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Electronic Supplementary Information

Electrochemical Reduction of 5-Benzylidene Thiazolidine-2,4-diones: A Greener Approach to the Preparation of Glitazone APIs

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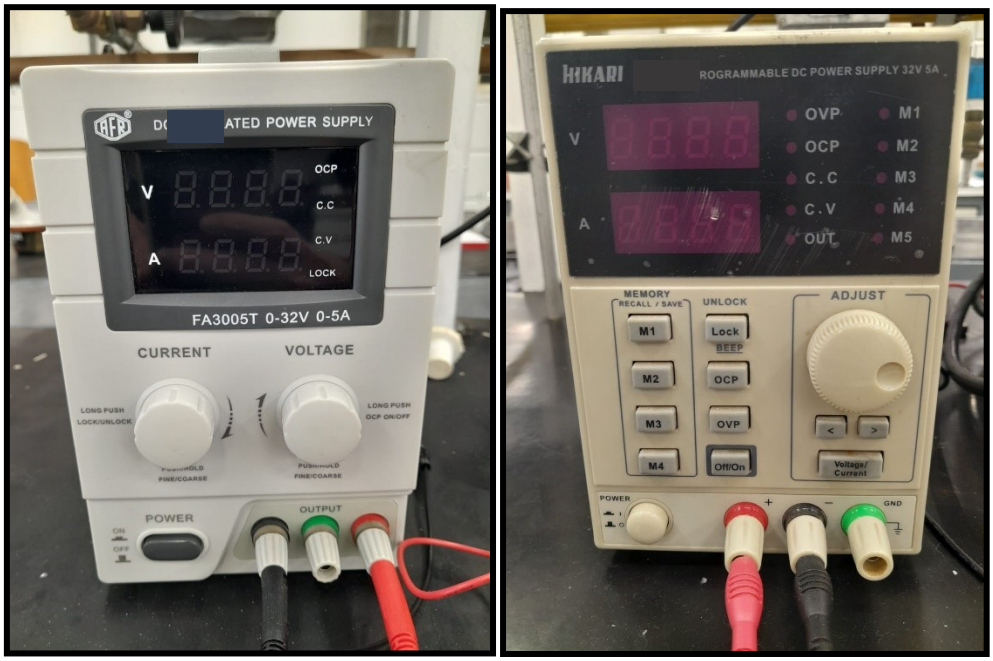
1. Experimental section

1.1. General remarks

All purchased chemicals were used as received without further purification. Analytical TLC was performed on TLC plates (silica gel 60 F254) and visualized employing a UV lamp and/or phosphomolybdic acid as revelator. Yields refer to chromatographically purified and spectroscopically pure compounds. Both ^{1}H and ^{13}C $\{^{1}H\}$ NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts for ^{1}H NMR were reported as δ (parts per million) relative to the solvents signals of $CDCl_3$ or DMSO-d_6 at 7.26 ppm (singlet) and 2.50 (quintet), respectively. Chemical shifts for ^{13}C NMR were reported as δ (parts per million) relative to the solvent signals of $CDCl_3$ or DMSO-d_6 at 77.0 (triplet) and 39.5 (septet), respectively. Chemical shifts are reported employing the following abbreviation pattern: *br* (broad), *s* (singlet), *d* (doublet), *dd* (doublet of doublet), *dt* (doublet of triplet), *t* (triplet), *q* (quartet), and *m* (multiplet).

Thiazolidine-2,4-dione was prepared following literature protocols.[1,2] 5-Substituted thiazolidine-2,4-diones were synthesized using a method previously developed by our research group.[3] The electrochemical reactions were carried out using a power supply (AFR – model FA3005P or Hikari – model HF-3205P).

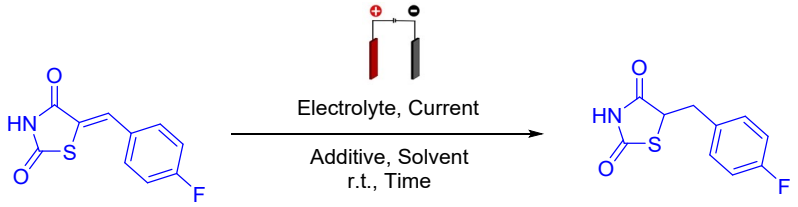
Figure S1. Power sources used in the electrochemical reactions.



1.2. Reaction optimization

For the preliminary optimization of the reaction conditions, the crude reaction mixture was diluted and directly analyzed by gas chromatography using a mass spectrometry detector (GC-MS). Since the formation of side-products was not detected during the synthesis (except for entry 1 of Table S1), the reported conversions refer to relative areas (in percentage) of product **1a** and the starting material (*Z*)-5-(4-fluorobenzylidene)thiazolidine-2,4-dione). After the selection of the best overall conditions, the samples were also analyzed through the ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard for the determination of the quantitative NMR yield (values in brackets in Tables S1 and S2).

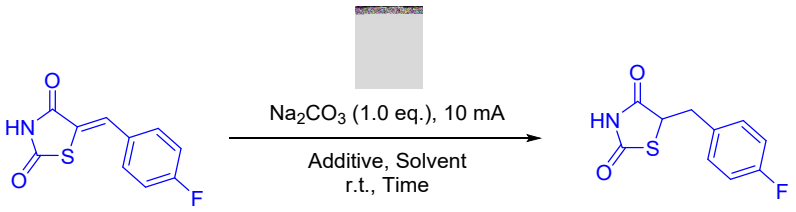
Table S1. Initial reaction optimization using a diversity of electrolytes.



Entry	Electrode	Electrolyte (eq.)	Current	Time	Solvent	Additive (eq.)	GC-MS conversion (^{1}H NMR yield)
1	C(+) | C(-)	Bu_4NBF_4 (1.0)	10 mA	2 h	DMSO	H_2O (5.5 eq.)	34% (31%)[a]
2	C(+) | C(-)	$LiClO_4$ (1.0)	10 mA	2 h	DMSO	H_2O (5.5 eq.)	70% (71%)
3	C(+) | C(-)	$LiClO_4$ (1.5)	10 mA	2 h	DMSO	H_2O (5.5 eq.)	67%
4	C(+) | C(-)	$LiClO_4$ (1.0)	5 mA	2 h	DMSO	H_2O (5.5 eq.)	10%
5	C(+) | C(-)	$LiClO_4$ (1.0)	15 mA	2 h	DMSO	H_2O (5.5 eq.)	65%
6	Pt(+) | Pt(-)	$LiClO_4$ (1.0)	10 mA	1 h	DMSO	H_2O (5.5 eq.)	6%
7	Pt(+) | Pt(-)	$LiClO_4$ (1.0)	10 mA	2 h	DMSO	H_2O (5.5 eq.)	9%
8	Pt(+) | C(-)	$LiClO_4$ (1.0)	10 mA	2 h	DMSO	H_2O (5.5 eq.)	41%
9	C(+) | Pt(-)	$LiClO_4$ (1.0)	10 mA	2 h	DMSO	H_2O (5.5 eq.)	4%
10	C(+) | C(-)	NaCl (1.0)	10 mA	2 h	DMSO	H_2O (5.5 eq.)	76% (78%)
11	C(+) | C(-)	NaCl (0.5)	10 mA	2 h	DMSO	H_2O (5.5 eq.)	65%
12	C(+) | C(-)	NaCl (1.5)	10 mA	2 h	DMSO	H_2O (5.5 eq.)	73%
13	C(+) | C(-)	NaCl (1.0)	10 mA	2 h	DMSO	None	35%
14	C(+) | C(-)	NaCl (1.0)	10 mA	2 h	H_2O	None	2%
15	C(+) | C(-)	NaCl (1.0)	10 mA	2 h	CH_3CN	H_2O (5.5 eq.)	25%

[a] This condition also led to the formation of undesirable *N*-alkylated side-products.

Table S2. Reaction optimization using a Na_2CO_3 as electrolyte.



Entry	Electrode	Time	Solvent	Additive (eq.)	GC-MS conversion (^{1}H NMR yield)
1	C(+) | C(-)	2 h	CH_3CN	H_2O (5.5 eq.)	35%
2	C(+) | C(-)	1 h	DMSO	H_2O (5.5 eq.)	75%
3	C(+) | C(-)	2 h	DMSO	H_2O (5.5 eq.)	89% (90%)[a]
4	C(+) |RVC(-)	1 h	DMSO	H_2O (5.5 eq.)	36%
5	C(+) |RVC(-)	2 h	DMSO	H_2O (5.5 eq.)	23%
6	C(+) |SS(-)	1 h	DMSO	H_2O (5.5 eq.)	3%
7	C(+) |SS(-)	2 h	DMSO	H_2O (5.5 eq.)	2% (0%)
8	C(+) |Pt(-)	1 h	DMSO	H_2O (5.5 eq.)	0%
9	C(+) |Pt(-)	2 h	DMSO	H_2O (5.5 eq.)	0% (0%)
10	C(+) | C(-)[b]	2 h	DMSO	H_2O (5.5 eq.)	43%
11	C(+) | C(-)	2 h	DMSO : H_2O (1:1 *v*/*v*)	None	27%
12	C(+) | C(-)	1 h	DMSO	H_2O (11.0 eq.)	72%
13	C(+) | C(-)	2 h	DMSO	H_2O (11.0 eq.)	84% (82%)
14	C(+) | C(-)	2 h	DMSO	None	29% (26%)

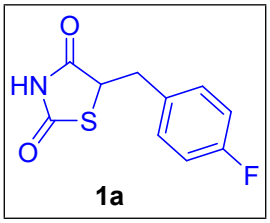
[a] 81% isolated yield; [b] Reaction with polarity reversal (30 seconds).

1.3. General procedure for the preparation of compounds 1a-1u

A 10 mL flask equipped with graphite in both electrodes (anode and cathode) was charged with 1.0 equivalent (0.5 mmol) of 5-arylidene-thiazolidine-2,4-dione and 1.0 equivalent (0.5 mmol) of sodium carbonate, followed by the addition of 5.0 mL of dimethylsulfoxide and 100 µL of distilled water (5.5 mmol). The reaction mixture was kept under constant current (10 mA) at room temperature for 2 hours. The resulting mixture was washed with 15 mL of a 0.1 mol L^{-1} HCl solution and extracted three times with ethyl acetate (3 × 15 mL). The combined organic phases were concentrated under reduced pressure, and the product purified through column chromatography.

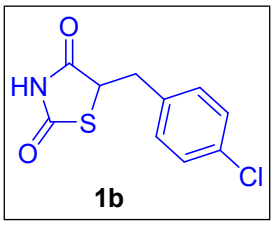
Figure S2. Reaction flask and graphite electrodes used in the electrochemical reactions.

1.4. Characterization data for compounds 1a-1u



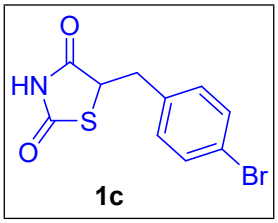
1a

5-(4-Fluorobenzyl)thiazolidine-2,4-dione (**1a**)[4]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1a** as a yellow solid (91.0 mg, 0.405 mmol, 81% yield). m.p.: 105.2-106.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (br, 1H), m (7.22-7.18, 2H), 6.95 (t, *J* = 8.4 Hz, 2H), 4.45 (dd, *J* = 9.4 Hz, *J* = 4.0 Hz, 1H), 3.41 (dd, *J* = 14.2 Hz, *J* = 3.9 Hz, 1H), 3.08 (dd, *J* = 14.2 Hz, *J* = 9.4 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.6, 170.8, 162.4 (d, *J* = 244.9 Hz), 131.4 (d, *J* = 3.4 Hz), 131.0 (d, *J* = 7.9 Hz), 115.9 (d, *J* = 21.3 Hz), 53.5, 37.8. ^{19}F NMR (377 MHz, CDCl3) δ 114.9. FT-IR (KBr): 3436, 3167, 3052, 2811, 1751, 1693, 1601, 1511, 1330, 1305, 1224, 1158, 1096, 829, 711.



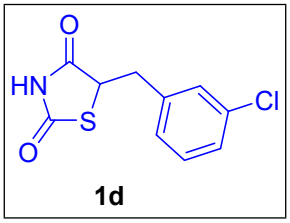
1b

5-(4-Chlorobenzyl)thiazolidine-2,4-dione (**1b**)[5]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1b** as a yellow solid (95.0 mg, 0.39 mmol, 78% yield). m.p.: 108.4-110.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br, 1H), 7.34-7.30 (m, 2H), 7.26-7.16 (m, 2H), 4.52 (dd, *J* = 9.4 Hz, *J* = 4.0 Hz, 1H), 3.47 (dd, *J* = 14.2 Hz, *J* = 3.9 Hz, 1H), 3.16 (dd, *J* = 14.2 Hz, *J* = 9.3 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.8, 170.0, 134.1, 133.9, 130.8, 129.2, 53.1, 38.0.



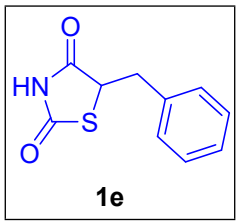
1c

5-(4-Bromobenzyl)thiazolidine-2,4-dione (**1c**)[4]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1c** as a white solid (122 mg, 0.425 mmol, 85% yield). m.p.: 224.0-225.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br, 1H), 7.37-7.29 (m, 2H), 7.25-7.23 (m, 2H), 4.55 (dd, *J* = 9.9 Hz, *J* = 3.8 Hz, 1H), 3.56 (dd, *J* = 14.1 Hz, *J* = 3.9 Hz, 1H), 3.14 (dd, *J* = 14.1 Hz, *J* = 9.9 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.2, 170.5, 135.9, 129.3, 129.0, 127.8, 53.6, 38.8.



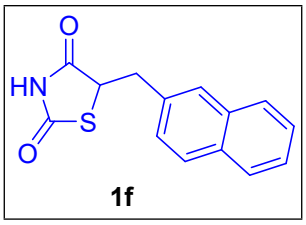
1d

5-(3-Chlorobenzyl)thiazolidine-2,4-dione (**1d**)[6]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1d** as a yellow solid (100 mg, 0.41 mmol, 82% yield). m.p.: 97.0-98.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br, 1H), 7.21-7.19 (m, 2H), 7.18-7.16 (m, 1H), 7.06-7.04 (m, 1H), 4.45 (dd, *J* = 9.7 Hz, *J* = 3.9 Hz, 1H), 3.44 (dd, *J* = 14.1 Hz, *J* = 4.0 Hz, 1H), 3.06 (dd, *J* = 14.1 Hz, *J* = 9.7 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.2, 170.4, 137.8, 134.8, 130.3, 129.5, 128.1, 127.5, 53.1, 38.3.



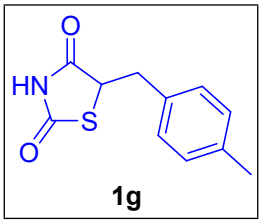
1e

5-Benzylthiazolidine-2,4-dione (**1e**)[4]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1e** as a white solid (89.0 mg, 0.43 mmol, 86% yield). m.p.: 77.6-78.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (br, 1H), 7.28-7.19 (m, 3H), 7.18-7.15 (m, 2H), 4.47 (dd, *J* = 9.9 Hz, *J* = 3.9 Hz, 1H), 3.48 (dd, *J* = 14.1 Hz, *J* = 3.9 Hz, 1H), 3.05 (dd, *J* = 14.0 Hz, *J* = 10.0 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.8, 171.1, 135.9, 129.3, 129.0, 127.8, 53.6, 38.8.



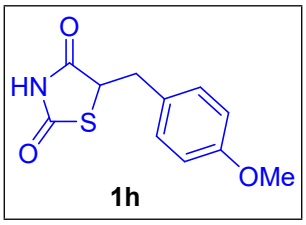
1f

5-(Naphthalen-2-ylmethyl)thiazolidine-2,4-dione (**1f**)[7]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1f** as a yellow solid (103 mg, 0.40 mmol, 80% yield). m.p.: 138.8-140.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (br, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.54-7.45 (m, 2H), 7.38-7.31 (m, 2H), 4.64 (dd, *J* = 11.4 Hz, *J* = 3.4 Hz, 1H), 4.25 (dd, *J* = 14.4 Hz, *J* = 3.3 Hz, 1H), 3.26 (dd, *J* = 14.3 Hz, *J* = 11.5 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.5, 170.6, 134.2, 132.3, 131.2, 129.4, 128.8, 127.4, 127.0, 126.3, 125.6, 122.9, 52.9, 36.9.



1g

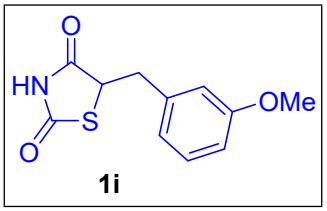
5-(4-Methylbenzyl)thiazolidine-2,4-dione (**1g**)[6]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1g** as a white solid (85.0 mg, 0.385 mmol, 77% yield). m.p.: 90.2-91.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br, 1H), 7.08-7.03 (m, 4H), 4.45 (dd, *J* = 9.8 Hz, *J* = 3.9 Hz, 1H), 3.43 (dd, *J* = 14.1 Hz, *J* = 3.9 Hz, 1H), 3.03 (dd, *J* = 14.1 Hz, *J* = 9.8 Hz, 1H), 2.26 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.2, 170.5, 137.4, 132.7, 129.6, 129.0, 53.6, 38.3, 21.1.



1h

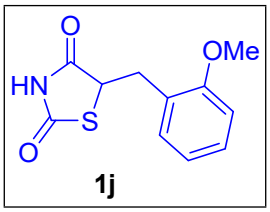
5-(4-Methoxybenzyl)thiazolidine-2,4-dione (**1h**)[4]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1h** as a white solid (107 mg, 0.45 mmol, 90% yield). m.p.: 113.2-114.8 °C. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 12.02 (br, 1H), 7.23-7.19 (m, 2H), 6.94-6.91 (m, 2H), 4.92 (dd, *J* = 9.0 Hz, *J* = 4.3 Hz, 1H), 3.71 (s, 3H), 3.35 (dd, *J* = 14.1 Hz, *J* = 4.3 Hz, 1H), 3.11 (dd, *J* = 14.2 Hz, *J* = 9.0 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 175.8, 171.8, 158.3, 130.4, 128.6, 113.8, 55.0, 53.1, 36.3.



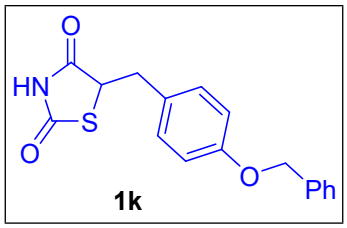
1i

5-(3-Methoxybenzyl)thiazolidine-2,4-dione (**1i**)[8]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1i** as a yellow oil (70.0 mg, 0.295 mmol, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (br, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.76-6.73 (m, 2H), 6.70-6.69 (m, 1H), 4.45 (dd, *J* = 10.1 Hz, *J* = 3.9 Hz, 1H), 3.72 (s, 3H), 3.46 (dd, *J* = 14.1 Hz, *J* = 3.9 Hz, 1H), 3.00 (dd, *J* = 14.0 Hz, *J* = 10.2 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.9, 171.3, 159.9, 137.6, 130.1, 121.4, 114.9, 113.0, 55.3, 53.6, 38.8.



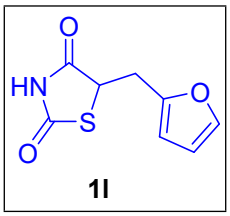
1j

5-(2-Methoxybenzyl)thiazolidine-2,4-dione (**1j**)[6]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1j** as a yellow solid (82.0 mg, 0.345 mmol, 69% yield). m.p.: 138.7-140.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (br, 1H), 7.23-7.19 (m, 1H), 7.09-7.06 (m, 1H), 6.89-6.79 (m, 2H), 4.68 (dd, *J* = 10.3 Hz, *J* = 4.4 Hz, 1H), 3.78 (s, 3H), 3.70 (dd, *J* = 13.7 Hz, *J* = 4.4 Hz, 1H), 2.86 (dd, *J* = 13.7 Hz, *J* = 10.3 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.0, 171.4, 157.5, 131.0, 129.3, 124.7, 120.8, 110.6, 55.4, 51.8, 34.6.



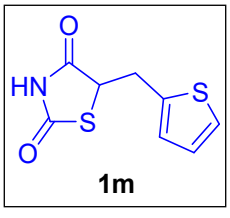
1k

5-(4-(benzyloxy)benzyl)thiazolidine-2,4-dione (**1k**): The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1k** as a yellow solid (127 mg, 0.41 mmol, 81% yield). m.p.: 137.6-138.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (br, 1H), 7.44-7.32 (m, 5H), 7.17-7.13 (m, 2H), 6.95-6.91 (m, 2H), 5.05 (s, 2H), 4.51 (dd, *J* = 9.5 Hz, *J* = 3.9 Hz, 1H), 3.46 (dd, *J* = 14.2 Hz, *J* = 3.9 Hz, 1H), 3.10 (dd, *J* = 14.2 Hz, *J* = 9.5 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.5, 170.8, 158.4, 136.9, 130.5, 128.8, 128.2, 128.0, 127.6, 115.3, 55.0, 53.1, 36.3. HRMS (ESI-TOF): *m/z* $[M + H]^+$ Calcd for $C_{17}H_{15}NO_3S$ 314.0851; Found 314.0843.



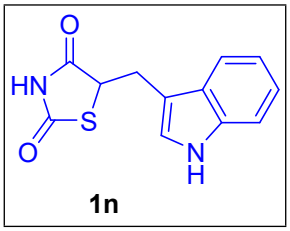
1l

5-(Furan-2-ylmethyl)thiazolidine-2,4-dione (**1l**): The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1l** as a red solid (80.0 mg, 0.405 mmol, 81% yield). m.p.: 81.5-83.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (br, 1H), 7.29-7.28 (m, 1H), 6.26-6.25 (m, 1H), 6.12-6.11 (m, 1H), 4.52 (dd, *J* = 9.2 Hz, *J* = 4.0 Hz, 1H), 3.47 (dd, *J* = 15.4 Hz, *J* = 4.0 Hz, 1H), 3.20 (dd, *J* = 15.5 Hz, *J* = 9.2 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.7, 170.3, 149.8, 142.7, 110.7, 108.4, 50.6, 31.5. FT-IR (KBr): 3447, 2966, 2920, 1751, 1680, 1636, 1617, 1384, 1338, 1261, 1099, 1026, 799, 744. HRMS (ESI-TOF): *m/z* $[M + H]^+$ Calcd for $C_8H_7NO_3S$ 198.0225; Found 198.0221.



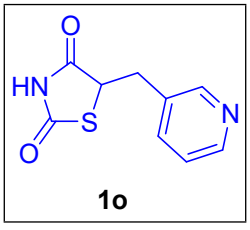
1m

5-(Thiophen-2-ylmethyl)thiazolidine-2,4-dione (**1m**): The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1m** as a yellow solid (75.0 mg, 0.35 mmol, 70% yield). m.p.: 139.4-141.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (br, 1H), 7.16 (d, *J* = 5.1 Hz, 1H), 6.90-6.89 (m, 1H), 6.87-6.86 (m, 1H), 4.49 (dd, *J* = 9.0 Hz, *J* = 3.8 Hz, 1H), 3.61 (dd, *J* = 15.1 Hz, *J* = 3.7 Hz, 1H), 3.39 (dd, *J* = 15.2 Hz, *J* = 9.1 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.9, 170.4, 137.3, 127.4, 127.3, 125.6, 53.4, 33.0. FT-IR (KBr): 3452, 3160, 3042, 2960, 2922, 2800, 1740, 1682, 1596, 1319, 1153, 802, 720, 699, 634. HRMS (ESI-TOF): *m/z* $[M + H]^+$ Calcd for $C_8H_7NO_2S_2$ 213.9996; Found 213.9989.



1n

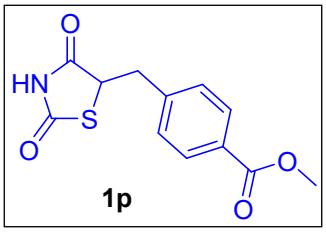
5-((1H-Indol-3-yl)methyl)thiazolidine-2,4-dione (**1n**)[6]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1n** as a red solid (69.0 mg, 0.28 mmol, 56% yield). m.p.: 134.2-135.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br, 1H), 8.09 (br, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.11-7.06 (m, 2H), 4.58 (dd, *J* = 9.7 Hz, *J* = 3.7 Hz, 1H), 3.64 (dd, *J* = 14.8 Hz, *J* = 3.7 Hz, 1H), 3.26 (dd, *J* = 14.7 Hz, *J* = 9.7 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.5, 170.9, 136.3, 126.9, 123.3, 122.7, 120.1, 118.7, 111.5, 110.5, 53.4, 29.1.



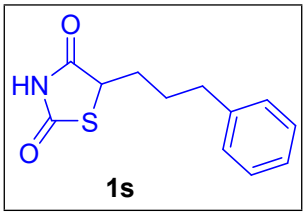
1o

5-(Pyridin-3-ylmethyl)thiazolidine-2,4-dione (**1o**): The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 6:4 hexanes/ethyl acetate) to afford product **1o** as a white solid (77.0 mg, 0.37 mmol, 74% yield). m.p.: 201.1-202.3 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br, 1H), 8.48-8.45 (m, 2H), 7.68 (dt, *J* = 7.8 Hz, *J* = 1.9 Hz, 1H), 7.36 (dd, *J* = 7.8 Hz, *J* = 4.8 Hz, 1H), 4.97 (dd, *J* = 8.4 Hz, *J* = 4.8 Hz, 1H), 3.38 (dd, *J* = 14.2 Hz, *J* = 4.8 Hz, 1H), 3.21 (dd, *J* = 14.2 Hz, *J* = 8.4 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 175.6,

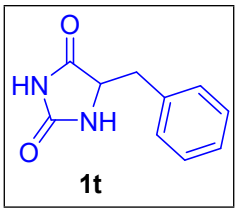
171.4, 150.4, 148.3, 137.1, 132.4, 123.5, 52.0, 34.1. FT-IR (KBr): 3436, 3011, 2963, 2923, 2868, 1742, 1690, 1602, 1428, 1317, 1177, 1025, 949, 800. HRMS (ESI-TOF): *m/z* $[M + H]^+$ Calcd for $C_9H_8N_2O_2S$ 209.0385; Found 209.0374.



Methyl 4-((2,4-dioxothiazolidin-5-yl)methyl)benzoate (**1p**): The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 6:4 hexanes/ethyl acetate) to afford product **1p** as a yelow oil (52.0 mg, 0.20 mmol, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (br, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.56 (dd, *J* = 9.5 Hz, *J* = 4.0 Hz, 1H), 3.92 (s, 3H), 3.57 (dd, *J* = 14.1 Hz, *J* = 4.0 Hz, 1H), 3.22 (dd, *J* = 14.1 Hz, *J* = 9.5 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.8, 170.0, 166.9, 140.9, 130.3, 129.8, 129.5, 52.8, 52.4, 38.6. HRMS (ESI-TOF): *m/z* $[M + H]^+$ Calcd for $C_{12}H_{11}NO_4S$ 266.0487; Found 266.0482.

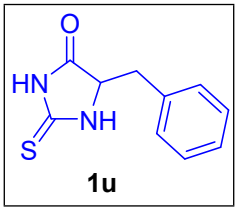


5-(3-Phenylpropyl)thiazolidine-2,4-dione (**1s**): The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1s** as a yellow oil (79.0 mg, 0.335 mmol, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (br, 1H), 7.34-7.29 (m, 2H), 7.26-7.10 (m, *3*H), 4.28 (dd, *J* = 8.7 Hz, *J* = 4.3 Hz, 1H), 2.68 (d, *J* = 7.4 Hz, 2H), 2.23-2.15 (m, 1H), 2.01-1.72 (m, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.8, 170.6, 141.1, 128.7, 128.5, 126.4, 51.7, 35.3, 32.5, 28.6. FT-IR (KBr): 3420, 3237, 3063, 3026, 2964, 2926, 2860, 1752, 1696, 1638, 1615, 1329, 1261, 1155, 1094, 1028, 803. HRMS (ESI-TOF): *m/z* $[M + H]^+$ Calcd for $C_{12}H_{13}NO_2S$ 236.0745; Found 236.0737.



