Supporting information for:

Discovery of Novel *N*-Isoxazolylphenyltriazinones as Promising Protoporphyrinogen IX Oxidase Inhibitors

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Contents:

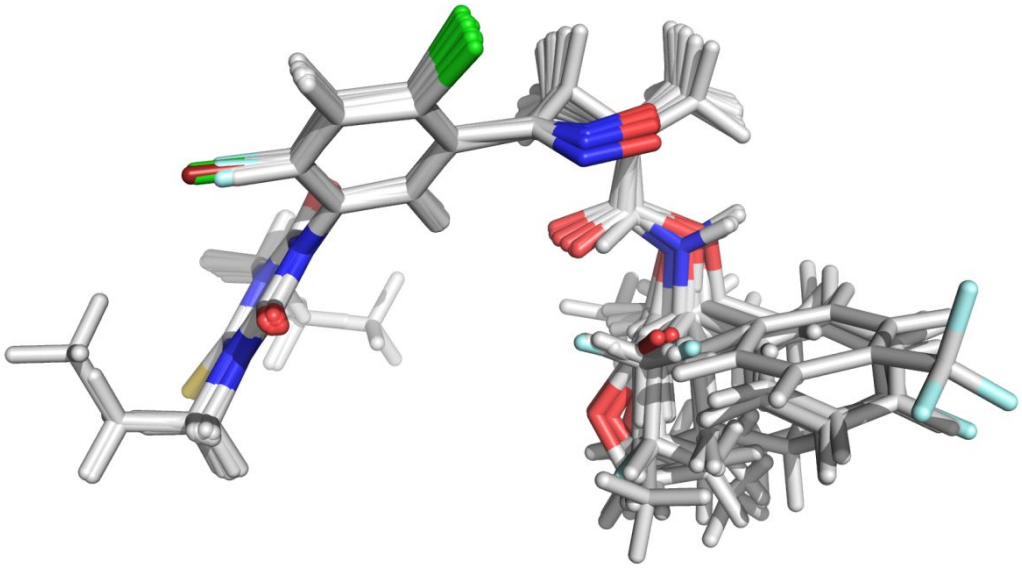

Figure S1. Superimposition of the structures 33 3D-QSAR training set compounds.

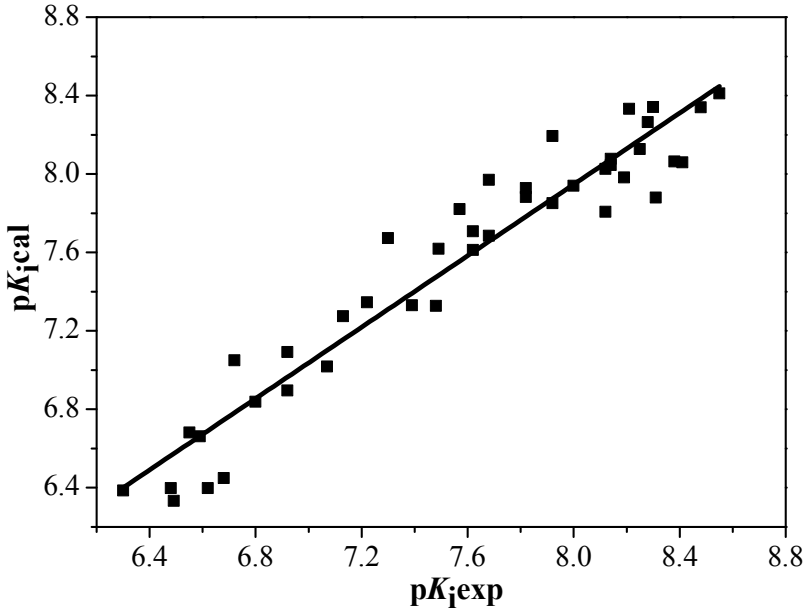

Figure S2. Plot of the Open3DQSAR calculated versus experimental pK_i values.

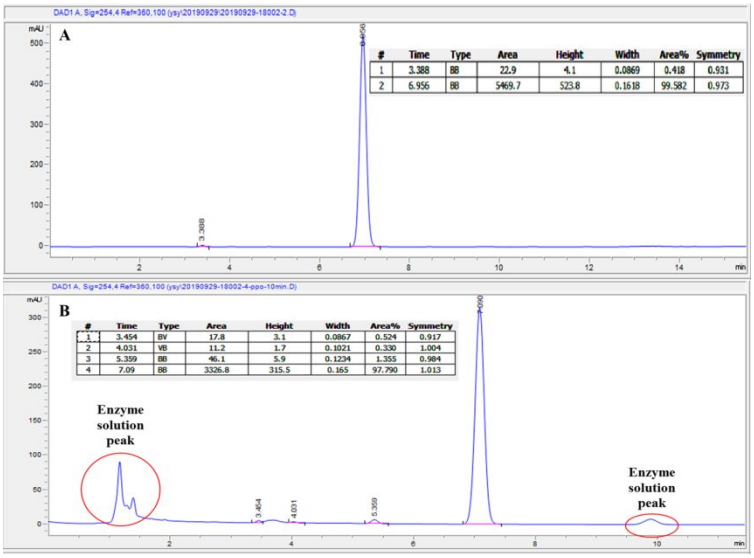

Figure S3. The results of HPLC analysis of **5a**. (A) Purity analysis of **5a**; (B) Analysis of the reaction solution at 10 min.

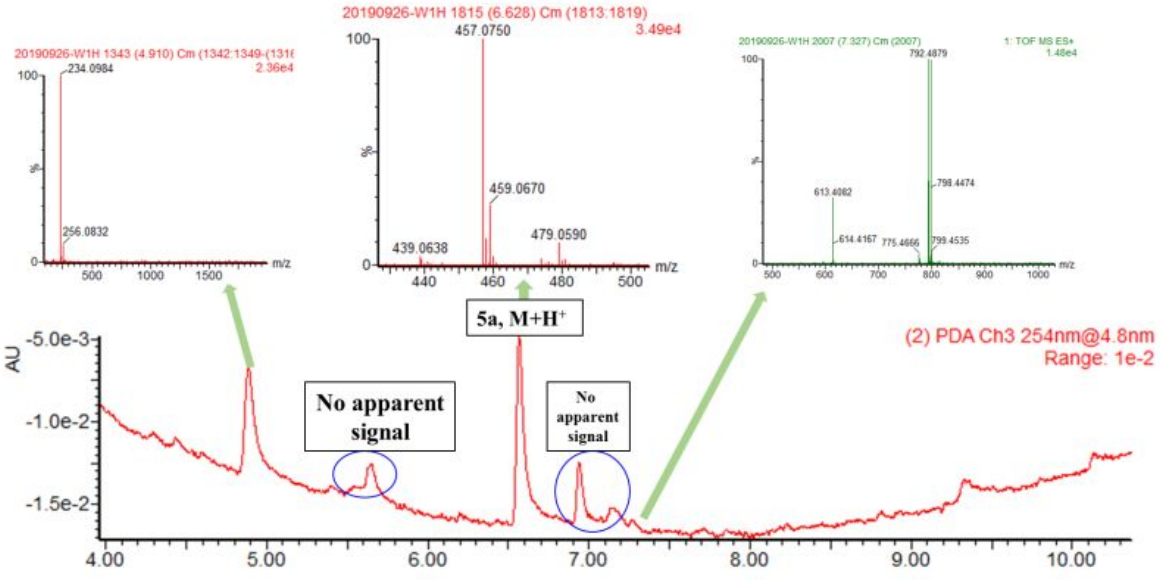

Figure S4. UPLC-HRMS analysis of the leaves extracts.

Table S1. Pre- and Post-emergent Herbicidal Activity of Compound 5a and Saflufenacil.

compds	dosage g ai/ha	%/inhibition (pre-emergence)				%/inhibition (post-emergence)			
		ABUJU[a]	AMATR	ECHCG	DIGSA	ABUJU[a]	AMATR	ECHCG	DIGSA
5a	150	100	100	100	100	100	100	100	100
	75	100	100	81	68	100	100	100	100
	37.5	100	100	44	65	100	100	100	100
	18.75	95	96	34	24	100	98	99	96
	9.375	31	33	30	20	96	97	83	81
saflufenacil	150	100	100	94	88	100	100	100	100
	75	100	100	79	63	100	100	100	100
	37.5	100	100	41	59	100	100	100	77
	18.75	100	100	34	19	100	100	90	50
	9.375	100	100	25	8	100	100	65	38

[a]Abbreviations: ABUJU, *Abutilon juncea*; AMATR, *Amaranthus tricolor*; ECHCG, *Echinochloa crus-galli*; DIGSA, *Digitaria sanguinalis*.

Table S2. Post-emergent Herbicidal Spectrum of Compound **5a** and Saflufenacil.

weeds		**5a** (g ai/ha)			saflufenacil (g ai/ha)		
		75	37.5	18.75	75	37.5	18.75
Cassia tora	CASTO	100	100	100	100	100	100
Leptochloa panicea	LEPPA	100	95	95	100	85	85
Aeschynomene indica	AESIN	100	100	100	100	100	100
Vicia gigantean	VICGI	95	85	80	95	95	90
Setaria faberii	SETFA	100	100	85	90	80	80
Sorghum halepense	SORHA	85	85	50	90	30	30
Pharbitis nil	PHANI	100	100	100	100	100	100
Xanthium sibiricum	XANSI	100	100	80	100	100	100
Bidens pilosa	BIDPI	100	90	85	100	100	100
Clinopodium chinense	CLICH	100	100	100	100	100	100
Eclipta prostrate	ECLPR	100	100	70	100	100	100
Commelina benghalensis	COMBE	100	100	100	100	100	100
Phytolacca acinosa	PHYAC	100	100	100	100	100	100
Beckmannia syzigachne	BECSY	95	85	0	90	30	0
Orychophragmus violaceus	ORYVI	90	85	80	100	100	100
Brassica juncea	BRAJU	85	80	70	100	100	100
Capsella bursa	CAPBU	95	85	80	100	100	100
Stellaria media	STEME	100	95	70	100	100	100
Veronica didyma	VERDI	100	100	100	100	100	100
Chenopodium serotinum	CHESE	100	100	100	100	100	100
Trifolium repens	TRIRE	100	100	100	100	100	100
Rumex acetosa	RUMAC	100	100	95	100	100	100
Descurainia sophia	DESSO	100	100	100	100	100	100
Polypogon fugax	POLFU	100	100	90	95	95	90
Poa annua	POAAN	100	100	95	95	90	85
Eleusine indica	ELEIN	95	90	70	70	60	60
Isodon serra	ISOSE	100	95	90	100	100	100
Boehmeria nivea	BOENI	100	100	100	100	100	100
Averaged inhibition percentage		97.9	95.4	85.2	97.3	91.6	90.0

Table S3. Calculated Binding Free Energies (kcal/mol) of *R*-**5a** and *S*-**5a** with NtPPO.

compds	ΔE_{ele}	ΔE_{VDW}	ΔE_{MM}	ΔG_{sol}	ΔE_{bind}	$-T\Delta S$	ΔG_{bind}
R-**5a**	-23.09	-59.44	-82.53	43.97	-38.66	9.55	-29.11
S-**5a**	-21.26	-60.65	-81.91	43.89	-38.02	9.43	-28.59

Table S4. Statistics of 3D-QSAR Model.

n (training set)	n (test set)	optimal PCs	r^2	q^2	r^2_{pred}	SDEC[a]	SDEP[b]
33	9	5	0.93	0.74	0.88	0.18	0.20

[a]SDEC: standard deviation of error of calculation, [b]SDEP: standard deviation of error of prediction.

Table S5. Calculated CLogP Values of Compounds **5-9**.

compds	X	R^1	R^2	R^3	CLogP[a]
5a	F	CH_3	$CO_2CH_2CH_3$	CH_3	3.78
5a1	F	CH_3	$CO_2CH_2CH_3$	CH_2CH_3	4.84
5a2	F	CH_3	$CO_2CH_2CH_3$	$CH_2CH_2CH_3$	5.90
5a3	F	H	$CO_2CH_2CH_3$	CH_3	3.26
5a4	F	CH_3	CH_2CH_3	CH_3	3.98
5a5	F	CH_3	CH_2OCOCH_3	CH_3	3.023
5b	F	CH_3	CO_2H	CH_3	2.78
5c	F	CH_3	CO_2CH_3	CH_3	3.25
5d	F	CH_3	$CO_2CH_2CH_2CH_3$	CH_3	4.31
5e	F	CH_3	$CO_2CH_2CH_2CH_3CH_3$	CH_3	4.84
5f	F	CH_3	$CO_2CH(CH_3)_2$	CH_3	4.09
5g	F	CH_3	$CO_2CH_2CH_2F$	CH_3	3.50
5h	F	CH_3	$CO_2CH_2CHF_2$	CH_3	3.83
5i	F	CH_3	$CO_2CH_2CH_2CH_2F$	CH_3	3.73
5j	F	CH_3	$CO_2CH_2CO_2C_2H_5$	CH_3	3.67
5k	F	CH_3	$CO_2CH(CH_3)CO_2C_2H_5$	CH_3	3.98
5l	F	CH_3	$CO_2C(CH_3)_2CO_2C_2H_5$	CH_3	4.29
5m	F	CH_3	$CO_2CHFCO_2C_2H_5$	CH_3	3.74
5n	F	CH_3	$CO_2CF_2CO_2C_2H_5$	CH_3	5.11
5o	F	CH_3	$CO_2CH_2C_6H_5$	CH_3	4.91
5p	F	CH_3	$CO_2CH_2C_6H_4(4\text{-}CF_3)$	CH_3	5.80
5q	F	CH_3	$CO_2CH_2C_6H_4(4\text{-}F)$	CH_3	5.06
5r	F	CH_3	$CO_2CH_2C_6H_4(4\text{-}CH_3)$	CH_3	5.41
6a	Cl	CH_3	$CO_2CH_2CH_3$	CH_3	4.35
6b	Cl	CH_3	CO_2H	CH_3	3.35
6c	Cl	CH_3	CO_2CH_3	CH_3	3.82
6d	Cl	CH_3	$CO_2CH_2CH_2CH_3$	CH_3	4.88
6e	Cl	CH_3	$CO_2CH_2CH_2CH_2CH_3$	CH_3	5.41
7a	Br	CH_3	$CO_2CH_2CH_3$	CH_3	4.50
7b	Br	CH_3	CO_2H	CH_3	3.50
7c	Br	CH_3	CO_2CH_3	CH_3	3.97
7d	Br	CH_3	$CO_2CH_2CH_2CH_3$	CH_3	5.03
7e	Br	CH_3	$CO_2CH_2CH_2CH_2CH_3$	CH_3	5.56
8a	H	CH_3	$CO_2CH_2CH_3$	CH_3	3.59
8b	H	CH_3	CO_2H	CH_3	2.59
8c	H	CH_3	CO_2CH_3	CH_3	3.06
8d	H	CH_3	$CO_2CH_2CH_2CH_3$	CH_3	4.12
8e	H	CH_3	$CO_2CH_2CH_2CH_2CH_3$	CH_3	4.65
9a	F	CH_3	$CONHCH_3$	CH_3	2.68
9b	F	CH_3	$CONHCH_2CH_3$	CH_3	3.21
9c	F	CH_3	$CONHCH_2CH_2CH_3$	CH_3	3.74
9d	F	CH_3	$CONHCH(CH_3)_2$	CH_3	3.52
9e	F	CH_3	$CONHCH_2CH_2CH_2CH_3$	CH_3	4.27

9f	F	CH_3	$CONHCH_2CH(CH_3)_2$	CH_3	4.14
9g	F	CH_3	$CONHC(CH_3)_3$	CH_3	3.92
9h	F	CH_3	$CONHCH_2C_6H_5$	CH_3	4.46
9i	F	CH_3	$CONHSO_2N(CH_3)CH(CH_3)_2$	CH_3	4.00

[a]CLogP values were predicted by ChemBioDraw Ultra 14.0.

1. General Methods

All chemical reagents and solvents were commercially available (Innochem, Science & Technology Co., Ltd. Beijing, China or J&K Scientific Ltd. Beijing, China) and used directly in the experiment without further purification. NMR spectra were recorded on a VARIAN Mercury-Plus 400 spectrometer (Bruker Corp., Switzerland) in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as the internal reference. High-resolution mass spectra (HRMS) were obtained on an FT-ICR mass spectrometer (Ionspec, 7.0 T). Melting points were taken on a Buchi B-565 melting point apparatus and are uncorrected.

2. Pre-emergence herbicidal Activity Evaluation Method.

Two representative broadleaf weeds: *A. juncea* and *A. tricolor*; and two representative monocotyledon weeds: *E. crusgalli* and *D. sanguinalis* were tested. Saflufenacil was used as a positive control. Before testing, compounds were dissolved in DMF and formulated with Tween-80 as emulsification reagent to a concentration of 100 g/L. Clay soil, pH 6.5, CEC 12.1 mol/kg, 37.3% clay particles, and 1.6% organic matter was used in the experiment. The active ingredient (g ai/ha) was calculated by the total amount of active ingredients in the formulation divided by the surface area of the pot. In the experiment, plastic pots with a diameter of 9 centimeters were filled with clay soil to a depth of 8 centimeters. About 20 of tested weeds seeds were sown in the pots at the depth of 1 to 3 centimeter and grown at 15 to 30 °C in the greenhouse. After sowing the seeds in the plastic pots, they were directly treated with **5a** and saflufenacil at 9.375-150 g ai/ha, with DMF+Tween-80-treated groups as solvent control. During the experiment, the air humidity was kept to about 50%. At 30th day post-treatment, fresh weight of the control group and testing groups above the tested soil was measured, and the inhibition rates were calculated by comparing to control values, with three replicates per treatment, the results are shown in Table S1.

3. Binding energy calculation.

After molecular docking, the best binding modes of *R*-**5a** and *S*-**5a** were used for the Binding energy calculation; the results are shown in Table S2. The binding free energy for each of the minimized inhibitor-protein was estimated using the molecular mechanics-Possion-Boltzmann surface area (MM-PBSA) method.[1] The binding free energy with receptor, ΔG_{bind}, was calculated according to the eq 1.

$$\Delta G_{bind} = G_{complex} - G_{receptor} - G_{ligand} \quad (1)$$

Where, $G_{complex}$ is the free energy of receptor−ligand complex, $G_{receptor}$ is the free energy of unbound receptor, G_{ligand} is the free energy of ligand.

The binding free energy ΔG_{bind} was calculate according to three items: MM gas-phase binding energy (ΔE_{MM}), solvation free energy (ΔG_{sol}) and entropic contribution ($-T\Delta S$), see eq2. The binding energy (ΔE_{bind}) is the sum of gas-phase binding energy (ΔE_{MM}) and solvation free energy (ΔG_{sol}), see eq3

$$\Delta G_{bind} = \Delta E_{bind} - T\Delta S \quad (2)$$

$$\Delta E_{bind} = \Delta EMM + \Delta G_{sol} \quad (3)$$

ΔE_{MM} was calculated by eq. 4, where, ΔE_{ele} and ΔE_{vdw} are electrostatic and van der Waals (vdw), respectively. ΔG_{sol} was calculated by eq. 5, where, ΔG_{PB} is the electrostatic contribution to the solvation free energy and ΔG_{np} is nonelectrostatic contribution to the solvation free energy.

$$\Delta E_{MM} = \Delta E_{ele} + \Delta E_{vdw} \quad (4)$$

$$\Delta G_{sol} = \Delta G_{PB} + \Delta G_{np} \quad (5)$$

The electrostatic contribution to the solvation free energy (ΔG_{PB}) was calculated by Poisson-Boltzmann (PB) method. ΔG_{np} is the nonelectrostatic contribution to the solvation free energy determined as a function of the solvent accessible surface area (SASA).

The entropic contribution to the binding free energy consists of two parts: ΔS_{sol} and ΔS_{conf}, see eq. 6. ΔS_{sol} is the solvation entropy change and ΔS_{conf} is the conformational entropy change.

$$\Delta S = \Delta S_{sol} + \Delta S_{conf} \quad (6)$$

The conformational entropy change is related to the change of the number of rotatable bonds during the binding process, and the solvation entropy is related to the tendency of water molecules to minimize their contacts with hydrophobic groups in protein.

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1 Huang, Z. Y.; Yang, J. F.; Song, K.; Chen, Q.; Zhou, S. L.; Hao, G. F.; Yang, G. F., One-pot approach to *N*-quinolyl 3'/4'-biaryl carboxamides by microwave-assisted suzuki-miyaura coupling and *N*-boc deprotection. *J. Org. Chem.* **2016**, *81*, 9647-9657.

4. PPO Inhibition Assay.

The expression and purification of *Nicotiana tabacum* mitochondrial PPO2 (*Nt*PPO) were performed as described previously[2-3] The enzyme substrate protoporphyrinogen IX was synthesized by reduction of protoporphyrin IX with freshly prepared sodium amalgam. Due to the chemical nature of protoporphyrin IX, it has a maximum excitation at 410 nm and a maximum emission of 630 nm. In the kinetic inhibition assays, we used a fluorescence detector to monitor the formation of the protoporphyrin IX by setting the emission wavelengths to 631 nm and excitation wavelengths to 410. Inhibitors were dissolved in dimethyl sulfoxide (DMSO) as a stock solution and diluted to the different concentration ranges from 0.05 μM to 50 mM just before using. The total volume of reaction solution was 200 μL, which consists of 0-40 μg PPO, 5 μM FAD, 5 mM DTT, 1 mM EDTA, 0.2 M imidazole, 0.1 M potassium phosphate buffer (pH 7.4), and 0.03% Tween 80 (v/v). To initiate the PPO reaction, 0-6.5 μM protoporphyrinogen IX was added to the assay solution.

The half maximal inhibitory concentration (IC_{50}) value of inhibitors was calculated by fitting *v* versus [*I*] data to a single binding site model (eq 1). The kinetic parameters were calculated by Sigma Plot software 10.0 (SPSS, Chicago, IL).

$$y = \min + \frac{\max - \min}{1 + 10^{\log IC_{50} - x}} \quad (1)$$

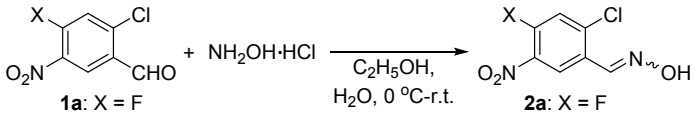
in this equation, y is the percentage of the maximal rate, min and max being the y values at which the curve levels off, x is the logarithm of inhibitor concentration. The inhibition constant of the enzymatic reaction (K_i) was calculated by using the following relationship among IC_{50}, K_i, and K_m at any saturated substrate concentration (eq 2).

$$K_i = \frac{IC_{50}}{S/K_m + 1} \quad (2)$$

1. Wang, D. W.; Li, Q.; Wen, K.; Ismail, I.; Liu, D. D.; Niu, C. W.; Wen, X.; Yang, G. F.; Xi, Z., Synthesis and herbicidal activity of pyrido[2,3-*d*]pyrimidine-2,4-dione-benzoxazinone hybrids as protoporphyrinogen oxidase inhibitors. *J. Agric. Food Chem.* **2017**, *65*, 5278-5286.
2. Hao, G. F.; Zuo, Y.; Yang, S. G.; Chen, Q.; Zhang, Y.; Yin, C. Y.; Niu, C. W.; Xi, Z.; Yang, G. F., Computational discovery of potent and bioselective protoporphyrinogen IX oxidase inhibitor via fragment deconstruction analysis. *J. Agric. Food Chem.* **2017**, *65*, 5581-5588.
3. Zuo, Y.; Wu, Q.; Su, S. W.; Niu, C. W.; Xi, Z.; Yang, G. F., Synthesis, herbicidal activity, and QSAR of novel *N*-benzothiazolyl-pyrimidine-2,4-diones as protoporphyrinogen oxidase inhibitors. *J. Agric. Food Chem.* **2016**, *64*, 552-562.

5. Experimental Procedures for the Synthesis of compounds 5-9.

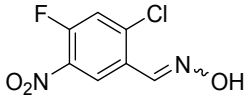
5.1 Synthesis of compounds 2.



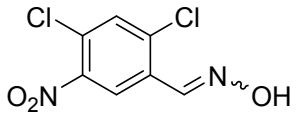
1a: X = F
1b: X = Cl
1c: X = Br
1d: X = H

2a: X = F
2b: X = Cl
2c: X = Br
2d: X = H

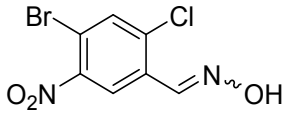
2-chloro-4-substituted-5-nitrobenzaldehyde **1 (**206 mmol**)** was dissolved in ethanol (200 mL) and cooled to 0 °C, and then a solution of hydroxylamine hydrochloride (250 mmol) in H_2O (20 mL) was added dropwise in 15 min with stirring. Then the reaction solution was moved to room temperature and stirred for another 2 h. After completing the reaction by TLC detection, the reaction solution was poured to H_2O (1000 mL) and stirred vigorously for 30 min. The resulting solid was filtered and washed with H_2O (300 mL), dried in vacuum to afford the corresponding compounds **2**.



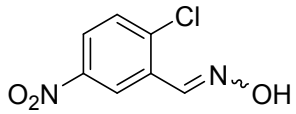
2-chloro-4-fluoro-5-nitrobenzaldehyde oxime (2a). White solid; m.p.: 89.6-90.9 °C; 91% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.34 (s, 1H), 8.01 (d, J = 11.2 Hz, 1H).



2,4-dichloro-5-nitrobenzaldehyde oxime (2b). White solid; m.p.: 108.0-109.8 °C; 96% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 8.12 (s, 1H).

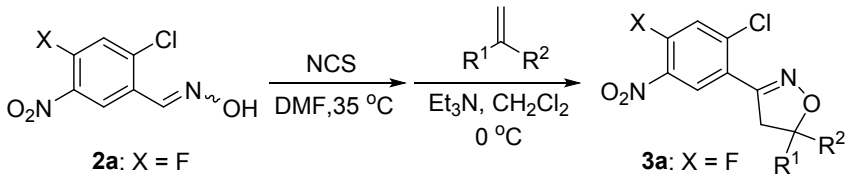


4-bromo-2-chloro-5-nitrobenzaldehyde oxime (2c). White solid; m.p.: 118.7-120.4°C; 95% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 8.35 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H).



2-chloro-5-nitrobenzaldehyde oxime (2d). Yellow solid; m.p.: 149.2-151.0 °C; 95% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 8.52 (d, J = 2.8 Hz, 1H), 8.40 (s, 1H), 8.22 (dd, J = 8.8, 2.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H).

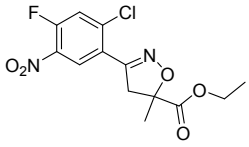
5.2 Synthesis of compounds 3.



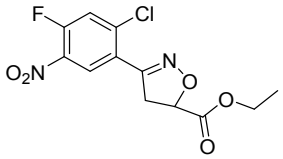
2a: X = F
2b: X = Cl
2c: X = Br
2d: X = H

3a: X = F
3b: X = Cl
3c: X = Br
3d: X = H

Compounds **2** (2.3 mmol) was dissolved in DMF (10 mL), and the solution was heated to 35 °C, and then *N*-chlorosuccinimide (NCS, 2.76 mmol) was added to solution in three portions with stirring. After stirring for another 1 h, the reaction was cooled to room temperature, CH_2Cl_2 (30 mL) and 1 M HCl solution (30 mL) were added to the solution. The organic layer was separated, and the water layer was extracted with another 20 mL of CH_2Cl_2. The combined organic layer was washed with H_2O (20 mL) and saturated NaCl solution (20 mL), dried with anhydrous Na_2SO_4, filtered to afford the intermediates solution, which can be used directly in the next step without further purification. The filtrate was cooled to 0 °C, and then a solution of $CH_2=CR^1R^2$ (3.0 mmol) and Et_3N (3.0 mmol) in CH_2Cl_2 (10 mL) was added in 10 min. After stirring for another one hour, 1 M HCl solution (30 mL) was added to the reaction solution and stirred vigorously for 10 min. The organic layer was separated and washed with saturated NaCl solution (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo, purified by flash chromatography to give compounds **3**.

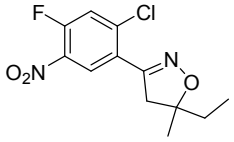


ethyl 3-(2-chloro-4-fluoro-5-nitrophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (**3a**). Yellow oil; 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 10.0 Hz, 1H), 4.30 (qd, J = 7.2, 1.2 Hz, 2H), 4.02 (d, J = 17.6 Hz, 1H), 3.40 (d, J = 17.6 Hz, 1H), 1.77 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H).

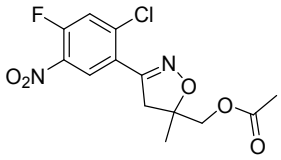


ethyl 3-(2-chloro-4-fluoro-5-nitrophenyl)-4,5-dihydroisoxazole-5-carboxylate (3a1). Yellow oil; 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 10.0 Hz, 1H),

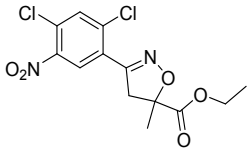
5.36 – 5.08 (m, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.90 – 3.71 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H).



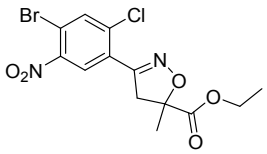
3-(2-chloro-4-fluoro-5-nitrophenyl)-5-ethyl-5-methyl-4,5-dihydroisoxazole (3a2). Yellow oil; 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 10.0 Hz, 1H), 3.29 (d, J = 17.2 Hz, 1H), 3.16 (d, J = 17.2 Hz, 1H), 1.79 (q, J = 7.6 Hz, 2H), 1.47 (s, 3H), 1.01 (t, J = 7.6 Hz, 3H).



(3-(2-chloro-4-fluoro-5-nitrophenyl)-5-methyl-4,5-dihydroisoxazol-5-yl)methyl acetate (3a3). Yellow oil; 20% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 10.0 Hz, 1H), 4.25 (d, J = 12.0 Hz, 1H), 4.15 (d, J = 11.6 Hz, 1H), 3.48 (d, J = 17.2 Hz, 1H), 3.24 (d, J = 17.2 Hz, 1H), 2.11 (s, 3H), 1.55 (s, 3H).

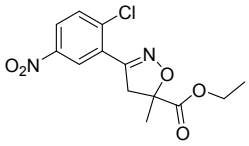


ethyl 3-(2,4-dichloro-5-nitrophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (3b). Yellow solid; m.p.: 75.7-76.5°C; 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.66 (s, 1H), 4.28 (d, J = 7.2 Hz, 2H), 4.01 (d, J = 17.6 Hz, 1H), 3.39 (d, J = 17.6 Hz, 1H), 1.74 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H).



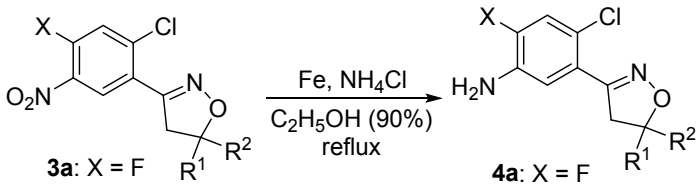
ethyl 3-(4-bromo-2-chloro-5-nitrophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (3c). Yellow solid; m.p.: 79.6-81.6°C; 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.85 (s,

1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.02 (d, *J* = 17.6 Hz, 1H), 3.39 (d, *J* = 17.2 Hz, 1H), 1.74 (s, 3H), 1.33 (d, *J* = 7.2 Hz, 3H).



ethyl 3-(2-chloro-5-nitrophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (3d). Yellow solid; m.p.: 55.7-57.0 °C; 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.4 Hz, 1H), 8.18 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 4.27 (tt, *J* = 8.0, 6.8 Hz, 2H), 4.00 (d, *J* = 17.2 Hz, 1H), 3.40 (d, *J* = 17.2 Hz, 1H), 1.73 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H).

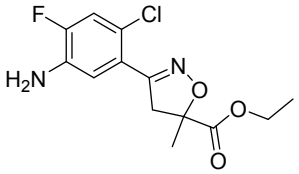
5.3 Synthesis of compounds 4.



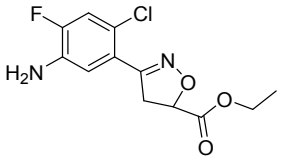
3a: X = F
3b: X = Cl
3c: X = Br
3d: X = H

4a: X = F
4b: X = Cl
4c: X = Br
4d: X = H

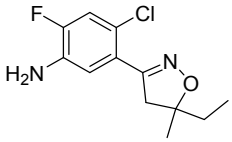
Compounds **4** (15.1 mmol), NH_4Cl (45.3 mmol), and EtOH (90%, 60 mL) were added to a flask, and the mixture was heated to reflux. Iron powder (45.3 mmol) was added portionwise to the solution in one hour, and the reaction mixture was refluxed for another 4 h. After completing the reaction, the hot reaction mixture was filtrated through a pad of celite, and the residue was washed with ethyl acetate (50 mL). H_2O (100 mL) was added to the filtrate, and the organic layer was separated. The water layer was extracted by 50 mL of ethyl acetate, the combined organic layer washed with water (30 mL) and saturated NaCl solution (30 mL), dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation to give compounds **4**.



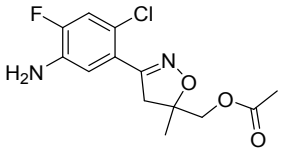
ethyl 3-(5-amino-2-chloro-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (**4a**). Yellow solid; m.p.: 78.2-80.2.0 °C; 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 10.0 Hz, 1H), 4.30 (qd, J = 7.2, 1.2 Hz, 2H), 4.02 (d, J = 17.6 Hz, 1H), 3.40 (d, J = 17.6 Hz, 1H), 1.77 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H).



