

The first example of α -ferrocenylalkylation of 2-thiohydantoin

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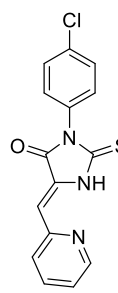
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1. General considerations

All reagents and solvents were purchased from commercial suppliers and used without further purification. Reactions were carried out in dry solvents and monitored in situ by thin-layer chromatography (TLC) carried out on silica gel plates (Merck KGaA; 60 F154), using UV light at 254 nm as the visualizing agent to assure consumption of starting materials prior to work up. NMR spectra were recorded on Bruker Avance II spectrometer (^1H : 400 MHz, ^{13}C : 100 MHz) at room temperature. Chemical shifts are reported in parts per million (ppm) calibrated using residual non deuterated solvent as internal reference. Integration is determined as the relative number of atoms. IR-spectra of compounds were recorded on a Nicolet iS5 FT-IR spectrometer (United States) by a frustrated total internal reflection (FTIR) method. High resolution mass spectra (HRMS) were recorded with a G3 QToF quadrupole-time-of-flight (Waters, USA) equipped with an ESI.

2. Synthesis and characterization.

**Synthesis of (Z)-3-(4-chlorophenyl)-5-(pyridin-2-ylmethylene)-2-thioxoimidazolidin-4-one (1).** Synthesis was performed according to the literature procedure.^{S1} From 200 mg (1.57 mmol) of 4-chloroaniline, by the reaction with 228 mg (1.57 mmol) of ethyl isothiocyanatoacetate, followed by addition of 185 mg (1.72 mmol) of pyridine-2-carbaldehyde and 97 mg (1.72 mmol) of solid KOH, **1** was obtained as a white-yellow powder. Yield: 401 mg (81%) after column chromatography in DCM:MeOH 20:1. ^1H NMR (400 MHz, CDCl_3) δ = 6.65 (s, 1H, $-\text{CH}=\text{}$) 7.30 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H, $\text{H}_\gamma\text{-Py}$) 7.34 - 7.39 (m, 2H, Ph) 7.46 (d, J = 7.8 Hz, 1H, $\text{H}_\alpha\text{-Py}$) 7.49–7.53 (m, 2H, Ph) 7.79 (td, J = 7.8, 1.8 Hz, 1H, $\text{H}_\beta\text{-Py}$) 8.72 (d, J = 4.0 Hz, 1H, $\text{H}_{\beta'}\text{-Py}$) 11.71 (br. s., 1H, NH) HRMS (ESI), m/z : calculated $\text{C}_{15}\text{H}_9\text{ClN}_3\text{OS}^-$: 314.0160 ($\text{M}-\text{H}^-$); found 314.0158 ($\text{M}-\text{H}^-$). Consistent with literature.^{S1}

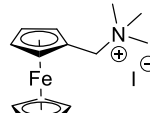
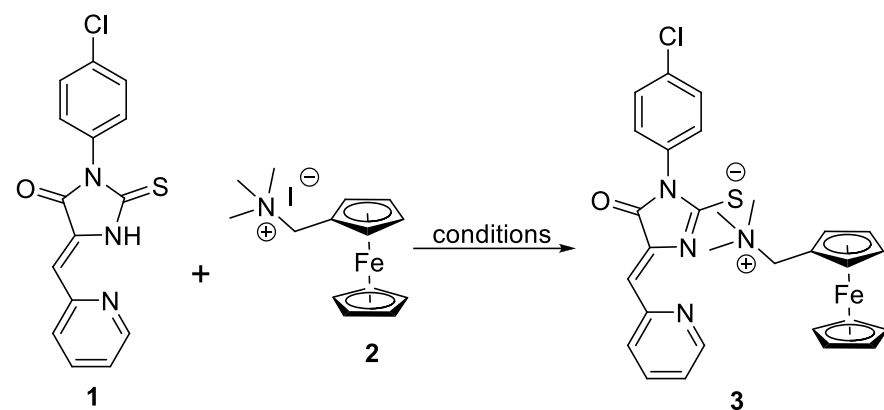
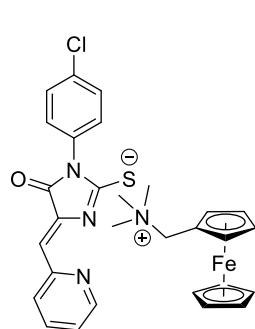
**Synthesis of *N,N,N*-trimethyl(ferrocenylmethyl) ammonium iodide (2).** To a stirred solution of 1.0 g (4.11 mmol) of *N,N*-dimethylaminomethylferrocene in 50 ml of dry diethyl ether was added 300 μL (4.82 mmol) of iodomethane. After 12 hours, the light yellow precipitate was filtered, washed with dry diethyl ether, and air-dried to constant weight. Yield: 1.5 g (95%), ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 2.90 (s, 9H, Me), 4.24 (s, 5H, C_5H_5), 4.34 - 4.38 (m, 2H, C_5H_4), 4.39 (s, 2H, CH_2), 4.49 (m, 2H, C_5H_4). Consistent with literature.^{S2}

Table S1. Optimization of alkylation conditions^a

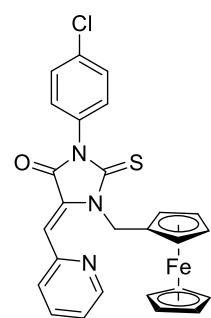
Entry	Base	Solvent	T/°C	Time/h	Result
1	KOH, 1 equiv.	MeOH	65	5	No reaction
2	MeONa, 1 equiv.	MeOH	65	5	No reaction
3	EtONa, 1 equiv.	EtOH	78	5	No reaction
4	K ₂ CO ₃ , 3 equiv.	MeCN	82	5	Decomposition
5	Et ₃ N, 1 equiv.	DMF	25	24	No reaction
6	Et ₃ N, 10 equiv.	DMF	25	24	Decomposition
7	K ₂ CO ₃ , 3 equiv.	DMF	25	24	Impure 3
8	KOH, 1 equiv.	EtOH/H ₂ O 1/1	25	2	Pure 3 ^b (90% yield)

^a All reactions were performed for compound **1** (0.32 mmol) and compound **2** (0.32 mmol). After completion of the reaction, the reaction mixture was diluted with twice the amount of water, the precipitate was filtered, dried, and analyzed by ¹H NMR. ^b Pure compound **3** precipitated spontaneously and was collected by filtration without additional workup.

