, 106.9, 46.4, 34.2, 18.3, 17.6, 11.3, 10.1. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{26}H_{27}N_3O_2Na$: 436.1995; found: 436.2013.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-methylbenzyl)-1H-pyrrole-3-carboxamide (**DM-16**)*. White solid (0.28 g, 61%). M.p. 235-236 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.51 (s, 1H), 7.16 (t, *J*=5.1 Hz, 1H), 7.12 (d, *J*=7.8 Hz, 2H), 6.94 (d, *J*=7.8 Hz, 2H), 6.49 (s, 1H), 5.85 (s, 1H), 4.94 (s, 2H), 4.22 (d, *J*=5.3 Hz, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 2.20 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.7, 163.8, 148.7, 143.0, 136.8, 135.7, 131.4, 129.6, 127.1, 123.0, 119.8, 116.4, 115.8, 108.0, 49.3, 35.3, 21.1, 19.4, 18.6, 12.3, 11.4. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{23}H_{27}N_3O_2Na$: 400.1995; found: 400.1995.

*2,4-Dimethyl-N-((4-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-17**)*. White solid (0.10 g, 32%). M.p. 150-152 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.54 (brs, 1H), 7.70 (d, *J*=8.3 Hz, 2H), 7.29 (t, *J*=5.4 Hz, 1H), 7.21 (d, *J*=8.2 Hz, 2H), 6.55 (s, 1H), 5.13 (s, 2H), 4.25 (d, *J*=5.4 Hz, 2H), 2.77 (t, *J*=5.2 Hz, 2H), 2.37 (t, *J*=4.8 Hz, 2H), 2.19 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 1.64-1.62 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.5, 161.2, 148.2, 142.7, 139.5, 130.3, 127.2 (*J*=31.3 Hz), 126.5, 124.9 (*J*=4.0 Hz), 123.6 (*J*=270.3 Hz), 121.2, 118.9, 115.7, 111.1, 48.0, 33.9, 25.9, 23.6, 21.5, 21.4, 15.3, 11.3, 10.2. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{26}H_{28}F_3N_3O_2Na$: 494.2026; found: 494.2028.

2,4-Dimethyl-N-((2-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-1

*H-pyrrole-3-carboxamide (**DM-18**)*. White solid (0.13 g, 43%). M.p. 171-173 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.82 (brs, 1H), 7.72 (d, *J*=8.0 Hz, 2H), 7.42 (t, *J*=5.6 Hz, 1H), 7.24-7.22 (m, 3H), 6.59 (s, 1H), 5.16 (s, 2H), 4.14 (d, *J*=5.5 Hz, 2H), 2.70 (t, *J*=7.2 Hz, 2H), 2.60 (t, *J*=7.1 Hz, 2H), 2.21 (s, 3H), 2.12 (s, 3H), 2.02-1.97 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 166.2, 163.0, 147.2, 143.7, 134.6, 131.1, 128.3 (*J*=31.6 Hz), 127.7, 126.5, 126.0 (*J*=3.4 Hz), 124.7 (*J*=270.3 Hz), 119.9, 117.2, 117.0, 116.5, 49.1, 39.1, 31.0, 29.7, 23.0, 12.3, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{24}H_{24}F_3N_3O_2Na$: 466.1713; found: 466.1719.

*2,4-Dimethyl-N-((4-methyl-2-oxo-6-propyl-1,2-dihydropyridin-3-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-19**)*. White solid (0.18 g, 60%). M.p. 152-154 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.49 (brs, 1H), 7.70 (d, *J*=8.2 Hz, 2H), 7.24 (t, *J*=5.3 Hz, 1H), 7.21 (d, *J*=8.0 Hz, 2H), 6.56 (s, 1H), 5.88 (s, 1H), 5.14 (s, 2H), 4.23 (d, *J*=5.4 Hz, 2H), 2.35 (t, *J*=7.4 Hz, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.08 (s, 3H), 1.59-1.53 (m, 2H), 0.86 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.6, 163.9, 148.8, 146.9, 143.7, 131.4, 128.3 (J=31.7 Hz), 127.6, 126.0 (3.4 Hz), 125.6, 123.8, 123.2, 120.0, 116.8, 116.3, 107.4, 49.0, 35.3, 34.3, 22.0, 19.4, 13.9, 12.3, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{25}H_{28}F_3N_3O_2Na$: 482.2026; found: 482.2034.

*N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-20**)*. White solid (0.17 g, 58%). M.p. 142-143 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.08 (brs, 1H), 7.71 (d, *J*=8.0 Hz, 2H), 7.65 (s, 1H), 7.22 (d, *J*=8.0 Hz, 2H), 6.60 (s, 1H), 6.31 (s, 1H), 5.16 (s, 2H), 4.25 (s, 2H), 3.86 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 166.5, 164.0, 147.1, 143.7, 131.9, 128.4, 128.2, 127.6, 126.1, 126.0, 125.6, 123.8, 120.2, 116.5, 116.2, 106.4, 95.7, 56.9, 49.1, 32.8, 19.3, 12.2, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{23}H_{24}F_3N_3O_3Na$: 470.1662; found: 470.1681.

*2,4-Dimethyl-N-((6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-(trifluoromethyl)benzyl-1H-pyrrole-3-carboxamide (**DM-21**)*. White solid (0.18 g, 64%). M.p. 206-208 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.63 (brs, 1H), 7.72 (d, *J*=8.2 Hz, 2H), 7.43 (t, *J*=5.8 Hz, 1H), 7.24 (d, *J*=7.9 Hz, 2H), 7.18 (d, *J*=6.8 Hz, 1H), 6.58 (s, 1H), 5.97 (d, *J*=6.9 Hz, 1H), 5.16 (s, 2H), 4.13 (d, *J*=5.7 Hz, 2H), 2.21 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 166.2, 163.1, 143.7, 136.9, 131.0, 128.3 (*J*=31.7 Hz), 127.7, 126.4, 126.0 (*J*=3.4 Hz), 125.6, 124.7 (*J*=270.3 Hz), 119.9, 117.2, 116.5, 104.1, 40.1, 38.5, 18.7, 12.3, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{22}H_{22}F_3N_3O_2Na$: 440.1556; found: 440.1571.

*N-((6-isobutyl-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-22**)*. White solid (0.15 g, 47%). M.p. 143-145 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.47 (brs, 1H), 7.70 (d, *J*=8.2 Hz, 2H), 7.24 (t, *J*=5.3 Hz, 1H), 7.21 (d, *J*=8.0 Hz, 2H), 6.56 (s, 1H), 5.85 (s, 2H), 5.14 (s, 2H), 4.24 (d, *J*=5.4 Hz, 2H), 2.25 (d, *J*=7.3 Hz, 2H), 2.22 (s, 3H), 2.19 (s, 3H), 2.08 (s, 3H), 1.93-1.87 (m, 1H), 0.85 (d, *J*=6.6 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.6, 162.8, 147.6, 145.1, 142.7, 130.3, 127.2 (*J*=31.5 Hz), 126.6, 124.9 (*J*=3.4 Hz), 123.6 (*J*=270.3 Hz), 122.1, 118.9, 115.8, 115.2, 107.1, 48.0, 40.4, 34.3, 27.1, 21.4, 18.4, 11.2, 10.2. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{26}H_{30}F_3N_3O_2Na$: 496.2182; found: 496.2202.

*N-((6-isobutyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-23**)*. White solid (0.13 g, 42%). M.p. 143-145 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.60 (brs, 1H), 7.72 (d, *J*=7.9 Hz, 2H), 7.45 (t, *J*=5.5 Hz, 1H), 7.25 (d, *J*=7.9 Hz, 2H), 7.21 (d, *J*=6.7 Hz, 1H), 6.59 (s, 1H), 5.97 (d, *J*=6.8 Hz, 1H), 5.16 (s, 2H), 4.15 (d, *J*=5.4 Hz, 2H), 2.30 (d, *J*=7.1 Hz, 2H), 2.22 (s, 3H), 2.13 (s, 3H), 1.93-1.88 (m, 1H), 0.86 (d, *J*=6.5 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 166.2, 163.2, 146.9, 143.7, 136.7, 131.1, 128.3 (*J*=31.6 Hz), 127.7, 126.7, 126.0 (*J*=3.4 Hz), 124.7 (*J*=270.3 Hz), 119.9, 117.2, 116.5, 104.3, 49.1, 41.5, 38.5, 28.3, 22.4, 12.3, 11.3. ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{25}H_{28}F_3N_3O_2Na$: 482.2026; found: 482.2043.

*2,4-Dimethyl-N-((2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-24**)*. White solid (0.16 g, 53%). M.p. 149-150 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm):

11.38 (brs, 1H), 7.72 (d, *J*=8.2 Hz, 2H), 7.45 (t, *J*=5.8 Hz, 1H), 7.24 (d, *J*=8.0 Hz, 2H), 7.02 (s, 1H), 6.59 (s, 1H), 5.16 (s, 2H), 4.13 (d, *J*=5.6 Hz, 2H), 2.44 (t, *J*=5.3 Hz, 2H), 2.35 (t, *J*=5.9 Hz, 2H), 2.21 (s, 3H), 2.12 (s, 3H), 1.67-1.62 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 166.2, 162.2, 143.7, 140.7, 138.8, 131.0, 128.3 (*J*=31.7 Hz), 127.7, 126.8, 126.0 (*J*=4.0 Hz), 124.7 (*J*=270.3 Hz), 119.9, 117.3, 116.5, 111.7, 49.1, 38.6, 26.2, 26.1, 22.6, 21.7, 12.2, 11.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{25}H_{26}F_3N_3O_2Na$: 480.1869; found: 480.1891.

*N-((6-ethyl-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-25**)*. White solid (0.16 g, 53%). M.p. 177-179 ºC. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.51 (brs, 1H), 7.70 (d, *J*=8.2 Hz, 2H), 7.24 (t, *J*=5.3 Hz, 1H), 7.21 (d, *J*=8.0 Hz, 2H), 6.56 (s, 1H), 5.88 (s, 1H), 5.14 (s, 2H), 4.23 (d, *J*=5.4 Hz, 2H), 2.42-2.38 (q, *J*=15.1 Hz, 7.5 Hz, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.08 (s, 3H), 1.12 (t, *J*=7.6 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 164.6, 162.8, 147.8, 147.3, 142.7, 130.3, 127.1 (J=31.7 Hz), 126.5, 124.9 (J=3.9 Hz), 124.5 (*J*=270.3 Hz), 122.7, 122.2, 118.9, 115.7, 115.2, 105.3, 48.0, 34.3, 24.6, 18.4, 12.3, 11.2, 10.2. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{24}H_{26}F_3N_3O_2Na$: 468.1869; found: 468.1887.

*N-((6-ethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl-1H-pyrrole-3-carboxamide (**DM-26**)*. White solid (0.07 g, 48%). M.p. 169-172 ºC. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.62 (brs, 1H), 7.72 (d, *J*=8.2 Hz, 2H), 7.44 (t, *J*=5.8 Hz, 1H), 7.24 (d, *J*=8.0 Hz, 2H), 7.21 (d, *J*=6.9 Hz, 1H), 6.59 (s, 1H), 5.99 (d, *J*=6.9 Hz, 1H), 5.16 (s, 2H), 4.14 (d, *J*=5.6 Hz, 2H), 2.46-2.42 (q, *J*=15.1 Hz, 7.5 Hz, 2H), 2.21 (s, 3H), 2.12 (s, 3H), 1.13 (t, *J*=7.6 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 166.2, 163.1, 149.2, 143.8, 136.9, 131.0, 128.3 (J=31.7 Hz), 127.7, 126.7, 126.0 (J=3.4 Hz), 124.7 (*J*=270.3 Hz), 119.9, 117.2, 116.5, 102.5, 49.1, 38.5, 25.7, 13.5, 12.3, 11.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{23}H_{24}F_3N_3O_2Na$: 454.1713; found: 454.1729.

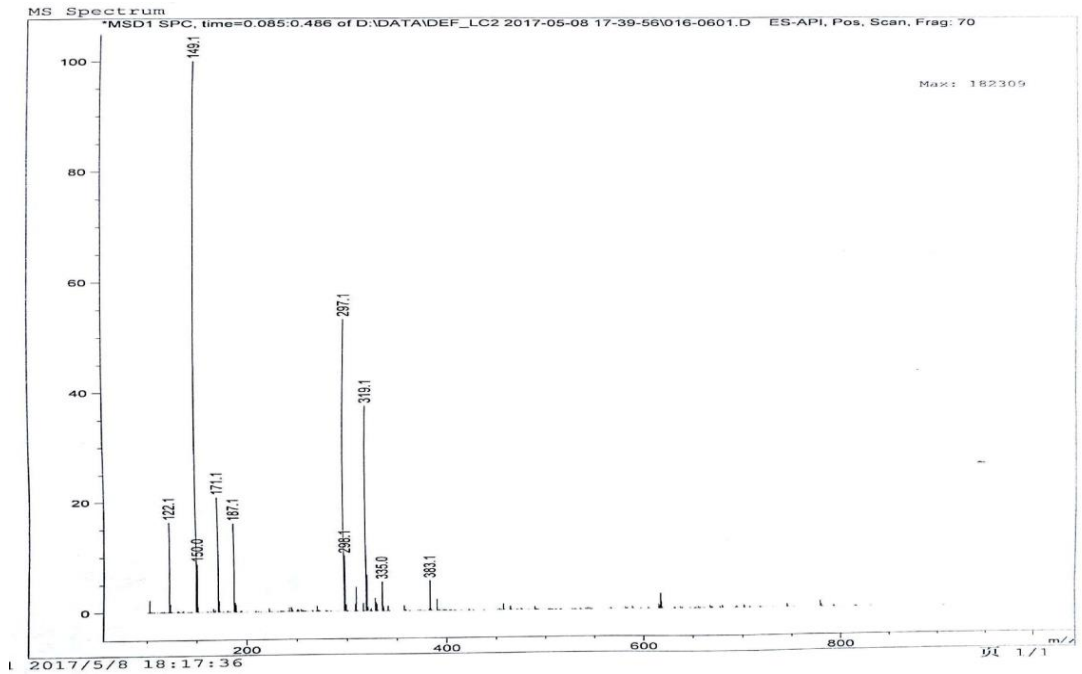
*N-((5,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-27**)*. White solid (0.08 g, 55%). M.p. 118-121 ºC. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.51 (brs, 1H), 7.72 (d, *J*=8.2 Hz, 2H), 7.45 (t, *J*=5.8 Hz, 1H), 7.25 (d, *J*=8.0 Hz, 2H), 7.10 (s, 1H), 6.60 (s, 1H), 5.16 (s, 2H), 4.14 (d, *J*=5.6 Hz, 2H), 2.22 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 166.2, 162.4, 143.7, 140.3, 140.1, 131.0, 128.3 (*J*=31.4 Hz), 127.7, 126.2, 126.0 (*J*=3.3 Hz), 124.7 (*J*=270.2 Hz), 119.9, 117.3, 116.5, 110.4, 49.1, 38.5, 16.5, 16.2, 12.2, 11.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{23}H_{24}F_3N_3O_2Na$: 454.1713; found: 454.1734.

*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(1-(4-(trifluoromethyl)benzyl)ethyl)-1H-pyrrole-3-carboxamide (**DM-28**)*. White solid (0.21 g, 73%). M.p. 135-137 ºC. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.53 (brs, 1H), 7.69 (d, *J*=8.2 Hz, 2H), 7.26 (d, *J*=8.1 Hz, 2H), 7.21 (t, *J*=5.4 Hz, 1H), 6.70 (s, 1H), 5.86 (s, 1H), 5.49-5.45 (q, *J*=13.9 Hz, 6.9 Hz, 1H), 4.25-4.18 (m, 2H), 2.20 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 1.71 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 165.7, 163.8, 148.8, 148.5, 14.0, 131.4, 128.2 (*J*=31.7 Hz), 127.1, 126.0 (*J*=3.9 Hz), 124.7 (*J*=270.4 Hz), 122.9, 116.8, 116.2, 116.0, 108.0, 53.8, 35.3, 22.0, 19.3, 18.6, 12.5, 11.3. ESI-HRMS: m/z [M+Na]$^+$ calcd for $C_{24}H_{26}F_3N_3O_2Na$: 468.1869; found: 468.1871.

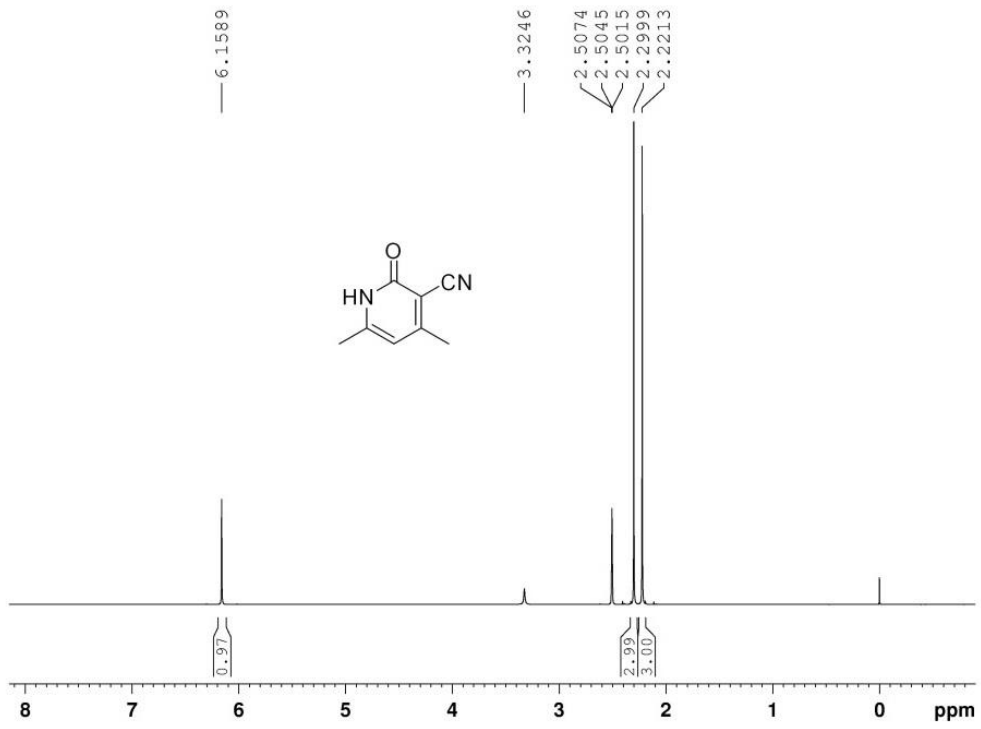
Spectrums of D and DM series compounds

*4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**2**)*

ESI-MS of compound 2

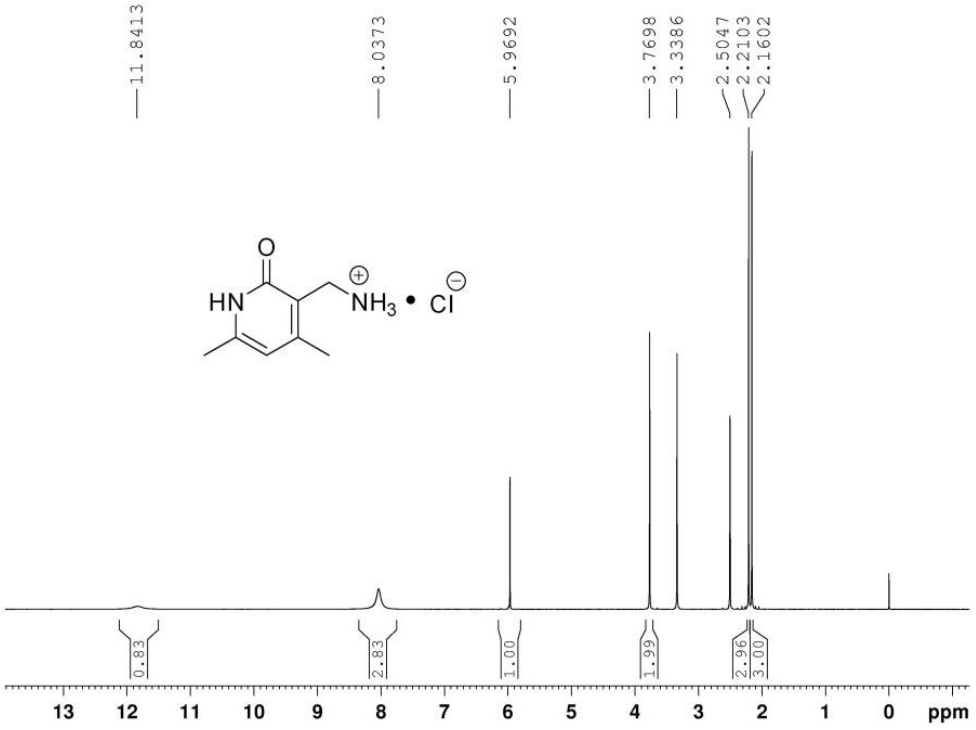


[1]H NMR of compound 2



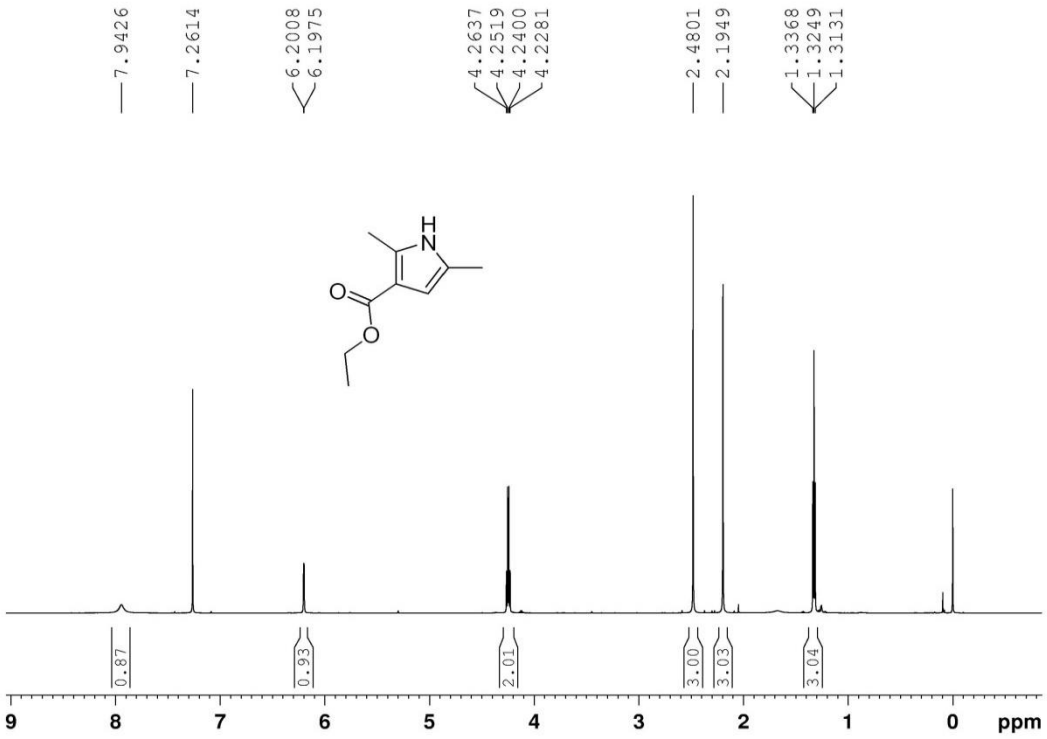
3-(Aminomethyl)-4,6-dimethylpyridin-2(1H)-one hydrochloride (3)

[1]H NMR of compound 3



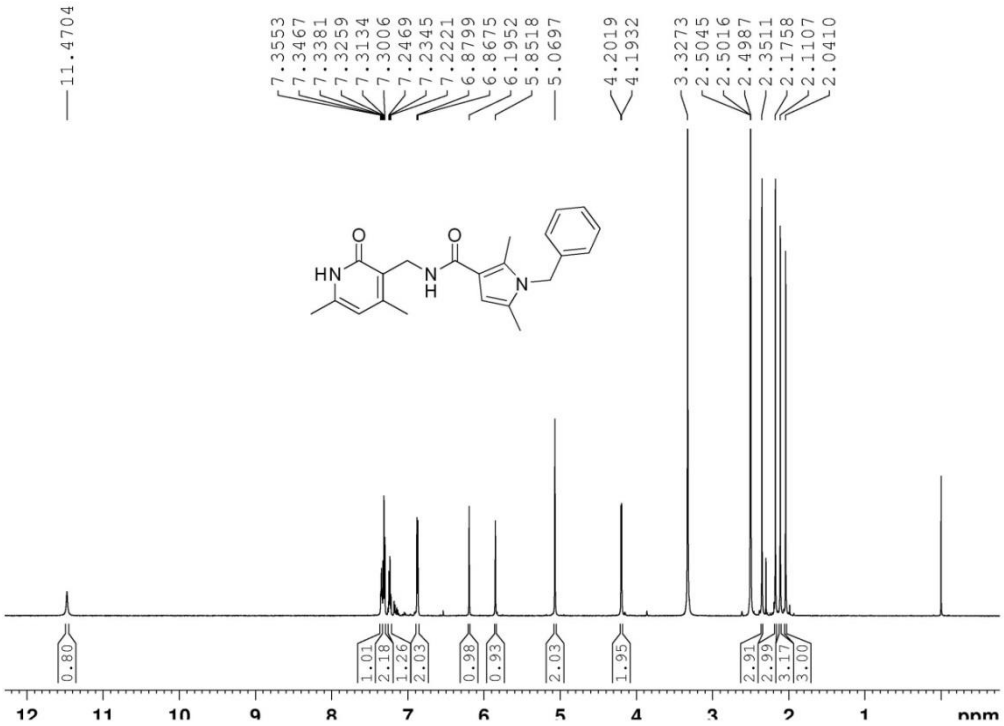
Ethyl 2,5-dimethyl-1H-pyrrole-3-carboxylate (5)

^{1}H NMR of compound 5

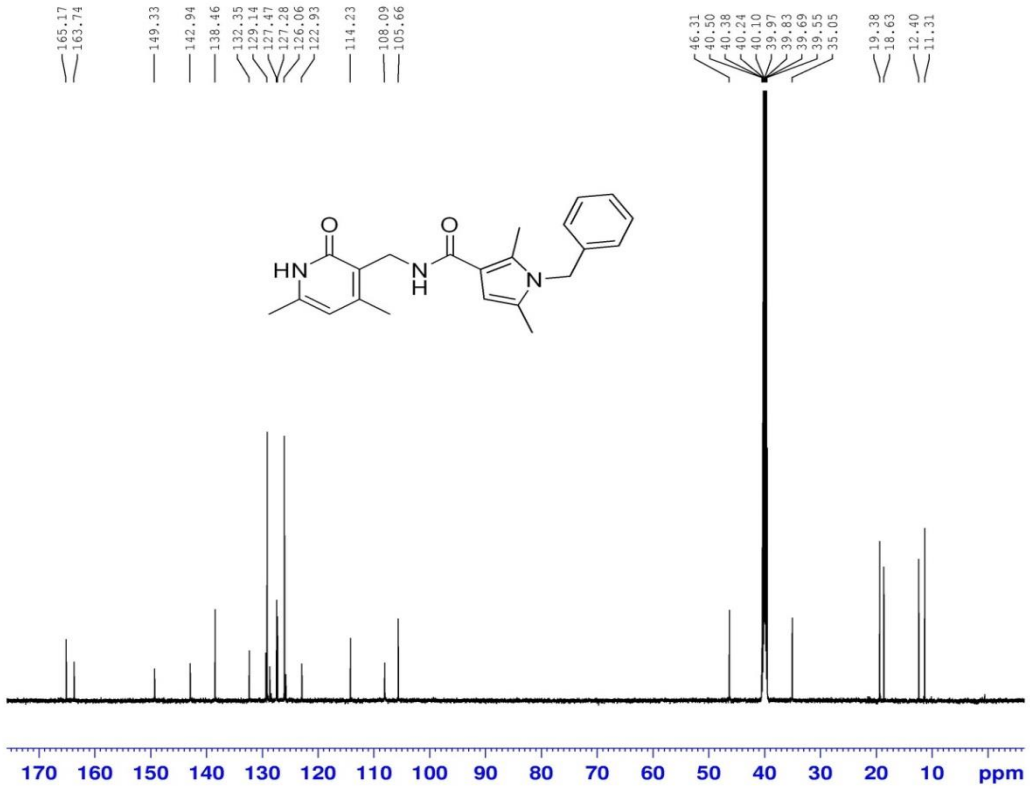


*1-Benzyl-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carbo xamide (**D-01**)*

^{1}H NMR of D-01

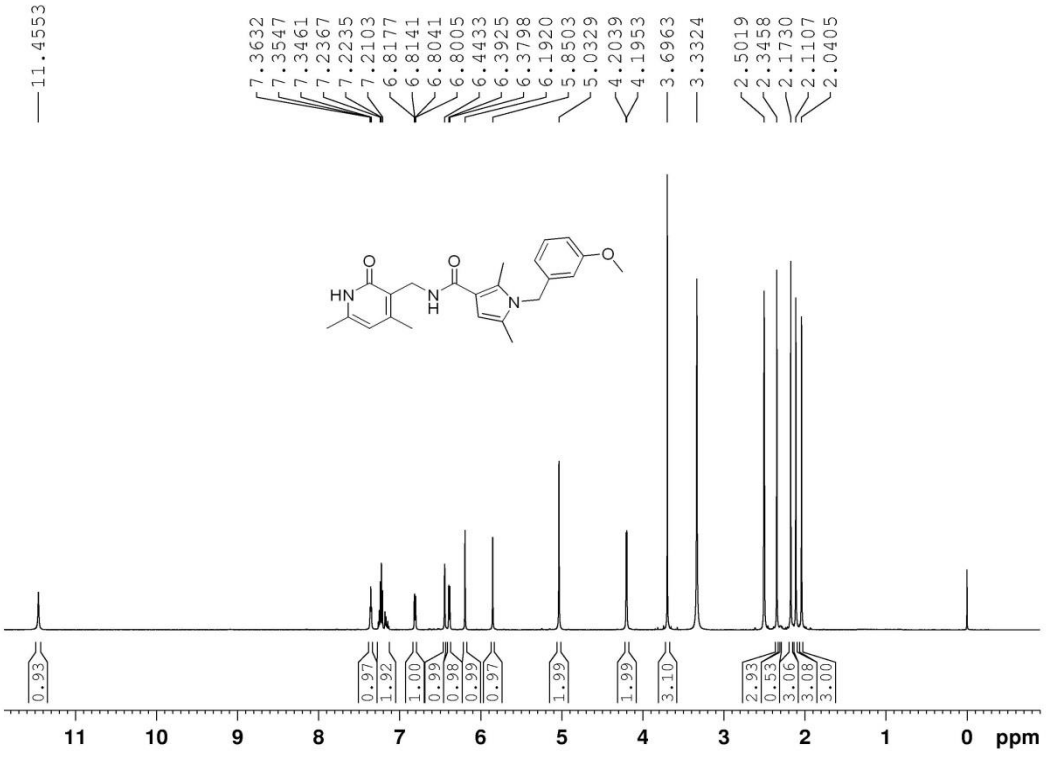


^{13}C NMR of D-01

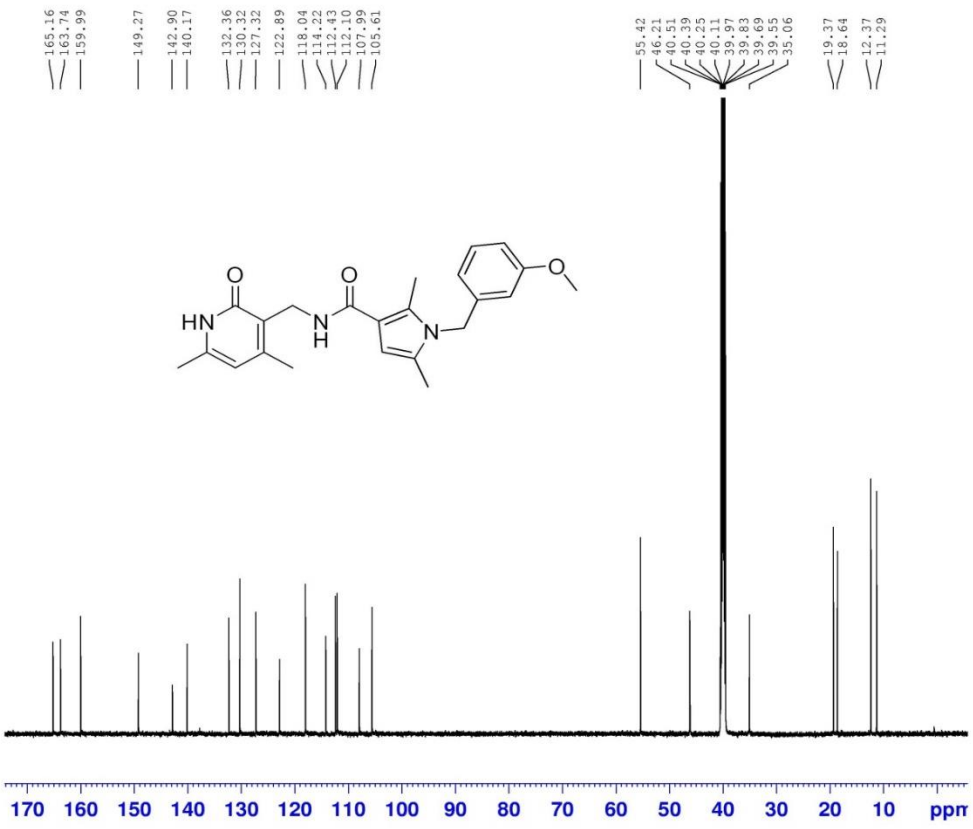


*N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(3-methoxybenzyl)-2,5-dimethyl-1H-pyrr ole-3-carboxamide (**D-02**)*

^{1}H NMR of D-02

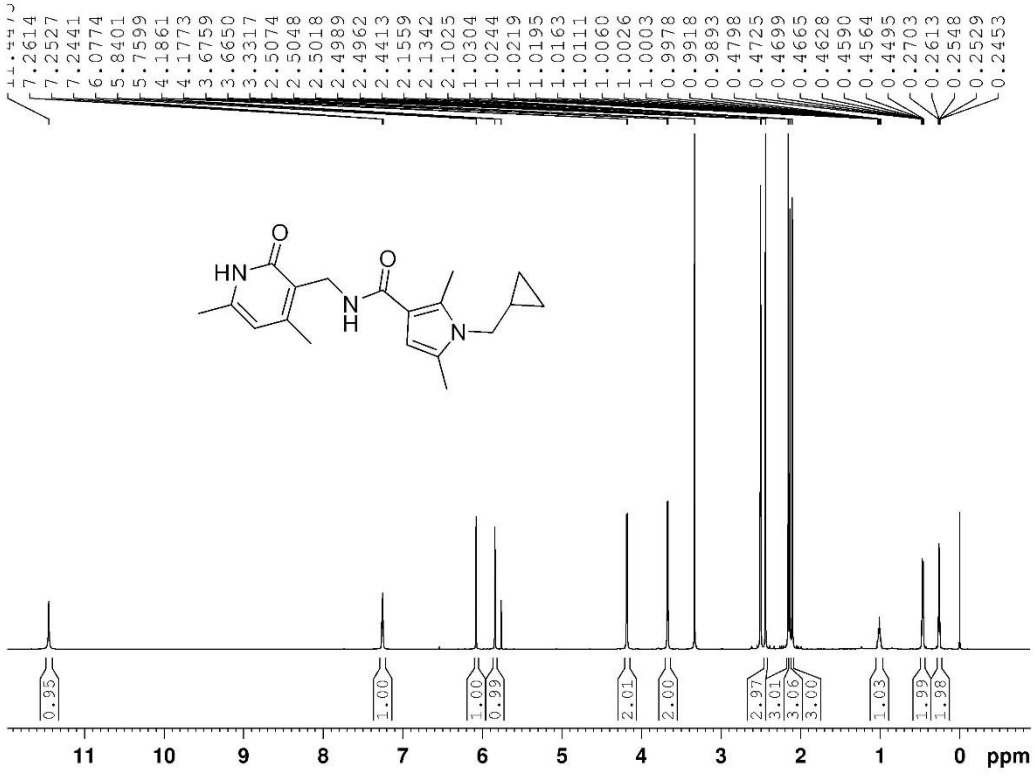


^{13}C NMR of D-02

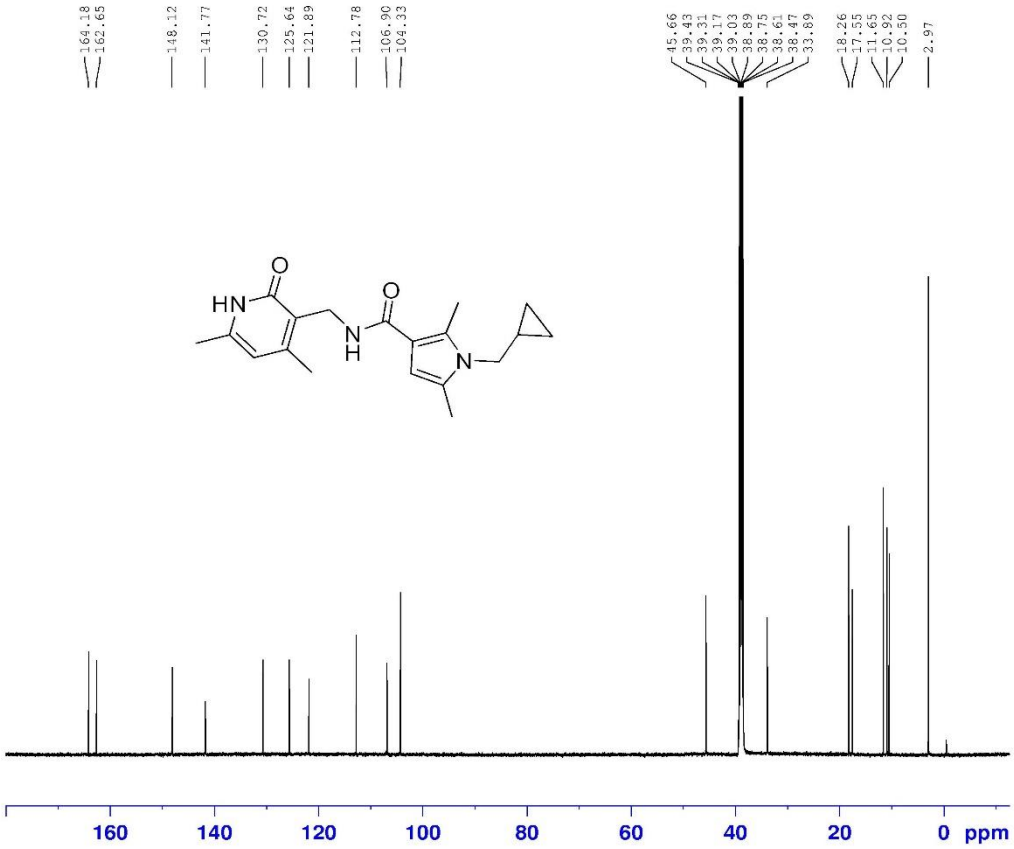


*N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(2,3,4-trimethoxybenzyl)-1 H-pyrrole-3-carboxamide (**D-03**)*

^{1}H NMR of D-03

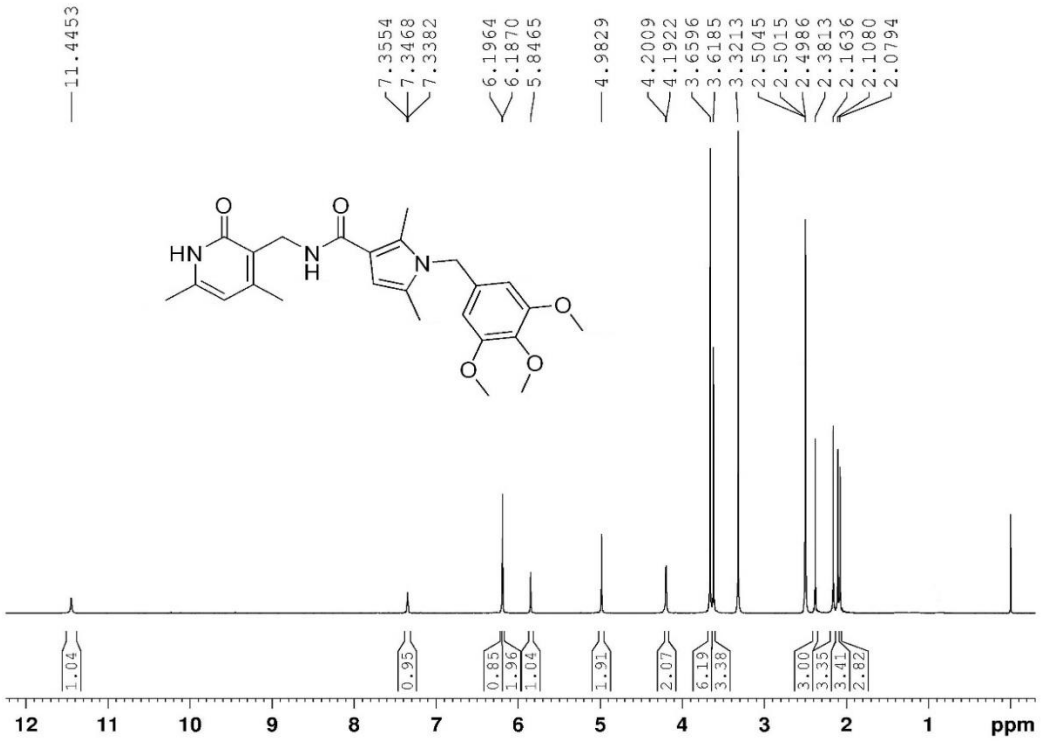


^{13}C NMR of D-03

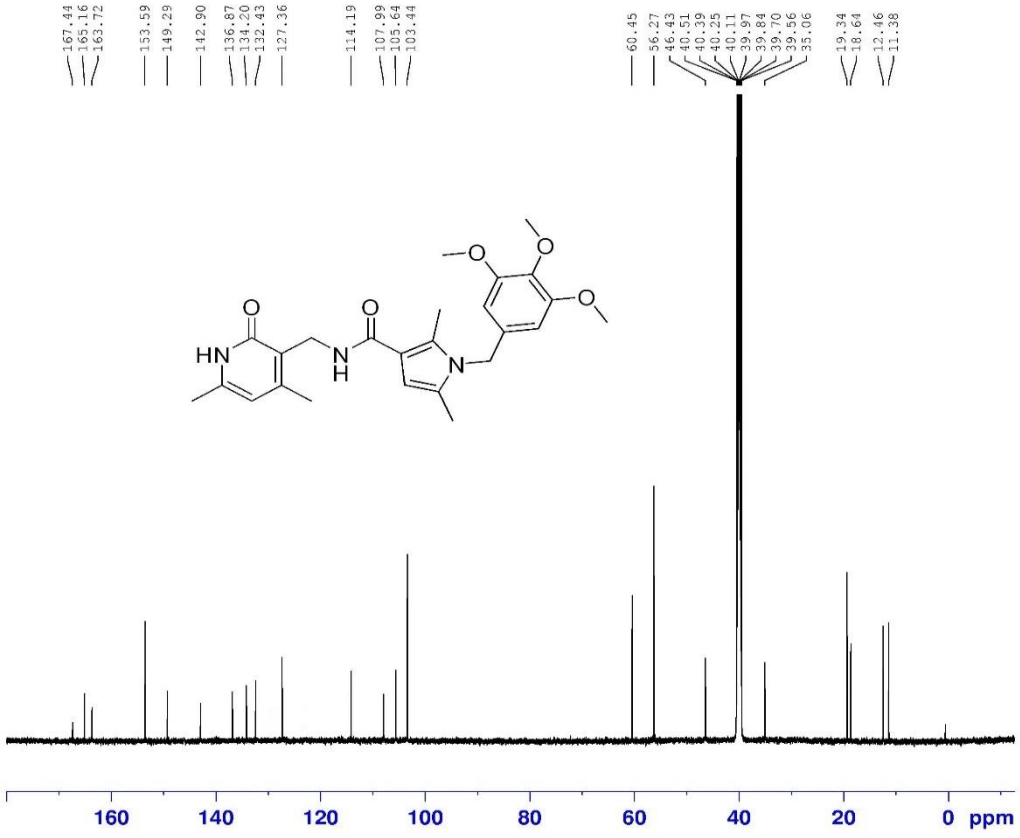


*N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(3,4,5-trimethoxybenzyl)-1 H-pyrrole-3-carboxamide (**D-04**)*