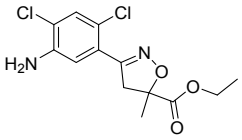
ethyl 3-(5-amino-2-chloro-4-fluorophenyl)-4,5-dihydroisoxazole-5-carboxylate (4a1). Yellow oil; 35% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 9.2 Hz, 1H), 7.08 (d, J = 10.4 Hz, 1H), 5.16 (dd, J = 11.2, 7.2 Hz, 1H), 4.31 – 4.25 (m, 2H), 3.76 (qd, J = 17.6, 11.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H).



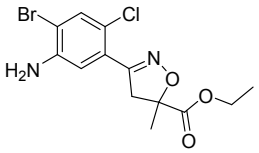
4-chloro-5-(5-ethyl-5-methyl-4,5-dihydroisoxazol-3-yl)-2-fluoroaniline (4a2). Yellow oil; 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.10 (m, 1H), 7.10 – 7.01 (m, 1H), 4.00 (s, 2H), 3.26 (d, J = 17.2 Hz, 1H), 3.14 (d, J = 17.2 Hz, 1H), 1.75 (q, J = 7.2 Hz, 2H), 1.43 (s, 3H), 0.99 (t, J = 7.6 Hz, 3H).



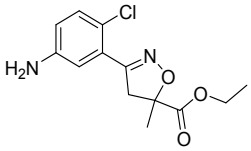
(3-(5-amino-2-chloro-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazol-5-yl)methyl acetate (4a3). Yellow oil; 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, J = 9.6 Hz, 1H), 7.05 (d, J = 10.4 Hz, 1H), 4.16 (d, J = 12.8 Hz, 2H), 3.44 (d, J = 17.2 Hz, 1H), 3.22 (d, J = 17.2 Hz, 1H), 2.09 (s, 3H), 1.50 (s, 3H).



ethyl 3-(5-amino-2,4-dichlorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (4b). Yellow solid; m.p.: 68.9-70.3 °C; 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.15 (s, 1H), 4.27 (dd, J = 14.4, 7.2 Hz, 2H), 3.94 (d, J = 17.6 Hz, 1H), 3.39 (d, J = 17.2 Hz, 1H), 1.73 (d, J = 13.6 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H).

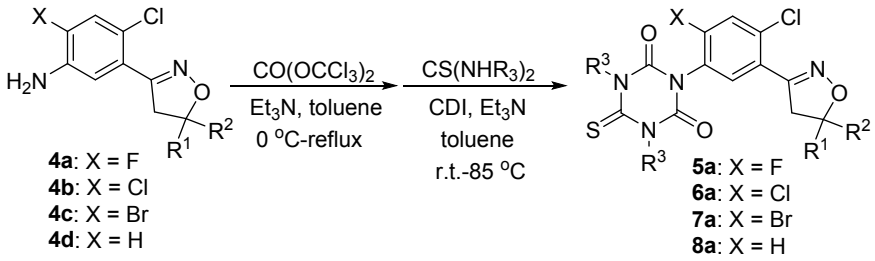


ethyl 3-(5-amino-4-bromo-2-chlorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (4c). Yellow oil; 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.07 (s, 1H), 4.26 (q, J = 7.2 Hz, 2H), 4.15 (s, 2H), 3.93 (d, J = 17.2 Hz, 1H), 3.39 (d, J = 17.2 Hz, 1H), 1.71 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H).



ethyl 3-(5-amino-2-chlorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (4d). Yellow oil; 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 3.2 Hz, 1H), 6.69 (dd, J = 8.8, 2.8 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.96 (d, J = 17.6 Hz, 1H), 3.70 (s, 2H), 3.42 (d, J = 17.2 Hz, 1H), 1.73 (s, 3H), 1.34 (t, J = 6.8 Hz, 3H).

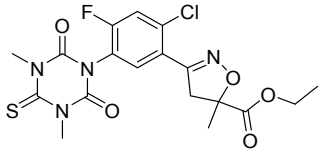
5.4 Synthesis of compounds 5a, 6a, 7a and 8a.



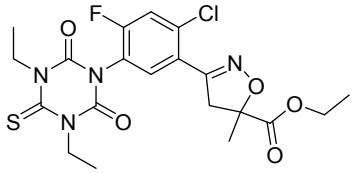
General method to synthesize of compounds **5a**, **6a**, **7a** and **8a**. $CO(OCCl_3)_2$ (8.4 mmol) and toluene (20 mL) were added to a 100 mL round bottom flask and cooled to 0 °C. A solution of **4** (16.7 mmol) and Et_3N (3.3 mmol) in toluene (20 mL) was added dropwise in 10 min, and then the mixture was heated slowly to reflux. After 10 h, the mixture was cooled to room temperature, and the solvent was removed by rotary evaporation.

Toluene (40 mL) and $CS(NHR^3)_2$ (20.1 mmol) were added successively to the residue, and the solution was stirred at room temperature for 30 min. Then CDI (33.4 mmol) was added to the solution, and the solution was heated slowly to 85 °C for 12 h. After the reaction was completed, the reaction solution was cooled to room temperature, ethyl acetate (20 mL) and H_2O (10 mL) were added to the solution. The organic layer was separated and wash with H_2O (20 mL) and saturated NaCl solution (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo,

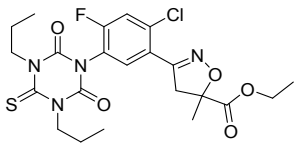
purified by flash chromatography to give **5a**, **6a**, **7a** or **8a.**



ethyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (5a). White solid; m.p.: 68.0-69.9 °C; 59% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 4.01 (d, J = 17.6 Hz, 1H), 3.77 (s, 6H), 3.39 (d, J = 17.6 Hz, 1H), 1.71 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.40, 171.55, 159.48, 156.90, 154.34, 146.54, 135.23, 135.13, 132.03, 126.00, 120.94, 120.80, 119.39, 119.16, 87.26, 62.18, 46.50, 36.80, 23.34, 14.09; HRMS (QFT-ESI) calcd for $C_{18}H_{18}ClFN_4NaO_5S$ $[M+Na]^+$ 479.0568, found: 479.0568.

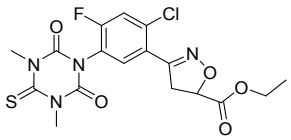


ethyl 3-(2-chloro-5-(3,5-diethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (5a1). White solid; m.p.: 58.4-59.5 °C; 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.50 (q, J = 6.8 Hz, 4H), 4.27 (q, J = 6.8 Hz, 2H), 4.01 (d, J = 17.2 Hz, 1H), 3.40 (d, J = 17.6 Hz, 1H), 1.71 (s, 3H), 1.33 (t, J = 6.8 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.25, 171.58, 159.46, 156.88, 154.41, 145.98, 135.07, 134.97, 132.09, 125.85, 125.81, 120.81, 120.68, 119.32, 119.09, 87.24, 62.18, 46.49, 45.14, 23.34, 14.09, 11.84; HRMS (QFT-ESI) calcd for $C_{20}H_{22}ClFN_4NaO_5S$ $[M+Na]^+$ 507.0881, found: 507.0880.

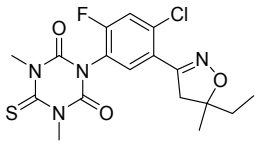


ethyl 3-(2-chloro-5-(2,6-dioxo-3,5-dipropyl-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (5a2). Colorless oil; 39% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.40 – 4.32 (m, 4H), 4.27 (q, J = 7.2 Hz, 2H), 4.01 (d, J = 17.2 Hz, 1H), 3.40 (d, J = 17.6 Hz, 1H), 1.86 – 1.73 (m, 4H), 1.72 (s, 3H), 1.33 (t, J = 6.8 Hz, 3H), 0.96 (t, J = 7.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.66,

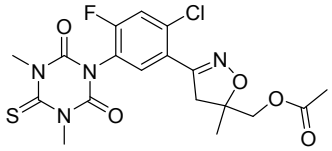
171.58, 159.46, 156.88, 154.41, 146.24, 135.07, 134.97, 132.08, 125.86, 125.82, 120.93, 120.79, 119.31, 119.08, 87.25, 62.18, 51.05, 46.52, 23.35, 19.86, 14.09, 11.00; HRMS (QFT-ESI) calcd for $C_{22}H_{27}ClFN_4O_5S$ $[M+H]^+$ 513.1369, found: 513.1374.



ethyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-4,5-dihydroisoxazole-5-carboxylate (5a3). White solid; m.p.: 73.0-74.9 °C; 64% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6H z, 1H), 7.37 (d, J = 9.2 Hz, 1H), 5.19 (dd, J = 10.4, 8.0 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.79 (dd, J = 10.8, 4.4 Hz, 2H), 3.76 (s, 6H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.44, 169.66, 159.59, 157.01, 154.20, 146.55, 135.28, 135.19, 132.25, 125.50, 121.01, 120.87, 119.44, 119.21, 78.99, 62.12, 40.60, 36.80, 21.06, 14.22, 14.13; HRMS (QFT-ESI) calcd for $C_{17}H_{16}ClFN_4NaO_5S$ $[M+Na]^+$ 465.0412, found:465.0411.

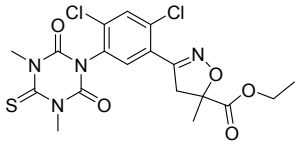


3-(4-chloro-5-(5-ethyl-5-methyl-4,5-dihydroisoxazol-3-yl)-2-fluorophenyl)-1,5-dimethyl-6-thioxo-1,3,5-triazinane-2,4-dione (5a4). White solid; m.p.: 153.7-155.4 °C; 64% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 3.78 (s, 6H), 3.32 (d, J = 17.2 Hz, 1H), 3.18 (d, J = 17.2 Hz, 1H), 1.77 (q, J = 7.2 Hz, 2H), 1.45 (s, 3H), 1.00 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.44, 159.13, 156.56, 154.09, 146.58, 135.03, 134.93, 131.73, 127.25, 127.20, 120.78, 120.64, 119.25, 119.02, 89.20, 65.87, 46.49, 36.80, 32.69, 25.05, 15.29; HRMS (QFT-ESI) calcd for $C_{17}H_{18}ClFN_4NaO_3S$ $[M+Na]^+$ 435.0670, found:435.0670.

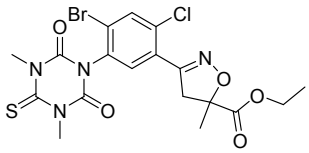


(3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazol-5-yl)methyl acetate (5a5). White solid; m.p.: 75.2-77.1 °C; 64% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 4.19 (dd, J = 27.6, 11.6 Hz, 2H), 3.79 (s, 6H), 3.52 (d, J = 17.2 Hz, 1H), 3.27 (d, J = 17.2 Hz, 1H), 2.11 (s,

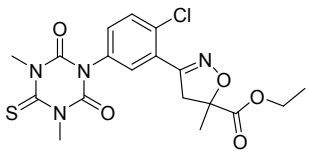
3H), 1.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.38, 170.69, 159.34, 156.76, 154.27, 146.56, 146.53, 135.09, 134.99, 131.88, 126.54, 126.50, 120.90, 120.76, 119.36, 119.13, 86.35, 67.67, 44.88, 36.80, 22.82, 20.83; HRMS (QFT-ESI) calcd for $C_{18}H_{18}ClFN_4NaO_5S$ $[M+Na]^+$ 479.0568, found:479.0567.



ethyl 3-(2,4-dichloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (6a). White solid; m.p.: 60.2-62.2 °C; 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.65 (t, J = 7.6 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 4.01 (d, J = 17.2 Hz, 1H), 3.78 (s, 6H), 3.40 (d, J = 17.6 Hz, 1H), 1.71 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.53, 171.47, 154.32, 146.50, 134.90, 134.60, 132.36, 132.15, 131.73, 131.65, 130.79, 128.75, 87.39, 62.20, 46.34, 36.75, 23.35, 14.10; HRMS (QFT-ESI) calcd for $C_{18}H_{18}Cl_2N_4NaO_5S$ $[M+Na]^+$ 495.0273, found: 495.0270.



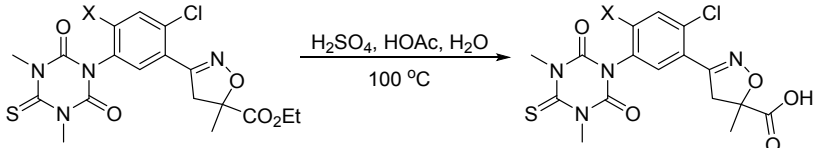
ethyl 3-(4-bromo-2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (7a). White solid; m.p.: 71.5-73.0 °C; 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.72 (s, 1H), 4.31 – 4.17 (m, 2H), 3.99 (d, J = 17.2 Hz, 1H), 3.76 (s, 6H), 3.37 (d, J = 17.6 Hz, 1H), 1.68 (s, 3H), 1.30 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.55, 171.43, 154.40, 146.45, 135.34, 135.13, 134.55, 132.57, 131.58, 131.41, 129.36, 124.78, 87.40, 62.18, 46.29, 36.74, 23.33, 14.10; HRMS (QFT-ESI) calcd for $C_{18}H_{18}BrClN_4NaO_5S$ $[M+Na]^+$ 538.9768, found: 538.9765.



ethyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate (8a). White solid; m.p.: 76.4-78.4 °C; 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.26 (dd, J = 8.4, 2.4 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 4.01 (d, J = 17. 2 Hz, 1H), 3.76 (s, 6H), 3.41 (d, J = 17.2 Hz, 1H),

1.70 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.65, 171.84, 155.26, 147.45, 134.06, 132.87, 132.03, 130.76, 130.60, 130.13, 87.37, 62.33, 46.77, 36.92, 23.55, 14.29; HRMS (QFT-ESI) calcd for $C_{18}H_{19}ClN_4NaO_5S$ $[M+Na]^+$ 461.0662, found: 461.0661.

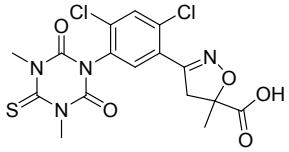
5.5 Synthesis of compounds 5b, 6b, 7b and 8b.



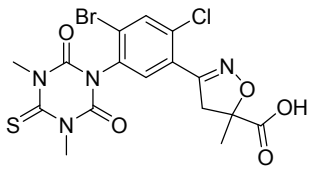
5a: X = F
6a: X = Cl
7a: X = Br
8a: X = H

5b: X = F
6b: X = Cl
7b: X = Br
8b: X = H

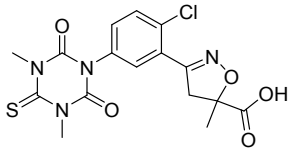
3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (5b). Compound **5a** (10 mmol) was dissolved in 20 mL of HOAc, then H_2O (10 mL) and H_2SO_4 (20 mL) were added to the solution with stirring, and the reaction solution was heated to 100 °C for 10 h. After completing the reaction, the reaction solution was cooled to room temperature and poured to 500 g of ice, and stirred vigorously for 30 min. The resulting solid was filtrated and washed with H_2O (50 mL), dried over in vacuum to give compound **5b**. White solid; m.p.: 120.4-122.2 °C; 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 4.04 (d, J = 17.6 Hz, 1H), 3.80 (s, 6H), 3.51 (d, J = 17.6 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.37, 175.80, 159.65, 157.06, 154.99, 146.59, 146.58, 135.30, 135.20, 132.13, 125.51, 125.47, 121.01, 120.87, 119.46, 119.23, 86.82, 46.68, 36.81, 22.99; HRMS (QFT-ESI) calcd for $C_{16}H_{13}ClFN_4O_5S$ $[M-H]^-$ 427.0285, found:427.0280.



3-(2,4-dichloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (6b). White solid; m.p.: 95.1-96.9 °C; 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.64 (s, 1H), 4.00 (d, J = 17.6 Hz, 1H), 3.76 (s, 6H), 3.44 (d, J = 17.6 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.51, 175.80, 154.84, 146.58, 135.19, 134.64, 132.16, 131.84, 130.84, 128.36, 86.96, 46.49, 36.77, 23.02; HRMS (QFT-ESI) calcd for $C_{16}H_{13}Cl_2N_4O_5S$ $[M-H]^-$ 442.9989, found: 442.9986.

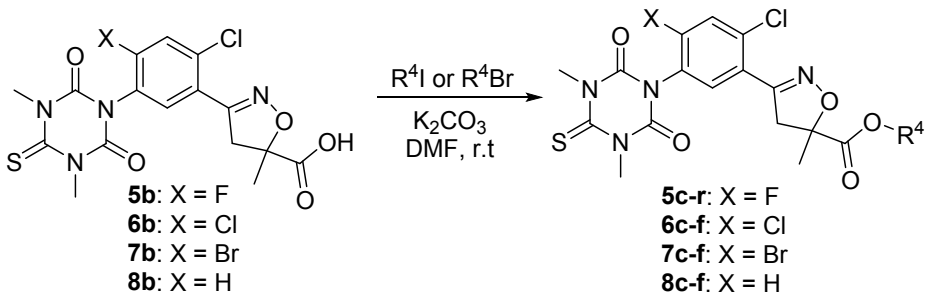


3-(4-bromo-2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (7b). White solid; m.p.: 113.9-115.9 °C; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) 9.93 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 3.99 (d, J = 17.6 Hz, 1H), 3.76 (s, 6H), 3.52 (d, J = 7.0 Hz, 1H), 1.73 (s, 3H);; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.52, 175.51, 154.91, 146.52, 146.50, 135.19, 134.65, 132.59, 131.66, 128.99, 125.10, 87.00, 46.47, 36.78, 23.04; HRMS (QFT-ESI) calcd for $C_{16}H_{13}BrClN_4O_5S$ $[M-H]^-$ 486.9479, found: 486.9482.



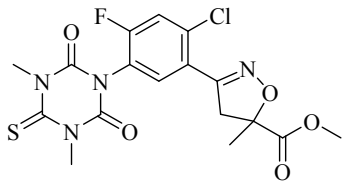
3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylic acid (8b). White solid; m.p.:117.5-119.5 °C; 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 4.4 Hz, 1H), 3.99 (d, J = 17.6 Hz, 1H), 3.74 (s, 6H), 3.48 (d, J = 17.6 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.48, 175.77, 155.70, 147.36, 133.87, 132.75, 131.86, 130.86, 130.49, 129.50, 86.76, 46.74, 36.75, 23.03; HRMS (QFT-ESI) calcd for $C_{16}H_{14}ClN_4O_5S$ $[M-H]^-$ 409.0379, found: 409.0375.

5.6 Synthesis of compounds 5c-r, 6c-f, 7c-f and 8c-f.

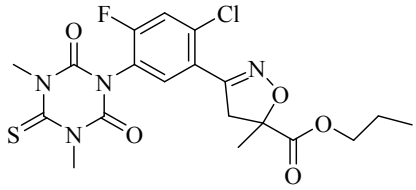


General method to synthesize of compounds **5c-r**, **6c-f**, **7c-f** and **8c-f**. To a stirred mixture of **5b, 6b**, **7b** or **8b** (2 mmol) in DMF (30 mL) was added K_2CO_3 (2.5 mmol) at room temperature. After 10 min, R^4I or R^4Br (1.25 mmol) was added to the mixture and then allowed to react for another 10 h. The reaction mixture was poured to water (150 mL), and extracted by ethyl acetate (60 mL).

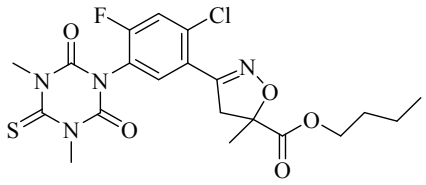
The organic layer was washed with water (40 mL) and saturated NaCl solution (40 mL), dried over Na_2SO_4. After removing the solvent in vacuum, the residue was purified by flash chromatography to give **5c-r**, **6c-e**, **7c-e** and **8c-e**.



methyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl) -5-methyl-4,5-dihydroisoxazole-5-carboxylate 5c. White solid; m.p.: 80.6-82.5 °C; 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.01 (d, J = 17.6 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 6H), 3.41 (d, J = 17.2 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.41, 172.09, 159.49, 156.91, 154.42, 146.55, 135.18, 135.08, 132.04, 125.87, 125.83, 120.96, 120.82, 119.40, 119.17, 87.22, 53.11, 46.58, 36.80, 23.38; HRMS (QFT-ESI) calcd for $C_{17}H_{16}ClFN_4NaO_5S$ $[M+Na]^+$ 465.0412, found: 465.0410.

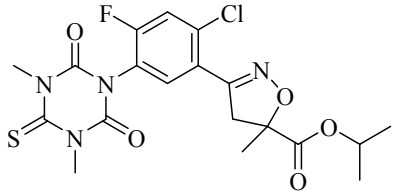


propyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl) -5-methyl-4,5-dihydroisoxazole-5-carboxylate 5d. White solid; m.p.: 60.6-62.6 °C; 56% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.17 (t, J = 6.8 Hz, 2H), 4.01 (d, J = 17.2 Hz, 1H), 3.77 (s, 6H), 3.39 (d, J = 17.2 Hz, 1H), 1.80 – 1.64 (m, 5H), 0.96 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.56, 171.73, 159.64, 157.06, 154.48, 146.69, 135.37, 135.28, 132.19, 126.17, 126.13, 121.10, 120.97, 119.54, 119.31, 87.49, 67.78, 46.66, 36.96, 23.49, 22.03, 10.44; HRMS (QFT-ESI) calcd for $C_{19}H_{20}ClFN_4NaO_5S$ $[M+Na]^+$ 493.0725, found: 493.0725.

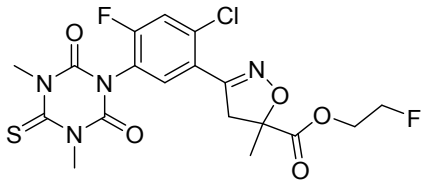


butyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl) -5-methyl-4,5-dihydroisoxazole-5-carboxylate 5e. White solid; m.p.:55.9-57.6 °C; 64% yield;

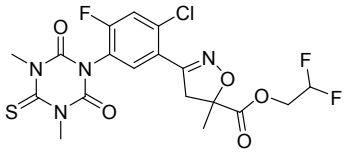
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 9.2 Hz, 1H), 4.25 (t, J = 6.8 Hz, 2H), 4.05 (d, J = 17.2 Hz, 1H), 3.81 (s, 6H), 3.43 (d, J = 17.2 Hz, 1H), 1.75 (s, 3H), 1.71 (dd, J = 14.8, 7.2Hz, 2H), 1.53 – 1.38 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.38, 171.58, 158.93, 156.25, 146.52, 135.19, 134.62, 132.02, 125.98, 120.84, 119.38, 119.23, 119.15, 87.31, 65.98, 46.48, 36.80, 30.48, 23.33, 19.04, 13.68; HRMS (QFT-ESI) calcd for $C_{20}H_{22}ClFN_4NaO_5S$ $[M+Na]^+$ 507.0881, found: 507.0881



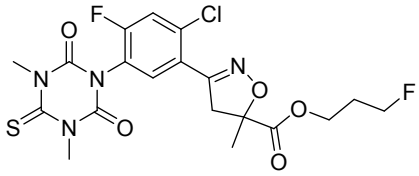
Isopropyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5f. White solid; m.p.: 62.5-64.1 °C; 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 5.09 (dt, J = 12.4, 6.0 Hz, 1H), 3.99 (d, J = 17.6 Hz, 1H), 3.77 (s, 6H), 3.37 (d, J = 17.2 Hz, 1H), 1.69 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.39, 171.00, 159.46, 156.88, 154.30, 146.55, 146.53, 135.24, 135.14, 132.03, 126.08, 126.04, 120.92, 120.78, 119.38, 119.15, 87.31, 69.89, 46.40, 36.81, 23.28, 21.64, 21.61; HRMS (QFT-ESI) calcd for $C_{19}H_{20}ClFN_4NaO_5S$ $[M+Na]^+$ 493.0725, found: 493.0723.



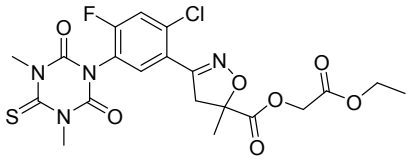
2-fluoroethyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5g. White solid; m.p.: 68.8-70.1 °C; 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 9.2 Hz, 1H), 4.66 (dt, J = 47.2, 4.0 Hz, 2H), 4.47 (ddd, J = 28.0, 8.0, 3.6 Hz, 2H), 4.04 (d, J = 17.2 Hz, 1H), 3.78 (s, 6H), 3.52 – 3.36 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.41, 171.32, 159.54, 156.96, 154.43, 146.54, 135.25, 135.15, 132.08, 125.86, 125.82, 120.98, 120.84, 119.39, 119.17, 87.13, 81.71, 80.00, 64.79, 64.59, 46.57, 36.81, 36.78, 23.22.; HRMS (QFT-ESI) calcd for $C_{18}H_{17}ClF_2N_4NaO_5S$ $[M+Na]^+$ 497.0474, found: 497.0472.



2,2-difluoroethyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5h. White solid; m.p.: 66.5-68.5 °C; 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 5.99 (tt, J = 54.8, 4.0 Hz, 1H), 4.38 (tdd, J = 13.6, 4.0, 2.4 Hz, 2H), 4.00 (d, J = 17.6 Hz, 1H), 3.74 (s, 6H), 3.44 (d, J = 17.6 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.46, 170.68, 159.59, 157.01, 154.53, 146.55, 135.17, 135.07, 132.09, 125.65, 125.61, 121.05, 120.92, 119.40, 119.17, 114.74, 112.34, 109.93, 86.95, 63.68, 63.39, 63.10, 46.55, 36.78, 36.75, 23.10; HRMS (QFT-ESI) calcd for $C_{18}H_{16}ClF_3N_4NaO_5S$ $[M+Na]^+$ 515.0380, found: 515.0378.

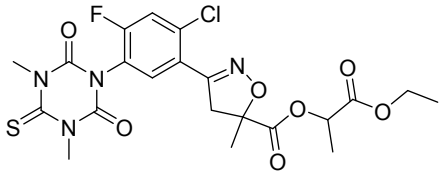


3-fluoropropyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5i. White solid; m.p.: 62.1-63.4 °C; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.53 (dt, J = 47.2, 5.2 Hz, 2H), 4.32 (t, J = 6.0 Hz, 2H), 3.99 (d, J = 17.6 Hz, 1H), 3.73 (s, 6H), 3.39 (d, J = 17.6 Hz, 1H), 2.16 – 1.97 (m, 2H), 1.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.48, 171.36, 159.48, 156.90, 154.48, 146.54, 135.09, 134.99, 132.04, 125.80, 121.00, 120.86, 119.36, 119.13, 87.17, 81.27, 79.63, 62.11, 62.06, 46.44, 36.75, 29.64, 29.44, 23.19; HRMS (QFT-ESI) calcd for $C_{19}H_{19}ClF_2N_4NaO_5S$ $[M+Na]^+$ 511.0630, found: 511.0630.

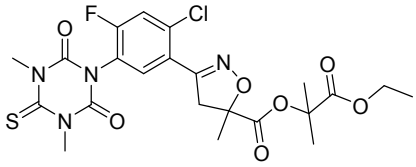


2-ethoxy-2-oxoethyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl) -4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5j. White solid; m.p.: 56.3-58.2 °C; 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.72 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 4.11 (d, J = 18.0 Hz, 1H), 3.76 (s, 6H), 3.47 (d, J = 17.6 Hz, 1H), 1.78 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.43, 171.13, 167.10, 159.51, 156.93, 154.44, 146.53, 135.21, 135.12, 132.09, 125.80, 125.76, 120.95,

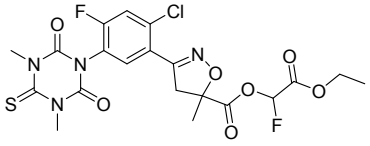
120.82, 119.39, 119.16, 86.97, 61.68, 61.48, 46.77, 36.79, 23.12, 14.09; HRMS (QFT-ESI) calcd for $C_{20}H_{20}ClFN_4NaO_7S$ $[M+Na]^+$ 537.0623, found: 537.0620.



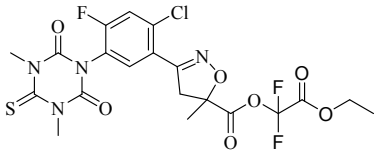
1-ethoxy-1-oxopropan-2-yl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan -1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5k. White solid; m.p.: 116.2-118.2 °C; 53% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.6, 4.8 Hz, 1H), 7.36 (dd, J = 9.2, 2.4 Hz, 1H), 5.15 (q, J = 7.2 Hz, 1H), 4.20 (qd, J = 7.2, 3.6 Hz, 2H), 4.11 (d, J = 17.2 Hz, 1H), 3.77 (s, 6H), 3.45 (d, J = 17.2 Hz, 1H), 1.77 (d, J = 17.6 Hz, 3H), 1.56 (t, J = 7.2 Hz, 3H), 1.26 (td, J = 7.2, 2.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.48, 171.03, 170.95, 170.12, 159.51, 156.93, 154.58, 154.23, 146.57, 146.55, 135.22, 135.12, 132.14, 132.09, 125.91, 125.87, 120.98, 120.84, 119.39, 119.16, 87.14, 86.79, 69.86, 69.82, 61.63, 47.01, 46.30, 36.80, 23.22, 22.98, 16.77, 16.74, 14.12; HRMS (QFT-ESI) calcd for $C_{21}H_{22}ClFN_4NaO_7S$ $[M+Na]^+$ 551.0779, found: 551.0778.



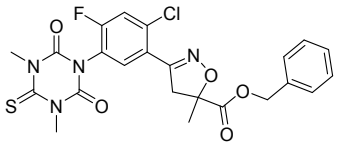
1-ethoxy-2-methyl-1-oxopropan-2-yl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo -1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5l. White solid; m.p.: 57.9-59.8 °C; 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.03 (d, J = 17.6 Hz, 1H), 3.77 (s, 6H), 3.38 (d, J = 17.6 Hz, 1H), 1.72 (s, 3H), 1.61 (d, J = 4.8 Hz, 6H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.41, 171.88, 170.31, 159.48, 156.90, 154.24, 146.55, 146.50, 135.21, 135.11, 132.03, 125.96, 125.92, 120.96, 120.82, 119.38, 119.14, 87.09, 79.98, 61.51, 46.47, 36.79, 24.57, 24.42, 23.03, 14.04; HRMS (QFT-ESI) calcd for $C_{22}H_{24}ClFN_4NaO_7S$ $[M+Na]^+$ 565.0936, found: 565.0935.



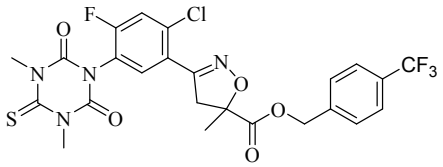
2-ethoxy-1-fluoro-2-oxoethyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5m. White solid; m.p.: 50.2-52.1 °C; 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 6.46 (d, J = 52.4 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.04 (dd, J = 17.6, 5.2 Hz, 1H), 3.77 (s, 6H), 3.49 (d, J = 17.6 Hz, 1H), 1.79 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.38, 169.02, 163.48, 159.67, 157.08, 154.39, 146.55, 146.50, 135.27, 135.18, 132.14, 125.50, 121.06, 120.92, 119.45, 119.22, 96.82, 94.47, 86.64, 63.03, 46.54, 36.81, 22.84, 13.95; HRMS (QFT-ESI) calcd for $C_{20}H_{19}ClF_2N_4NaO_7S$ $[M+Na]^+$ 555.0529, found: 555.0527.



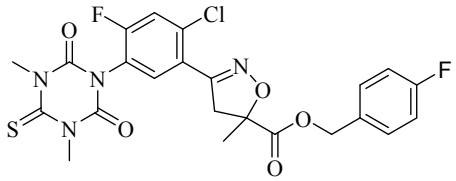
2-ethoxy-1,1-difluoro-2-oxoethyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5n. White solid; m.p.: 62.0-64.0 °C; 25% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 9.2 Hz, 1H), 4.20 (tt, J = 13.6, 6.8 Hz, 2H), 3.92 (d, J = 17.6 Hz, 1H), 3.68 (s, 6H), 3.32 (d, J = 17.6 Hz, 1H), 1.62 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.42, 170.50, 166.66, 158.45, 155.87, 153.34, 145.52, 134.15, 134.05, 131.30, 131.02, 129.89, 127.82, 124.95, 124.92, 119.95, 119.82, 118.34, 118.10, 86.21, 61.12, 45.47, 35.75, 22.29, 13.07, 12.71; HRMS (QFT-ESI) calcd for $C_{20}H_{18}ClF_3N_4NaO_7S$ $[M+Na]^+$ 573.0435, found: 573.0433.



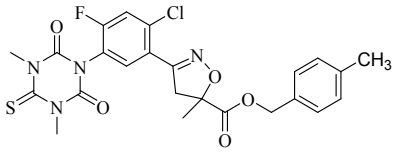
benzyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5o. White solid; m.p.: 173.8-175.8 °C; 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.6 Hz, 1H), 7.43 – 7.31 (m, 6H), 5.23 (d, J = 0.8 Hz, 2H), 3.98 (d, J = 17.2 Hz, 1H), 3.77 (s, 6H), 3.39 (d, J = 17.2 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.38, 171.29, 159.49, 156.91, 154.38, 146.52, 146.49, 135.25, 135.19, 135.15, 132.03, 128.64, 128.45, 128.18, 128.16, 128.15, 125.93, 125.89, 120.92, 120.78, 119.36, 119.13, 87.26, 67.59, 46.55, 36.79, 23.20; HRMS (QFT-ESI) calcd for $C_{23}H_{20}ClFN_4NaO_5S$ $[M+Na]^+$ 541.0725, found: 541.0724.