1t

5-Benzylimidazolidine-2,4-dione (**1t**)[9]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1t** as a white solid (81.0 mg, 0.425 mmol, 85% yield). m.p.: 174.2-175.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (br, 1H), 7.92 (br, 1H), 7.31-7.23 (m, 3H), 7.22-7.15 (m, 2H), 4.33 (t, J = 4.7 Hz, 1H), 2.99-2.85 (m, 2H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 175.2, 157.1, 135.6, 129.7, 128.1, 126.7, 58.4, 36.4.



1u

5-Benzyl-2-thioxoimidazolidin-4-one (**1u**)[10]: The reaction was purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1u** as a yellow solid (68.0 mg, 0.33 mmol, 66% yield). m.p.: 184.3-185.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (br, 1H), 10.07 (br, 1H), 7.29-7.22 (m, 3H), 7.19-7.14 (m, 2H), 4.56 (t, J = 4.5 Hz, 1H), 2.98 (d, J = 3.8 Hz, 2H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 182.3, 175.7, 135.0, 129.6, 128.2, 126.9, 61.4, 35.6.

1.5. General procedure for the preparation of Pioglitazone and Pioglitazone hydrochloride

A 10 mL flask equipped with graphite in both electrodes (anode and cathode) was charged with 1.0 equivalent (0.5 mmol) of intermediate **2** and 1.0 equivalent (0.5 mmol) of sodium carbonate, followed by the addition of 5.0 mL of dimethylsulfoxide and 100 µL of distilled water (5.5 mmol). The reaction mixture was kept under constant current (10 mA) at room temperature for 3 hours. The crude reaction mixture was concentrated under reduced pressure, and the product purified through column chromatography or recrystallization using water/methanol. The reaction was also carried out at a 1.7 mmol scale (reaction time of 10.2 hours at a constant current of 10 mA).

Figure S3. A) Reaction flask charged with 1.7 mmol of intermediate **2**; B) Reaction setup synthesis.

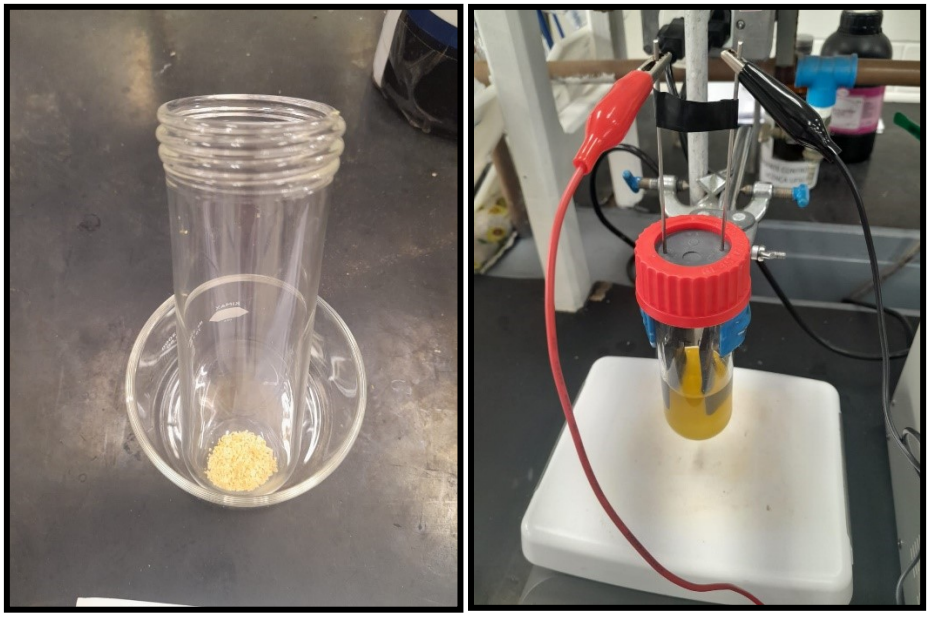
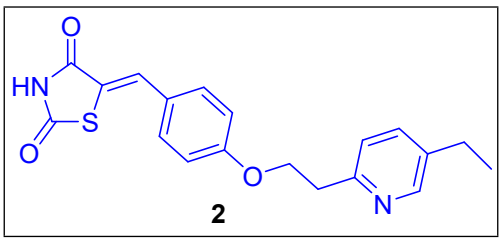


Figure S4. A) Crude reaction mixture after 10.2 hours; B) Isolated product after purification.

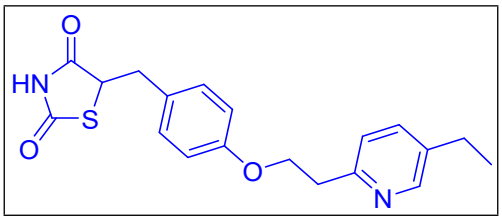
Pioglitazone hydrochloride was prepared following a literature method.[11] In a 10 mL flask, 1.0 mmol of Pioglitazone was added, followed by the addition of 1.8 mL of isopropyl alcohol and 0.5 mL of hydrochloric acid. The reaction was heated to 80 °C and kept for 30 minutes. The reaction was cooled to room temperature and the solid was filtered and dried under vacuum.

1.6. Characterization data for intermediate 2, Pioglitazone and Pioglitazone hydrochloride

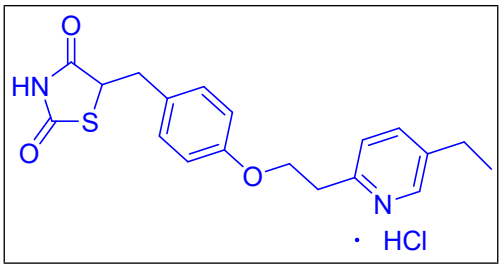


2

(Z)-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (**2**) prepared according to the literature.[12] Pale yellow solid m.p.: 158.7-159.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.51 (br, 1H), 8.38 (s, 1H), 7.75 (s, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 2H), 4.42 (t, *J* = 6.6 Hz, 2H), 3.17 (t, *J* = 6.5 Hz, 2H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 167.9, 167.4, 160.2, 155.1, 148.4, 136.9, 136.0, 132.1, 131.8, 125.5, 123.2, 120.3, 115.4, 67.1, 36.4, 24.9, 15.4.



Pioglitazone[13]: The reaction was purified through recrystallization on water/methanol or column chromatography on silica gel (elution: 1:1 hexanes/ethyl acetate to ethyl acetate) to afford Pioglitazone as a yellow solid (144 mg, 0.405 mmol, 81% yield working with 0.5 mmol-scale; or 458 mg, 1,29 mmol, 76% yield working with 1.7 mmol-scale). m.p.: 181.5-182.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (br, 1H), 8.72 (d, *J* = 1.6 Hz, 1H), 8.40 (dd, *J* = 8.3 Hz, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.86 (dd, *J* = 8.9 Hz, *J* = 4.4 Hz, 1H), 4.39 (t, *J* = 6.2 Hz, 2H), 3.49 (t, *J* = 6.2 Hz, 2H), 3.28 (dd, *J* = 14.2 Hz, *J* = 4.3 Hz, 1H), 3.05 (dd, *J* = 14.2 Hz, *J* = 9.0 Hz, 1H), 2.78 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 188.9, 180.3, 156.9, 155.6, 148.5, 136.6, 135.7, 131.8, 129.8, 123.0, 114.1, 66.7, 58.4, 39.9, 36.8, 25.0, 15.4.



Pioglitazone hydrochloride[11]: The reaction was purified through filtration to afford Pioglitazone hydrochloride as a pale yellow solid (380 mg, 0.97 mmol, 97% yield). m.p.: 191.8-193.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (br, 1H), 8.72 (d, *J* = 1.6 Hz, 1H), 8.40 (dd, *J* = 8.3 Hz, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.86 (dd, *J* = 8.9 Hz, *J* = 4.4 Hz, 1H), 4.39 (t, *J* = 6.2 Hz, 2H), 3.49 (t, *J* = 6.2 Hz, 2H), 3.28 (dd, *J* = 14.2 Hz, *J* = 4.3 Hz, 1H), 3.05 (dd, *J* = 14.2 Hz, *J* = 9.0 Hz, 1H), 2.78 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 175.7, 171.7, 157.0, 151.3, 145.1, 141.2, 140.3, 130.4, 129.1, 127.0, 114.4, 65.5, 53.0, 36.2, 32.4, 24.6, 14.6. FT-IR (KBr): 3480, 3412, 3083, 2966, 2927, 2878, 2742, 1741, 1691, 1616, 1510, 1475, 1335, 1312, 1229, 1150, 1037, 849.

1.7. General procedure for the gram scale preparation of compound 1a

A 100 mL flask equipped with graphite in both electrodes (anode and cathode) was charged with 1.0 equivalent (6 mmol, 1339 mg) of (*Z*)-5-(4-fluorobenzylidene)thiazolidine-2,4-dione and 1.0 equivalent (6 mmol, 636 mg) of sodium carbonate, followed by the addition of 60.0 mL of dimethylsulfoxide and 1.2 mL of distilled water (66 mmol). The reaction mixture was kept under constant current (10 mA) at room temperature for 24 hours. The resulting mixture was washed with 180 mL of a 0.1 M HCl solution and extracted three times with ethyl acetate (3 × 180 mL). The combined organic phases were concentrated under reduced pressure, and the product purified through column chromatography on silica gel (elution: 9:1 hexanes/ethyl acetate to 7:3 hexanes/ethyl acetate) to afford product **1a** as a yellow solid (1044 mg, 4.68 mmol, 78% yield).

Figure S5. A) 100 mL reaction flask charged with 6 mmol of (*Z*)-5-(4-fluorobenzylidene)thiazolidine-2,4-dione; B) Reaction setup for the gram scale synthesis.

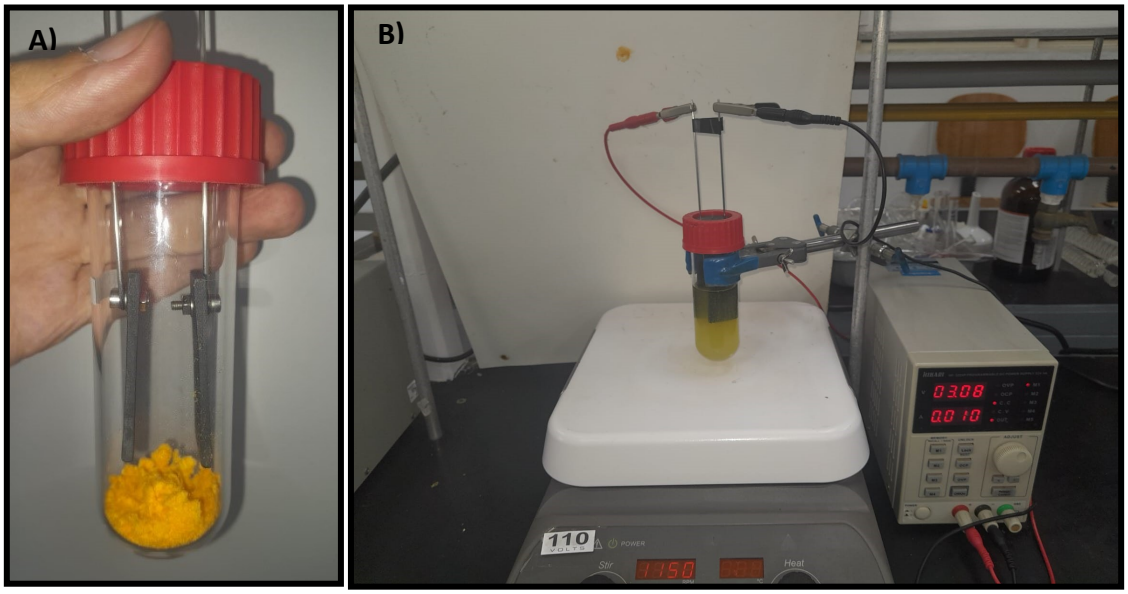
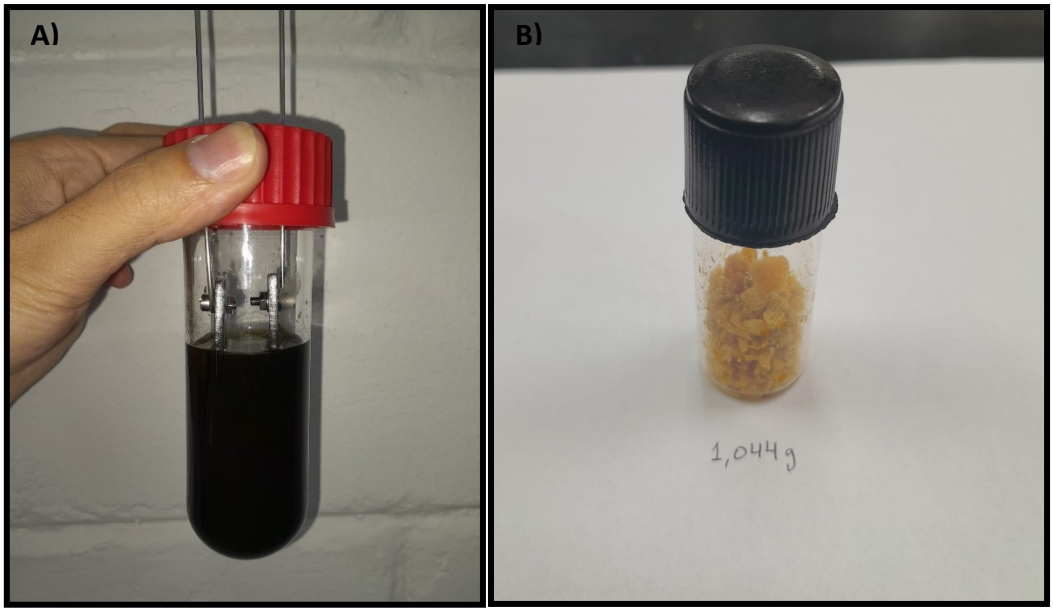


Figure S6. A) Crude reaction mixture after 24 hours; B) Isolated product **1a** after purification.



1.8. Cyclic voltammetry of (*Z*)-5-(4-fluorobenzylidene)thiazolidine-2,4-dione

Cyclic voltammetry data was acquired using a scan rate of 50 mV s^{-1} (Ag/Ag^+ reference electrode and glassy carbon working electrodes). The data was acquired in an undivided cell reactor using 0.5 mmol of (*Z*)-5-(4-fluorobenzylidene)thiazolidine-2,4-dione or 2.75 mmol of water, 0.5 mmol of Na_2CO_3 in 5 mL of dimethylsulfoxide (concentration of thiazolidine-2,4-dione and sodium carbonate of 0.1 M, concentration of water 0.55 M).

Figure S7. Cyclic voltammogram (IUPAC convention) of (*Z*)-5-(4-fluorobenzylidene)thiazolidine-2,4-dione (black) and background (red).

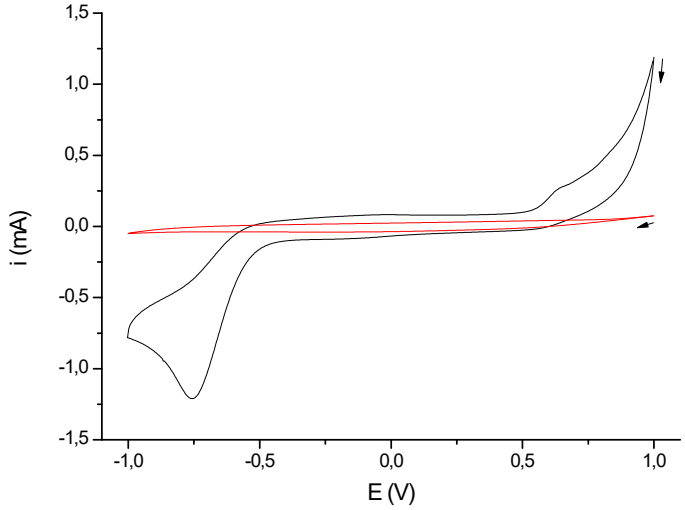
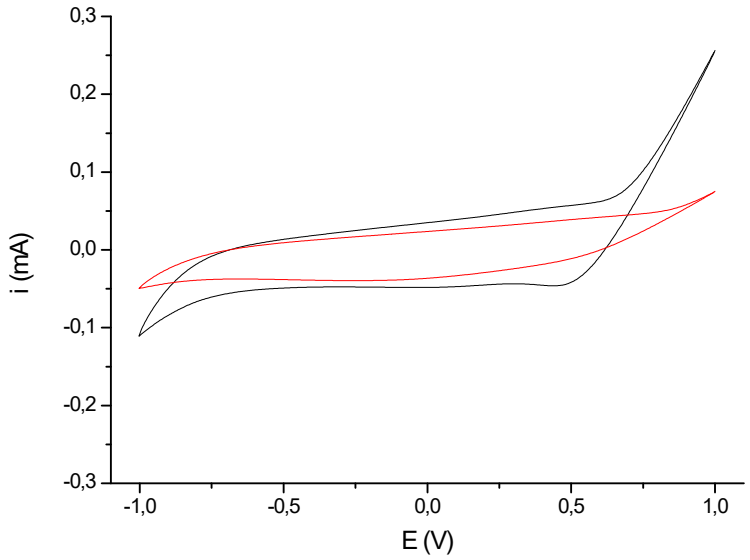
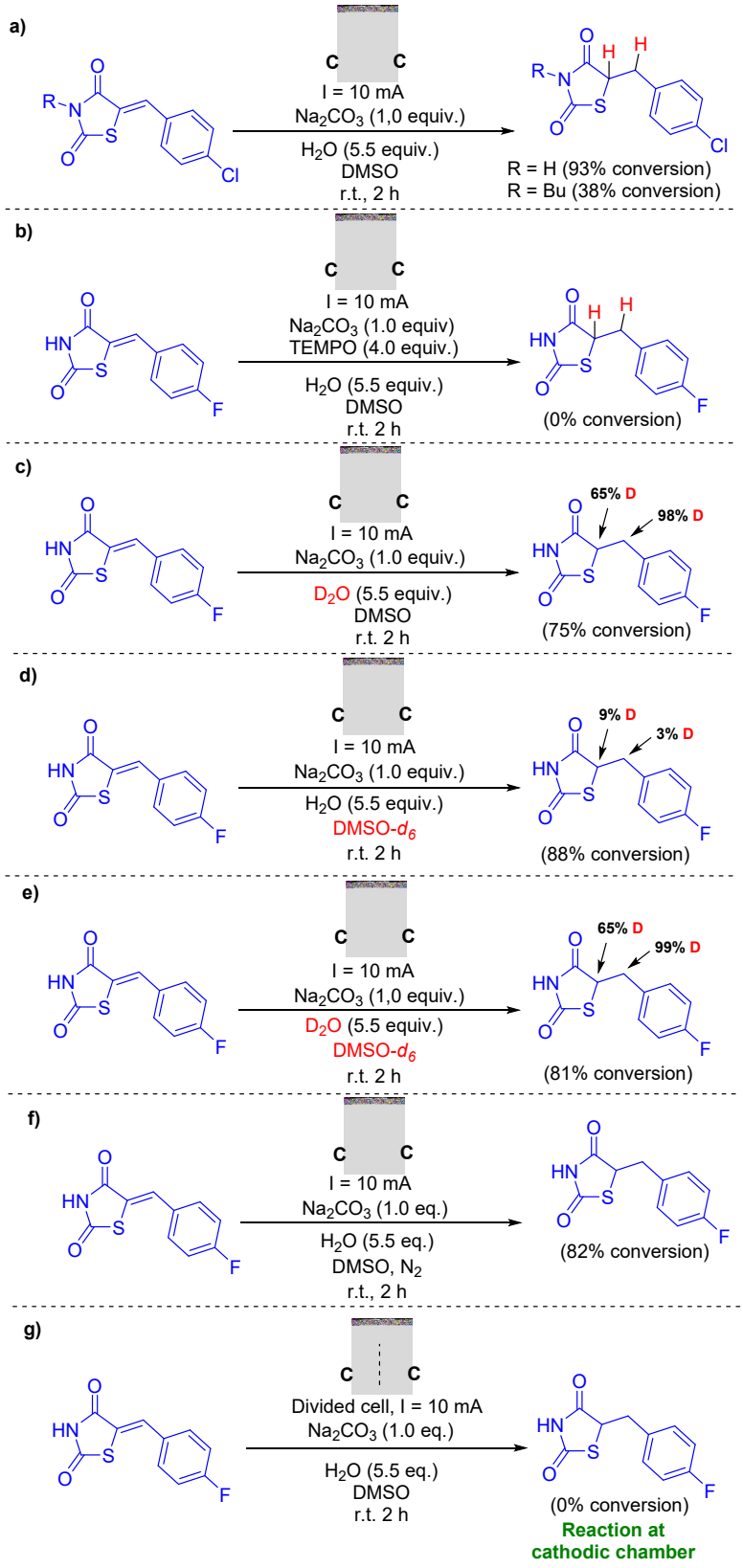


Figure S8. Cyclic voltammogram (IUPAC convention) of water (black) and background (red).



1.9. Control experiments

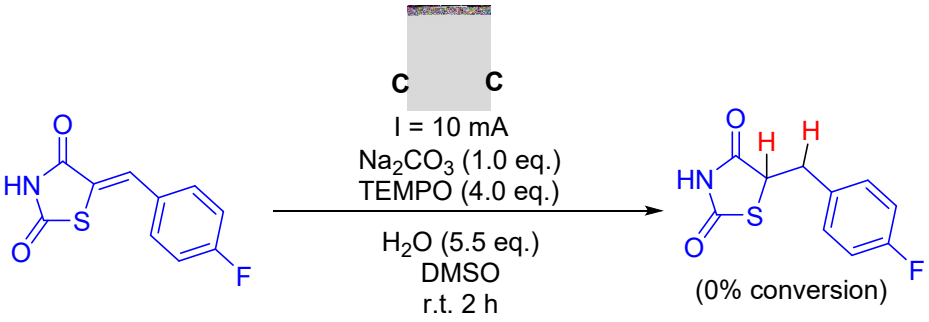
Scheme S1. Control experiments.[a]



[a] Conversions calculated through the ^{1}H NMR analysis of the crude reaction mixture.

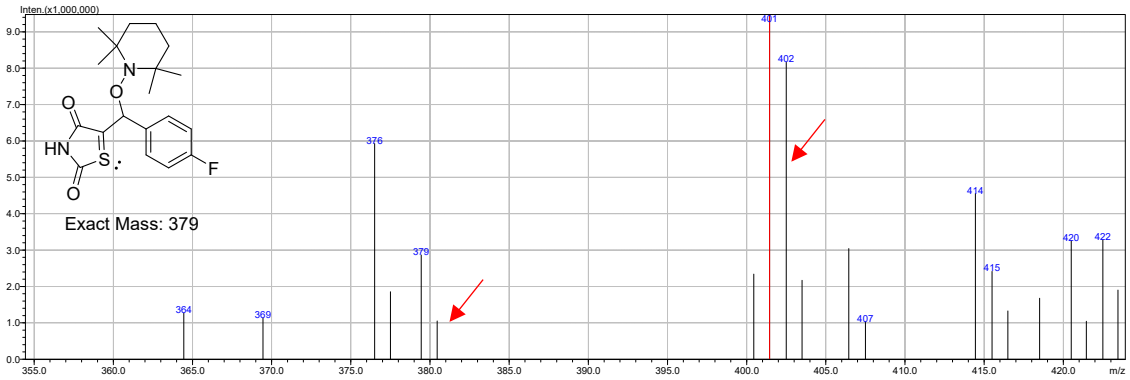
- Radical scavenger experiment analysis through mass spectrometry

Scheme S2. Control experiment detailed in Scheme S1.



The analysis of the intermediate species were performed directly from crude reaction mixture by ESI(+) MS in order to intercept the TEMPO-trapped intermediate. The crude reaction mixture was diluted in formic acid 1%/methanol (7:3 v/v) and directly analyzed by ESI(+)-MS. Signals of *m/z* 380 and 402 were detected, corresponding to the expected substrate-TEMPO intermediate ($[M + H]^+$ and $[M + Na]^+$, respectively).

Figure S9. ESI(+)-MS of the crude reaction mixture.



2. NMR and IR spectra of compounds 1a-1u

Figure S10. FT-IR (KBr) of compound **1a**.

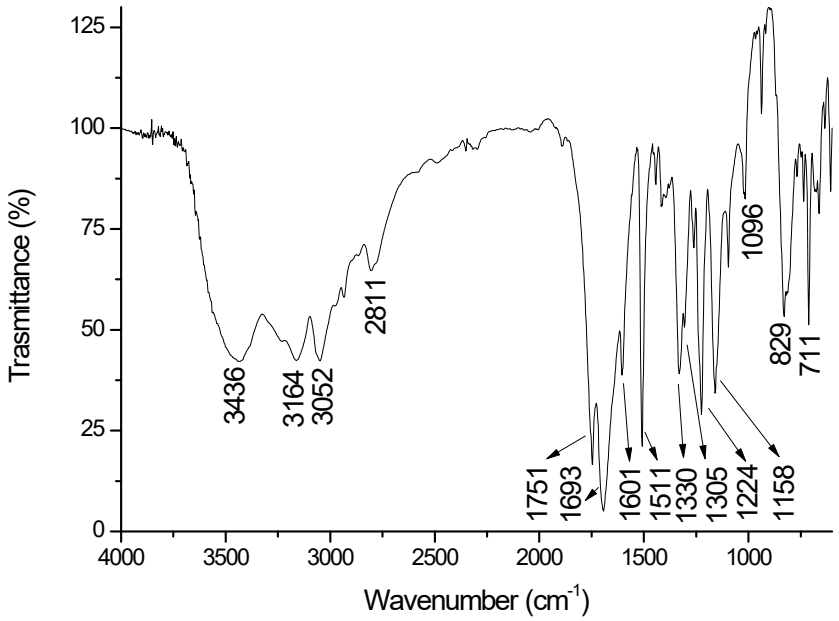


Figure S11. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1a**.

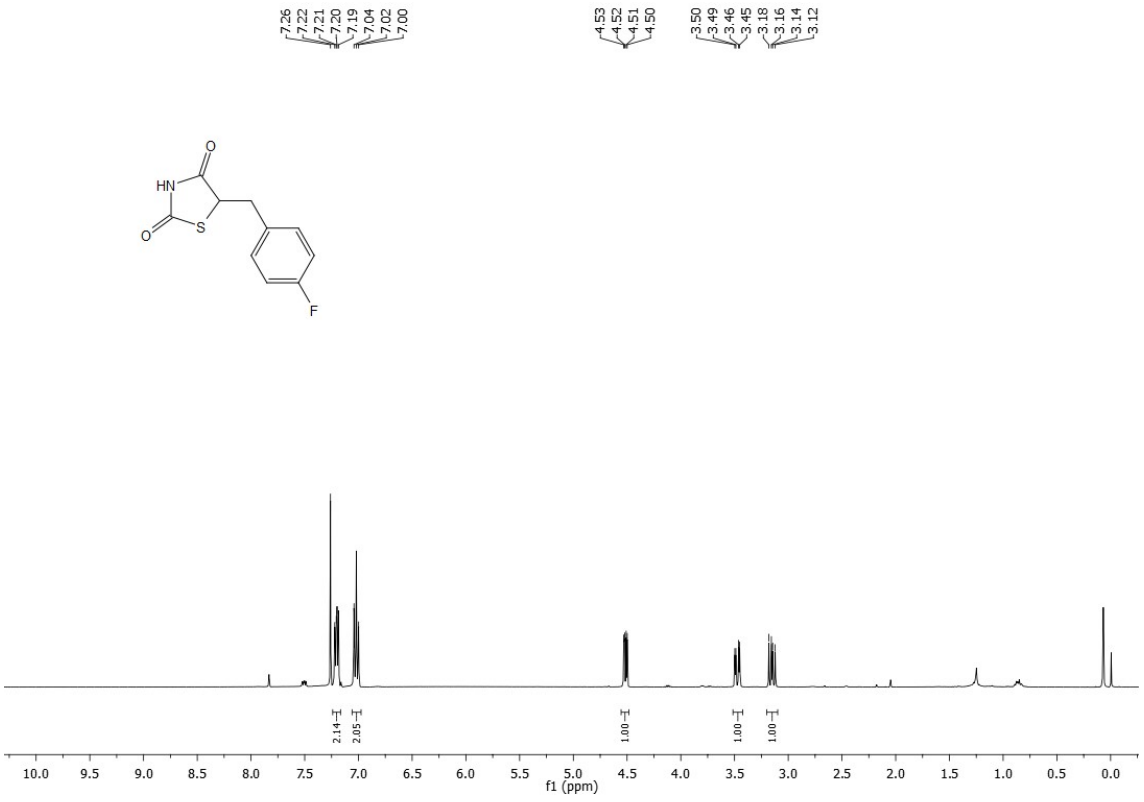


Figure S12. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1a**.