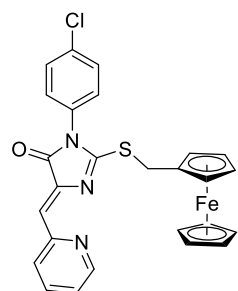


Synthesis of compound (3). 200 mg (0.62 mmol) of (Z)-3-(4-chlorophenyl)-5-(pyridin-2-ylmethylene)-2-thioxoimidazolidin-4-one **1** was added to a solution of 72 mg (1.28 mmol) of KOH in 20 ml of 50% aqueous ethanol. The resulting mixture was shaken in an ultrasonic bath until a completely transparent bright red solution formed. A solution of 244 mg (0.62 mmol) of *N,N,N*-trimethyl(ferrocenylmethyl) ammonium iodide **2** in 3 ml of 50% aqueous ethanol was added to the resulting solution with stirring. After 2 hours, the resulting light orange precipitate was filtered, washed with water until the washings were colorless, and dried in air to constant weight. Yield: 326 mg (90%). Crystals suitable for X-ray diffraction were obtained by recrystallization from 95% aqueous ethanol. Mp 184–186 °C (dec.), ¹H NMR (400 MHz, DMSO-*d*₆) δ = 2.89 (s, 9H, Me) 4.23 (s, 5H, C₅H₅) 4.35 (s, 2H, CH₂) 4.37 (br. s., 2H, C₅H₄) 4.47 (s, 2H, C₅H₄) 6.20 (br. s., 1H, –CH=) 7.15 (br. s., 1H, H_γ-Py) 7.29 (d, *J* = 8.3 Hz, 2H, Ph) 7.46 (d, *J* = 8.3 Hz, 2H, Ph) 7.77 (t, *J* = 7.7 Hz, 1H, H_{β'}-Py) 8.50 (br. s., 1H, H_β-Py) 8.81 (br. s., 1H, H_α-Py). ¹³C NMR (109 MHz, DMSO-*d*₆) δ = 51.4, 65.4, 68.9, 70.0, 71.9, 73.1, 108.9, 116.5, 120.9, 125.0, 128.0, 130.3, 132.0, 134.9, 135.8, 149.2, 154.5, 155.5, 185.6. IR (neat, ν/cm^{–1}): 3050 (CH), 1689 (cyclic amide), 1495 (ferrocene), 1416 (C=S), 1329 (Py), 870 (ferrocene), 825 (1,4-Ar). HRMS (ESI), *m/z*: calculated for C₁₄H₂₀FeN: 258.0945 (M_{cation})⁺; found, 258.0947 (M_{cation})⁺. calculated for C₁₅H₉ClN₃OS[–]: 314.0160 (M_{anion})[–]; found, 314.0156 (M_{anion})[–].

Self-alkylation of compound 3. Solution of 100 mg (0.175 mmol) of compound **3** in 1.5 ml of dry DMSO was heated at 150 °C in oil bath for 1 hour. After completion of the reaction, the reaction mixture was diluted with 3 ml of water and extracted into methylene chloride (2 × 2 ml). The organic extracts were combined, washed with water (3 × 4 ml), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The products were isolated and purified by column chromatography on silica gel using hexane:ethyl acetate (1:1) as eluent.



(Z)-1-ferrocenylmethyl-3-(4-chlorophenyl)-5-(pyridin-2-ylmethylene)-2-thioxoimidazolidin-4-one (4). First bright orange band with $R_f = 0.75$. Yield: 27 mg (30%) as a light orange powder. Mp 194–195 °C (dec.), ^1H NMR (400 MHz, CDCl_3) $\delta = 3.78$ (s, 2H, C_5H_4) 3.95 (t, $J = 1.8$ Hz, 2H, C_5H_4) 4.06 (s, 5H, C_5H_5) 6.02 (s, 2H, CH_2) 6.87 (s, 1H, $-\text{CH}=\text{}$) 7.27 - 7.31 (m, 2H, Ph) 7.42 (dd, $J = 7.6, 4.9$ Hz, 1H, $\text{H}\beta'$ -Py) 7.45 - 7.49 (m, 2H, Ph) 7.59 (d, $J = 8.0$ Hz, 1H, $\text{H}\gamma$ -Py) 7.86 (td, $J = 7.8, 1.8$ Hz, 1H, $\text{H}\beta$ -Py) 8.89 (d, $J = 4.2$ Hz, 1H, $\text{H}\alpha$ -Py). ^{13}C NMR (109 MHz, CDCl_3) $\delta = 45.3, 68.1, 68.6, 69.5, 81.8, 112.6, 123.1, 127.7, 128.4, 129.3, 129.6, 131.9, 135.1, 137.0, 149.2, 151.2, 152.3, 178.9$. IR (neat, ν/cm^{-1}): 3051 (CH), 1734 (cyclic amide), 1724 (cyclic amide), 1496 (ferrocene), 1392 (C=S), 1259 (Py), 1015 (ferrocene), 812 (1,4-Ar). HRMS (ESI), m/z : calculated for $\text{C}_{26}\text{H}_{20}\text{ClFeN}_3\text{OS}$: 513.0366 (M) $^+$; found, 513.0370 (M) $^+$.



(Z)-3-(4-chlorophenyl)-2-((ferrocenylmethyl)thio)-5-(pyridin-2-ylmethylene)-3,5-dihydro-4H-imidazol-4-one (5). Second yellow band with $R_f = 0.5$. Yield: 18 mg (20%) as a dark yellow powder. Mp 227–229 °C (dec.), ^1H NMR (400 MHz, CDCl_3) $\delta = 4.19$ (t, $J = 1.8$ Hz, 2H, C_5H_4) 4.26 (s, 5H, C_5H_5) 4.55 (t, $J = 1.8$ Hz, 2H, C_5H_4) 5.28 (s, 2H, CH_2) 6.98 (s, 1H, $-\text{CH}=\text{}$) 7.22 - 7.26 (m, 1H, $\text{H}\beta'$ -Py) 7.28 - 7.31 (m, 2H, Ph) 7.46 - 7.50 (m, 2H, Ph) 7.70 (td, $J = 7.8, 1.8$ Hz, 1H, $\text{H}\beta$ -Py) 8.62 (d, $J = 8.1$ Hz, 1H, $\text{H}\gamma$ -Py) 8.68 (d, $J = 4.0$ Hz, 1H, $\text{H}\alpha$ -Py). ^{13}C NMR (109 MHz, CDCl_3) $\delta = 43.3, 68.6, 68.9, 70.0, 80.5, 120.9, 123.5, 125.6, 129.1, 129.3, 129.7, 131.4, 135.1, 136.1, 149.6, 151.2, 161.0, 176.0$. IR (neat, ν/cm^{-1}): 3062 (CH), 1724 (cyclic amide), 1714 (cyclic amide), 1490 (ferrocene), 1339 ($\text{CH}_2\text{-S}$), 1257 (Py), 1013 (ferrocene), 812 (1,4-Ar), 630 (S-C). HRMS (ESI), m/z : calculated for $\text{C}_{26}\text{H}_{21}\text{ClFeN}_3\text{OS}$: 514.0444 ($\text{M}+\text{H}$) $^+$; found, 514.0448 ($\text{M}+\text{H}$) $^+$.