4-(trifluoromethyl)benzyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5p. White solid; m.p.: 158.8-159.9 °C; 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 9.2 Hz, 1H), 5.29 (s, 2H), 4.01 (d, J = 17.6 Hz, 1H), 3.77 (s, 6H), 3.42 (d, J = 17.6 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.50, 171.15, 162.50, 159.54, 156.96, 154.53, 146.57, 139.25, 135.07, 134.98, 132.05, 128.02, 125.63, 125.60, 121.10, 120.96, 119.36, 119.13, 87.17, 66.46, 46.52, 36.70, 23.07; HRMS (QFT-ESI) calcd for $C_{24}H_{19}ClFN_4NaO_5S$ $[M+Na]^+$ 609.0599, found: 609.0598.

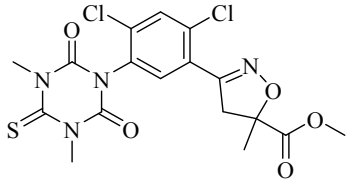


4-fluorobenzyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5q. White solid; m.p.: 141.8-143.8 °C; 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.6 Hz, 1H), 7.35 (dt, J = 5.2, 2.4 Hz, 3H), 7.04 (t, J = 8.8 Hz, 2H), 5.20 (s, 2H), 3.96 (d, J = 17.6 Hz, 1H), 3.77 (d, J = 1.6 Hz, 6H), 3.61 – 3.30 (m, 1H), 1.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.40, 171.30, 163.99, 161.53, 159.51, 156.93, 154.45, 146.54, 135.21, 135.11, 132.02, 131.08, 131.04, 130.33, 130.24, 125.86, 125.81, 120.97, 120.83, 119.38, 119.15, 115.73, 115.51, 87.22, 66.88, 46.53, 36.80, 23.14; HRMS (QFT-ESI) calcd for $C_{23}H_{19}ClF_2N_4NaO_5S$ $[M+Na]^+$ 559.0630, found: 559.0630.

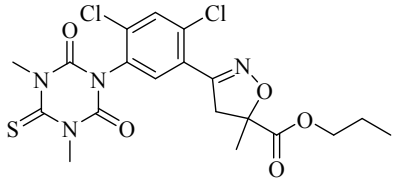


4-methylbenzyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 5r. White solid; m.p.: 167.1-168.6 °C; 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 5.19 (d, J = 1.2 Hz, 2H), 3.97 (d, J

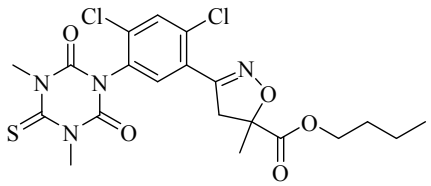
= 17.2 Hz, 1H), 3.76 (d, *J* = 1.2 Hz, 6H), 3.37 (d, *J* = 17.6 Hz, 1H), 2.34 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.46, 171.28, 159.49, 156.91, 154.36, 146.56, 146.53, 138.34, 135.19, 135.10, 132.25, 132.07, 129.32, 129.19, 128.32, 127.05, 125.96, 125.92, 120.99, 120.85, 119.34, 119.11, 87.26, 67.58, 46.53, 36.80, 36.77, 23.24, 21.24; HRMS (QFT-ESI) calcd for $C_{24}H_{22}ClFN_4NaO_5S$ $[M+Na]^+$ 555.0881, found: 555.0882.



methyl 3-(2,4-dichloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl -4,5-dihydroisoxazole-5-carboxylate 6c. White solid; m.p.: 76.4-78.4 °C; 63% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.58 (s, 1H), 3.94 (d, *J* = 17.6 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 6H), 3.34 (d, *J* = 17.6 Hz, 1H), 1.64 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.53, 171.99, 154.34, 146.49, 134.94, 134.57, 132.15, 131.73, 130.81, 128.67, 87.36, 53.08, 46.45, 36.74, 23.37; HRMS (QFT-ESI) calcd for $C_{17}H_{16}Cl_2N_4NaO_5S$ $[M+Na]^+$ 481.0116, found: 481.0115.

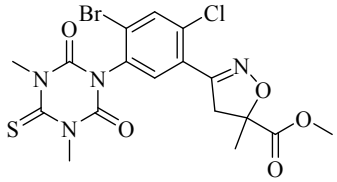


propyl 3-(2,4-dichloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl -4,5-dihydroisoxazole-5-carboxylate 6d. White solid; m.p.: 55.5-57.2 °C; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.63 (s, 1H), 4.15 (t, *J* = 6.4 Hz, 2H), 4.00 (d, *J* = 17.2 Hz, 1H), 3.76 (s, 6H), 3.37 (d, *J* = 17.6 Hz, 1H), 1.75 – 1.64 (m, 5H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.57, 171.44, 154.31, 146.50, 134.86, 134.53, 132.09, 131.75, 130.83, 128.76, 87.43, 67.59, 46.32, 36.71, 23.30, 21.86, 10.29; HRMS (QFT-ESI) calcd for $C_{19}H_{20}Cl_2N_4NaO_5S$ $[M+Na]^+$ 509.0429, found: 509.0428.

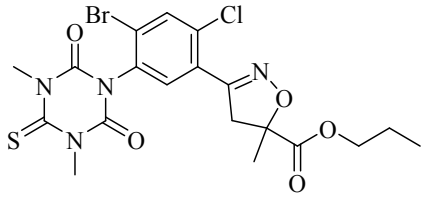


butyl 3-(2,4-dichloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-

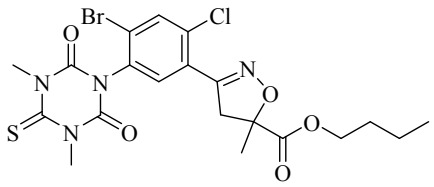
methyl-4,5-dihydroisoxazole-5-carboxylate 6e. White solid; m.p.: 52.7-54.6 °C; 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.65 (s, 1H), 4.21 (t, J = 6.4 Hz, 2H), 4.01 (d, J = 17.6 Hz, 1H), 3.78 (s, 6H), 3.39 (d, J = 17.2 Hz, 1H), 1.76 – 1.62 (m, 5H), 1.40 (dq, J = 14.8, 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.55, 171.46, 154.29, 146.49, 134.87, 134.56, 132.11, 131.74, 130.81, 128.77, 87.44, 65.96, 46.33, 36.73, 30.48, 23.31, 19.03, 13.67; HRMS (QFT-ESI) calcd for $C_{20}H_{22}Cl_2N_4NaO_5S$ $[M+Na]^+$ 523.0586, found: 523.0584.



methyl 3-(4-bromo-2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl) -5-methyl-4,5-dihydroisoxazole-5-carboxylate 7c. White solid; m.p.: 86.5-88.4 °C; 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75 (s, 1H), 4.02 (d, J = 17.6 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 6H), 3.42 (d, J = 17.6 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.56, 171.96, 154.46, 146.46, 135.13, 134.52, 132.59, 131.57, 129.26, 124.83, 87.36, 53.10, 46.38, 36.74, 23.36; HRMS (QFT-ESI) calcd for $C_{17}H_{17}BrClN_4O_5S$ $[M+H]^+$ 502.9792, found: 502.9790.

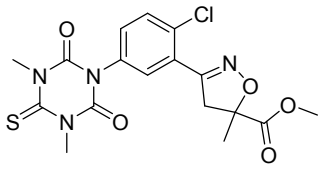


propyl 3-(4-bromo-2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl) phenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxylate 7d. White solid; m.p.: 61.7-63.2 °C; 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.76 (s, 1H), 4.19 (t, J = 6.8 Hz, 2H), 4.04 (d, J = 17.2 Hz, 1H), 3.80 (s, 6H), 3.42 (d, J = 17.6 Hz, 1H), 1.81 – 1.67 (m, 5H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.56, 171.44, 154.40, 146.46, 146.44, 135.10, 134.52, 132.58, 131.58, 129.36, 124.77, 87.46, 67.60, 46.27, 36.73, 23.32, 21.87, 10.31; HRMS (QFT-ESI) calcd for $C_{19}H_{20}BrClN_4NaO_5S$ $[M+H]^+$ 552.9924, , found: 552.9923.

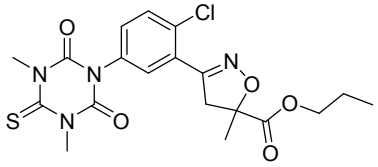


butyl 3-(4-bromo-2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)

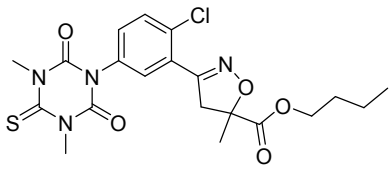
-5-methyl-4,5-dihydroisoxazole-5-carboxylate 7e. White solid; m.p.: 58.2-60.0 °C; 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.74 (s, 1H), 4.21 (t, J = 6.4 Hz, 2H), 4.01 (d, J = 17.2 Hz, 1H), 3.78 (s, 6H), 3.39 (d, J = 17.2 Hz, 1H), 1.71 (s, 3H), 1.66 (dd, J = 14.8, 6.8 Hz, 2H), 1.40 (dq, J = 15.2, 7.6 Hz, 2H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.58, 171.39, 154.41, 146.46, 146.43, 135.05, 134.46, 132.61, 131.59, 129.34, 124.75, 87.42, 65.91, 46.23, 36.70, 30.46, 23.28, 19.04, 13.71; HRMS (QFT-ESI) calcd for $C_{20}H_{23}BrClN_4O_5S$ $[M+H]^+$ 545.0261, found: 545.0260.



methyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl -4,5-dihydroisoxazole-5-carboxylate 8c. White solid; m.p.: 86.6-88.4 °C; 78% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 2.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.30 – 7.26 (m, 1H), 4.02 (d, J = 17.6 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 6H), 3.44 (d, J = 17.6 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.46, 172.17, 155.11, 147.25, 133.82, 132.69, 131.85, 130.62, 130.40, 129.82, 87.14, 53.07, 46.67, 36.72, 23.39; HRMS (QFT-ESI) calcd for $C_{17}H_{17}ClN_4NaO_5S$ $[M+Na]^+$ 447.0506, found: 447.0504.

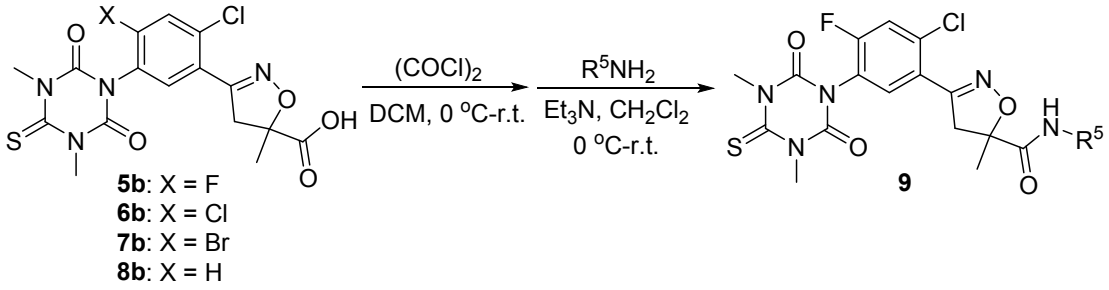


propyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl -4,5-dihydroisoxazole-5-carboxylate 8d. White solid; m.p.: 64.1-65.9 °C; 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.4, 2.4 Hz, 1H), 4.17 (t, J = 6.8 Hz, 2H), 4.03 (d, J = 17.6 Hz, 1H), 3.76 (s, 6H), 3.42 (d, J = 17.6 Hz, 1H), 1.82 – 1.67 (m, 5H), 0.96 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.47, 171.69, 155.07, 147.26, 133.87, 132.68, 131.84, 130.58, 130.42, 129.97, 87.26, 67.60, 46.59, 36.74, 23.37, 21.88, 10.31; HRMS (QFT-ESI) calcd for $C_{19}H_{21}ClN_4NaO_5S$ $[M+Na]^+$ 475.0819, found: 475.0818.



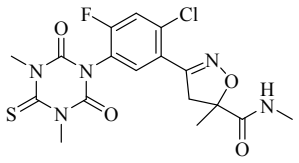
butyl 3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)phenyl)-5-methyl -4,5-dihydroisoxazole-5-carboxylate 8e. White solid; m.p.: 61.2-63.0 °C; 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.26 (dd, J = 8.4, 2.4 Hz, 1H), 4.21 (t, J = 6.4 Hz, 2H), 4.02 (d, J = 17.2 Hz, 1H), 3.76 (s, 6H), 3.42 (d, J = 17.6 Hz, 1H), 1.71 (s, 3H), 1.70 – 1.59 (m, 2H), 1.49 – 1.31 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.47, 171.69, 155.05, 147.26, 133.87, 132.68, 131.84, 130.58, 130.42, 129.97, 87.24, 77.37, 77.25, 77.05, 76.74, 65.96, 46.59, 36.74, 30.49, 23.37, 19.05, 13.70; HRMS (QFT-ESI) calcd for $C_{20}H_{23}ClN_4NaO_5S$ $[M+Na]^+$ 489.0975, found: 489.0975.

5.7 Synthesis of compounds 9.

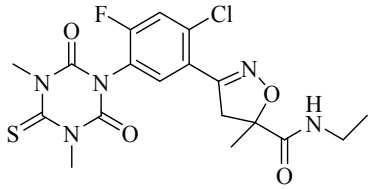


5b: X = F
6b: X = Cl
7b: X = Br
8b: X = H

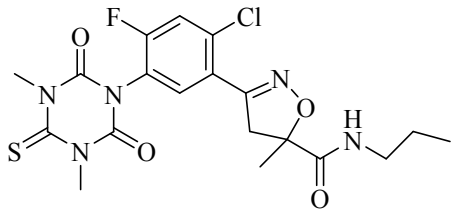
General method to synthesize of compounds **9**. Compound **5b**, **6b**, **7b**, or **8b** (1 mmol) was dissolved in CH_2Cl (20 mL) and cooled to 0 °C, $(COCl)_2$ (1.25 mmol) was added dropwise to the solution. Then the reaction solution was stirred at 0 °C for 1 h, and moved to the room temperature for another 2 hours. After removing the solvent by rotary evaporation, CH_2Cl (30 mL) was added to the flask to dissolve the residue, and the resulting solution was cooled to 0 °C, R^5NH_2 (1.05 mmol) was added to the solution. The reaction solution was stirred for 30 min at 0 °C, and then moved to room temperature for another 3 hours. After completing the reaction, H_2O (20 mL) was added to the solution, the organic layer was separated and washed with water (40 mL) and saturated NaCl solution (40 mL), dried over Na_2SO_4. After removing the solvent in vacuum, the residue was purified by flash chromatography to give compounds **9**.



3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-N,5-dimethyl-4,5-dihydroisoxazole-5-carboxamide 9a. White solid; m.p.: 102.0-104.0 °C; 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 6.84 (d, J = 4.8 Hz, 1H), 3.97 (d, J = 17.6 Hz, 1H), 3.76 (s, 6H), 3.38 (d, J = 17.6 Hz, 1H), 2.83 (d, J = 5.2 Hz, 3H), 1.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.37, 173.51, 159.51, 156.93, 155.92, 146.57, 135.43, 135.33, 131.81, 125.65, 125.61, 120.88, 120.74, 119.60, 119.37, 88.52, 47.15, 36.81, 26.12, 23.83; HRMS (QFT-ESI) calcd for $C_{17}H_{17}ClFN_5NaO_4S$ $[M+Na]^+$ 464.0572, found: 464.0570.

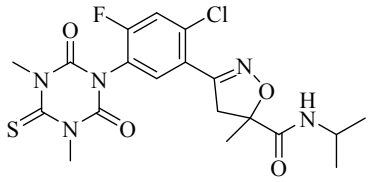


3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-N-ethyl-5-methyl-4,5-dihydroisoxazole-5-carboxamide 9b. White solid; m.p.: 97.9-99.9 °C; 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 9.2 Hz, 1H), 6.80 (s, 1H), 3.99 (d, J = 17.6 Hz, 1H), 3.79 (s, 6H), 3.39 (d, J = 17.6 Hz, 1H), 3.31 (dd, J = 14.0, 6.8 Hz, 2H), 1.73 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.39, 172.68, 159.52, 156.94, 155.90, 146.55, 135.47, 135.37, 131.81, 125.73, 125.69, 120.90, 120.76, 119.59, 119.36, 88.44, 65.84, 47.13, 36.80, 34.31, 23.81, 14.67; HRMS (QFT-ESI) calcd for $C_{18}H_{19}ClFN_5NaO_4S$ $[M+Na]^+$ 478.0728, found: 478.0726.

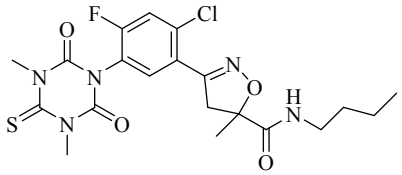


3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-N-propyl-4,5-dihydroisoxazole-5-carboxamide 9c. White solid; m.p.: 85.0-87.0 °C; 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 6.81 (t, J = 5.6 Hz, 1H), 3.97 (d, J = 18.0 Hz, 1H), 3.77 (s, 6H), 3.36 (d, J = 17.6 Hz, 1H), 3.32 – 3.14 (m,

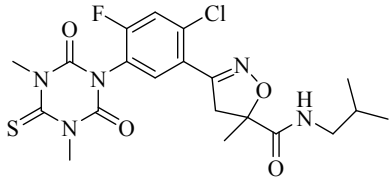
2H), 1.71 (s, 3H), 1.54 (h, J = 7.2 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.38, 172.82, 159.52, 156.94, 155.96, 146.54, 135.48, 135.38, 131.80, 125.73, 125.69, 120.89, 120.75, 119.58, 119.35, 88.50, 47.13, 41.03, 36.80, 23.82, 22.69, 11.26; HRMS (QFT-ESI) calcd for $C_{19}H_{21}ClFN_5NaO_4S$ $[M+Na]^+$ 492.0885, found: 492.0883.



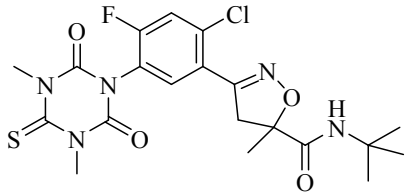
3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-N-isopropyl-5-methyl-4,5-dihydroisoxazole-5-carboxamide 9d. White solid; m.p.: 87.9-89.9 °C; 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 4.04 (dd, J = 13.2, 6.8 Hz, 1H), 3.96 (d, J = 17.2 Hz, 1H), 3.77 (s, 6H), 3.45 – 3.30 (m, 1H), 1.70 (s, 3H), 1.17 (dd, J = 14.0, 6.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.34, 171.88, 159.49, 156.91, 155.90, 146.55, 146.50, 135.50, 135.40, 131.75, 125.74, 125.70, 120.85, 120.71, 119.58, 119.35, 88.36, 47.05, 41.42, 36.81, 23.77, 22.62, 22.55. 3H), 1.17 (dd, J = 14.1, 6.4 Hz, 6H); HRMS (QFT-ESI) calcd for $C_{19}H_{21}ClFN_5NaO_4S$ $[M+Na]^+$ 492.0885, found: 492.0885.



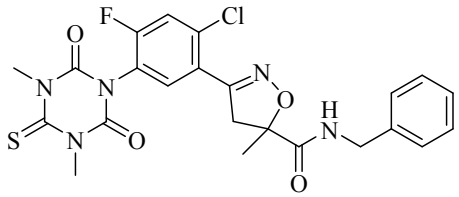
N-butyl-3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxamide 9e. White solid; m.p.: 72.0-74.0 °C; 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 6.79 (t, J = 5.6 Hz, 1H), 3.97 (d, J = 18.0 Hz, 1H), 3.77 (s, 6H), 3.36 (d, J = 17.6 Hz, 1H), 3.26 (qd, J = 13.2, 6.0 Hz, 2H), 1.71 (s, 3H), 1.56 – 1.46 (m, 2H), 1.34 (dd, J = 15.2, 7.6 Hz, 2H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.36, 172.77, 159.52, 156.94, 155.97, 146.54, 146.53, 135.49, 135.39, 131.80, 125.73, 125.69, 120.87, 120.74, 119.59, 119.36, 88.50, 47.12, 39.11, 36.81, 31.47, 23.81, 19.99, 13.71; HRMS (QFT-ESI) calcd for $C_{20}H_{23}ClFN_5NaO_4S$ $[M+Na]^+$ 506.1041, found: 506.1039.



3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-N-isobutyl-5-methyl-4,5-dihydroisoxazole-5-carboxamide 9f. White solid; m.p.: 86.3-88.2 °C; 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 6.86 (t, J = 6.0 Hz, 1H), 3.98 (d, J = 18.0 Hz, 1H), 3.77 (s, 6H), 3.36 (d, J = 18.0 Hz, 1H), 3.18 – 3.01 (m, 2H), 1.80 (td, J = 13.2, 6.8 Hz, 1H), 1.72 (s, 3H), 0.94 – 0.87 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.36, 172.88, 159.53, 156.94, 156.07, 146.55, 146.51, 135.51, 135.41, 131.81, 125.72, 125.68, 120.87, 120.73, 119.60, 119.37, 88.55, 47.11, 46.56, 36.82, 28.48, 23.82, 20.02, 19.99; HRMS (QFT-ESI) calcd for $C_{20}H_{23}ClFN_5NaO_4S$ $[M+Na]^+$ 506.1041, found: 506.1038.

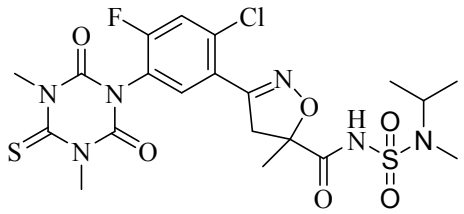


N-(tert-butyl)-3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxamide 9g. White solid; m.p.: 94.3-95.8 °C; 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 6.62 (s, 1H), 3.96 (d, J = 18.0 Hz, 1H), 3.77 (s, 6H), 3.31 (d, J = 17.6 Hz, 1H), 1.68 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.34, 171.97, 159.48, 156.90, 155.88, 146.55, 146.49, 135.53, 135.43, 131.74, 125.81, 125.77, 120.83, 120.70, 119.56, 119.33, 88.52, 51.13, 46.95, 36.80, 28.58, 23.77; HRMS (QFT-ESI) calcd for $C_{20}H_{23}ClFN_5NaO_4S$ $[M+Na]^+$ 506.1041, found: 506.1040.



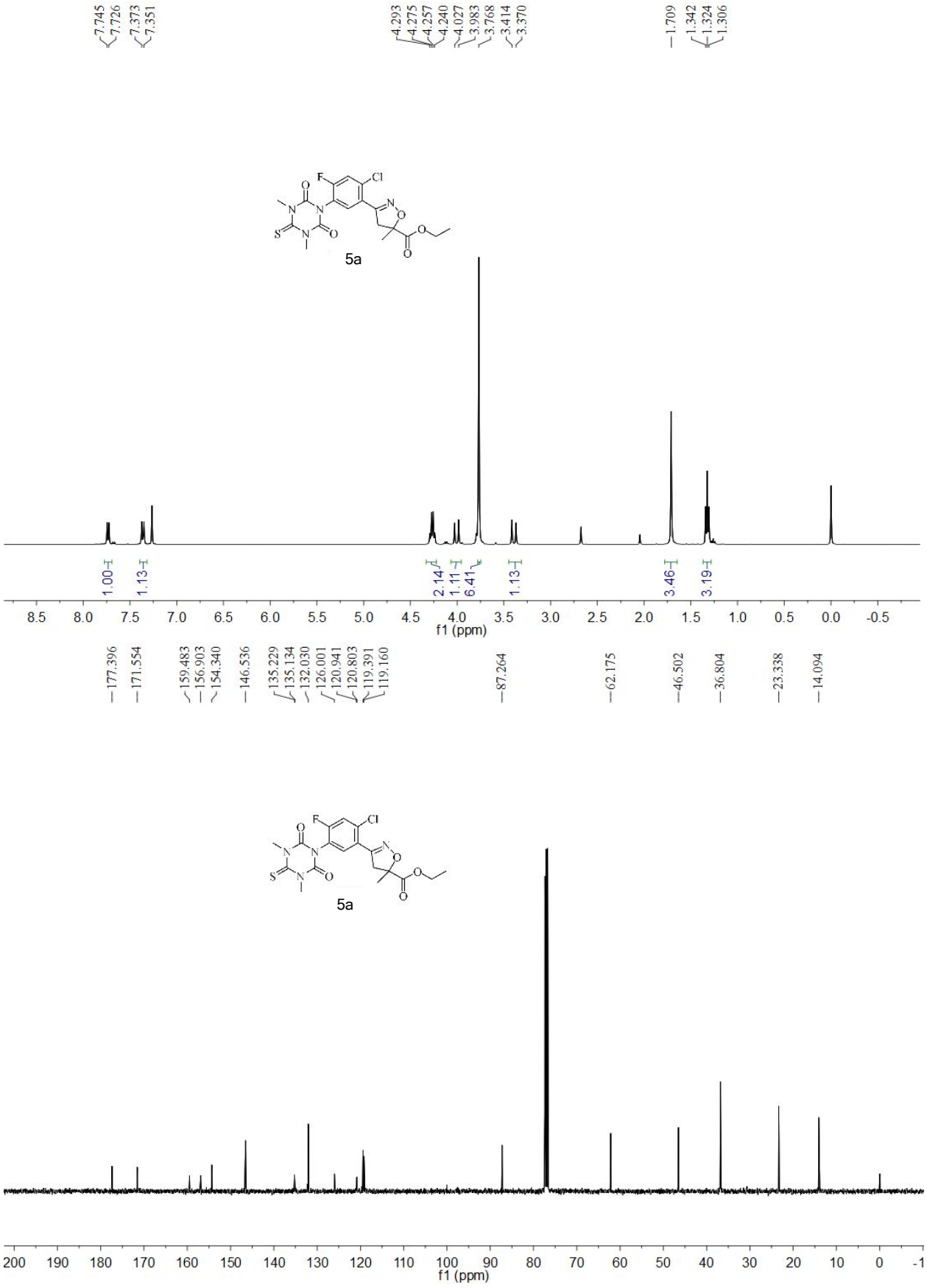
N-benzyl-3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-5-methyl-4,5-dihydroisoxazole-5-carboxamide 9h. White solid; m.p.: 96.0-98 °C; 86% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.31 (dd, J = 14.4, 6.8 Hz, 3H), 7.24 (d, J = 8.0 Hz, 2H), 7.13 (t, J = 5.2 Hz, 1H), 4.45 (qd, J = 14.8, 6.0 Hz,

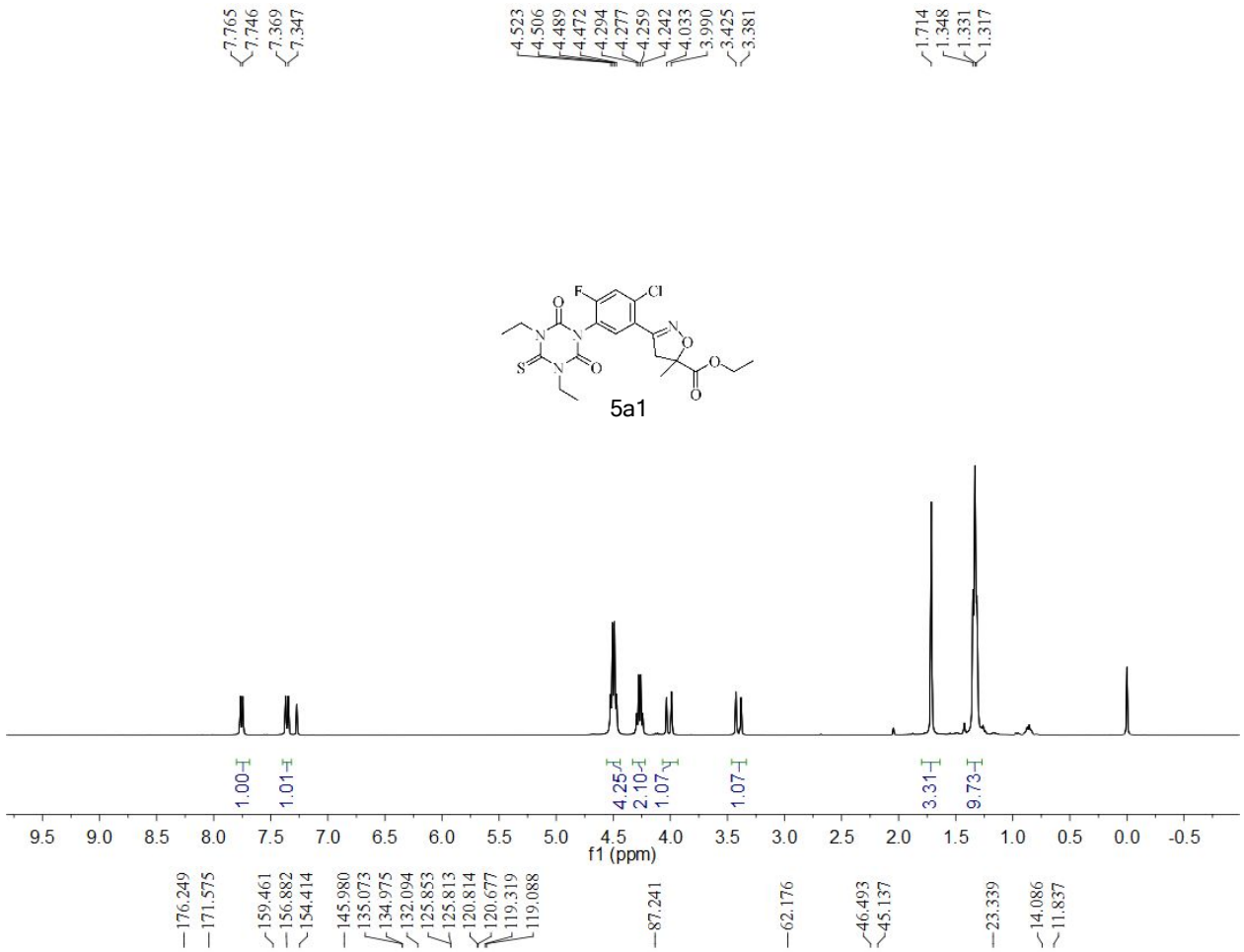
2H), 4.01 (d, *J* = 17.6 Hz, 1H), 3.77 (d, *J* = 3.2 Hz, 6H), 3.40 (d, *J* = 18.0 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.40, 172.88, 159.56, 156.98, 156.07, 146.53, 137.70, 135.44, 135.34, 131.82, 128.75, 127.61, 127.55, 125.68, 125.64, 120.92, 120.79, 119.56, 119.33, 88.53, 47.16, 43.32, 36.79, 23.73; HRMS (QFT-ESI) calcd for $C_{23}H_{21}ClFN_5NaO_4S$ $[M+Na]^+$ 540.0885, found: 540.0884.



3-(2-chloro-5-(3,5-dimethyl-2,6-dioxo-4-thioxo-1,3,5-triazinan-1-yl)-4-fluorophenyl)-N-(N-isopropyl-N-methylsulfamoyl)-5-methyl-4,5-dihydroisoxazole-5-carboxamide 9i. White solid; m.p.: 87.6-88.9 °C; 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 4.18 (dt, *J* = 13.6, 6.8 Hz, 1H), 4.00 (d, *J* = 18.0 Hz, 1H), 3.77 (s, 6H), 3.41 (d, *J* = 17.6 Hz, 1H), 2.88 (s, 3H), 1.73 (s, 3H), 1.18 – 1.09 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.38, 171.72, 159.84, 157.25, 156.25, 146.58, 146.48, 135.38, 135.28, 132.09, 125.06, 125.02, 121.14, 121.00, 119.61, 119.38, 88.26, 49.80, 46.76, 36.81, 28.58, 23.13, 19.92, 19.84, 19.78; HRMS (QFT-ESI) calcd for $C_{20}H_{24}ClFN_6NaO_6S_2$ $[M+Na]^+$ 585.0769, found: 585.0768.

Representative ^{1}H NMR and ^{13}C NMR Spectrum.