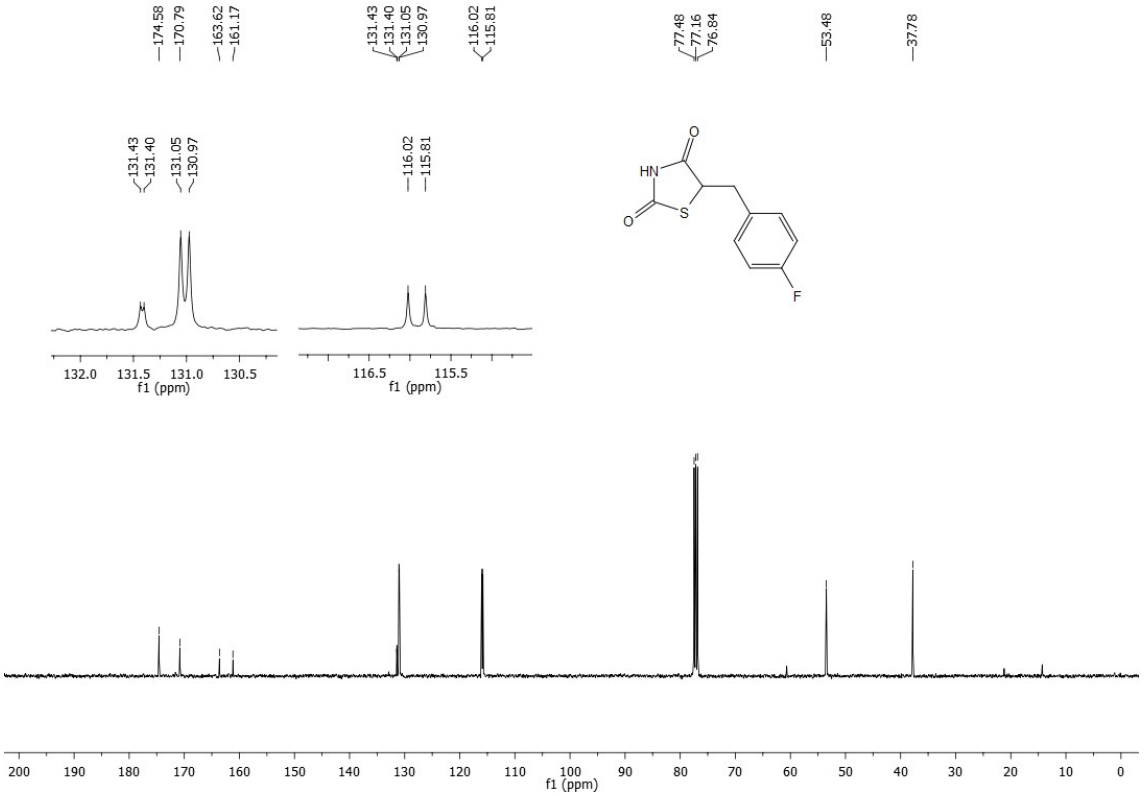


Figure S13. ^{19}F NMR (377 MHz, $CDCl_3$) of compound **1a**.

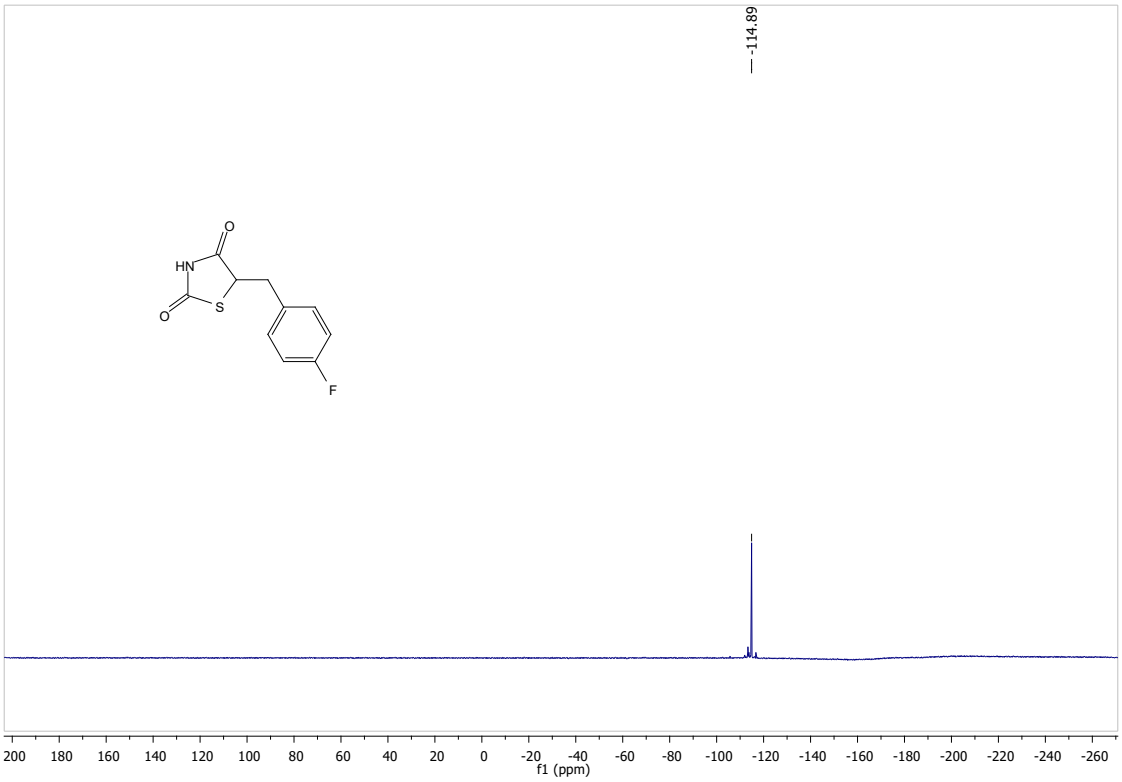


Figure S14. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1b**.

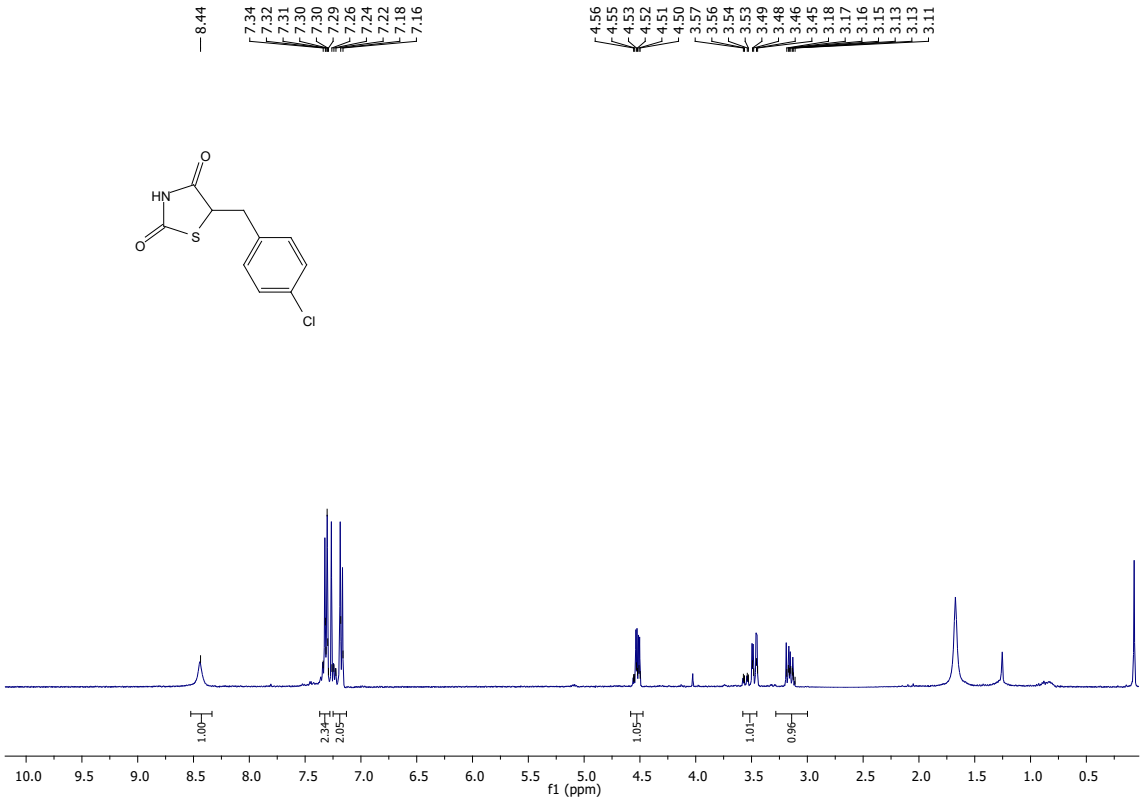


Figure S15. ^{13}C $\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **1b**.

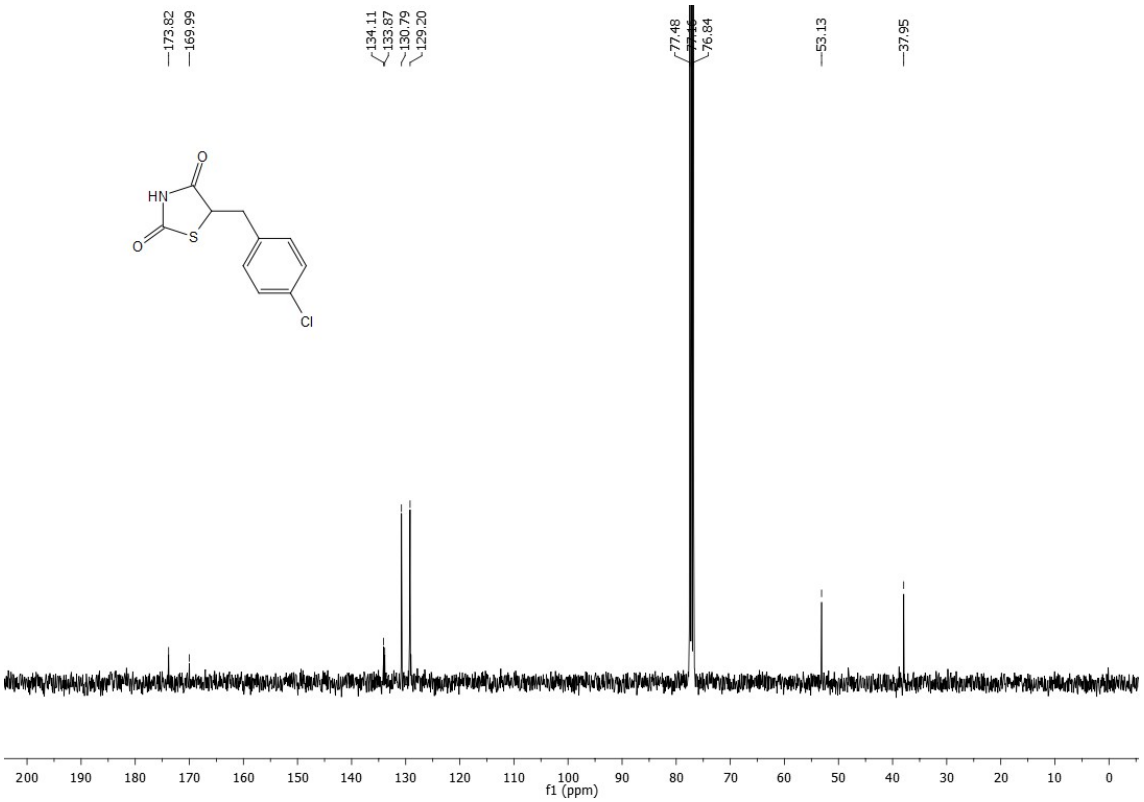


Figure S16. DEPT135 (100 MHz, $CDCl_3$) of compound **1b**.

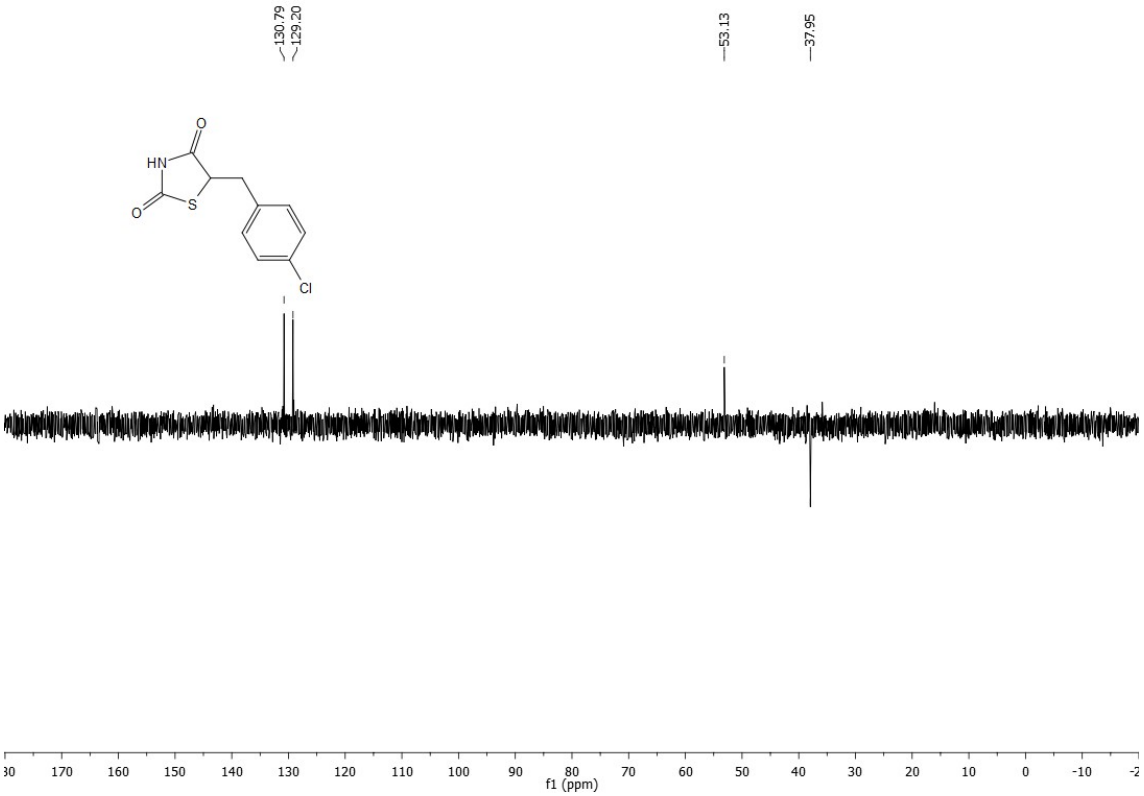


Figure S17. ^1H NMR (400 MHz, $CDCl_3$) of compound **1c**.

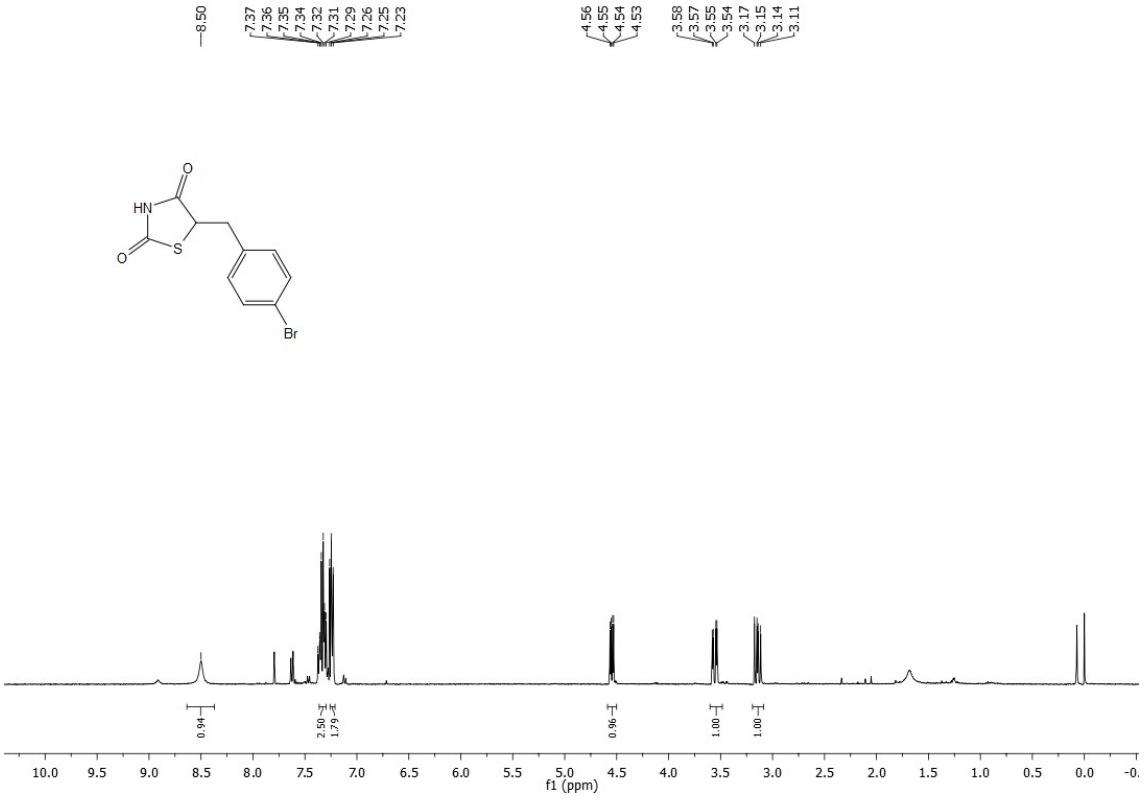


Figure S18. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1c**.

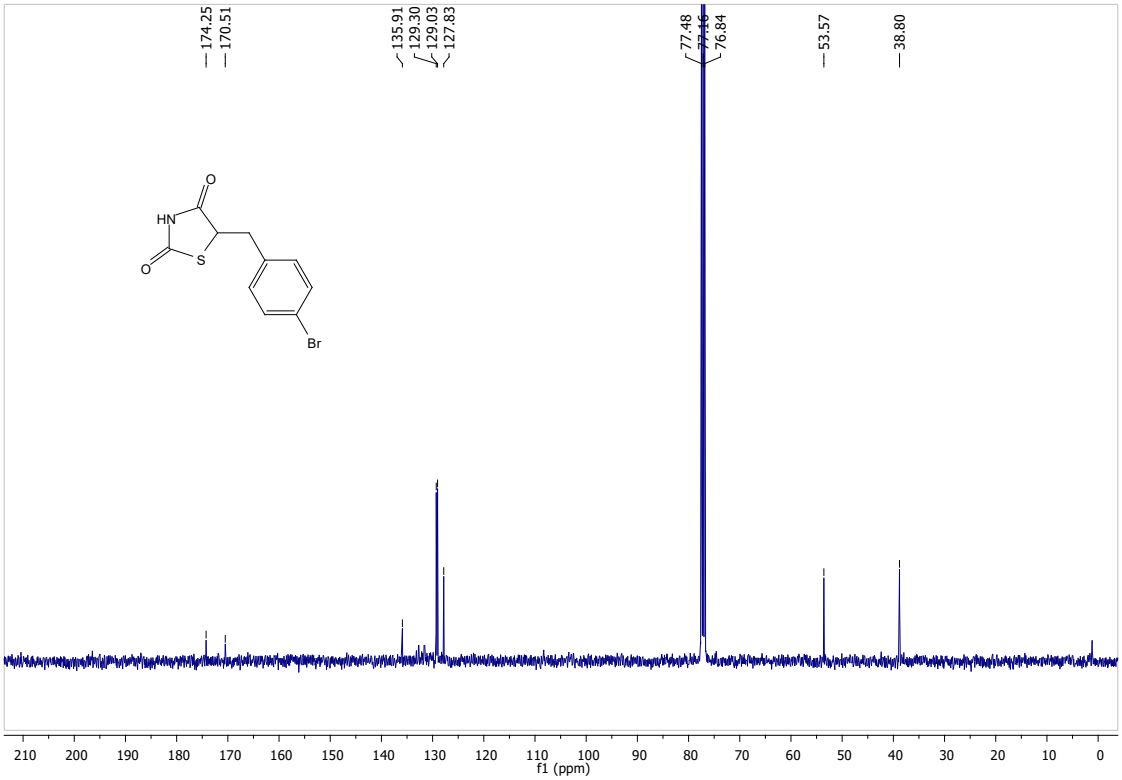


Figure S19. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1d**.

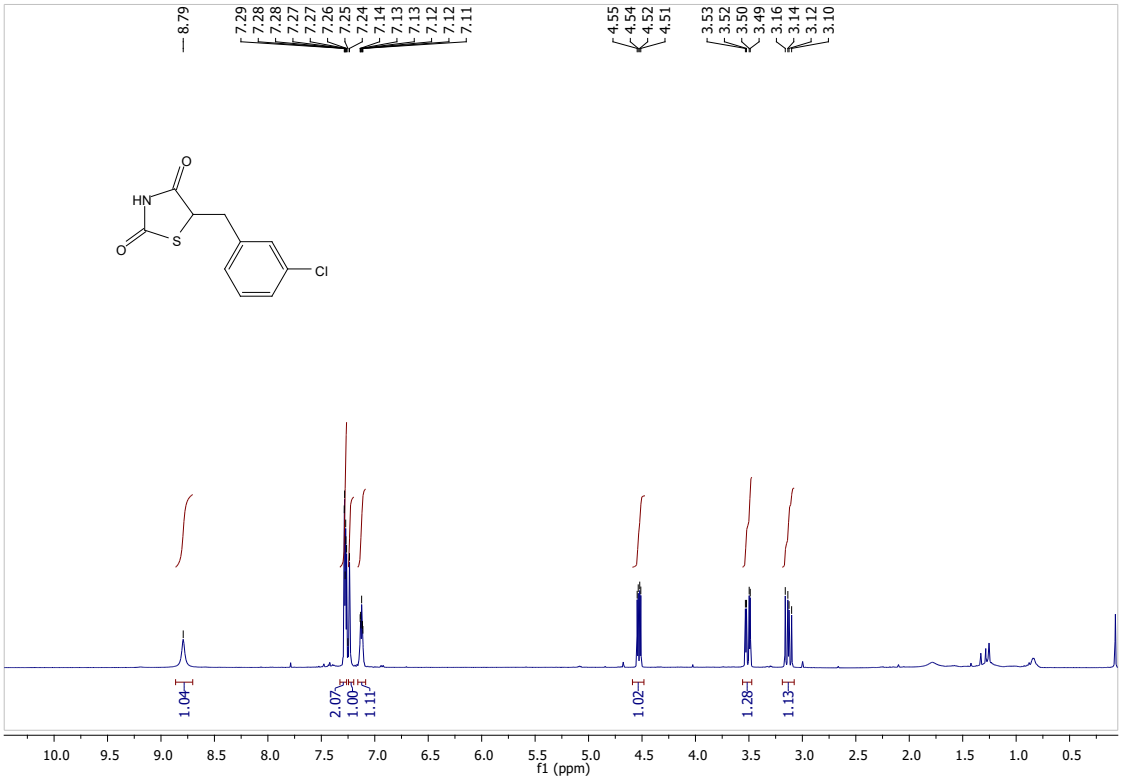


Figure S20. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1d**.

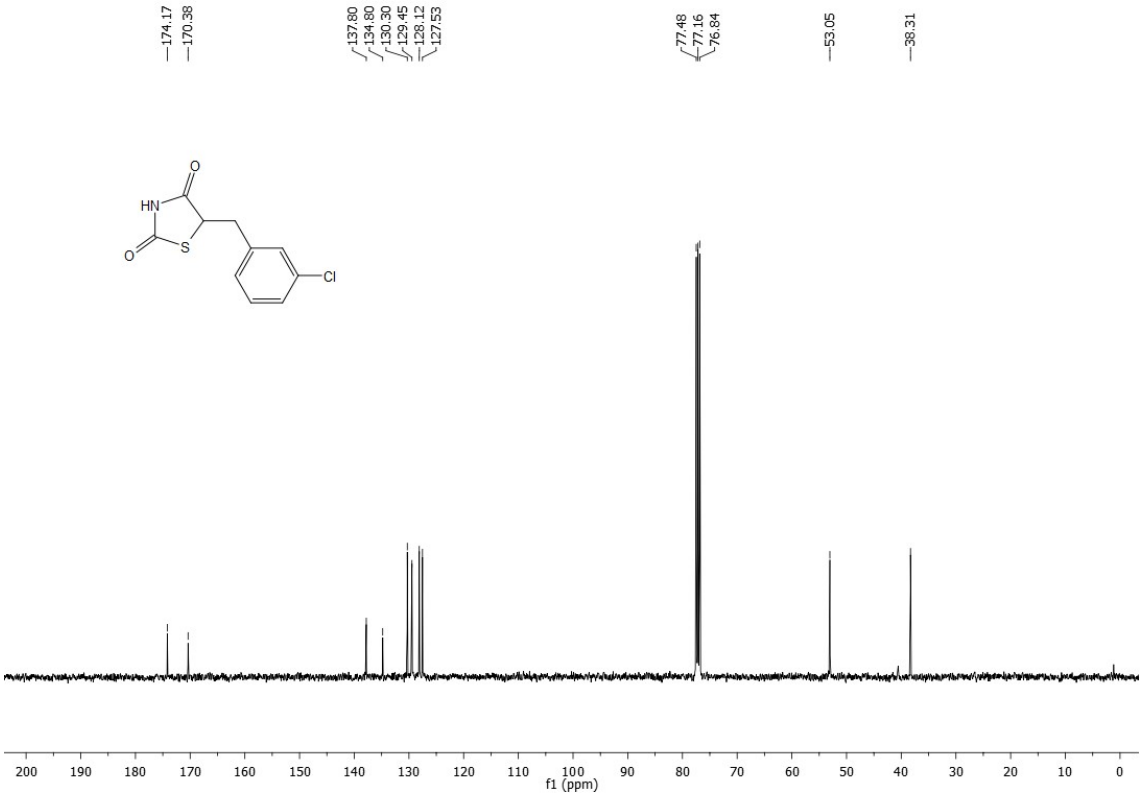


Figure S21. DEPT135 (100 MHz, $CDCl_3$) of compound **1d**.

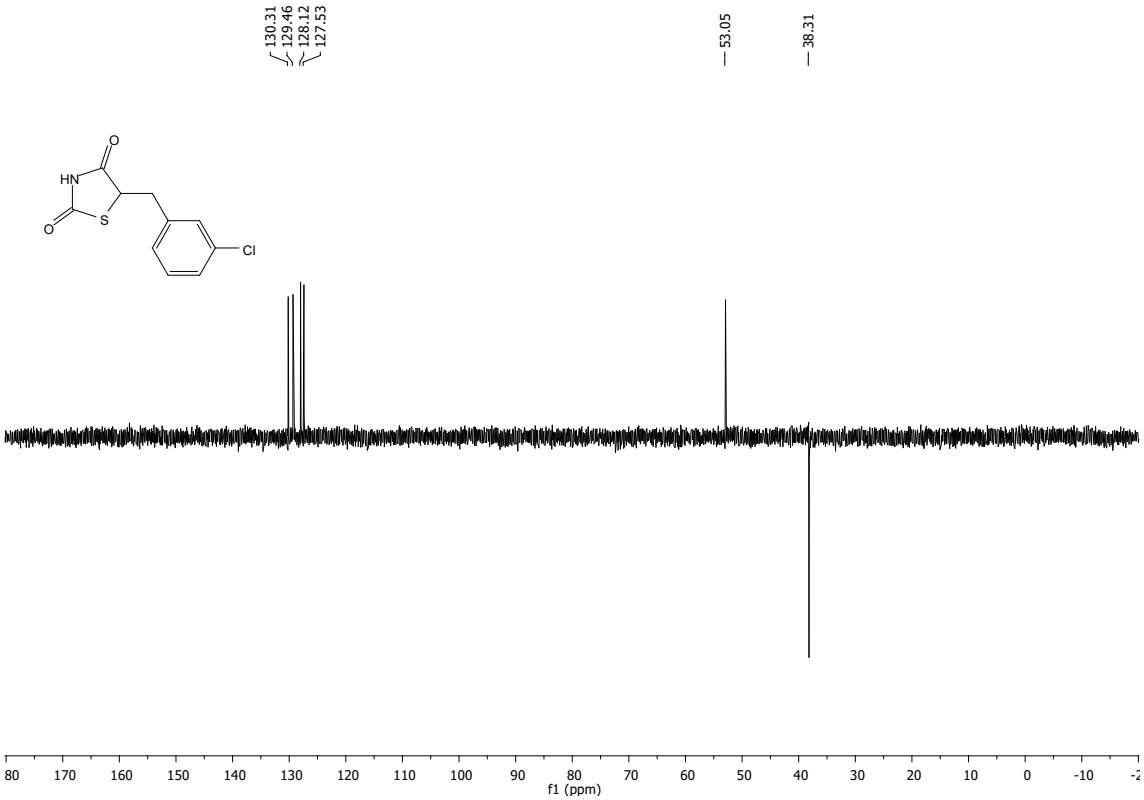


Figure S22. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1e**.