^{1}H NMR of D-04

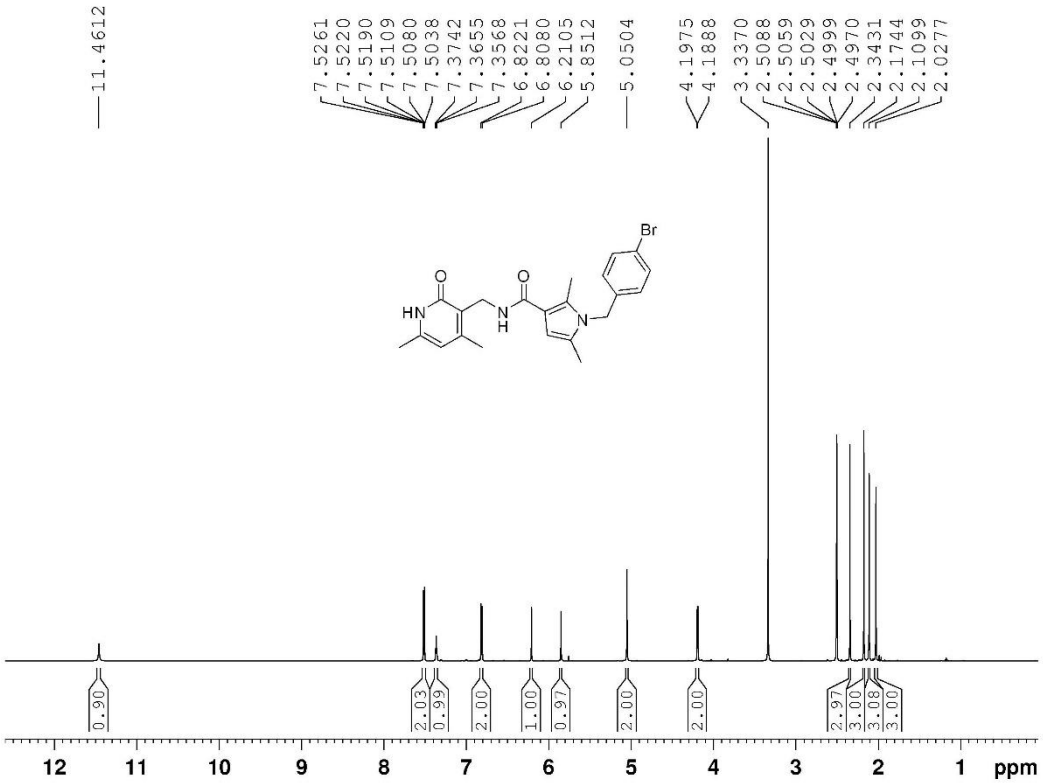


^{13}C NMR of D-04

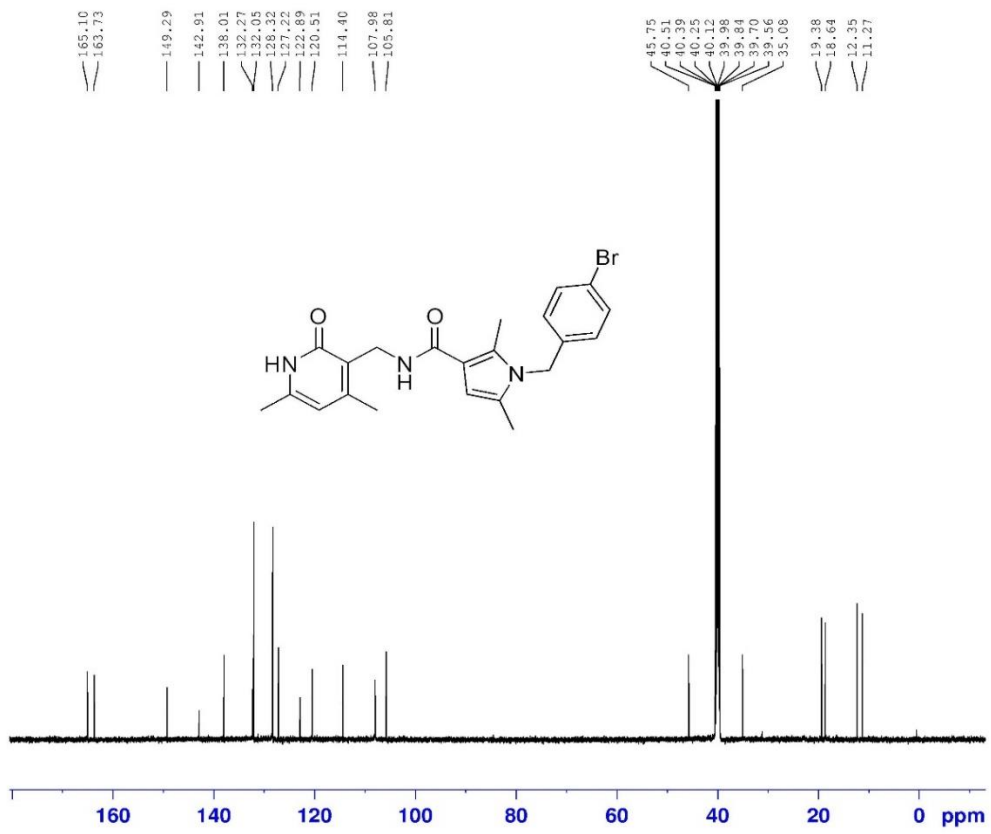


*1-(4-bromobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-05**)*

^{1}H NMR of D-05

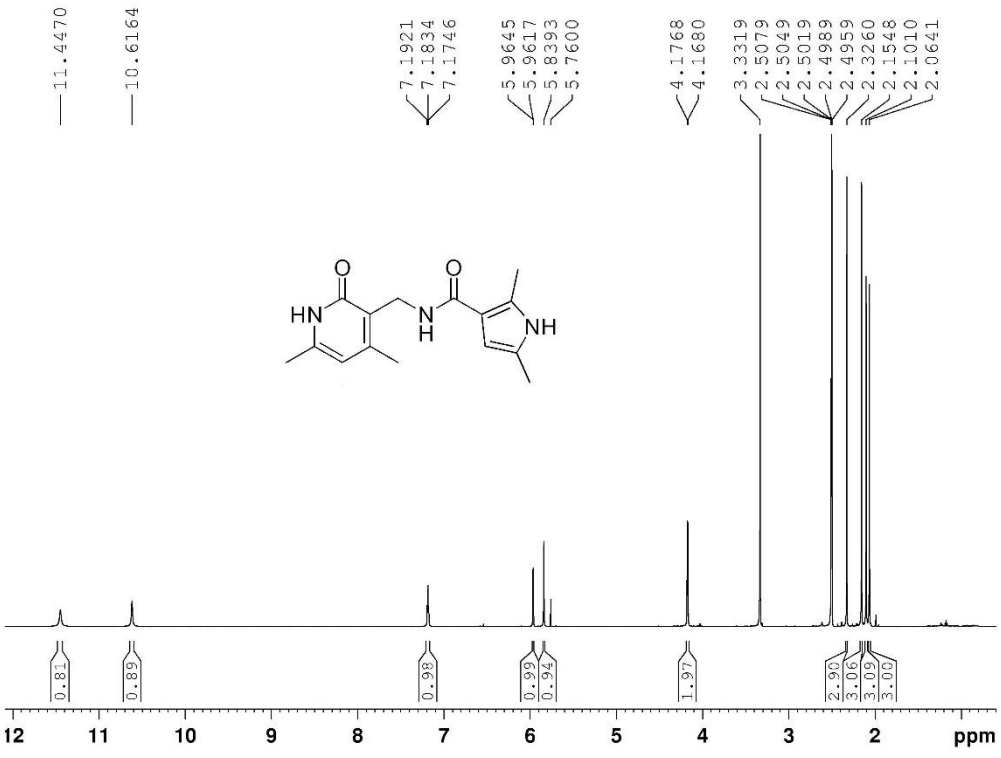


^{13}C NMR of D-05

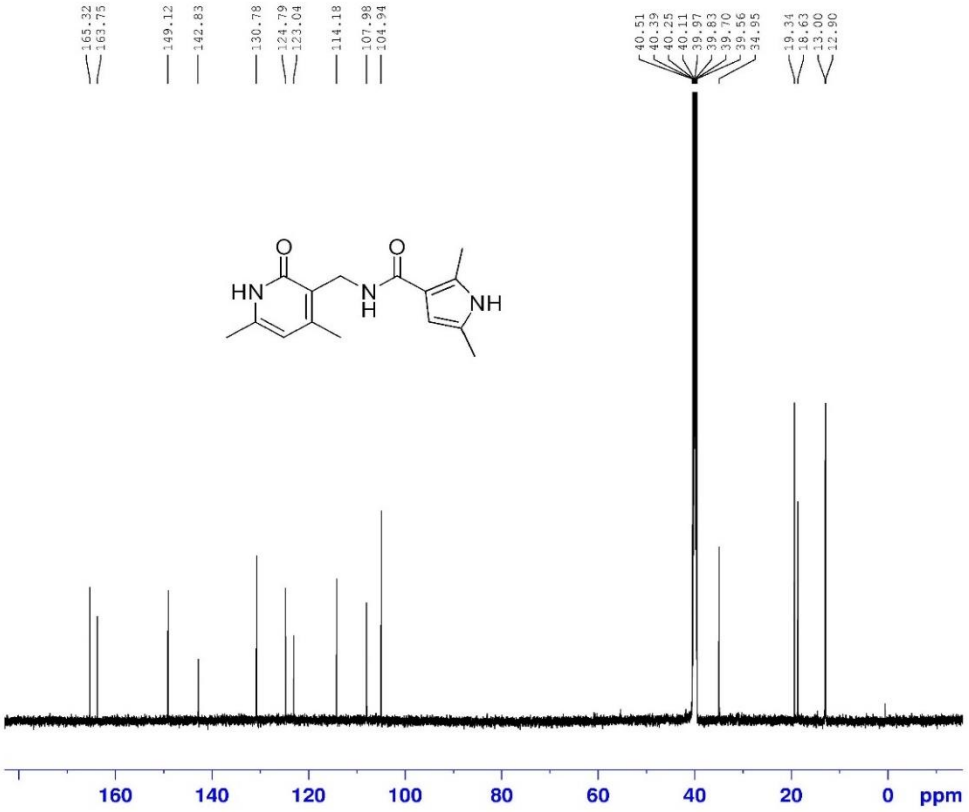


N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide ***(D-06)***

^{1}H NMR of D-06

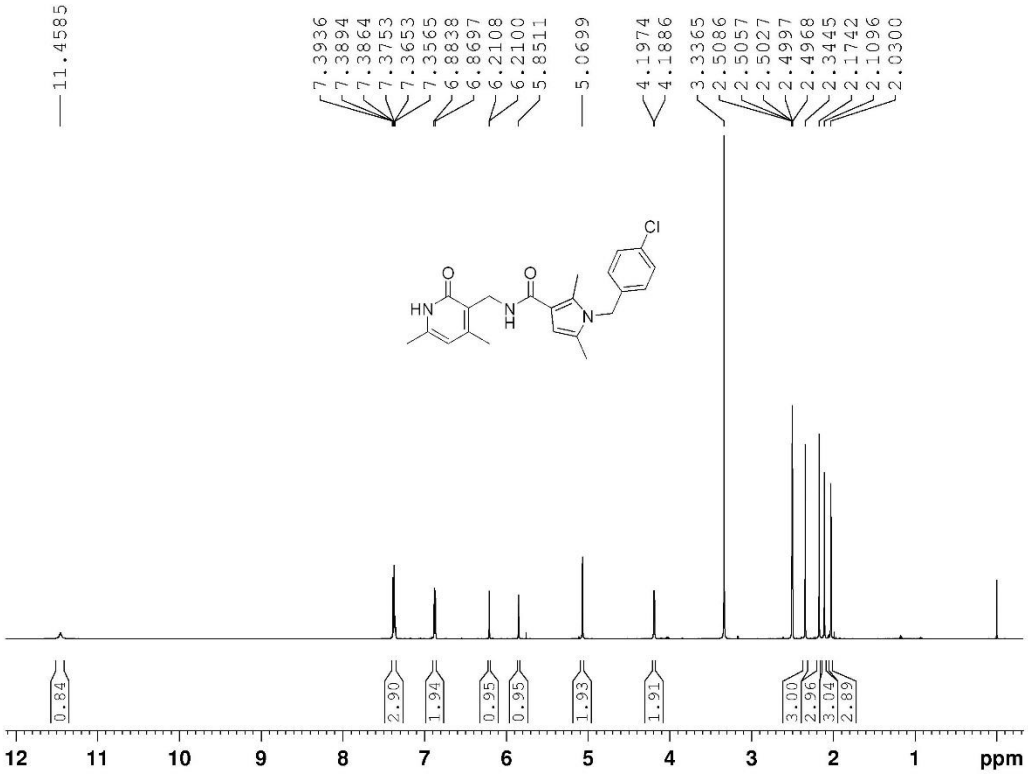


^{13}C NMR of D-06

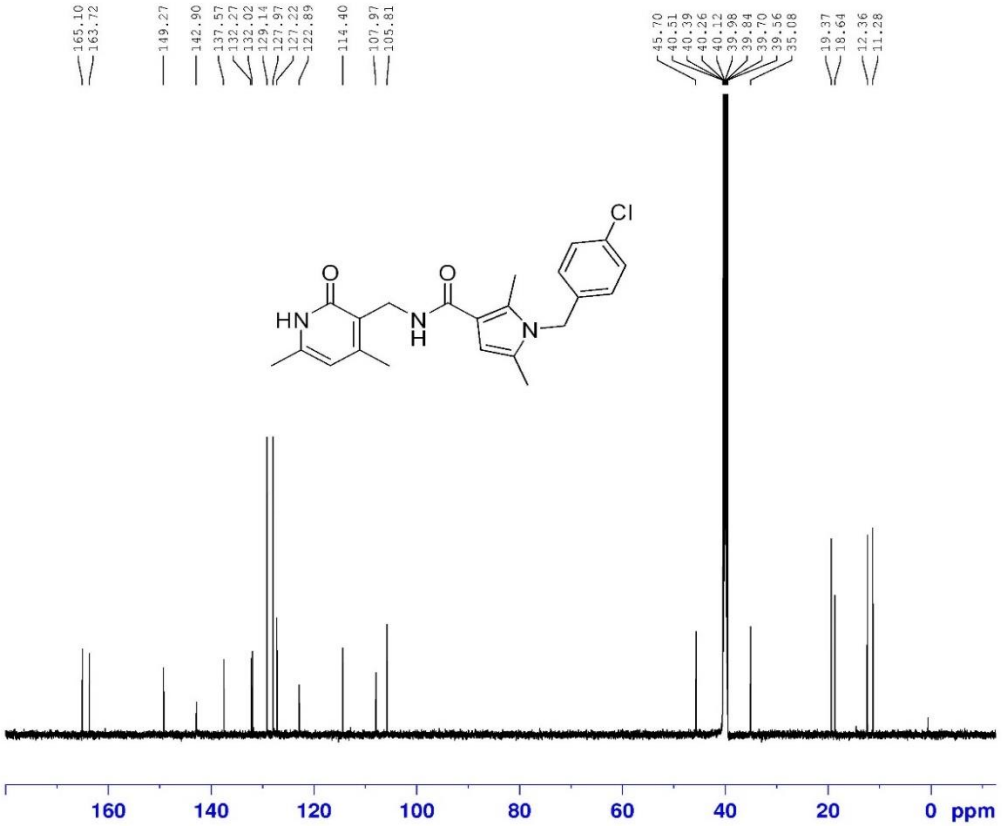


*1-(4-chlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrol e-3-carboxamide (**D-07**)*

^{1}H NMR of D-07

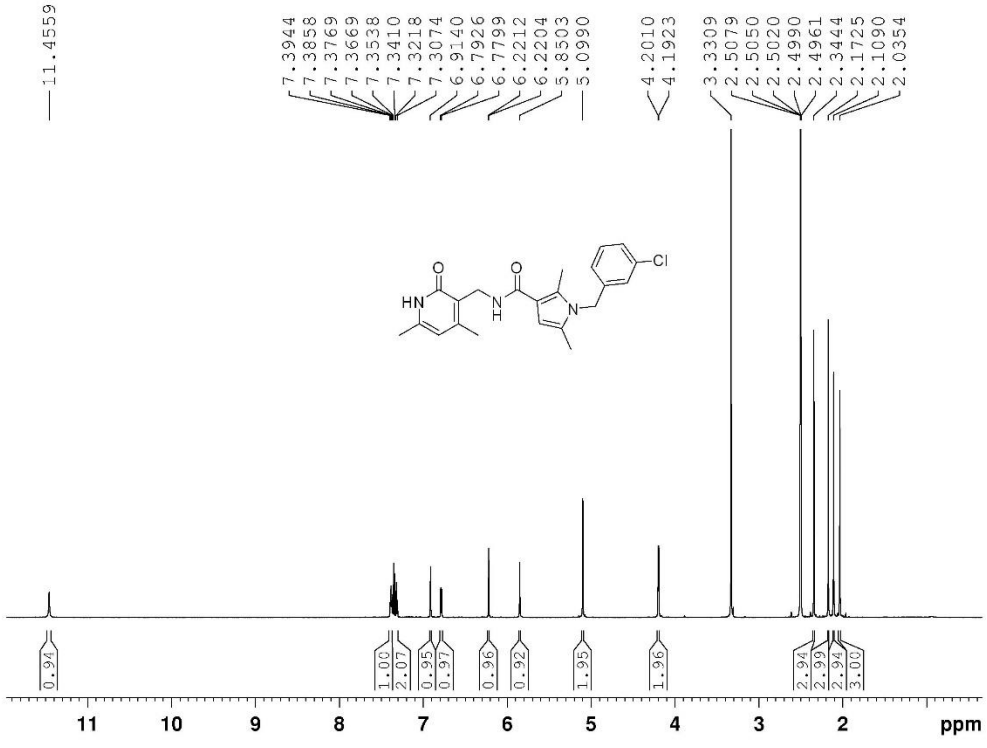


^{13}C NMR of D-07

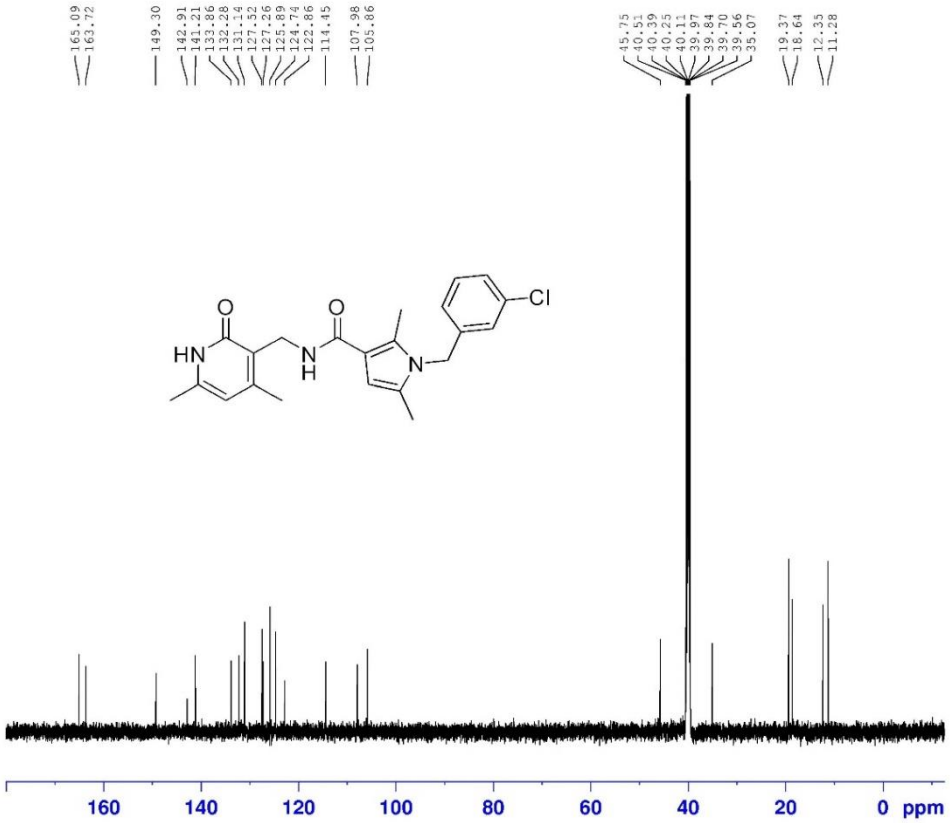


*1-(3-chlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-08**)*

^{1}H NMR of D-08

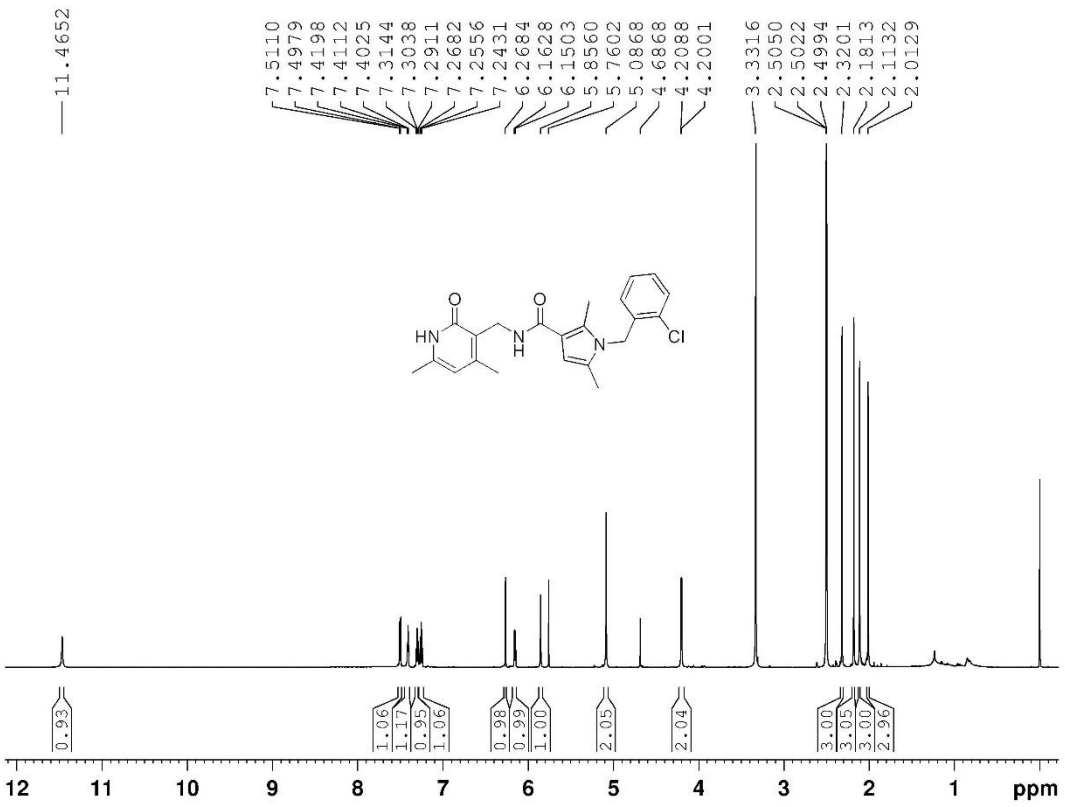


^{13}C NMR of D-08

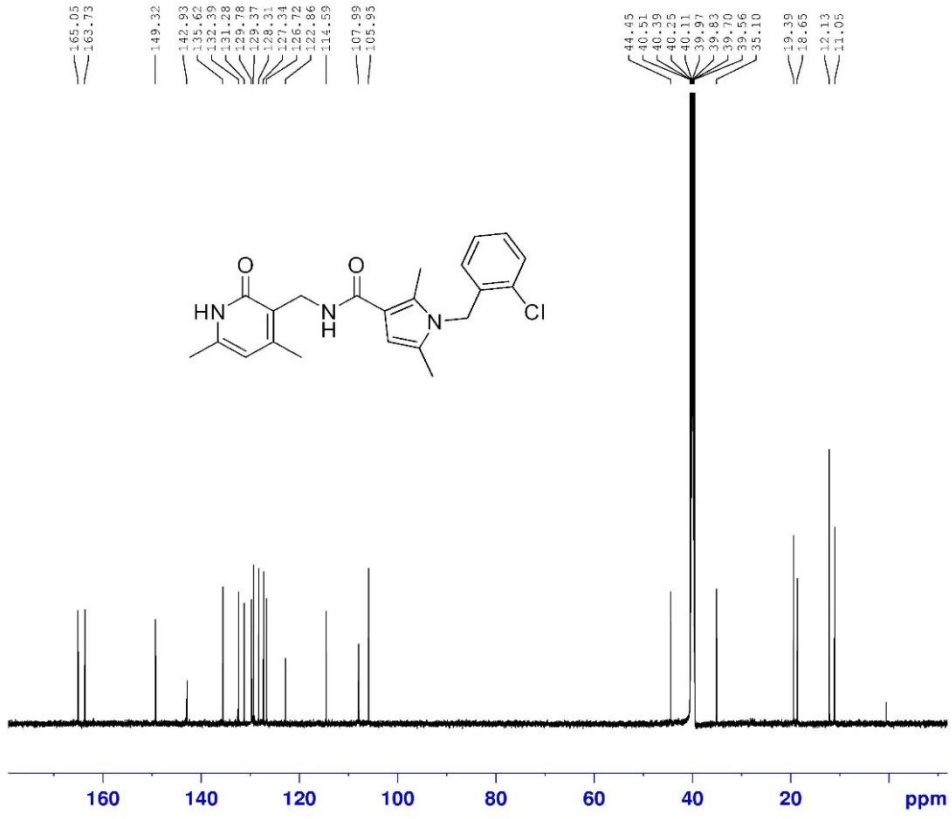


*1-(2-chlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-09**)*

^{1}H NMR of D-09

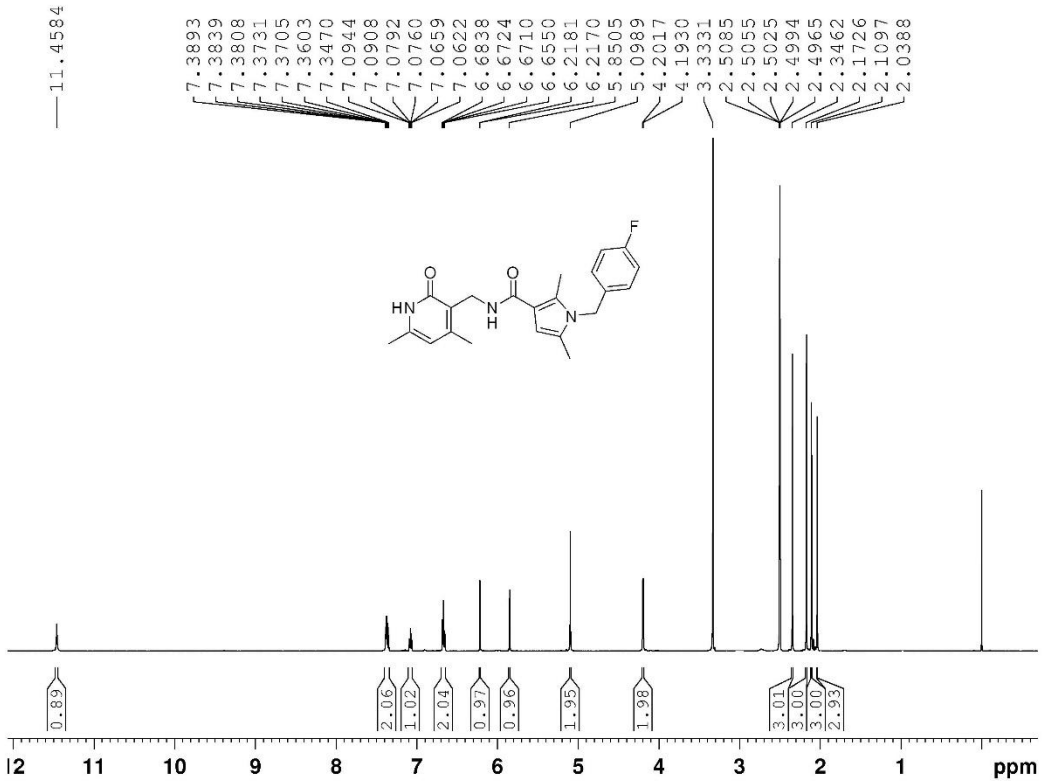


^{13}C NMR of D-09

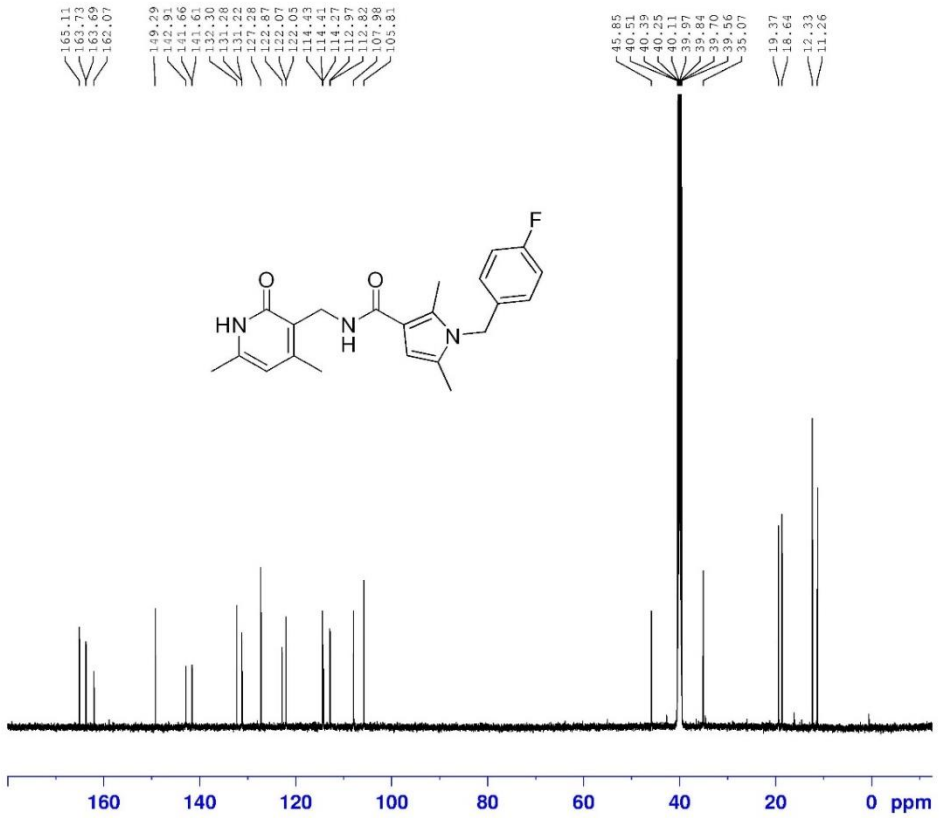


*N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-10**)*

^{1}H NMR of D-10

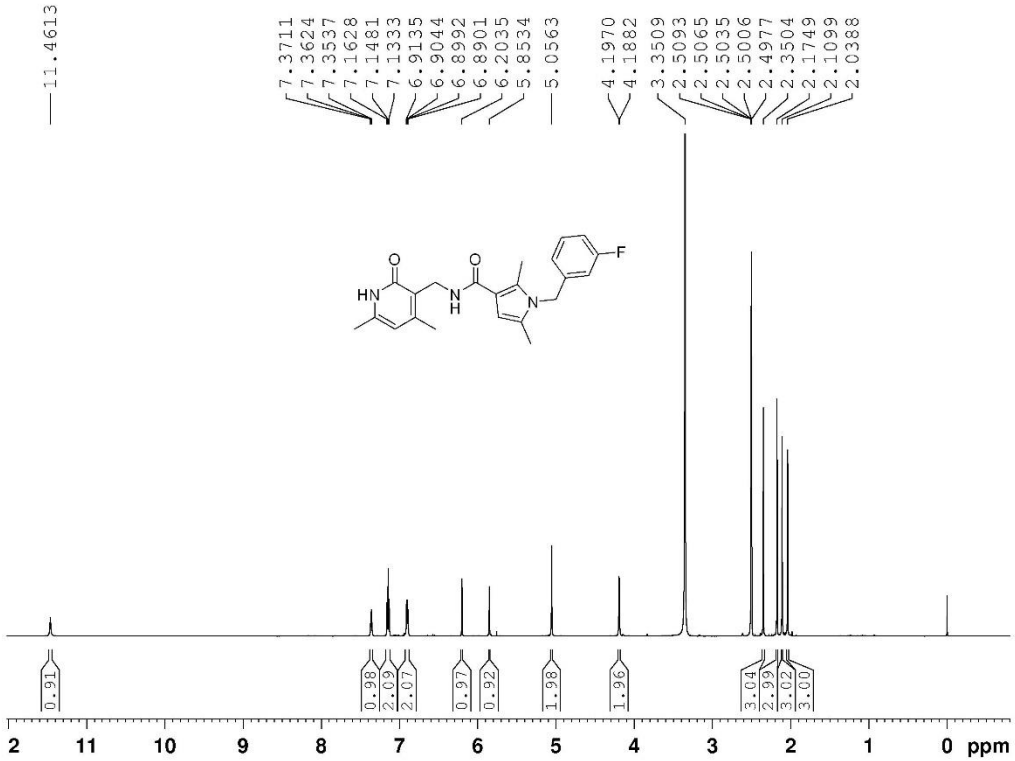


^{13}C NMR of D-10

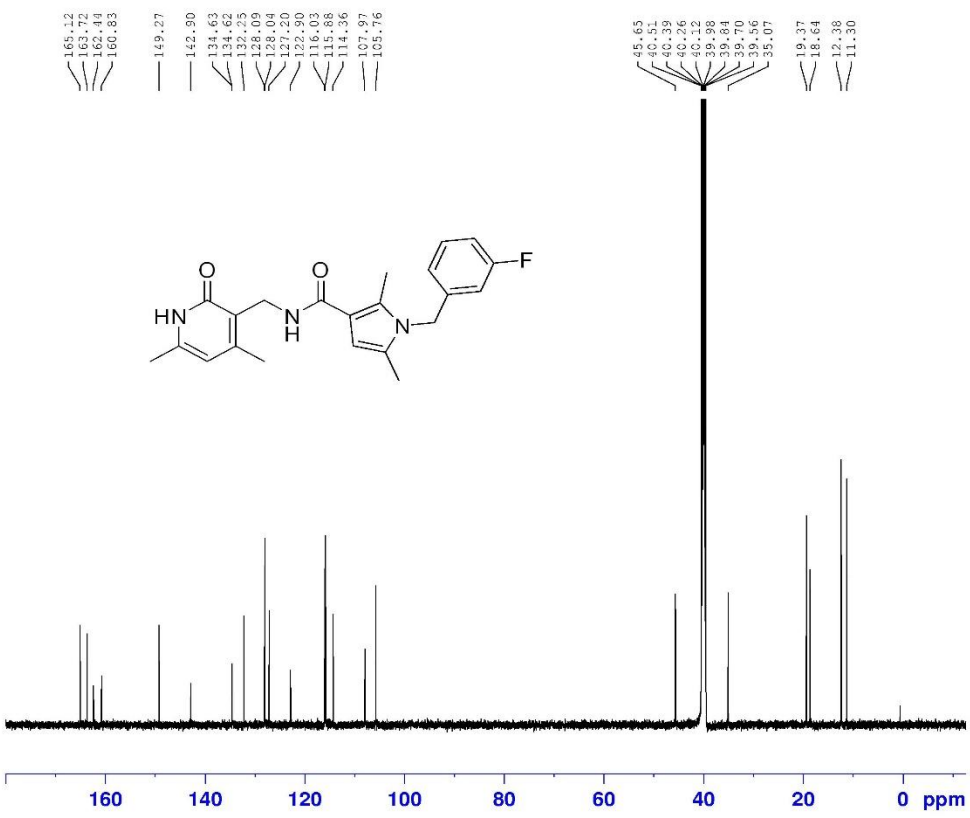


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-11**)*

^{1}H NMR of D-11

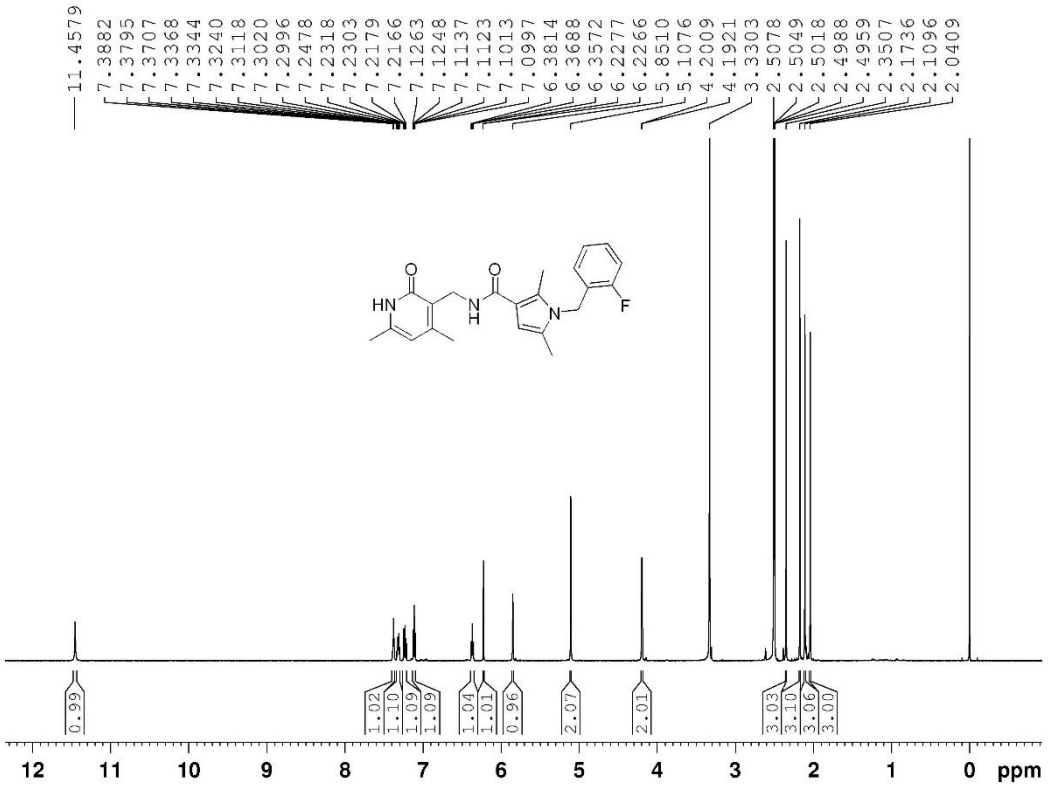


^{13}C NMR of D-11

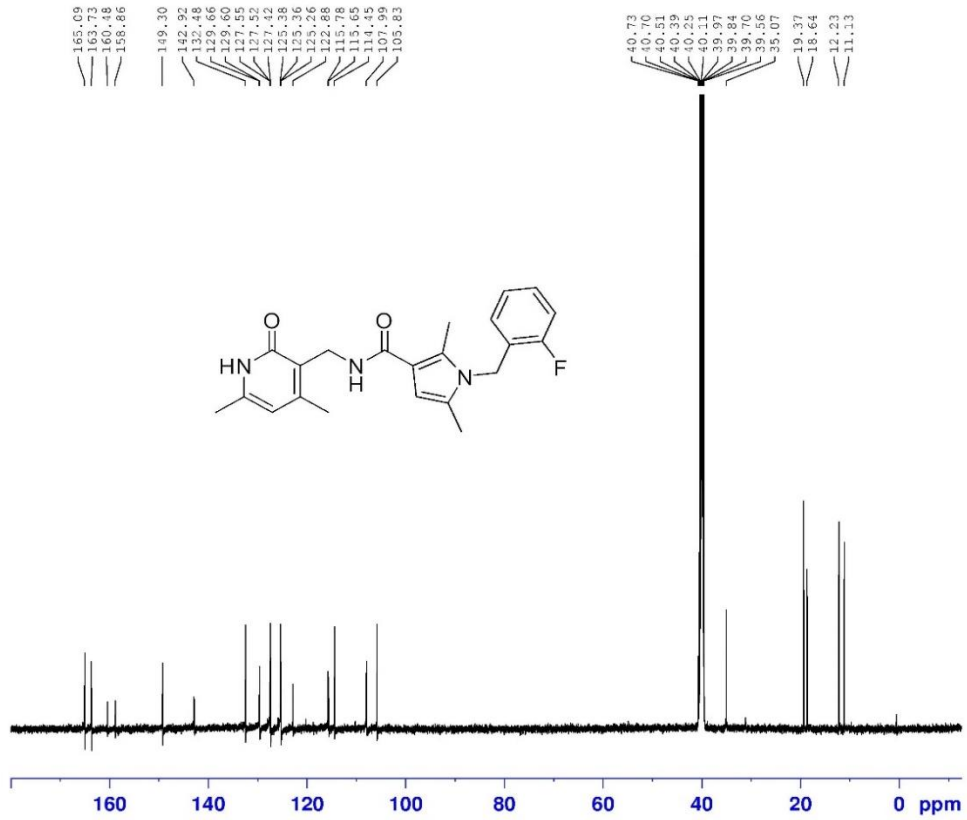


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-fluorobenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-12**)*