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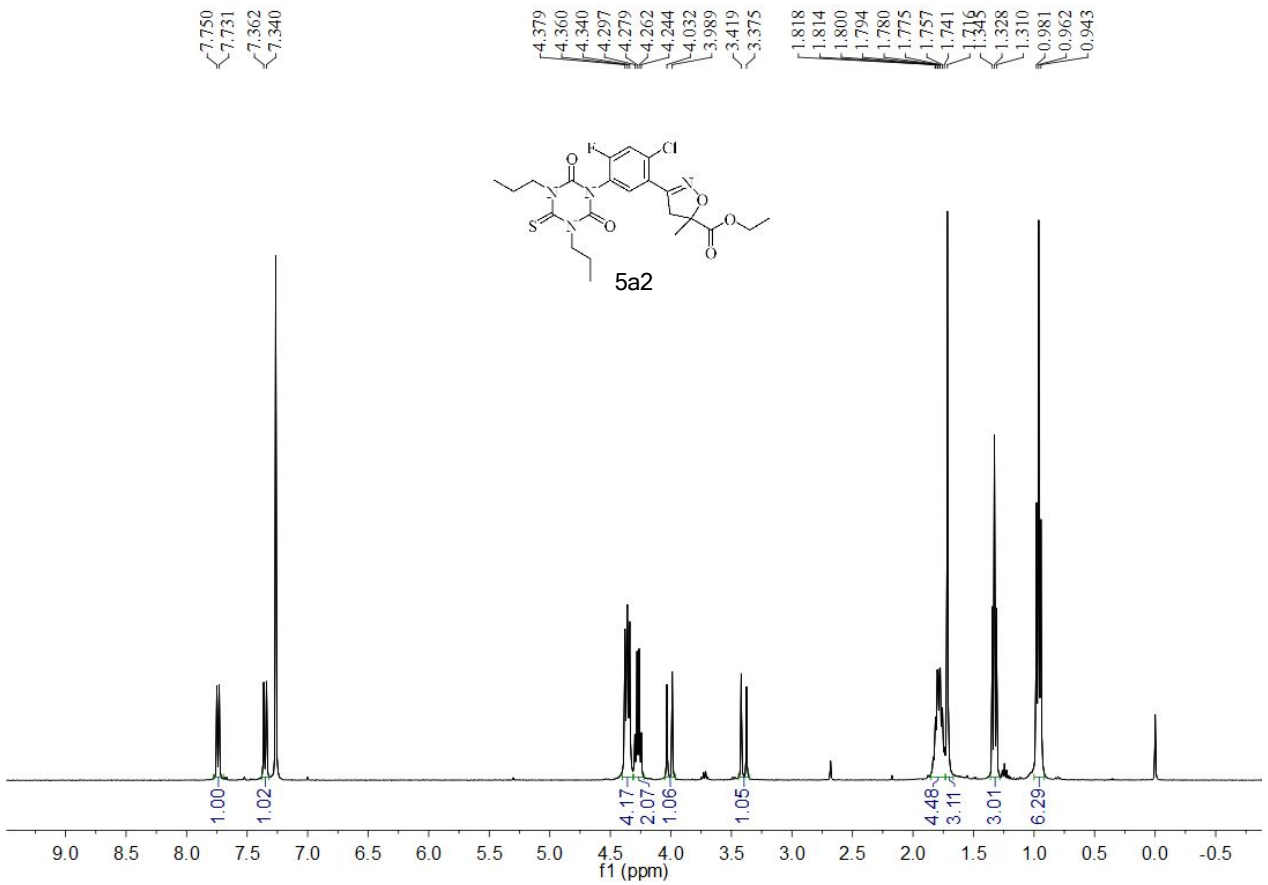
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1.818
1.814
1.800
1.794
1.780
1.775
1.757
1.741
1.328
1.310
0.981
0.962
0.943
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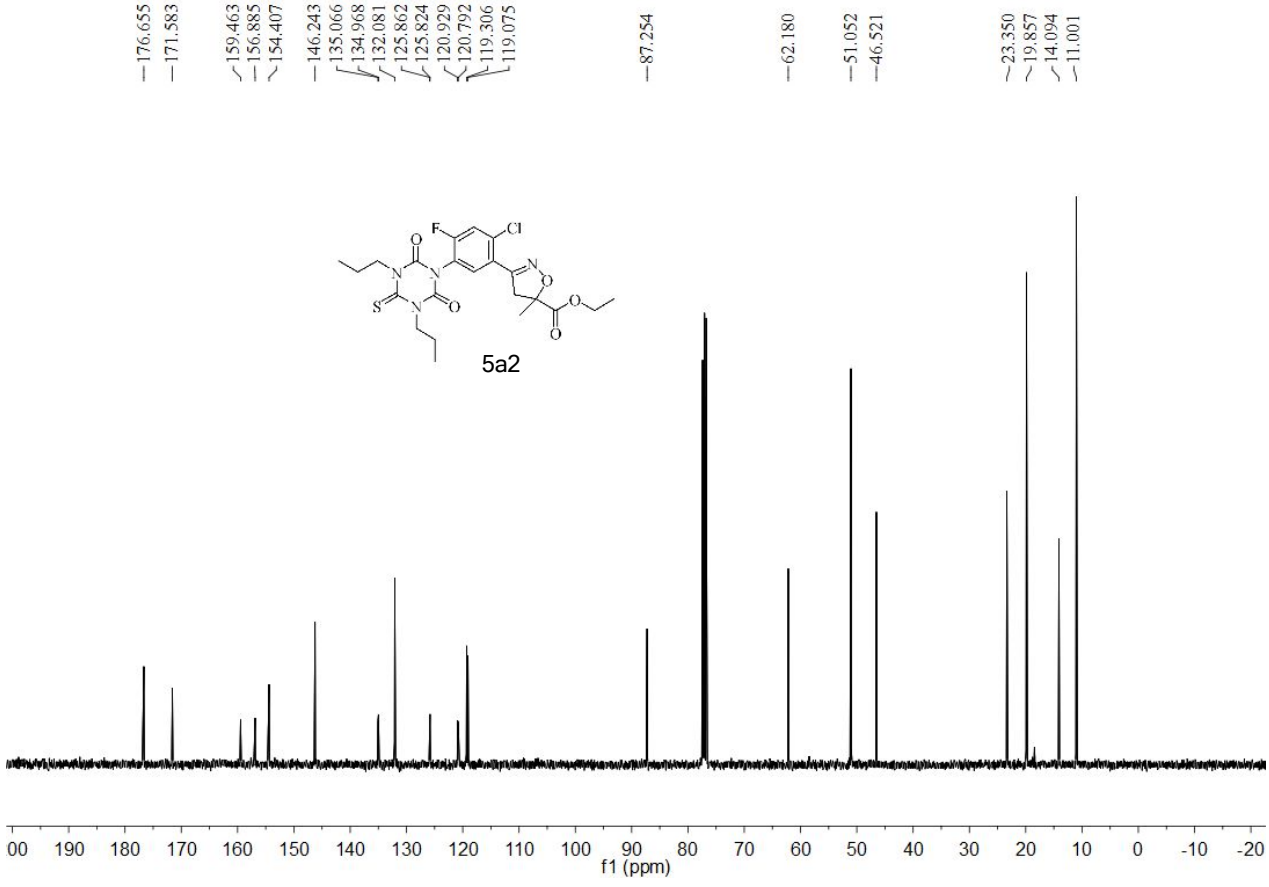
2.07
1.06
1.05
4.48
3.11
3.01
6.29
f1 (ppm)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46.521
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14.094
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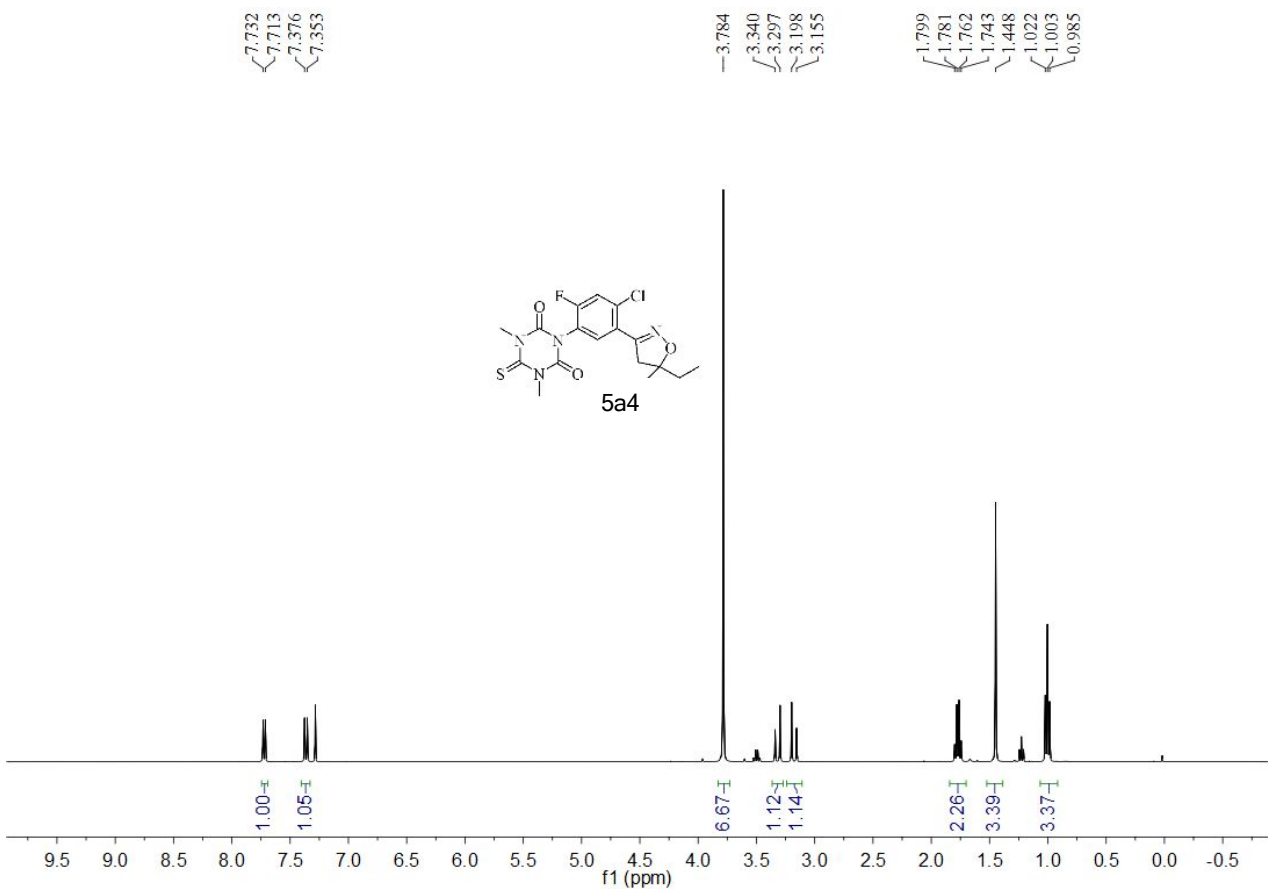
5a2
f1 (ppm)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3.198
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1.743
1.448
1.022
1.003
0.985
F
Cl
O
N
S
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1.00
1.05
6.67
1.12
1.14
2.26
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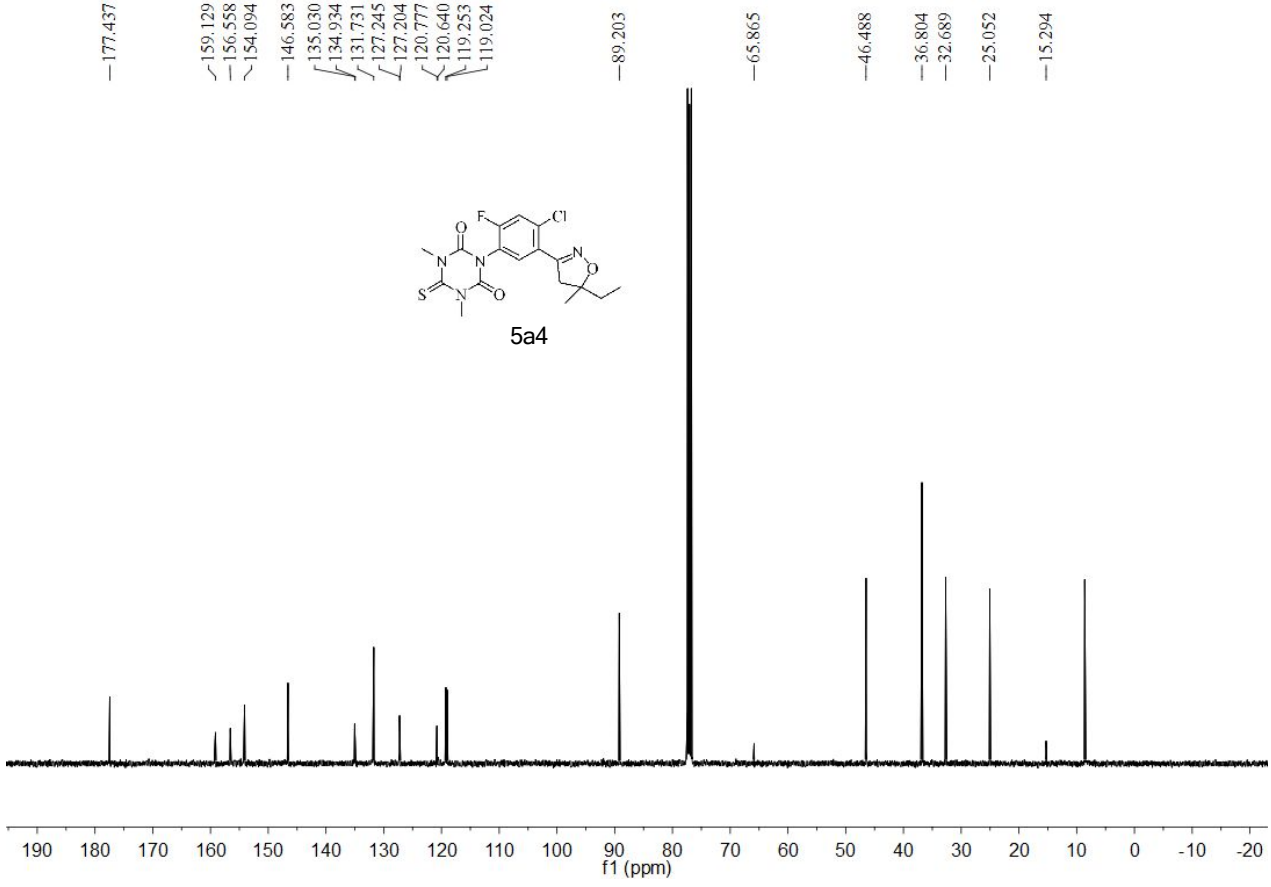
3.37
f1 (ppm)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120.640
119.253
119.024
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32.689
25.052
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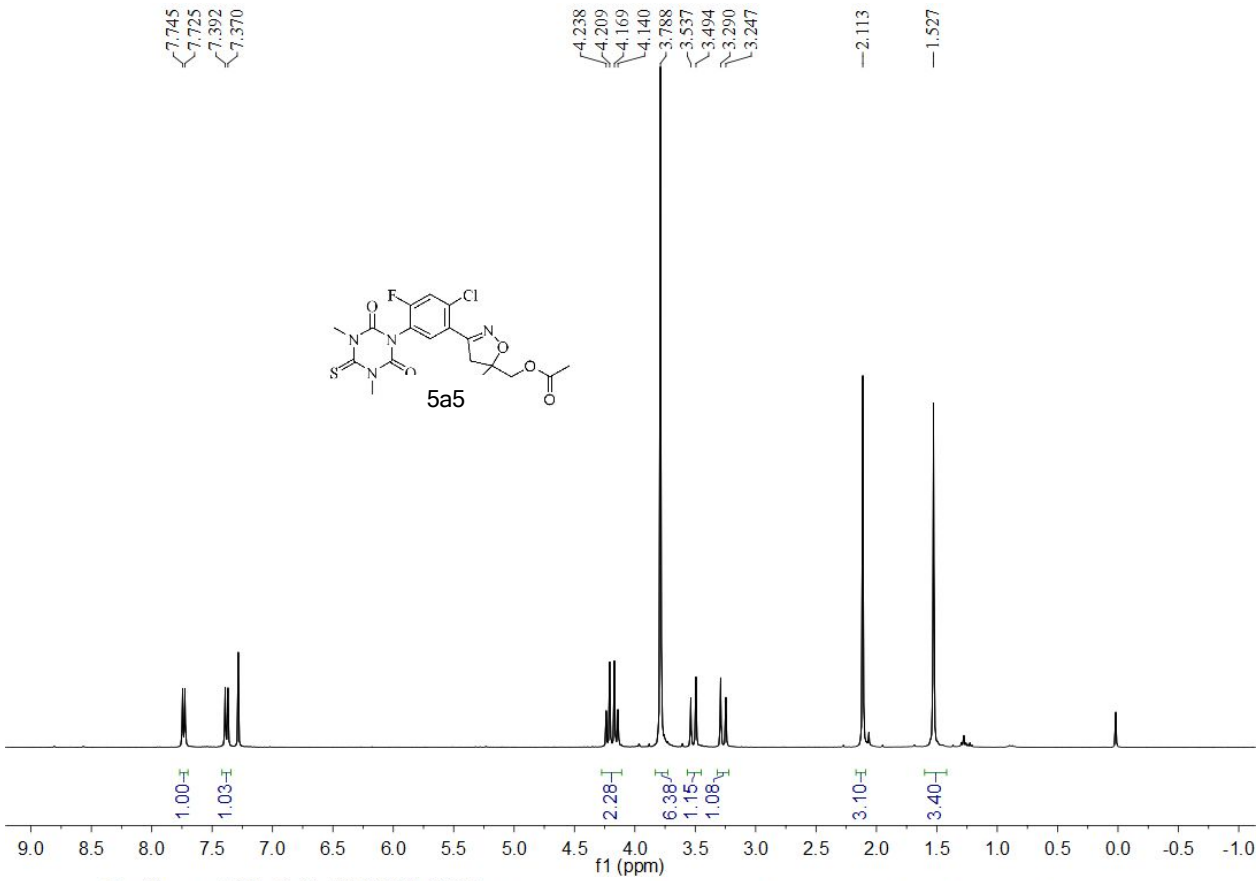
F
Cl
O
N
S
5a4
f1 (ppm)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4.140
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3.494
3.290
3.247
2.113
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6.38
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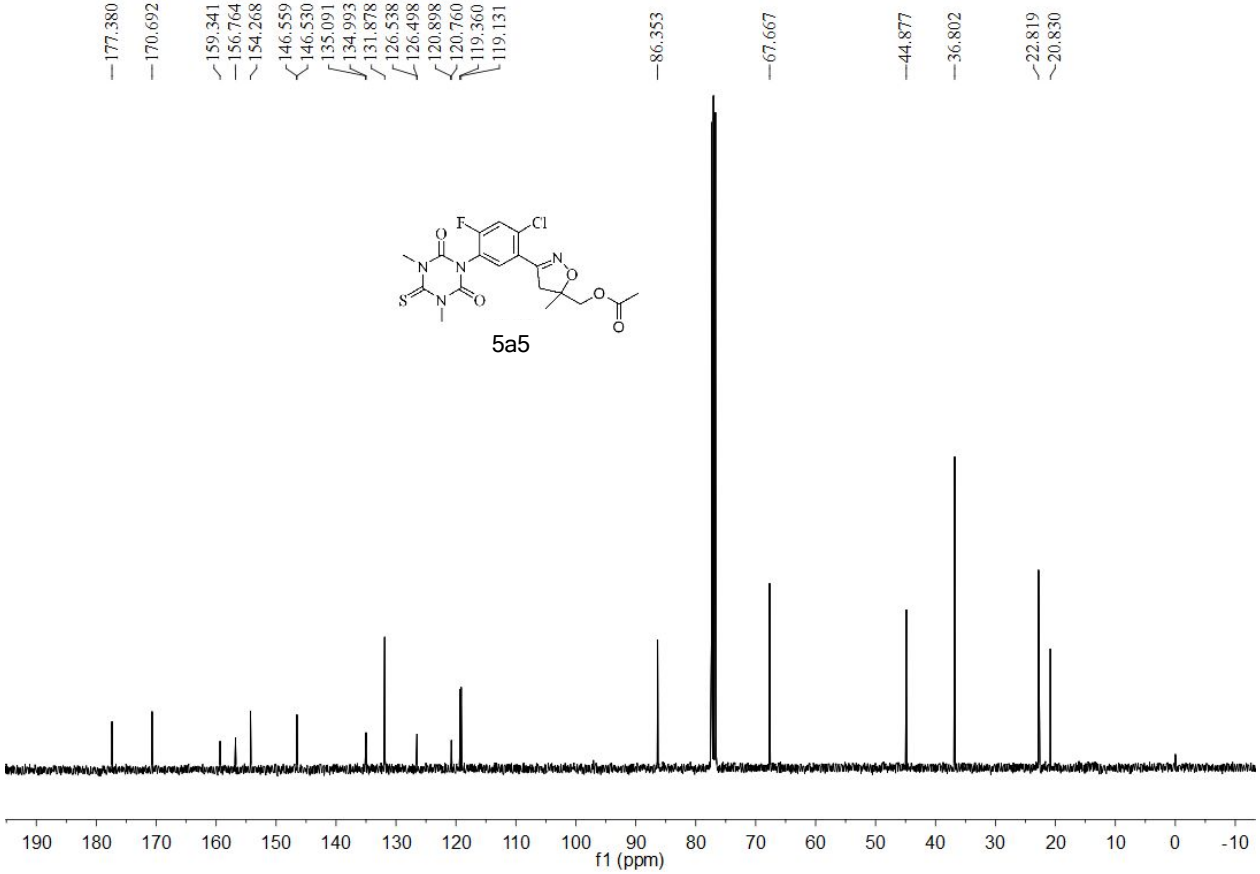
1.08
3.10
3.40
f1 (ppm)

5a5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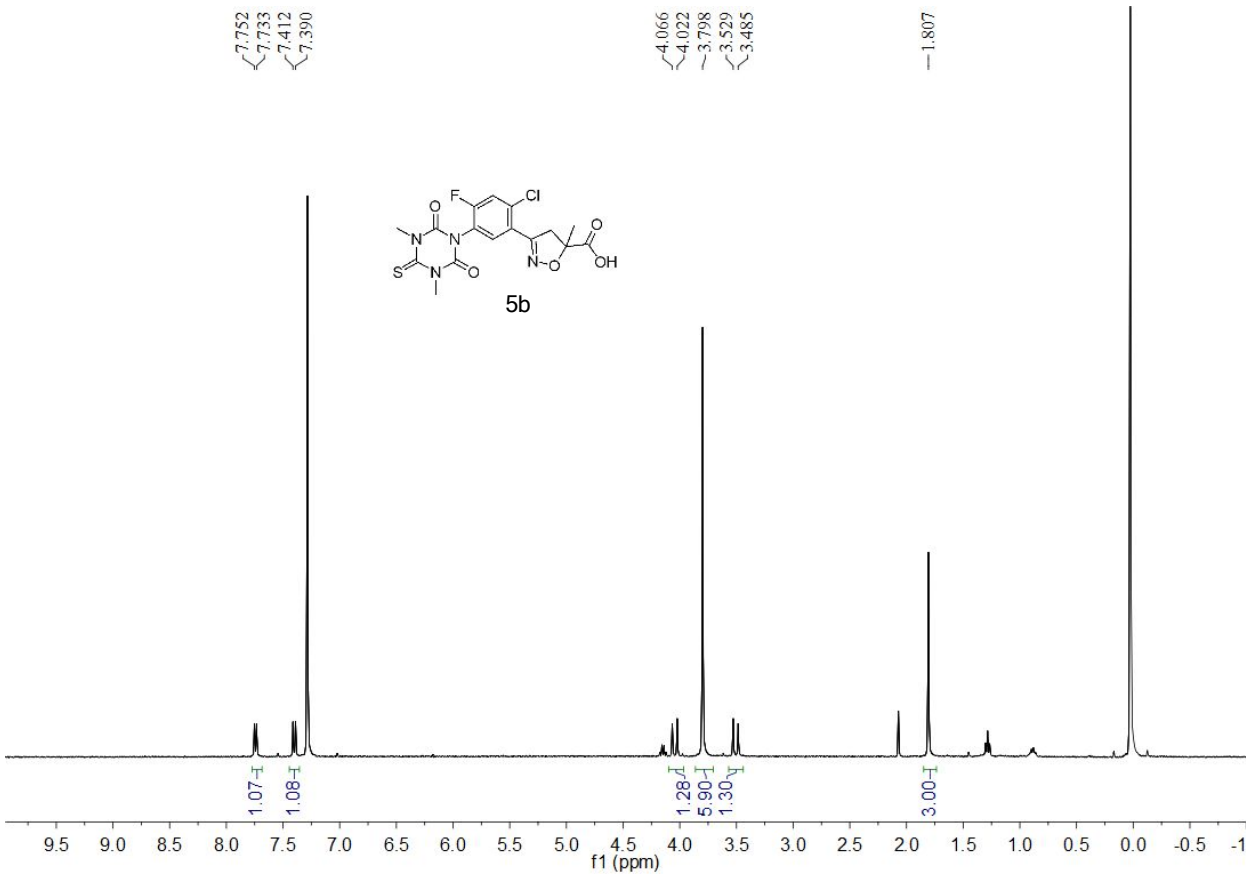
20.830
f1 (ppm)