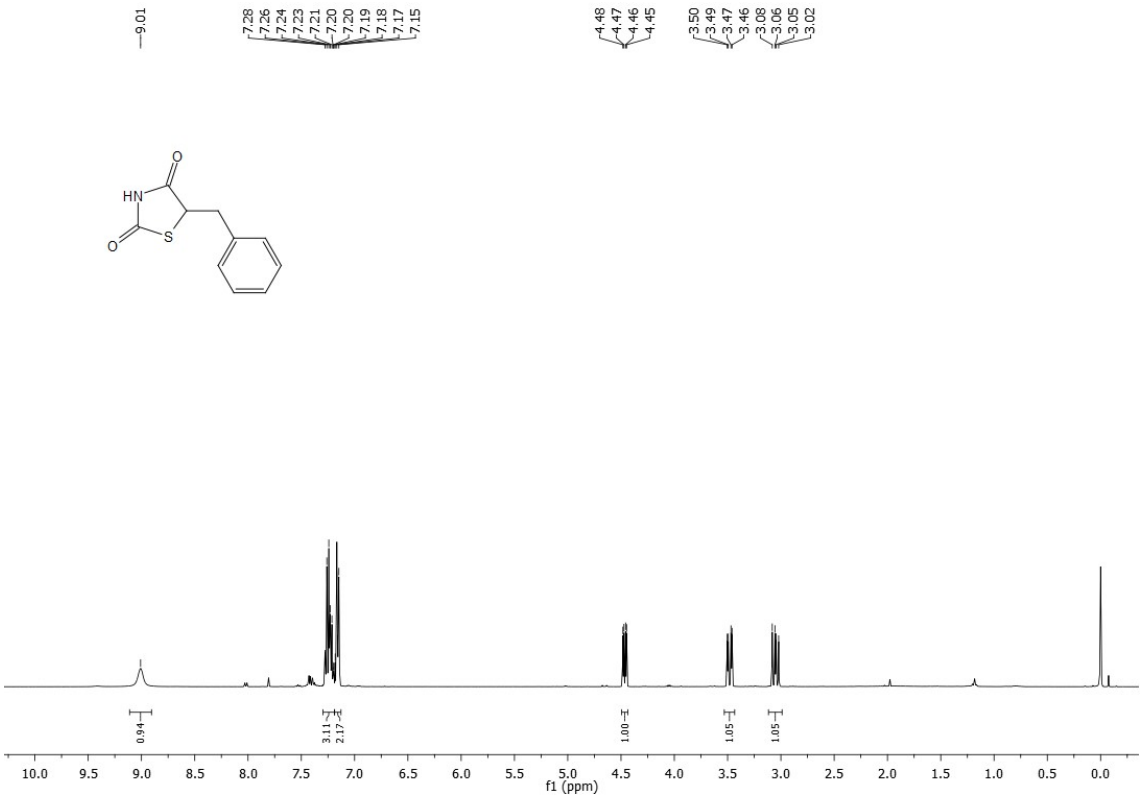


Figure S23. ^{13}C $\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **1e**.

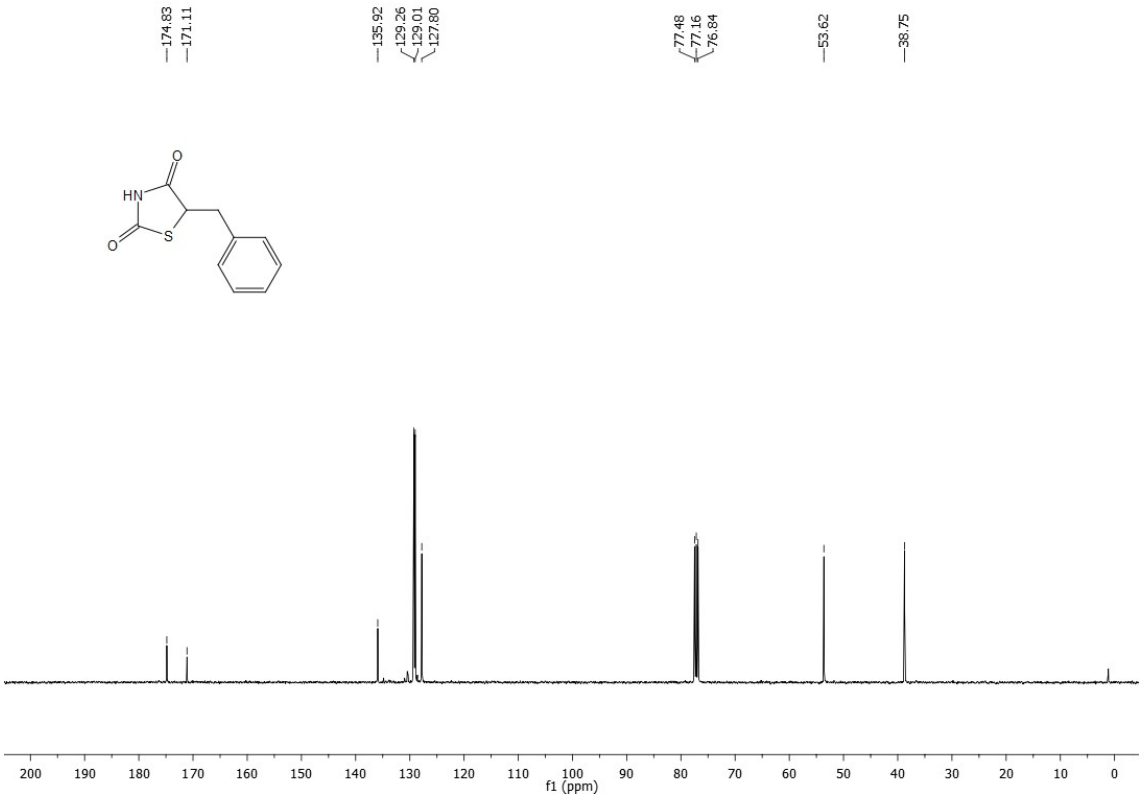


Figure S24. DEPT135 (100 MHz, $CDCl_3$) of compound **1e**.

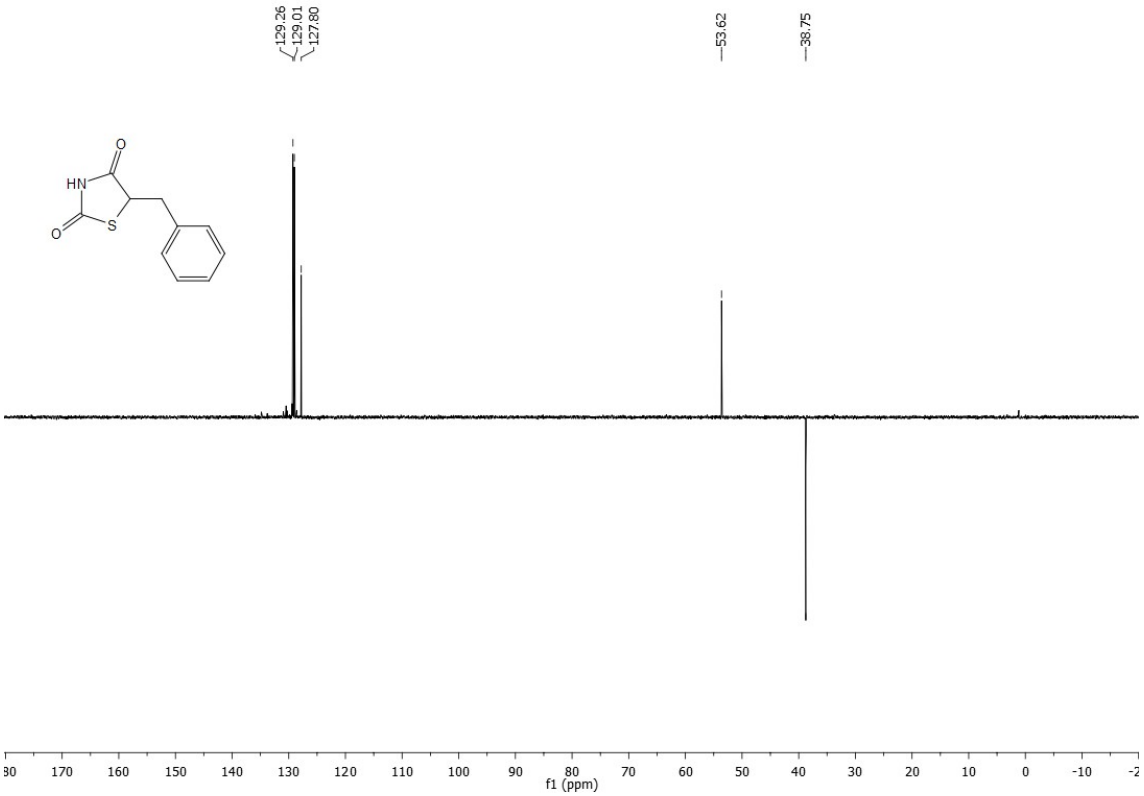


Figure S25. ^1H NMR (400 MHz, $CDCl_3$) of compound **1f**.

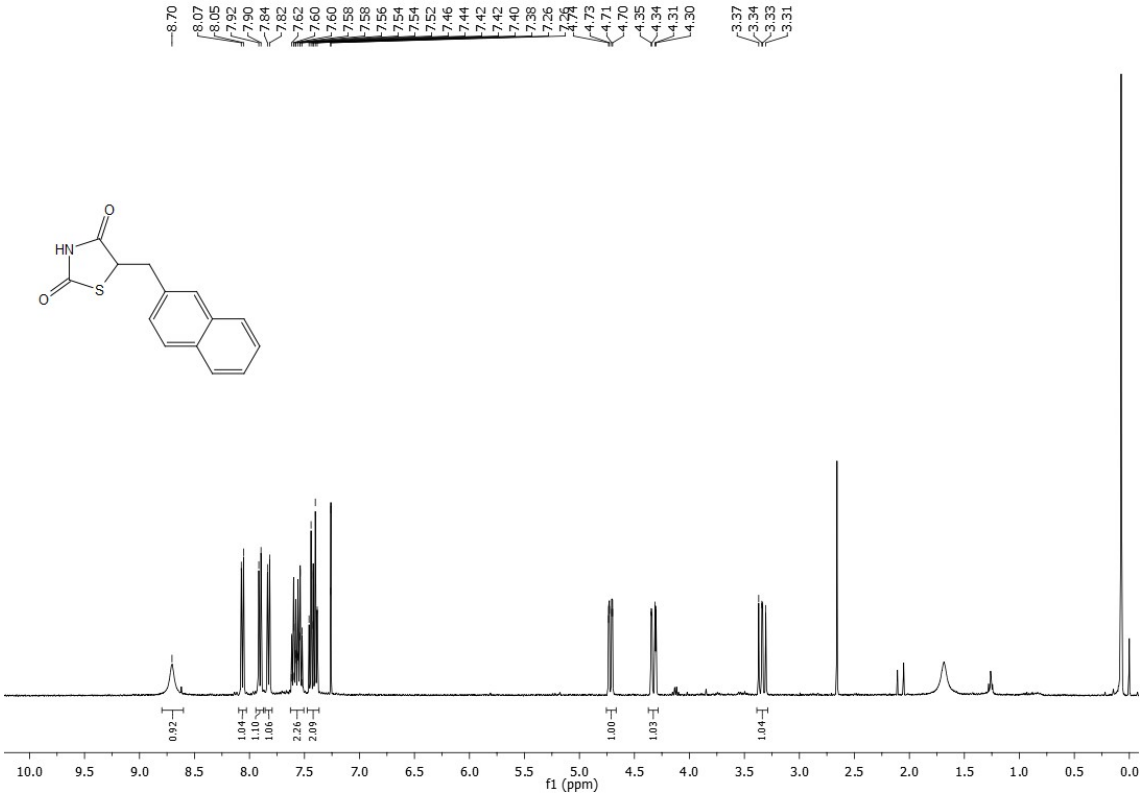


Figure S26. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1f**.

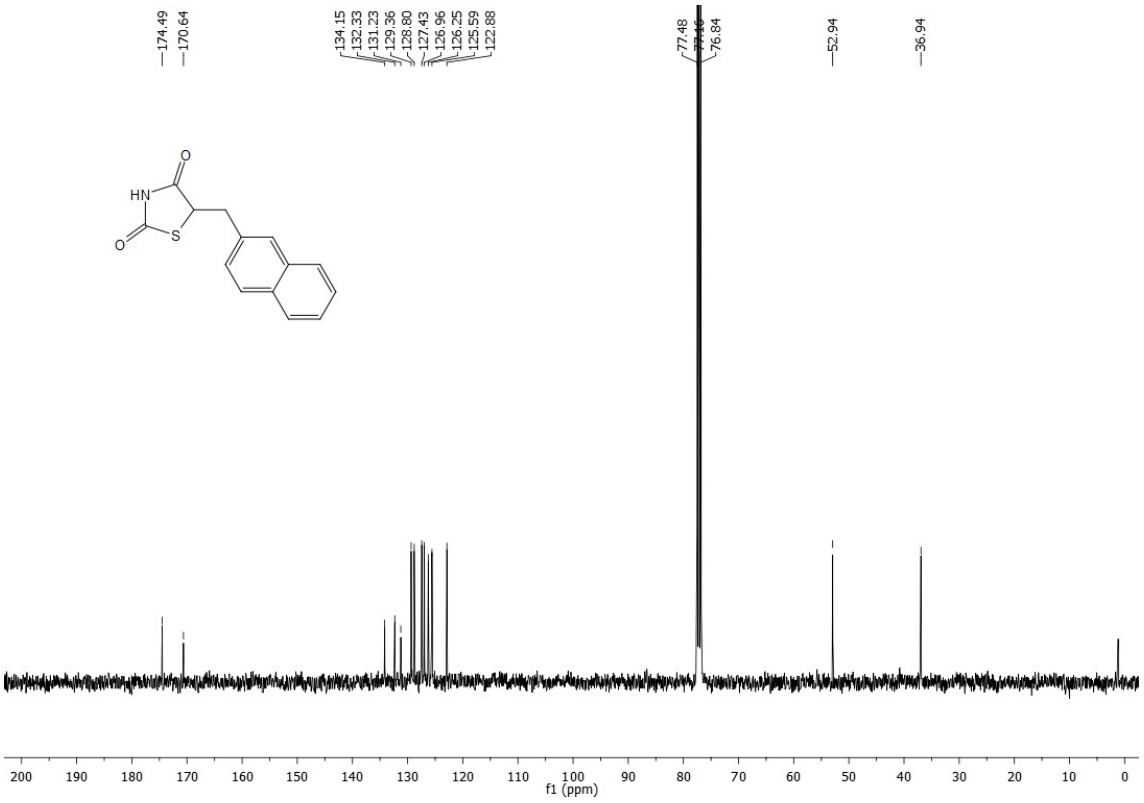


Figure S27. DEPT135 (100 MHz, $CDCl_3$) of compound **1f**.

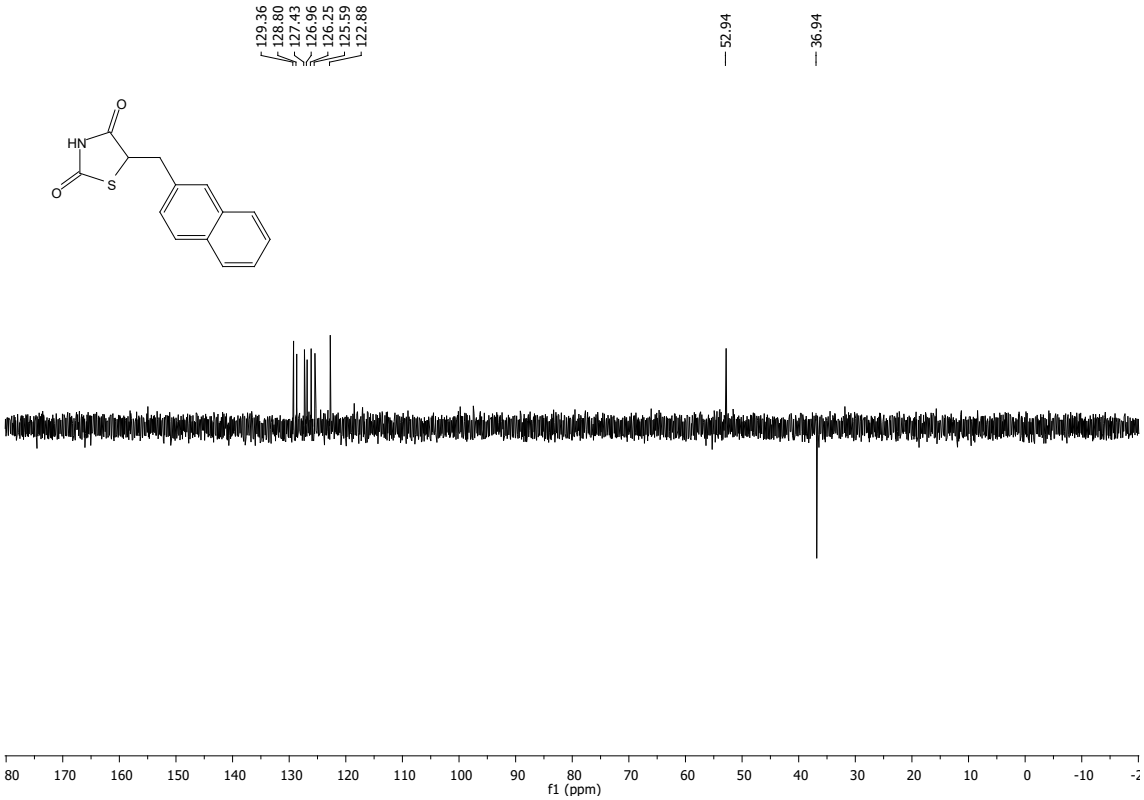


Figure S28. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1g**.

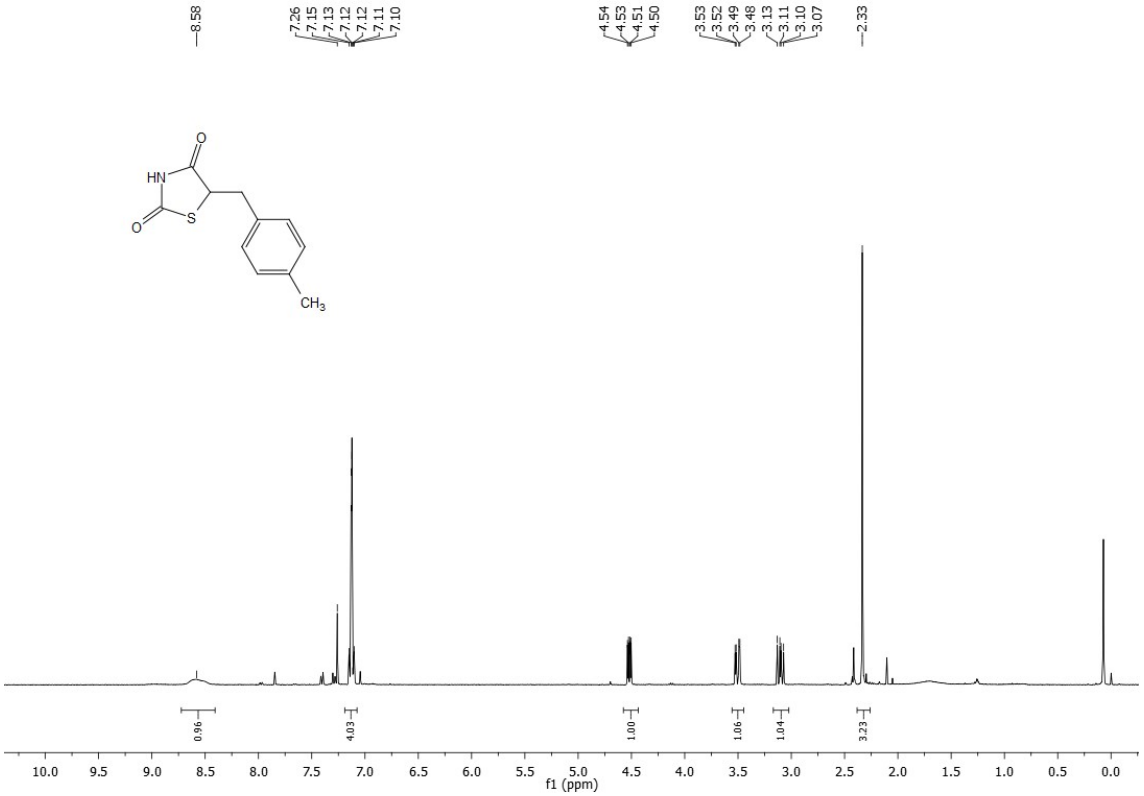


Figure S29. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1g**.

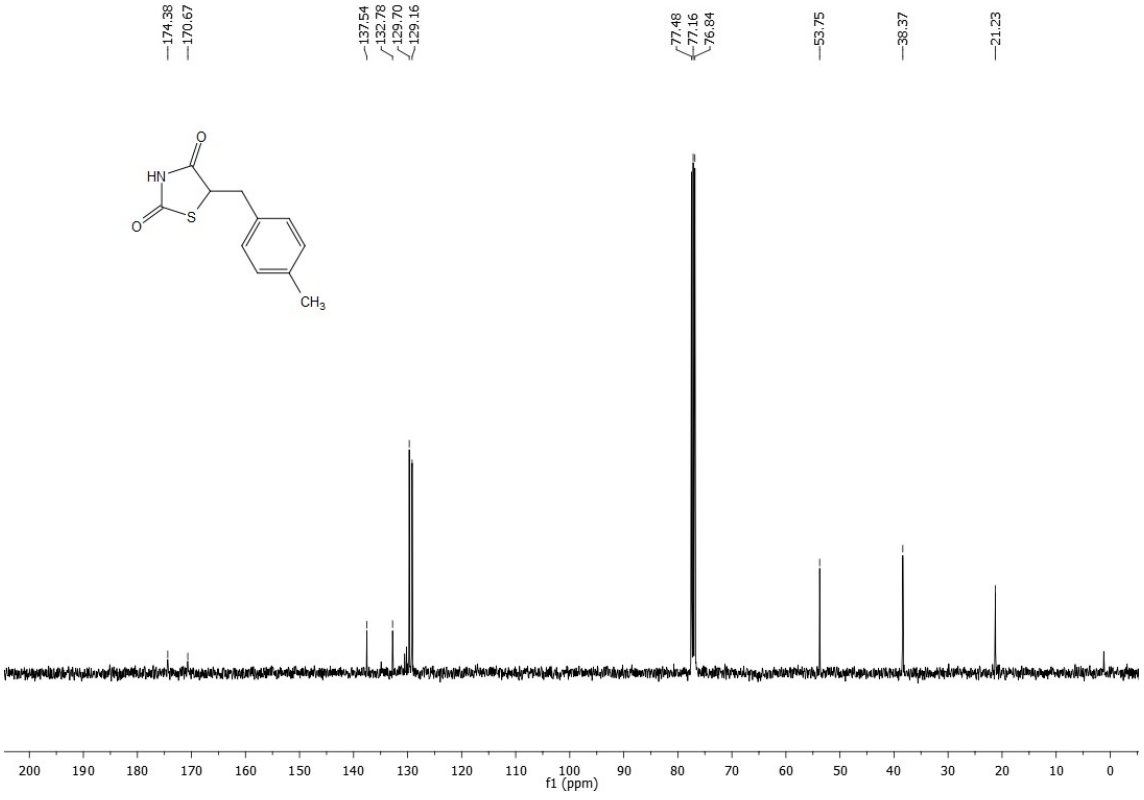


Figure S30. DEPT135 (100 MHz, $CDCl_3$) of compound **1i**.

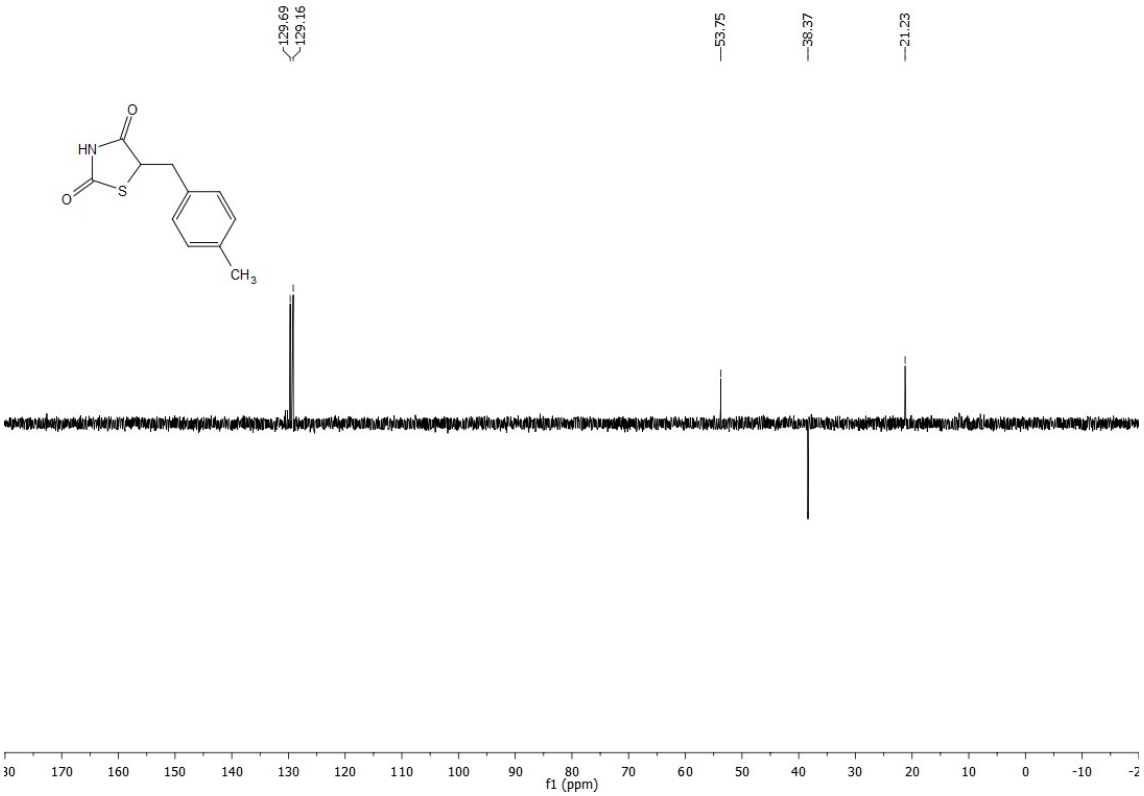


Figure S31. ^1H NMR (400 MHz, DMSO-d_6) of compound **1h**.