^{1}H NMR of D-12

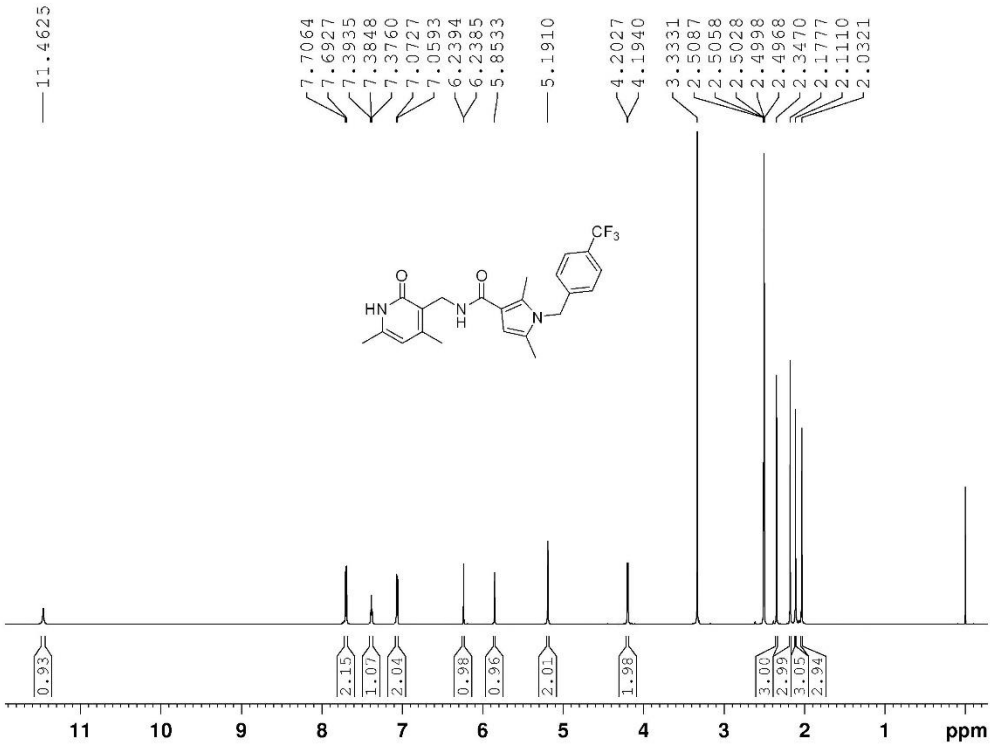


^{13}C NMR of D-12

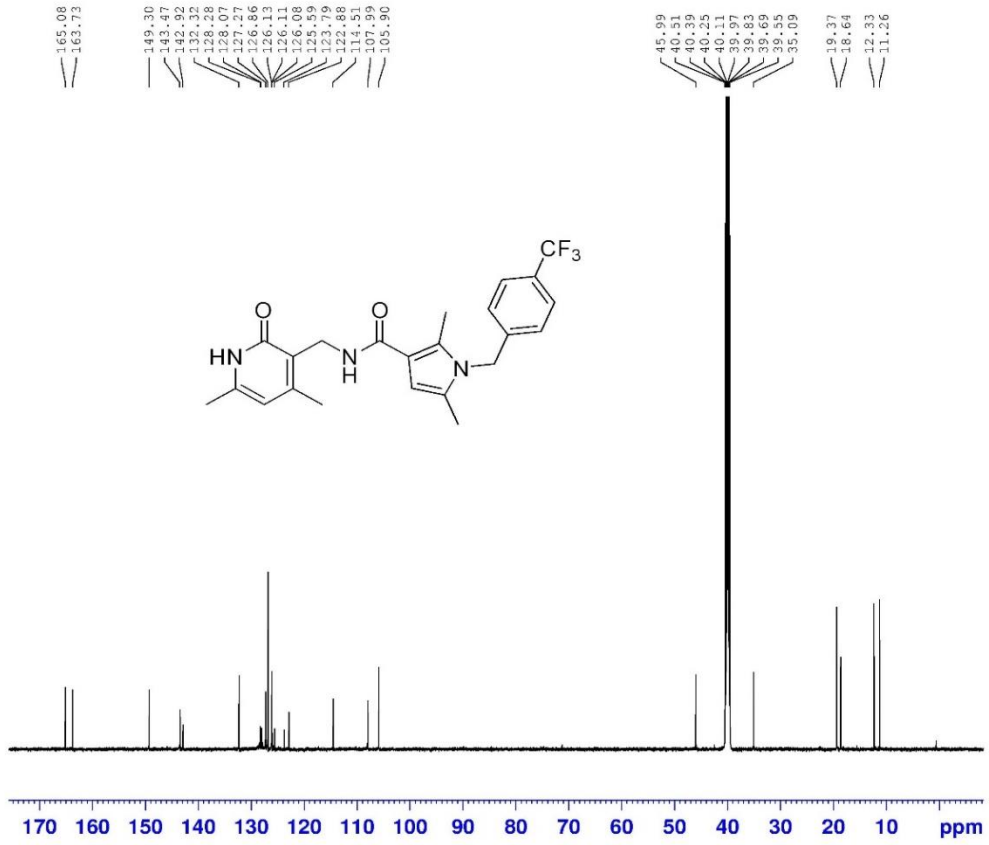


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(4-(trifluoromethyl)benzyl) -1H-pyrrole-3-carboxamide (**D-13**)*

^{1}H NMR of D-13

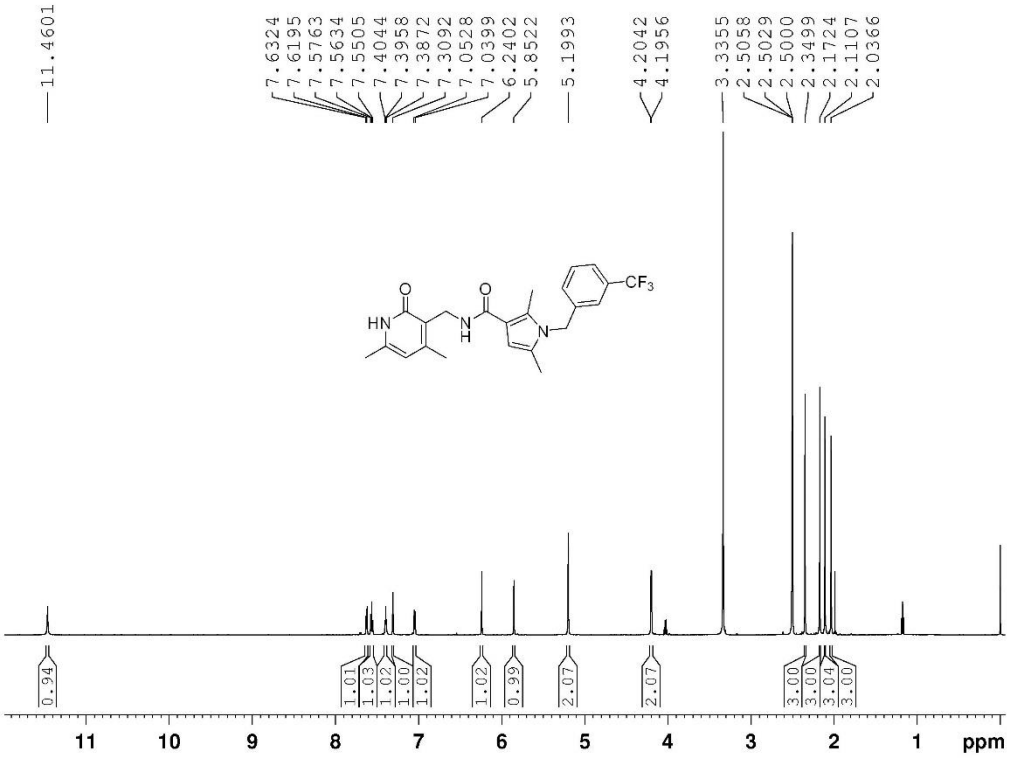


^{13}C NMR of D-13

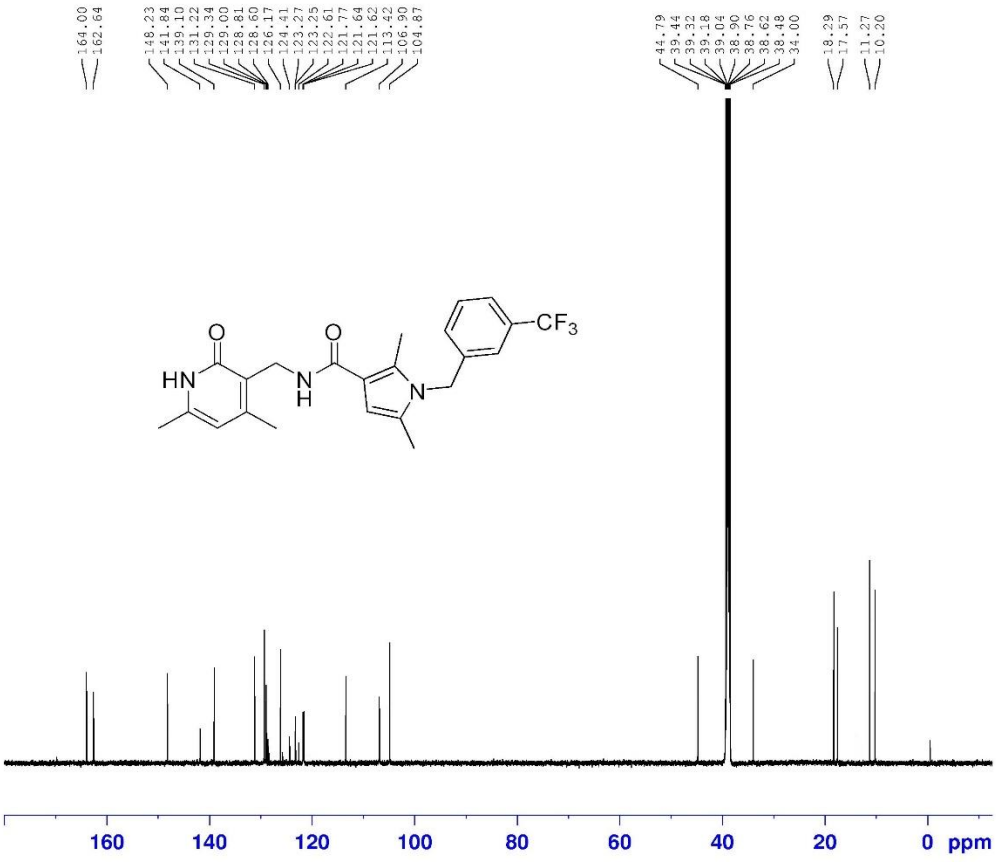


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(3-(trifluoromethyl)benzyl) -1H-pyrrole-3-carboxamide (**D-14**)*

^{1}H NMR of D-14

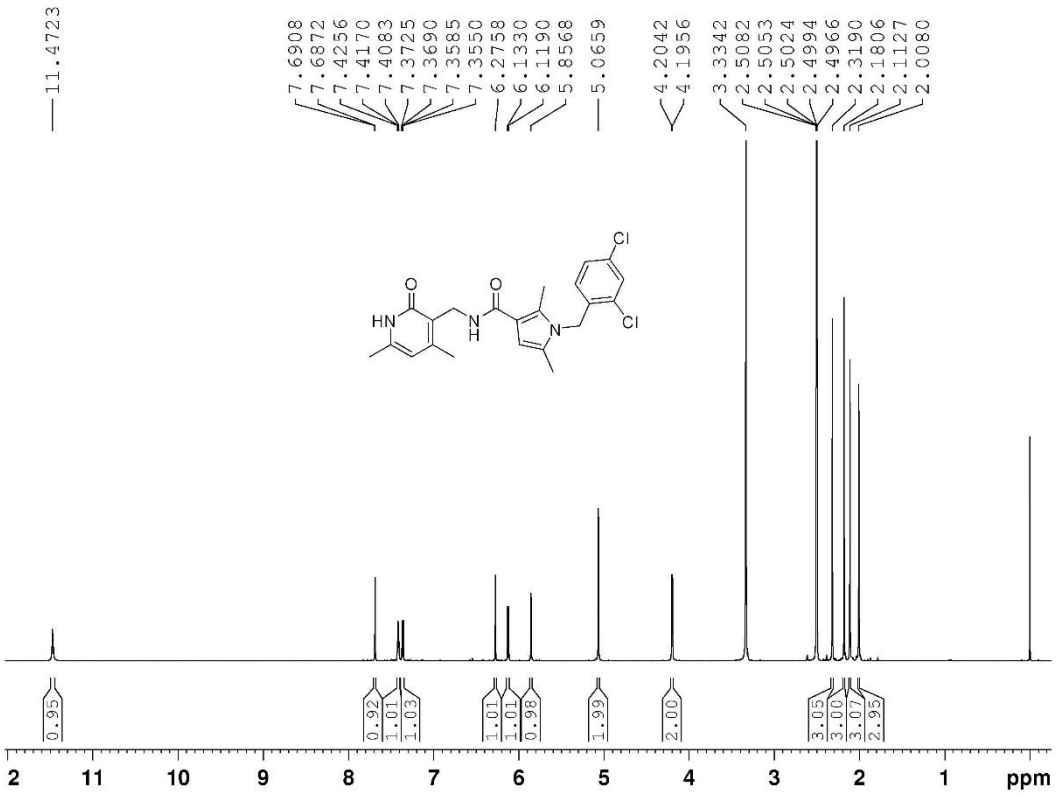


^{13}C NMR of D-14

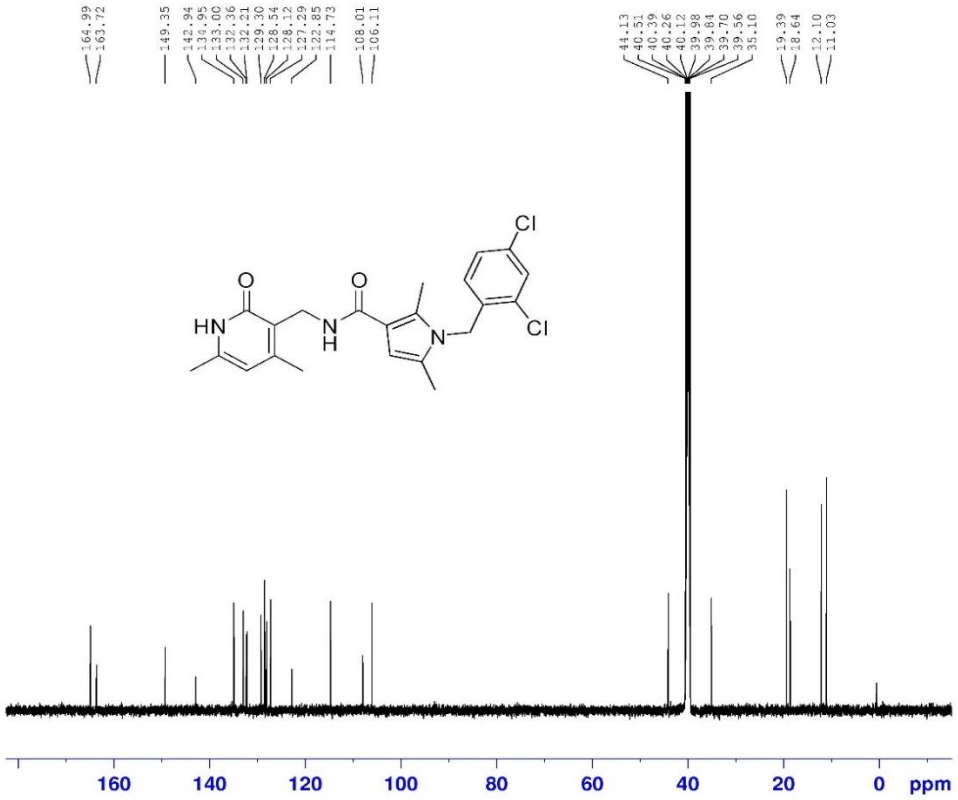


*1-(2,4-Dichlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-py rrole-3-carboxamide (**D-15**)*

^{1}H NMR of D-15

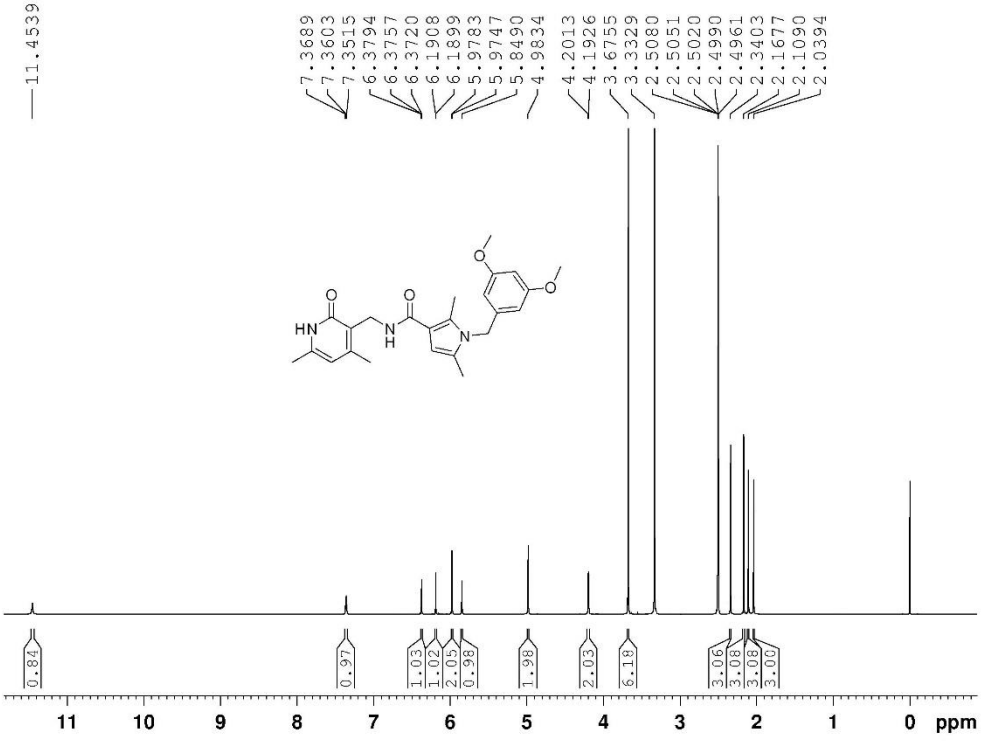


^{13}C NMR of D-15

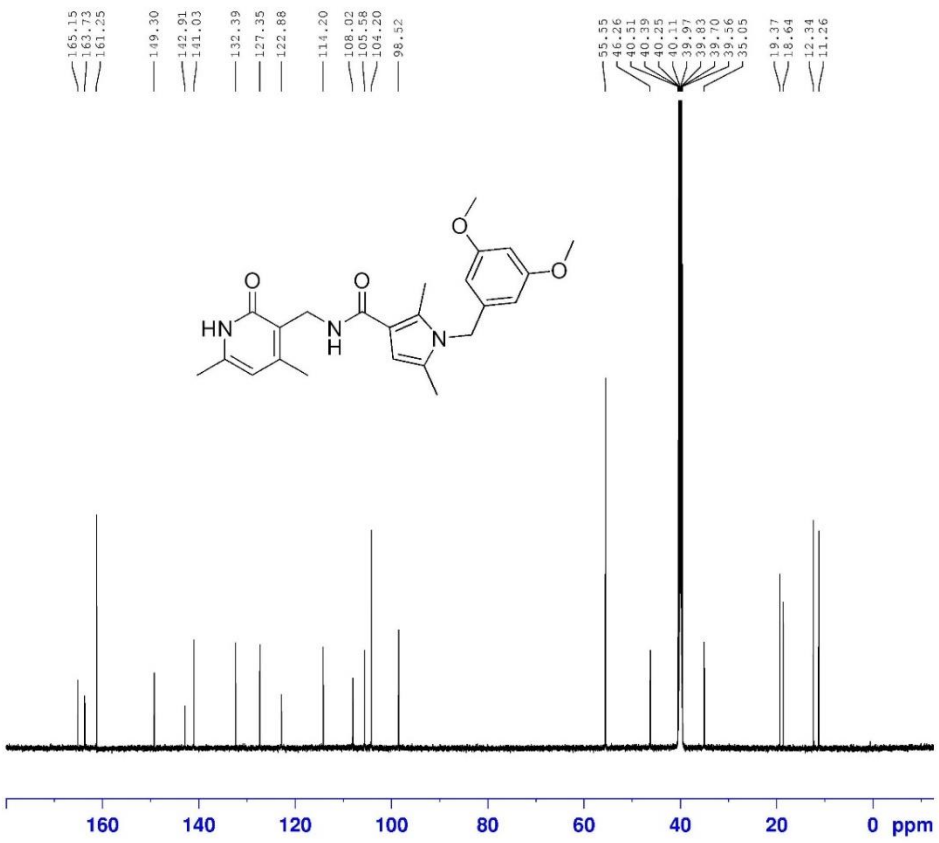


1-(3,5-Dimethoxybenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (D-16)

^{1}H NMR of D-16

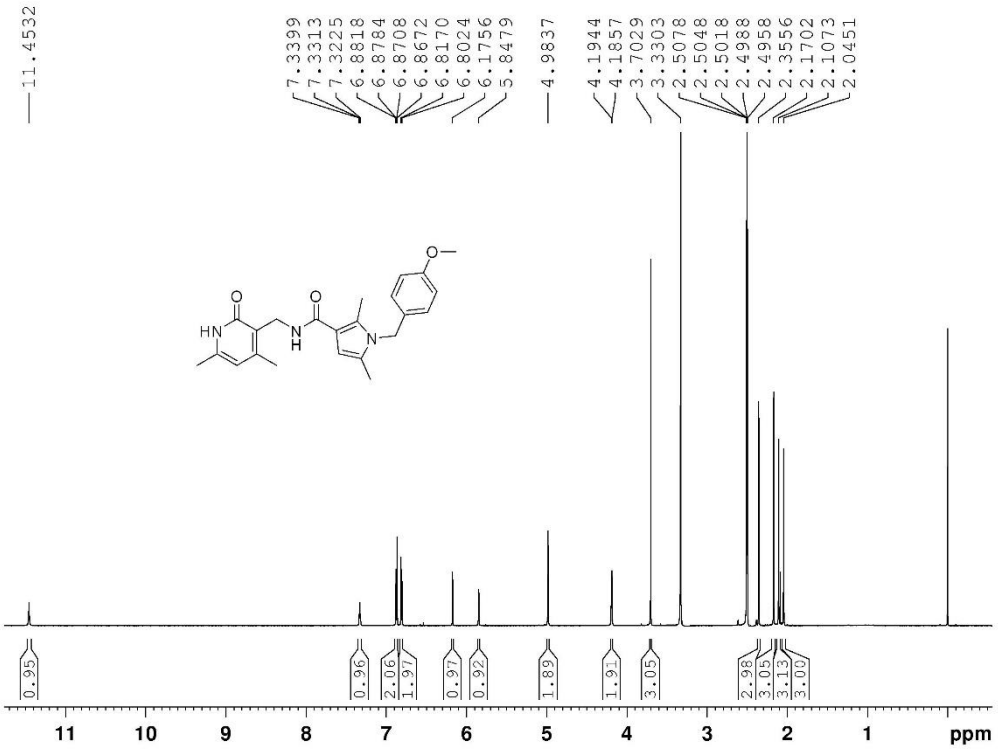


^{13}C NMR of D-16

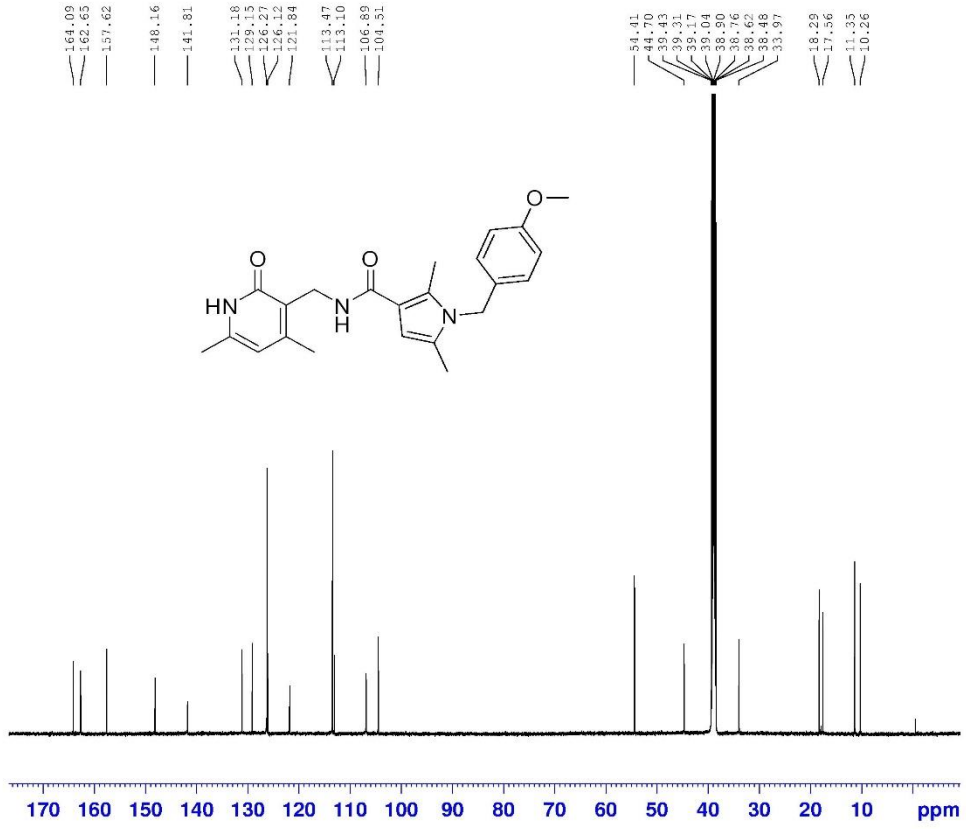


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-methoxybenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-17**)*

^{1}H NMR of D-17

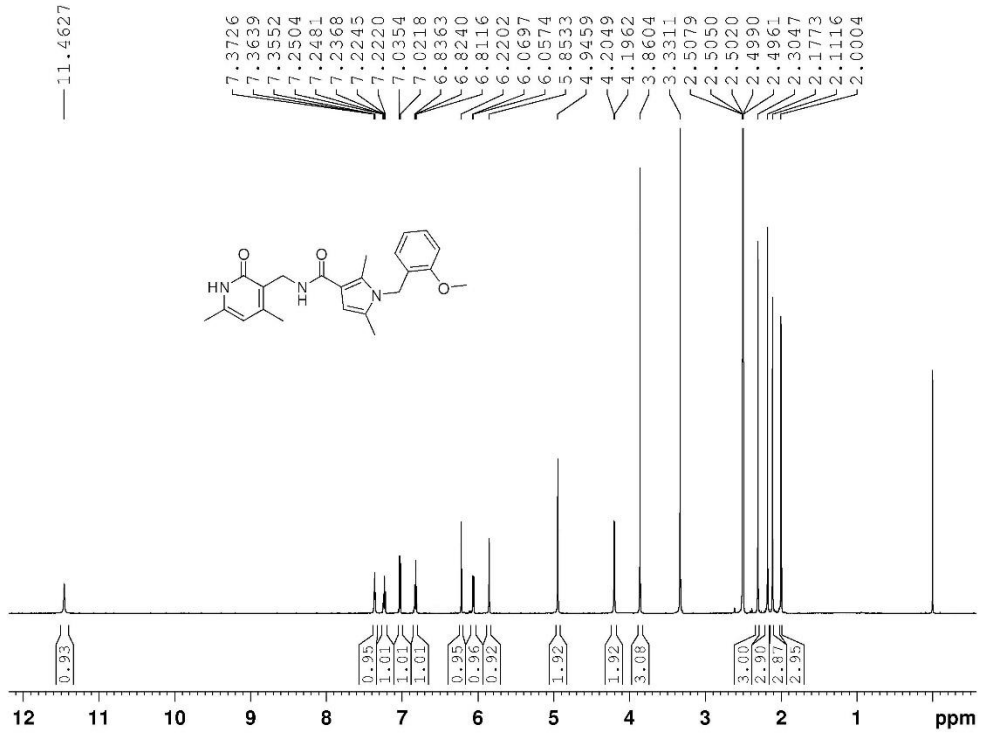


^{13}C NMR of D-17

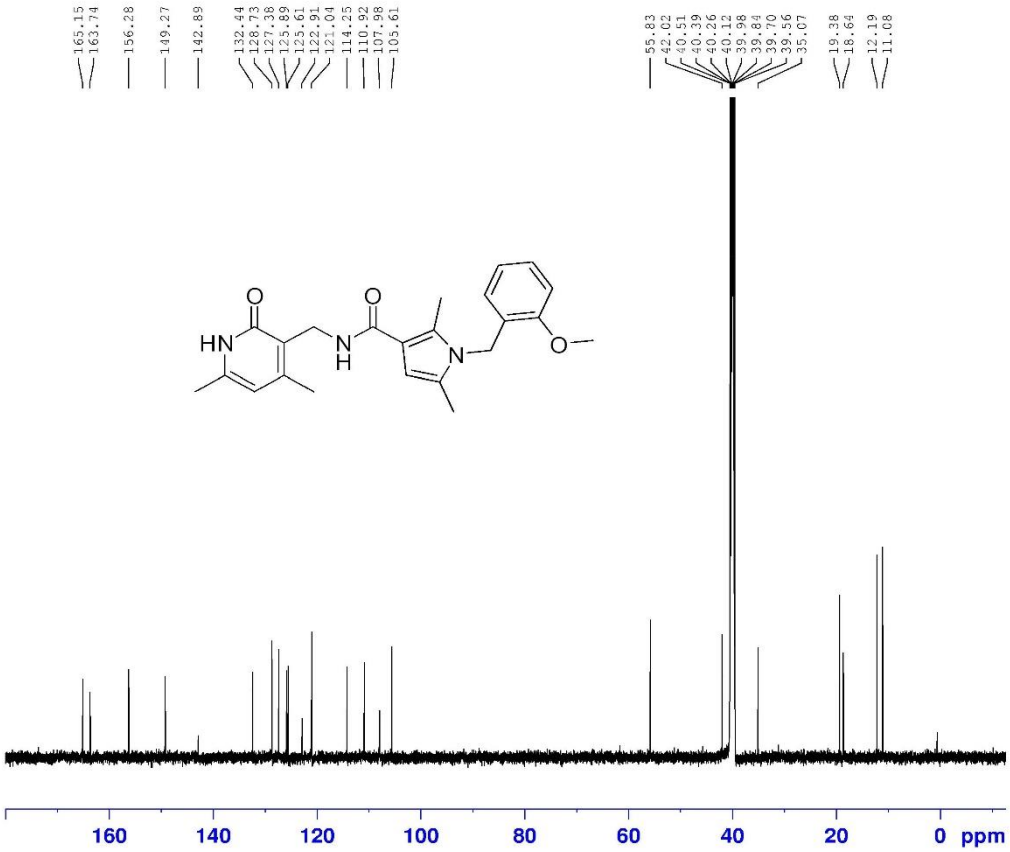


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-methoxybenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-18**)*

^{1}H NMR of D-18

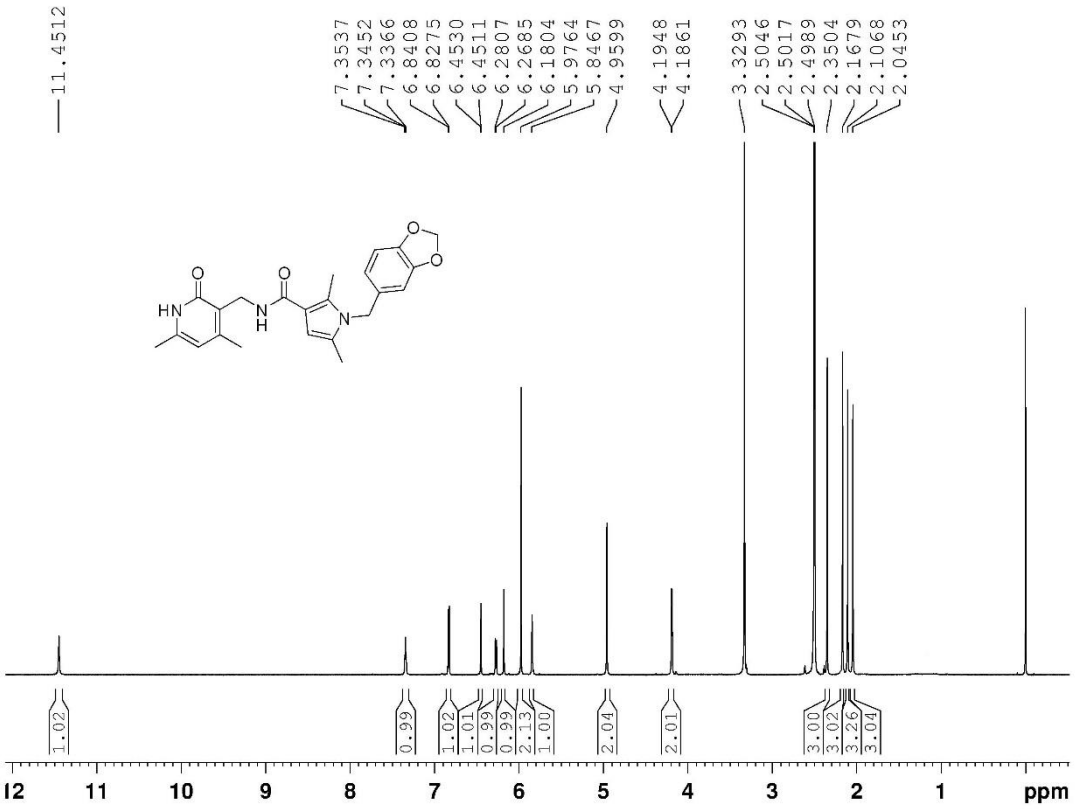


^{13}C NMR of D-18

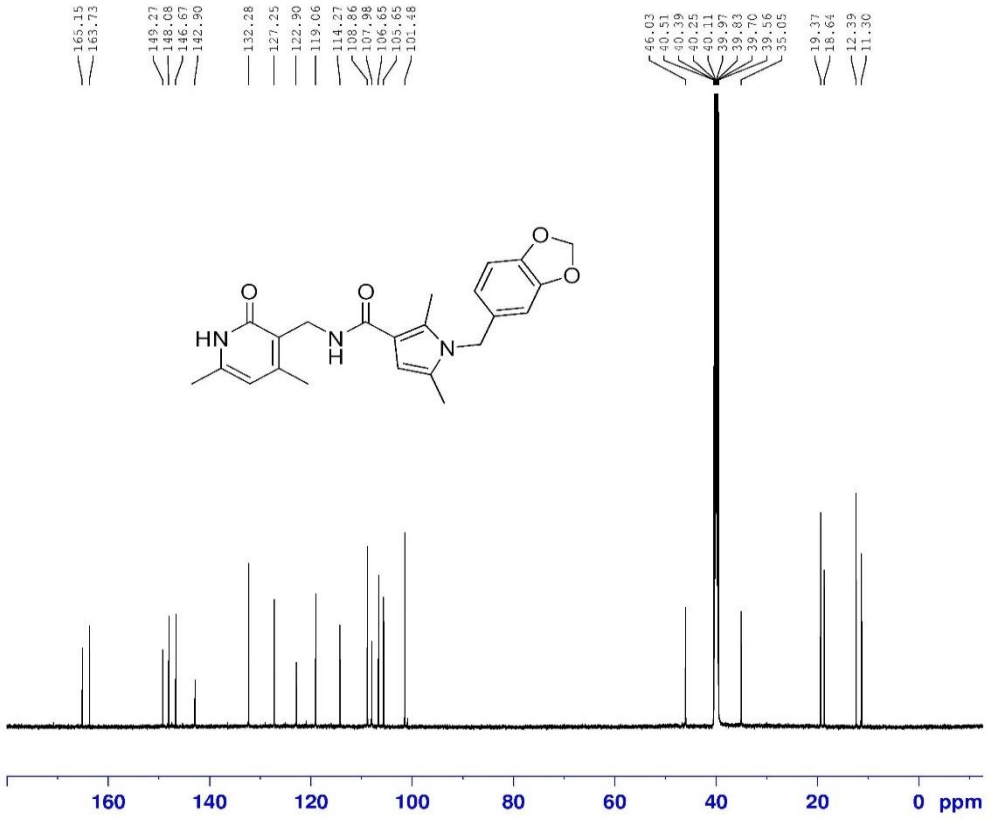


*1-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydro)pyridin-3-yl)methyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-19**)*

^{1}H NMR of D-19

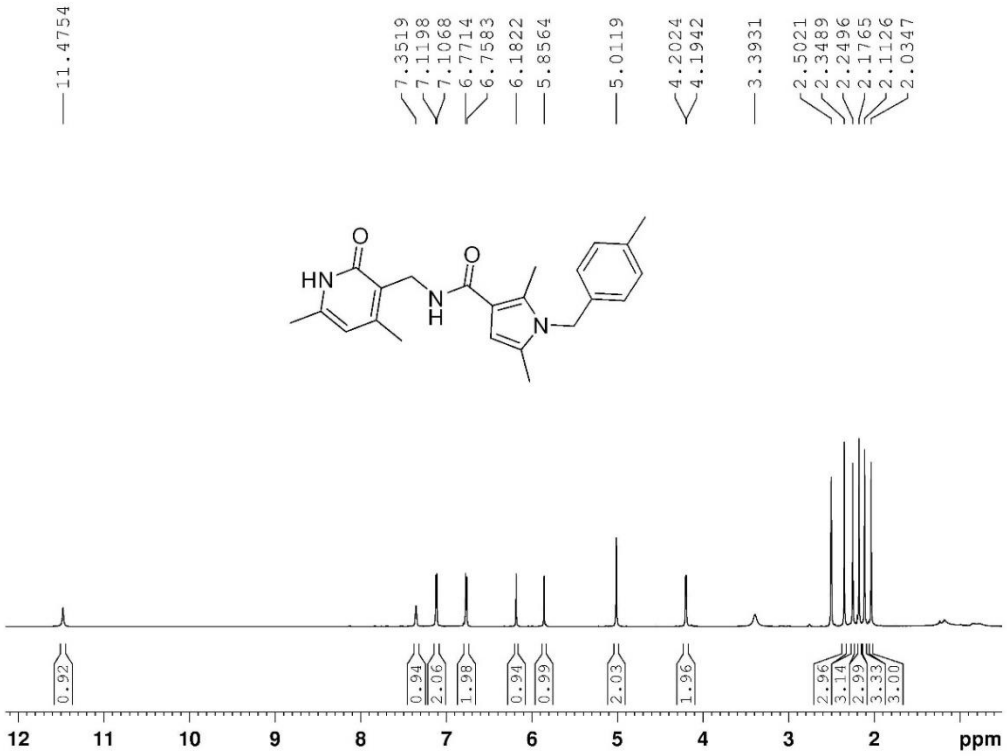


^{13}C NMR of D-19

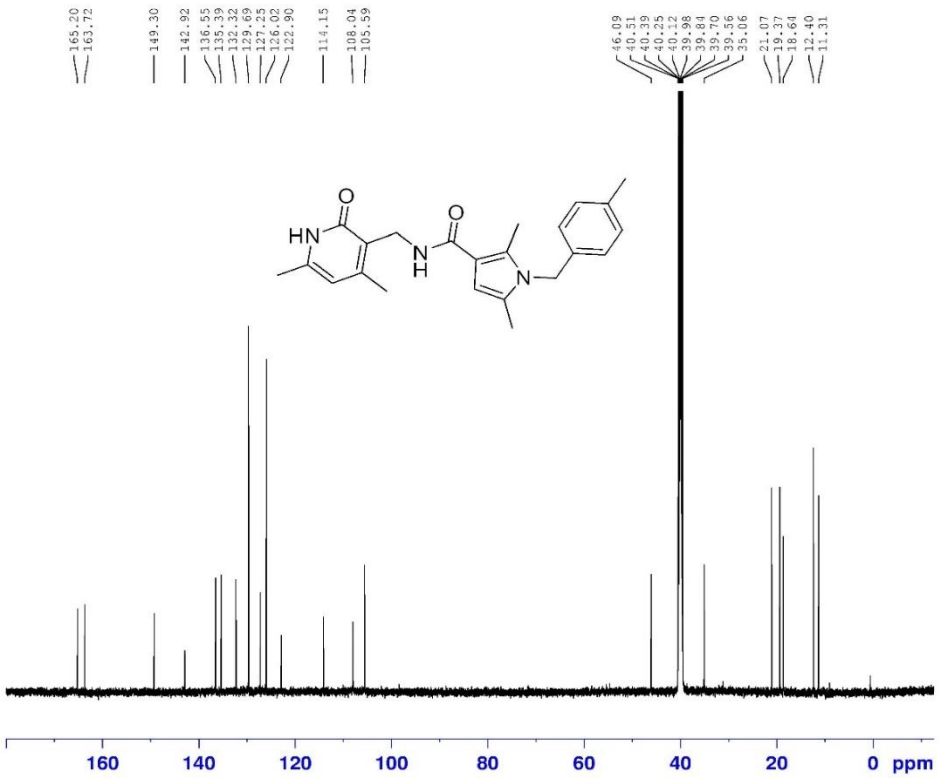


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(4-methylbenzyl)-1H-pyrrole-3-carboxamide (**D-20**)*

^{1}H NMR of D-20

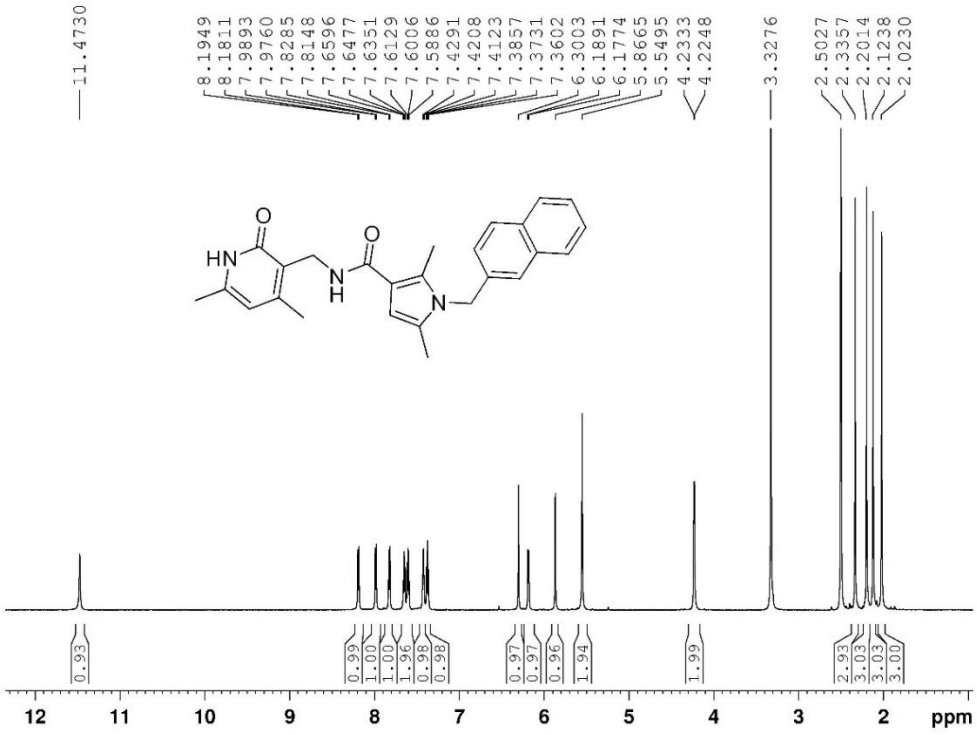


^{13}C NMR of D-20

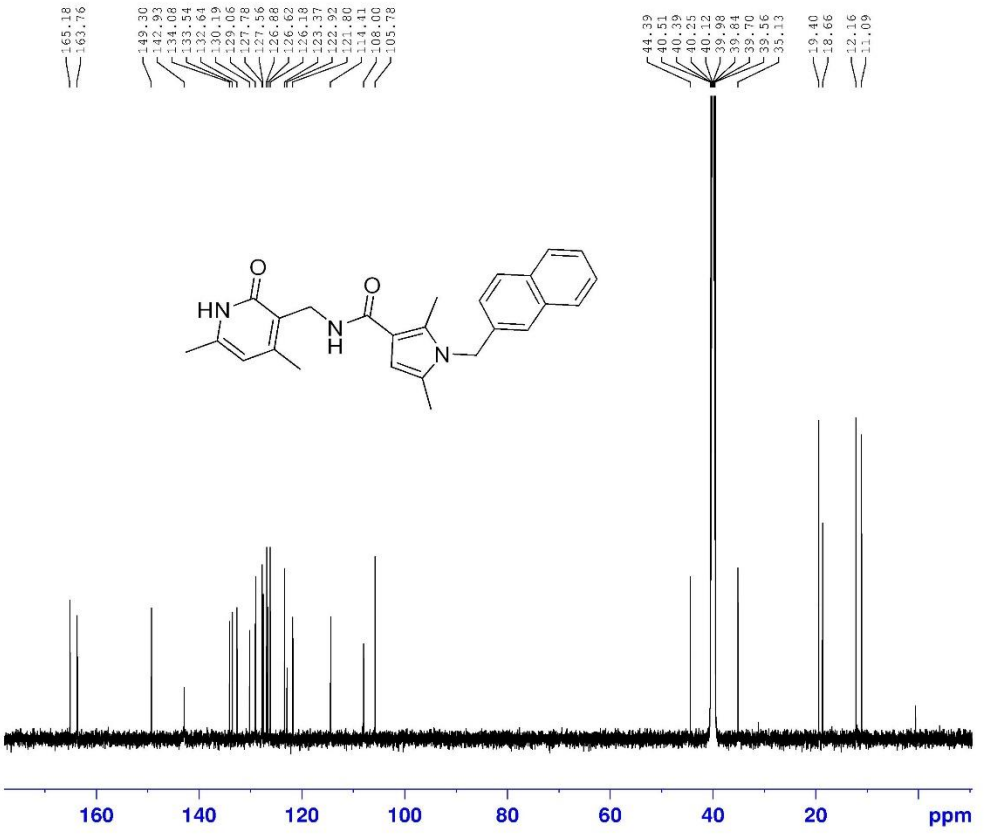


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,5-dimethyl-1-(naphthalen-2-ylmethyl) -1H-pyrrole-3-carboxamide (**D-21**)*