5a5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3.529
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1.807
F
Cl
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S
OH
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1.08
1.28
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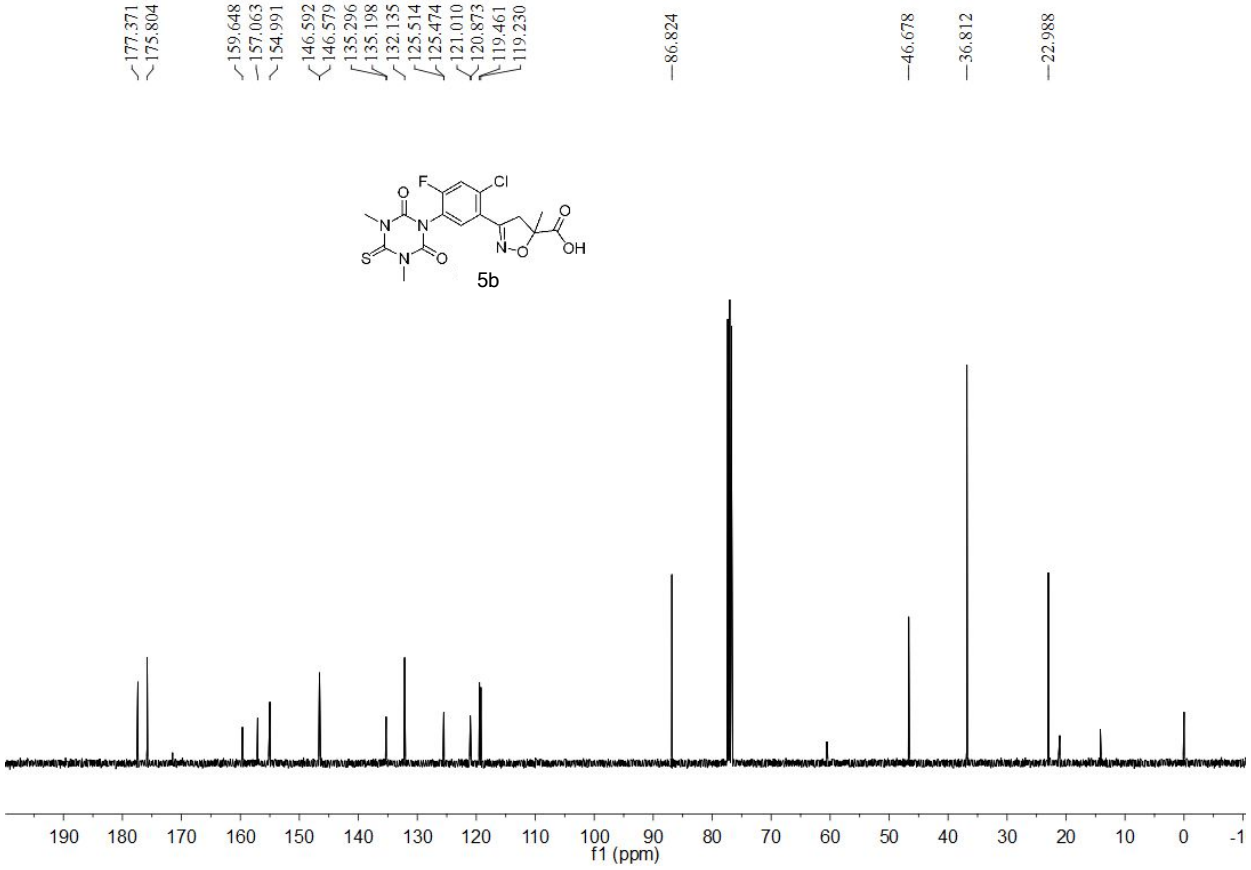
1.30
3.00
f1 (ppm)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125.474
121.010
120.873
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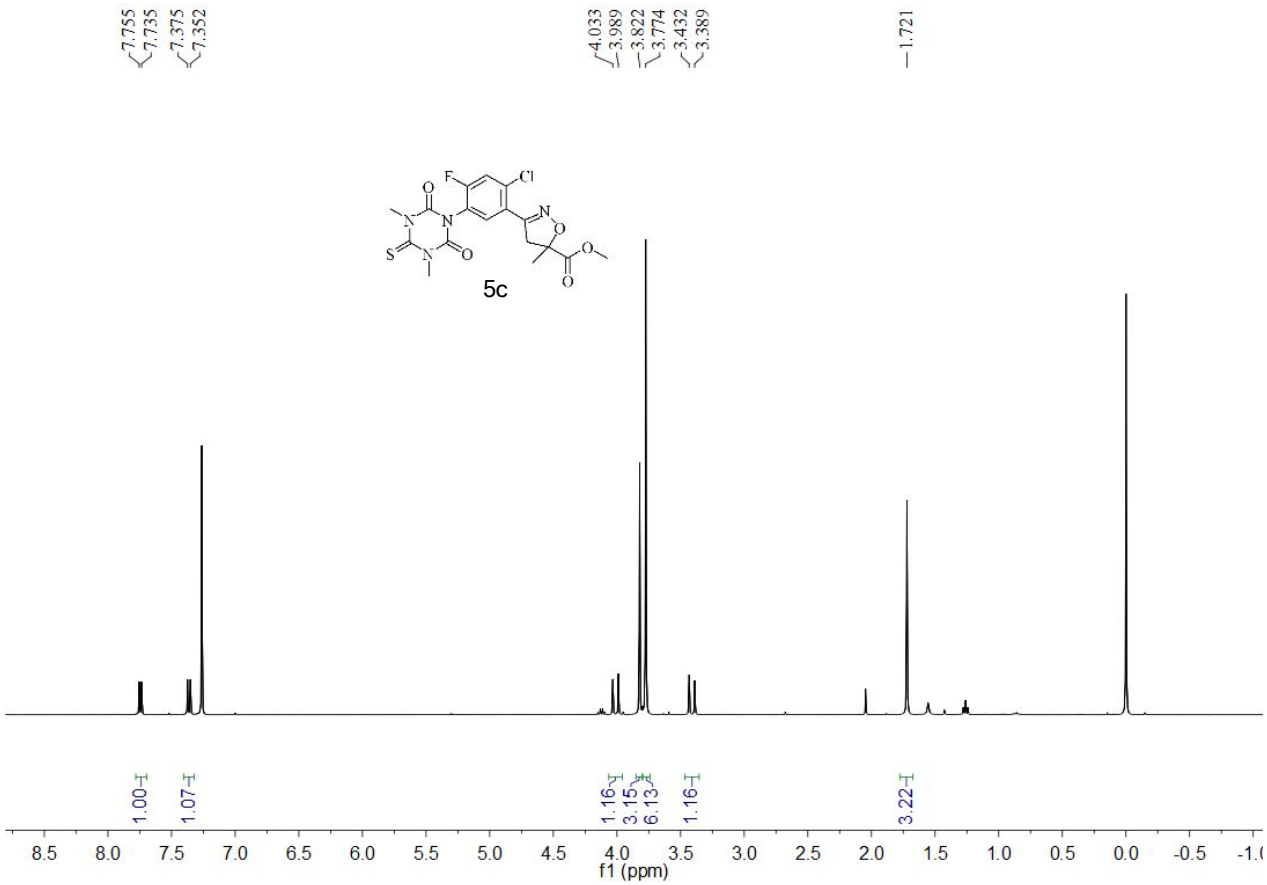
46.678
36.812
22.988
F
Cl
O
N
S
OH
5b
f1 (ppm)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3.774
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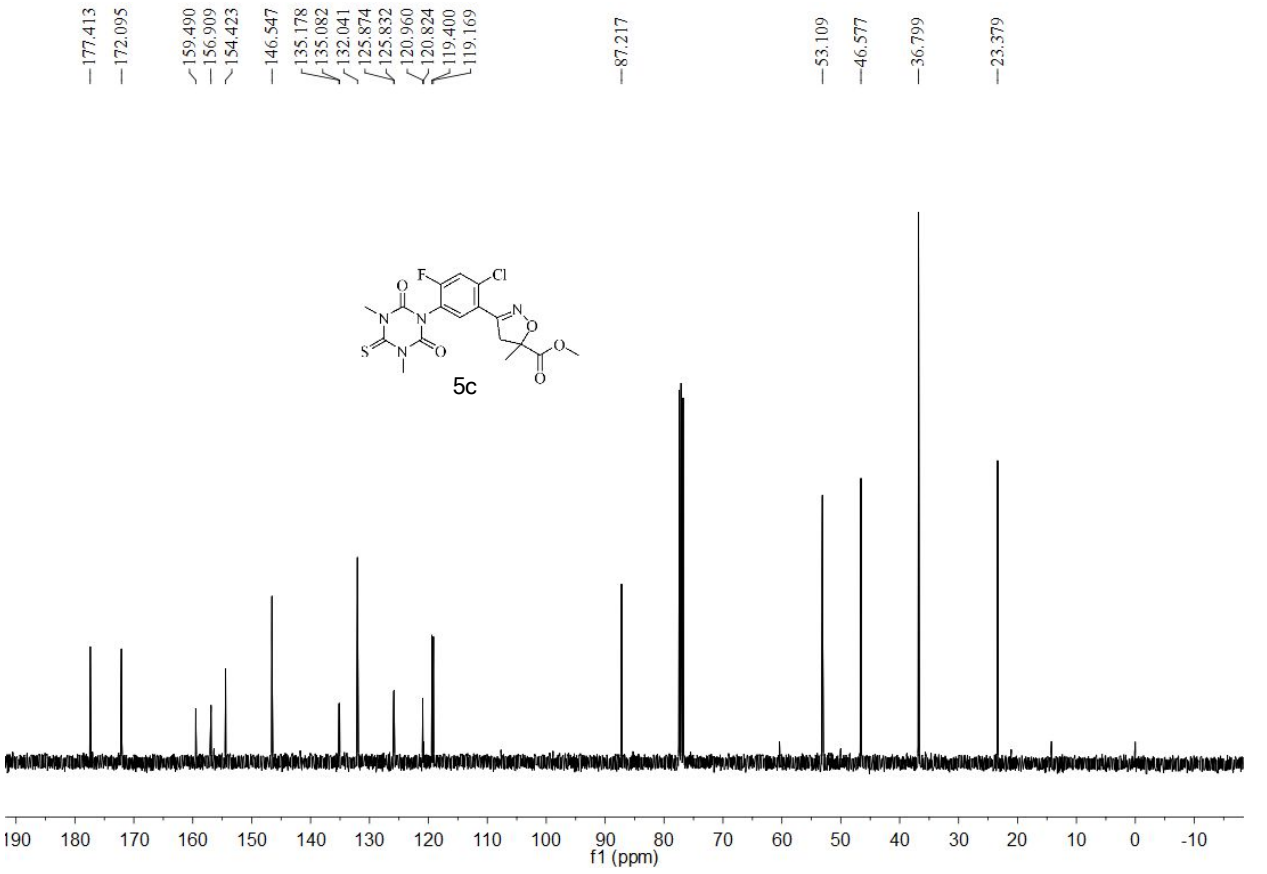
1.16
3.15
6.13
1.16
3.22
f1 (ppm)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135.082
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125.874
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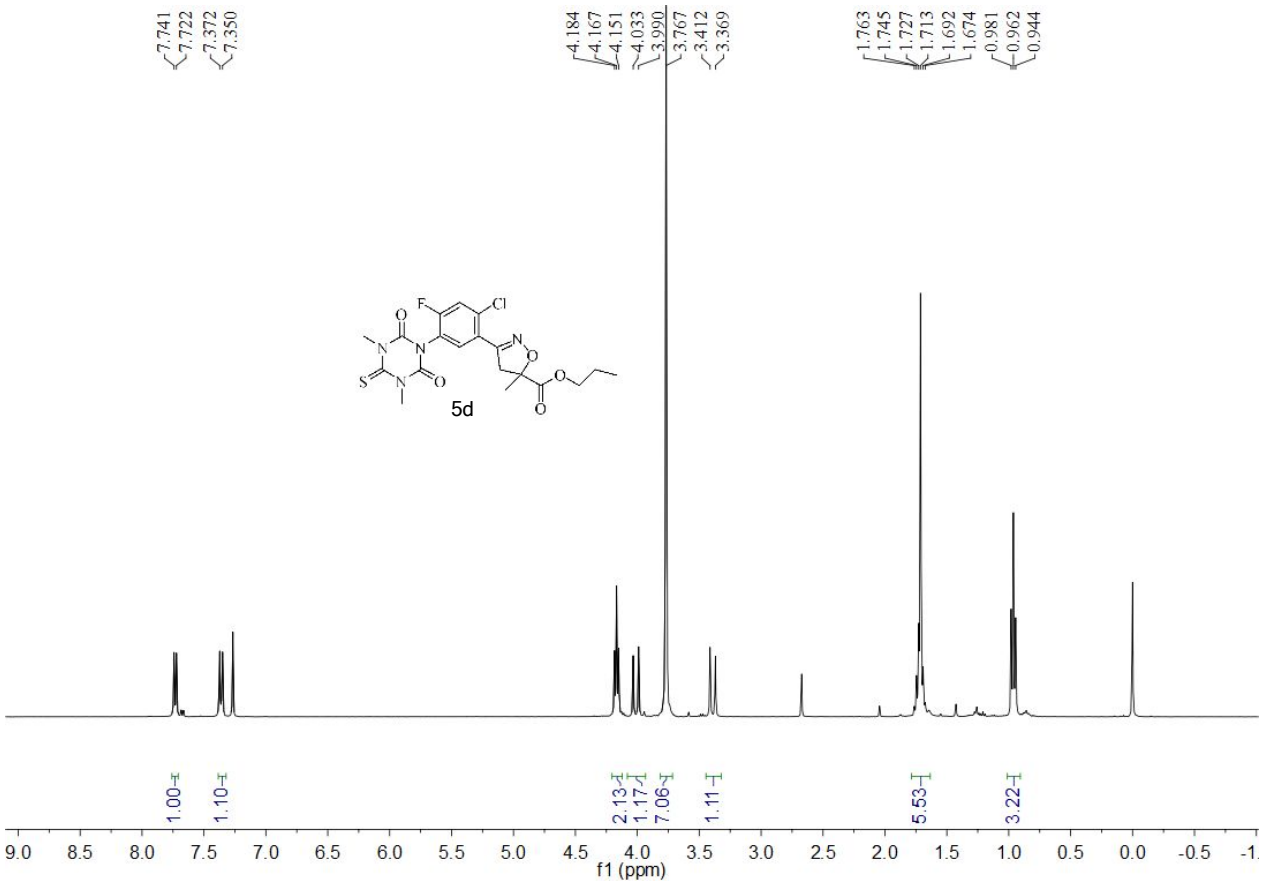
119.400
119.169
87.217
53.109
46.577
36.799
23.379
5c
f1 (ppm)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3.369
1.763
1.745
1.727
1.713
1.692
1.674
0.981
0.962
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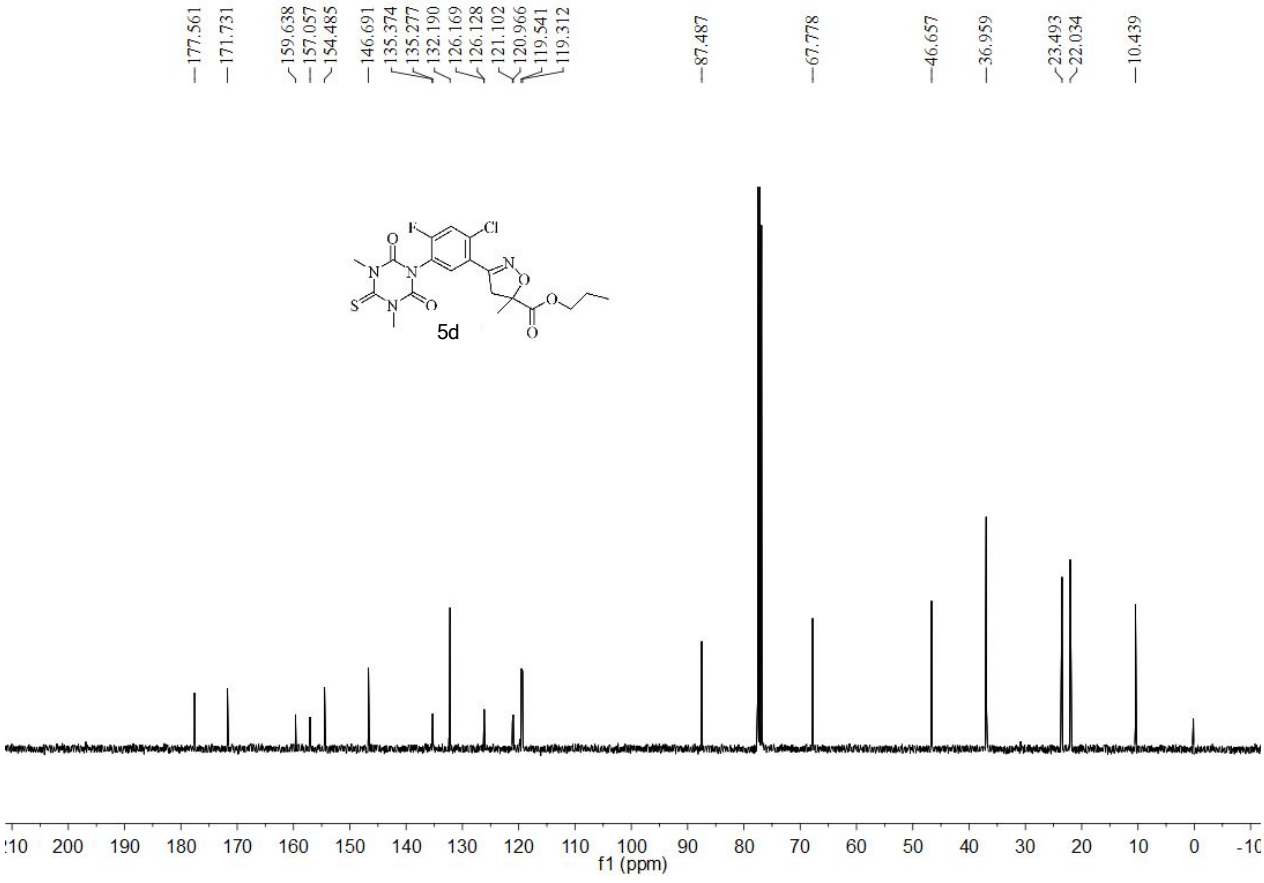
1.00
1.10
2.13
1.17
7.06
1.11
5.53
3.22
f1 (ppm)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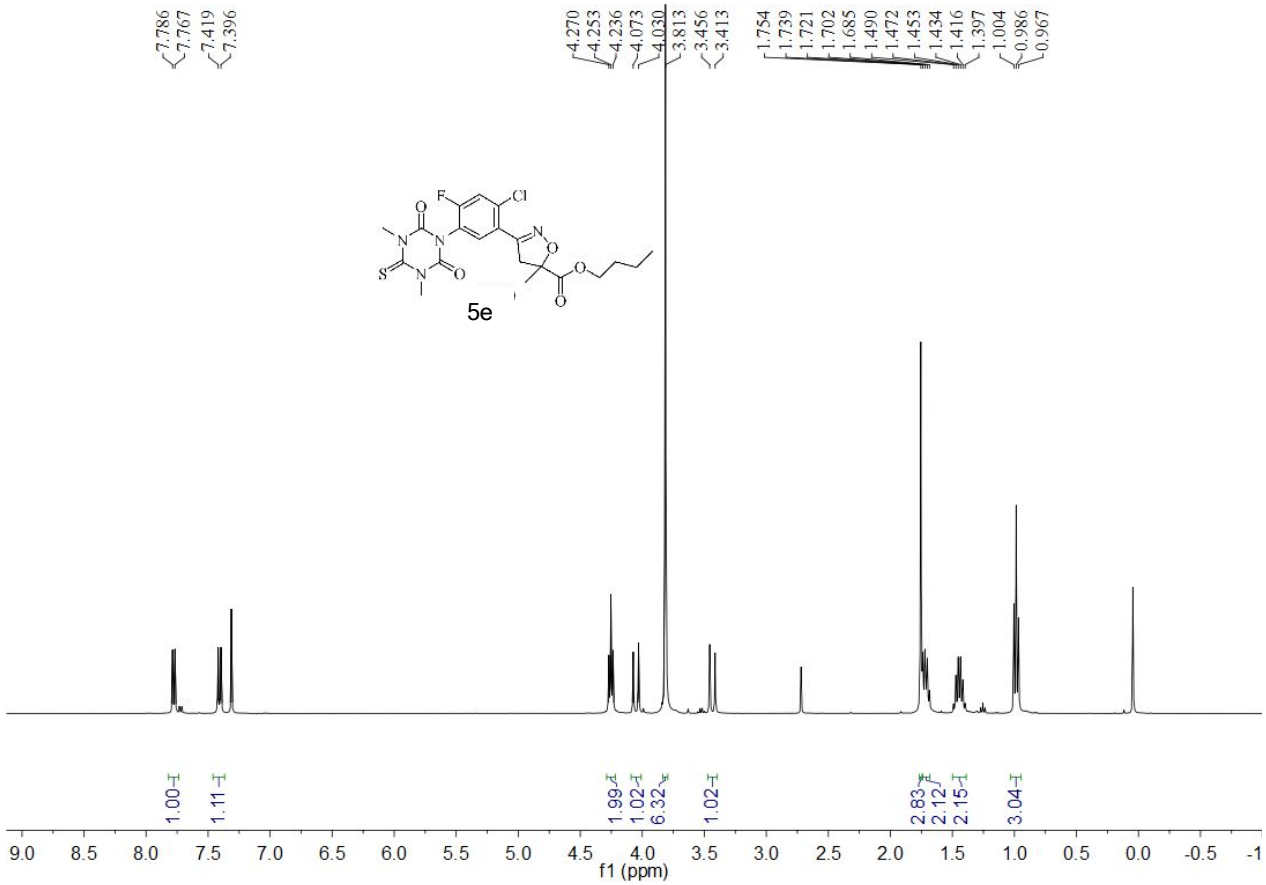
f1 (ppm)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1.754
1.739
1.721
1.702
1.685
1.490
1.472
1.453
1.434
1.416
1.397
1.004
0.986
0.967
F
Cl
O
N
S
5e
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1.99
1.02
6.32
1.02
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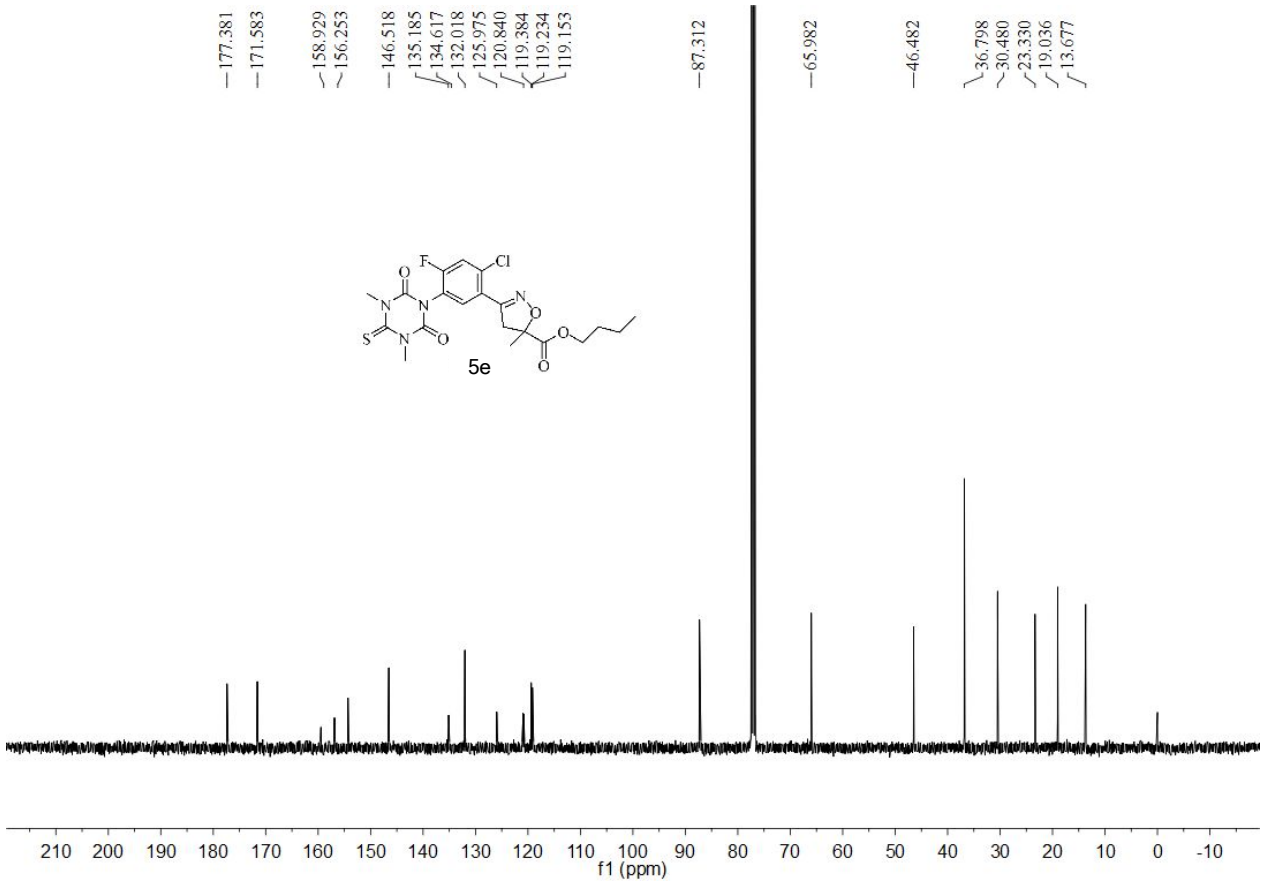
2.12
2.15
3.04
f1 (ppm)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119.234
119.153
87.312
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30.480
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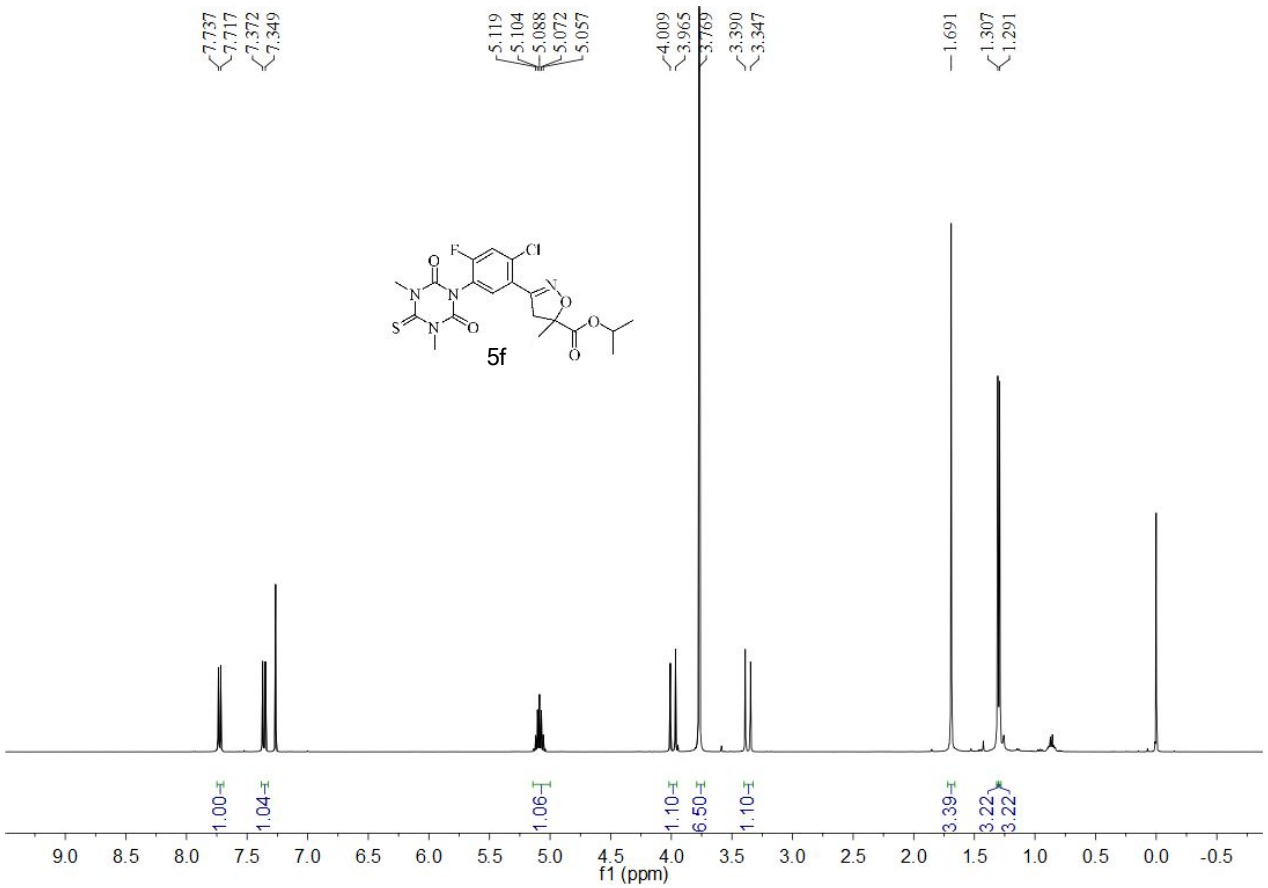
19.036
13.677
F
Cl
O
N
S
5e
f1 (ppm)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3.965
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3.390
3.347
1.691
1.307
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1.10
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1.10
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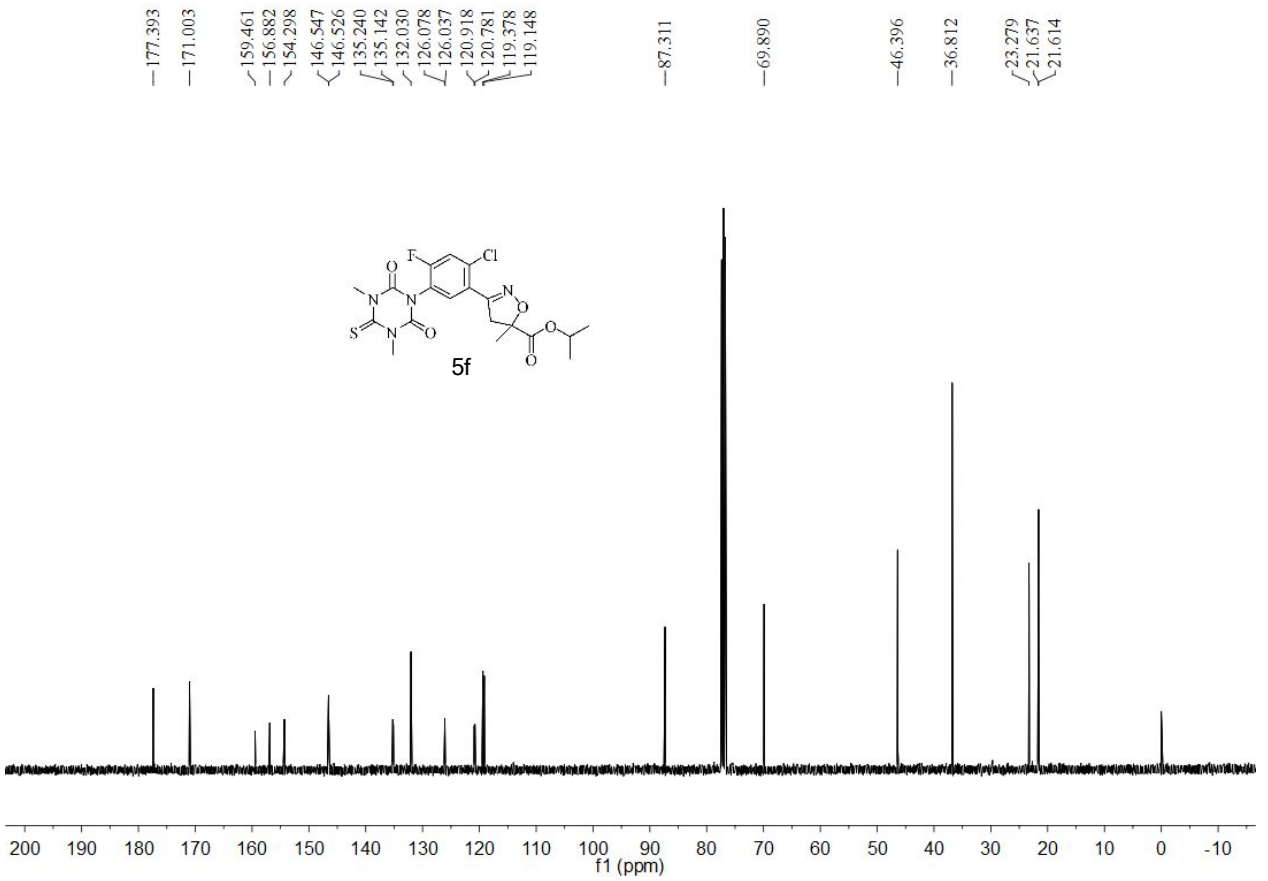
3.22
3.22
f1 (ppm)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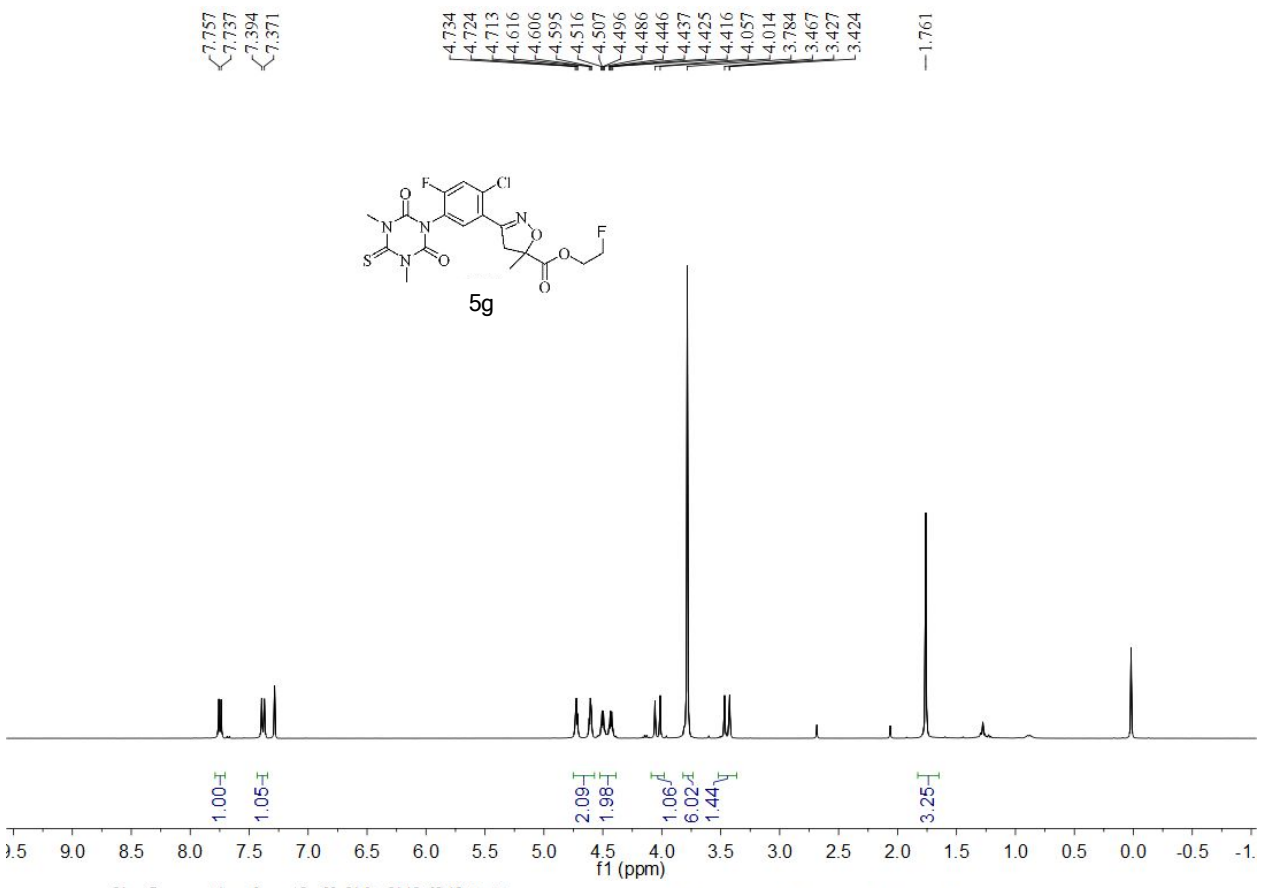
5f
f1 (ppm)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4.496
4.486
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4.057
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3.784
3.467
3.427
3.424
1.761
F
Cl
O
N
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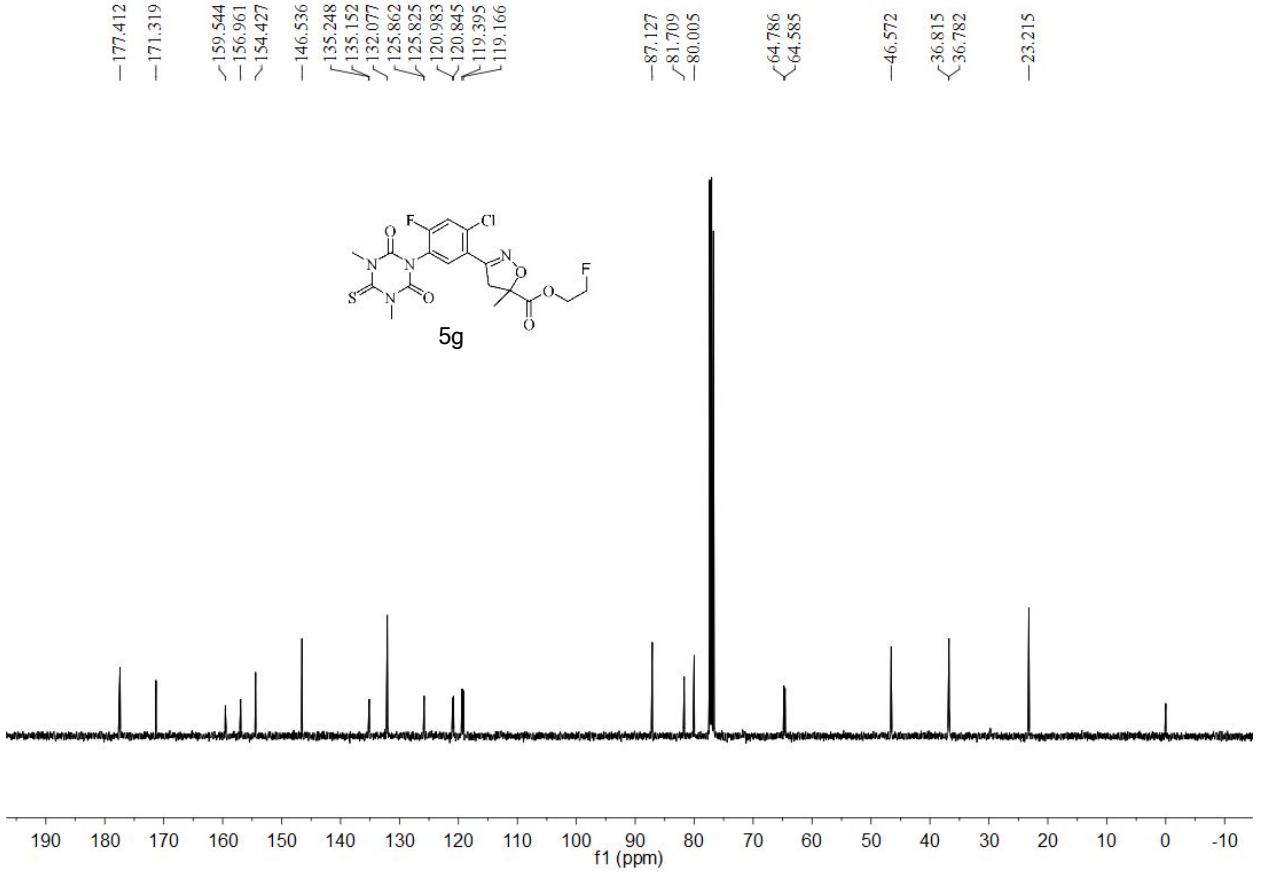
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81.709
80.005
64.786
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36.782
23.215
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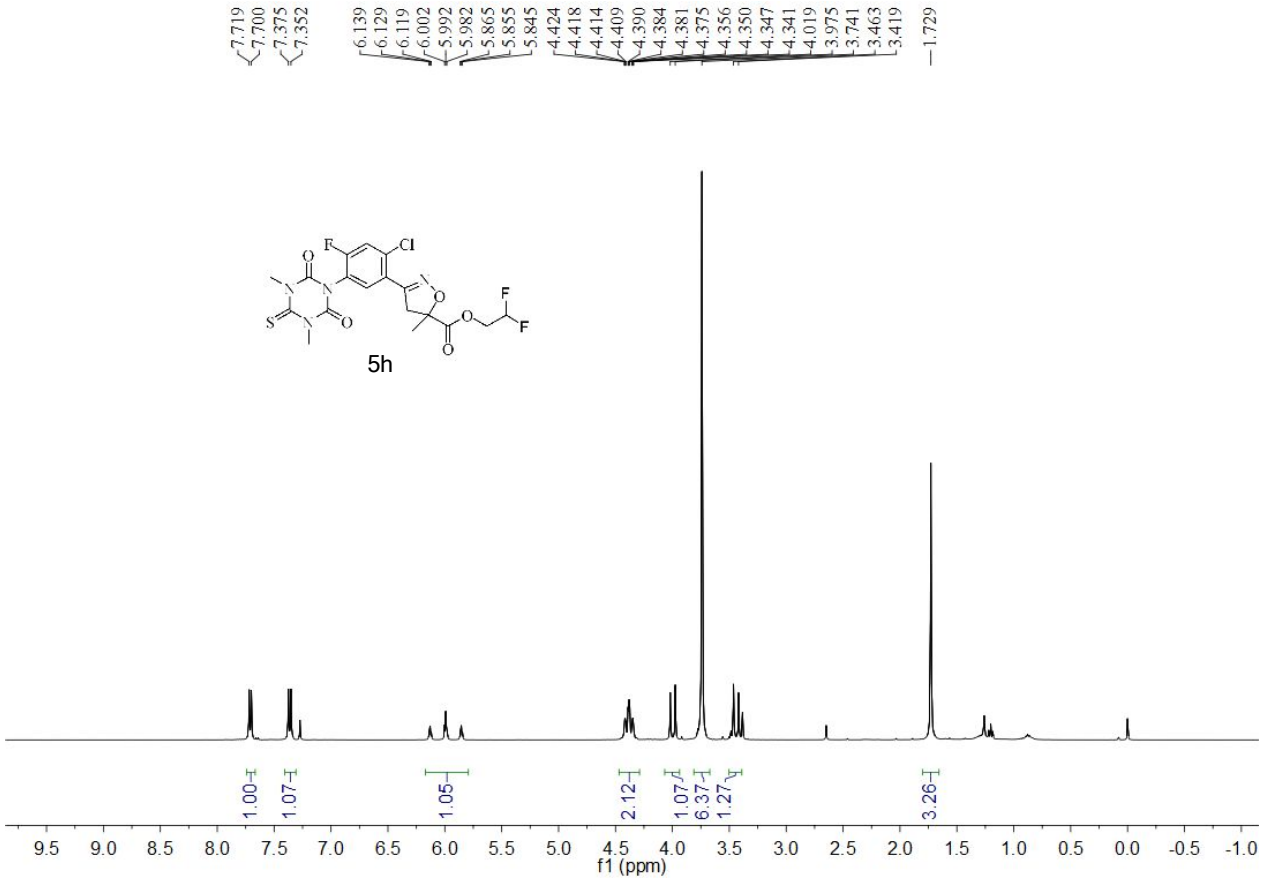
Cl
O
N
S
O
F
O
5g
f1 (ppm)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4.409
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4.375
4.356
4.350
4.347
4.341
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3.741
3.463