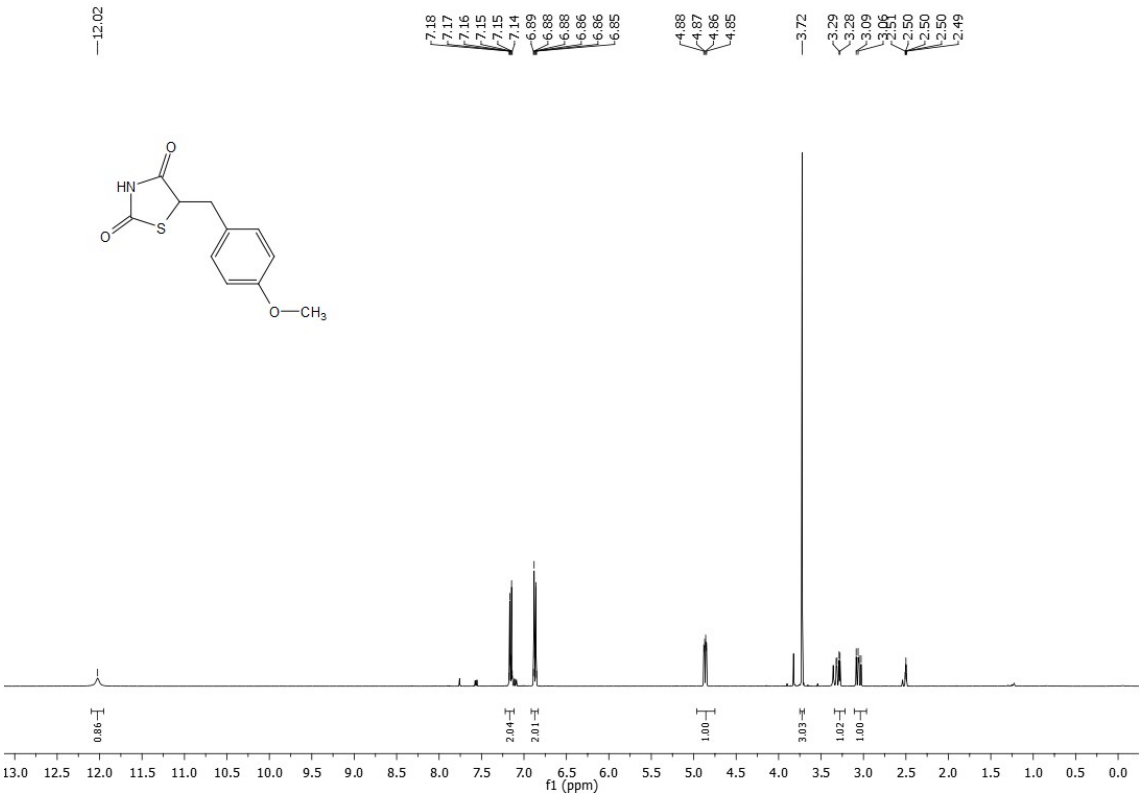


Figure S32. ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) of compound **1h**.

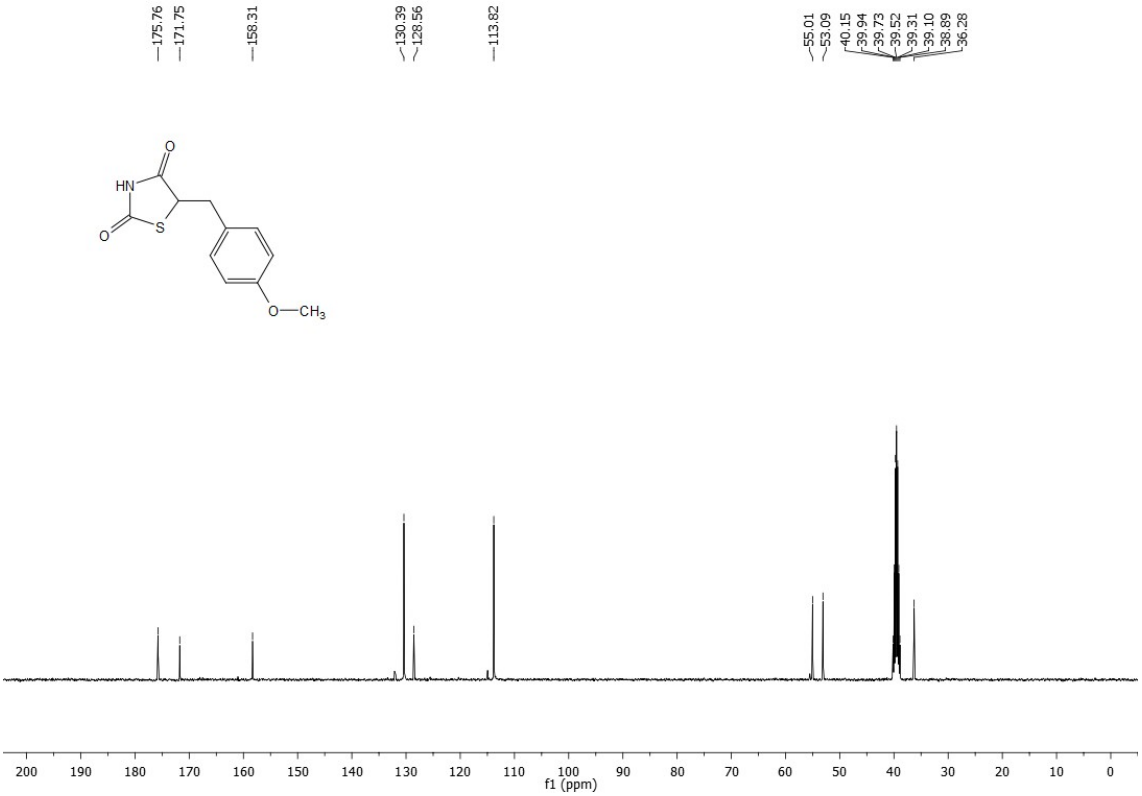


Figure S33. DEPT135 (100 MHz, DMSO-d_6) of compound **1h**.

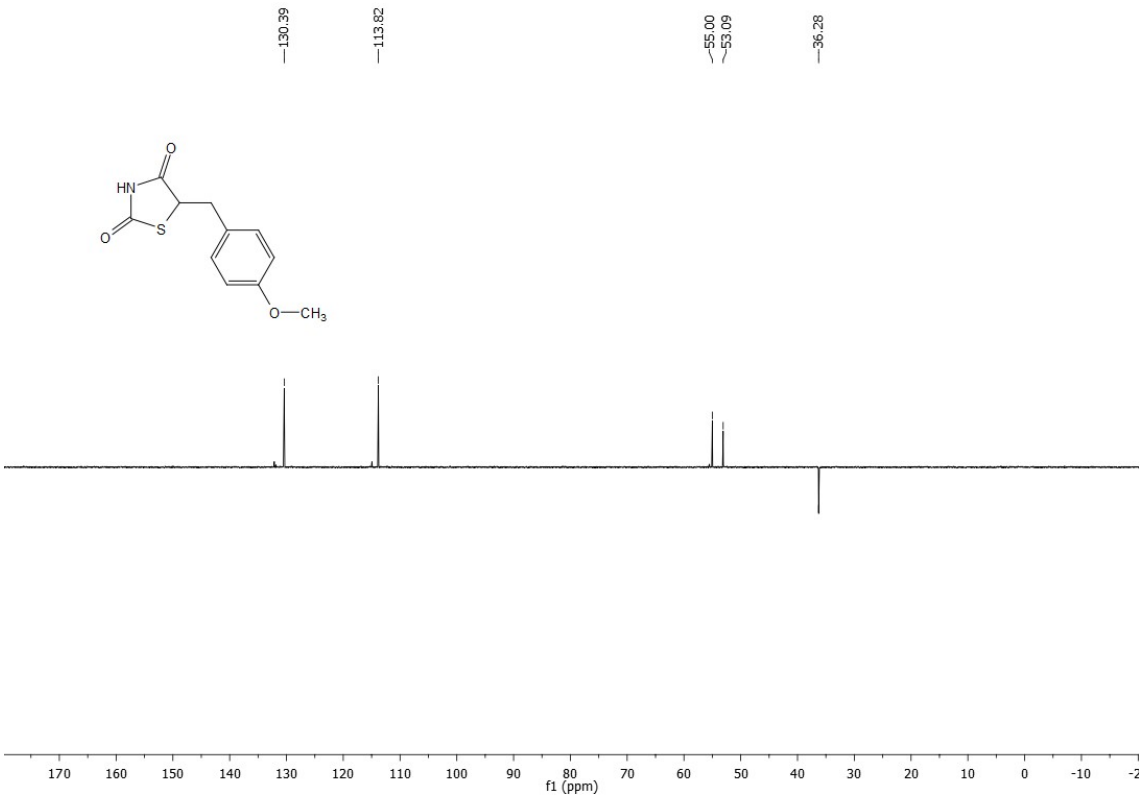


Figure S34. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1i**.

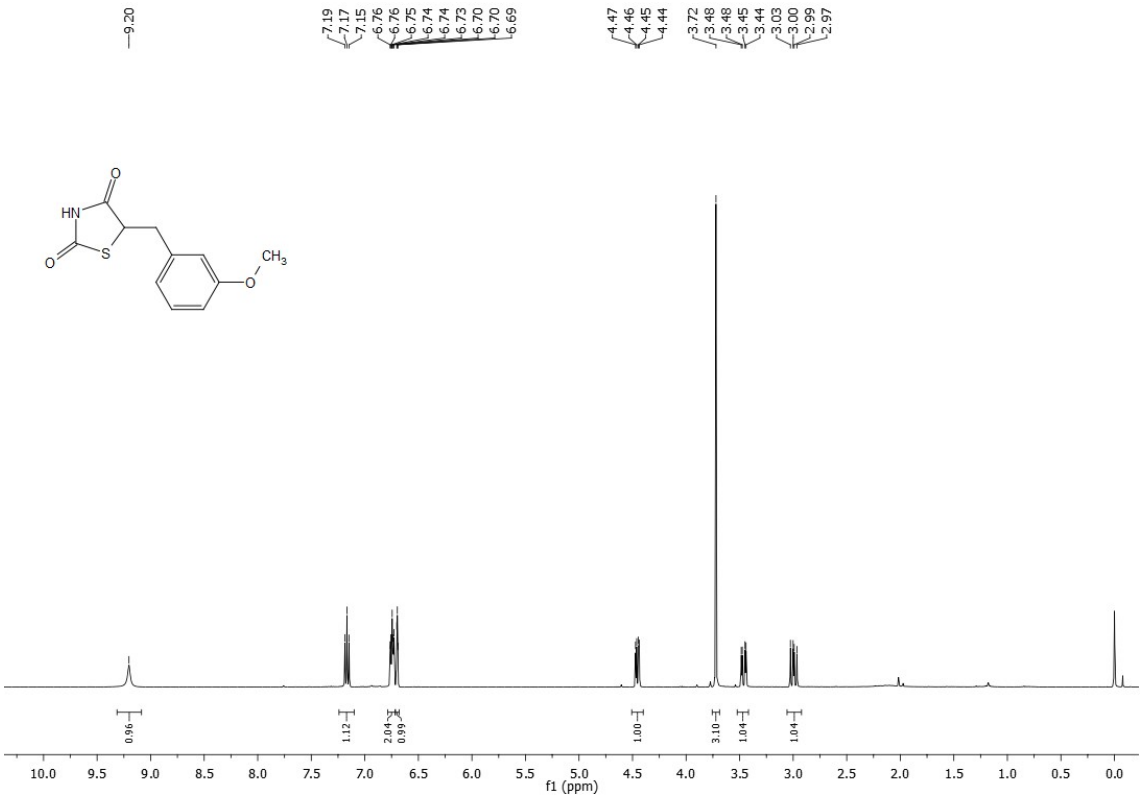


Figure S35. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1i**.

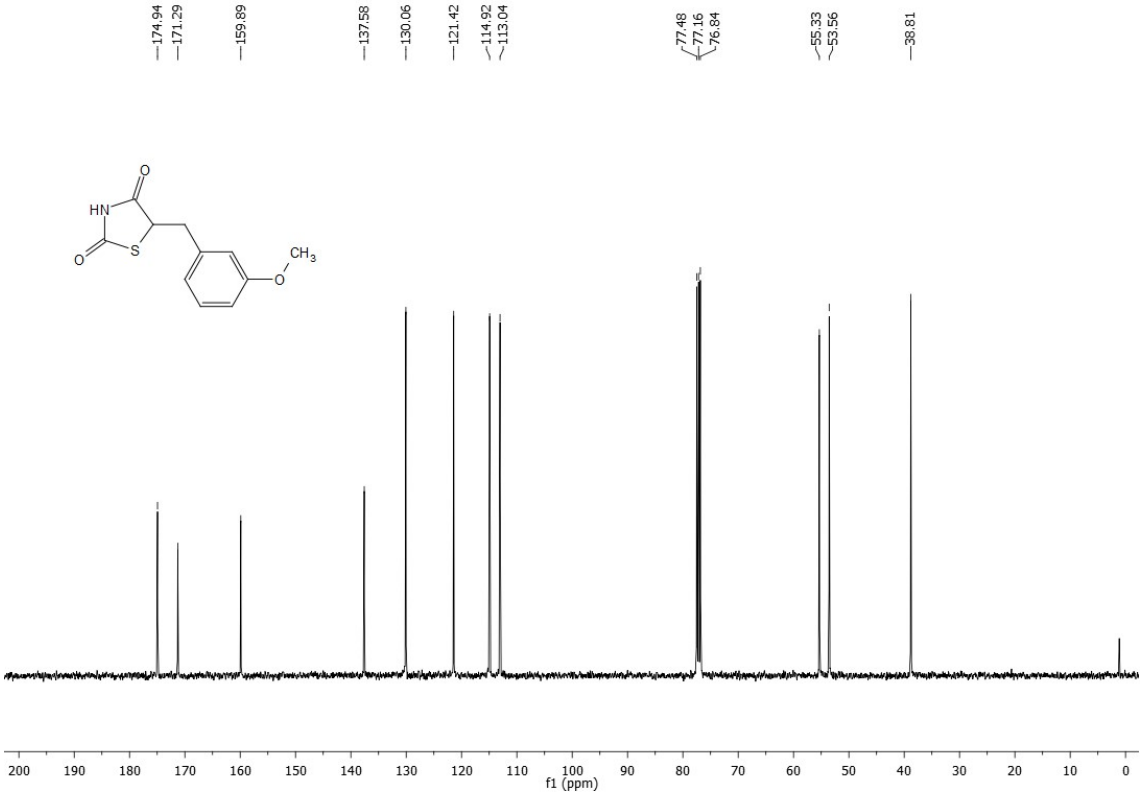


Figure S36. DEPT135 (100 MHz, $CDCl_3$) of compound **1i**.

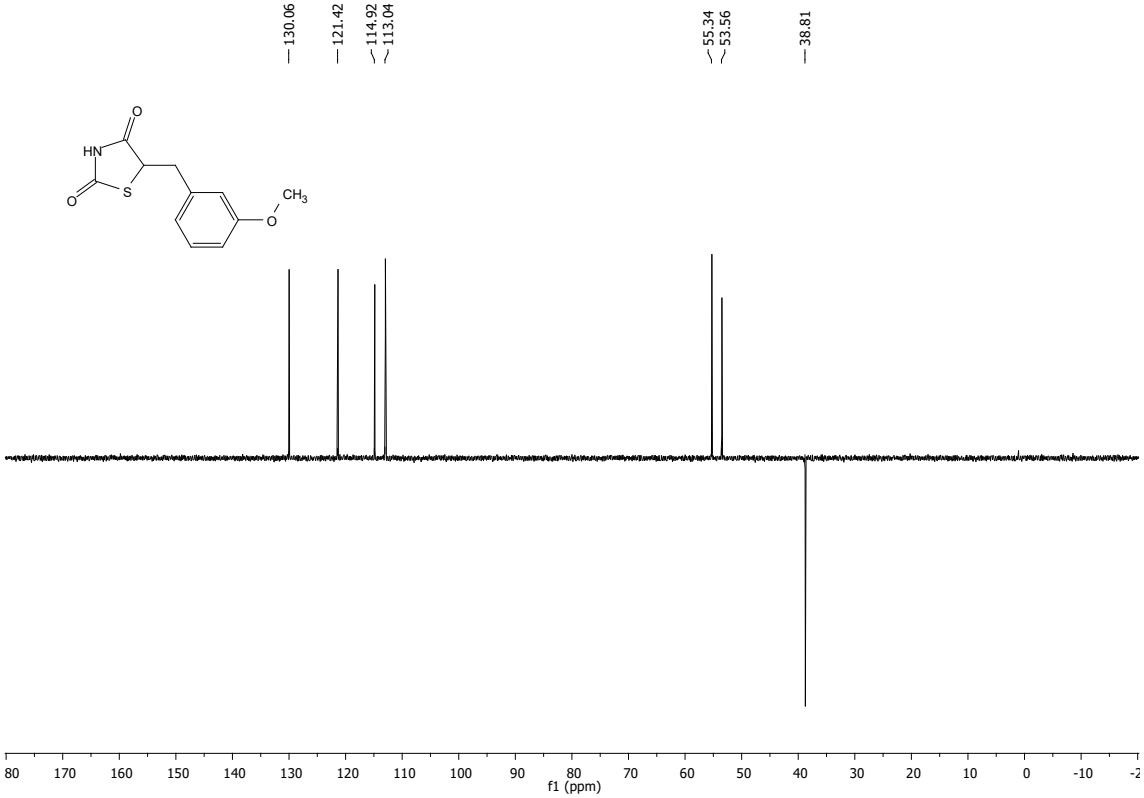


Figure S37. ^1H NMR (400 MHz, $CDCl_3$) of compound **1j**.

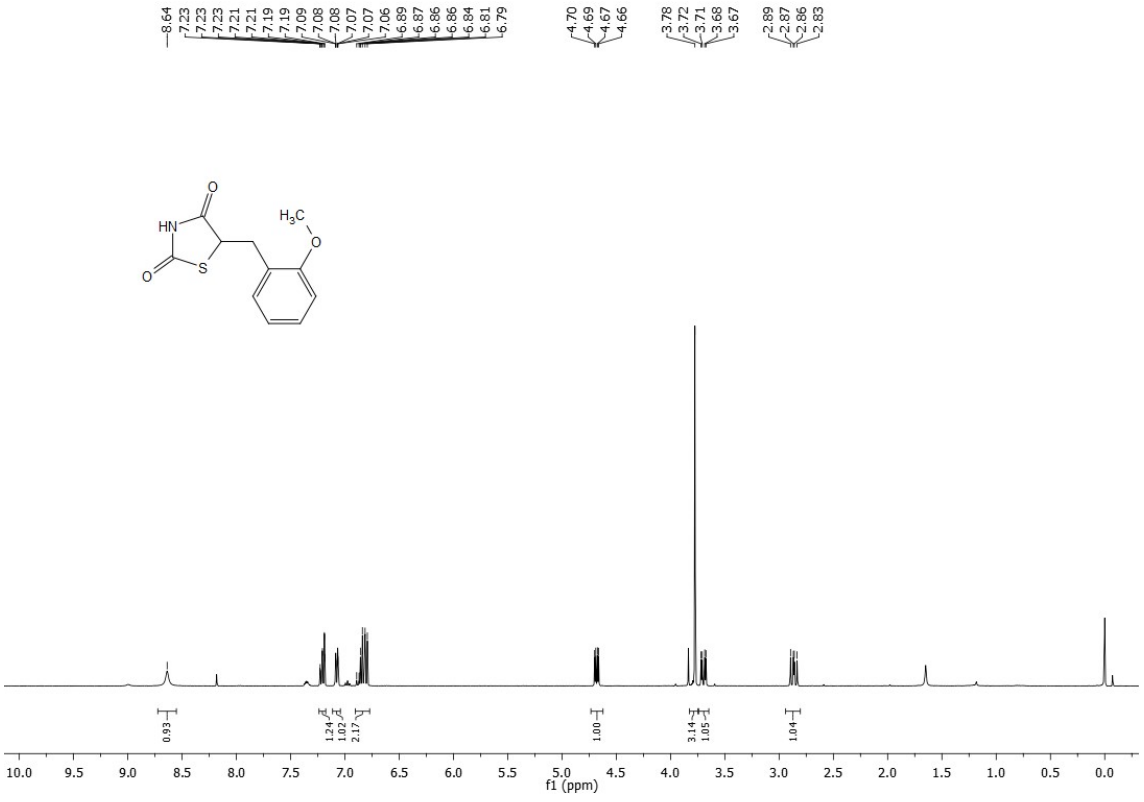


Figure S38. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1j**.

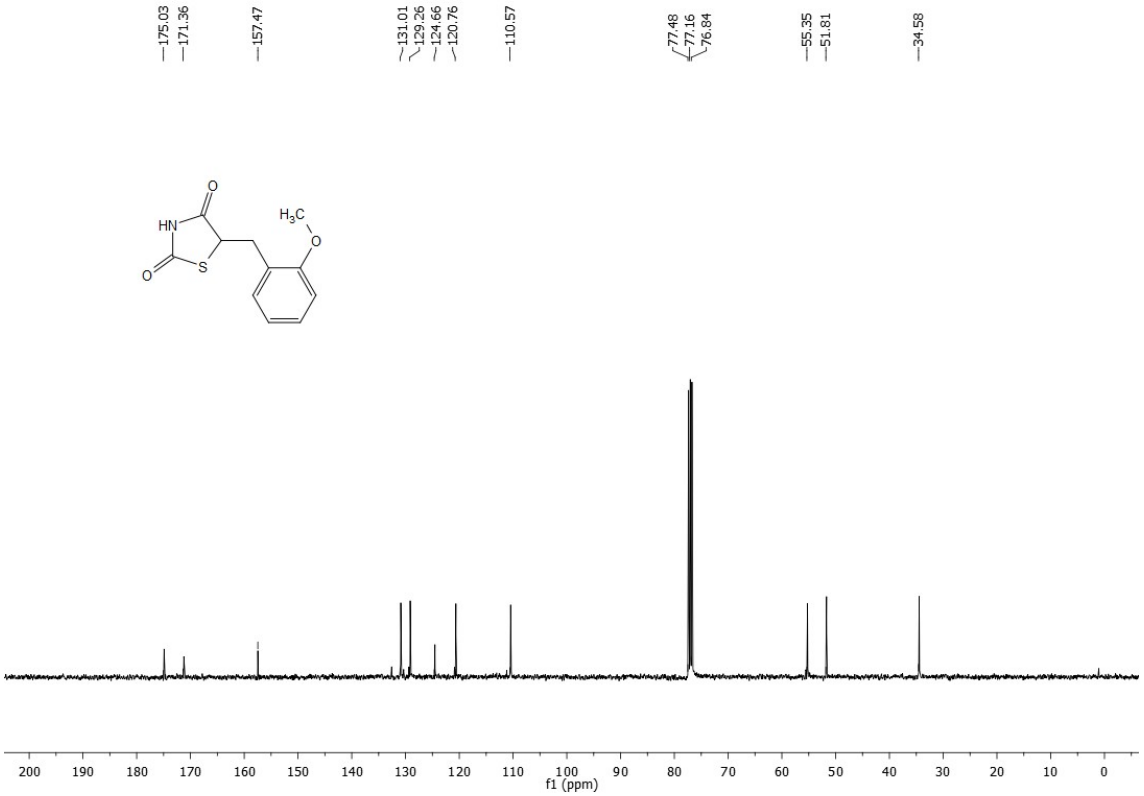


Figure S39. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1k**.

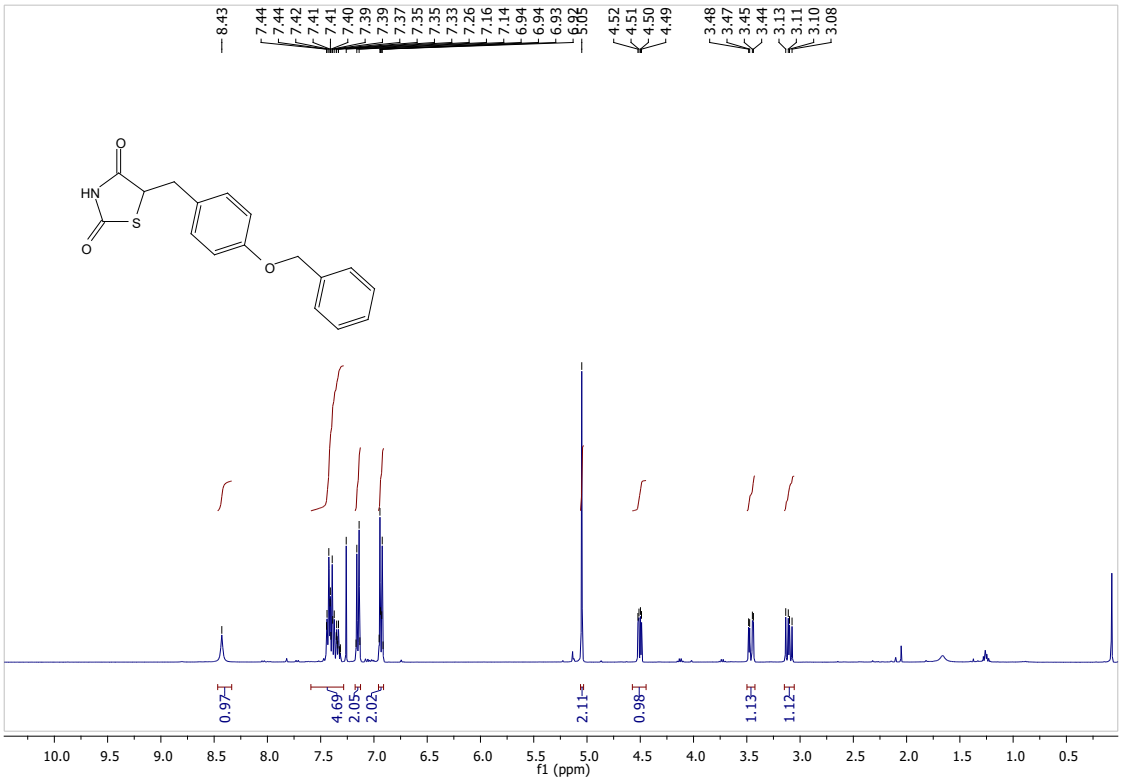


Figure S40. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1k**.

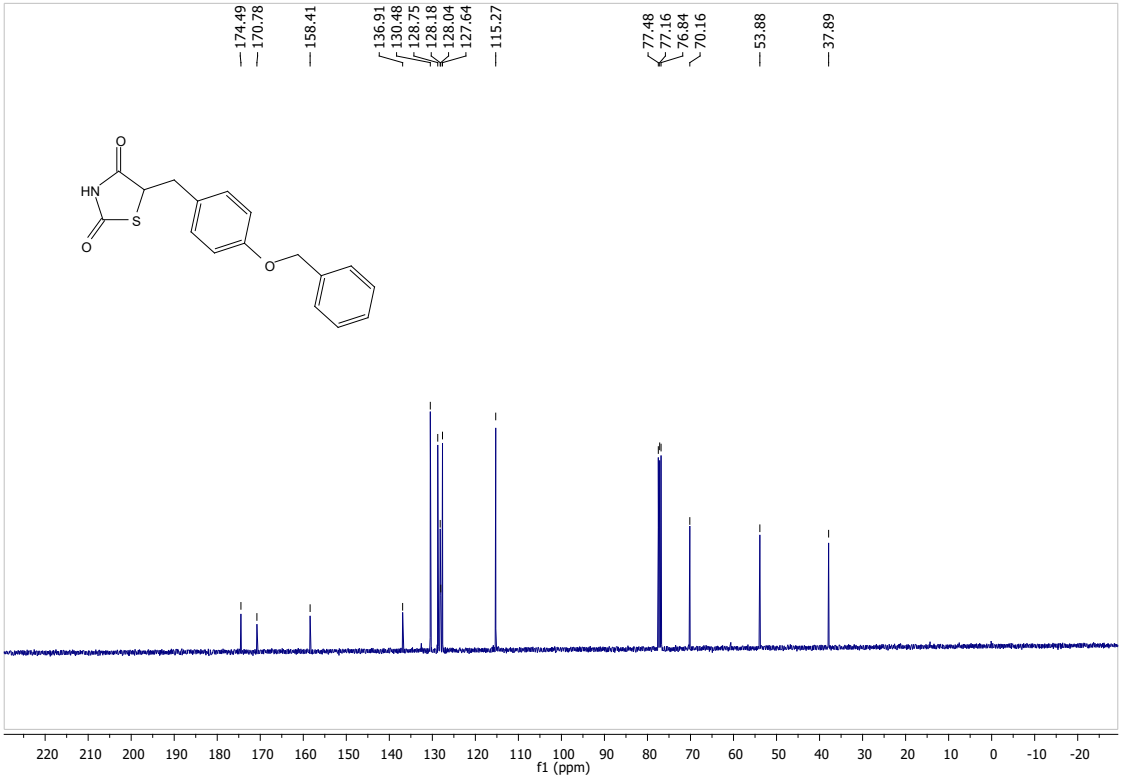


Figure S41. FT-IR (KBr) of compound **1l**.