^{1}H NMR of D-21

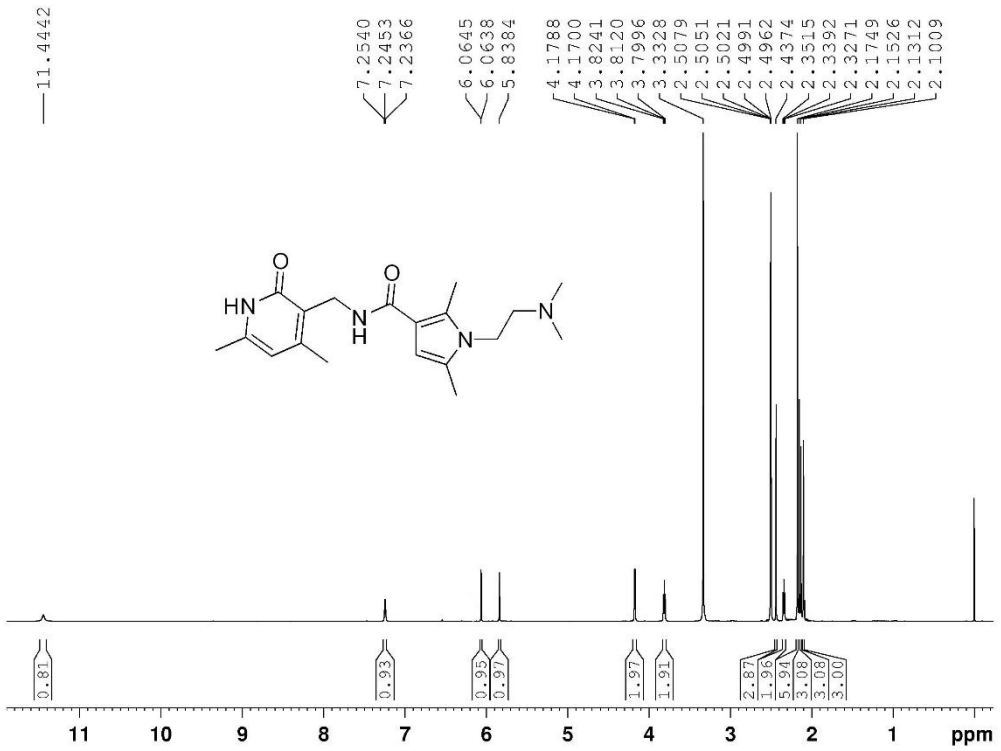


^{13}C NMR of D-21

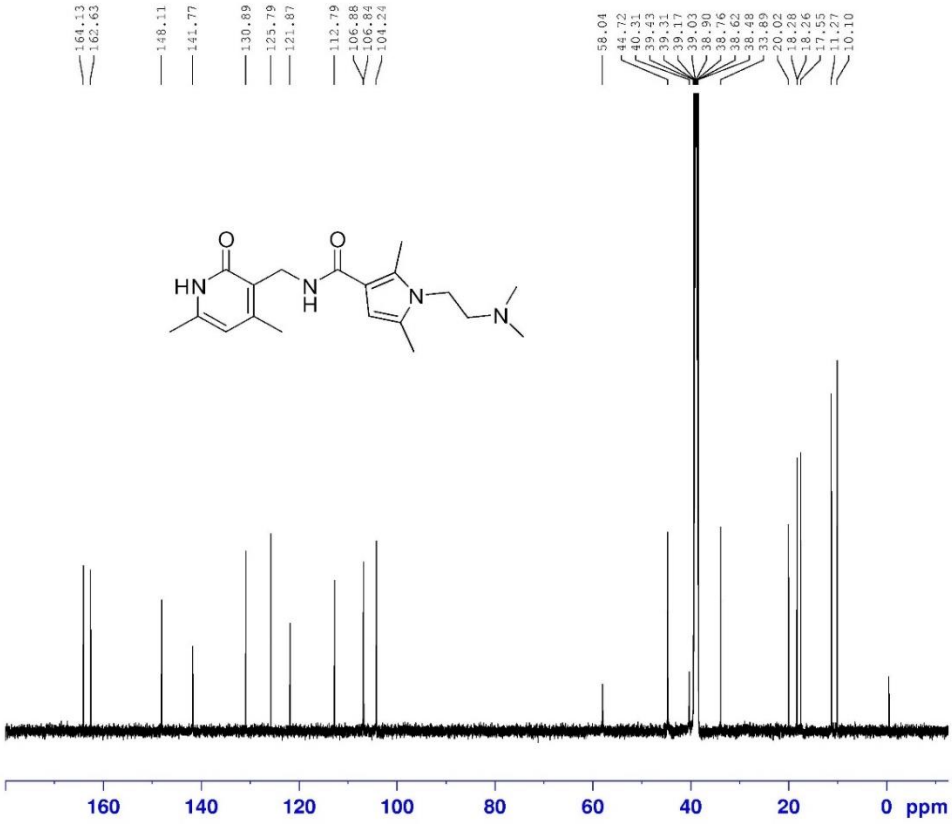


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-(dimethylamino)ethyl)-2,5-dimethyl-1H-pyrrole-3-carboxamide (**D-22**)*

^{1}H NMR of D-22

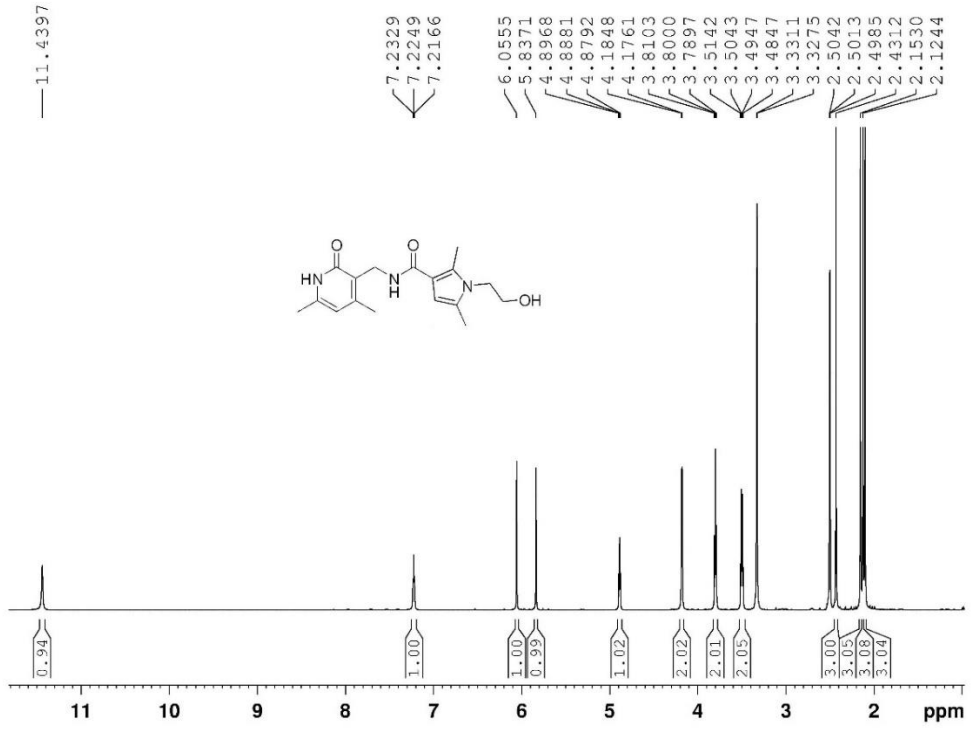


^{13}C NMR of D-22

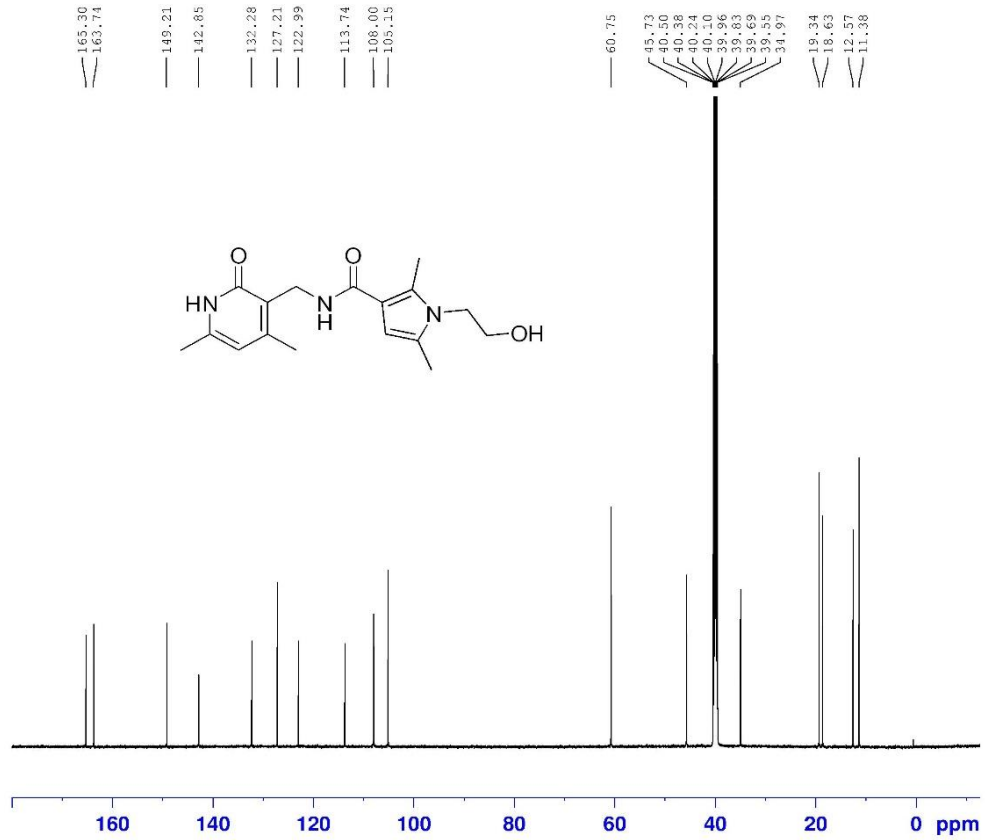


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-hydroxyethyl)-2,5-dimethyl -1H-pyrrole-3-carboxamide (**D-23**)*

^{1}H NMR of D-23

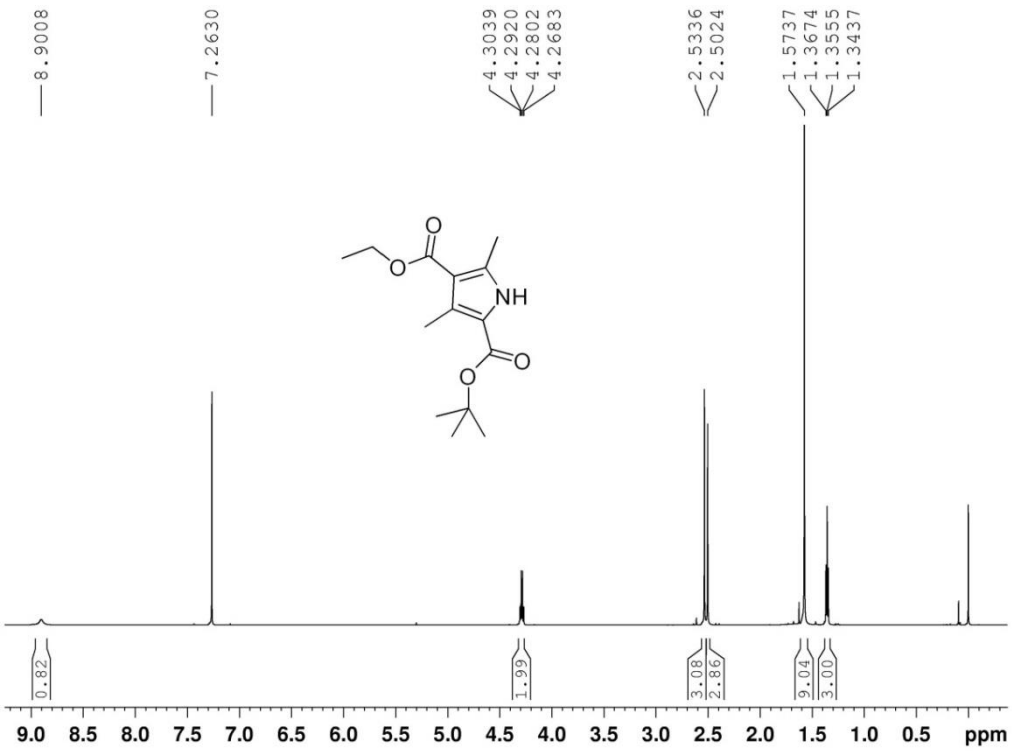


^{13}C NMR of D-23



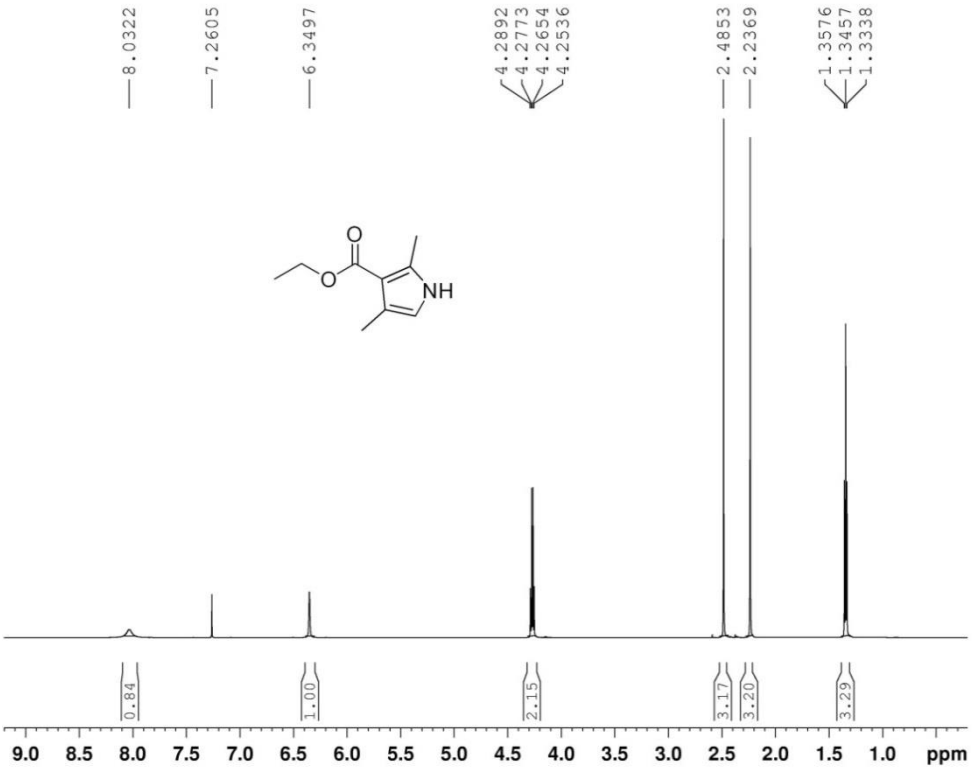
*2-(tert-Butyl) 4-ethyl 3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (**29**)*

^{1}H NMR of compound 29



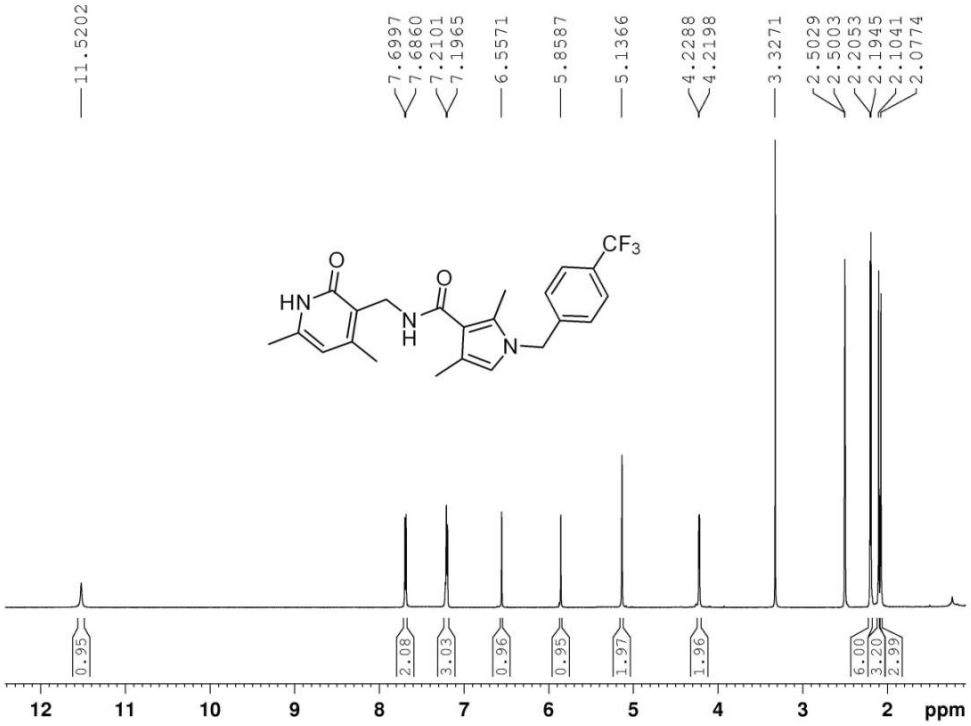
Ethyl 2,4-dimethyl-1H-pyrrole-3-carboxylate ***(30)***

^{1}H NMR of compound 30

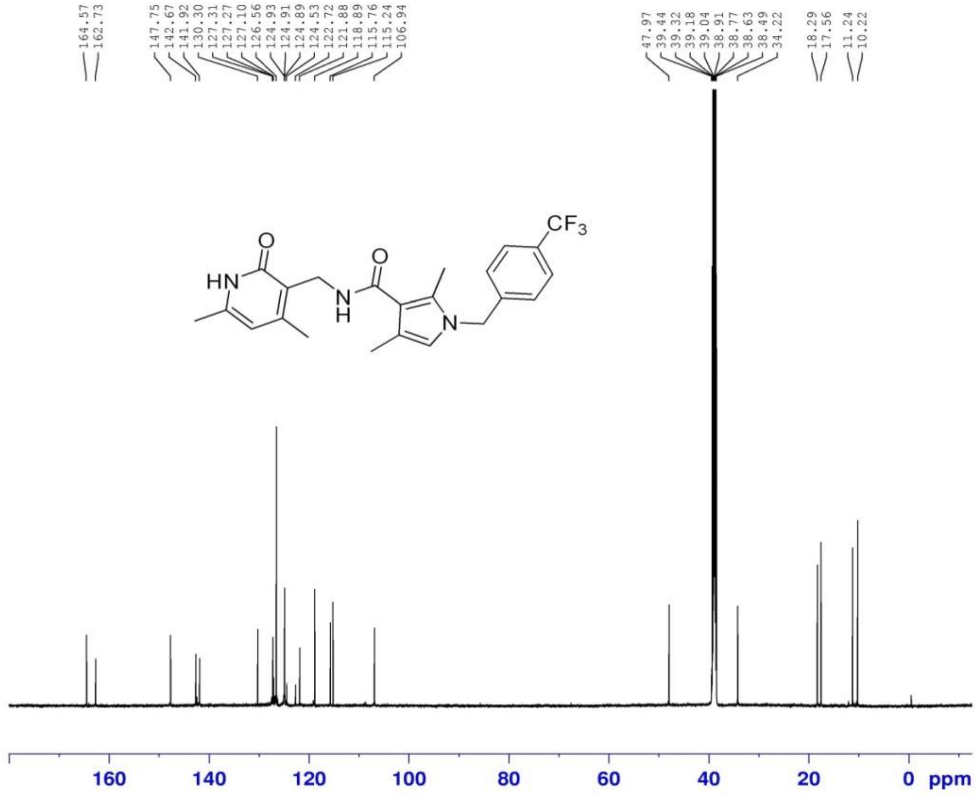


*N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide(**DM-01**)*

^{1}H NMR of DM-01

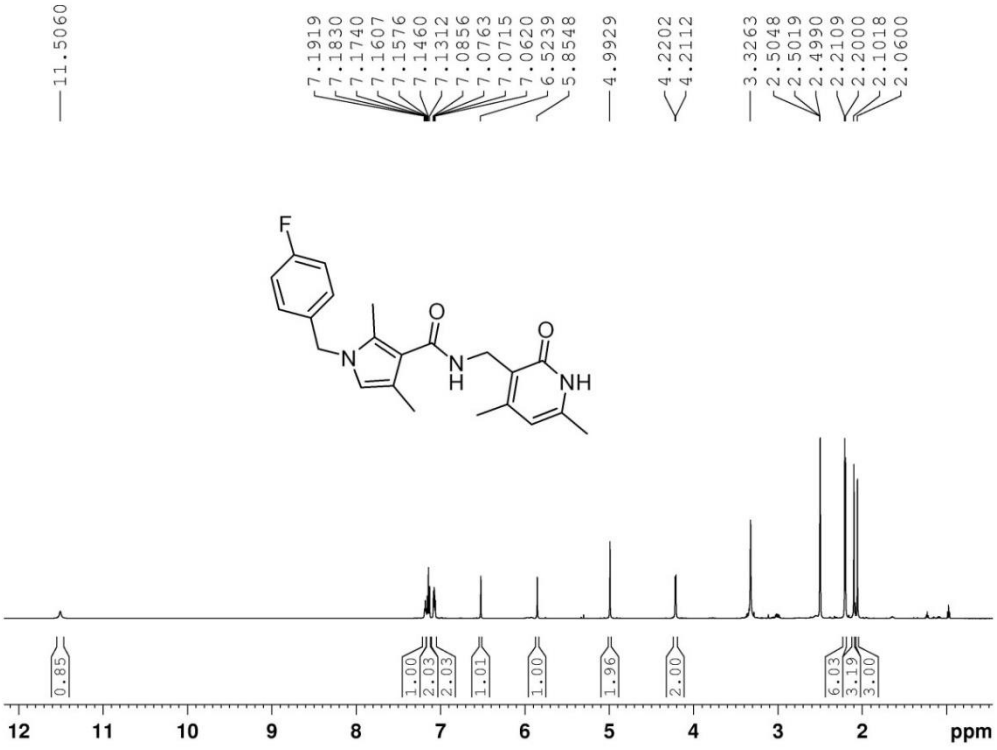


^{13}C NMR of DM-01

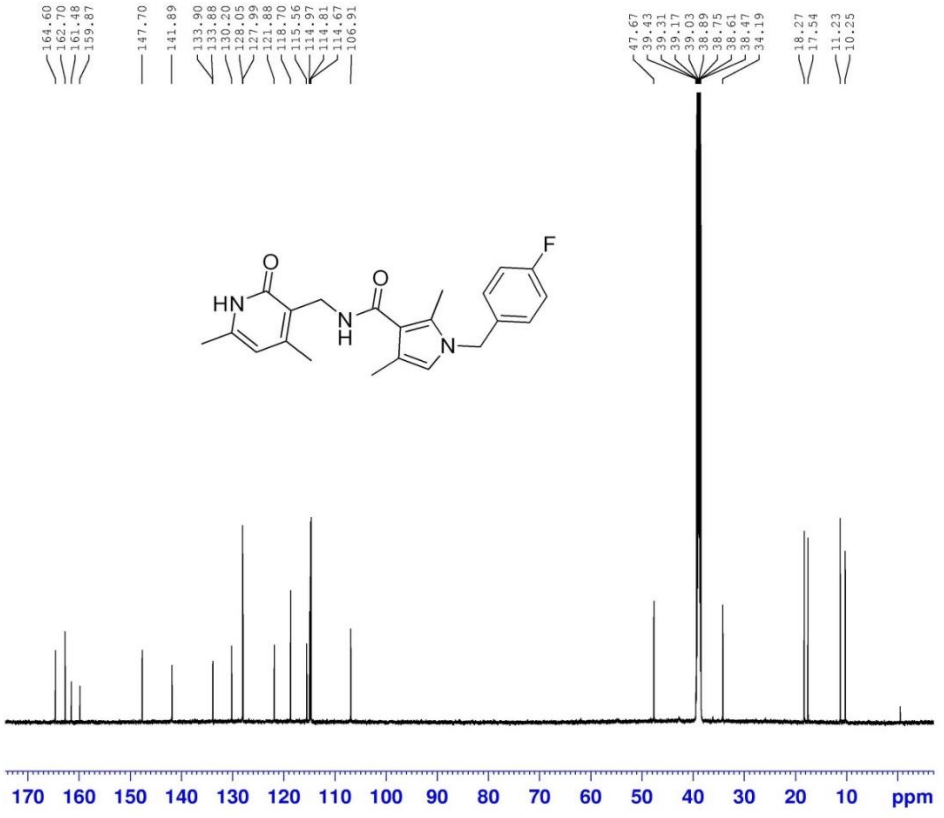


*N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-fluorobenzyl)-2,4-dimethyl-1H-pyrrol-3-carboxamide (**DM-02**)*

^{1}H NMR of DM-02

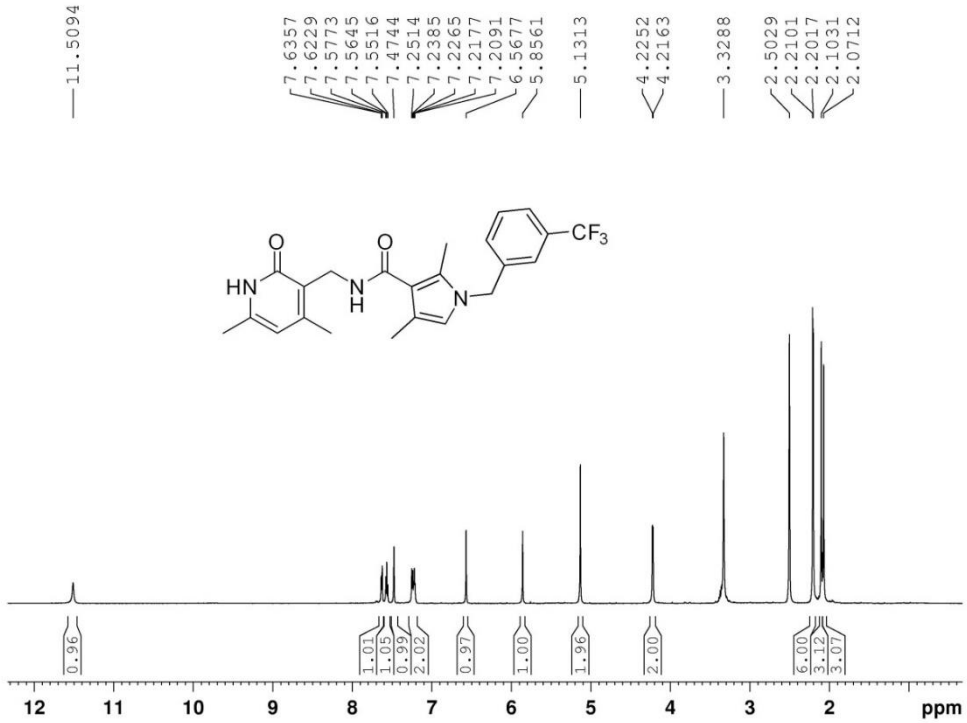


^{13}C NMR of DM-02

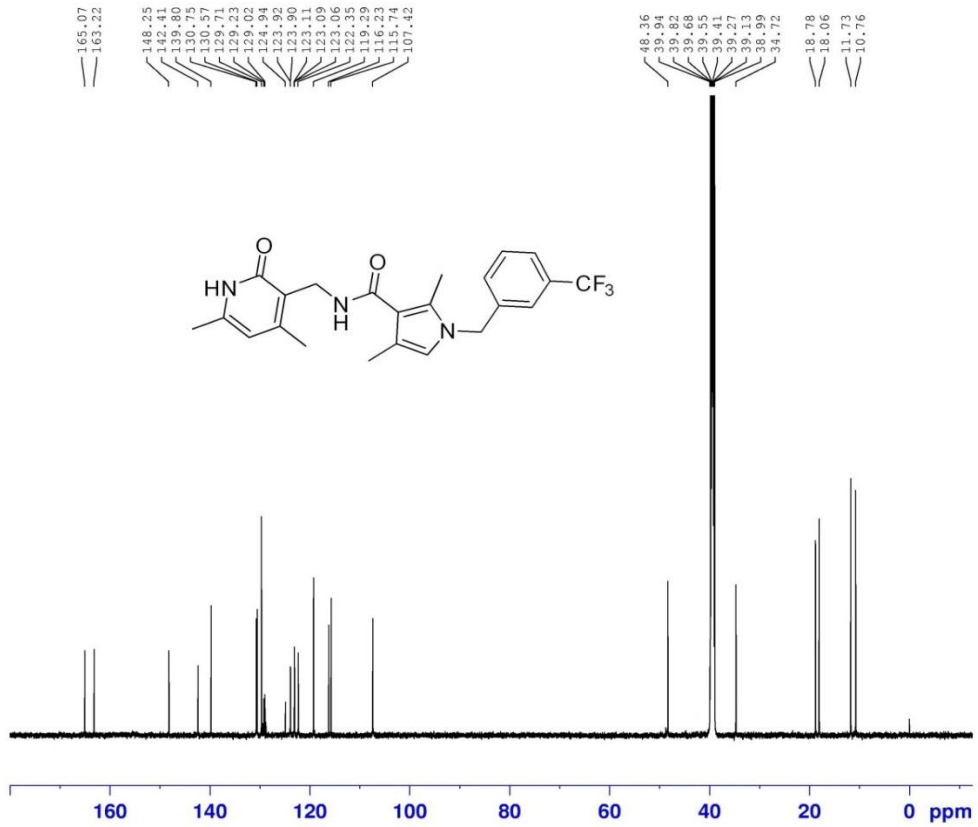


*N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(3-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-03**)*

^{1}H NMR of DM-03

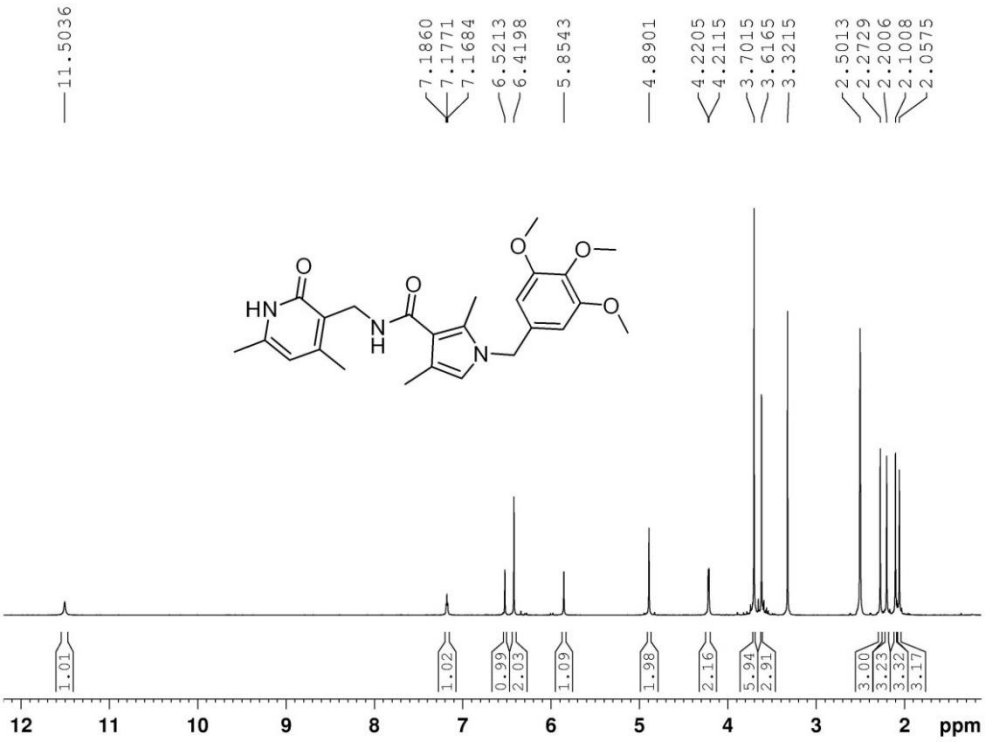


^{13}C NMR of DM-03

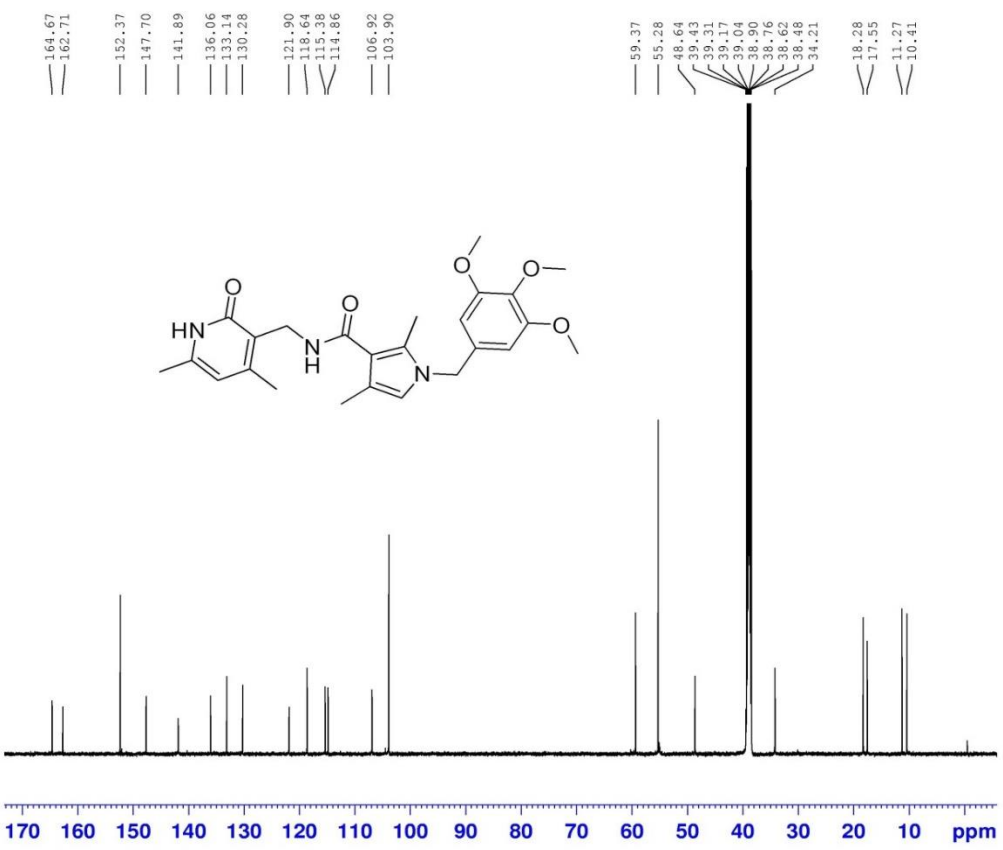


*N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(3,4,5-trimethoxybenzyl)-1 H-pyrrole-3-carboxamide (**DM-04**)*

^{1}H NMR of DM-04

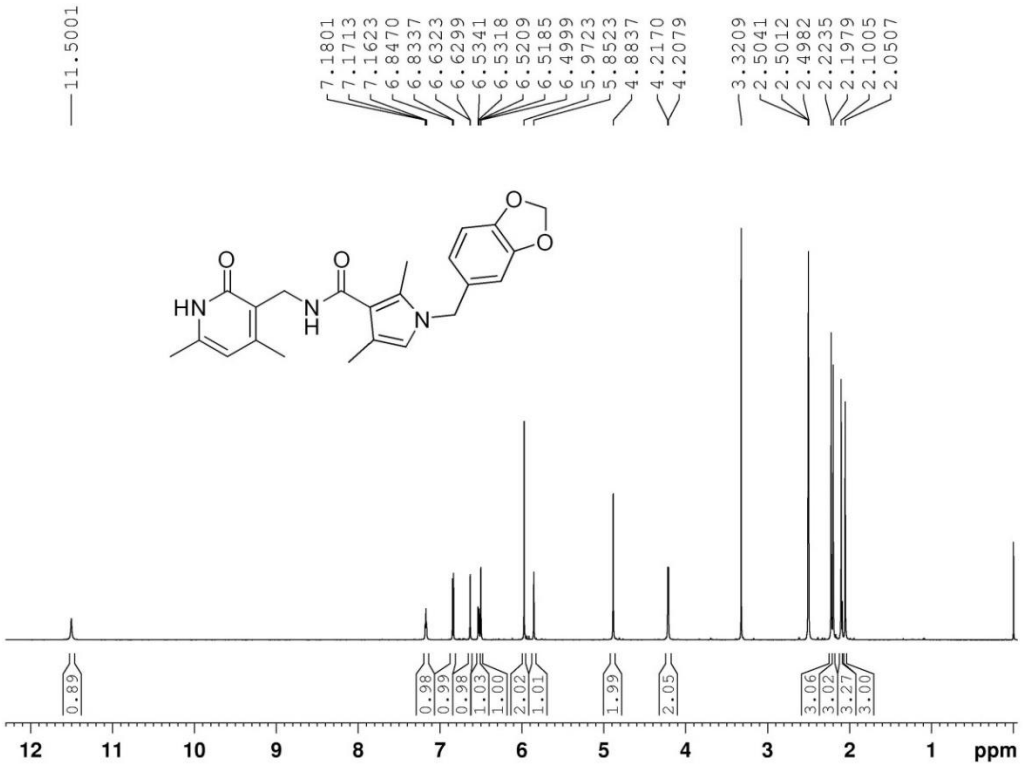


^{13}C NMR of DM-04

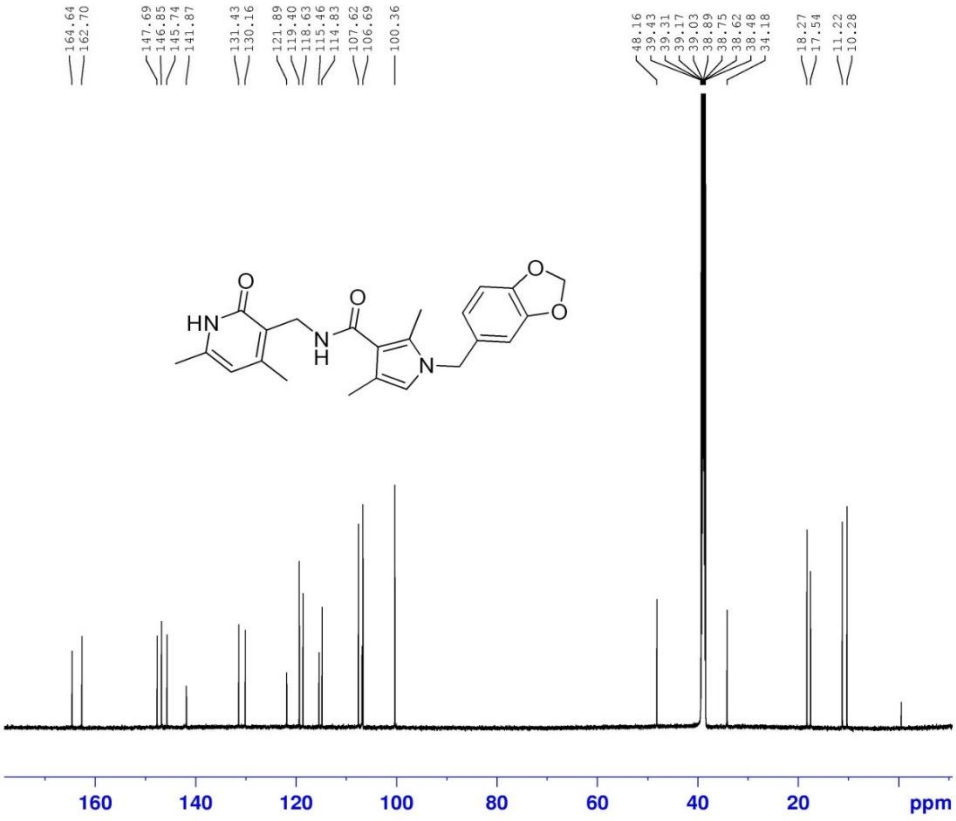


*1-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-di methyl-1H-pyrrole-3-carboxamide (**DM-05**)*

^{1}H NMR of DM-05

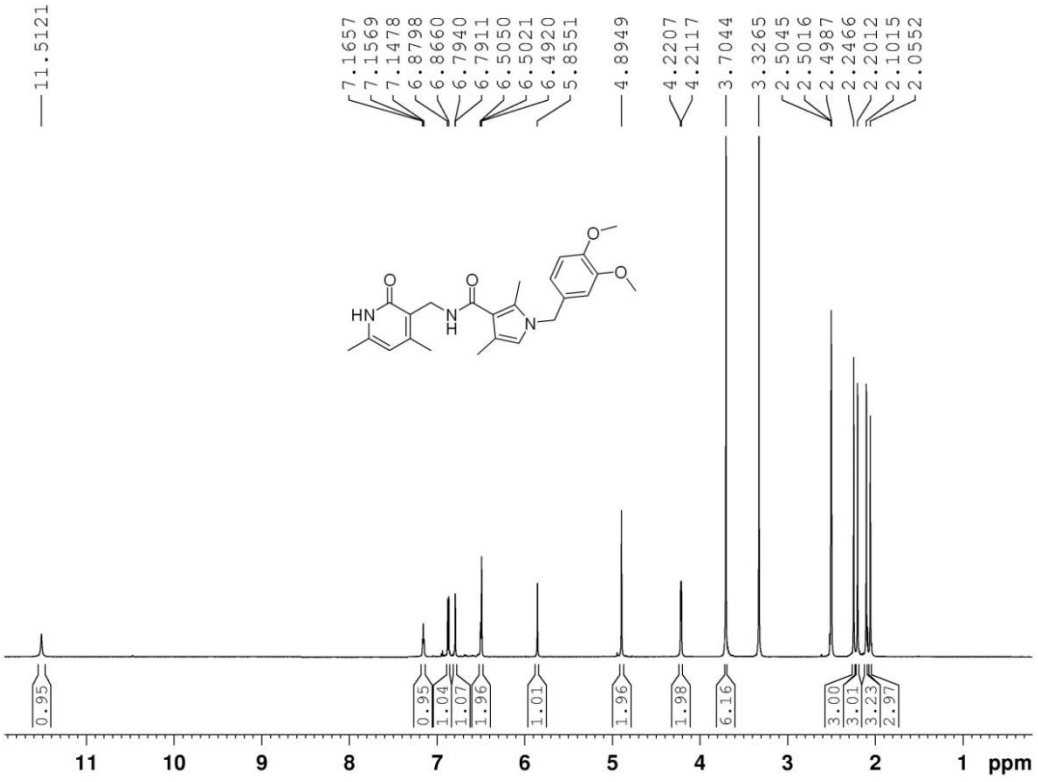


^{13}C NMR of DM-05

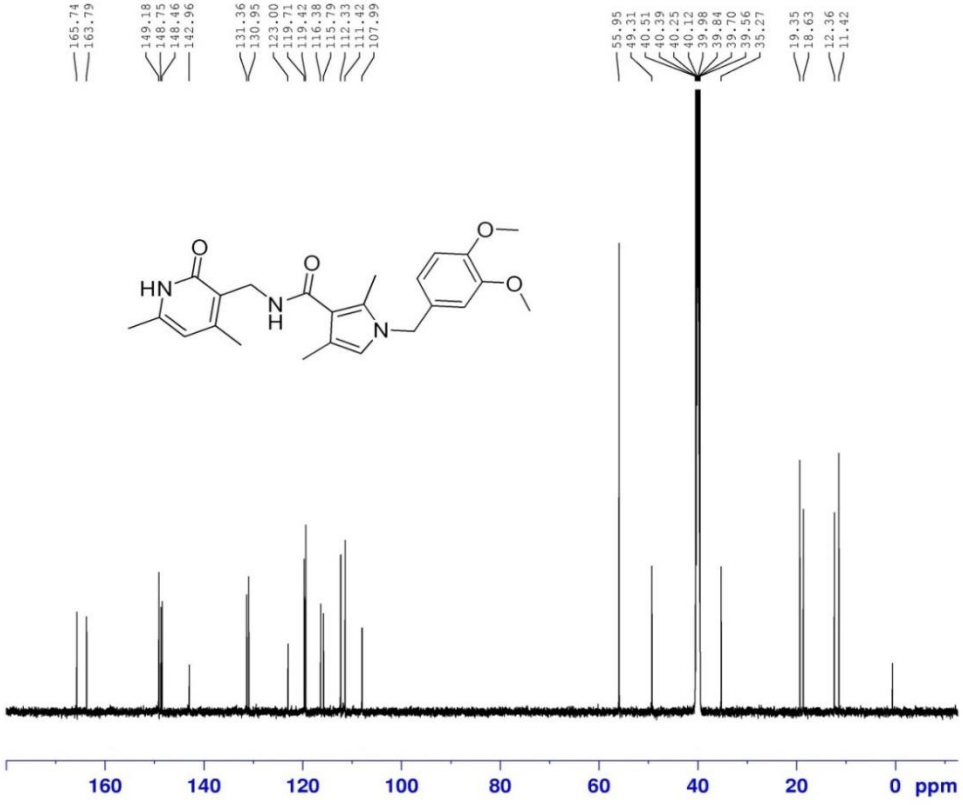


*1-(3,4-Dimethoxybenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide(**DM-06**)*