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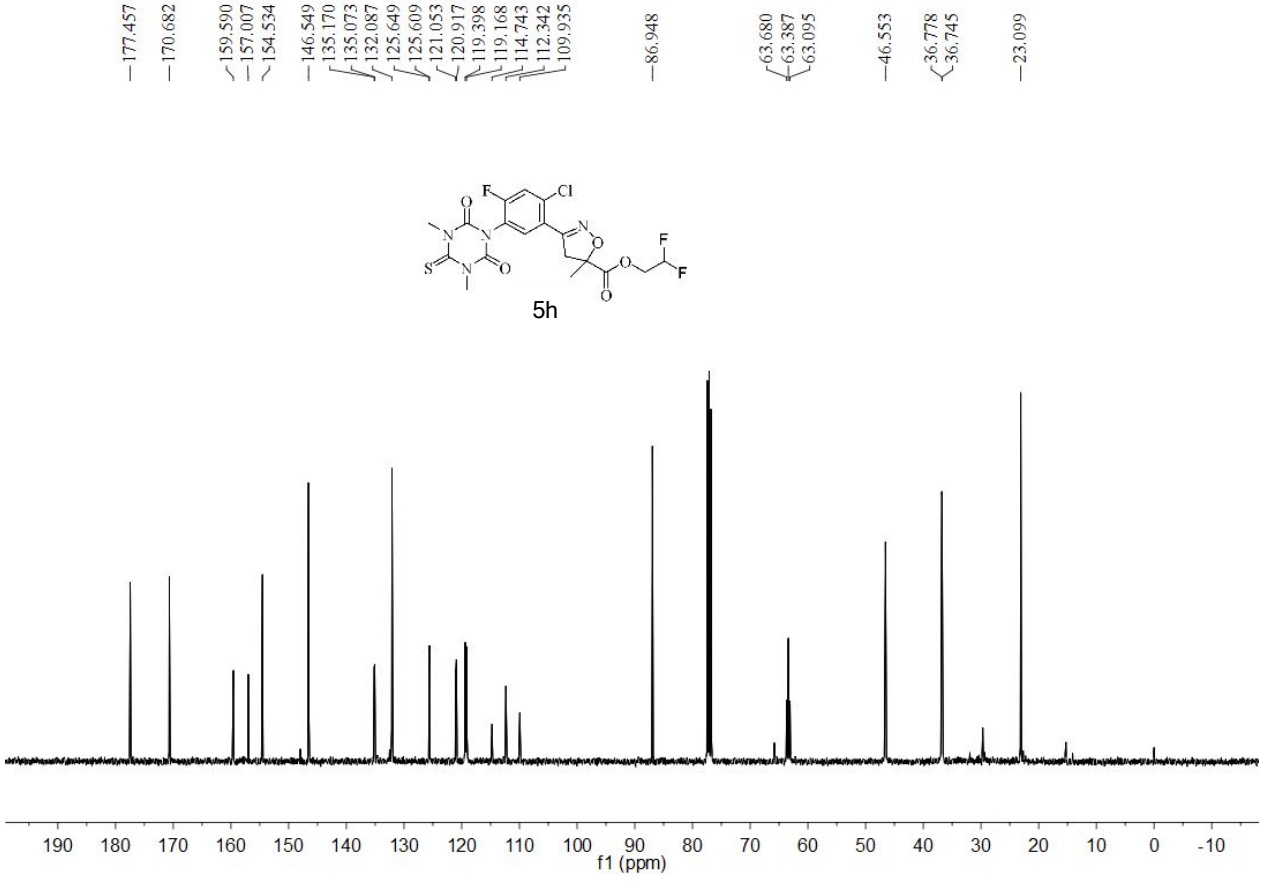
f1 (ppm)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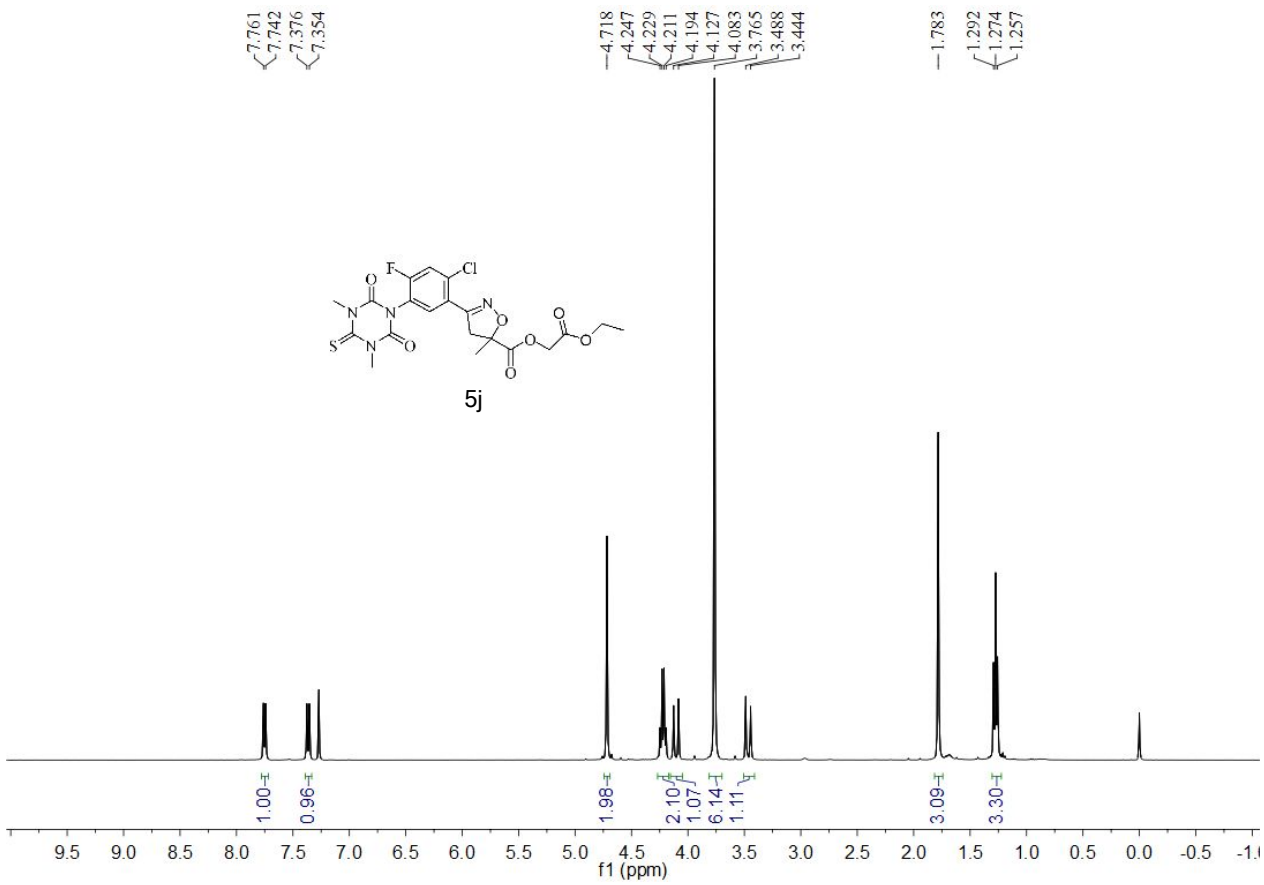
f1 (ppm)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3.444
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1.292
1.274
1.257
F
Cl
O
N
S
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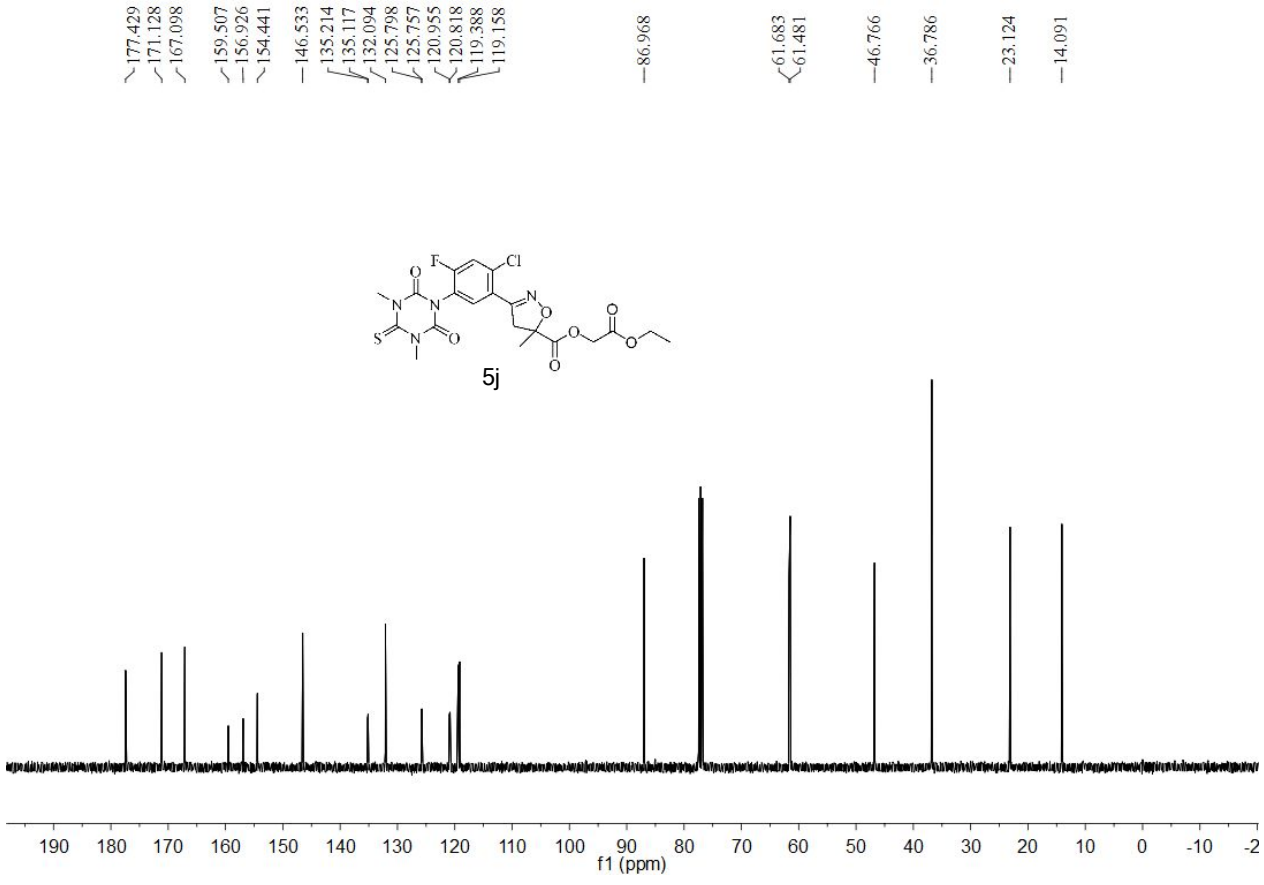
1.11
3.09
3.30
f1 (ppm)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Cl
O
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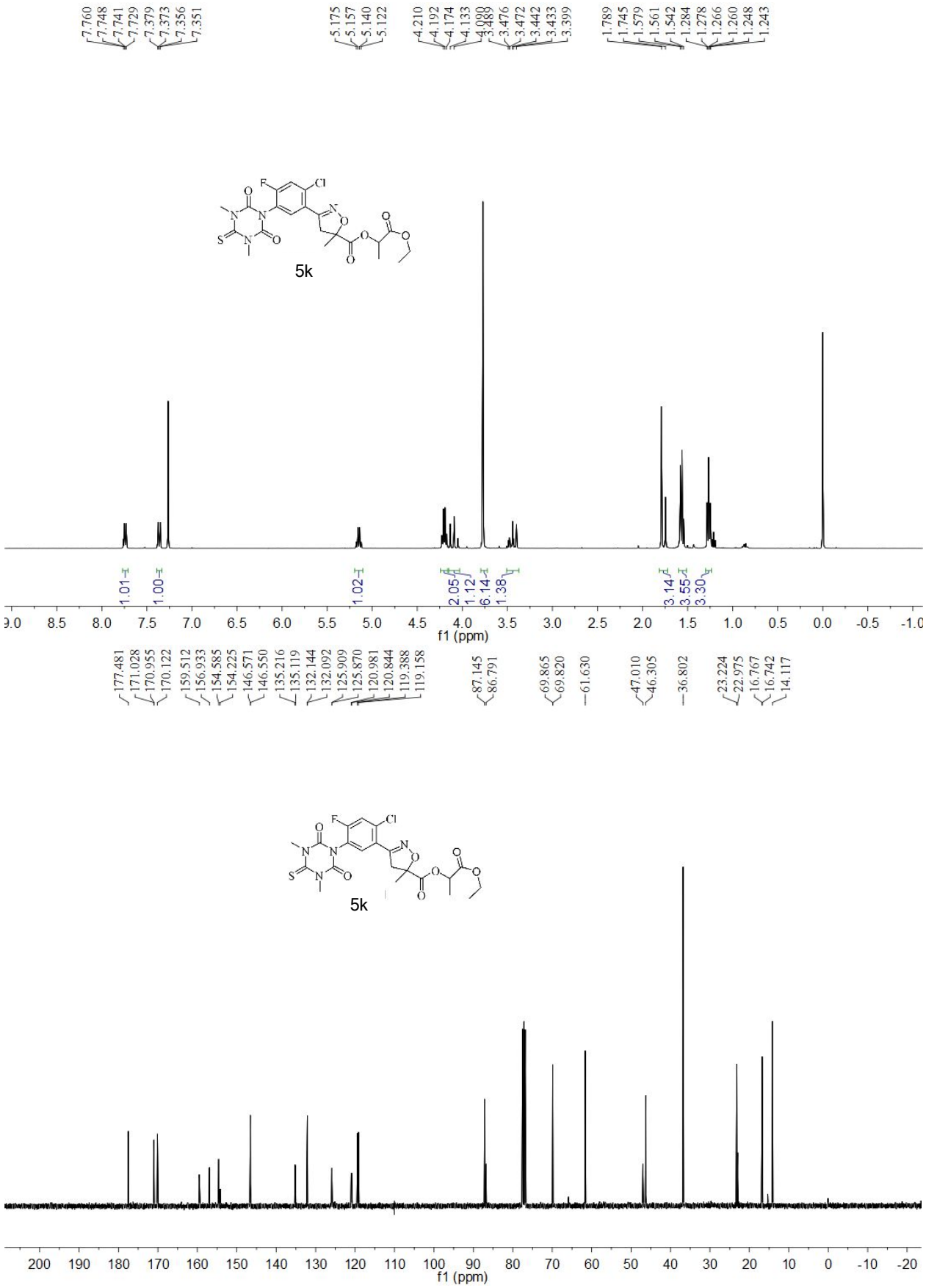
S
5j
f1 (ppm)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1.542
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F
Cl
N
O
S
O
O
O
O
O
5k
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1.00
1.02
2.05
1.12
6.14
1.38
3.14
3.55
3.30
f1 (ppm)
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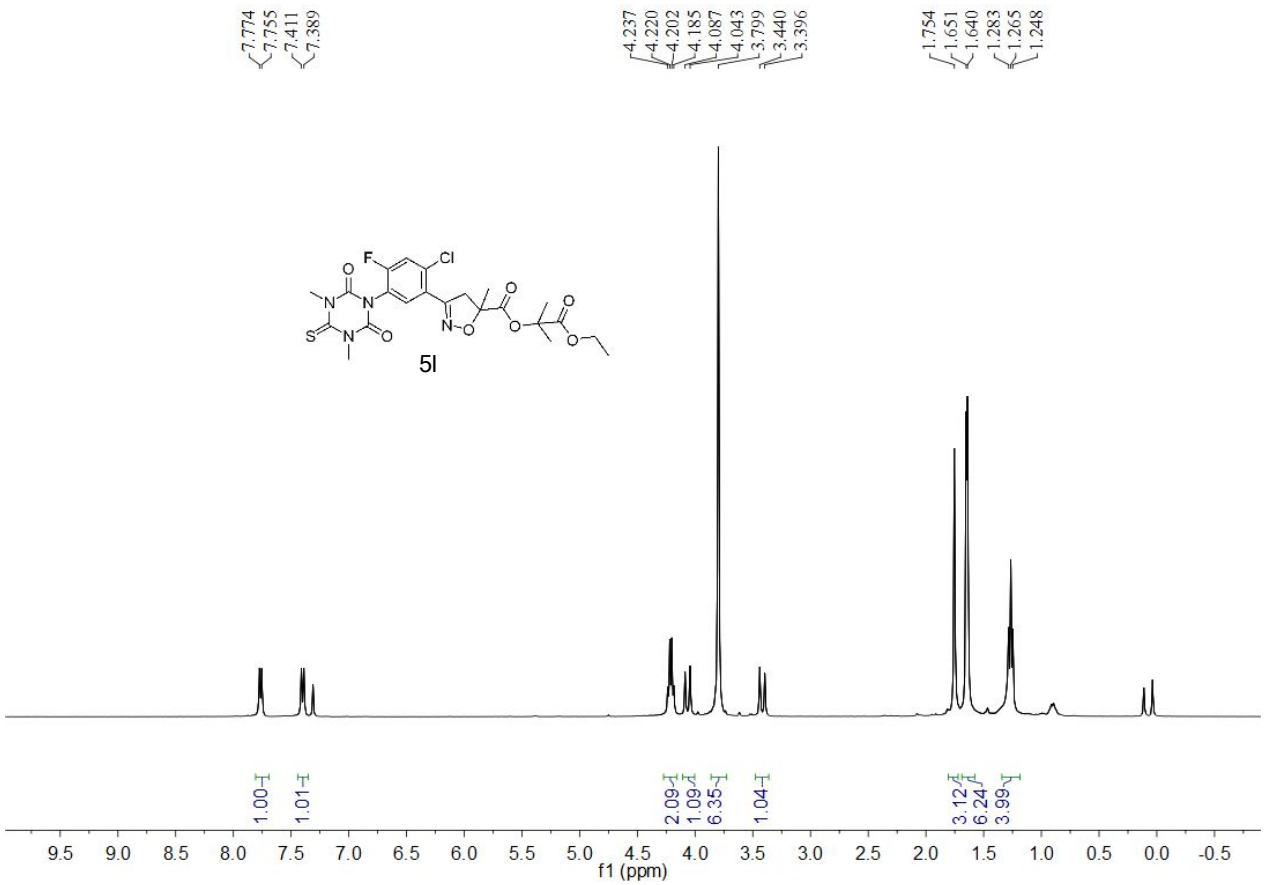
f1 (ppm)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3.396
1.754
1.651
1.640
1.283
1.265
1.248
F
Cl
O
N
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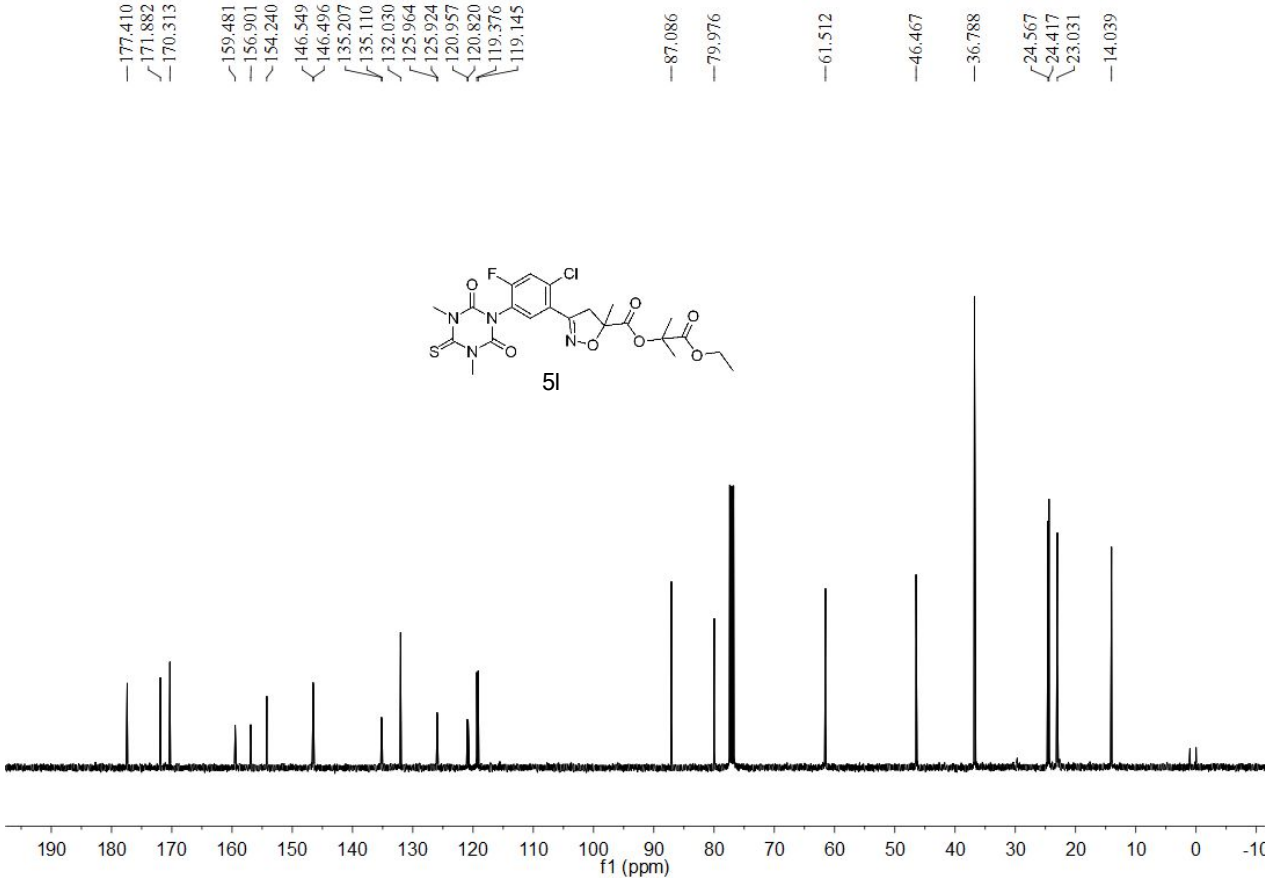
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125.924
120.957
120.820
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119.145
87.086
79.976
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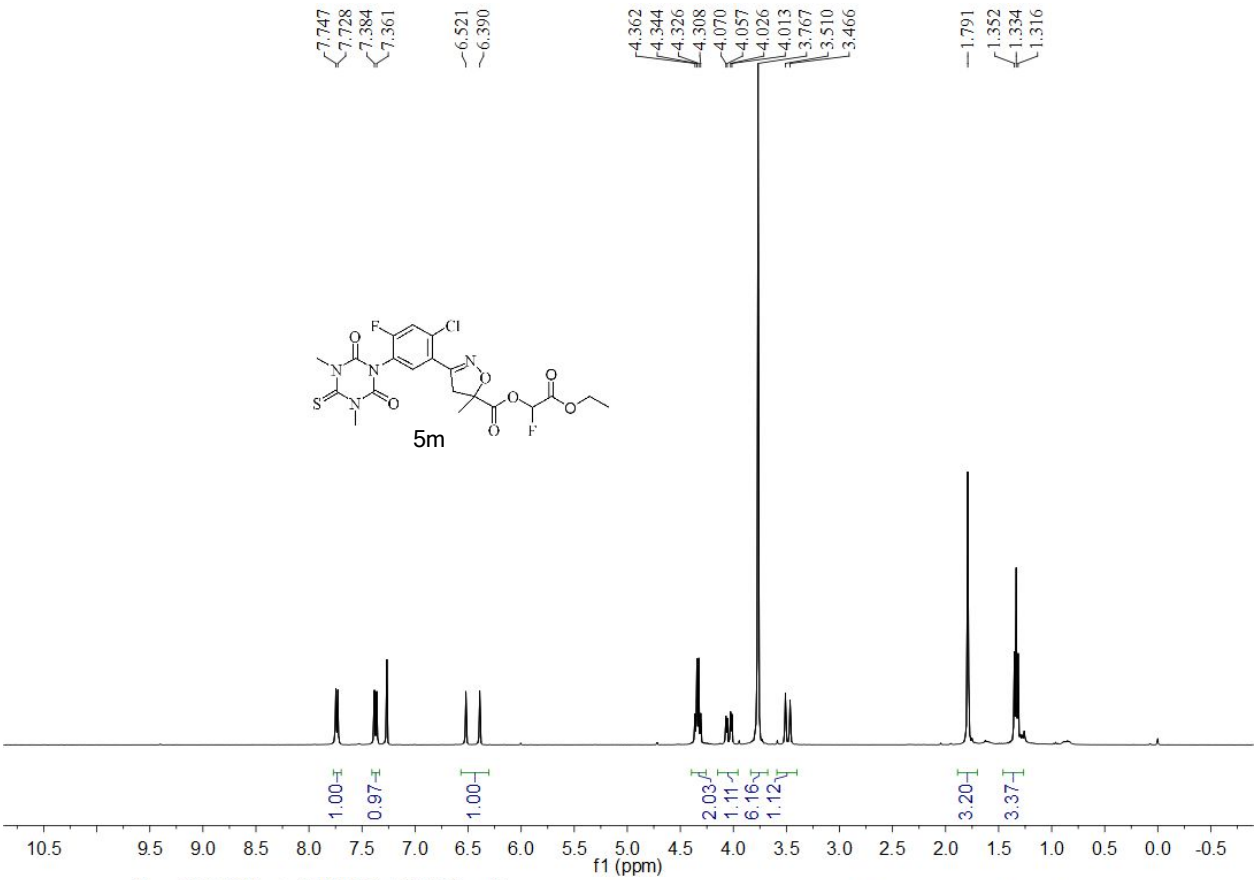
Cl
O
N
S
5l
f1 (ppm)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4.026
4.013
3.767
3.510
3.466
1.791
1.352
1.334
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1.12
3.20
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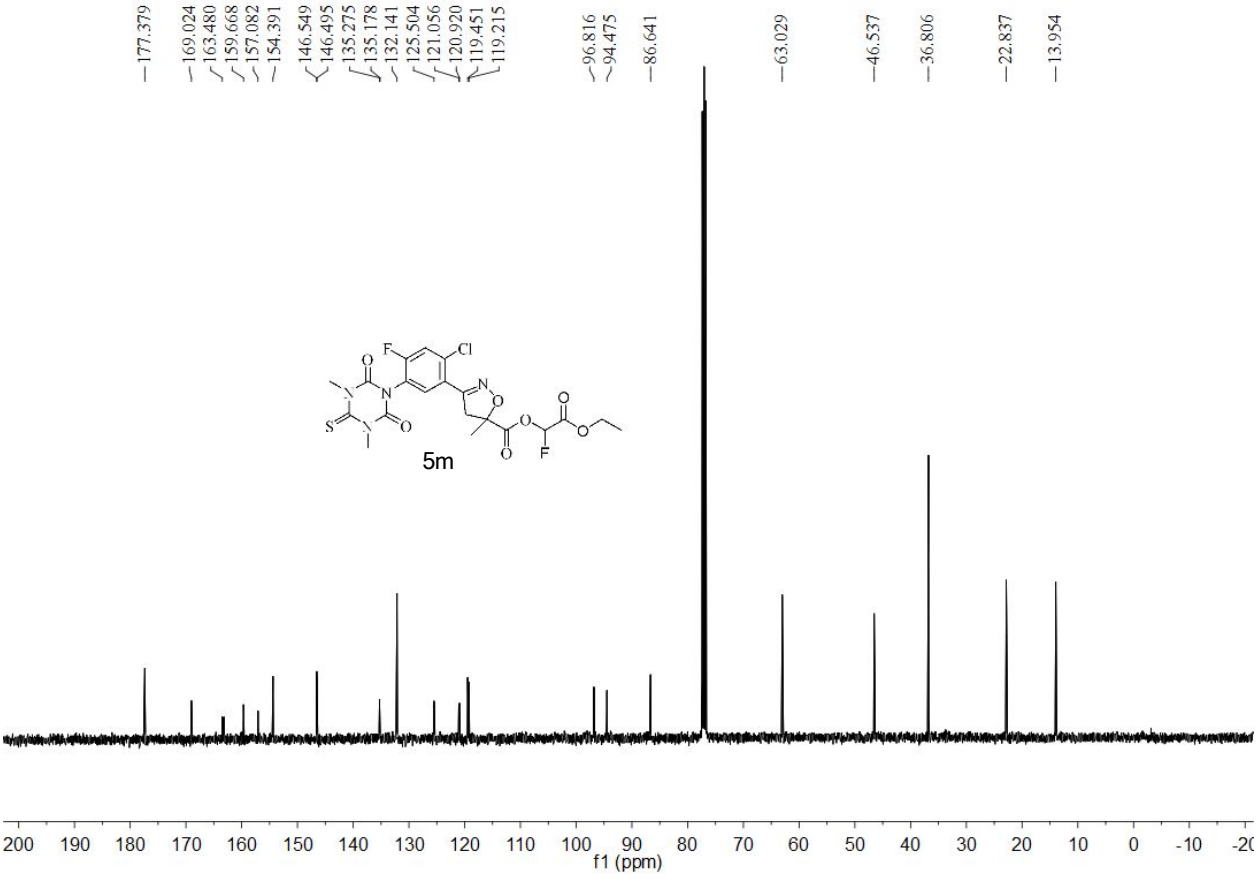
f1 (ppm)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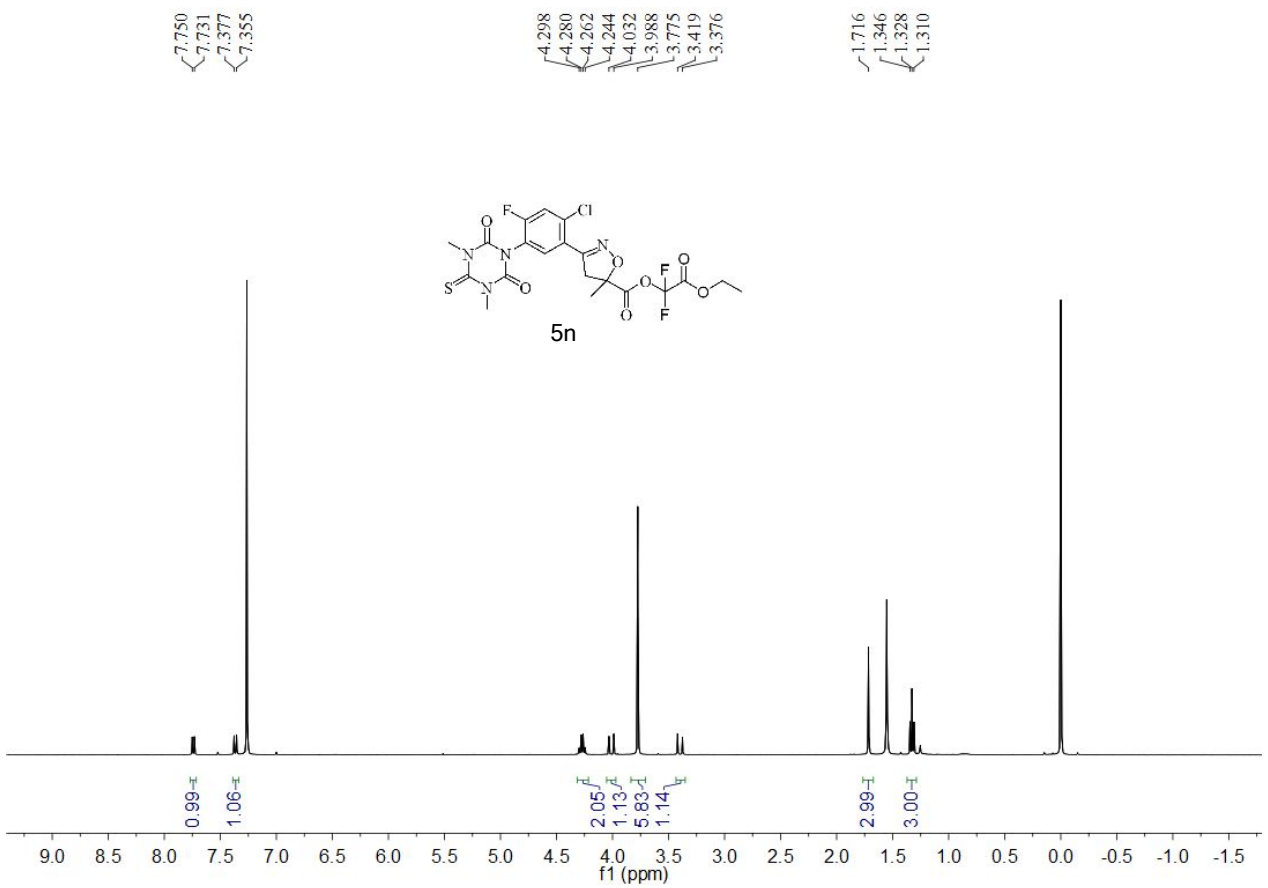
5m
f1 (ppm)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1.716
1.346
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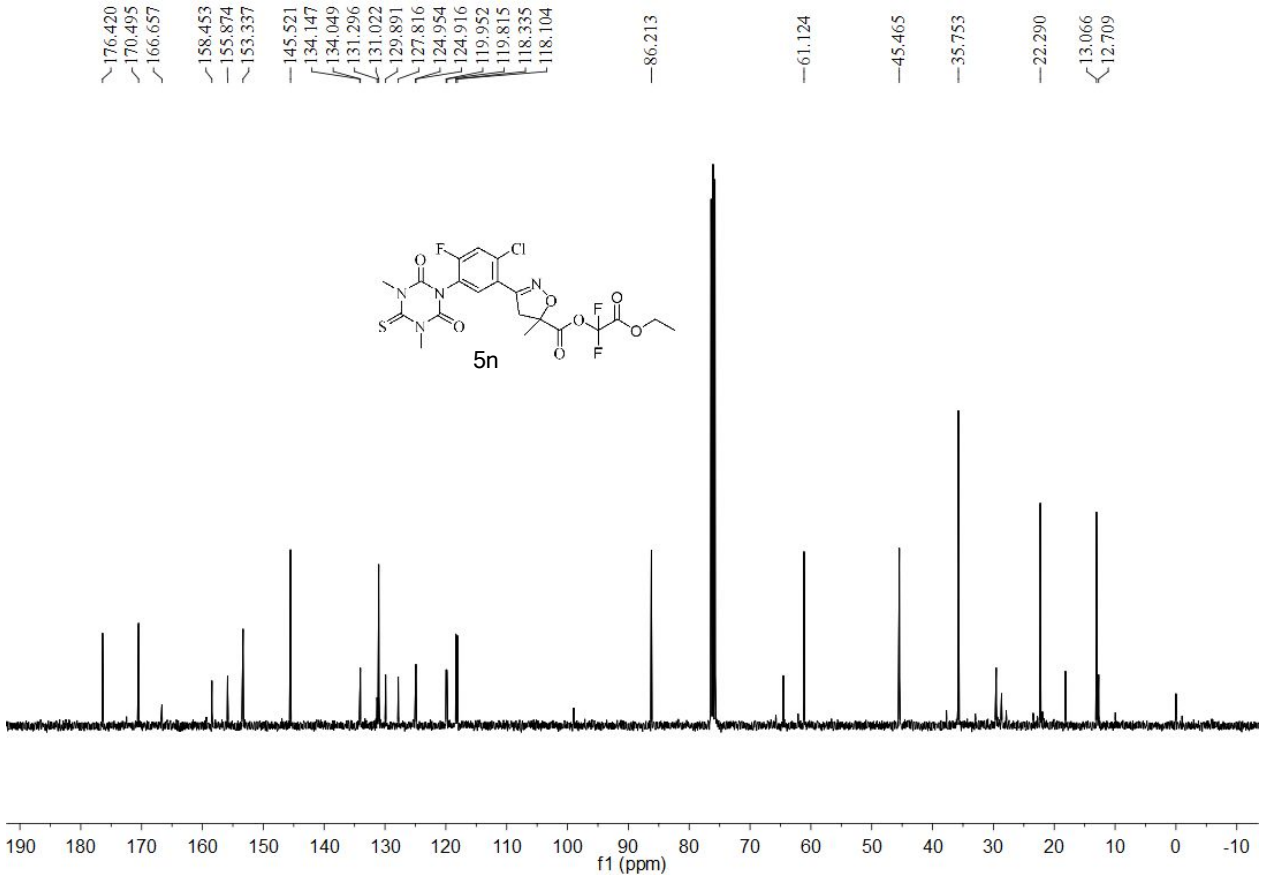
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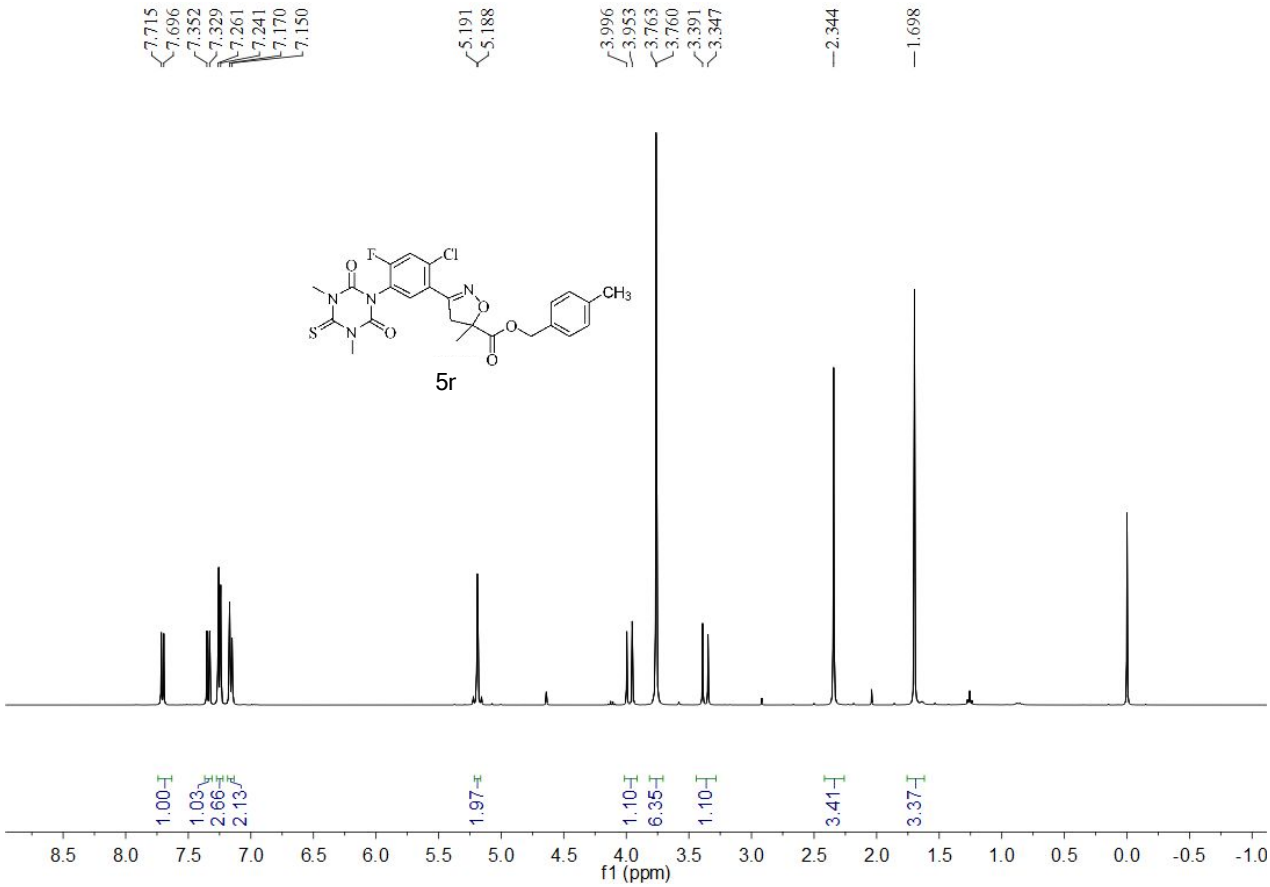
131.296
131.022
129.891
127.816
124.954
124.916
119.952
119.815
118.335
118.104
86.213
61.124
45.465
35.753
22.290
13.066
12.709
5n
f1 (ppm)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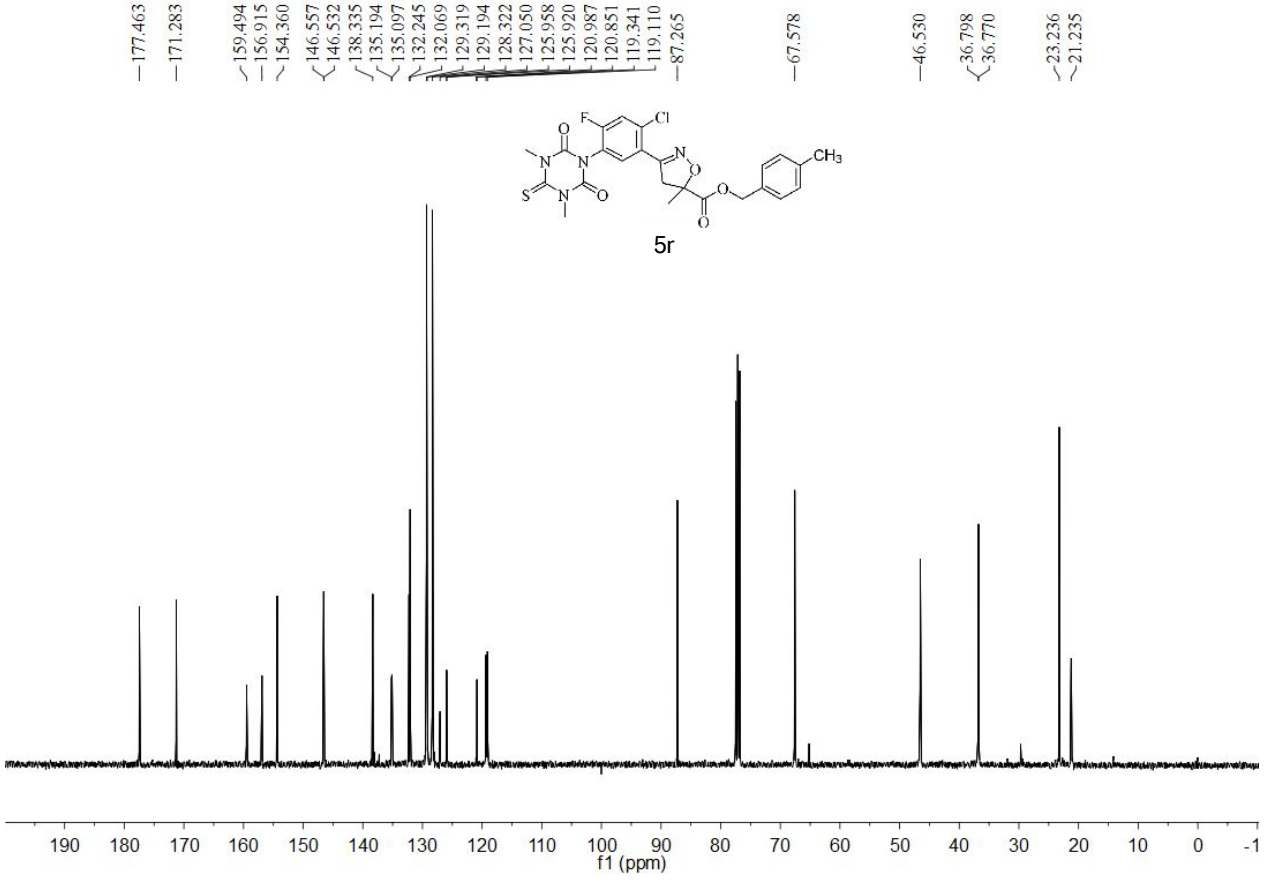
7.696
7.352
7.329
7.261
7.241
7.170
7.150
5.191
5.188
3.996
3.953
3.763
3.760
3.391
3.347
2.344
1.698
F
Cl
O
N
CH3
S
5r
1.00
1.03
2.66
2.13
1.97
1.10
6.35
1.10
3.41
3.37
f1 (ppm)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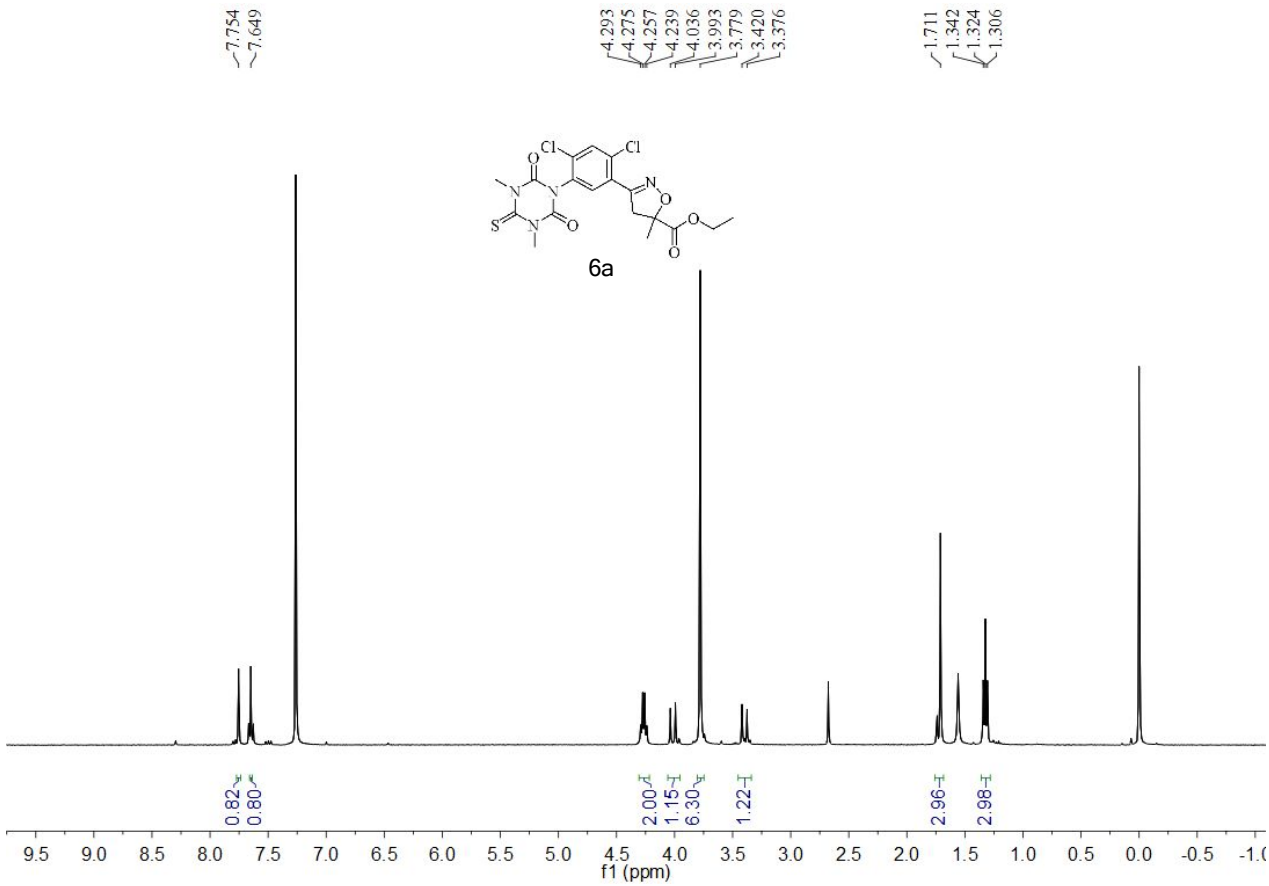
159.494
156.915
154.360
146.557
146.532
138.335
135.194
135.097
132.245
132.069
129.319
129.194
128.322
127.050
125.958
125.920
120.987
120.851
119.341
119.110
87.265
67.578
46.530
36.798
36.770
23.236
21.235
F
Cl
O
N
CH3
S
5r
f1 (ppm)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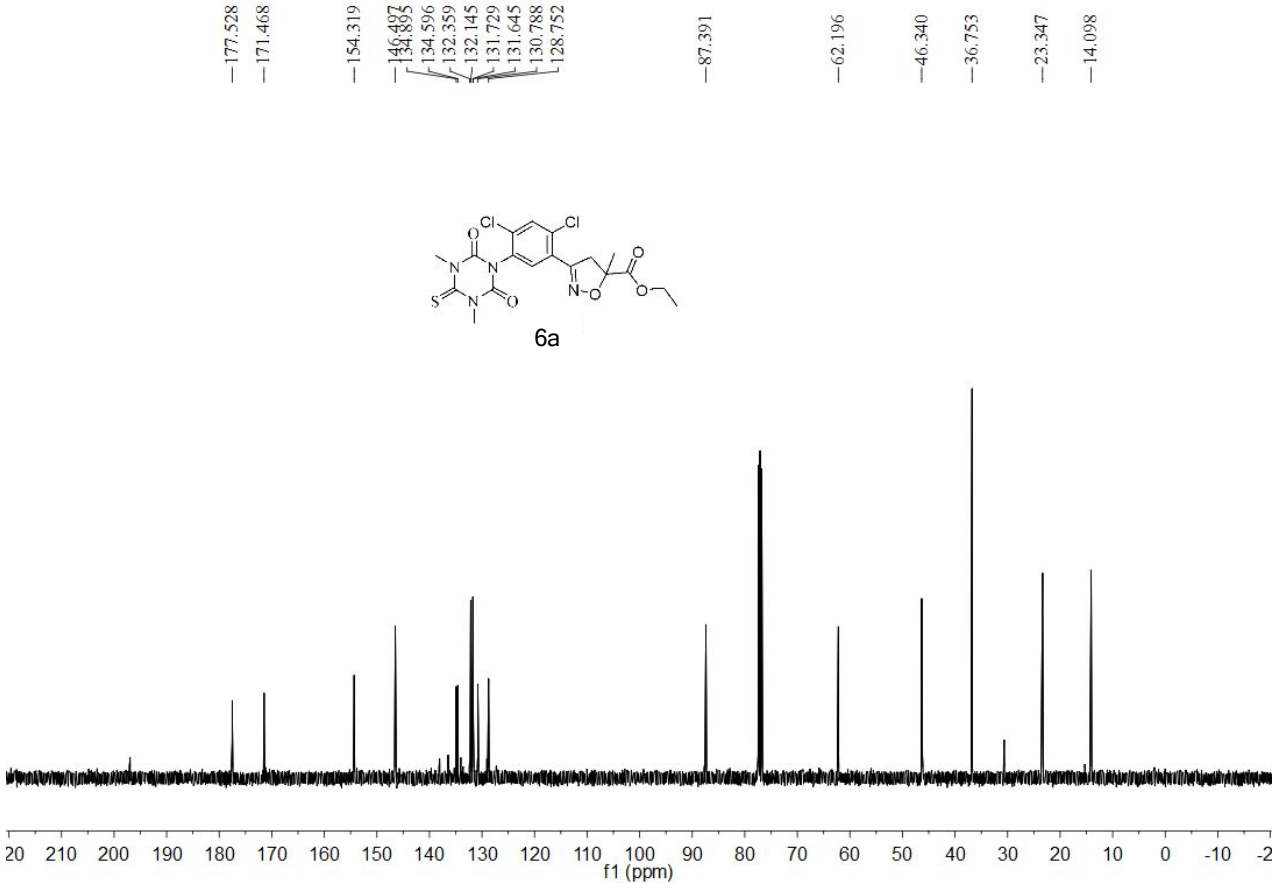
4.275
4.257
4.239
4.036
3.993
3.779
3.420
3.376
1.711
1.342
1.324
1.306
6a
0.82
0.80
2.00
1.15
6.30
1.22
2.96
2.98
f1 (ppm)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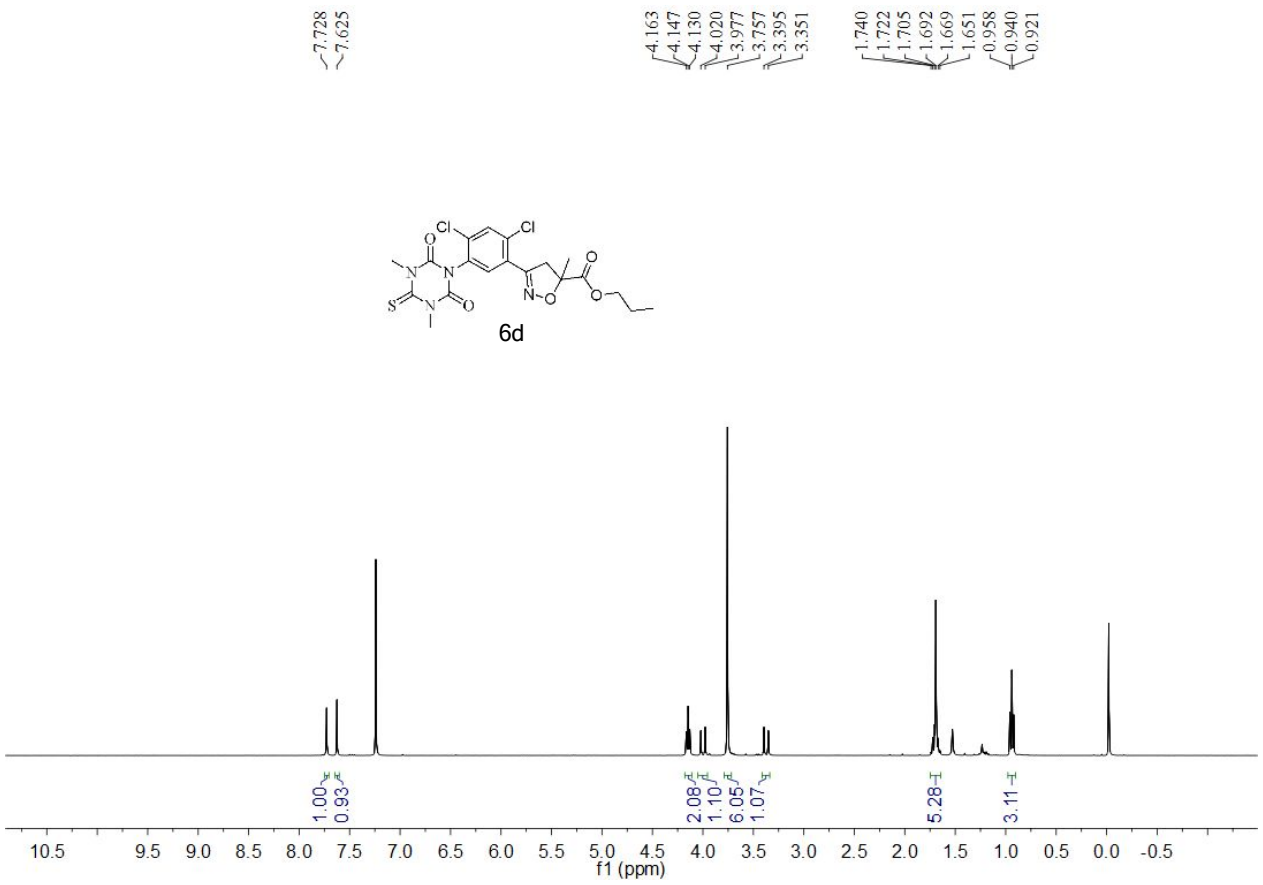
171.468
154.319
146.497
134.895
134.596
132.359
132.145
131.729
131.645
130.788
128.752
87.391
62.196
46.340
36.753
23.347
14.098
6a
f1 (ppm)