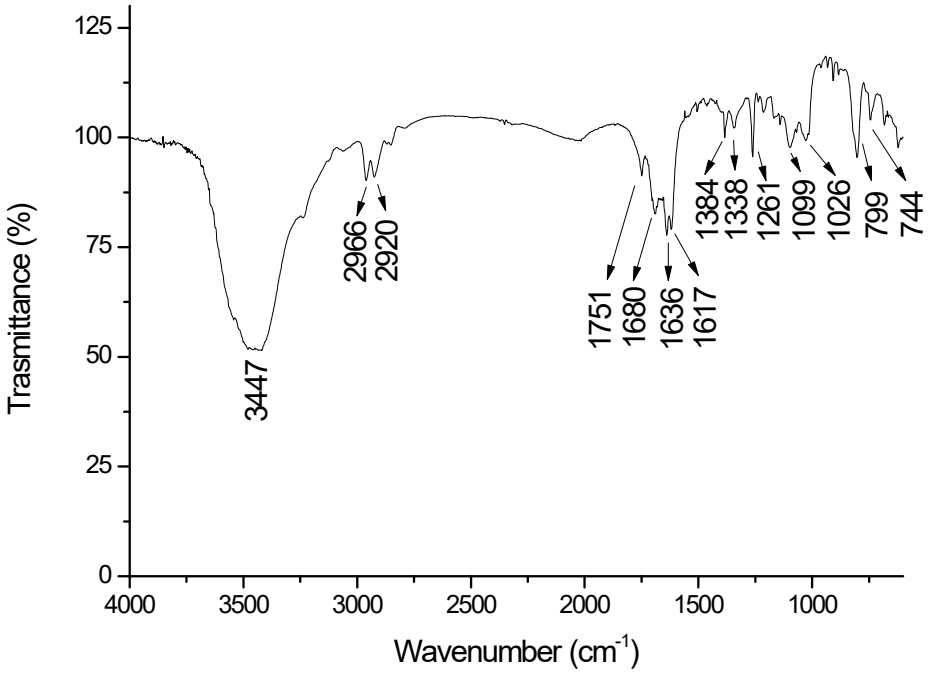


Figure S42. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1l**.

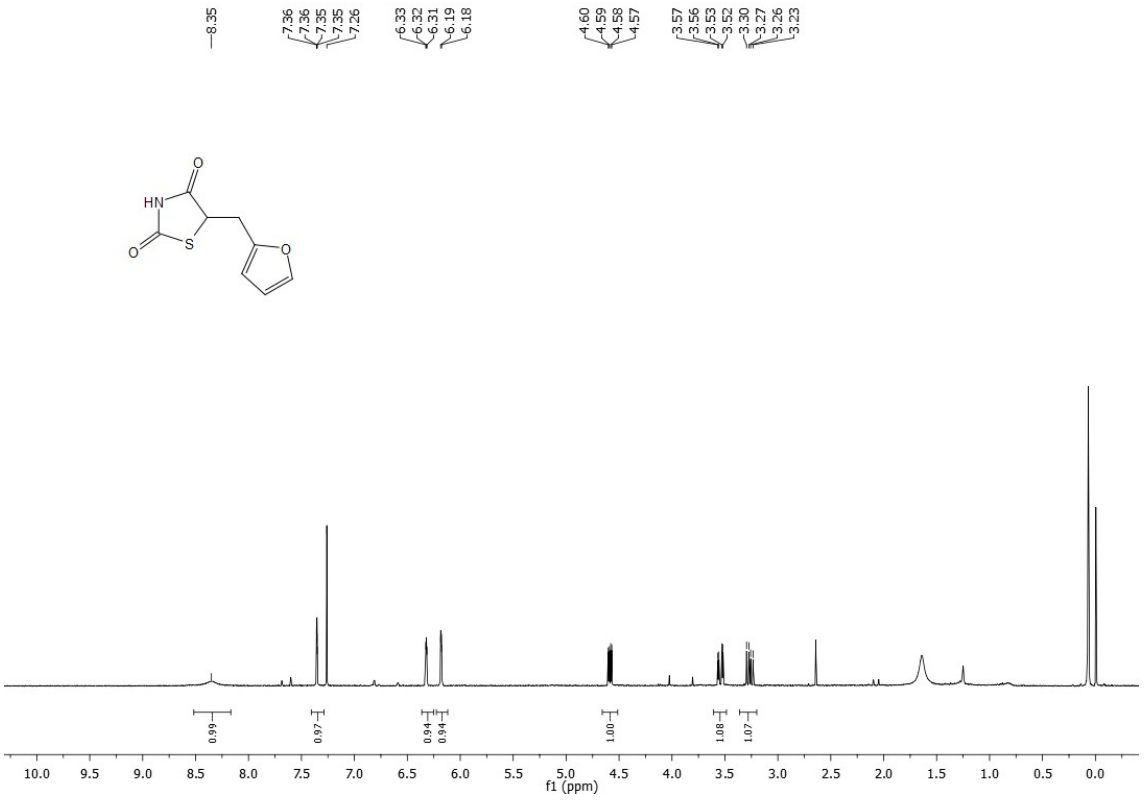


Figure S43. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1l**.

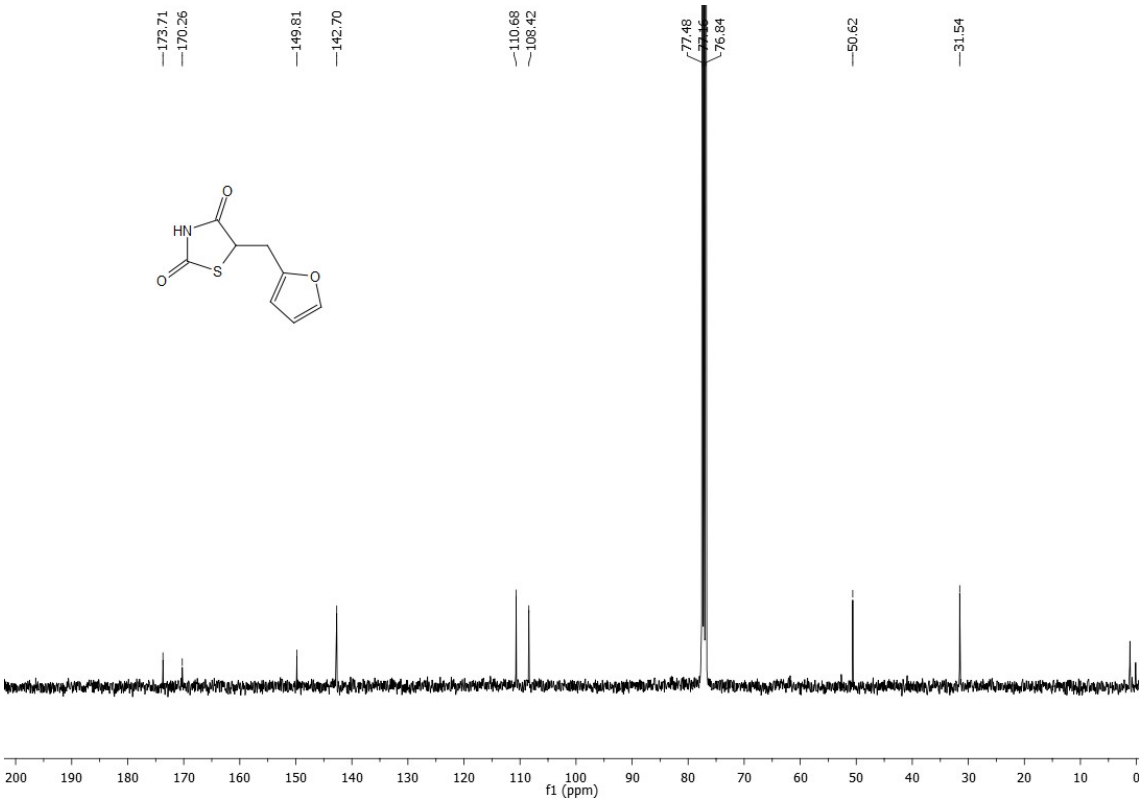


Figure S44. DEPT135 (100 MHz, $CDCl_3$) of compound **1l**.

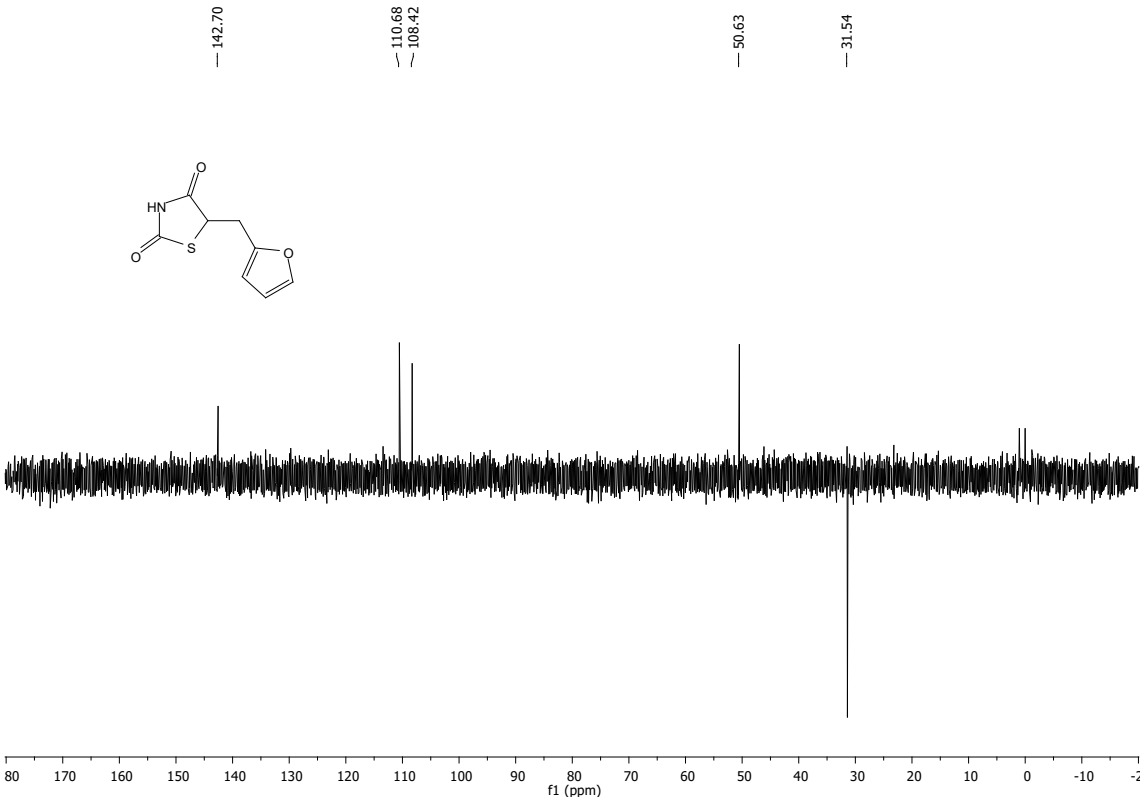


Figure S45. FT-IR (KBr) of compound **1m**.

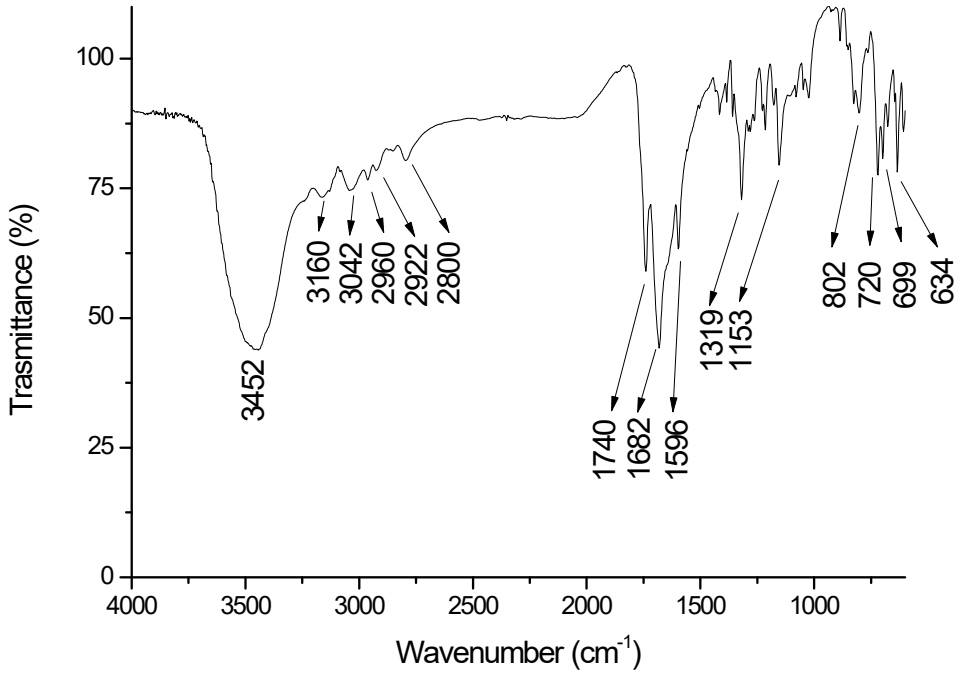


Figure S46. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1m**.

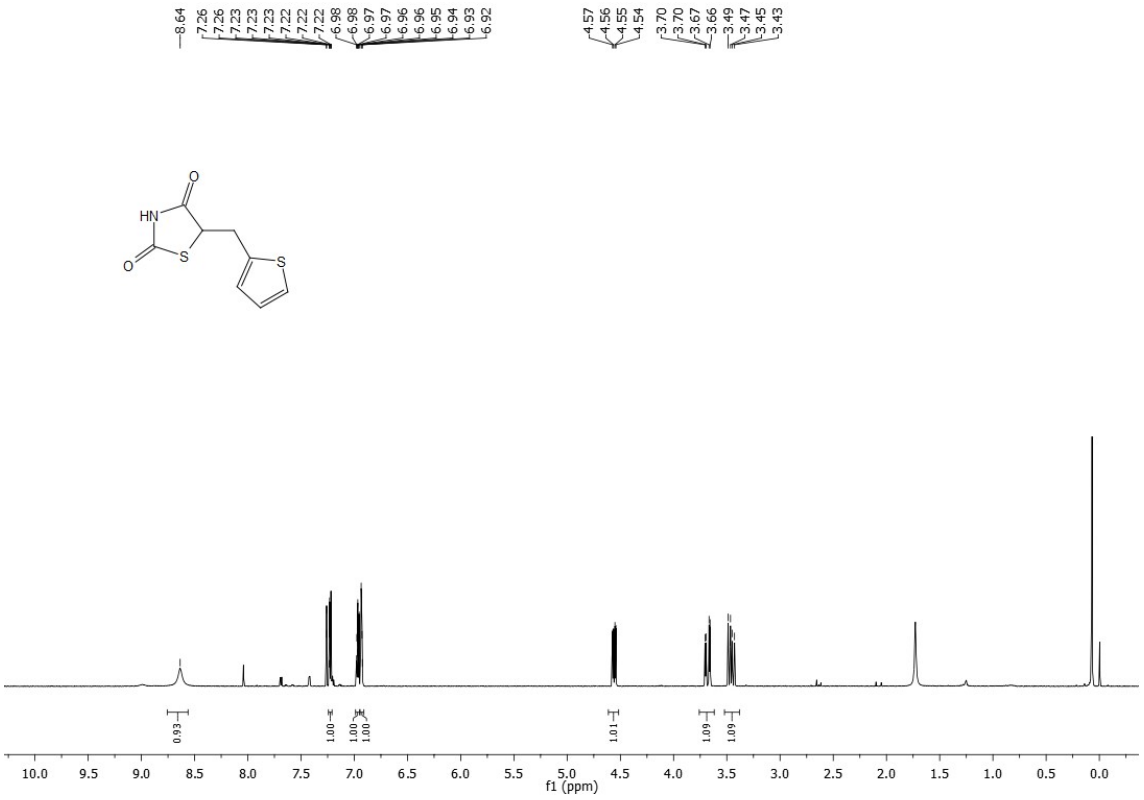


Figure S47. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1m**.

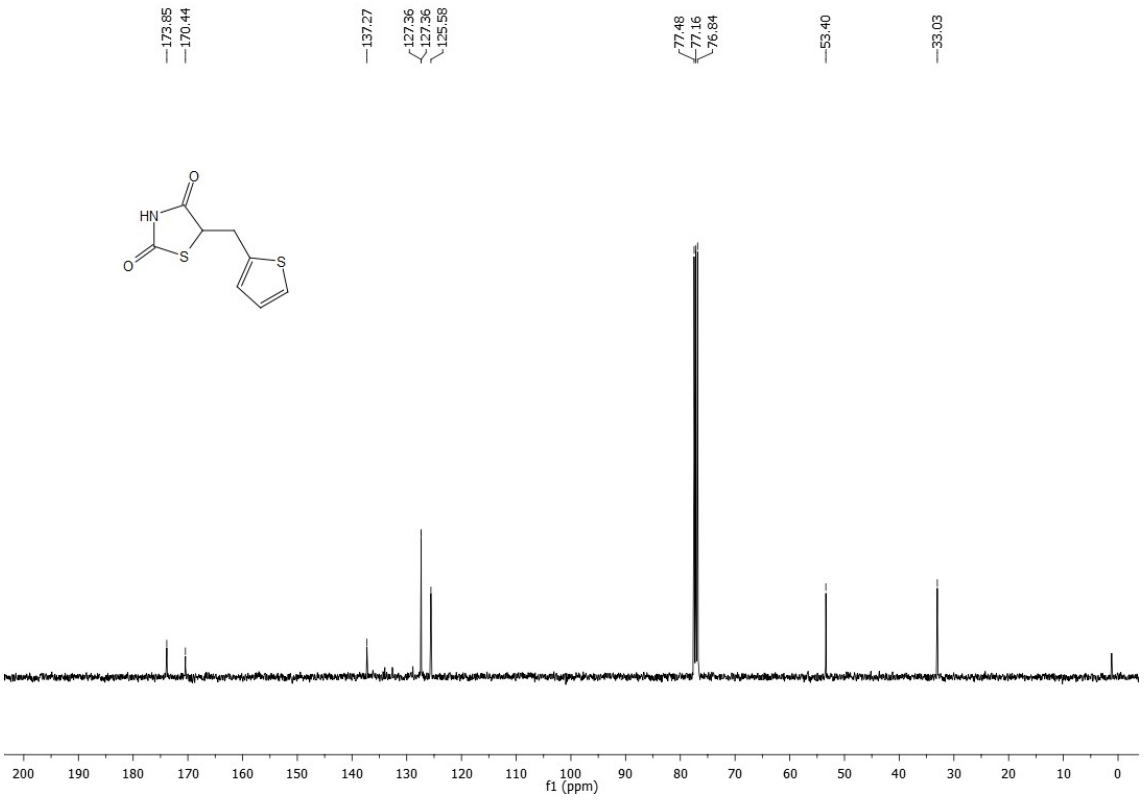


Figure S48. DEPT135 (100 MHz, $CDCl_3$) of compound **1m**.

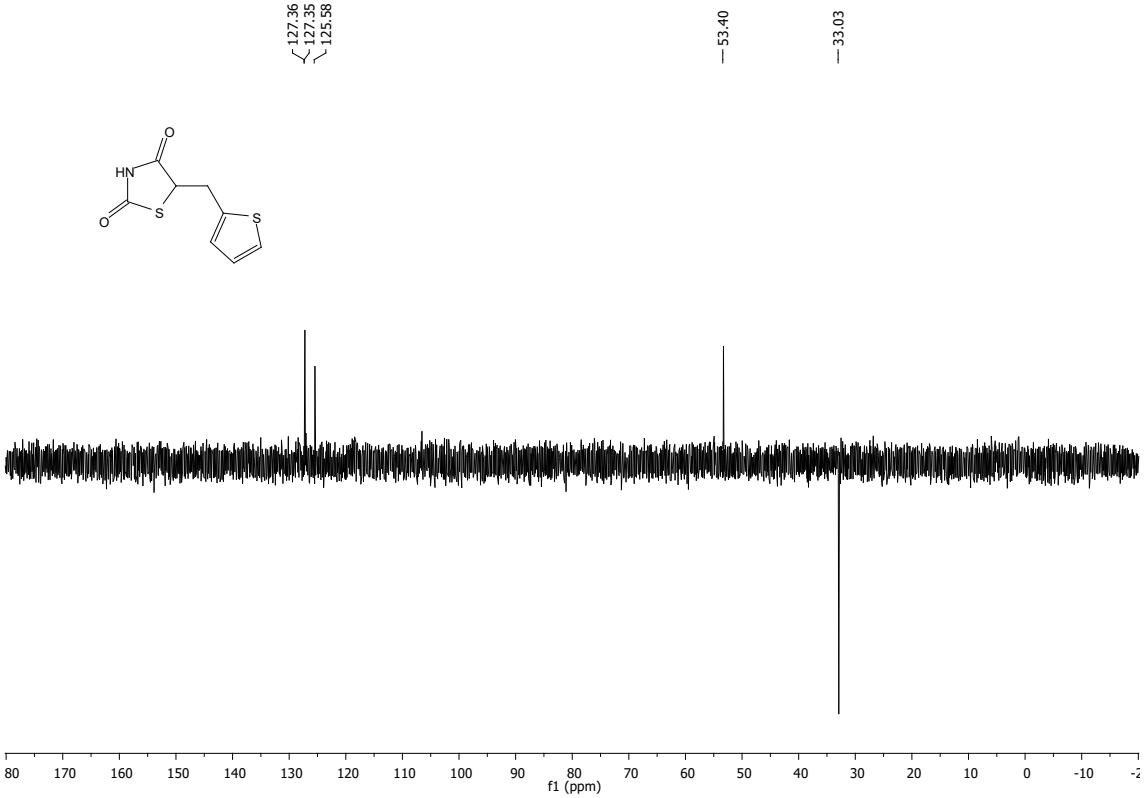


Figure S49. ^1H NMR (400 MHz, $CDCl_3$) of compound **1n**.

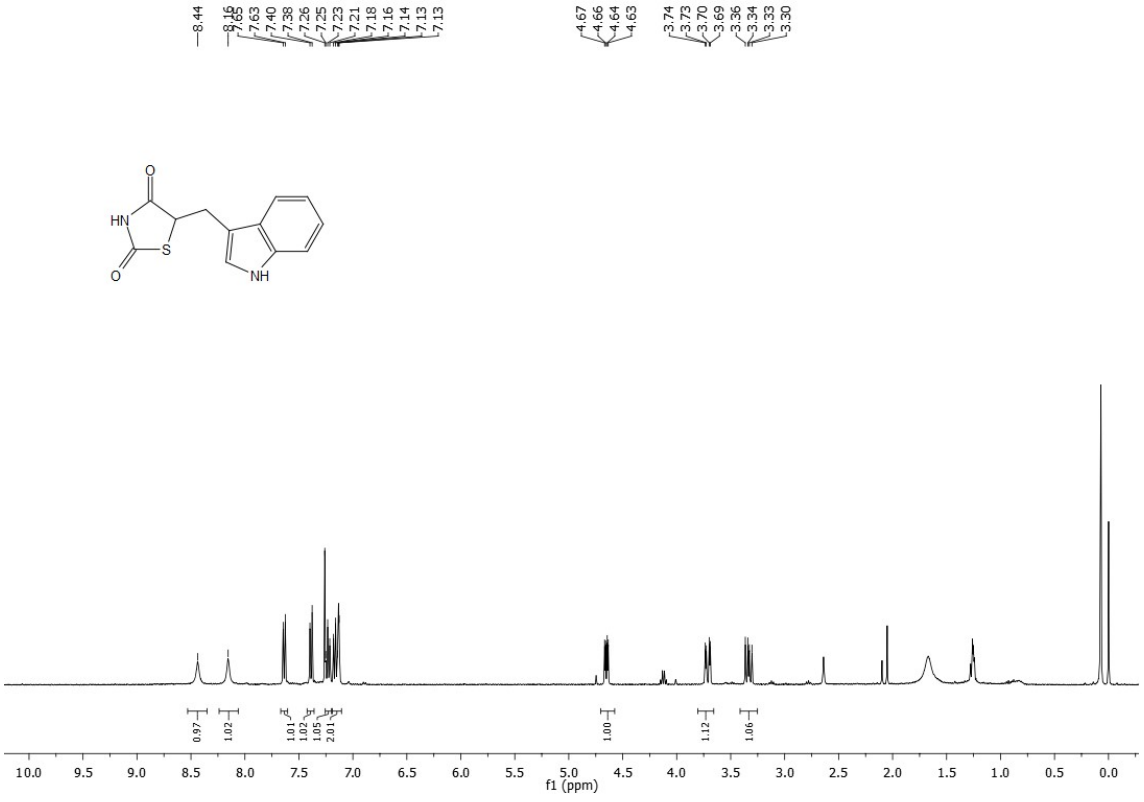


Figure S50. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1n**.

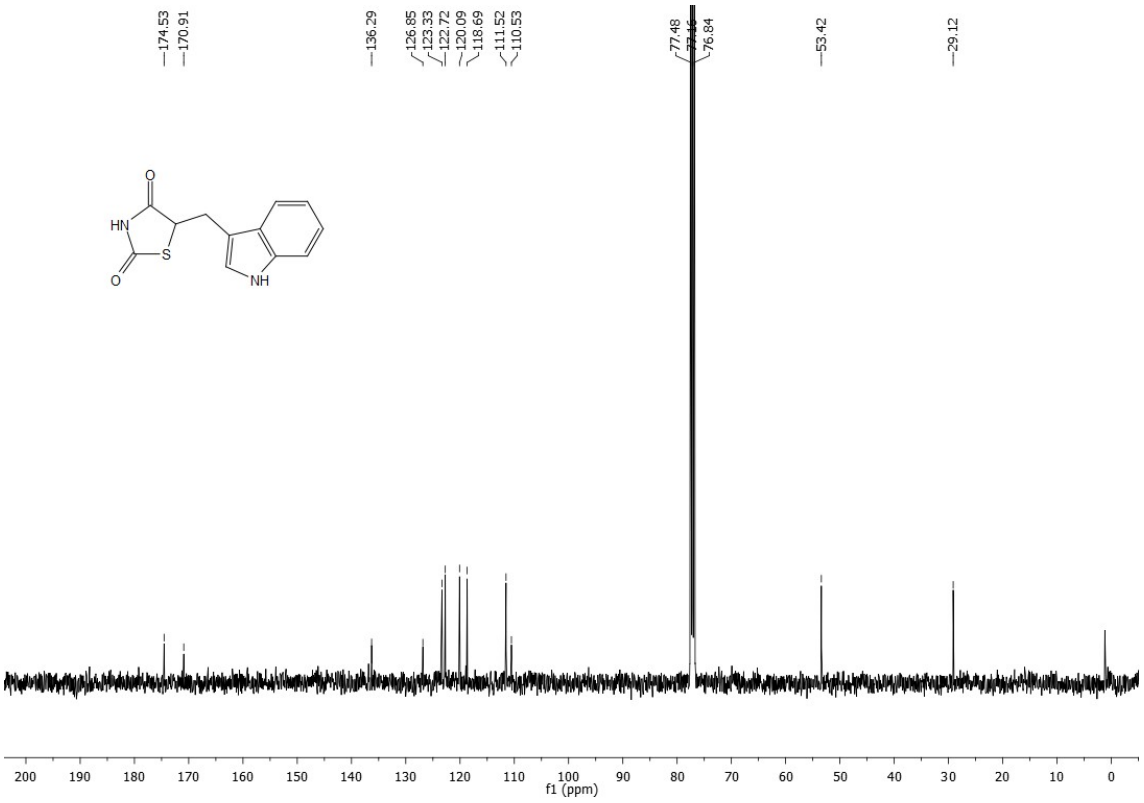


Figure S51. DEPT135 (100 MHz, $CDCl_3$) of compound **1n**.