3. Figures:

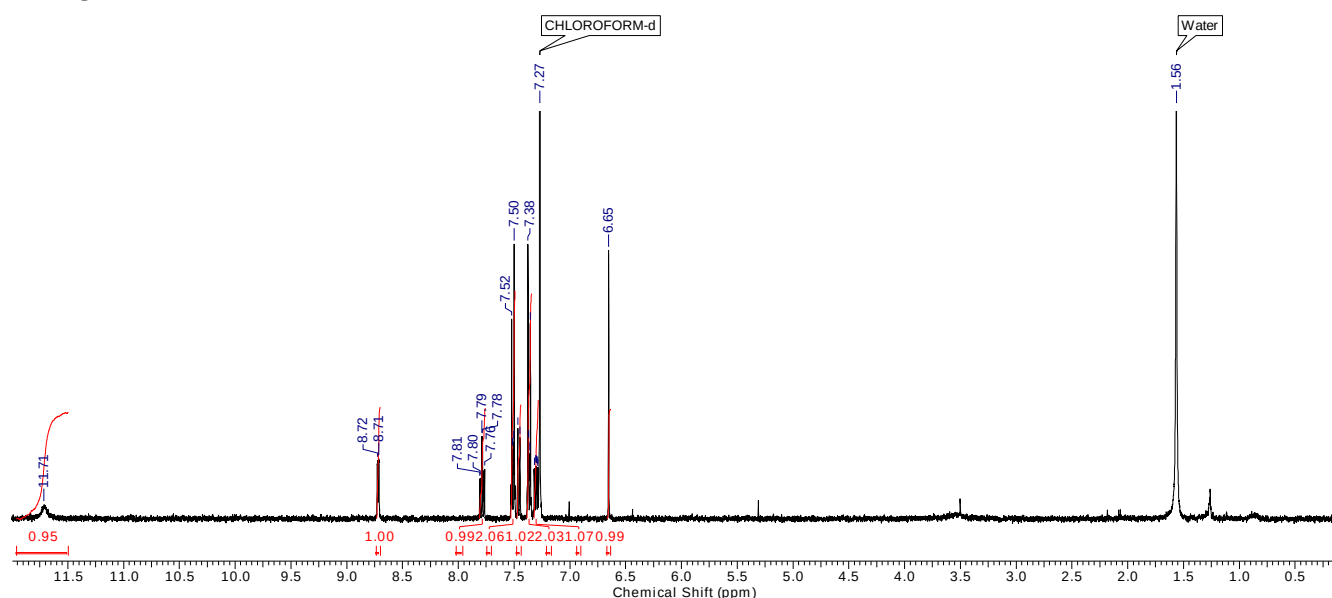


Figure S1. ^1H NMR spectra of **1**.

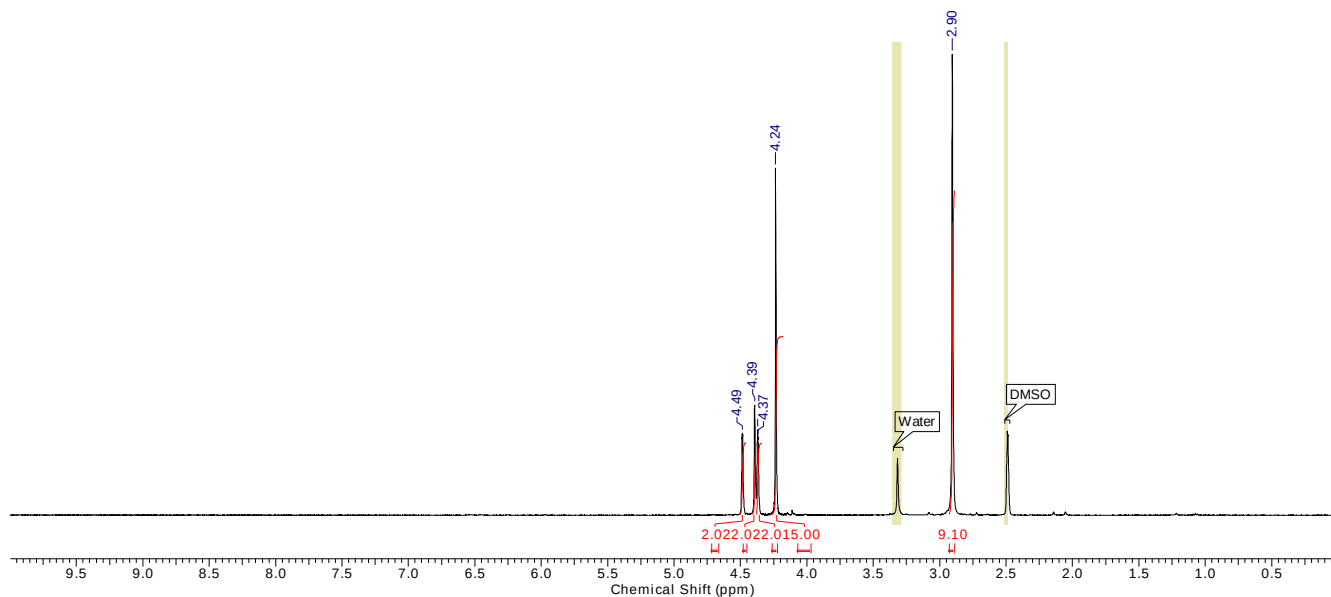


Figure S2. ¹H NMR spectra of **2**.