7.728
7.625
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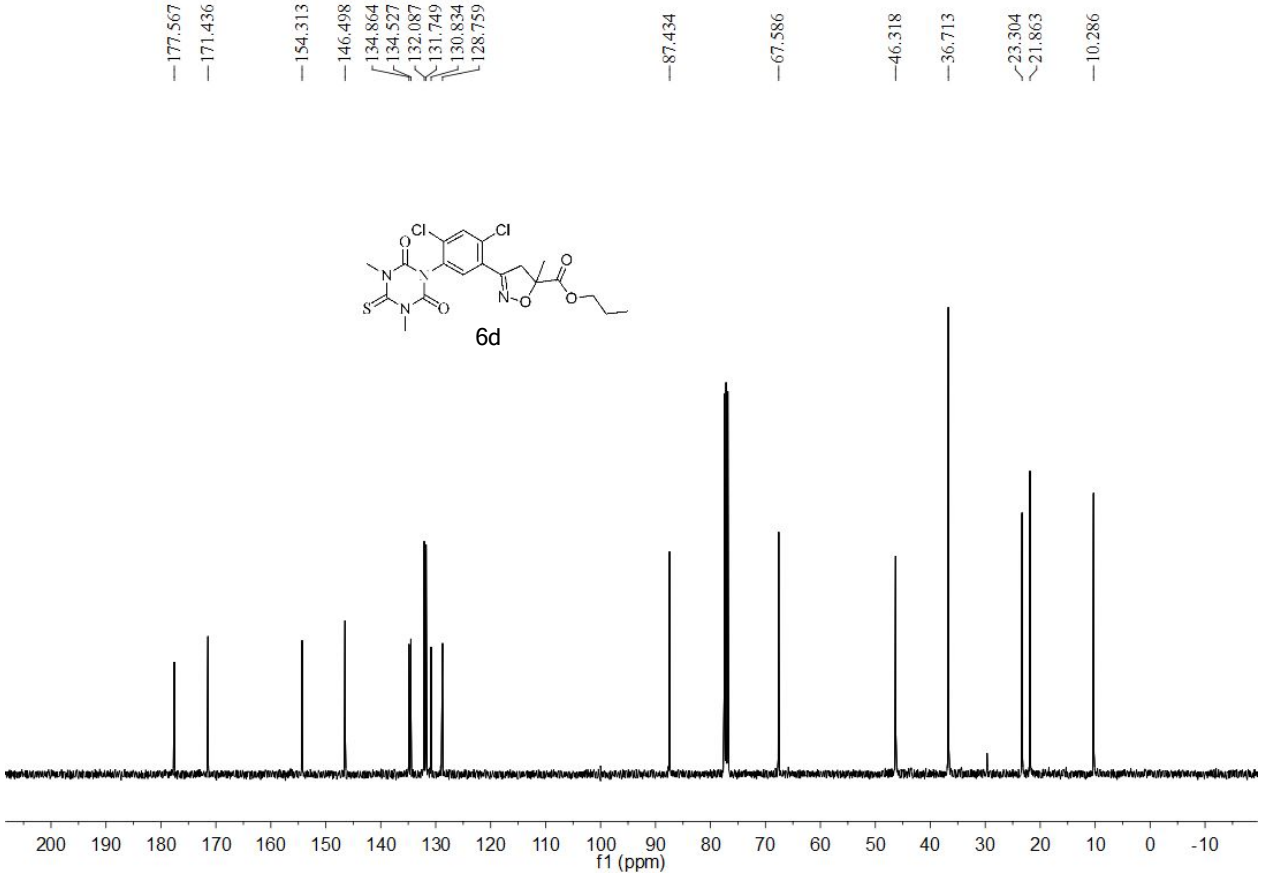
4.147
4.130
4.020
3.977
3.757
3.395
3.351
1.740
1.722
1.705
1.692
1.669
1.651
0.958
0.940
0.921
6d
1.00
0.93
2.08
1.10
6.05
1.07
5.28
3.11
f1 (ppm)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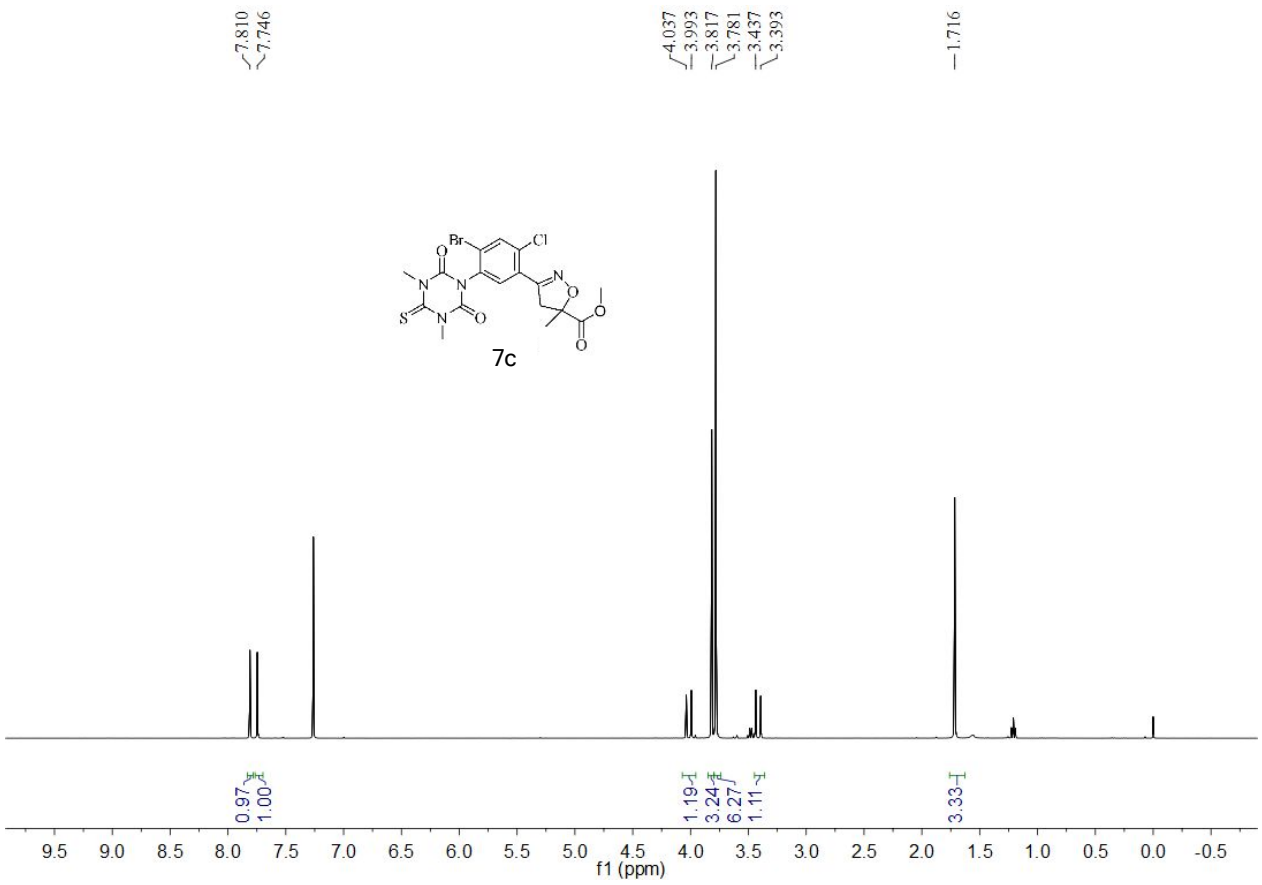
154.313
146.498
134.864
134.527
132.087
131.749
130.834
128.759
87.434
67.586
46.318
36.713
23.304
21.863
10.286
6d
f1 (ppm)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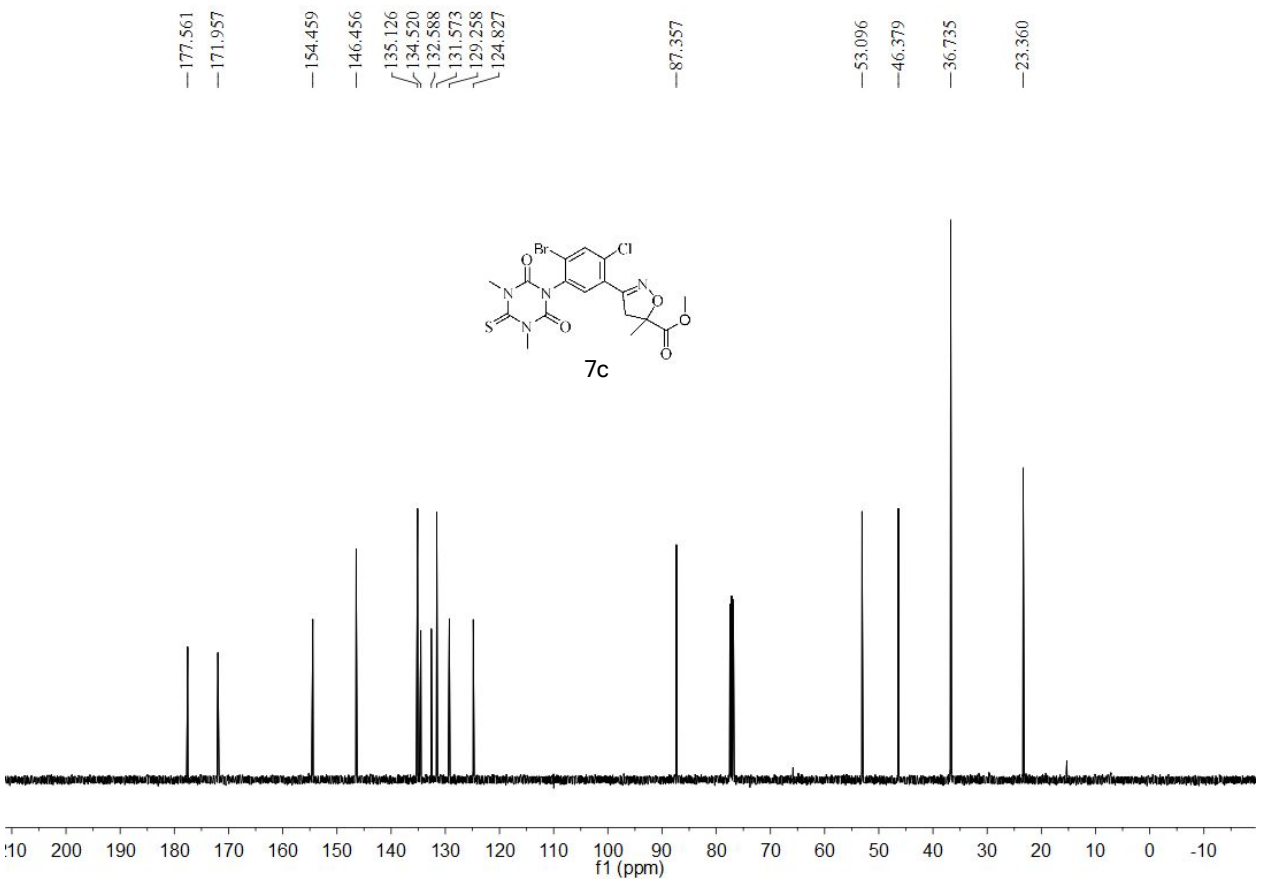
7.746
4.037
3.993
3.817
3.781
3.437
3.393
1.716
Br
Cl
O
N
S
O
O
O
7c
0.97
1.00
1.19
3.24
6.27
1.11
3.33
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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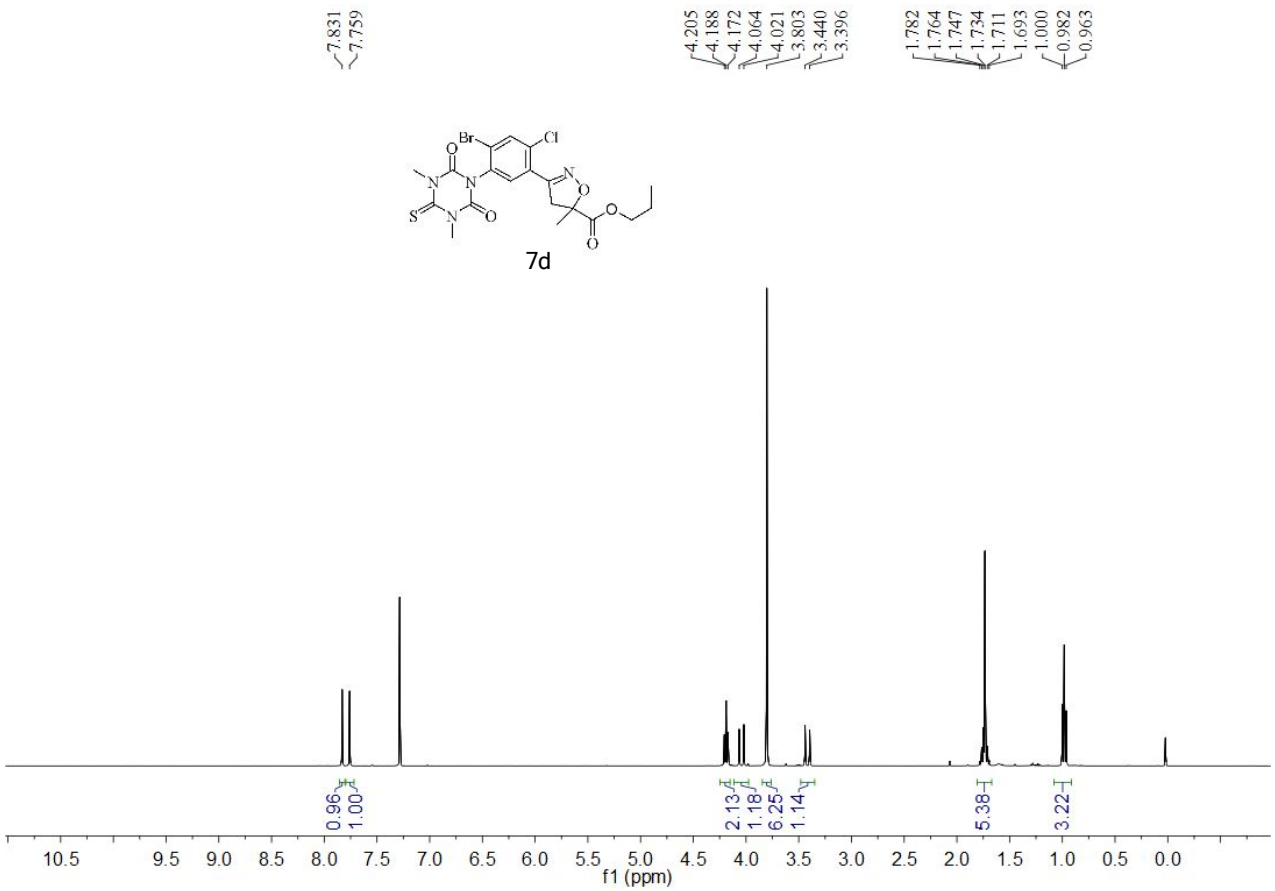
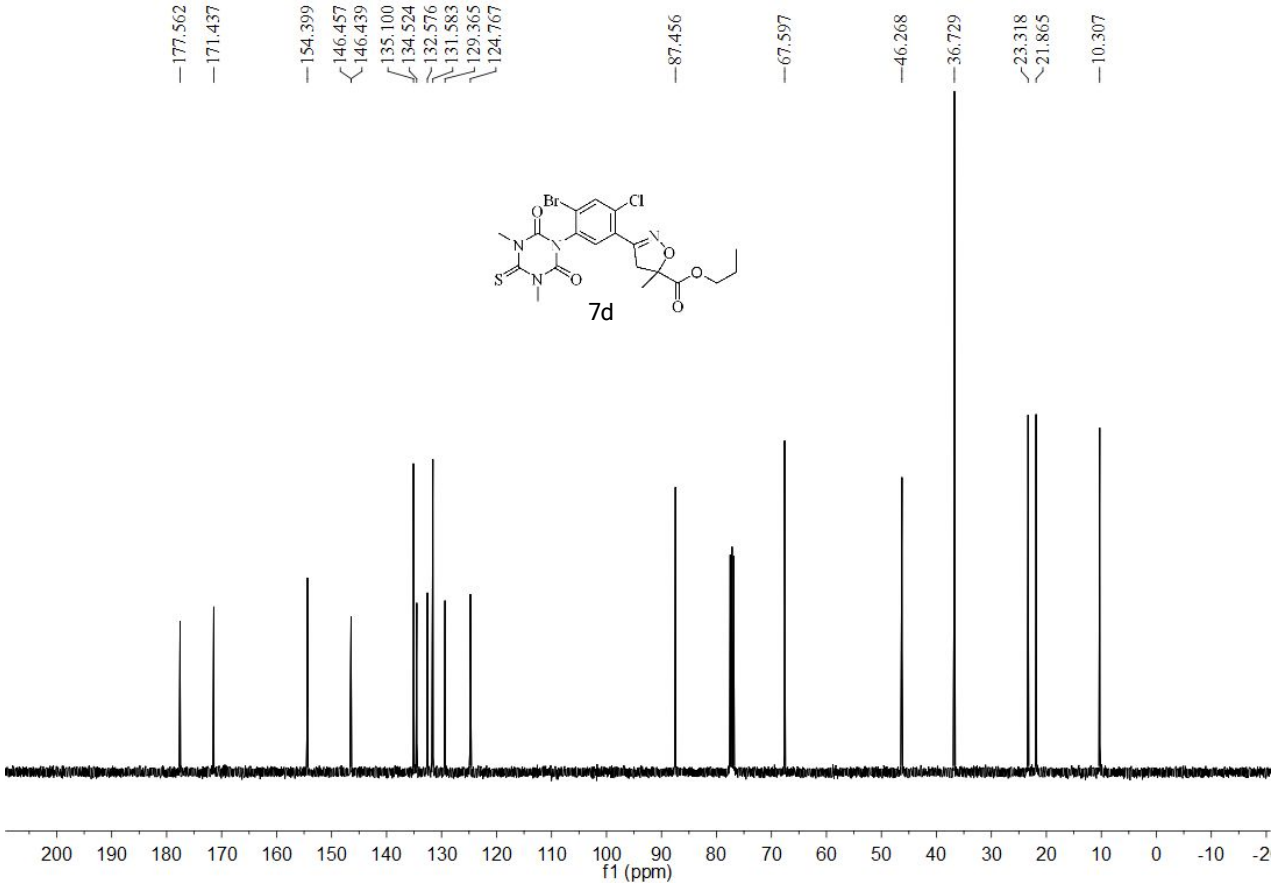
171.957
154.459
146.456
135.126
134.520
132.588
131.573
129.258
124.827
87.357
53.096
46.379
36.735
23.360
Br
Cl
O
N
S
O
O
O
7c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.831
7.759
4.205
4.188
4.172
4.064
4.021
3.803
3.440
3.396
1.782
1.764
1.747
1.734
1.711
1.693
1.000
0.982
0.963
Br
Cl
O
N
S
O
O
O
7d
0.96
1.00
2.13
1.18
6.25
1.14
5.38
3.22
10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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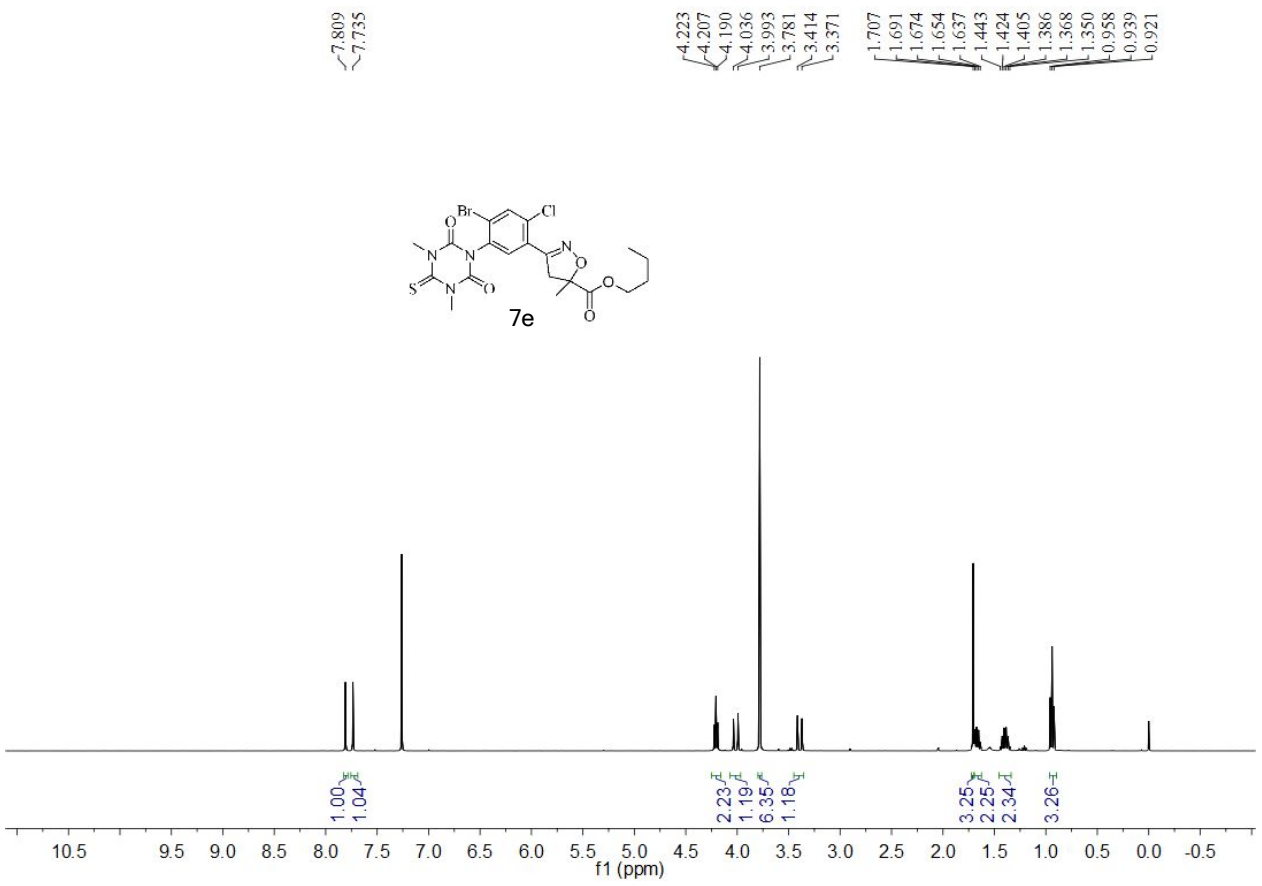
171.437
154.399
146.457
146.439
135.100
134.524
132.576
131.583
129.365
124.767
87.456
67.597
46.268
36.729
23.318
21.865
10.307
Br
Cl
O
N
S
O
O
O
7d
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2
f1 (ppm)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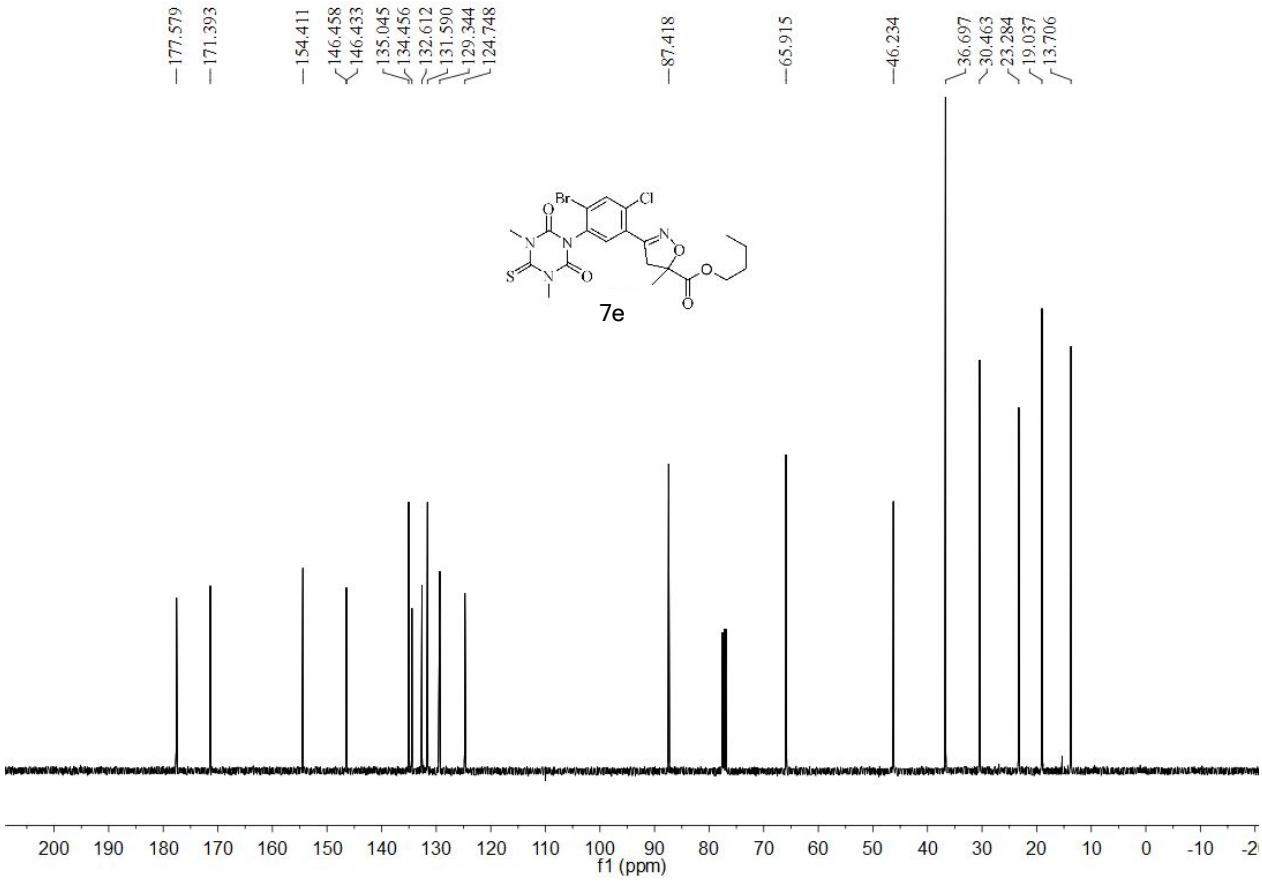
7.735
4.223
4.207
4.190
4.036
3.993
3.781
3.414
3.371
1.707
1.691
1.674
1.654
1.637
1.443
1.424
1.405
1.386
1.368
1.350
0.958
0.939
0.921
Br
Cl
O
N
S
7e
1.00
1.04
2.23
1.19
6.35
1.18
3.25
2.25
2.34
3.26
f1 (ppm)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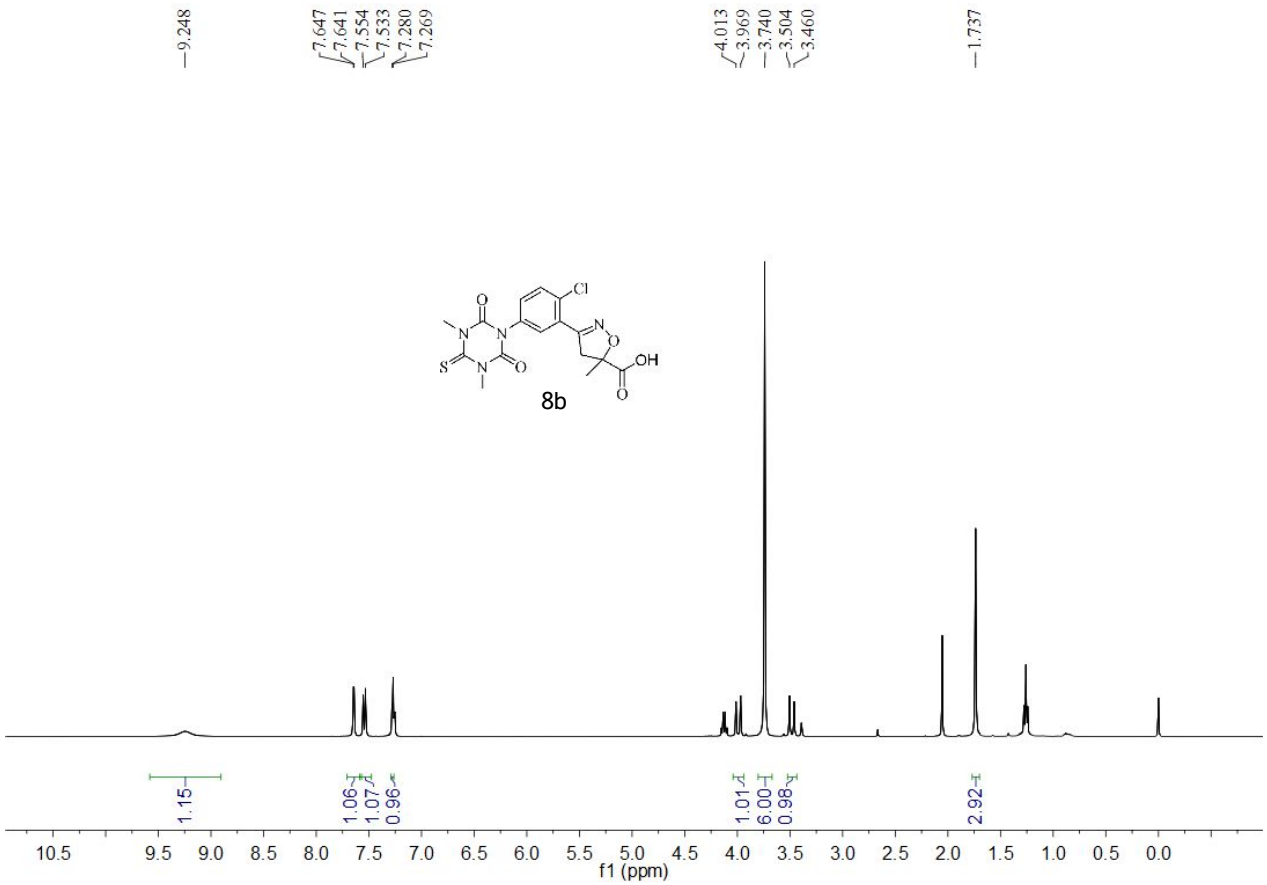
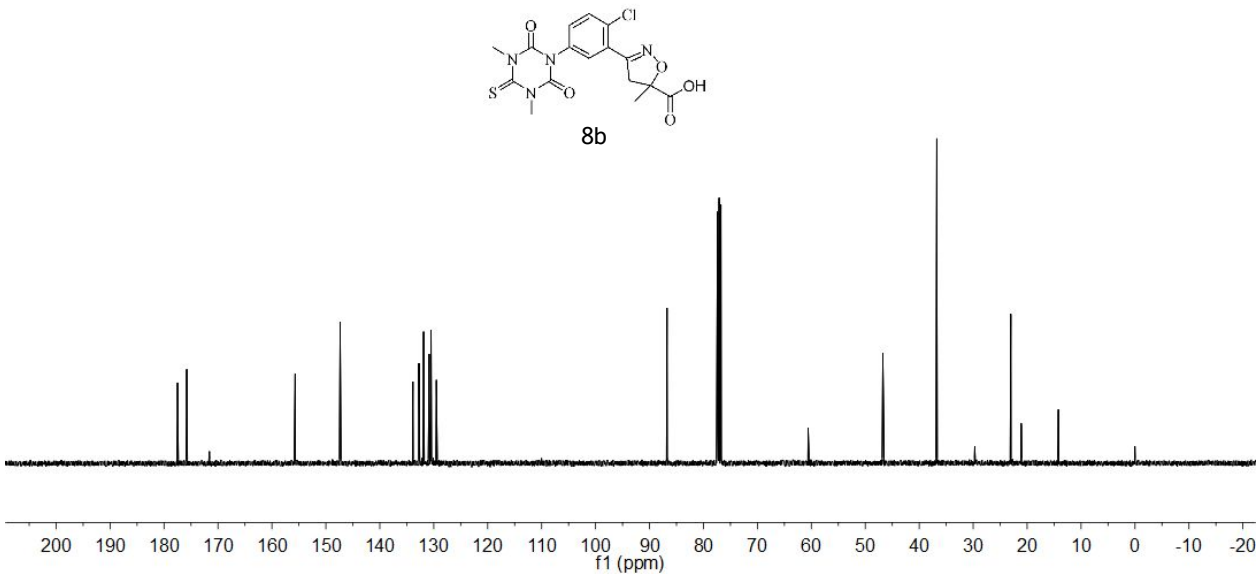
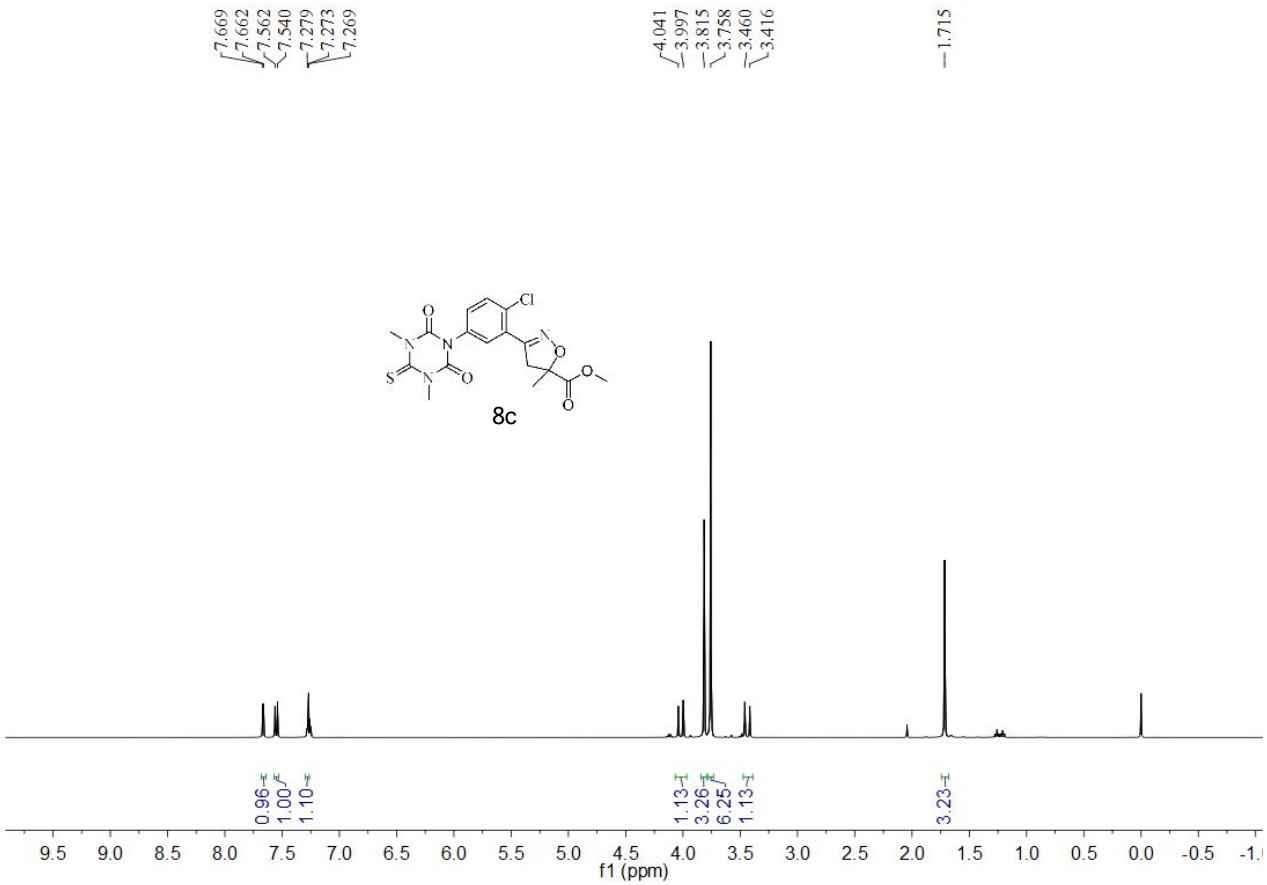
146.433
135.045
134.456
132.612
131.590
129.344
124.748
87.418
65.915
46.234
36.697
30.463
23.284
19.037
13.706
Br
Cl
O
N
S
7e
f1 (ppm)