^{1}H NMR of DM-06

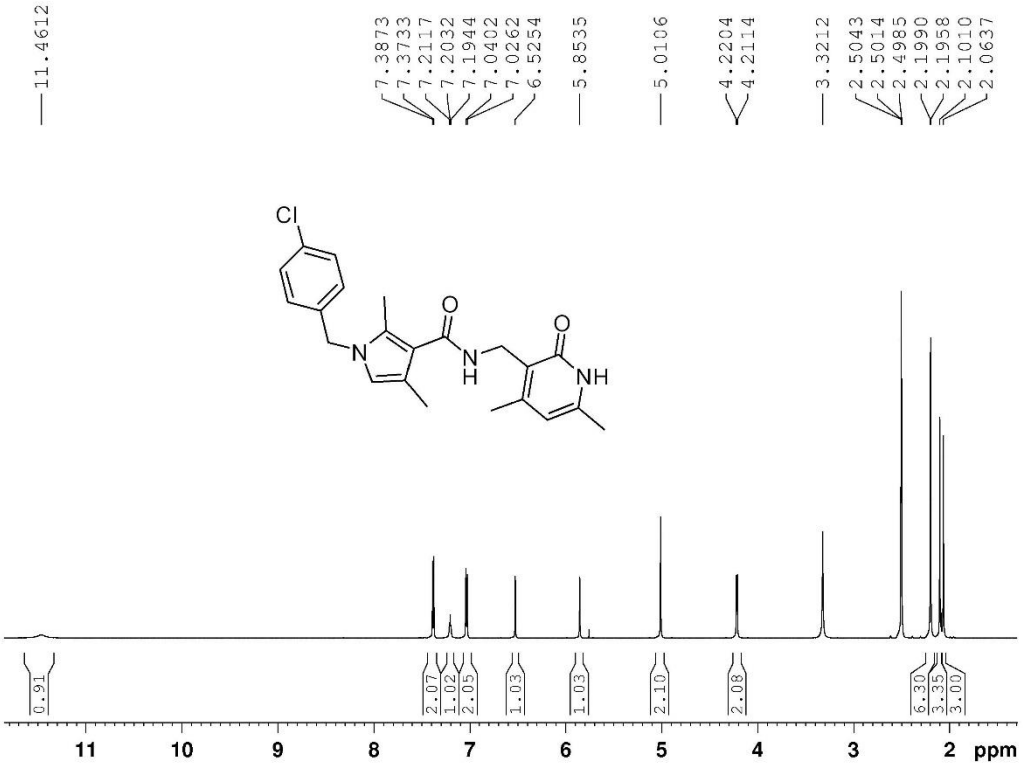


^{13}C NMR of DM-06

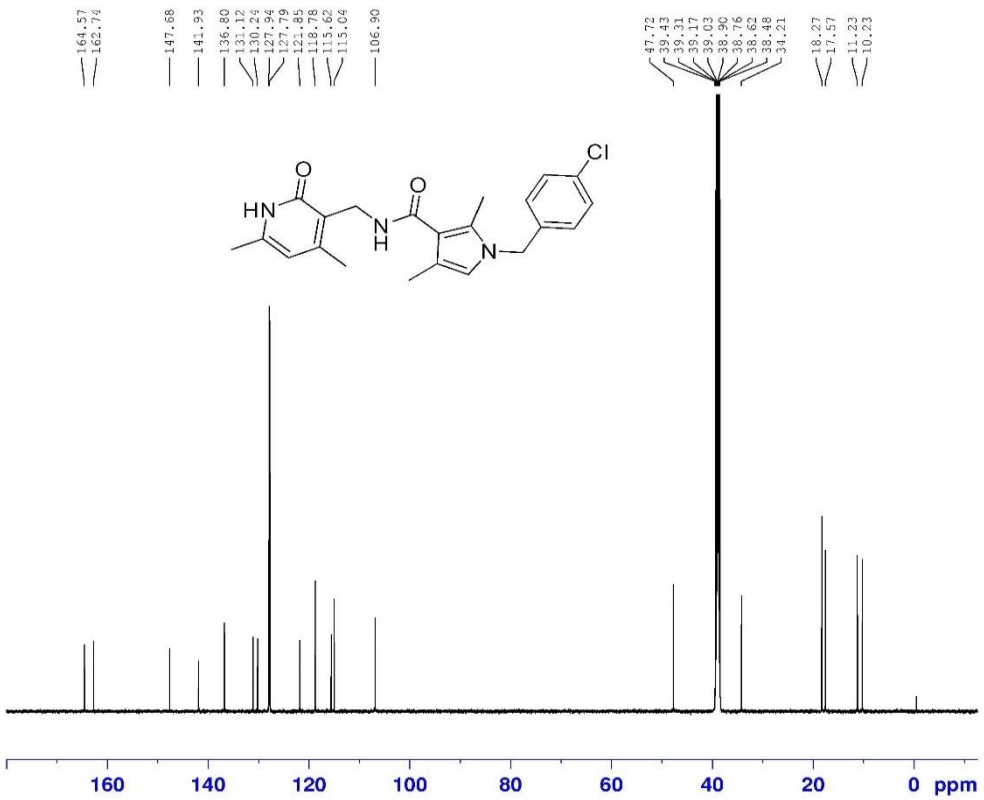


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(3-fluorobenzyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-07**)*

^{1}H NMR of DM-07

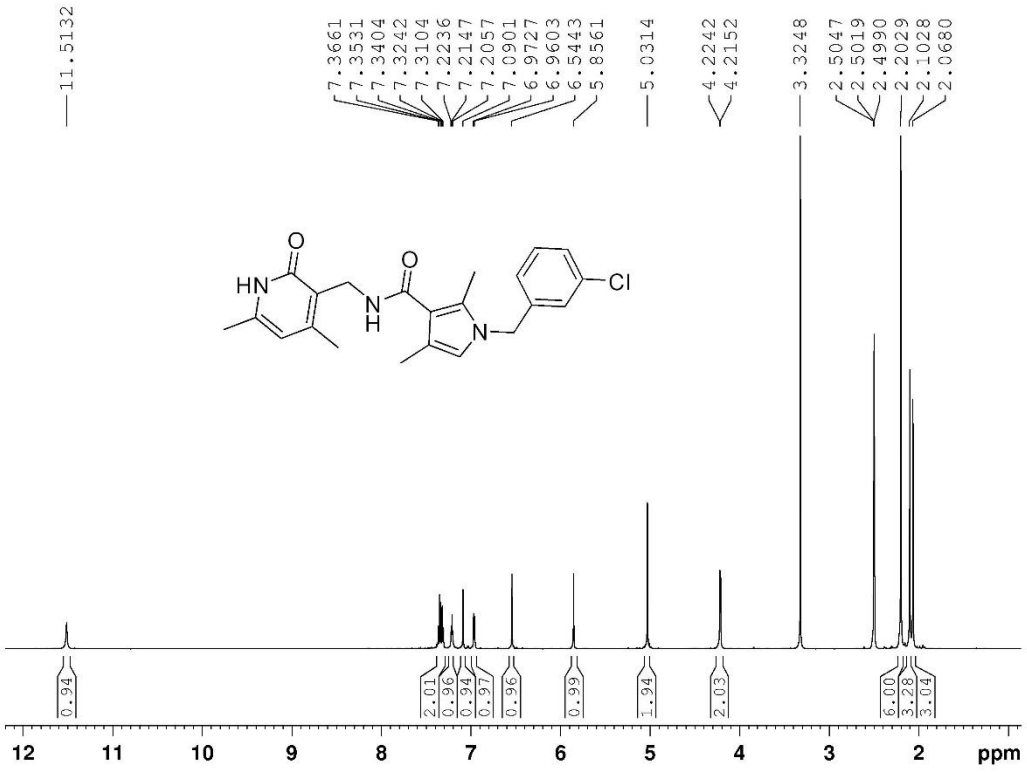


^{13}C NMR of DM-07

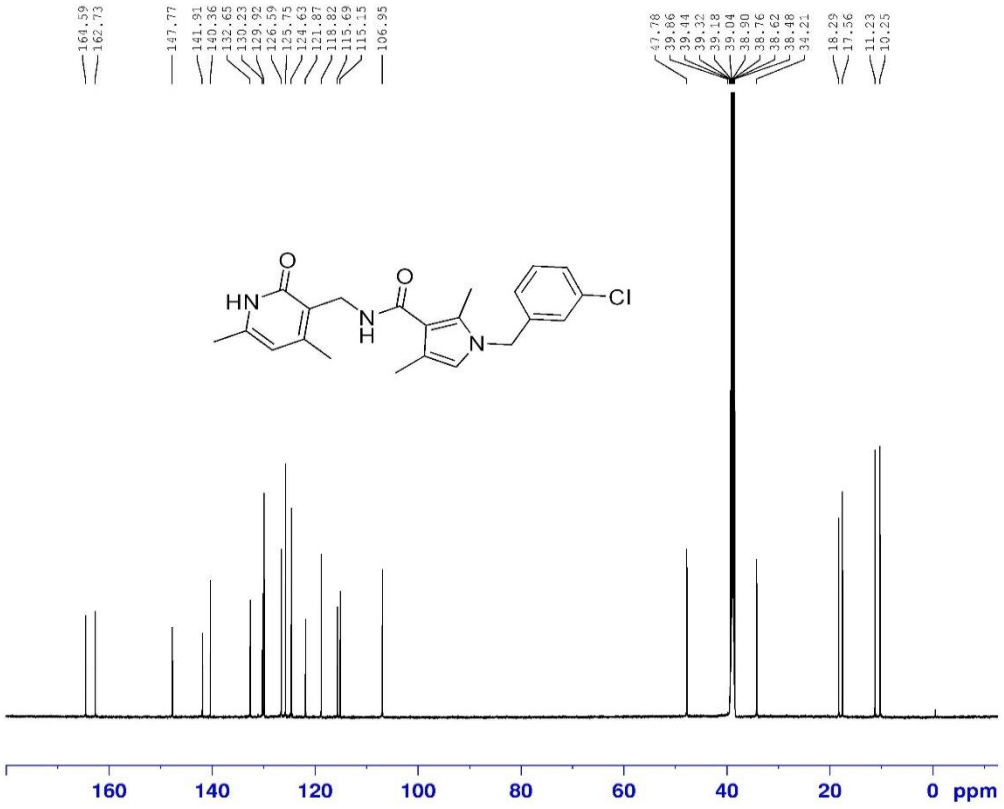


*1-(3-Chlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl -1H-pyrrole-3-carboxamide (**DM-08**)*

^{1}H NMR of DM-08

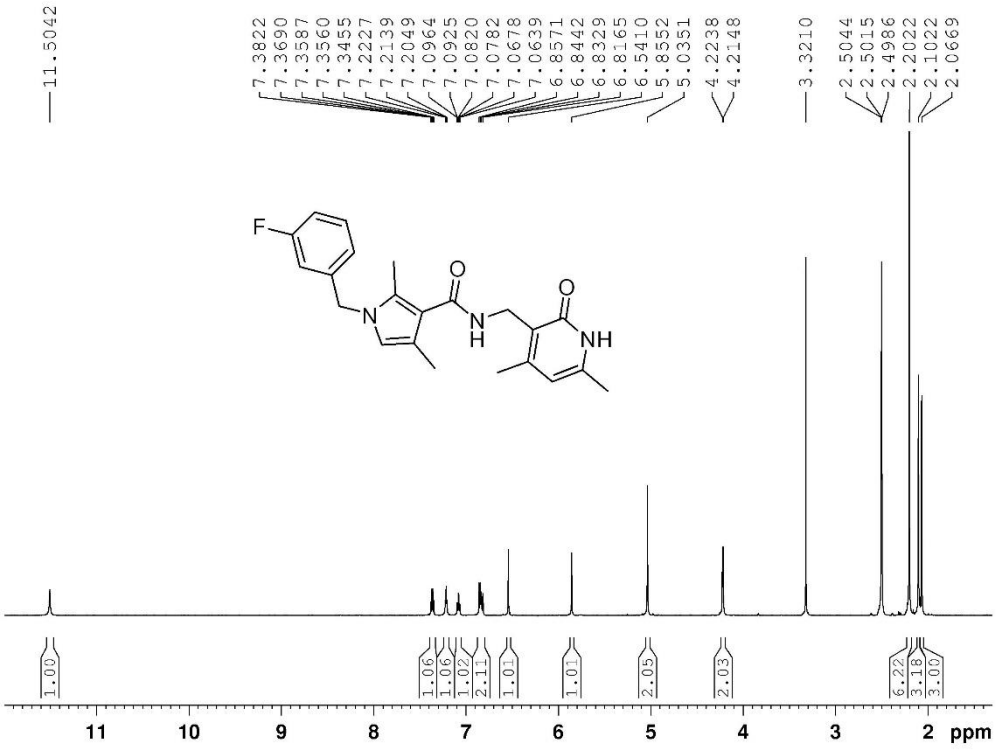


^{13}C NMR of DM-08

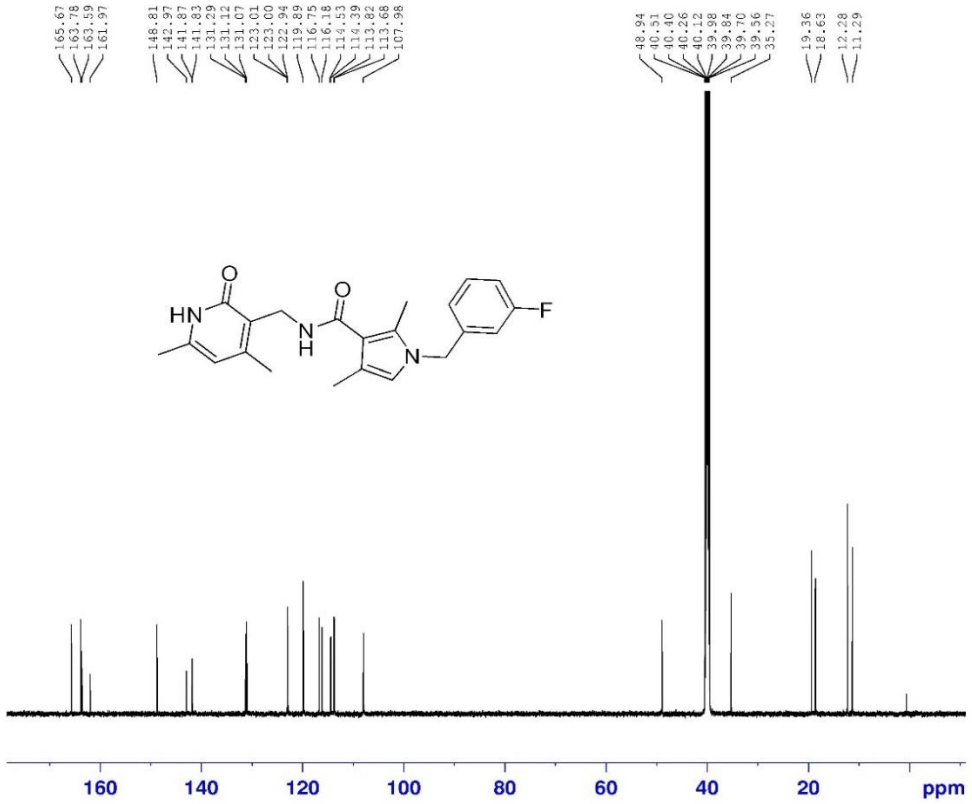


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(3-fluorobenzyl)-2,4-dimethyl -1H-pyrrole-3-carboxamide (**DM-09**)*

^{1}H NMR of DM-09

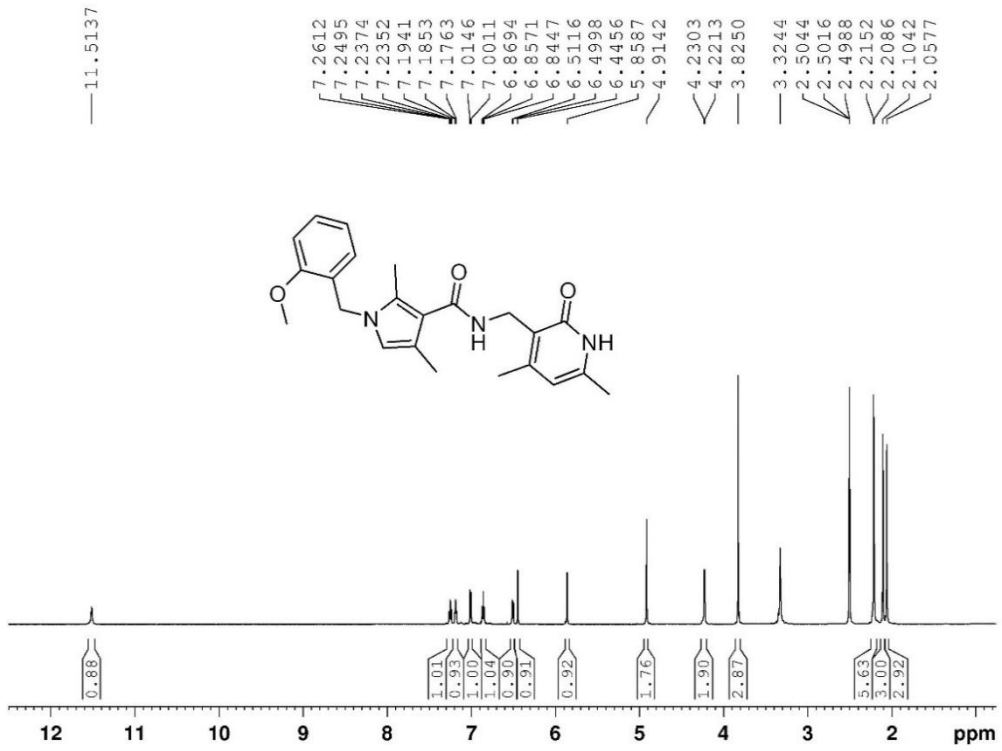


^{13}C NMR of DM-09

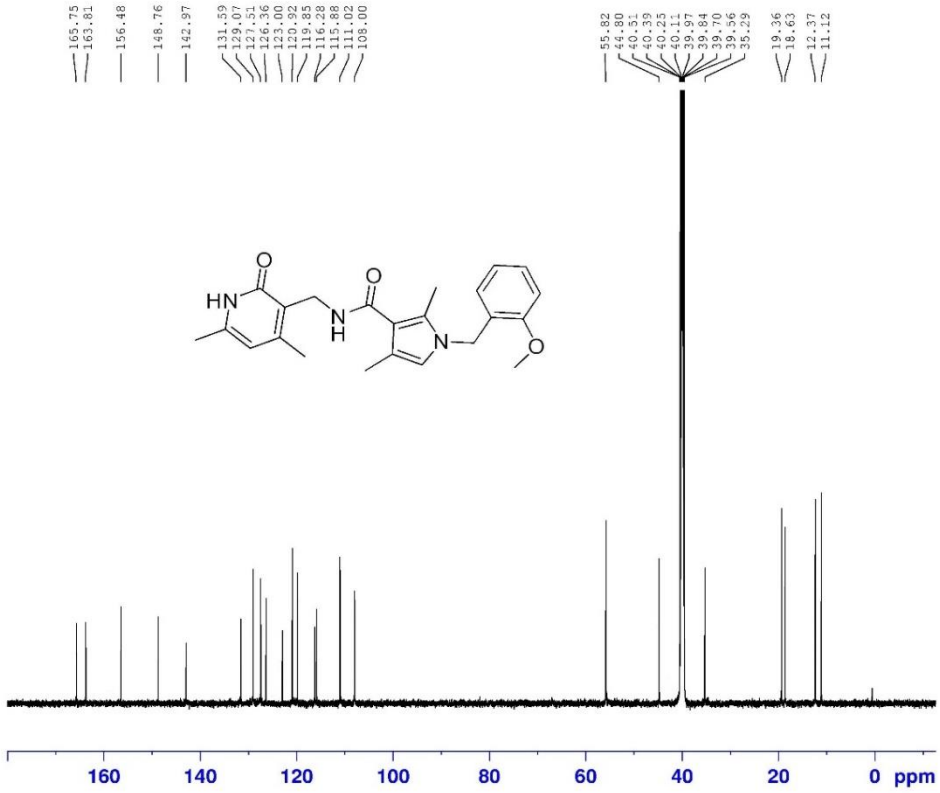


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(2-methoxybenzyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-10**)*

^{1}H NMR of DM-10

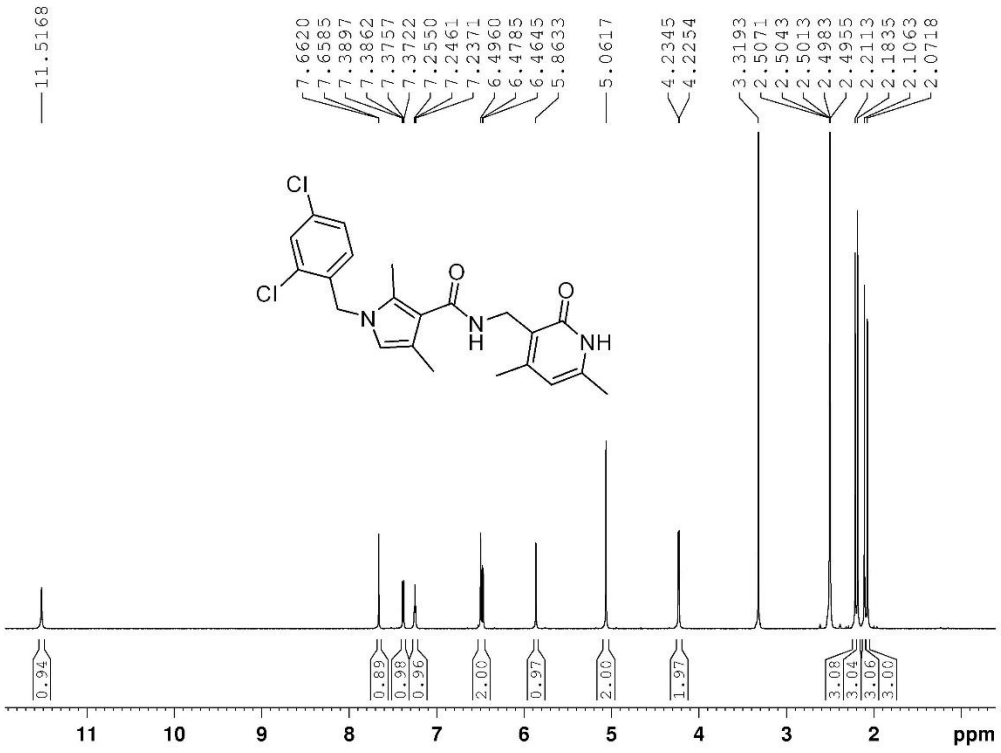


^{13}C NMR of DM-10

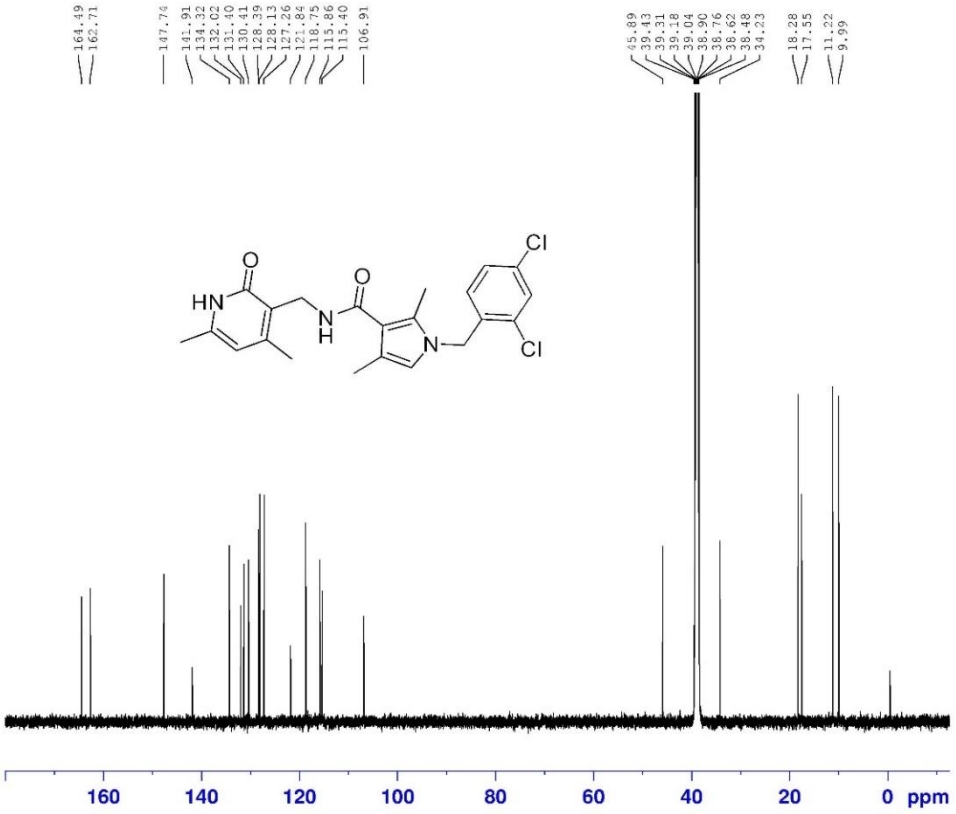


*1-(2,4-Dichlorobenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1H-py rrole-3-carboxamide (**DM-11**)*

^{1}H NMR of DM-11

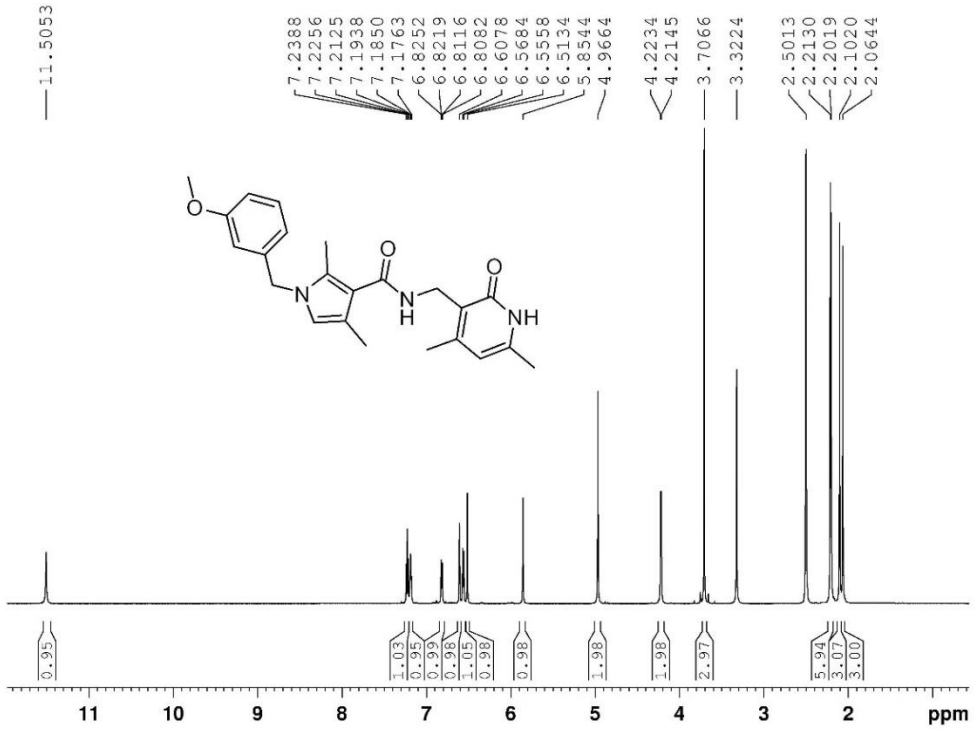


^{13}C NMR of DM-11

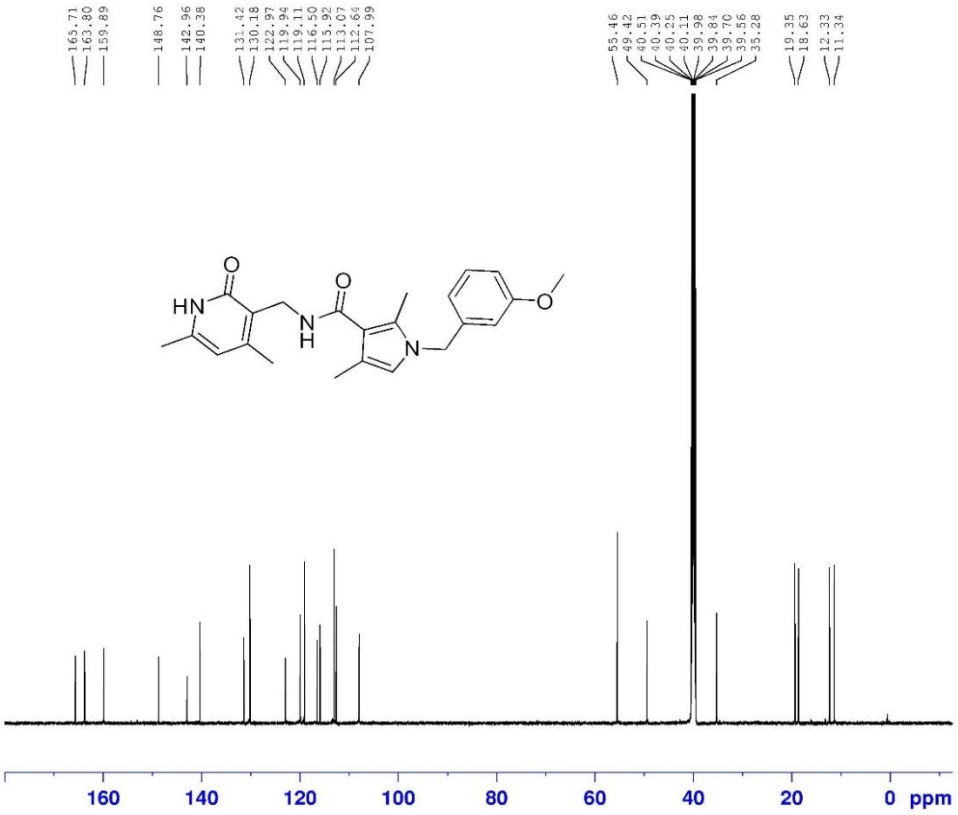


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(3-methoxybenzyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-12**)*

^{1}H NMR of DM-12

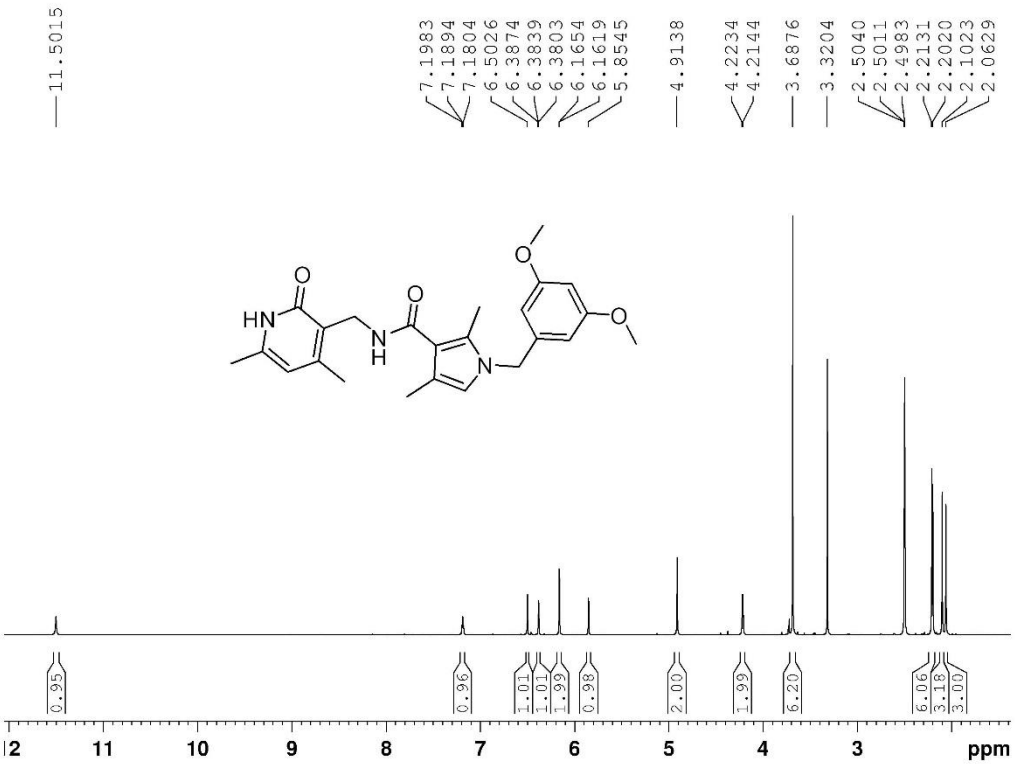


^{13}C NMR of DM-12

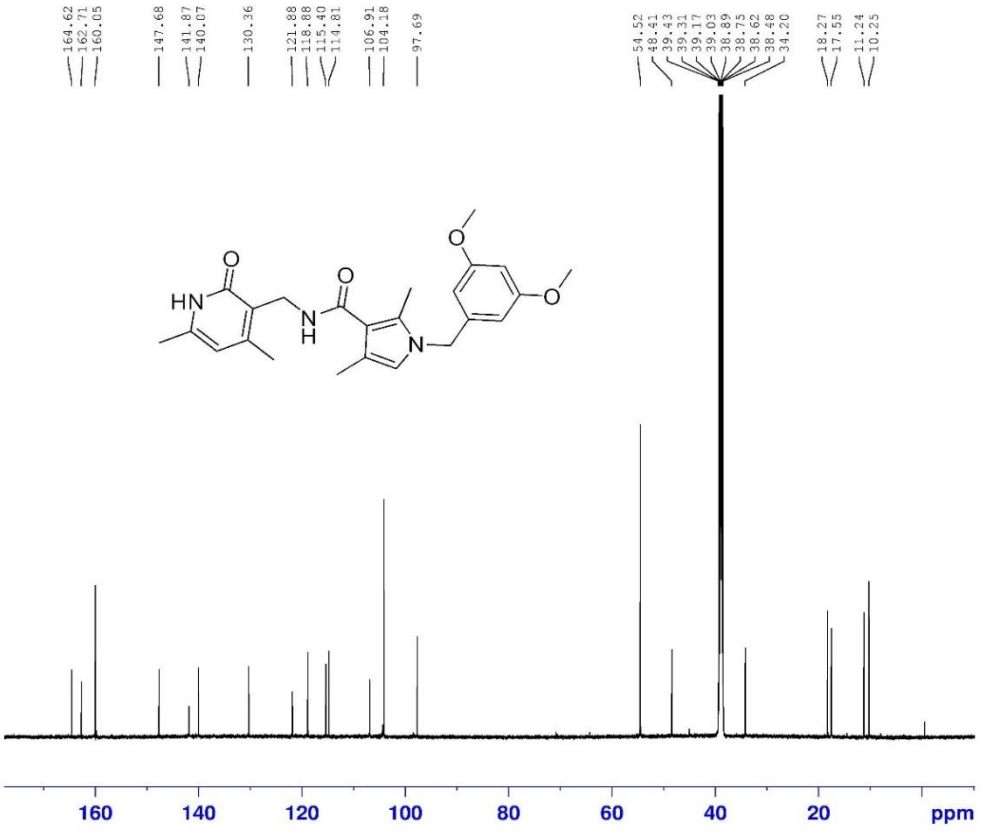


*1-(3,5-Dimethoxybenzyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**DM-13**)*

^{1}H NMR of DM-13

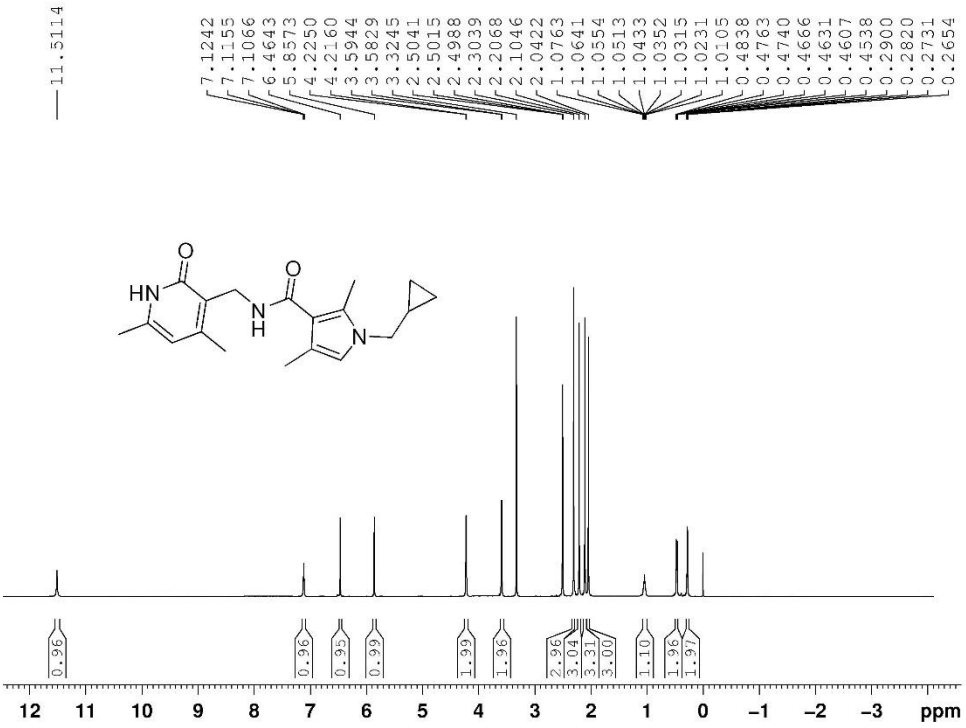


^{13}C NMR of DM-13

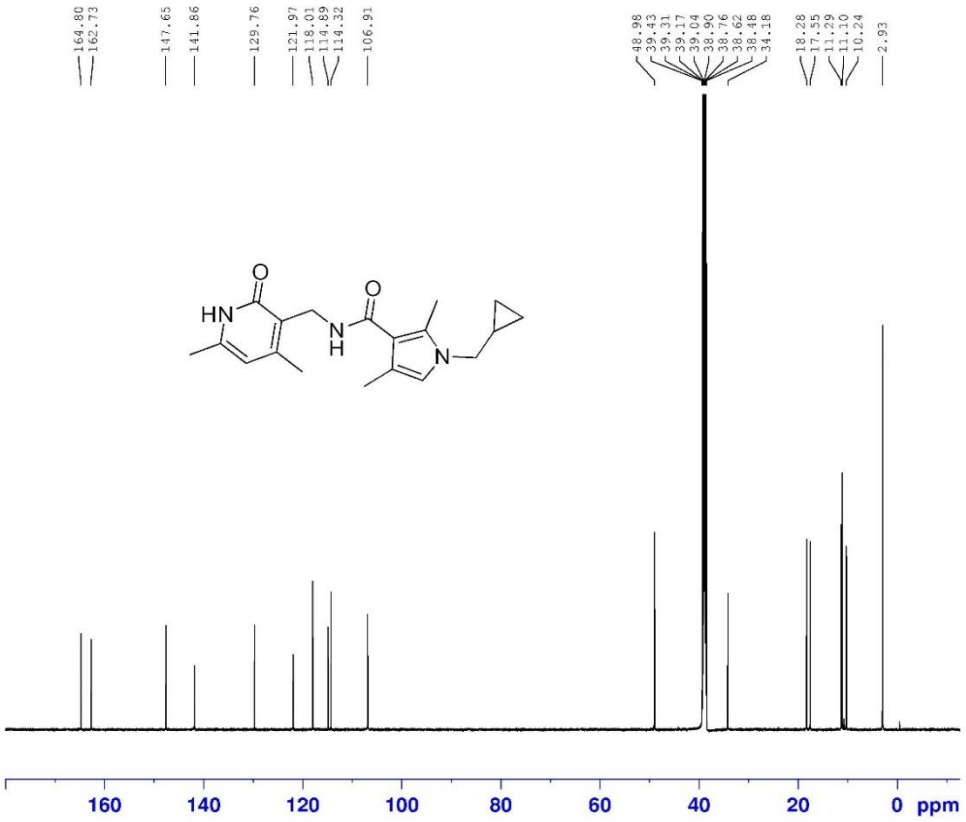


*1-(cyclopropylmethyl)-N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl -1H-pyrrole-3-carboxamide (**DM-14**)*