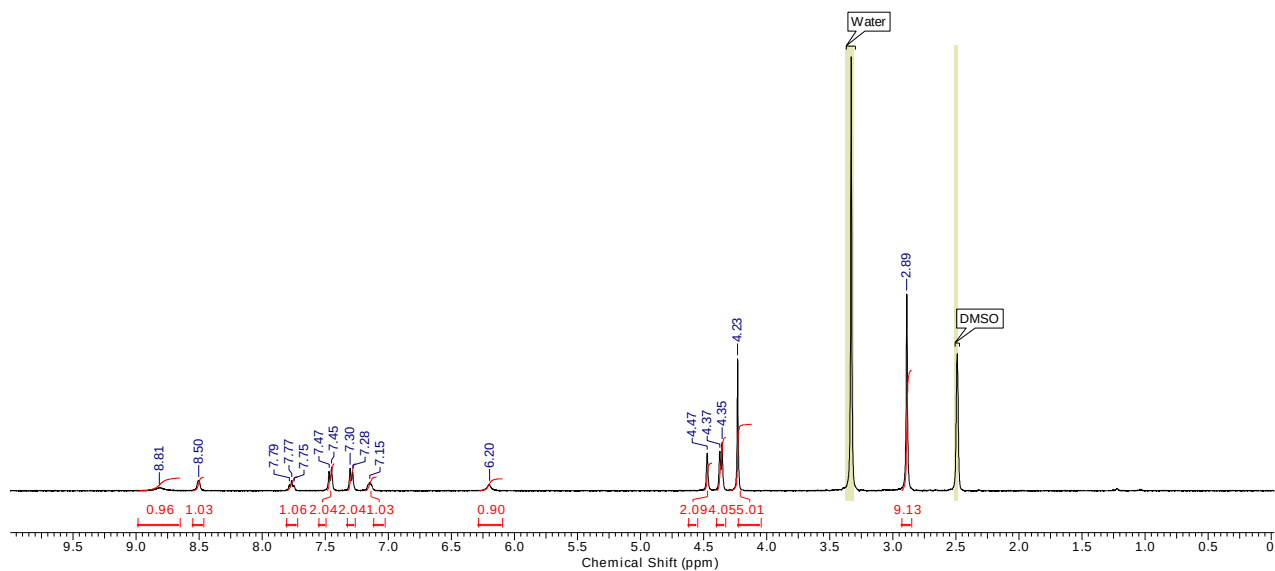


Figure S3. ¹H NMR spectra of **3**.

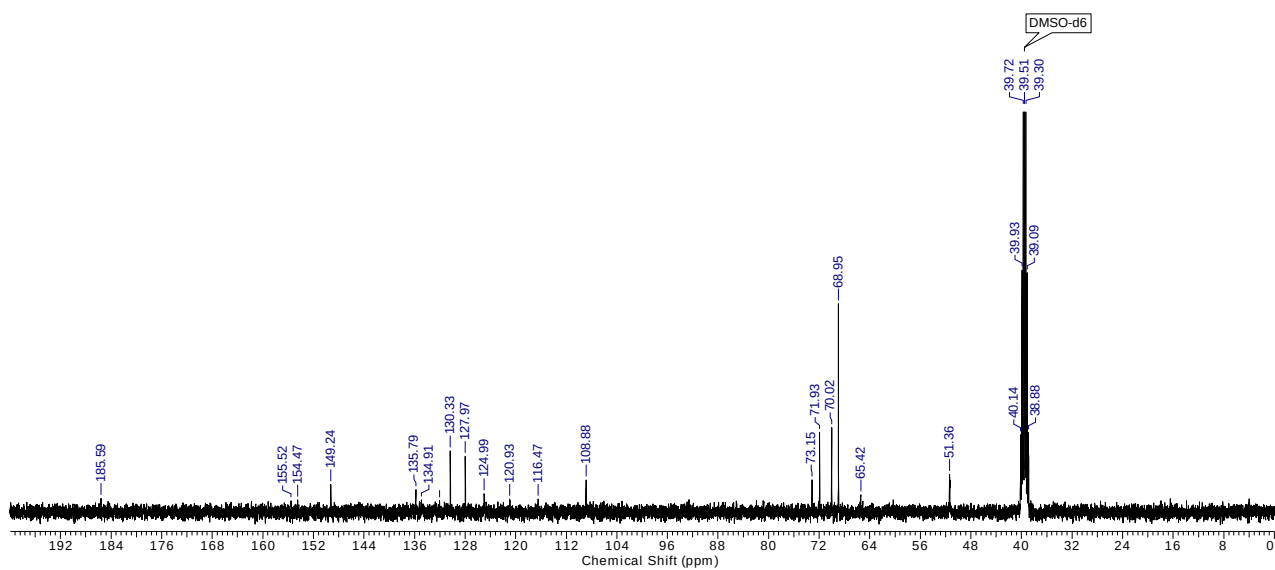


Figure S4. ¹³C NMR spectra of **3**.

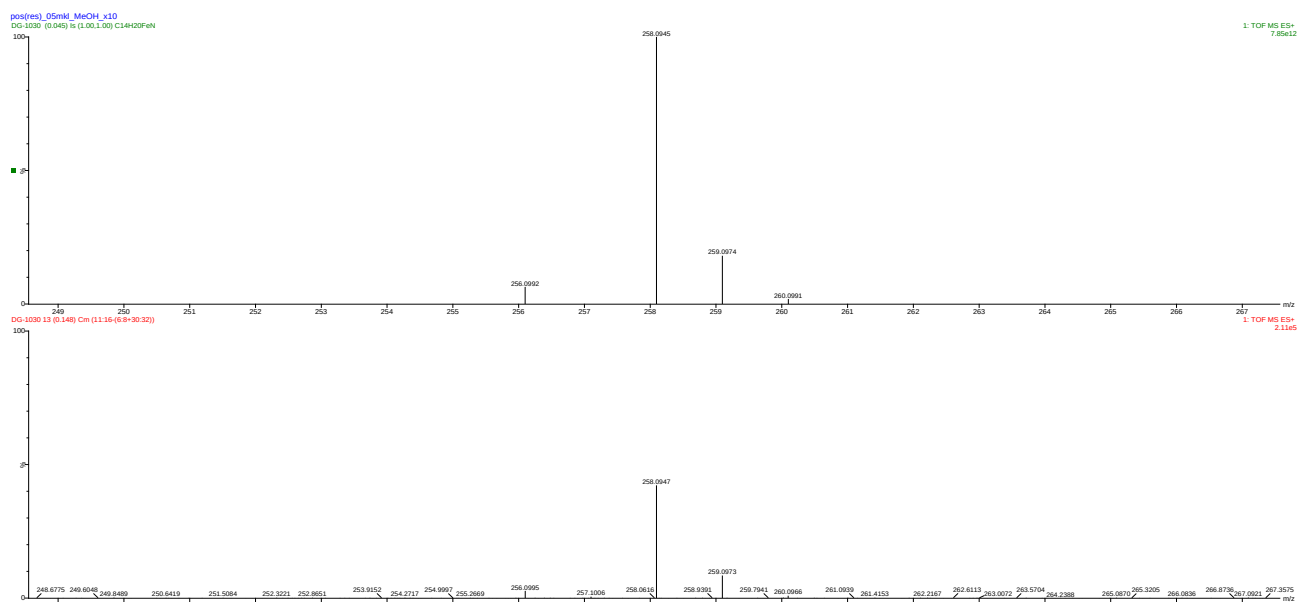


Figure S5. Predicted (top) and experimental (bottom) HRMS spectra of compound **3** (positive mod).