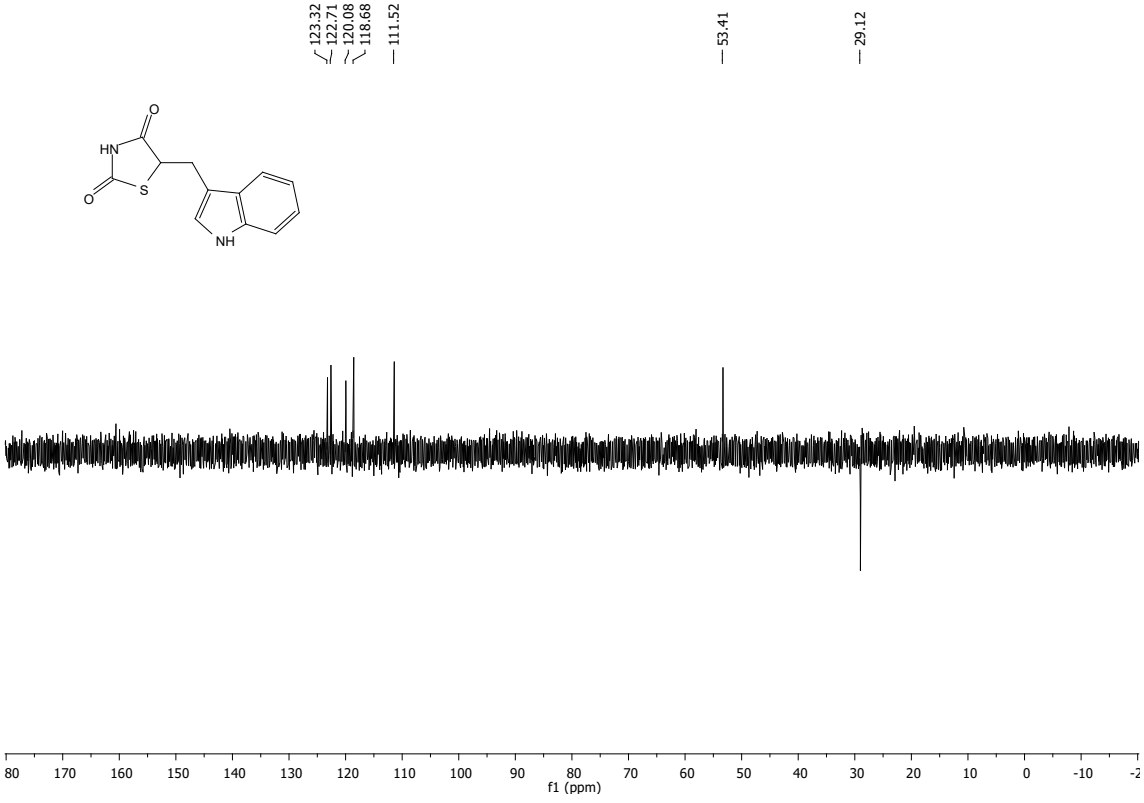


Figure S52. FT-IR (KBr) of compound **1o**.

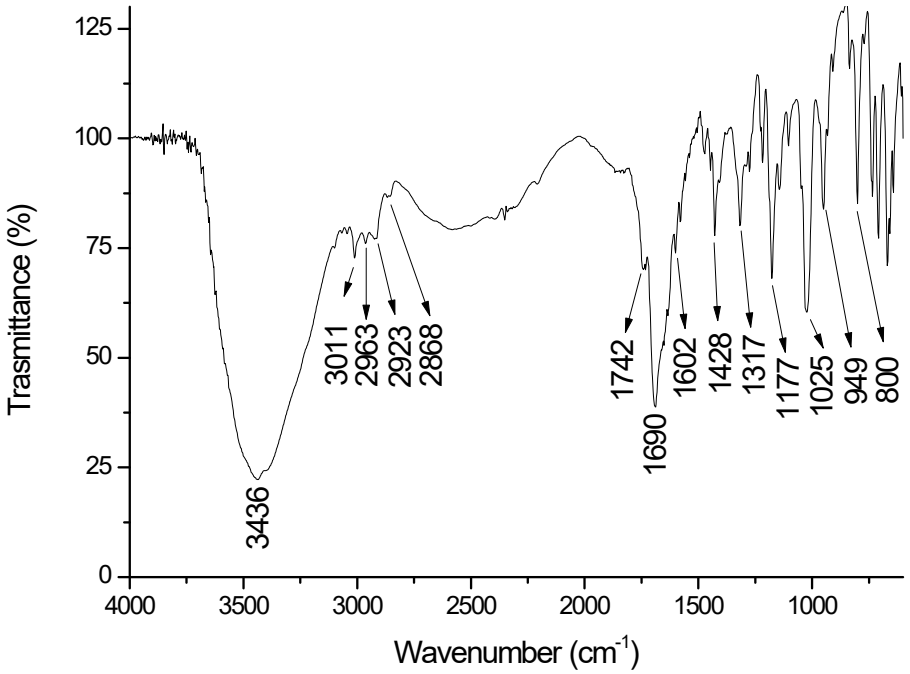


Figure S53. ^{1}H NMR (400 MHz, DMSO-d_6) of compound **1o**.

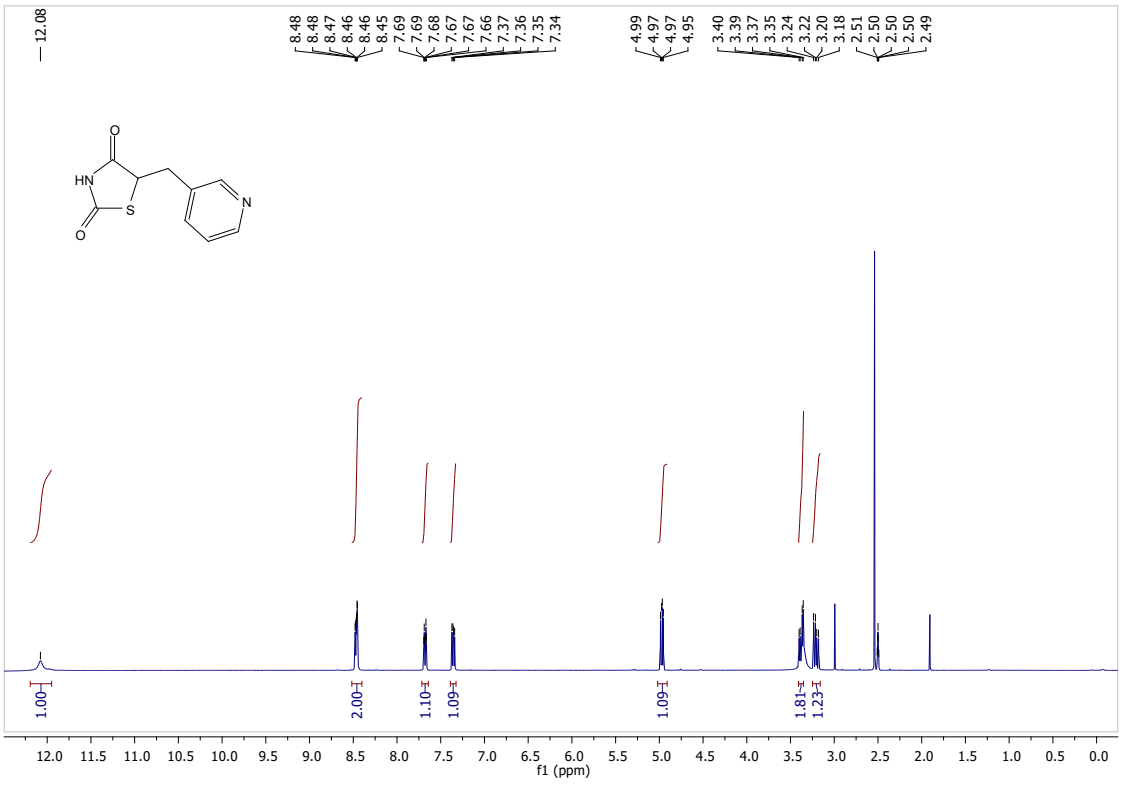


Figure S54. ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) of compound **1o**.

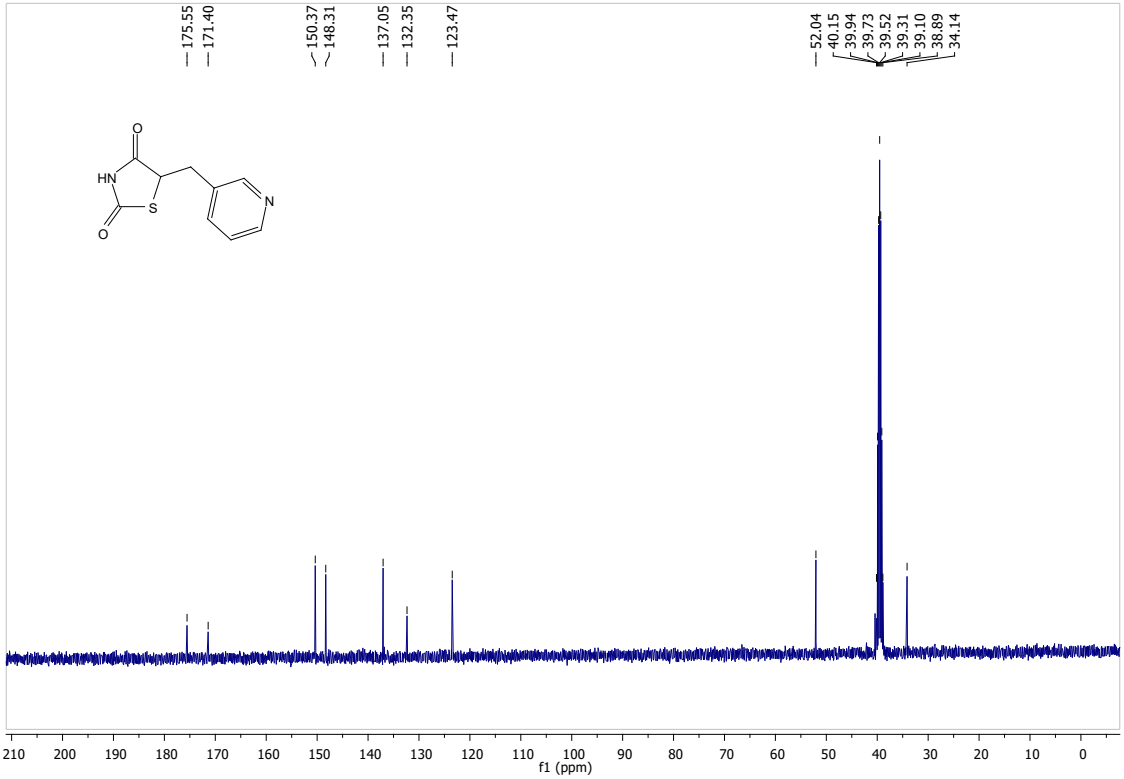


Figure S55. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1p**.

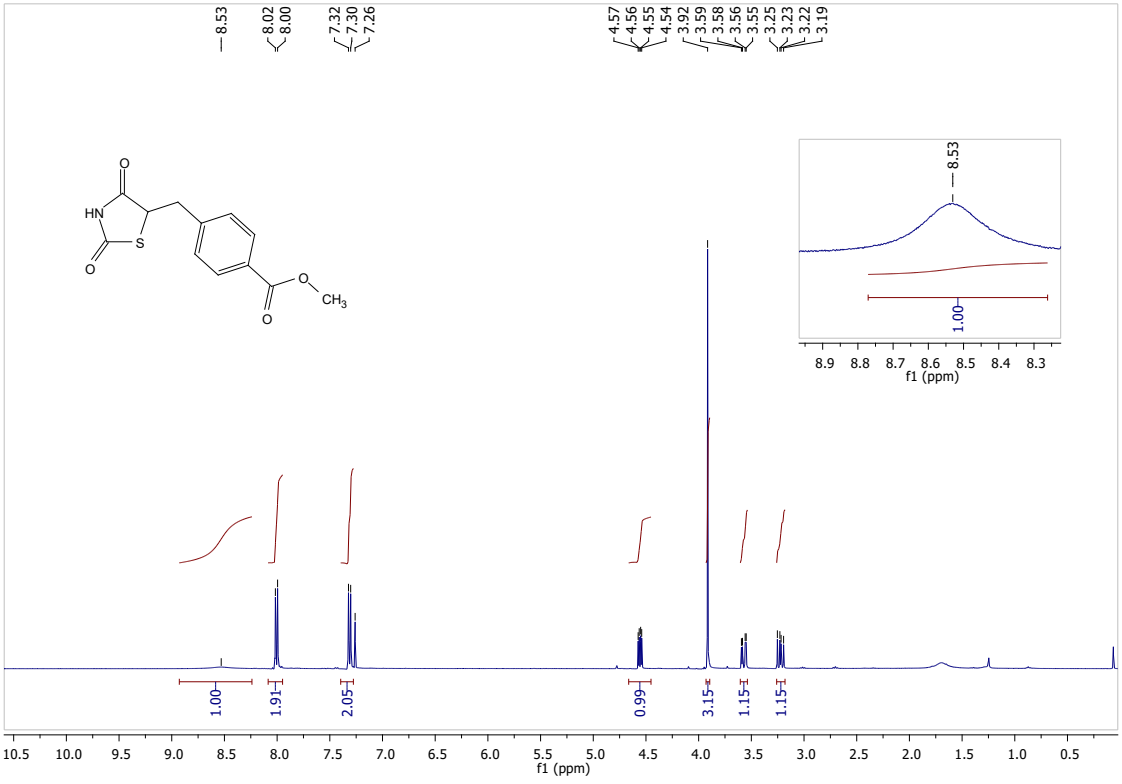


Figure S56. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1p**.

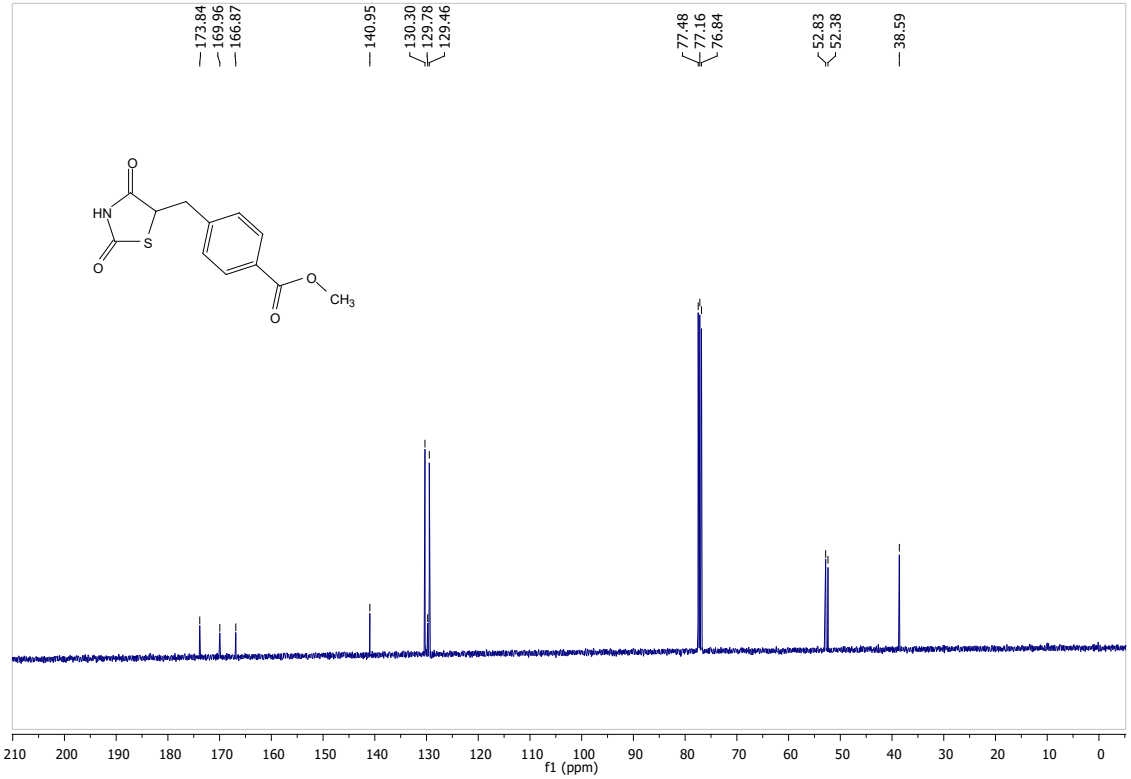


Figure S57. FT-IR (KBr) of compound **1s**.

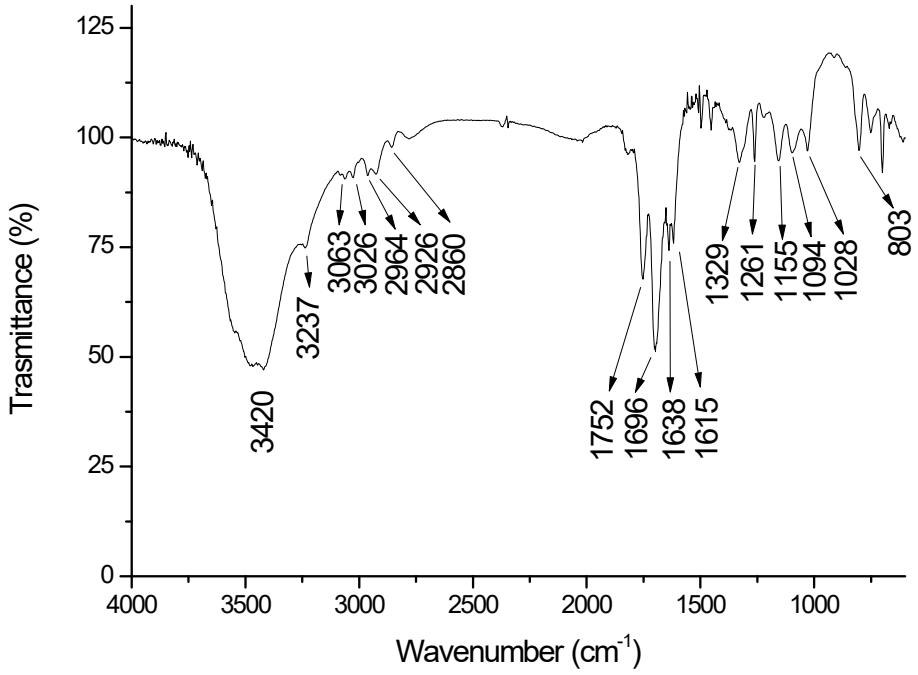


Figure S58. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1s**.

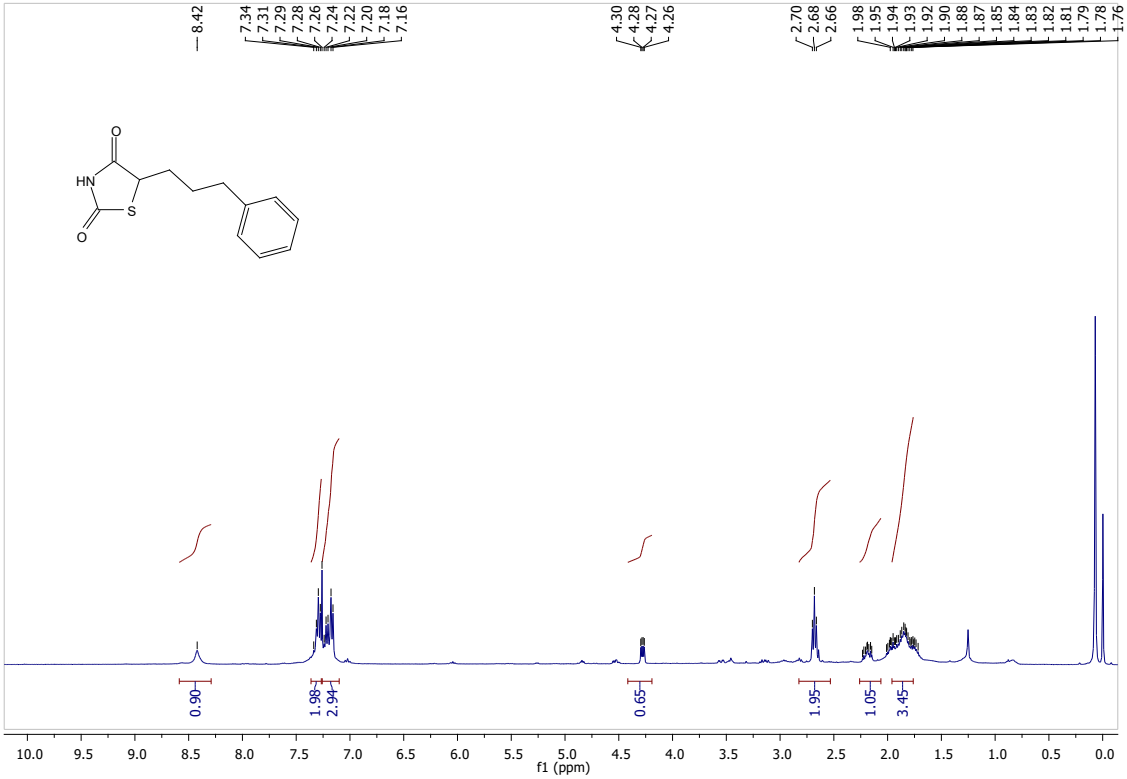


Figure S59. ^{13}C $\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **1s**.

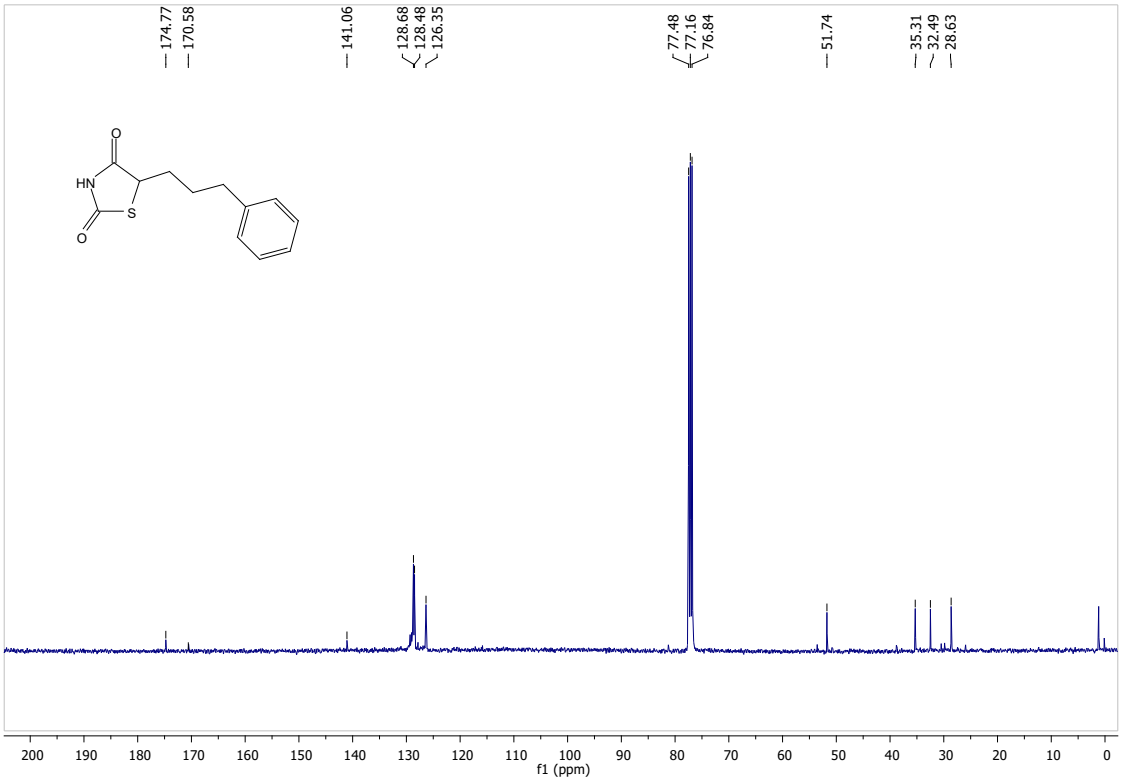


Figure S60. ^{1}H NMR (400 MHz, DMSO-d_6) of compound **1t**.

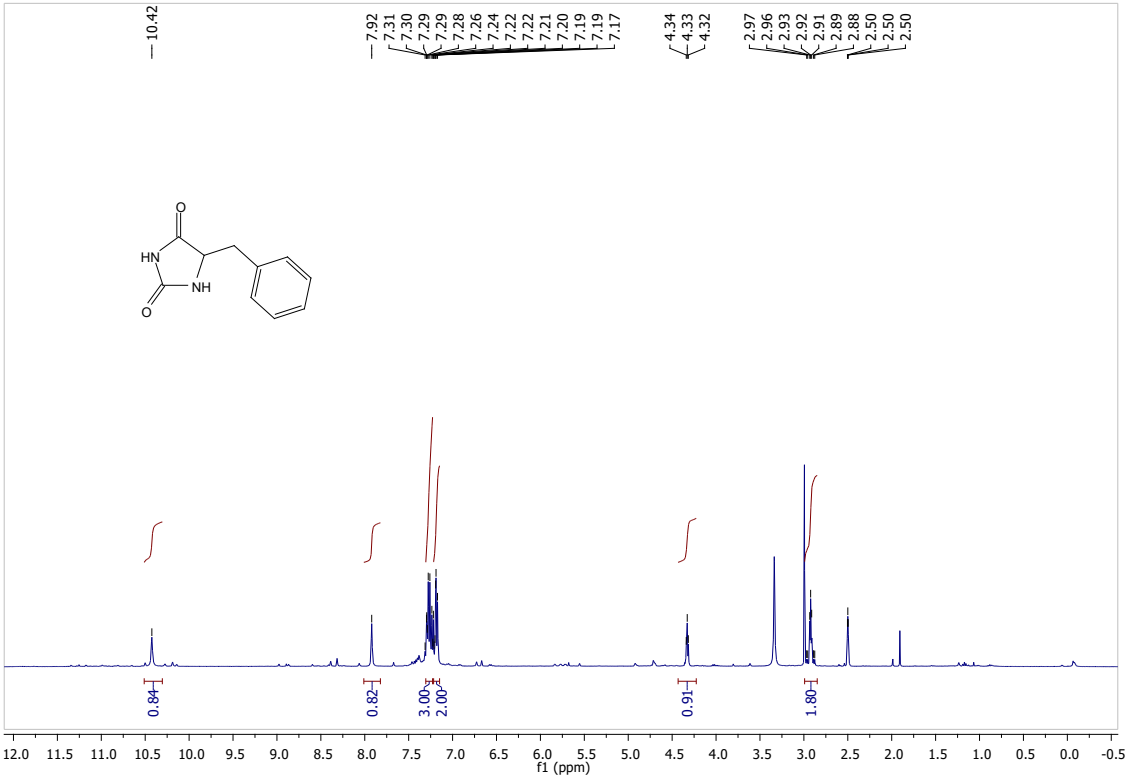


Figure S61. ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) of compound **1t**.

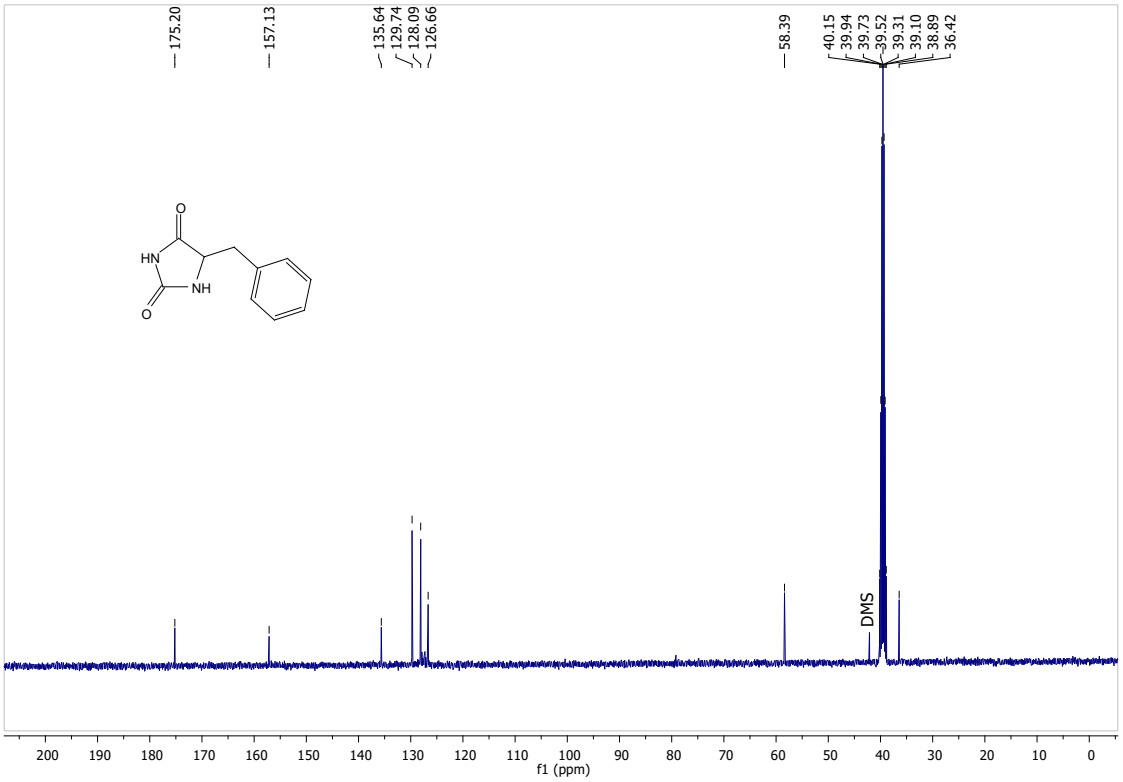


Figure S62. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1u**.