^{1}H NMR of DM-14

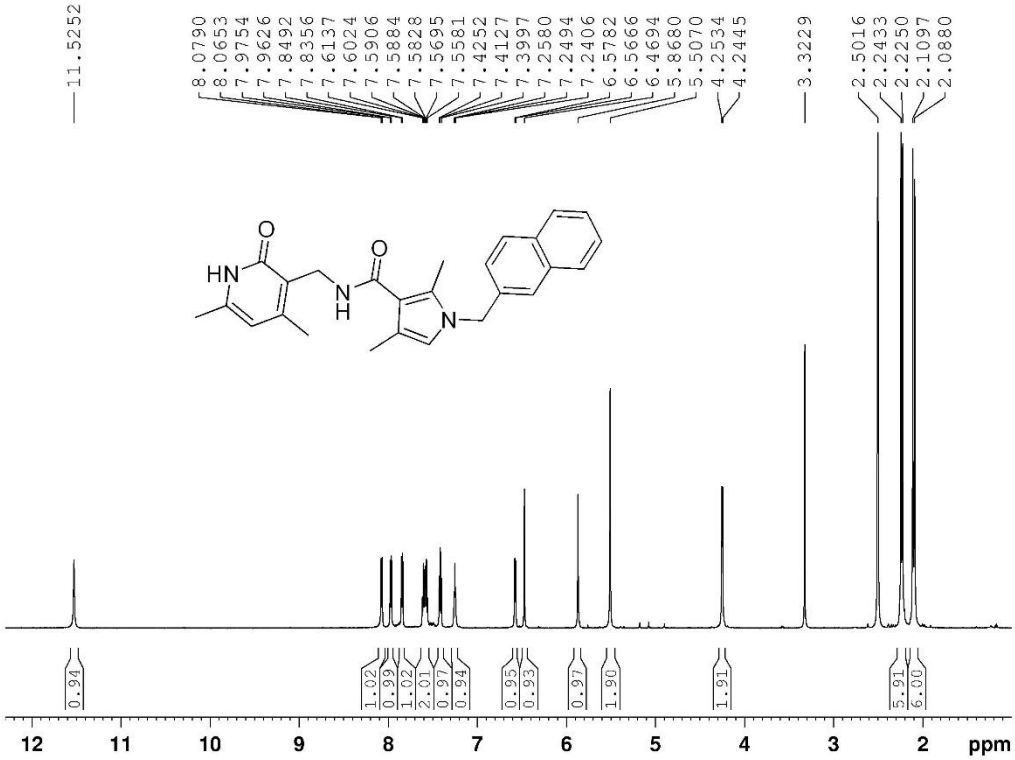


^{13}C NMR of DM-14

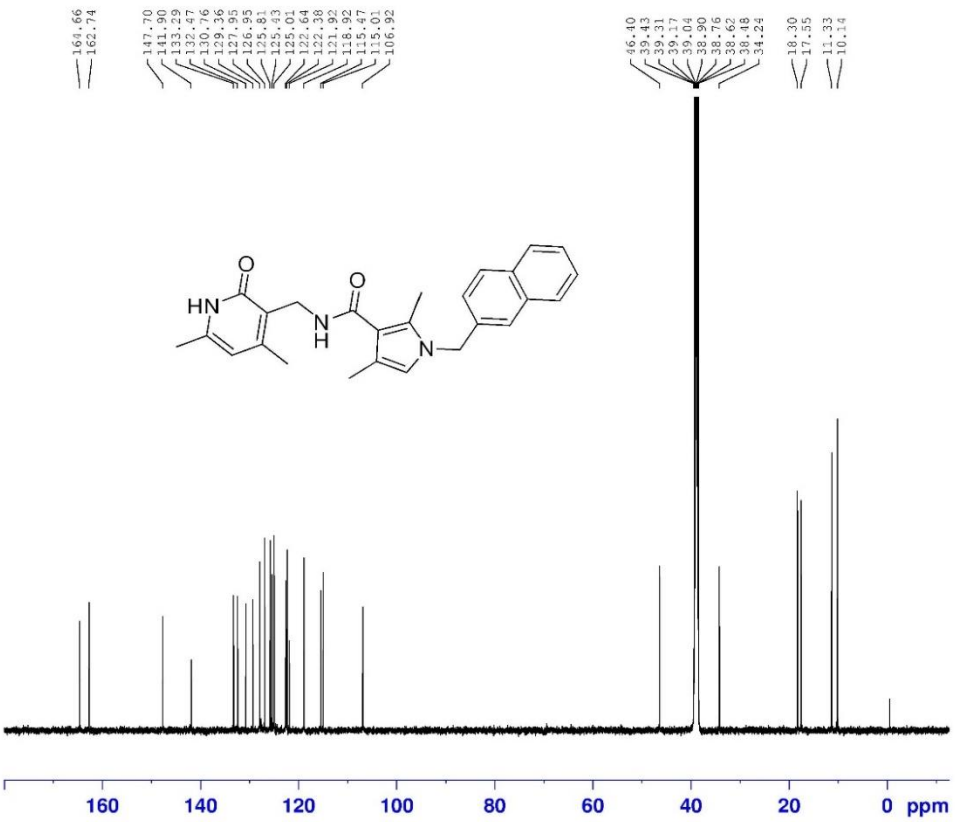


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(naphthalene-2-yl-methyl) -1H-pyrrole-3-carboxamide (**DM-15**)*

^{1}H NMR of DM-15

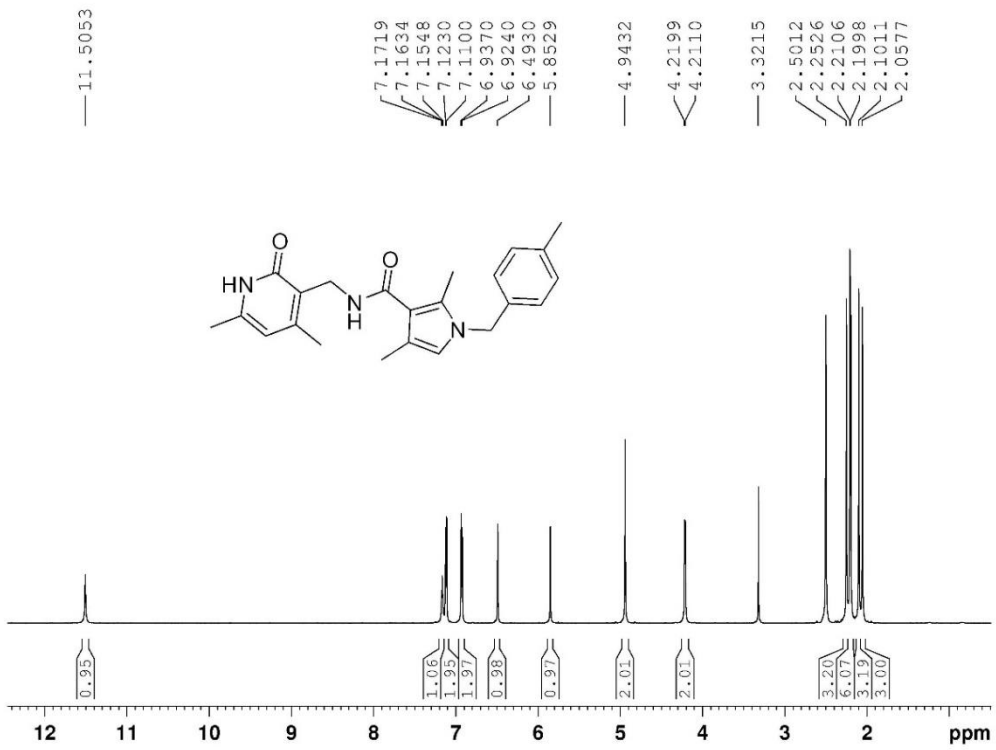


^{13}C NMR of DM-15

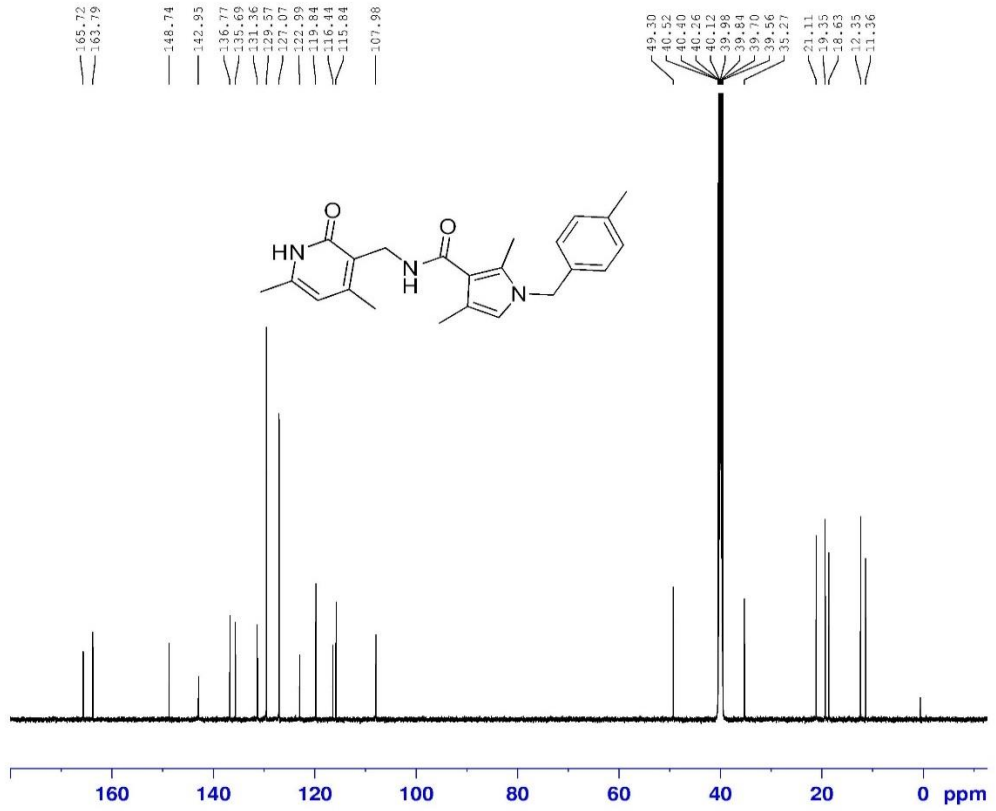


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-methylbenzyl)-1H-pyrr ole-3-carboxamide (**DM-16**)*

^{1}H NMR of DM-16

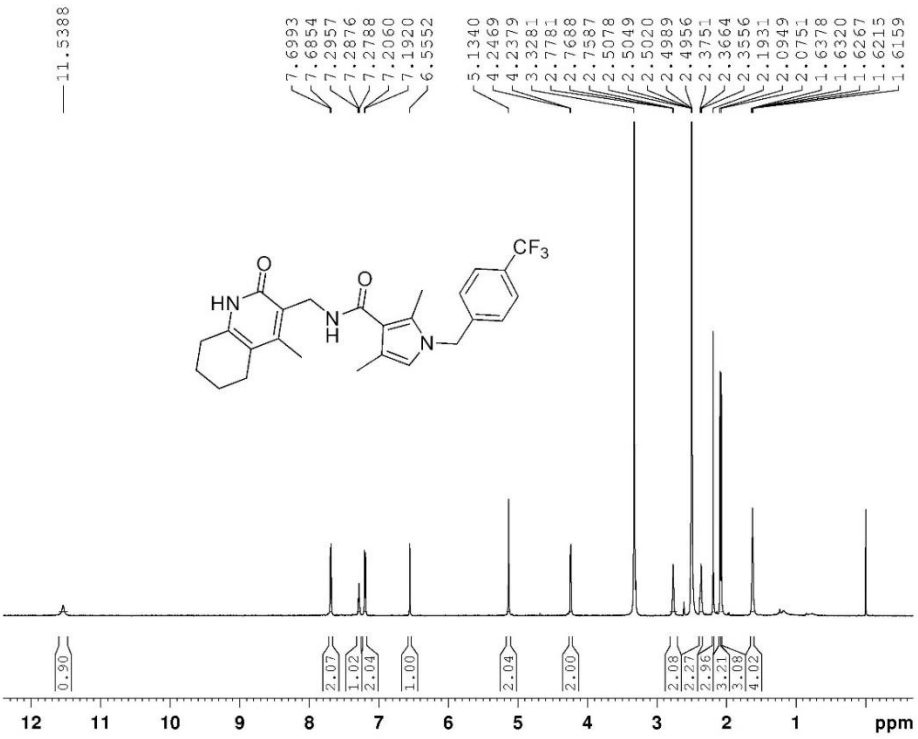


^{13}C NMR of DM-16

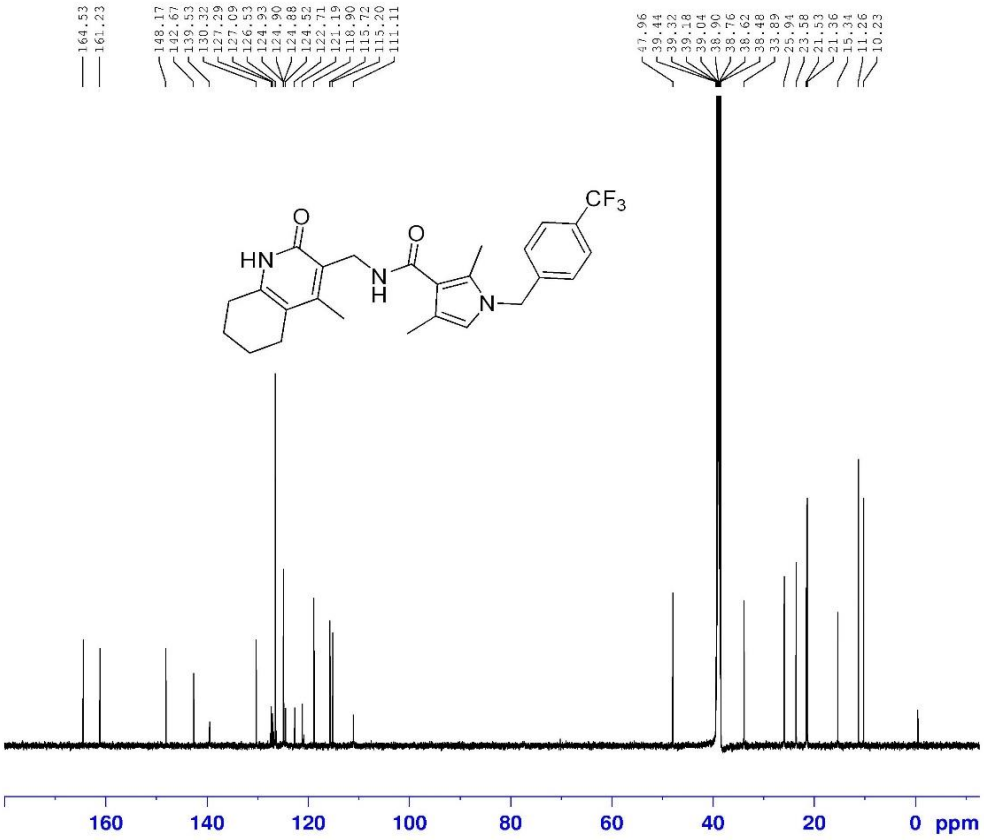


*2,4-Dimethyl-N-((4-methyl-2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-17**)*

^{1}H NMR of DM-17

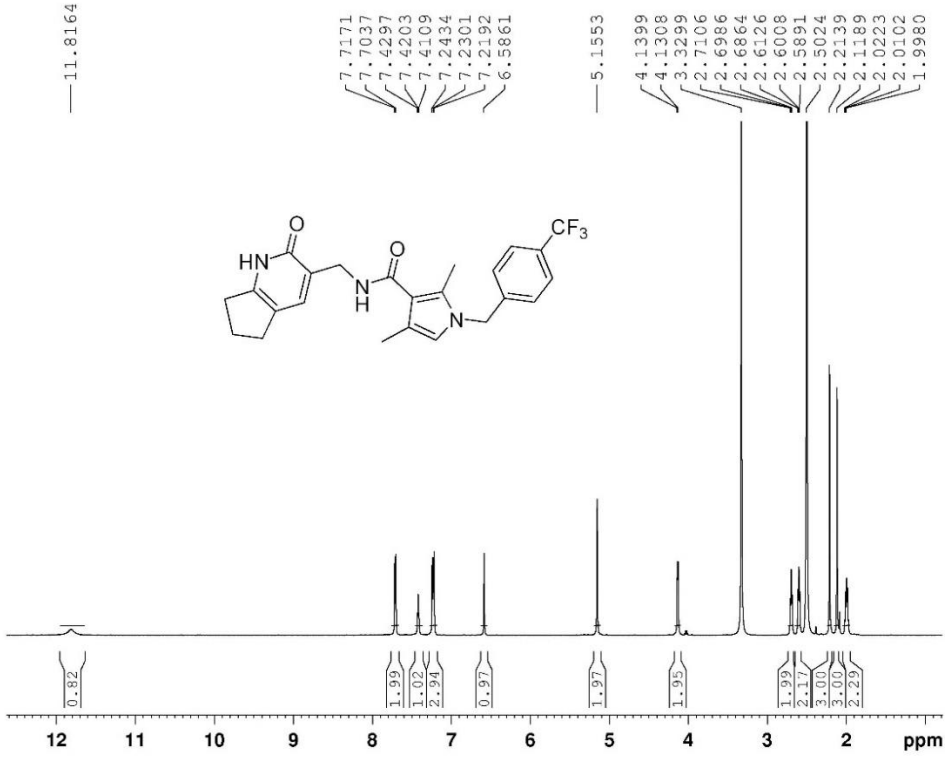


^{13}C NMR of DM-17

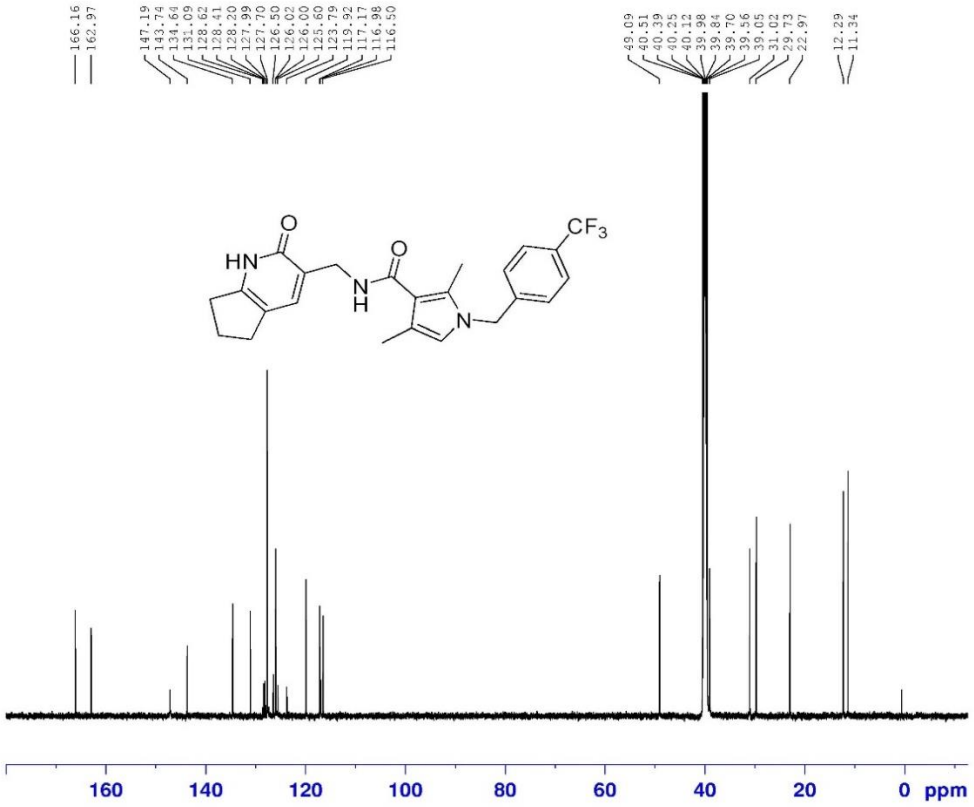


*2,4-Dimethyl-N-((2-oxo-2,5,6,7-tetrahydro-1H-cyclopenta[b]pyridin-3-yl)methyl)-1-(4-(trifluorome thyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-18**)*

^{1}H NMR of DM-18

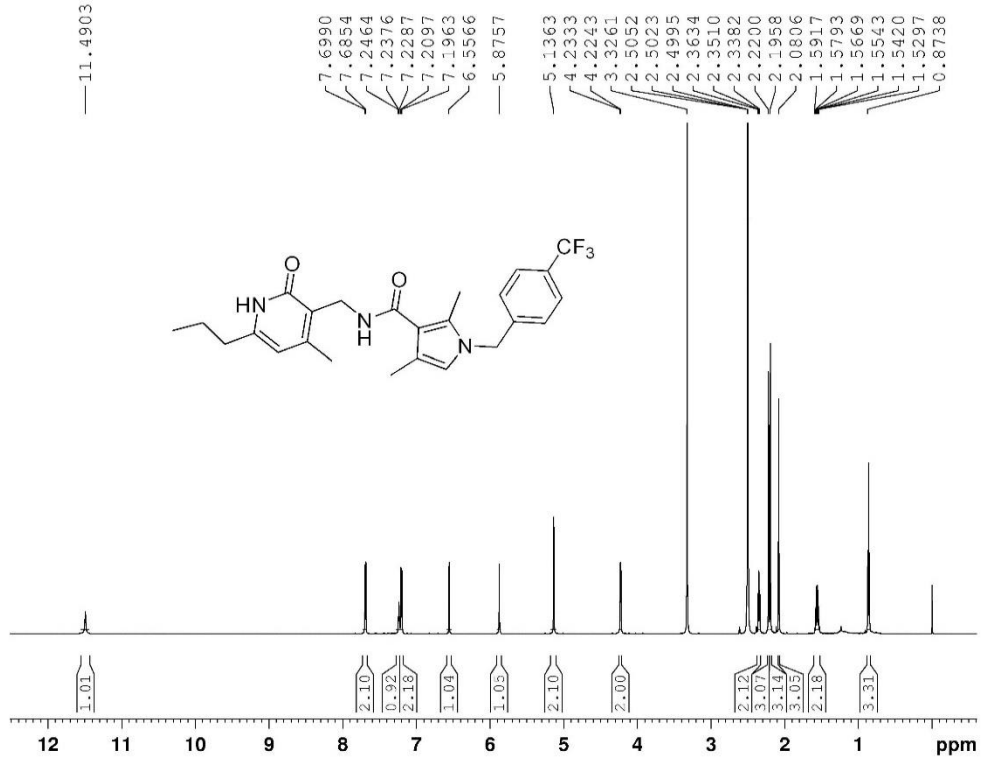


^{13}C NMR of DM-18

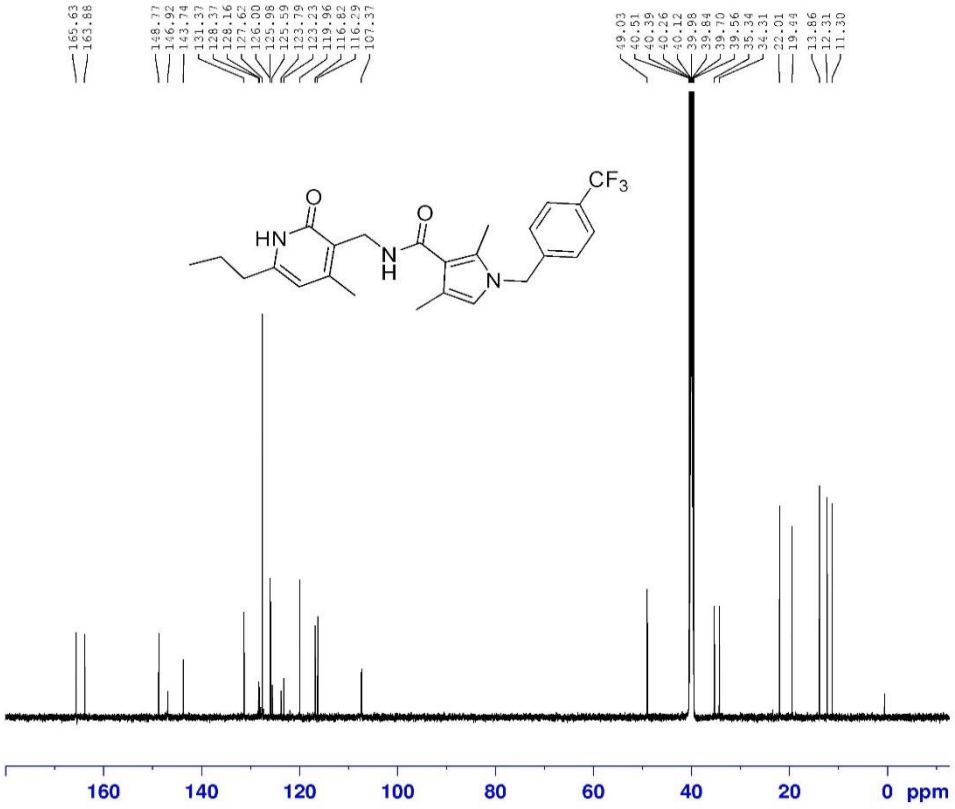


*2,4-Dimethyl-N-((4-methyl-2-oxo-6-propyl-1,2-dihydropyridin-3-yl)methyl)-1-(4-(trifluoromethyl)be nzyl)-1H-pyrrole-3-carboxamide (**DM-19**)*

^{1}H NMR of DM-19

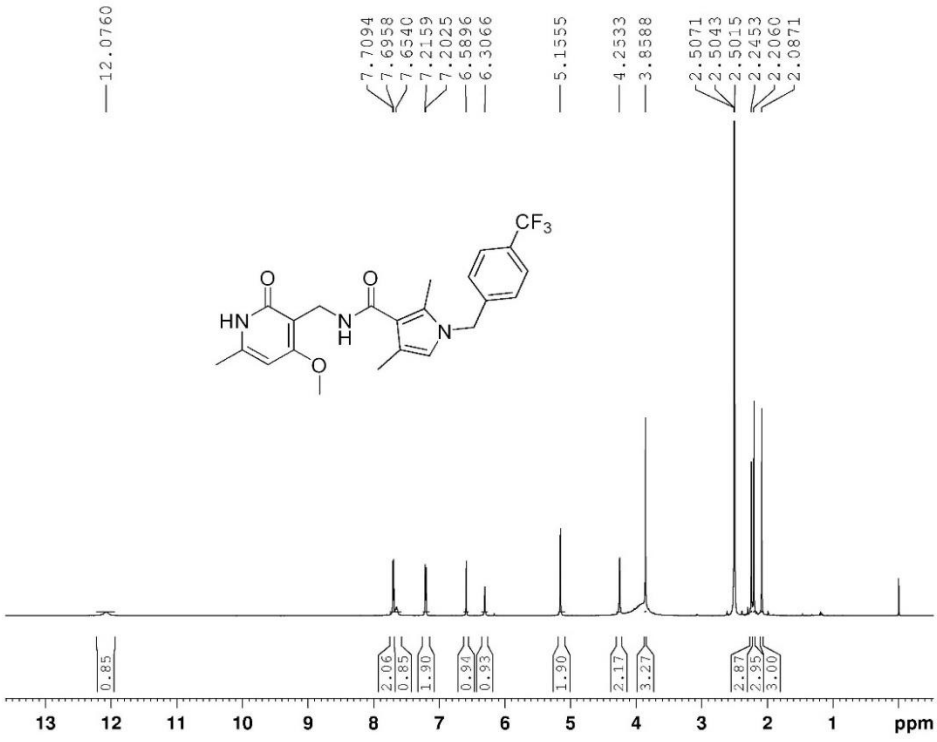


^{13}C NMR of DM-19

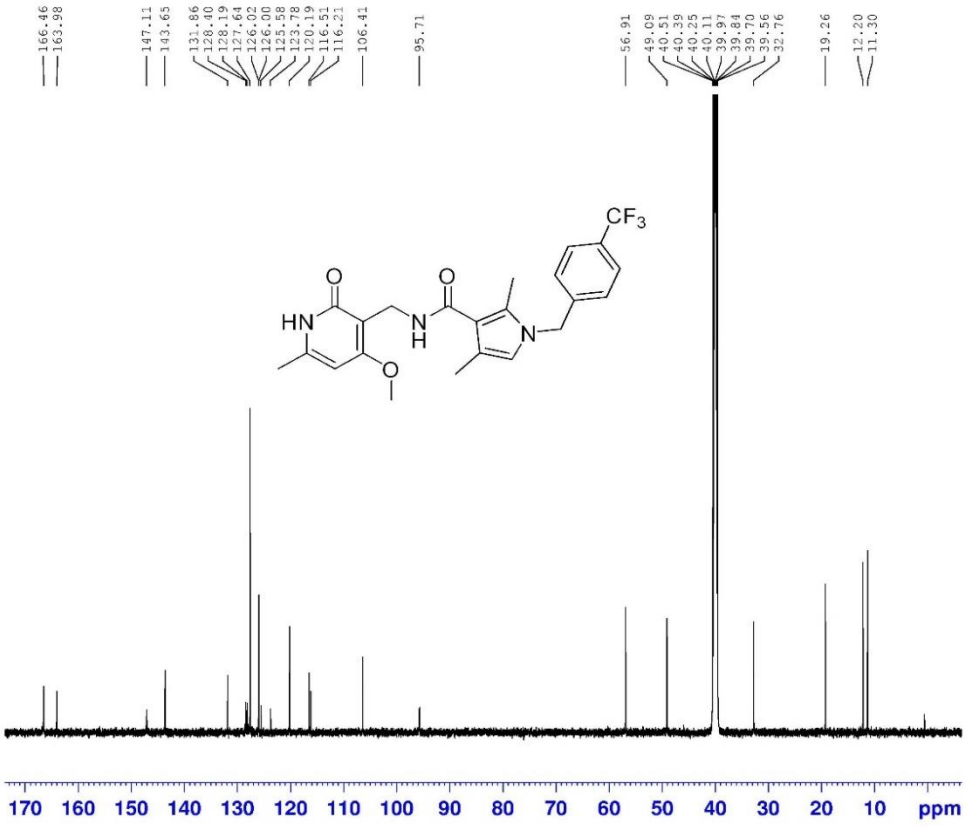


*N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl) benzyl)-1H-pyrrole-3-carboxamide (**DM-20**)*

^{1}H NMR of DM-20

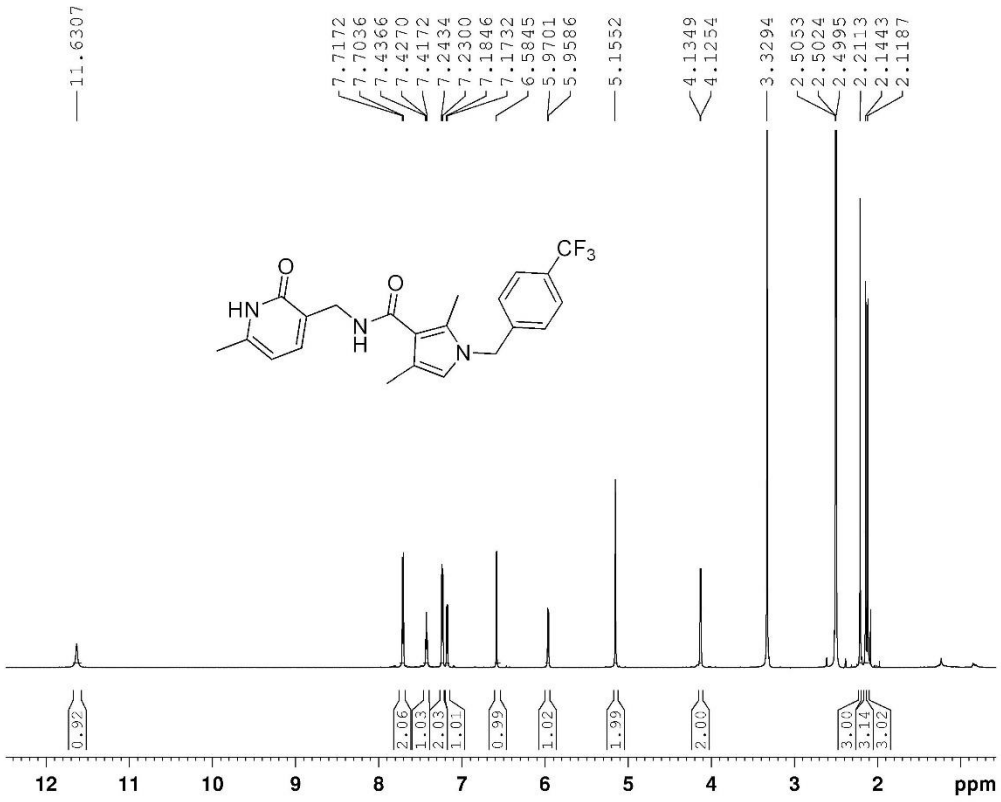


^{13}C NMR of DM-20

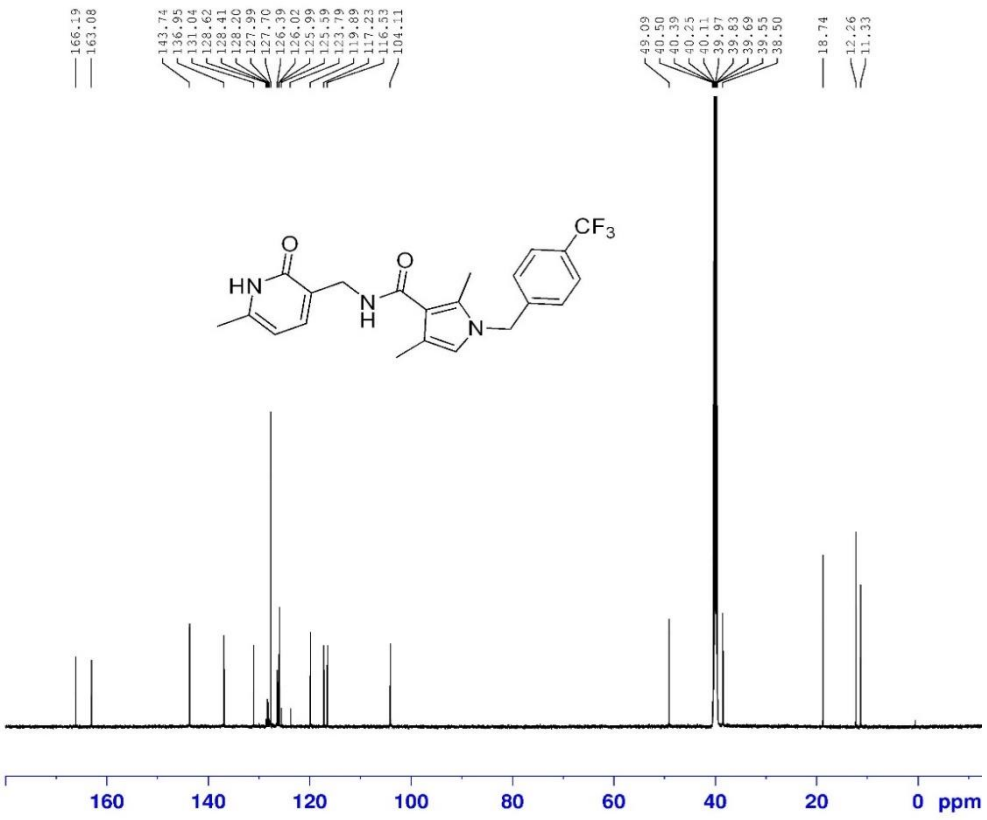


*2,4-Dimethyl-N-((6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-1-(4-(trifluoromethyl)benzyl -1H-pyrrole-3-carboxamide (**DM-21**)*

^{1}H NMR of DM-21

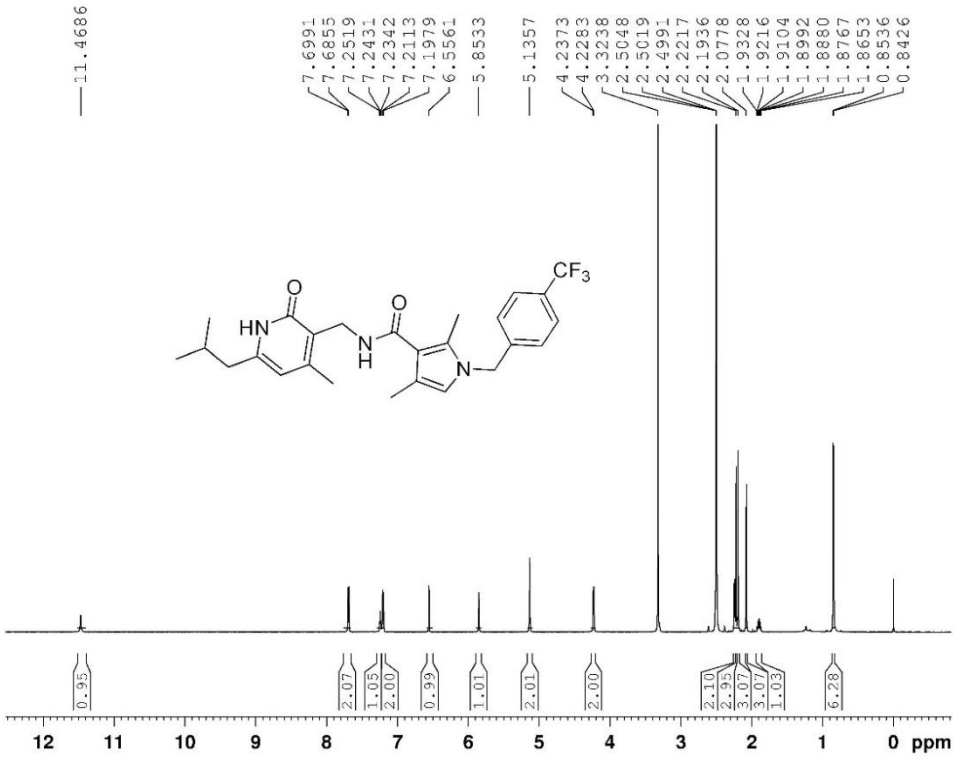


^{13}C NMR of DM-21

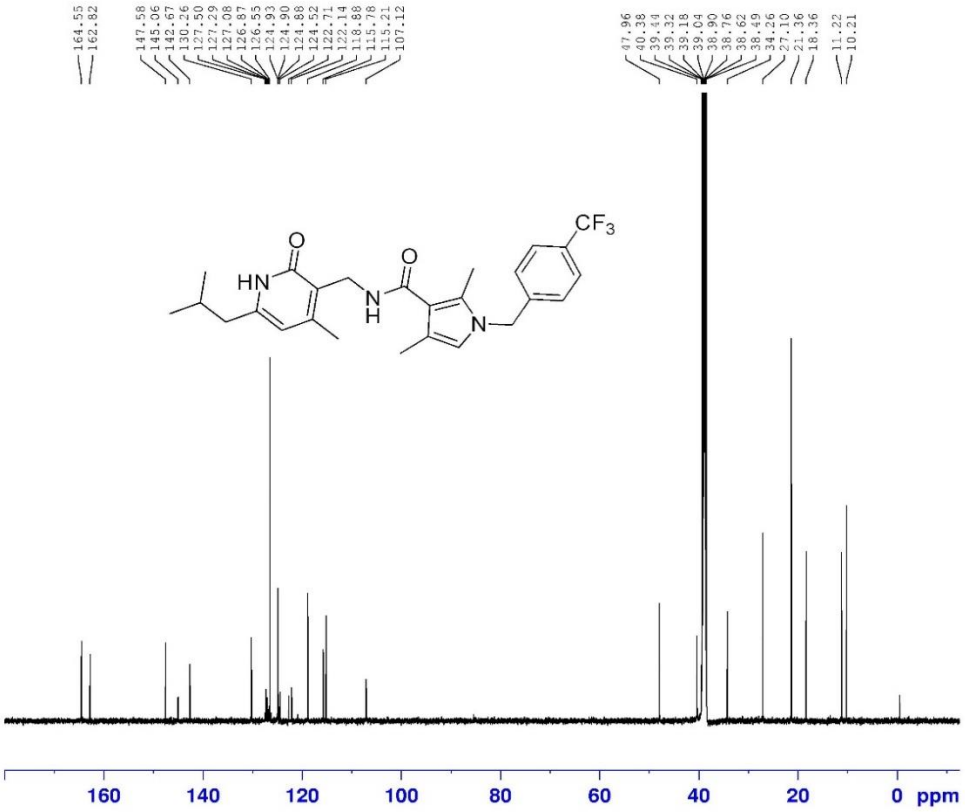


*N-((6-isobutyl-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-22**)*

^{1}H NMR of DM-22

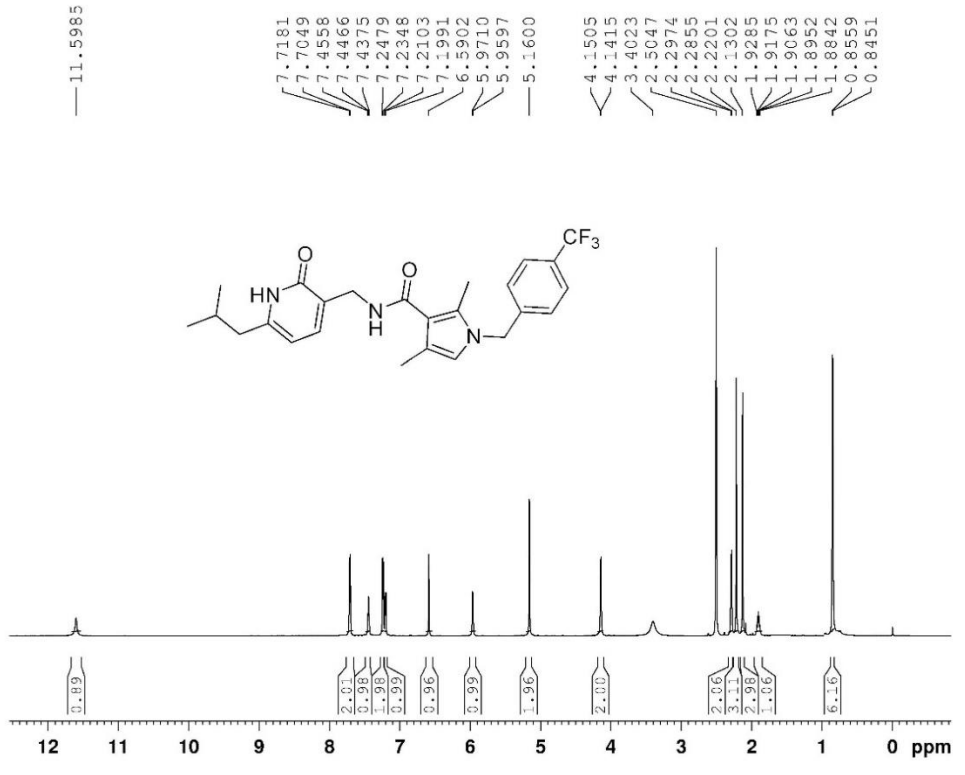


^{13}C NMR of DM-22

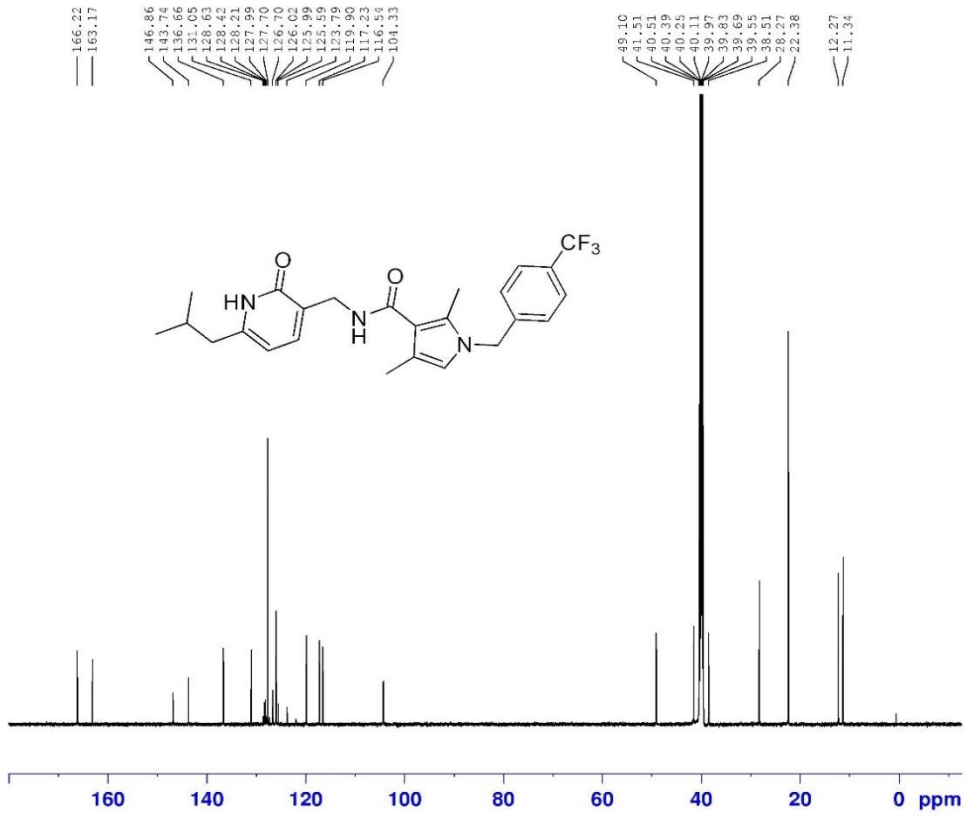


*N-((6-isobutyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1 H-pyrrole-3-carboxamide (**DM-23**)*