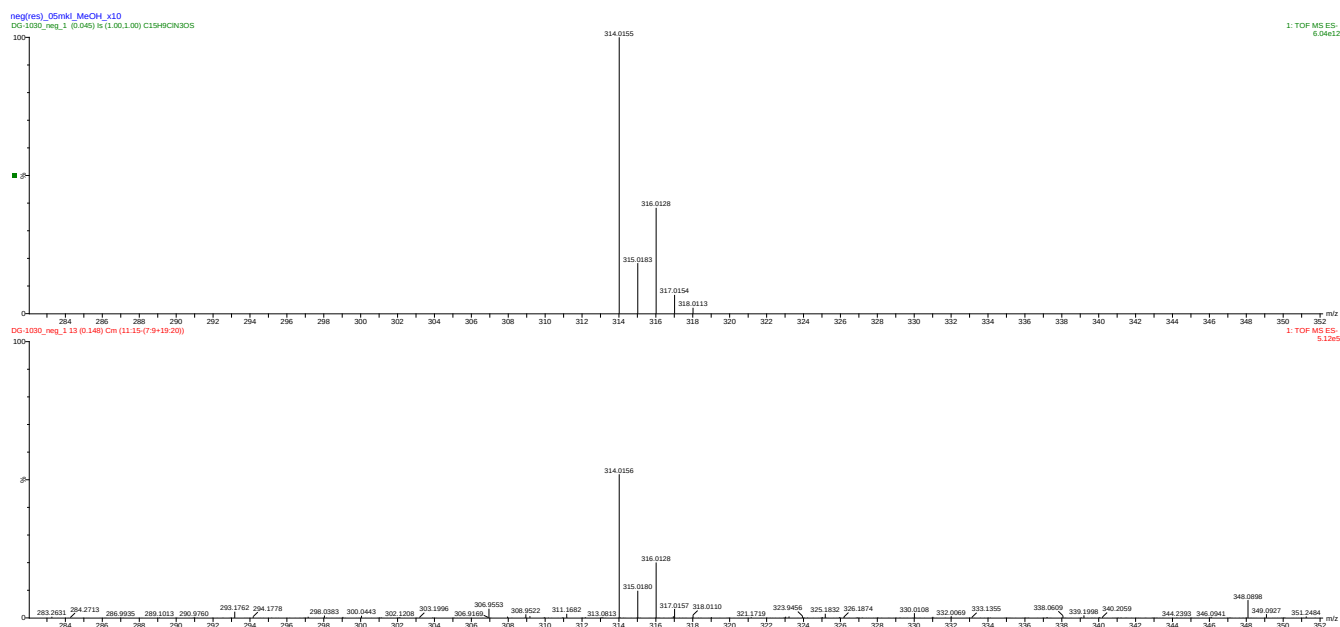


Figure S6. Predicted (top) and experimental (bottom) HRMS spectra of compound **3** (negative mod).

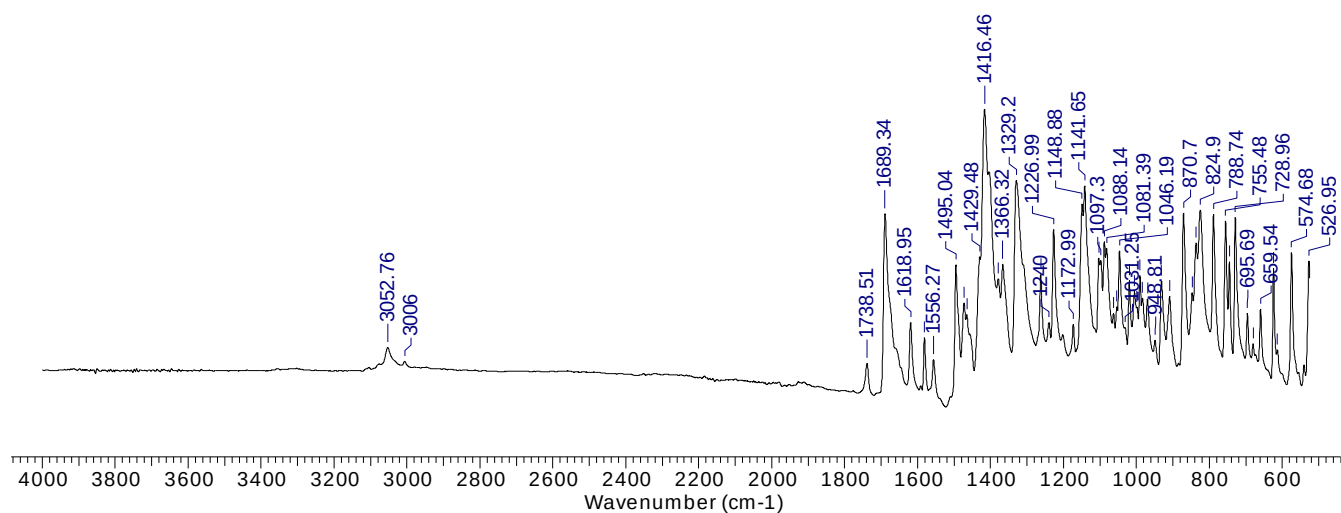


Figure S7. IR spectrum of compound **3**.