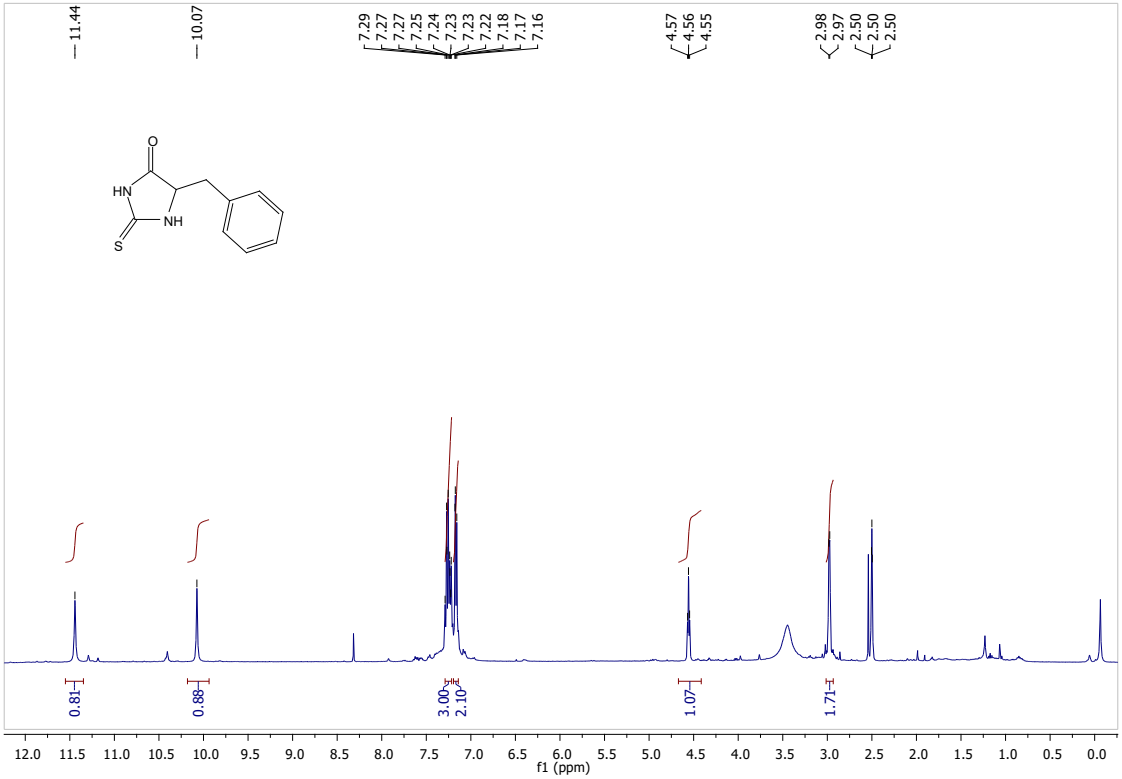
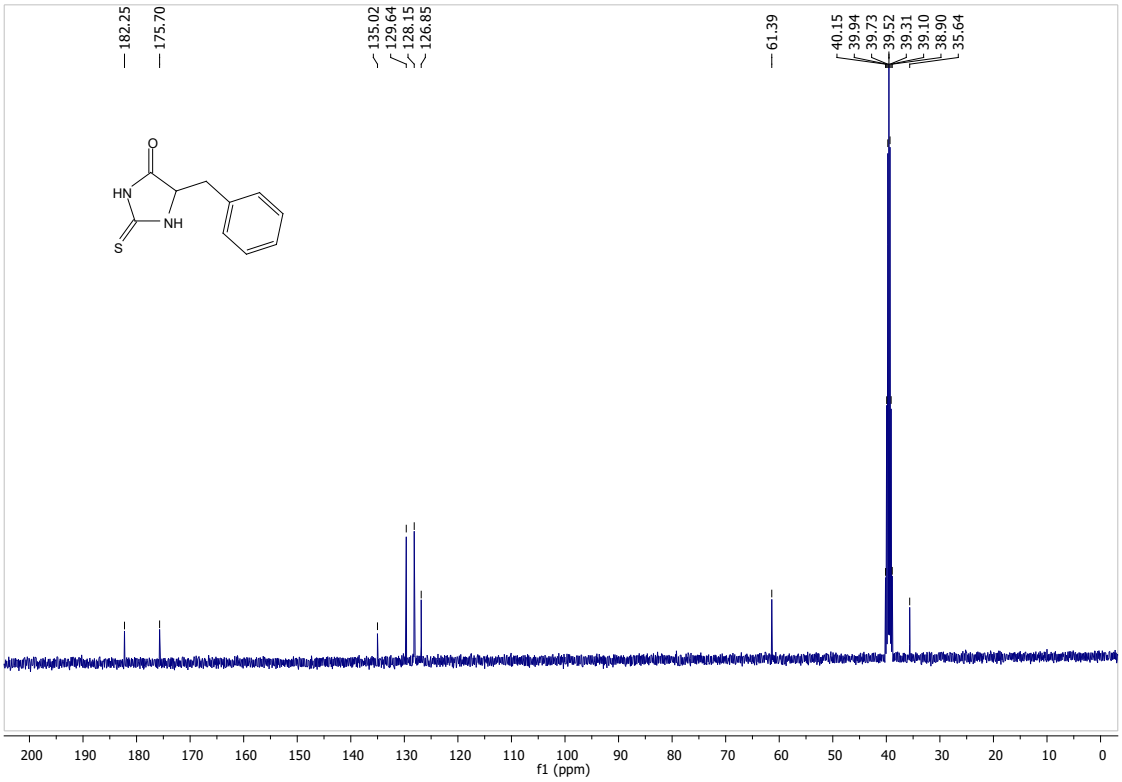


Figure S63. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) of compound **1u**.



3. NMR and IR spectra of intermediate 2, Pioglitazone and Pioglitazone hydrochloride

Figure S64. ^{1}H NMR (400 MHz, DMSO-d_6) of intermediate **2**.

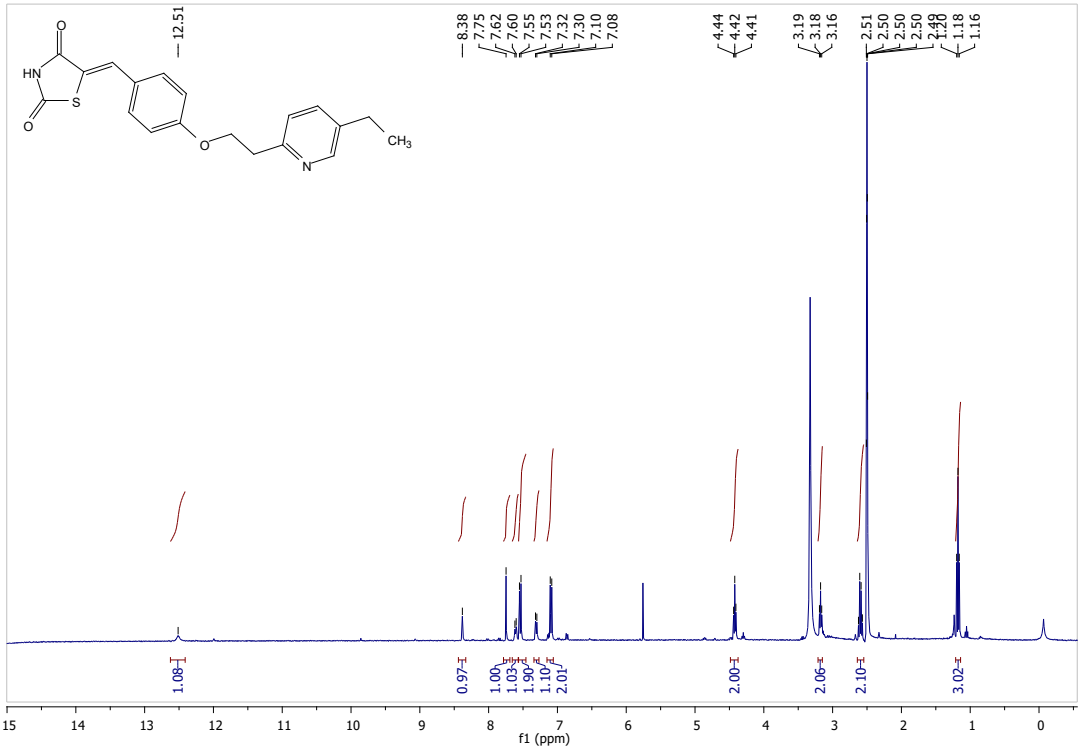


Figure S65. ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) of intermediate **2**.

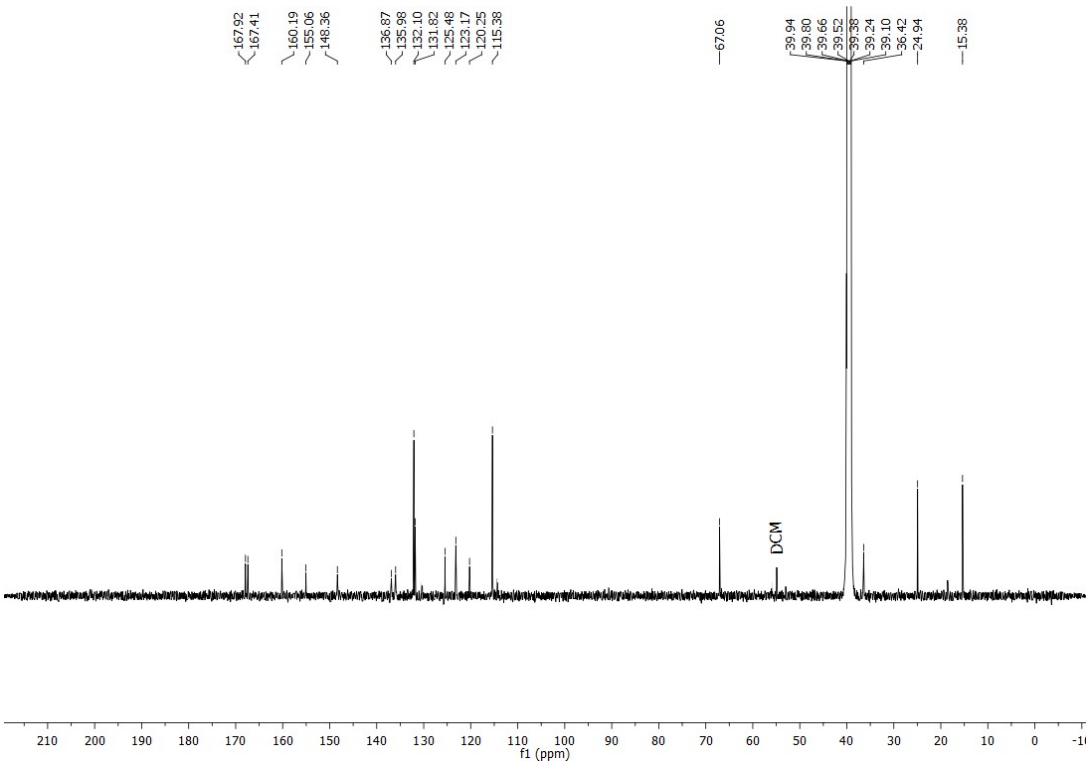


Figure S66. ^{1}H NMR (400 MHz, DMSO-d_6) of Pioglitazone.

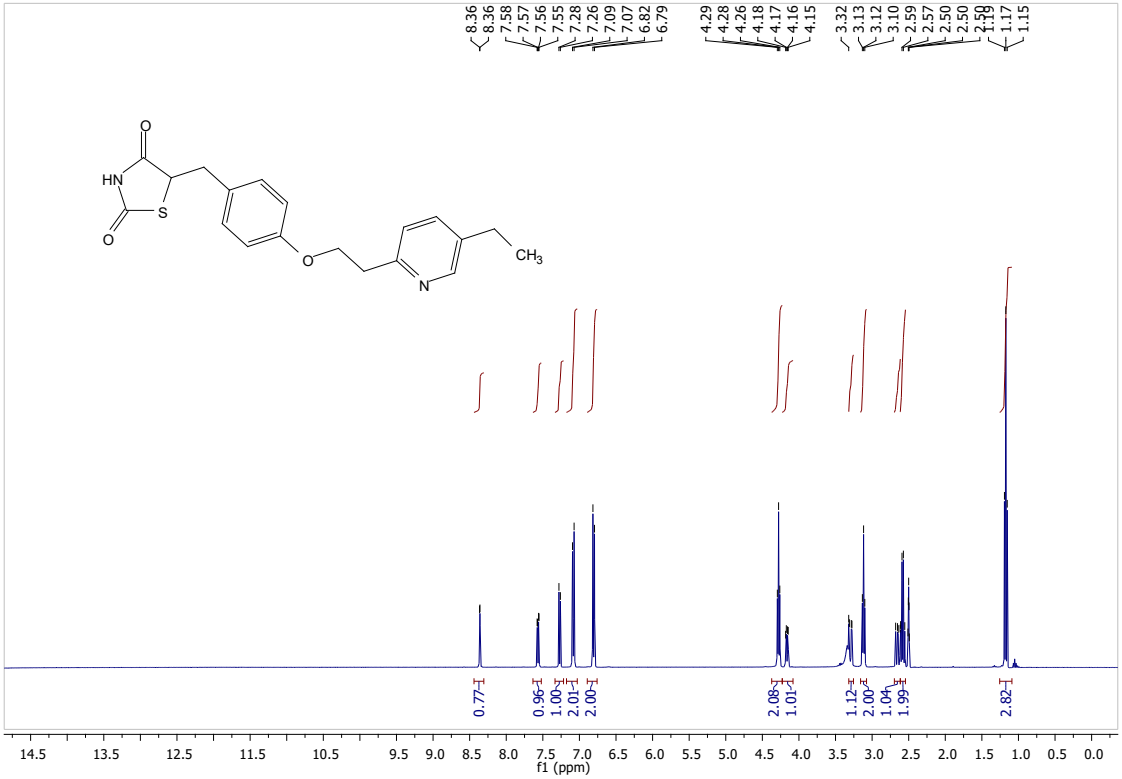


Figure S67. ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) of Pioglitazone.

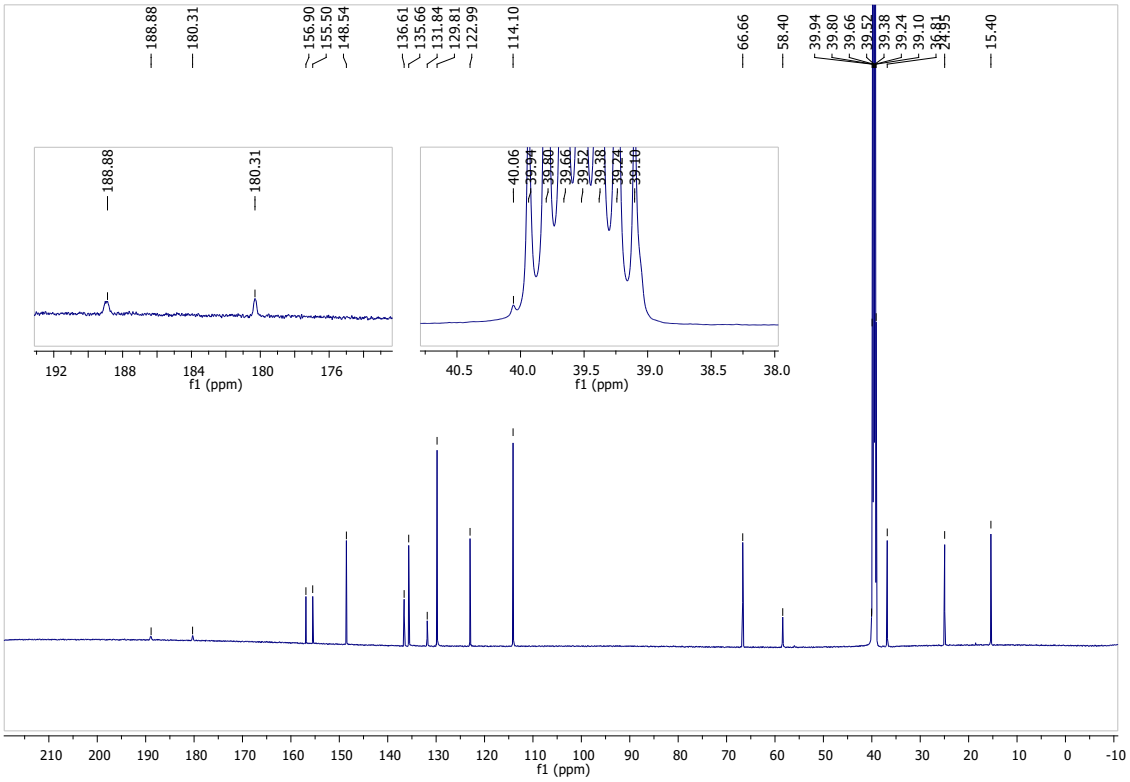


Figure S68. DEPT135 (100 MHz, DMSO-d_6) of Pioglitazone.

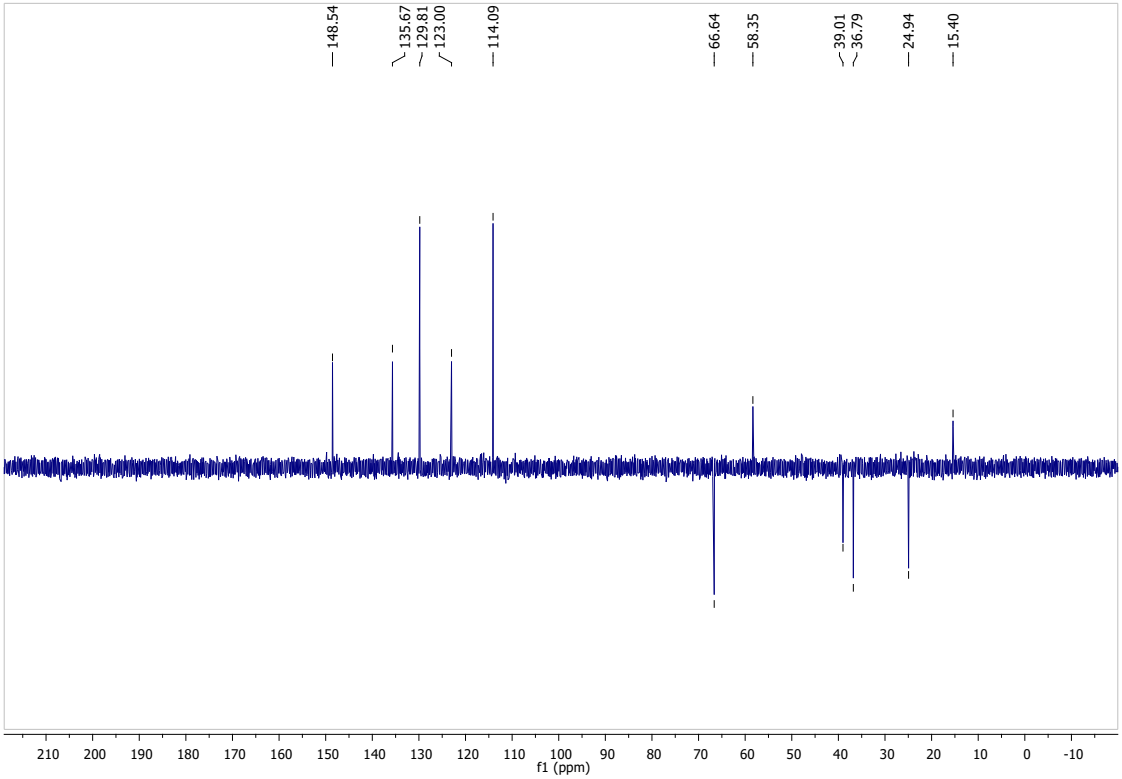


Figure S69. FT-IR (KBr) of Pioglitazone hydrochloride.

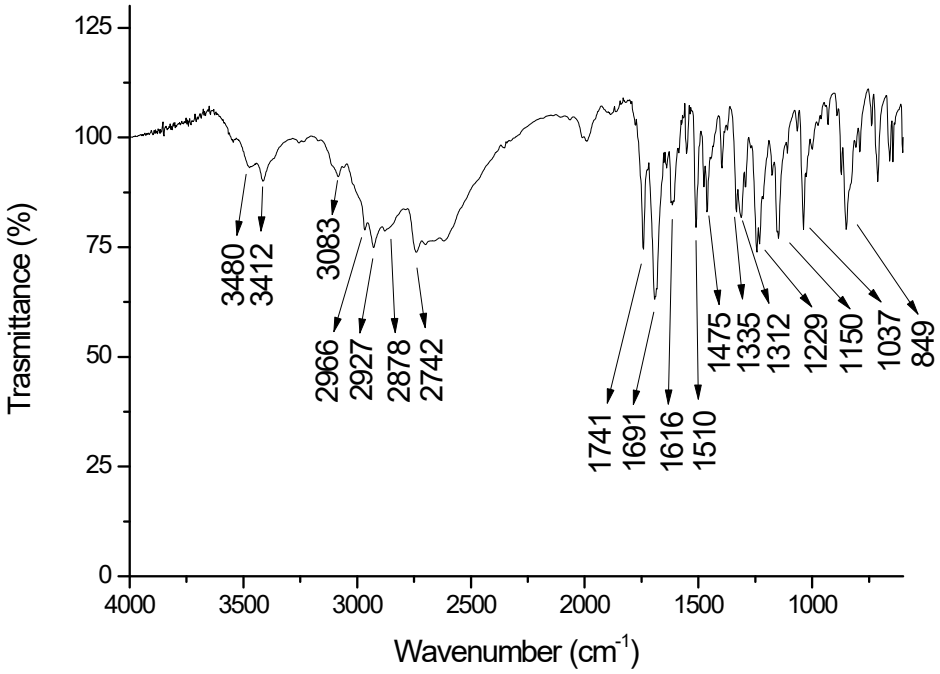


Figure S70. ^{1}H NMR (400 MHz, DMSO-d_6) of Pioglitazone hydrochloride.

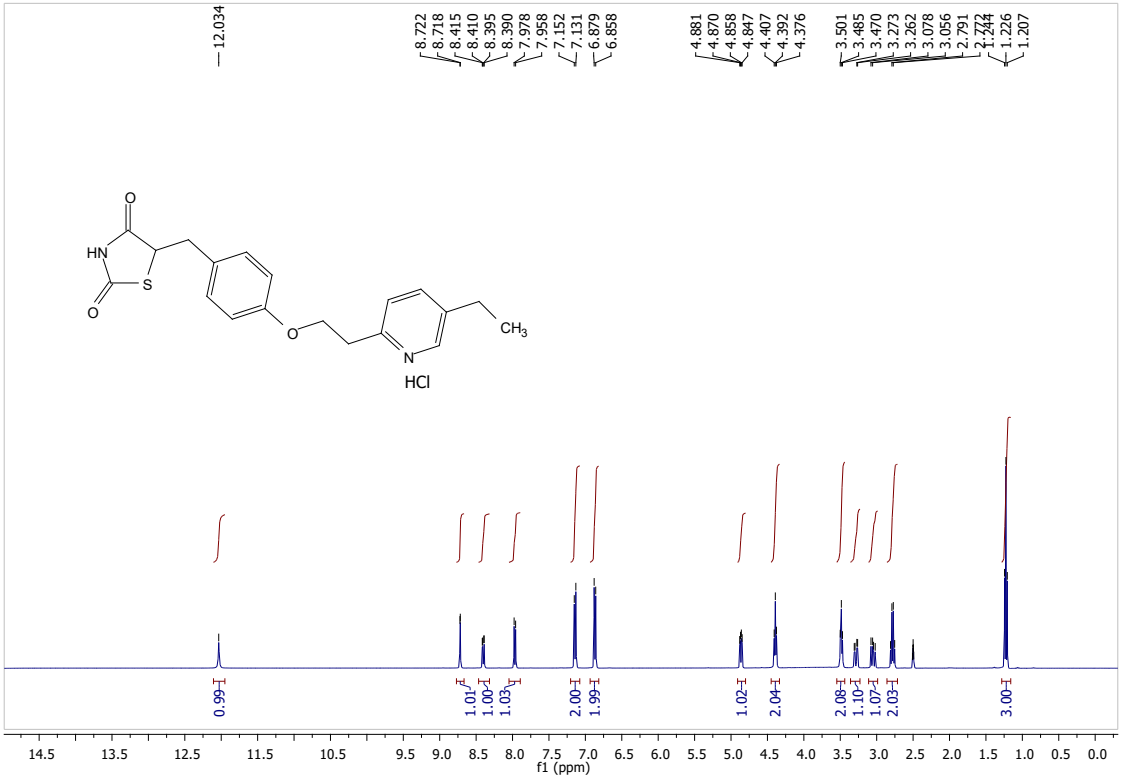
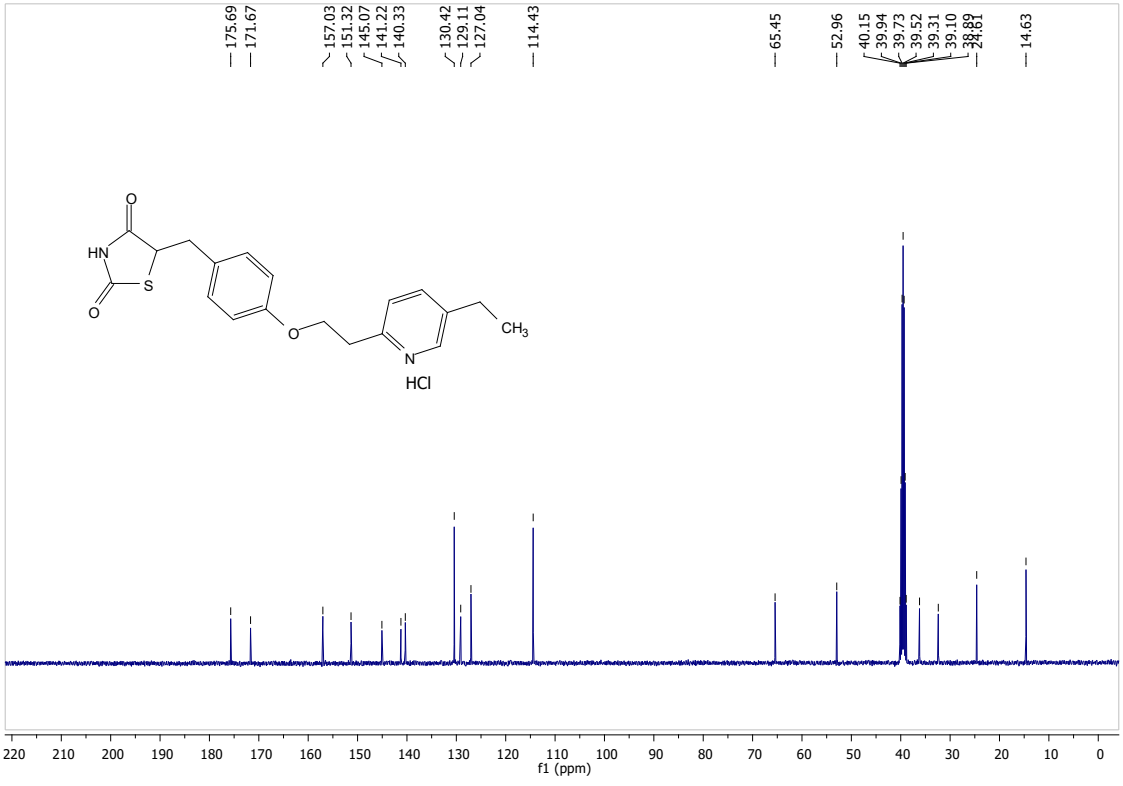


Figure S71. ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) of Pioglitazone hydrochloride.



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