^{1}H NMR of DM-23

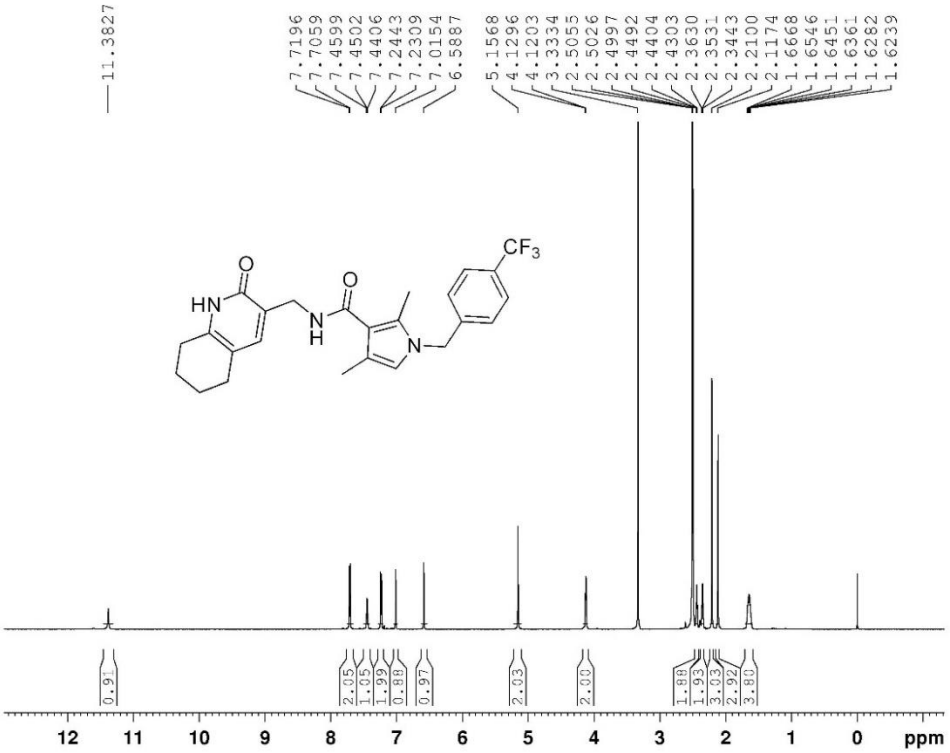


^{13}C NMR of DM-23

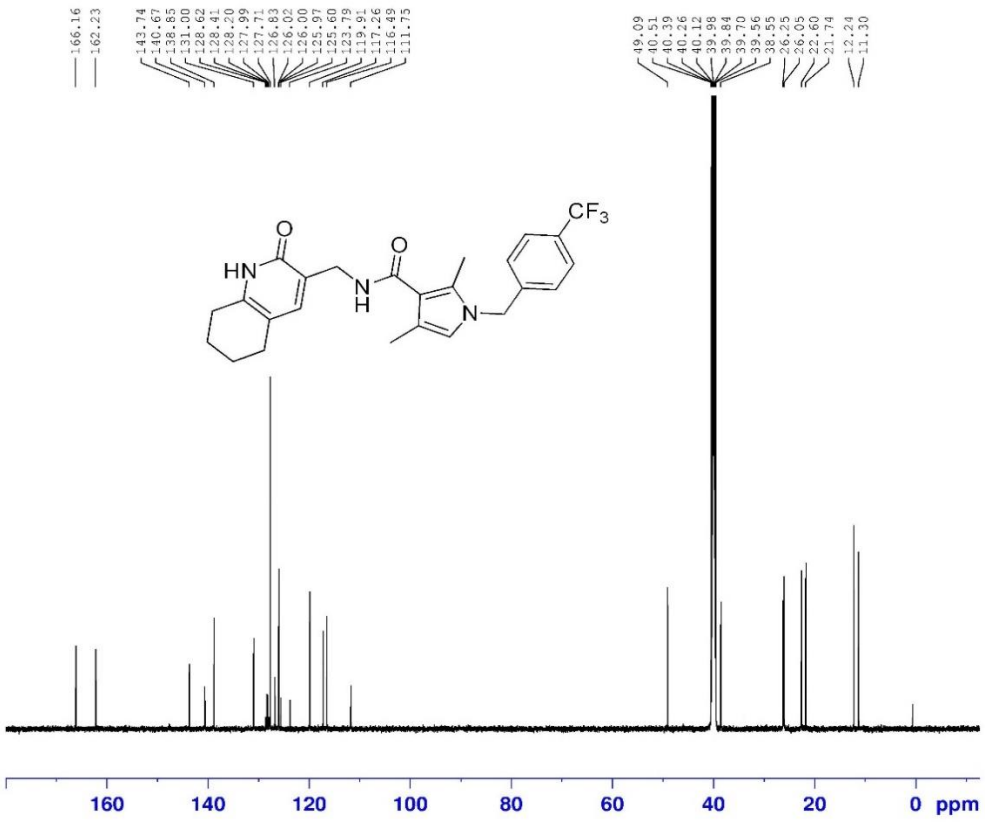


*2,4-Dimethyl-N-((2-oxo-1,2,5,6,7,8-hexahydroquinolin-3-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-1 H-pyrrole-3-carboxamide (**DM-24**)*

^{1}H NMR of DM-24

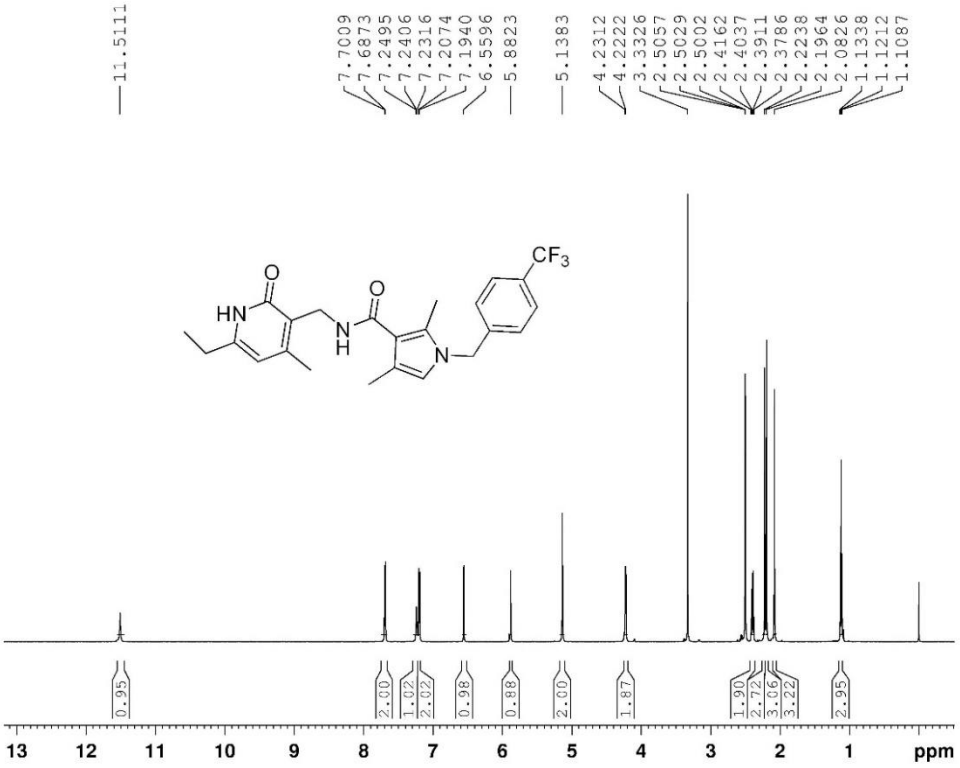


^{13}C NMR of DM-24

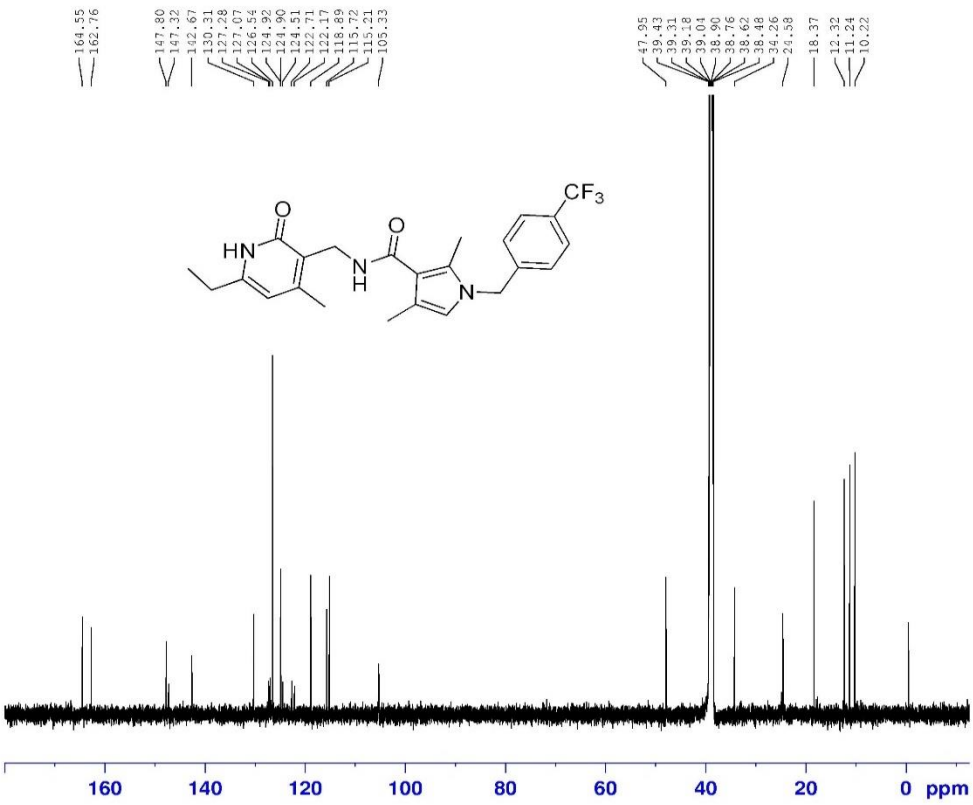


*N-((6-ethyl-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-pyrrole-3-carboxamide (**DM-25**)*

^{1}H NMR of DM-25

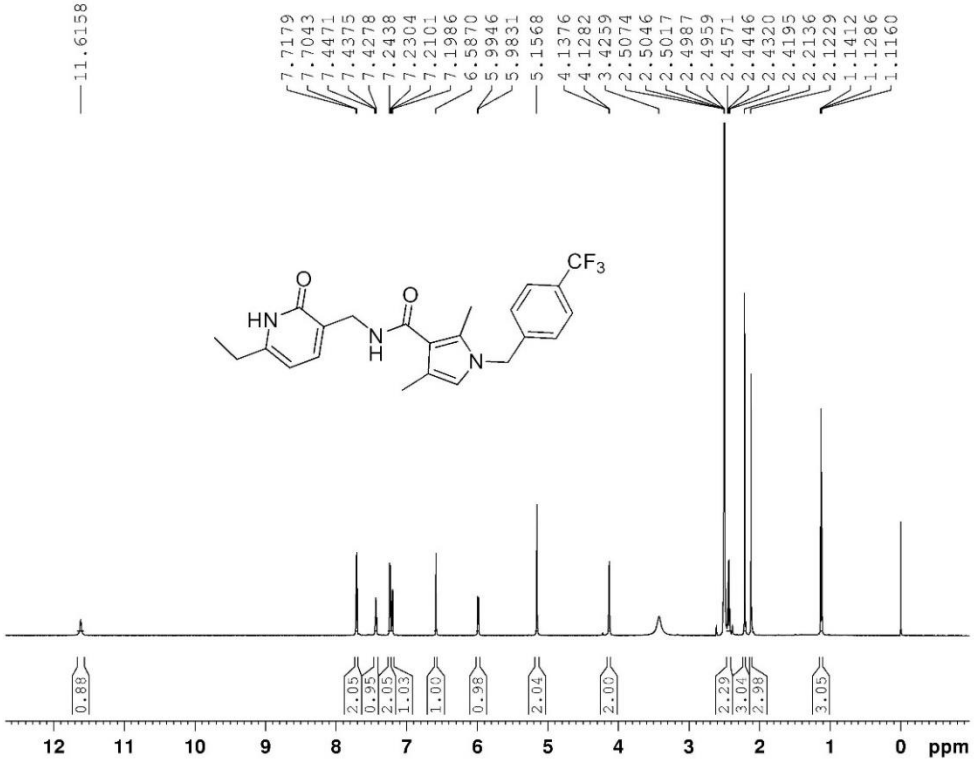


^{13}C NMR of DM-25

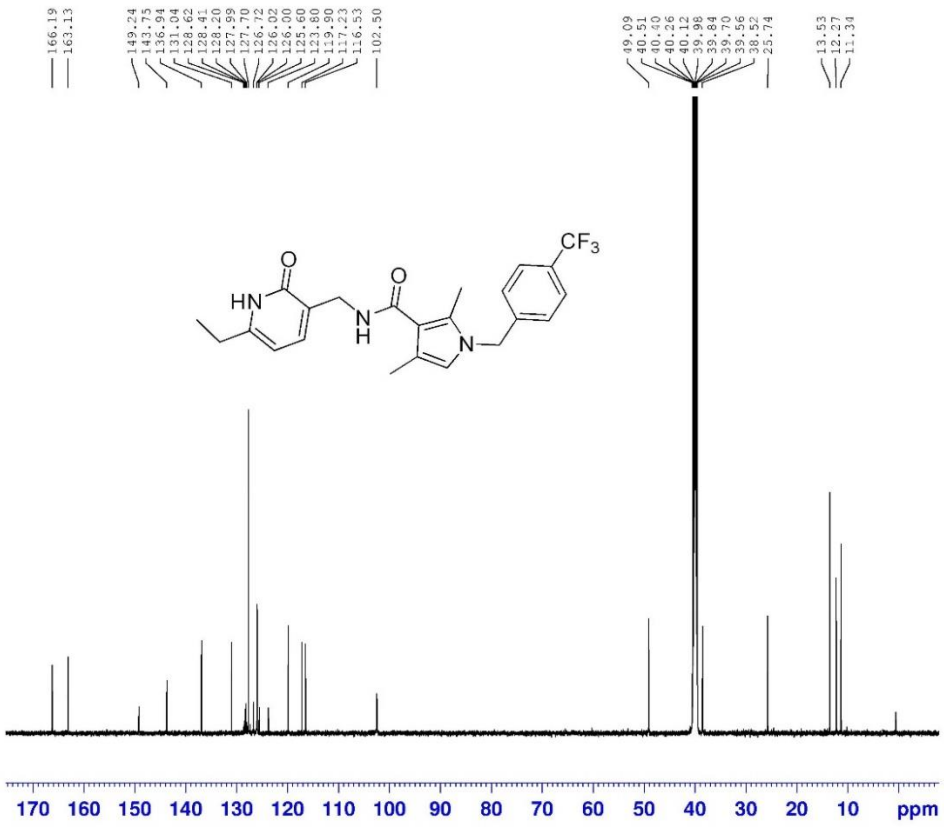


*N-((6-ethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl-1H-py rrole-3-carboxamide (**DM-26**)*

^{1}H NMR of DM-26

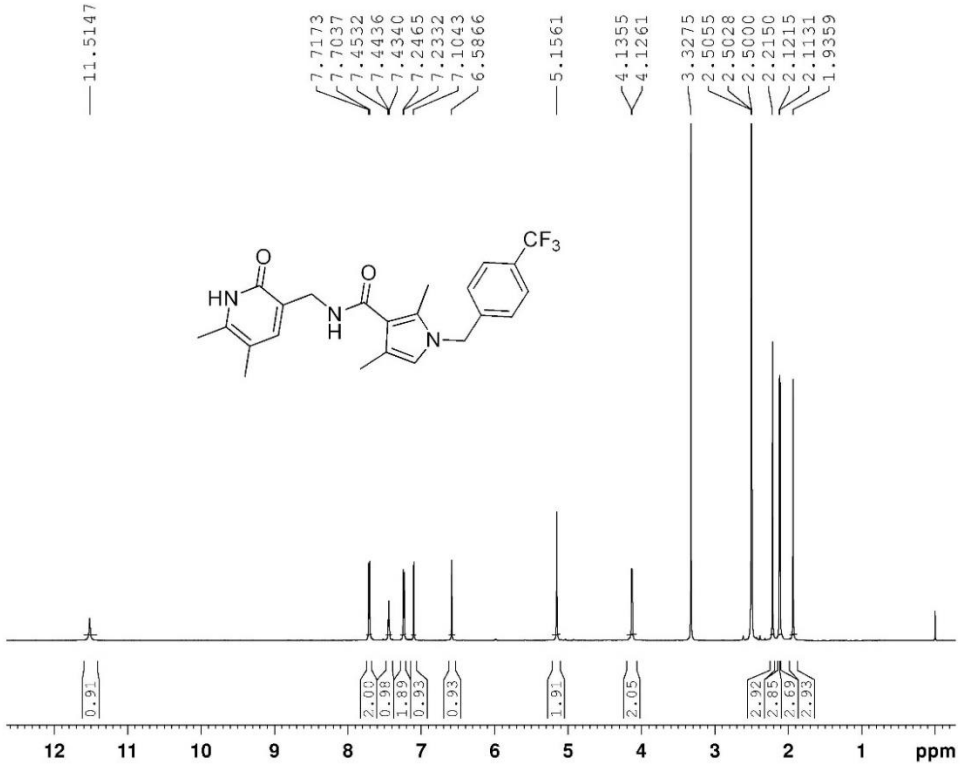


^{13}C NMR of DM-26

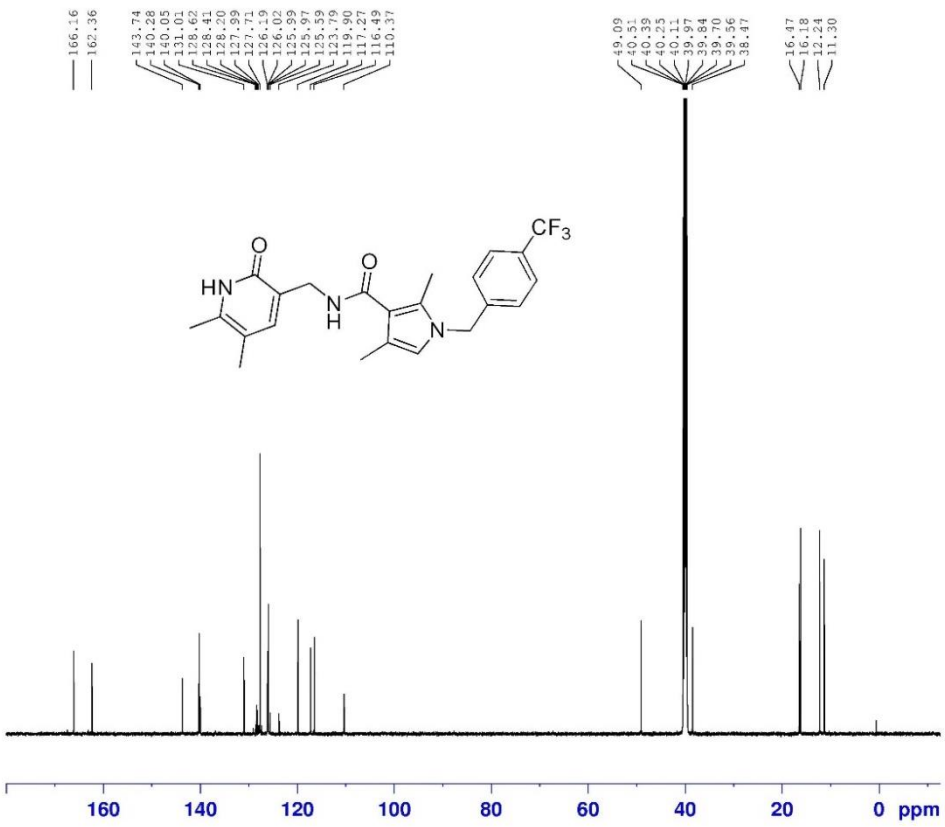


*N-((5,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(4-(trifluoromethyl)benzyl) -1H-pyrrole-3-carboxamide (**DM-27**)*

^{1}H NMR of DM-27

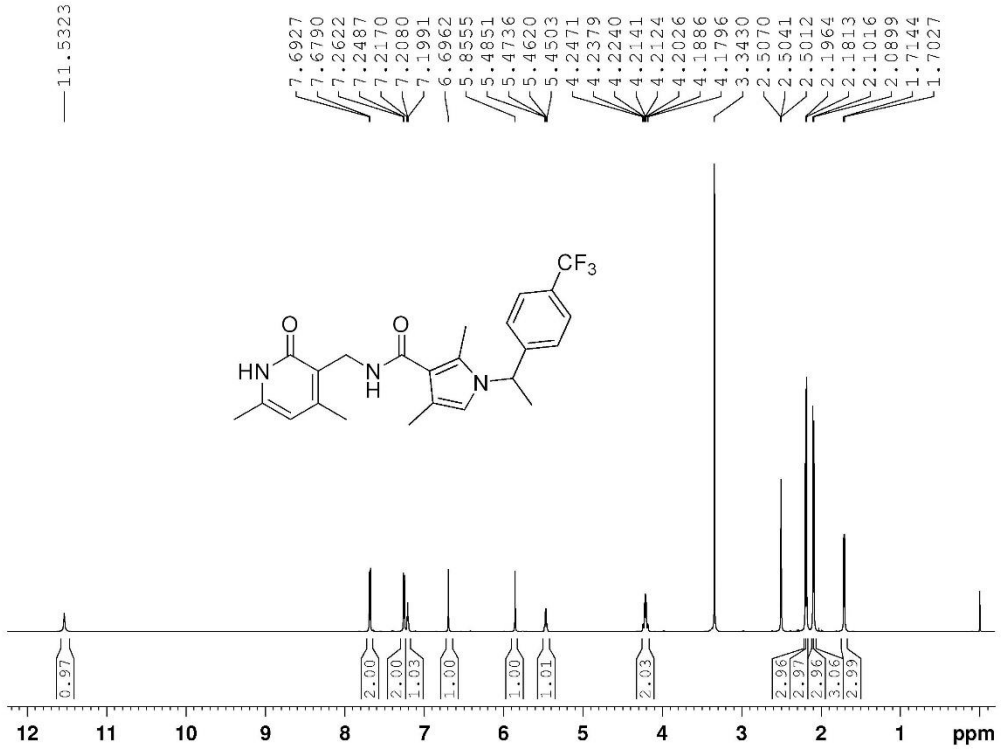


^{13}C NMR of DM-27

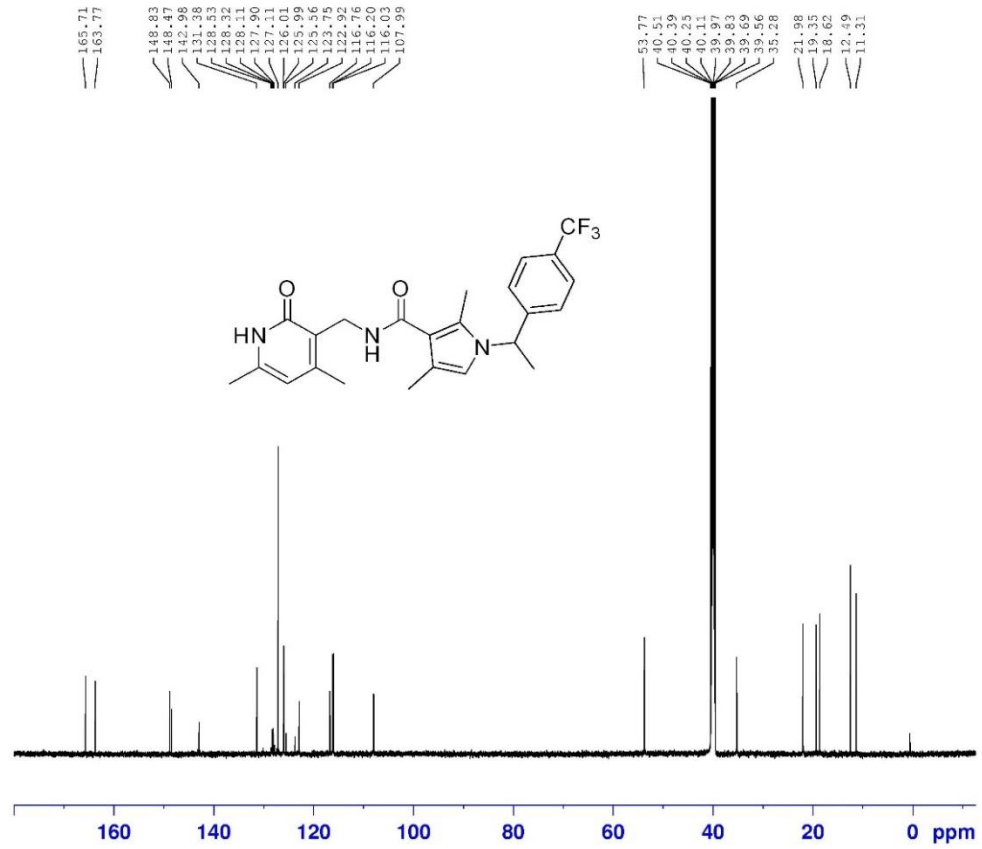


*N-((4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2,4-dimethyl-1-(1-(4-(Trifluoromethyl)phe nyl)ethyl)-1H-pyrrole-3-carboxamide (**DM-28**)*