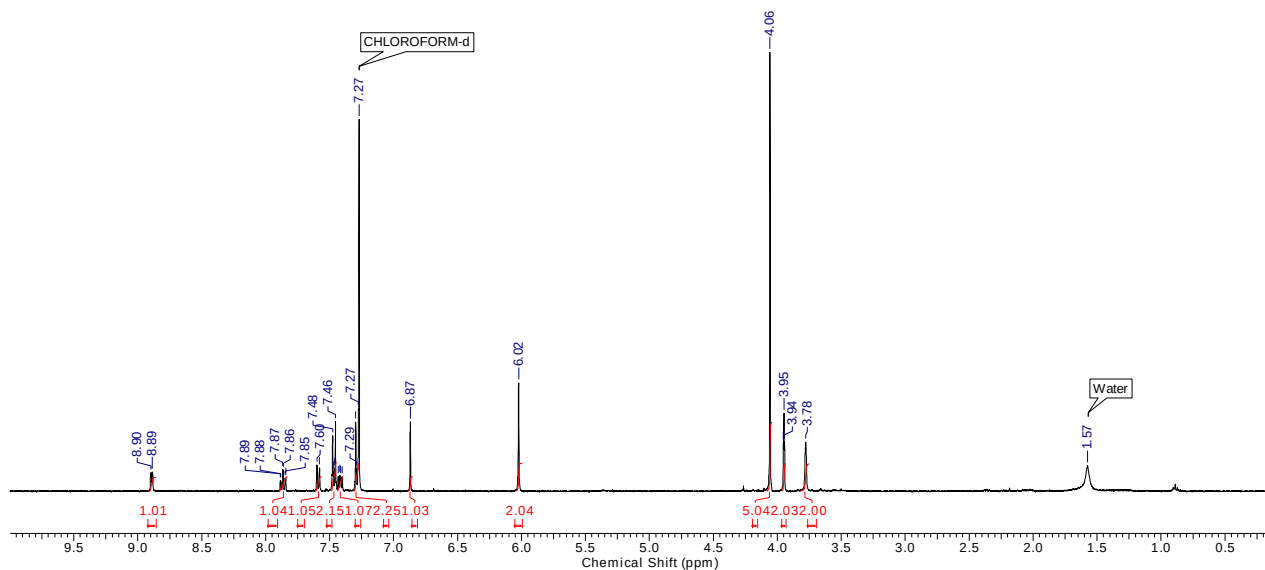


Figure S8. ^1H NMR spectra of **4**.

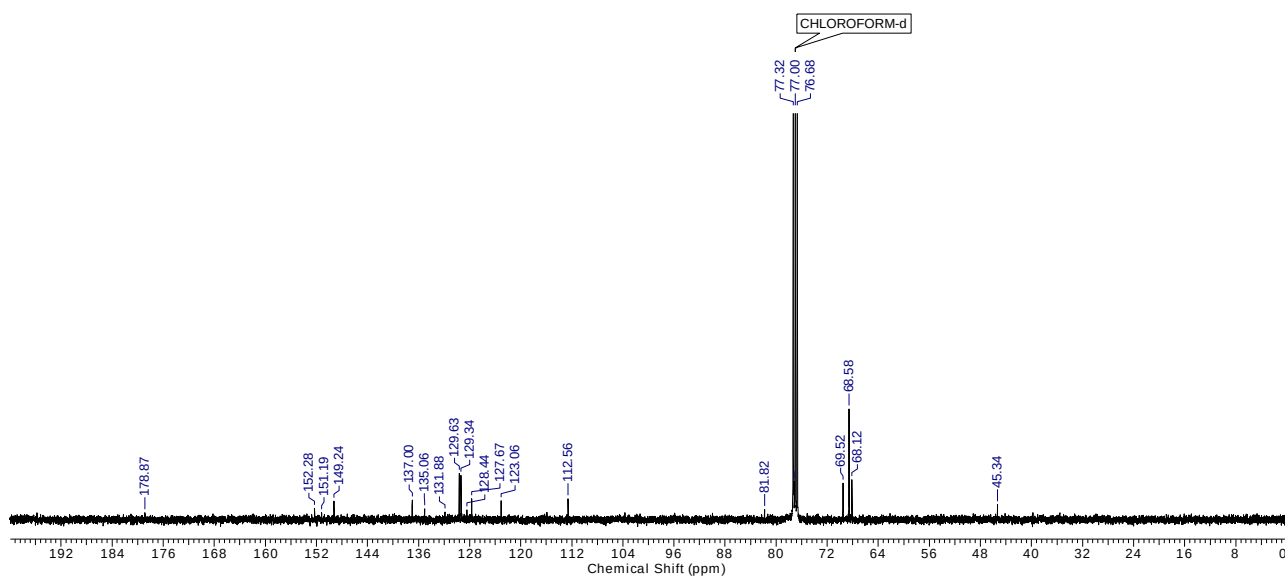


Figure S9. ^{13}C NMR spectra of **4**.

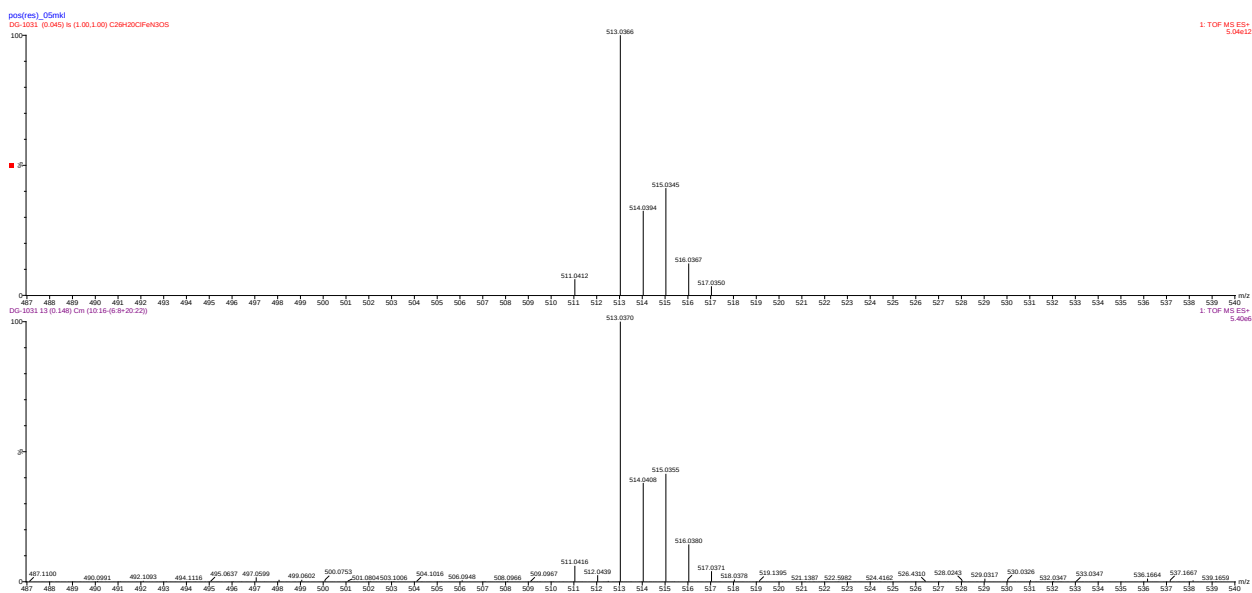


Figure S10. Predicted (top) and experimental (bottom) HRMS spectra of compound **4** (positive mod).