^{1}H NMR of DM-28

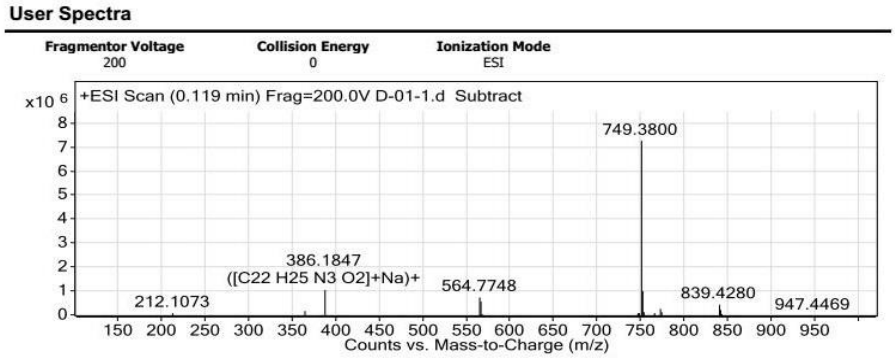


^{13}C NMR of DM-28

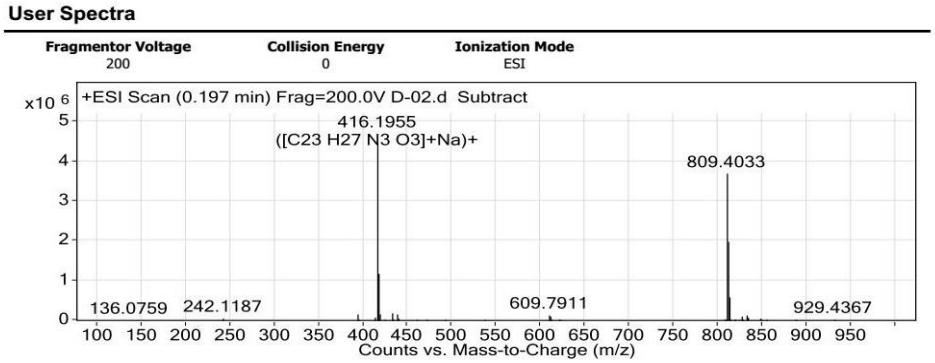


ESI-HRMS spectrums of D and DM series compounds

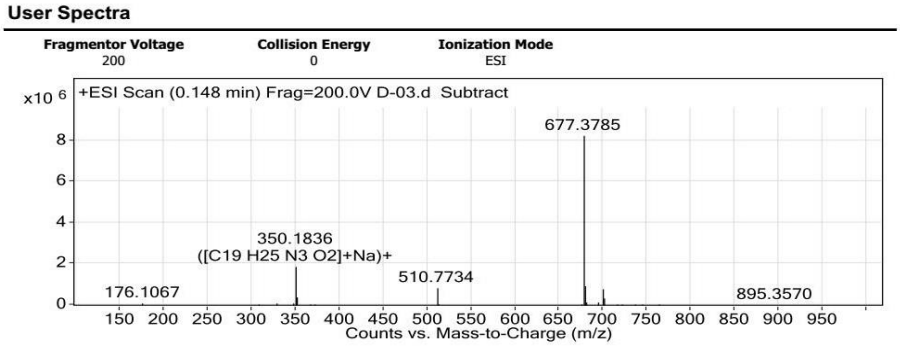
ESI-HRMS spectrum of D-01



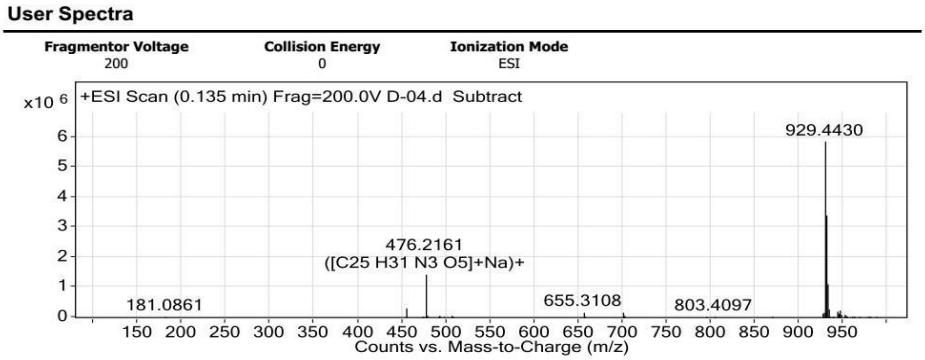
ESI-HRMS spectrum of D-02



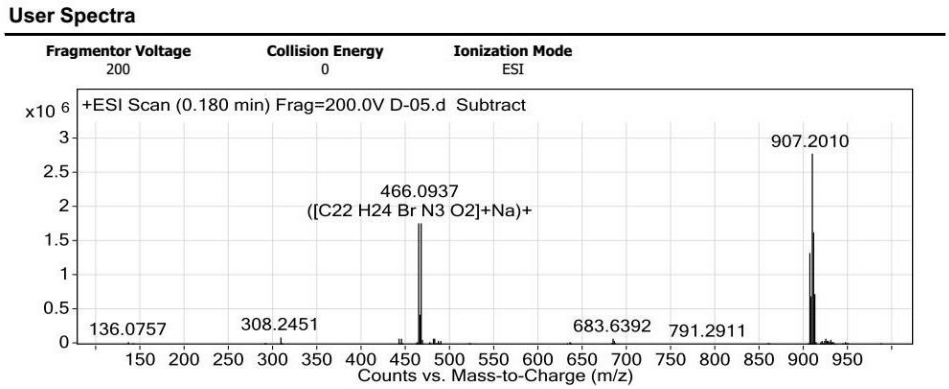
ESI-HRMS spectrum of D-03



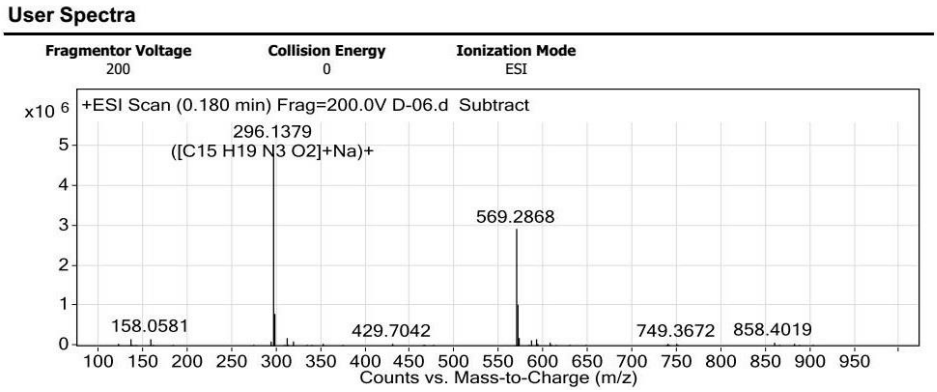
ESI-HRMS spectrum of D-04



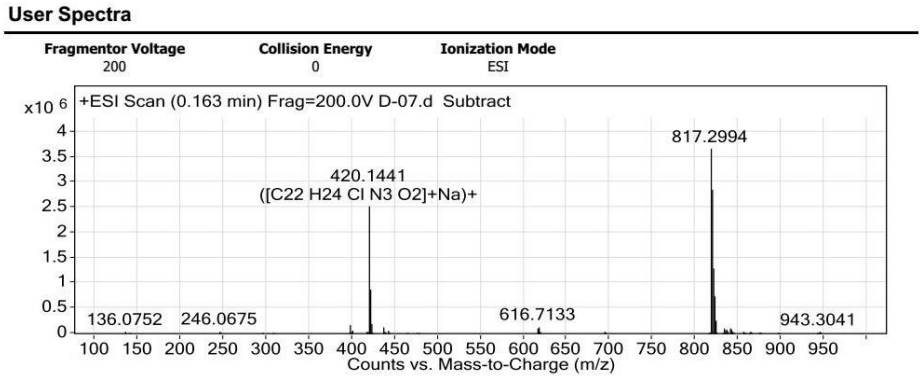
ESI-HRMS spectrum of D-05



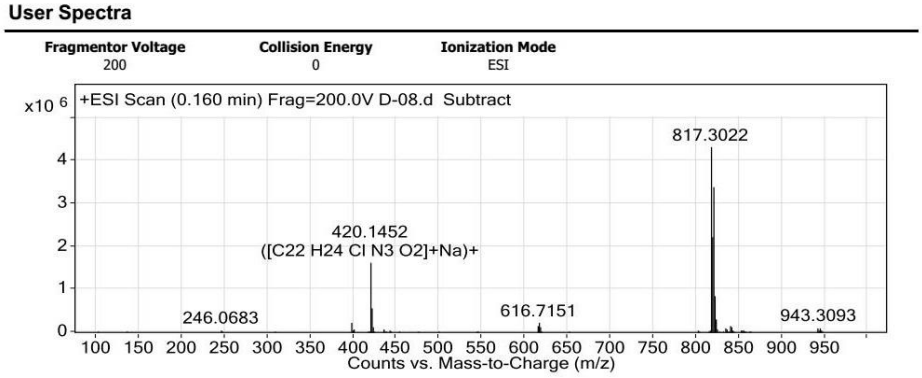
ESI-HRMS spectrum of D-06



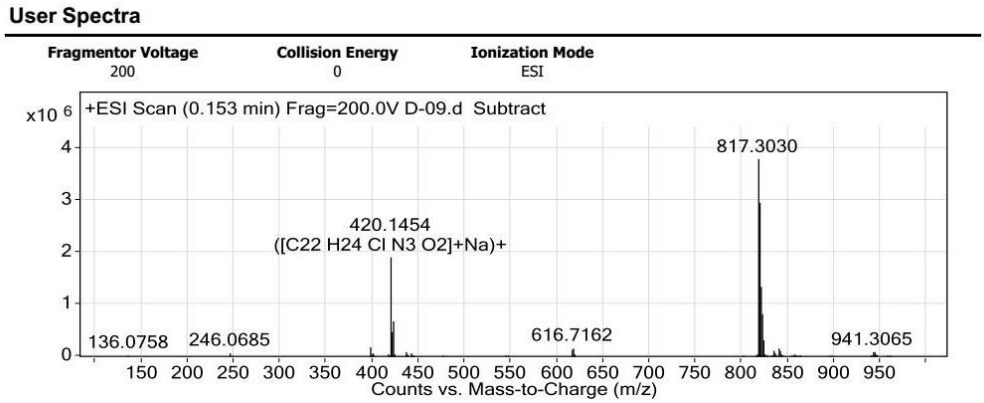
ESI-HRMS spectrum of D-07



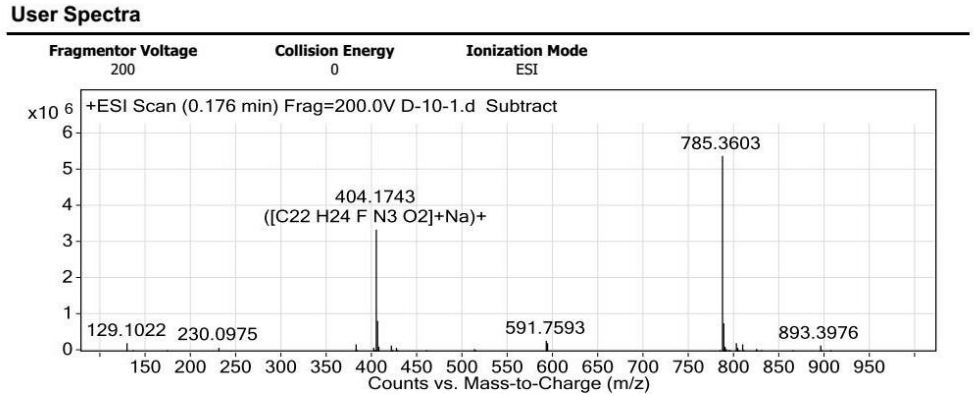
ESI-HRMS spectrum of D-08



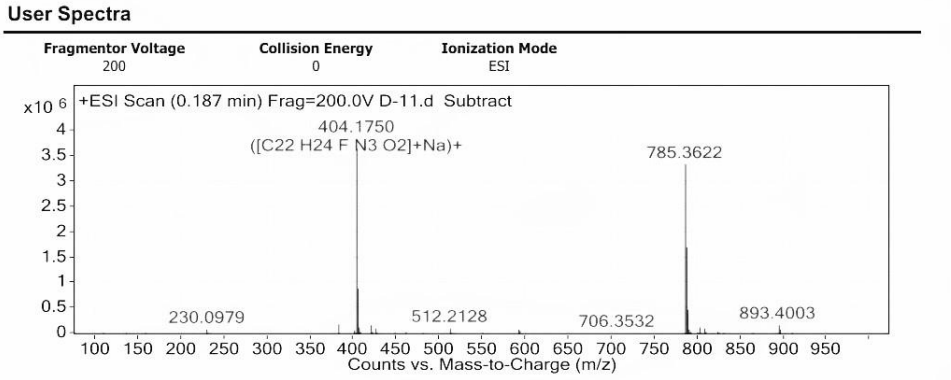
ESI-HRMS spectrum of D-09



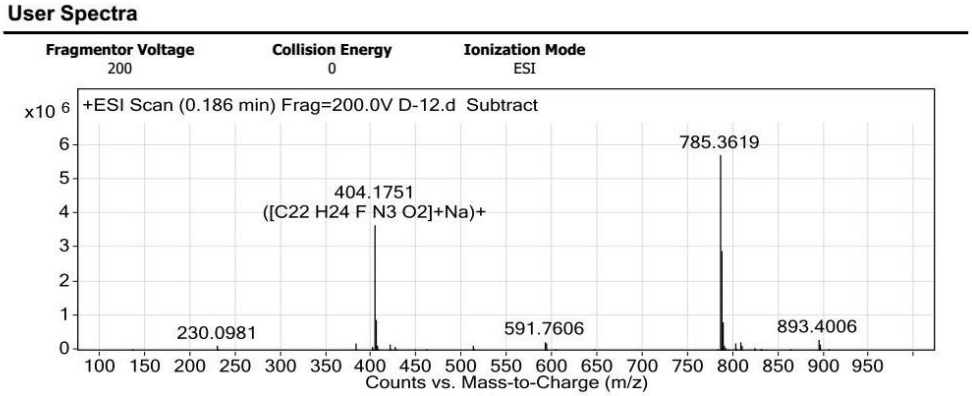
ESI-HRMS spectrum of D-10



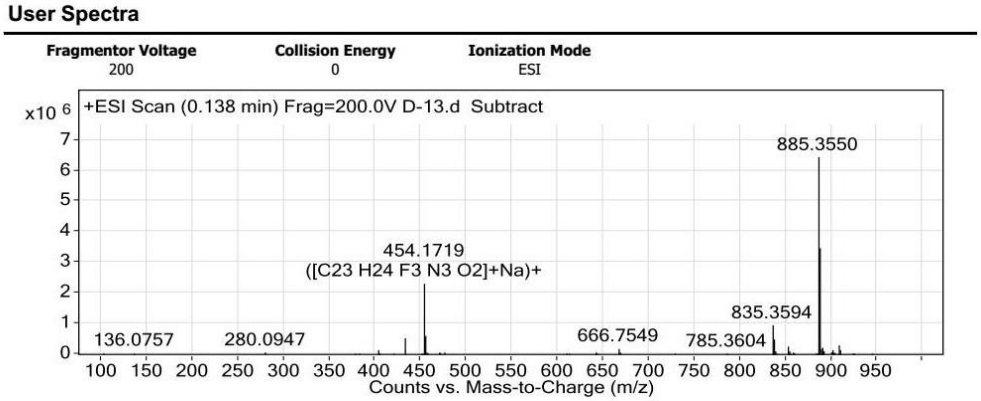
ESI-HRMS spectrum of D-11



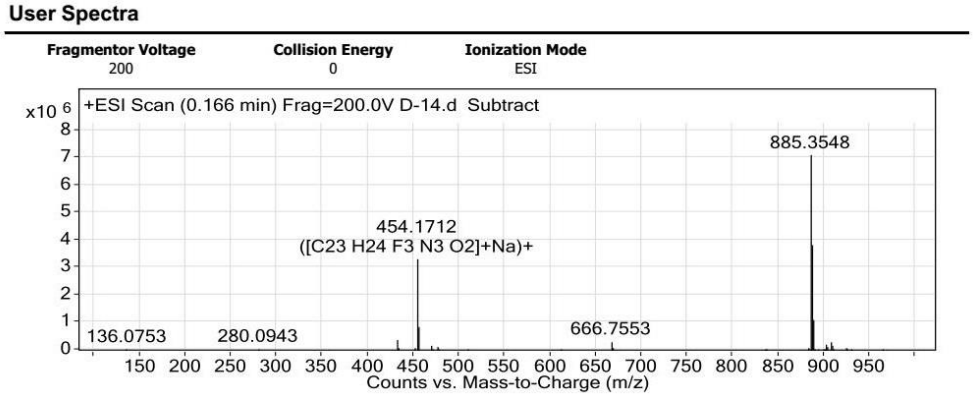
ESI-HRMS spectrum of D-12



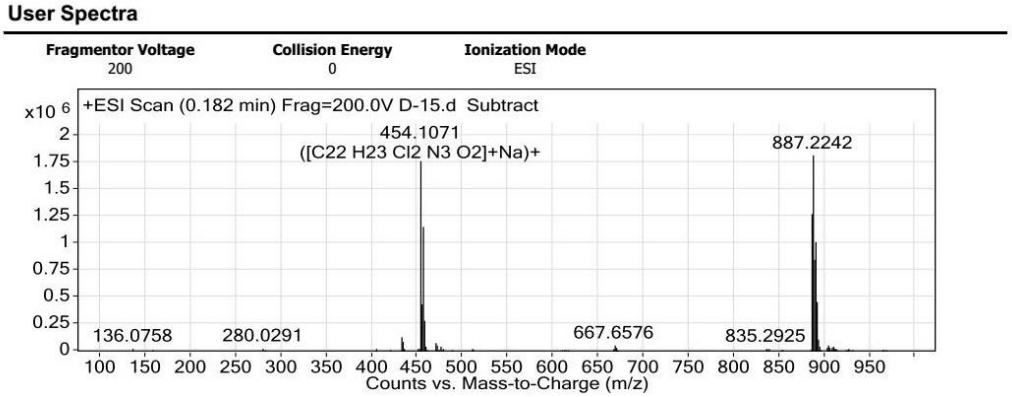
ESI-HRMS spectrum of D-13



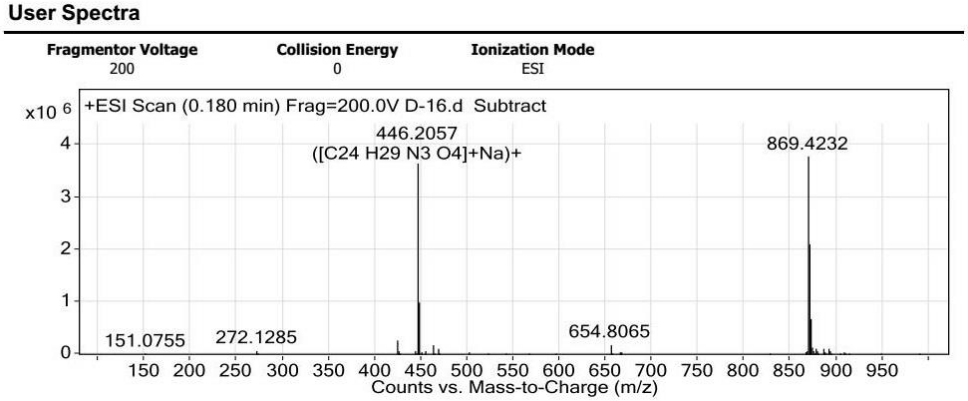
ESI-HRMS spectrum of D-14



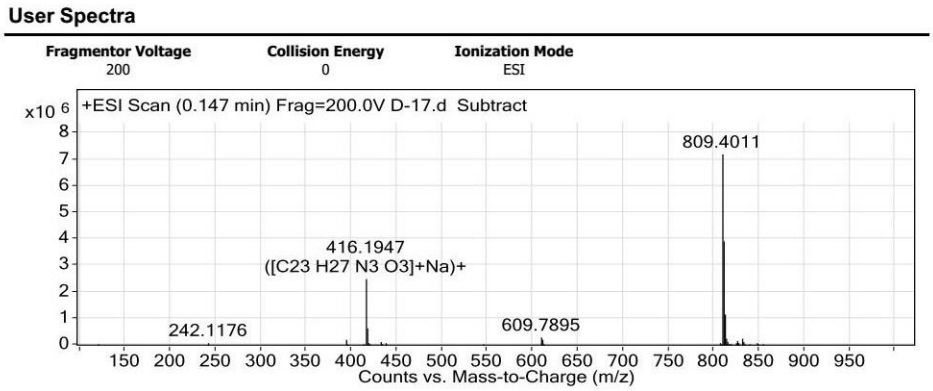
ESI-HRMS spectrum of D-15



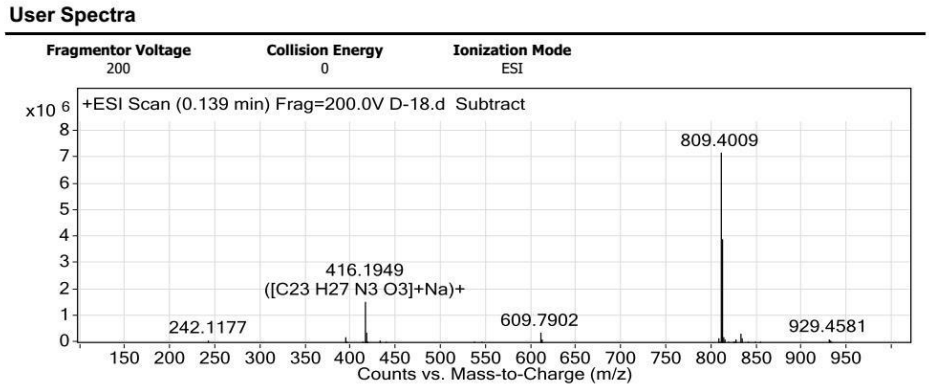
ESI-HRMS spectrum of D-16



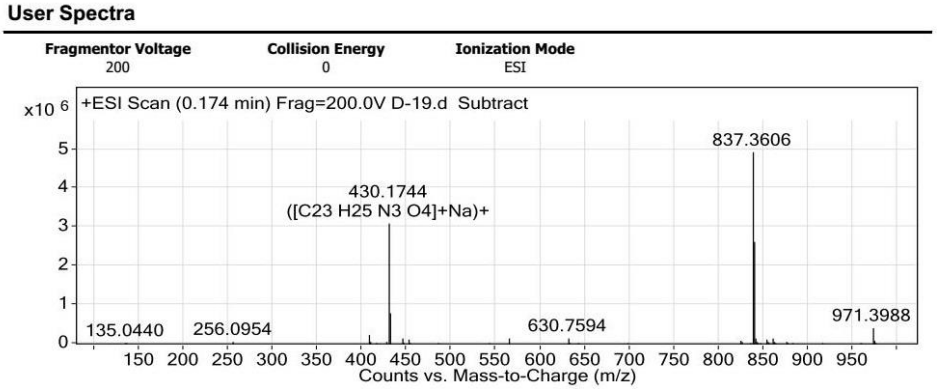
ESI-HRMS spectrum of D-17



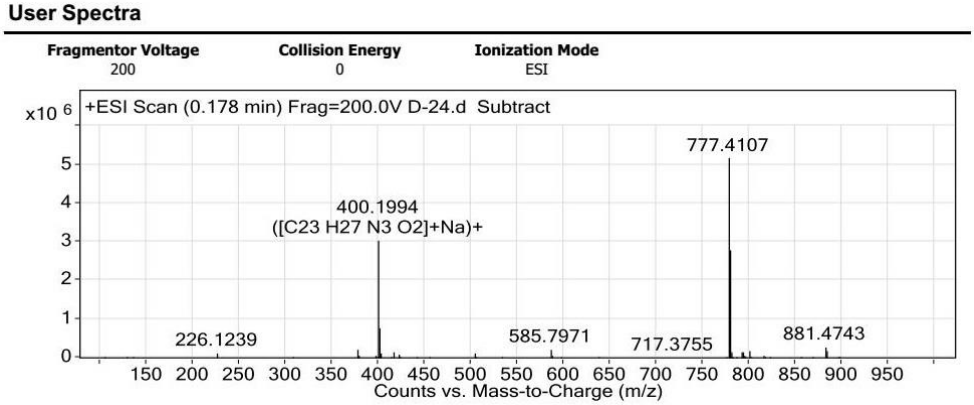
ESI-HRMS spectrum of D-18



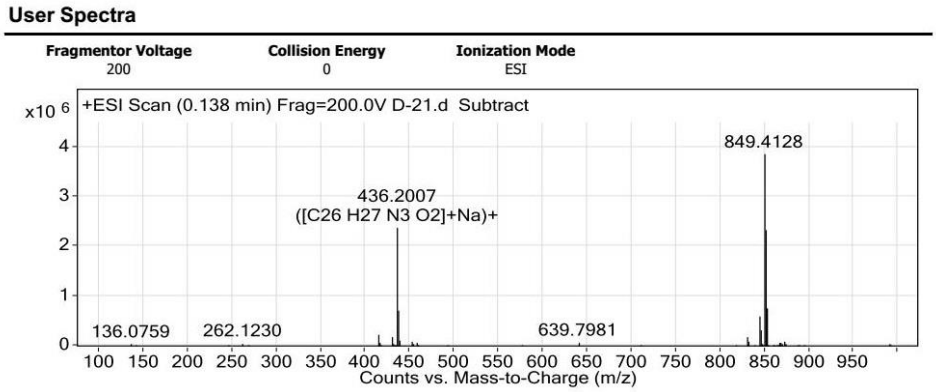
ESI-HRMS spectrum of D-19



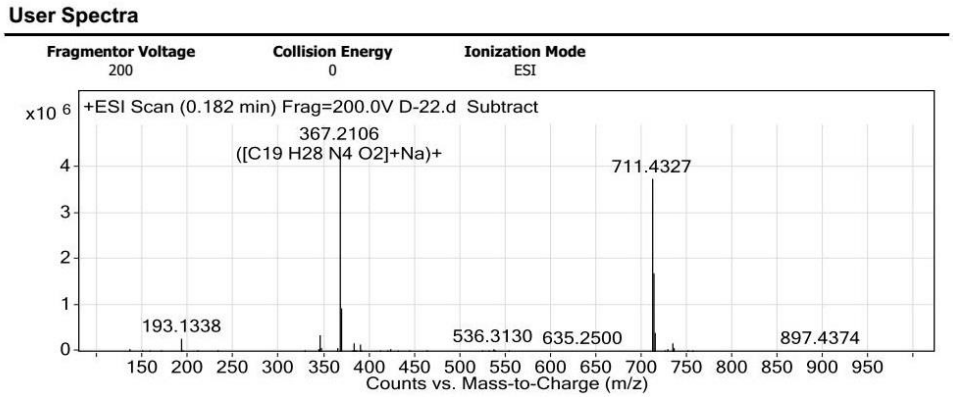
ESI-HRMS spectrum of D-20



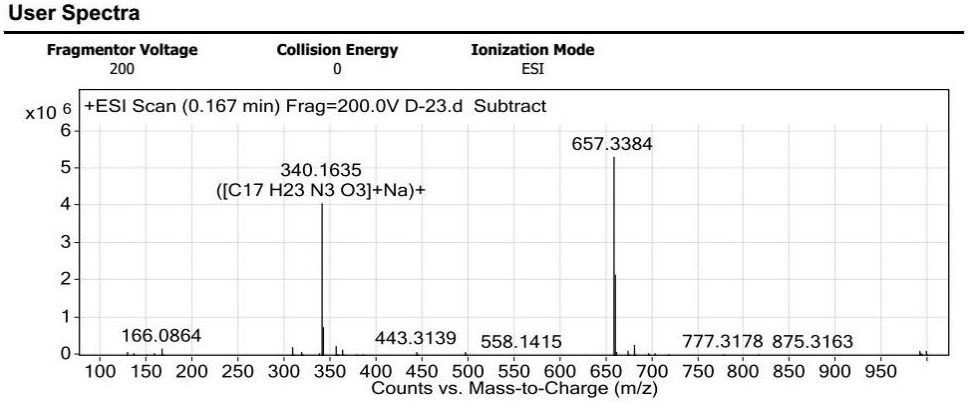
ESI-HRMS spectrum of D-21



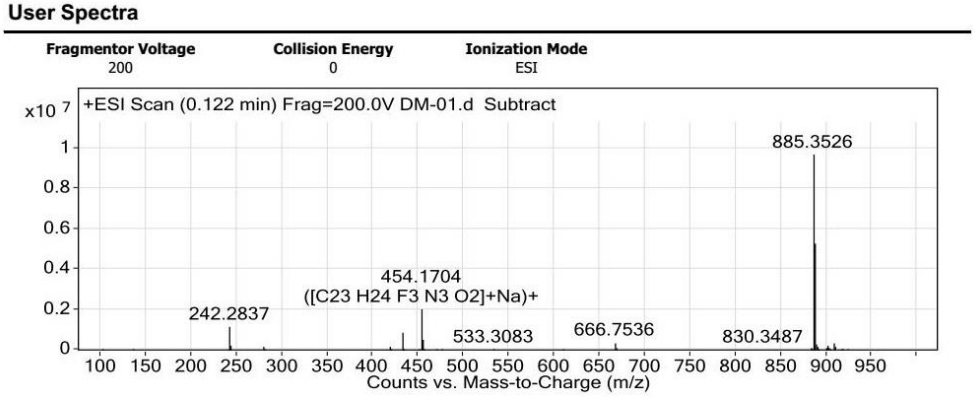
ESI-HRMS spectrum of D-22



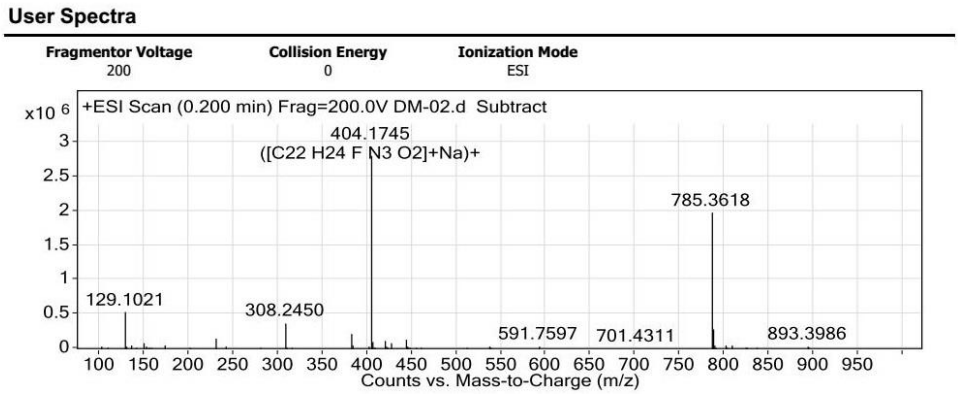
ESI-HRMS spectrum of D-23



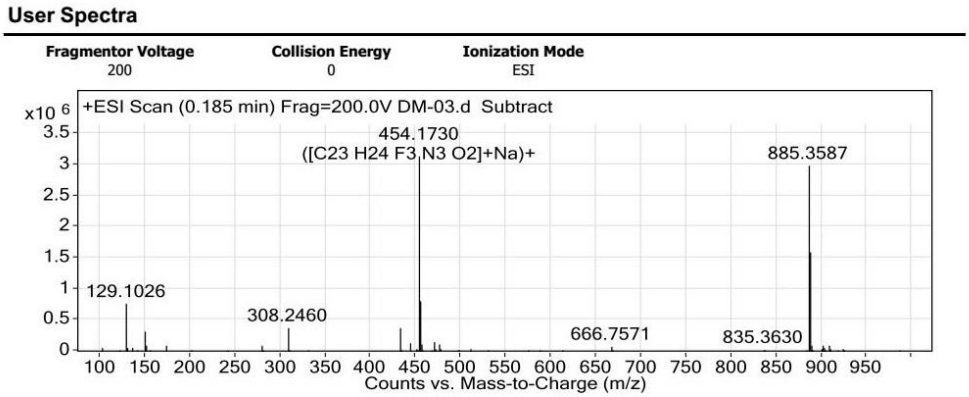
ESI-HRMS spectrum of DM-01



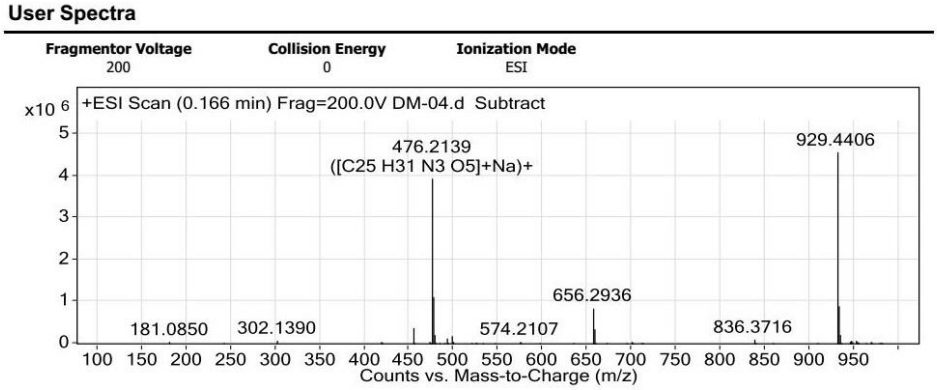
ESI-HRMS spectrum of DM-02



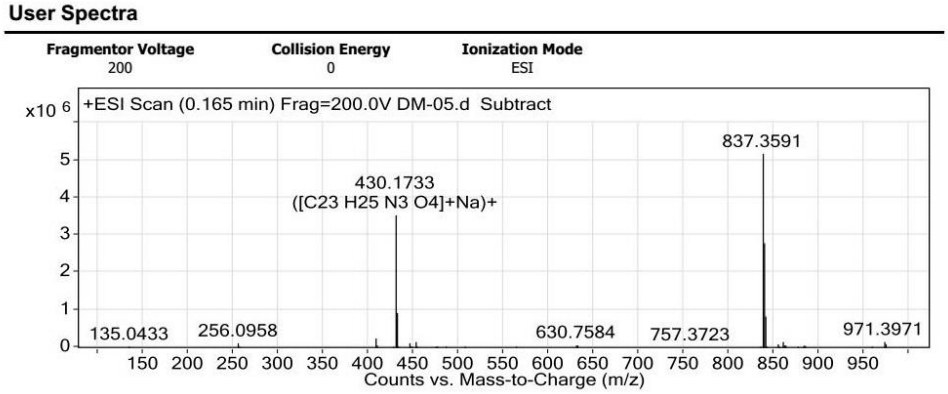
ESI-HRMS spectrum of DM-03



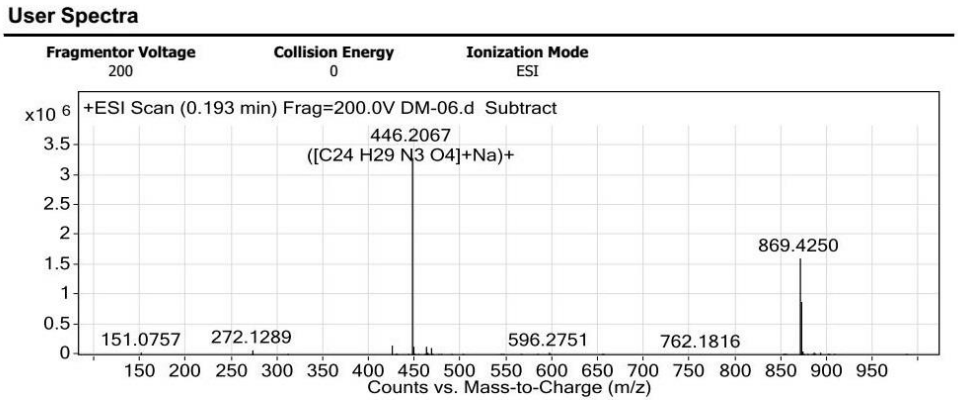
ESI-HRMS spectrum of DM-04



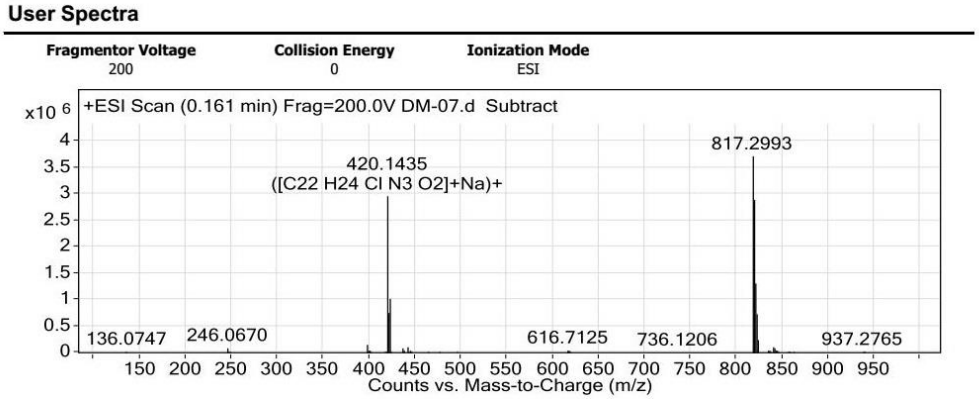
ESI-HRMS spectrum of DM-05



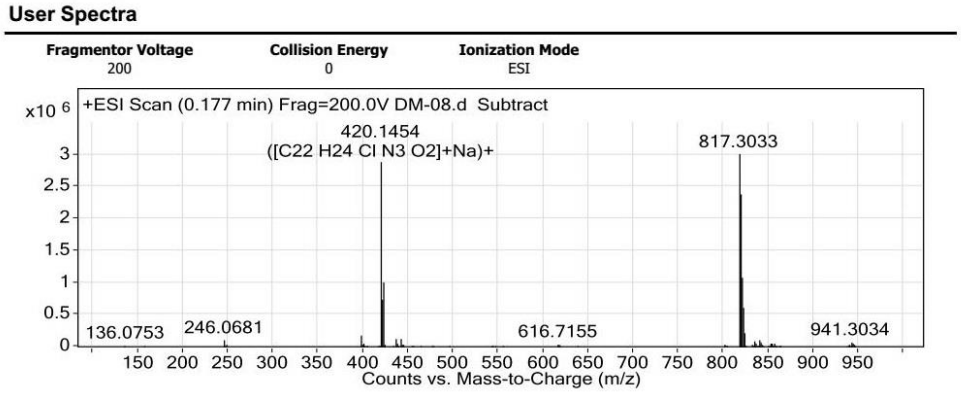
ESI-HRMS spectrum of DM-06



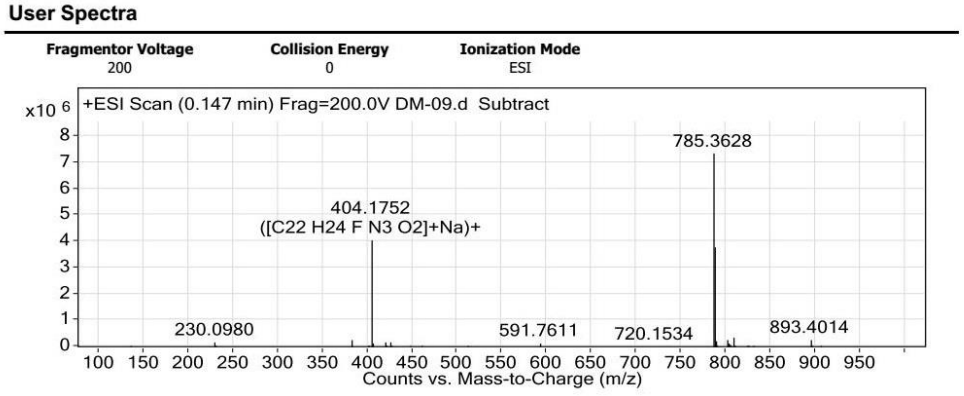
ESI-HRMS spectrum of DM-07



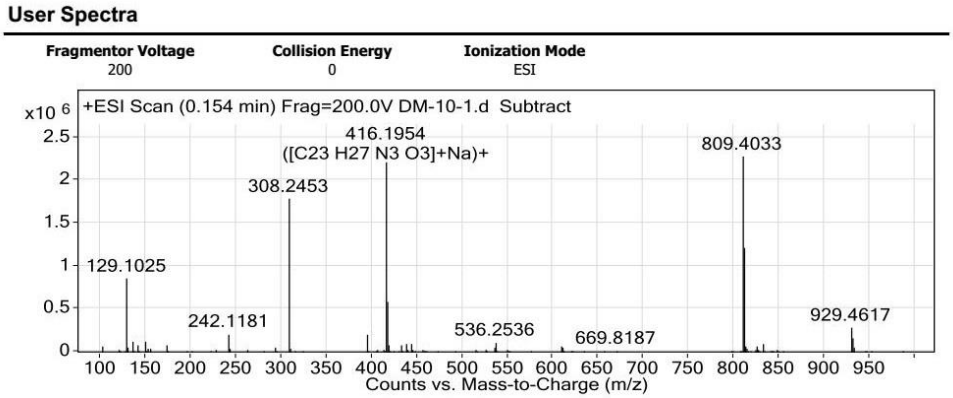
ESI-HRMS spectrum of DM-08



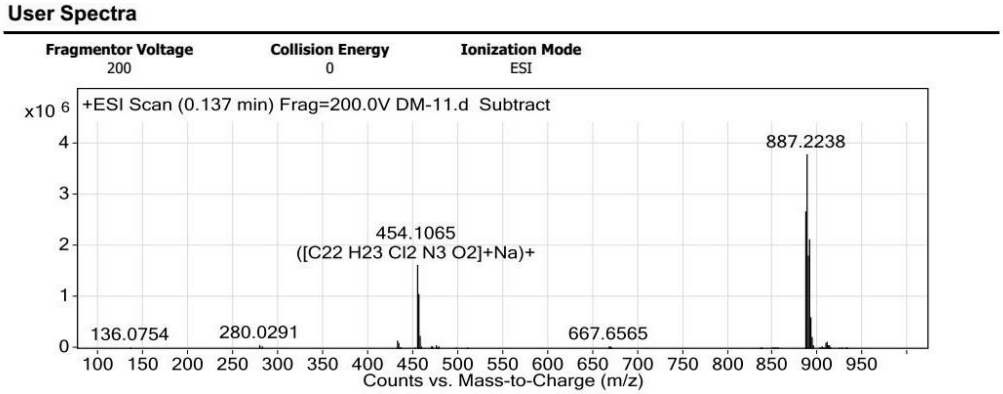
ESI-HRMS spectrum of DM-09



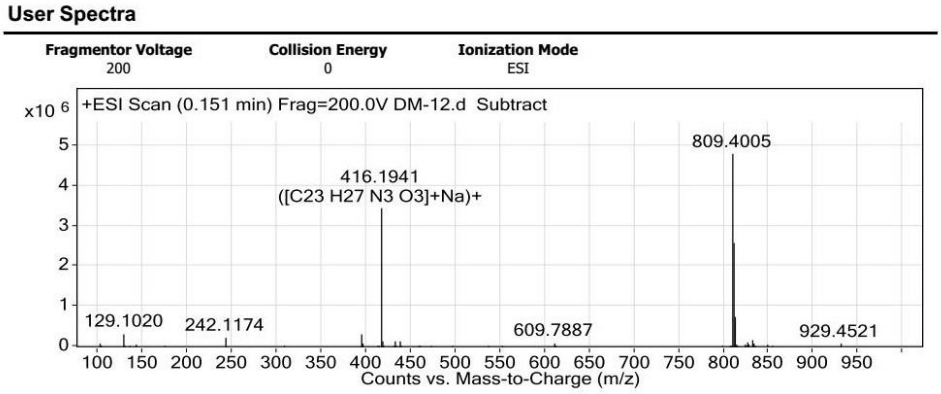
ESI-HRMS spectrum of DM-10



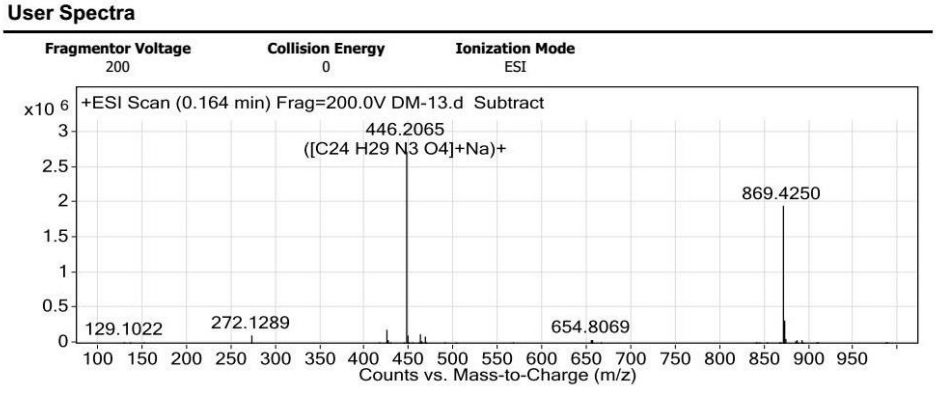
ESI-HRMS spectrum of DM-11



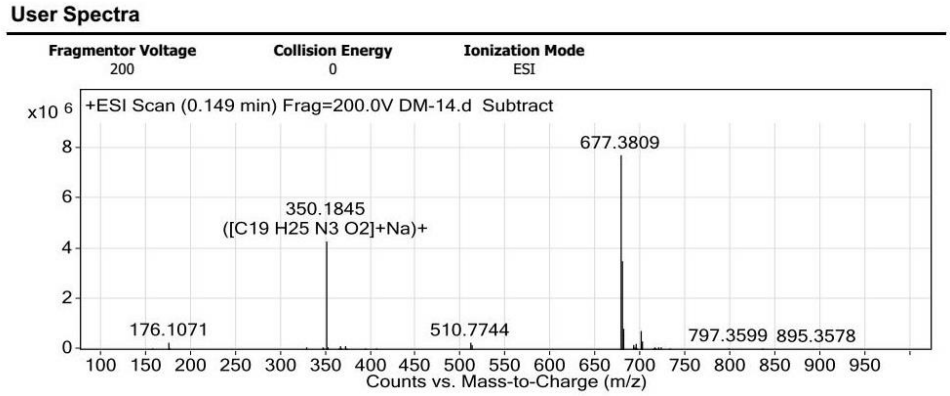
ESI-HRMS spectrum of DM-12



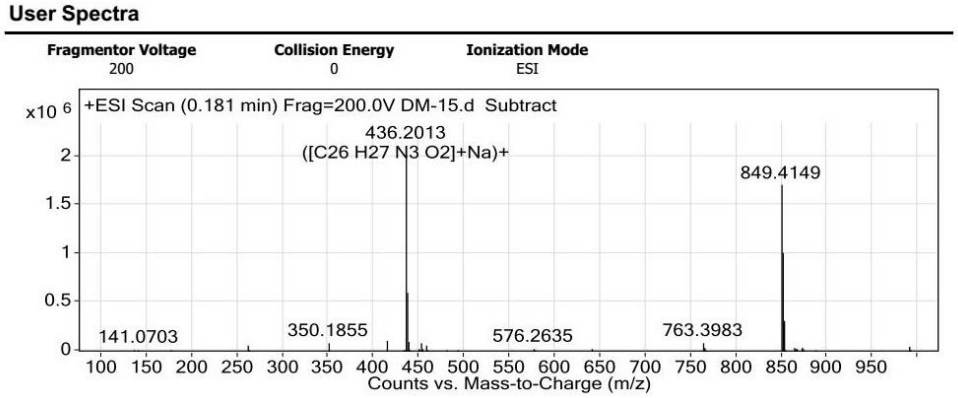
ESI-HRMS spectrum of DM-13



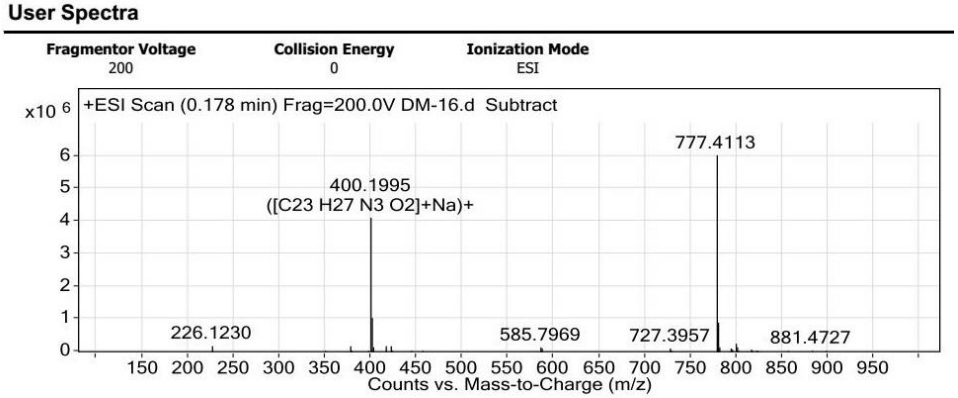
ESI-HRMS spectrum of DM-14



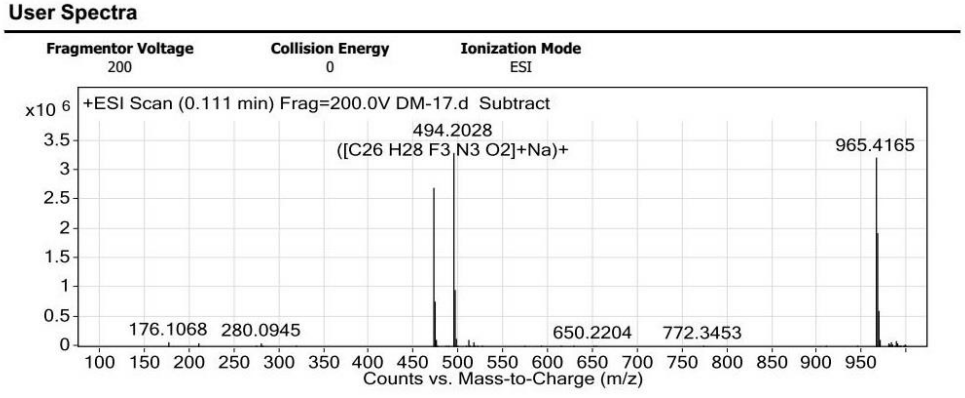
ESI-HRMS spectrum of DM-15



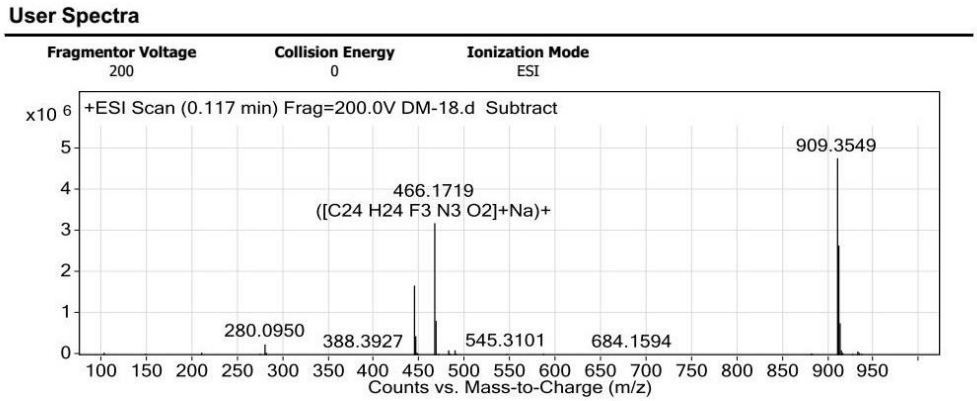
ESI-HRMS spectrum of DM-16



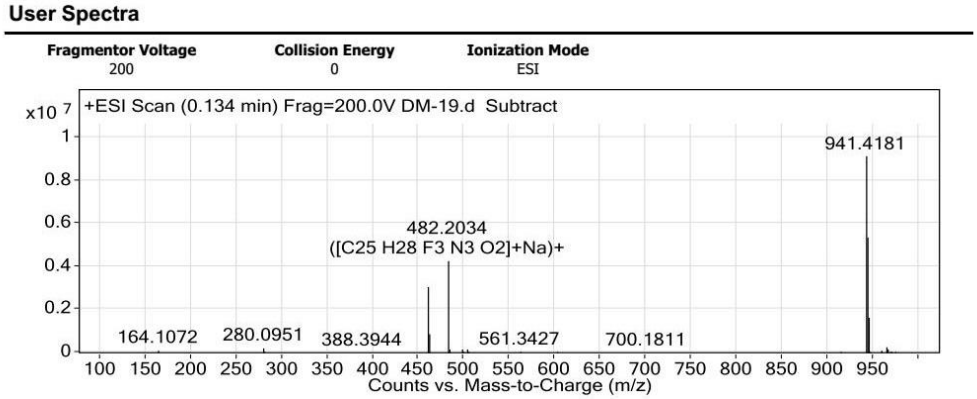
ESI-HRMS spectrum of DM-17



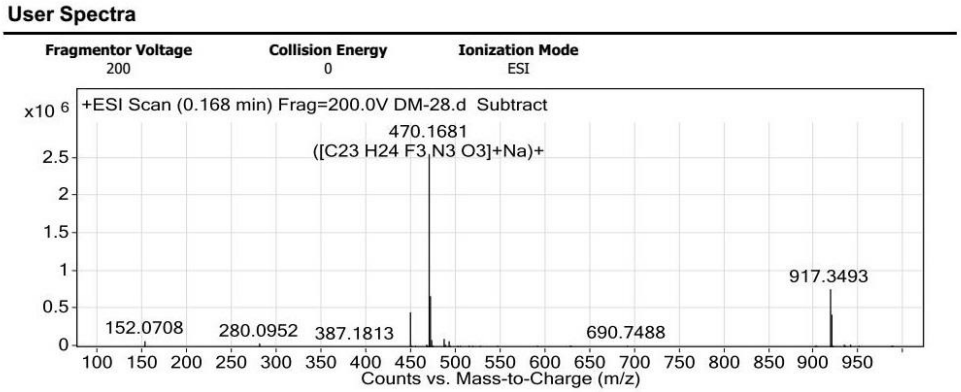
ESI-HRMS spectrum of DM-18



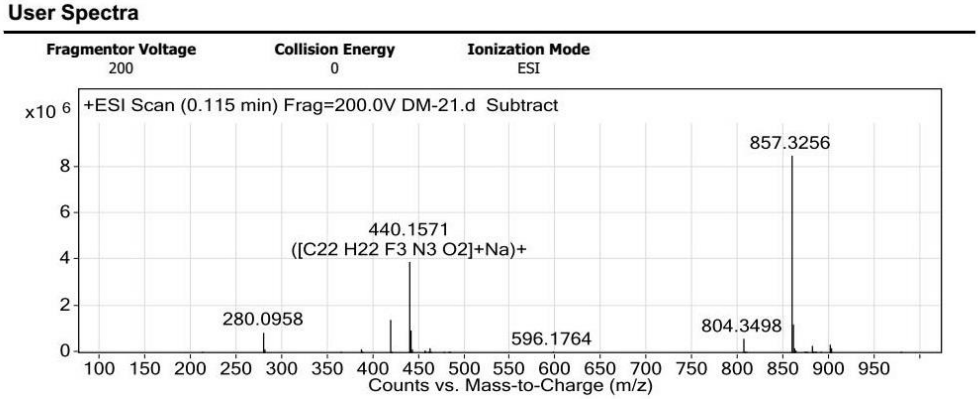
ESI-HRMS spectrum of DM-19



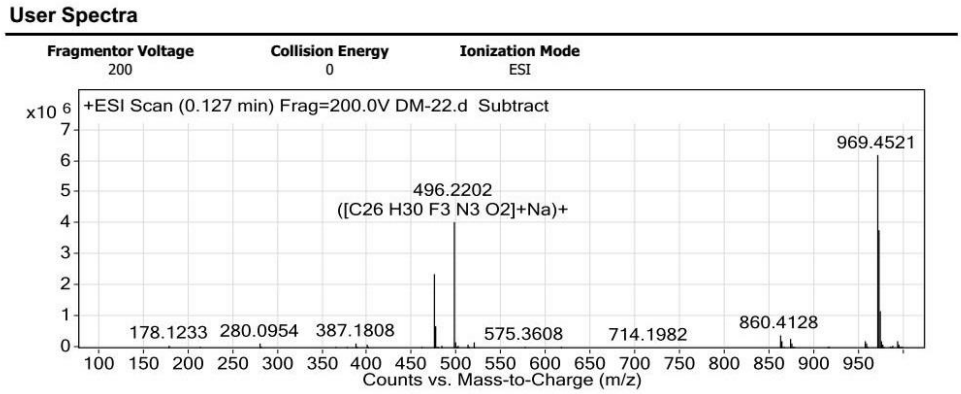
ESI-HRMS spectrum of DM-20



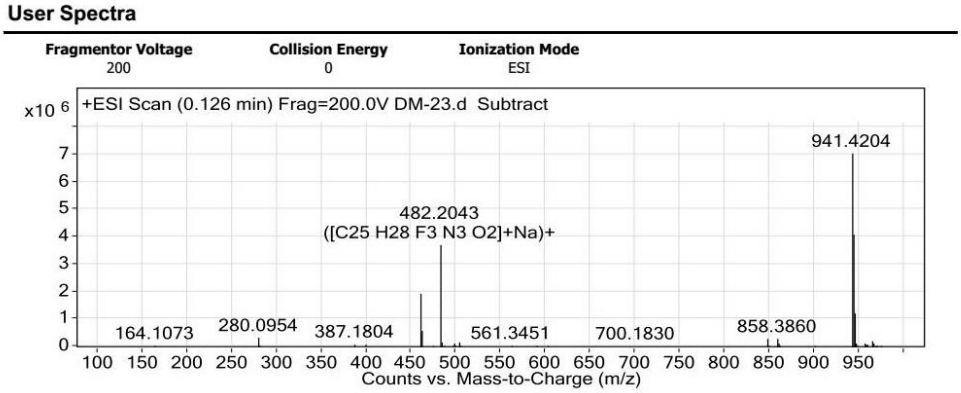
ESI-HRMS spectrum of DM-21



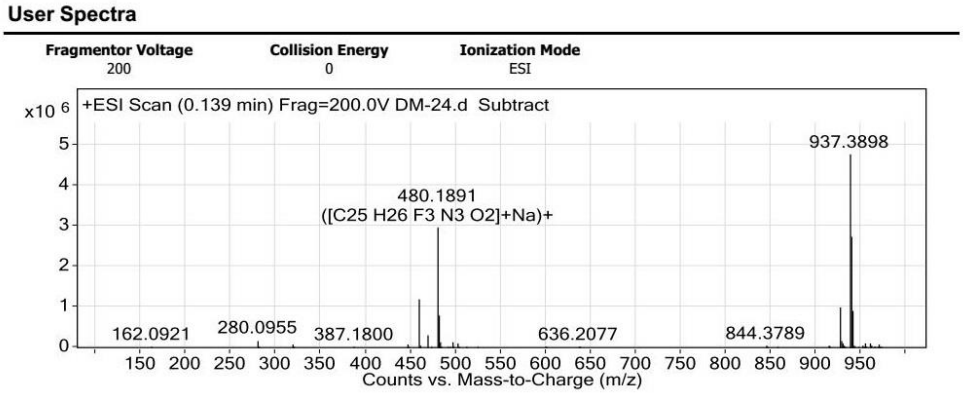
ESI-HRMS spectrum of DM-22



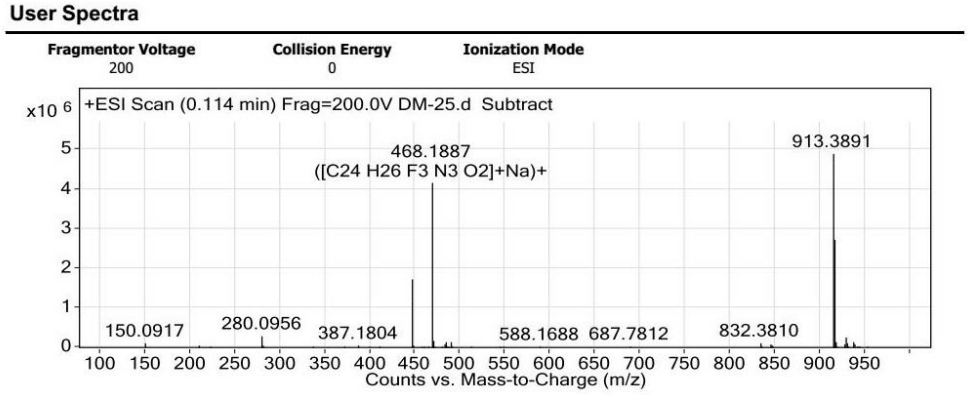
ESI-HRMS spectrum of DM-23



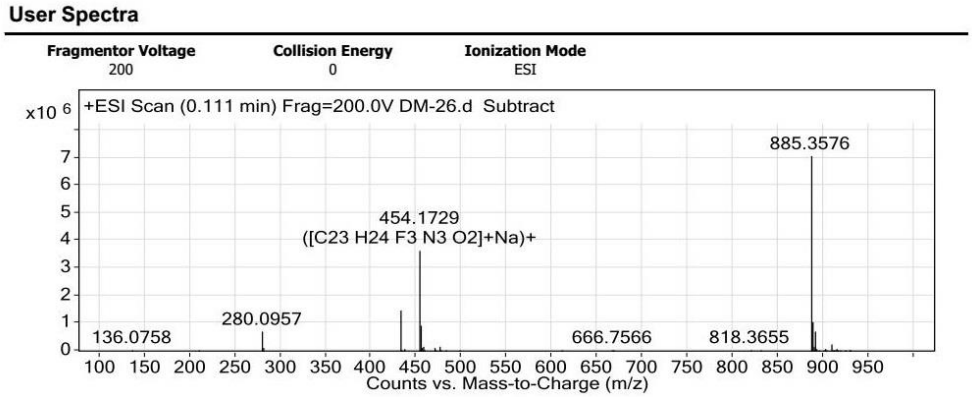
ESI-HRMS spectrum of DM-24



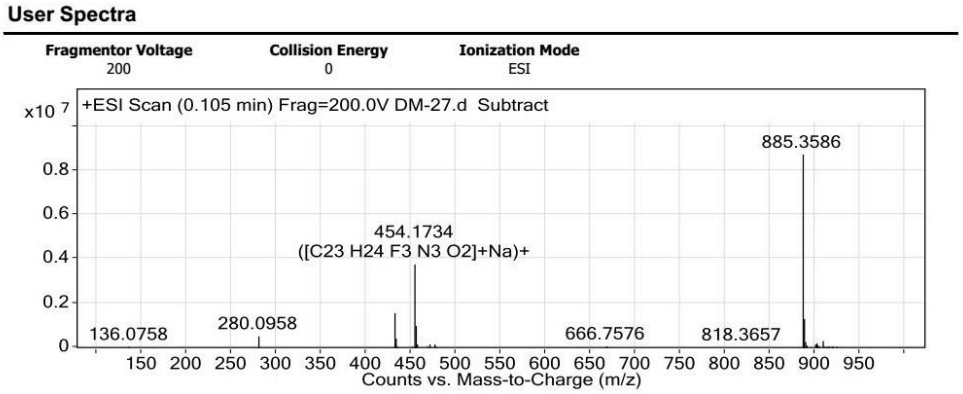
ESI-HRMS spectrum of DM-25



ESI-HRMS spectrum of DM-26



ESI-HRMS spectrum of DM-27



ESI-HRMS spectrum of DM-28