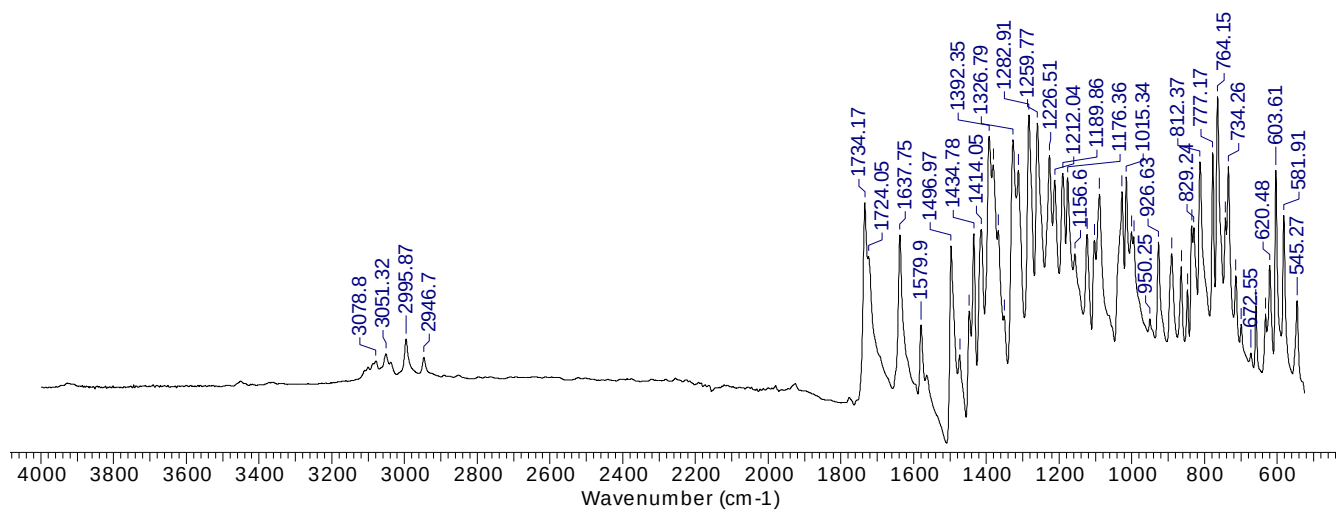


Figure S11. IR spectrum of compound 4.

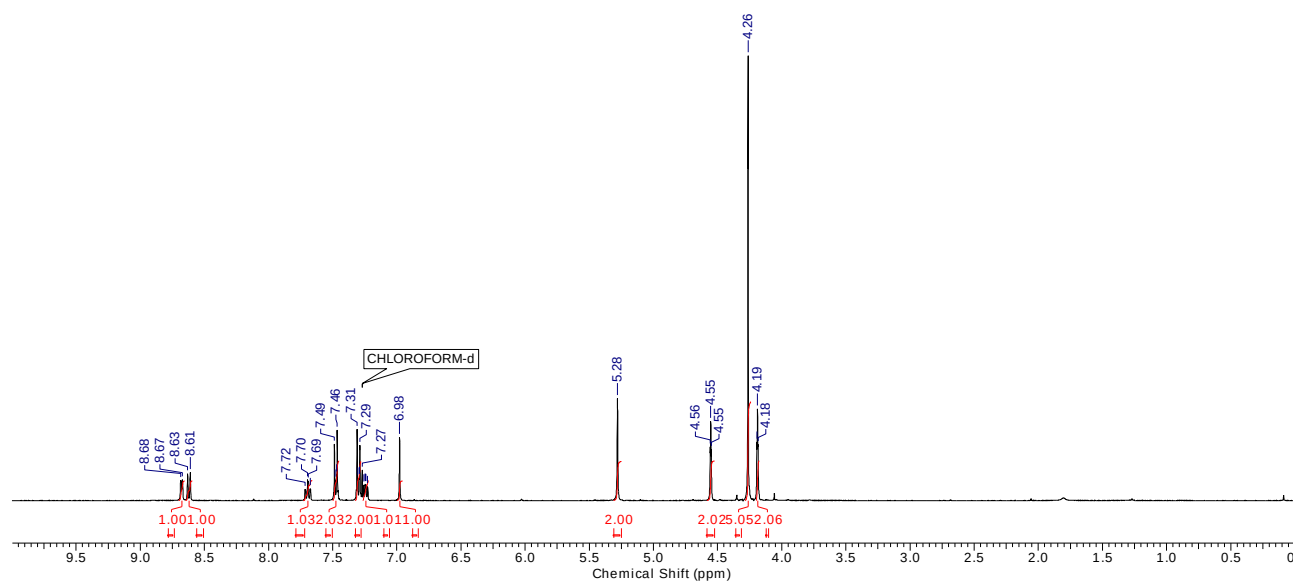


Figure S12. ¹H NMR spectra of 5.

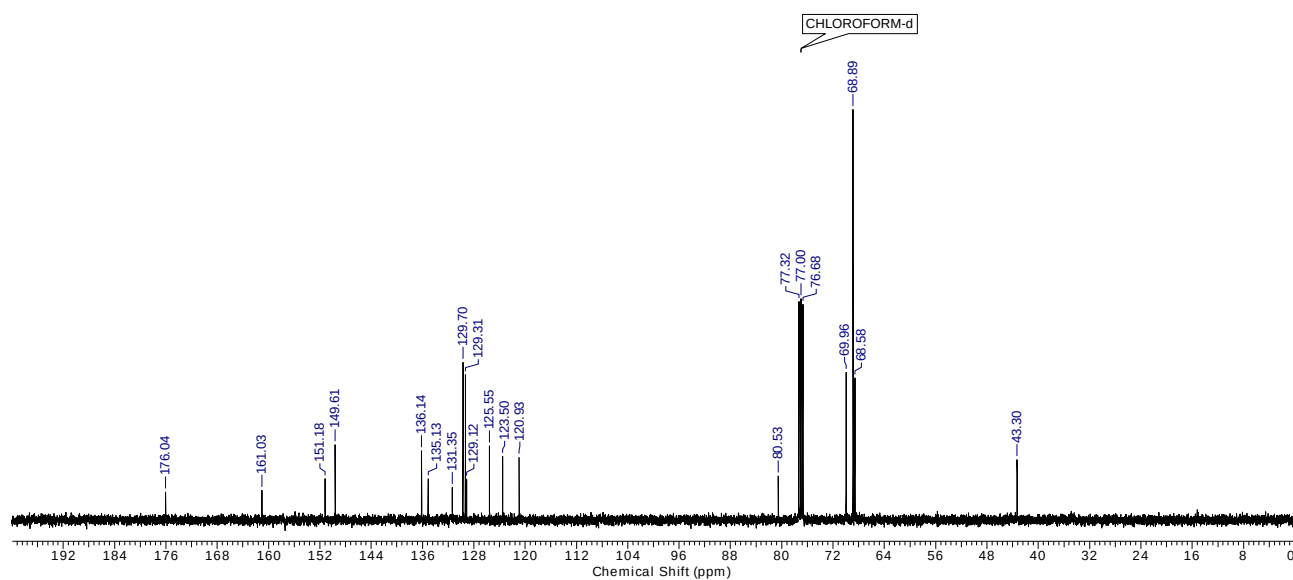


Figure S13. ¹³C NMR spectra of 5.

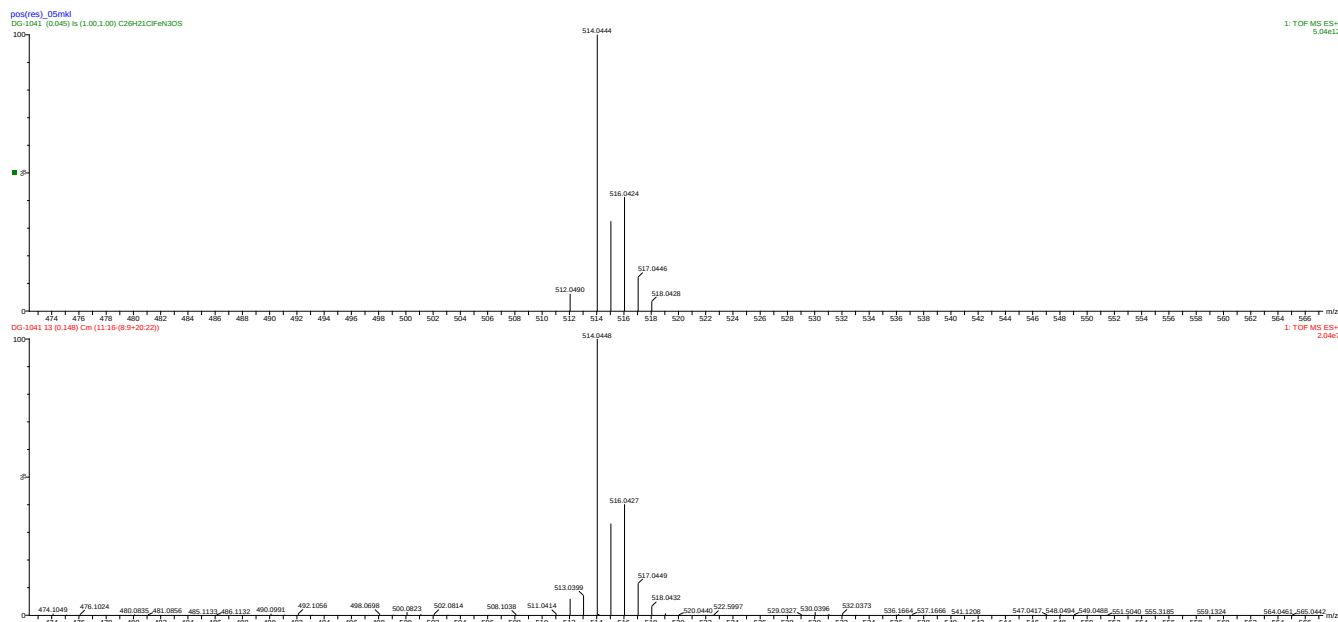


Figure S14. Predicted (top) and experimental (bottom) HRMS spectra of compound **5** (positive mod).

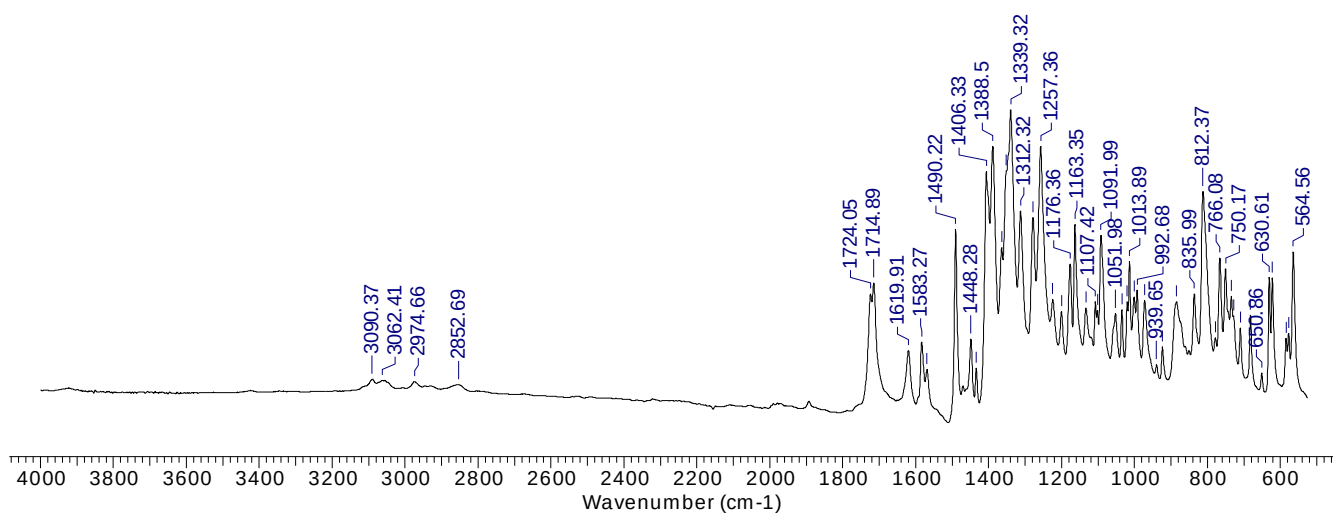


Figure S15. IR spectrum of compound **5**.

References

- S1.** O. O. Krasnovskaya, D. A. Guk, A. E. Naumov, V. N. Nikitina, A. S. Semkina, K. Yu. Vlasova, V. Pokrovsky, O. O. Ryabaya, S. S. Karshieva, D. A. Skvortsov, I. V. Zhirkina, R. R. Shafikov, P. V. Gorelkin, A. N. Vaneev, A. S. Erofeev, D. M. Mazur, V. A. Tafenko, V. I. Pergushov, M. Ya. Melnikov, M. A. Soldatov, V. V. Shapovalov, A. V. Soldatov, R. A. Akasov, V. M. Gerasimov, D. A. Sakharov, A. A. Moiseeva, N. V. Zyk, E. K. Beloglazkina, A. G. Majouga, *J. Med. Chem.*, 2020, **63**, 13031; <https://doi.org/10.1021/acs.jmedchem.0c01196>.
- S2.** Z. Li, G. Li, L. Jiang, J. Li, G. Sun, C. Xia, F. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 1494; <https://doi.org/10.1002/anie.201409579>.