9.248
7.647
7.641
7.554
7.533
7.280
7.269
4.013
3.969
3.740
3.504
3.460
1.737
1.15
1.06
1.07
0.96
1.01
6.00
0.98
2.92
f1 (ppm)

8b


177.476
175.774
155.696
147.355
133.869
132.751
131.862
130.862
130.490
129.496
86.764
46.744
36.748
23.032
f1 (ppm)

8b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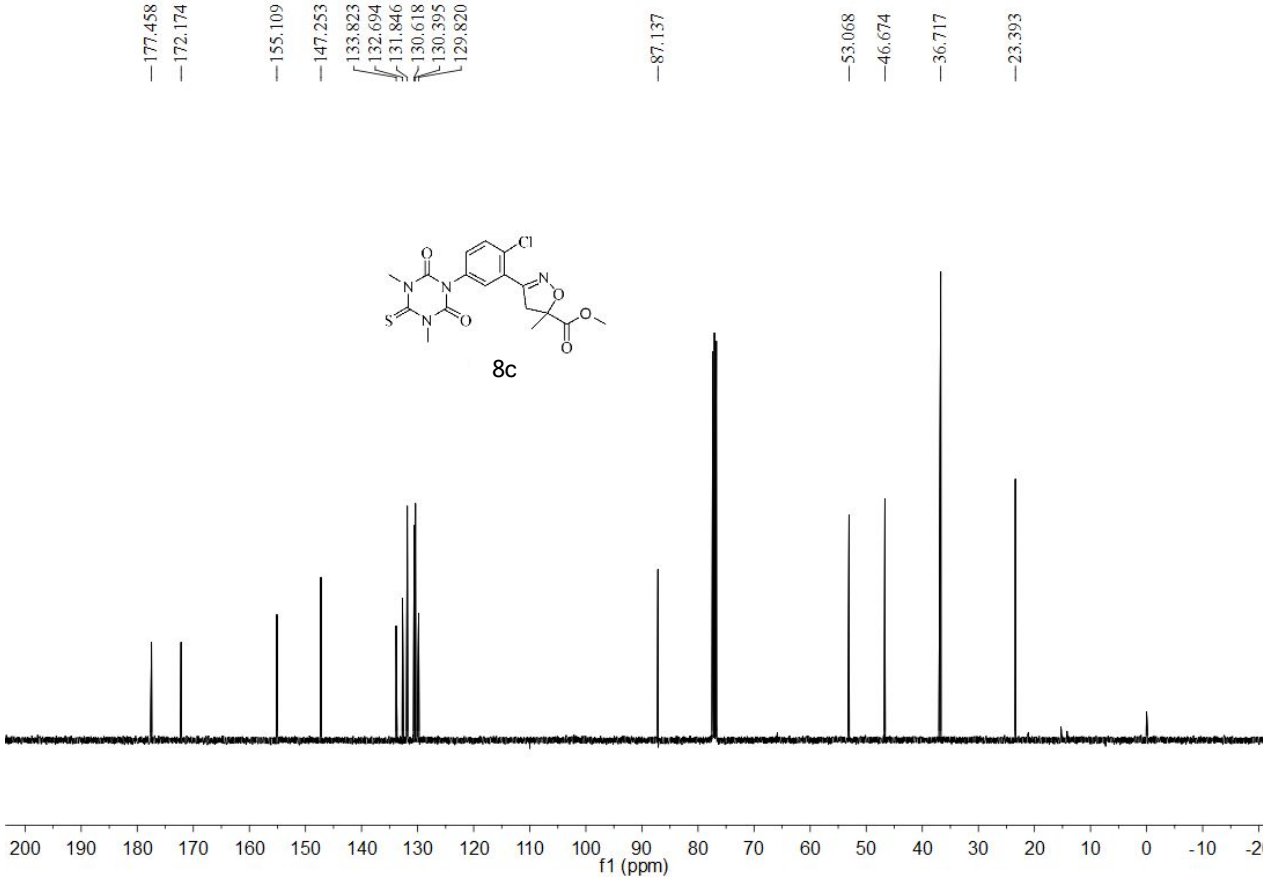
7.662
7.562
7.540
7.279
7.273
7.269
4.041
3.997
3.815
3.758
3.460
3.416
1.715
Cl
O
N
S
O
O
8c
0.96
1.00
1.10
1.13
3.26
6.25
1.13
3.23
f1 (ppm)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172.174
155.109
147.253
133.823
132.694
131.846
130.618
130.395
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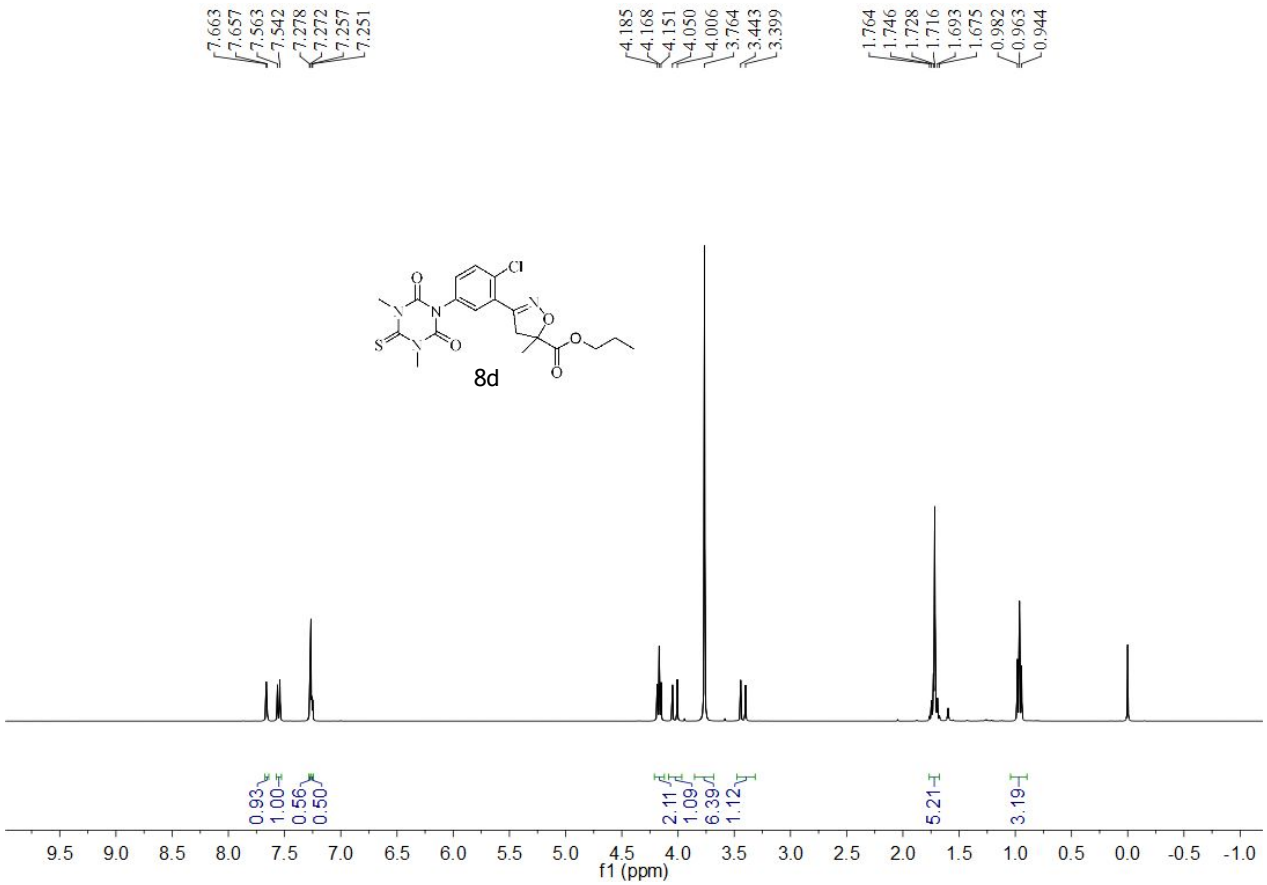
87.137
53.068
46.674
36.717
23.393
Cl
O
N
S
O
O
8c
f1 (ppm)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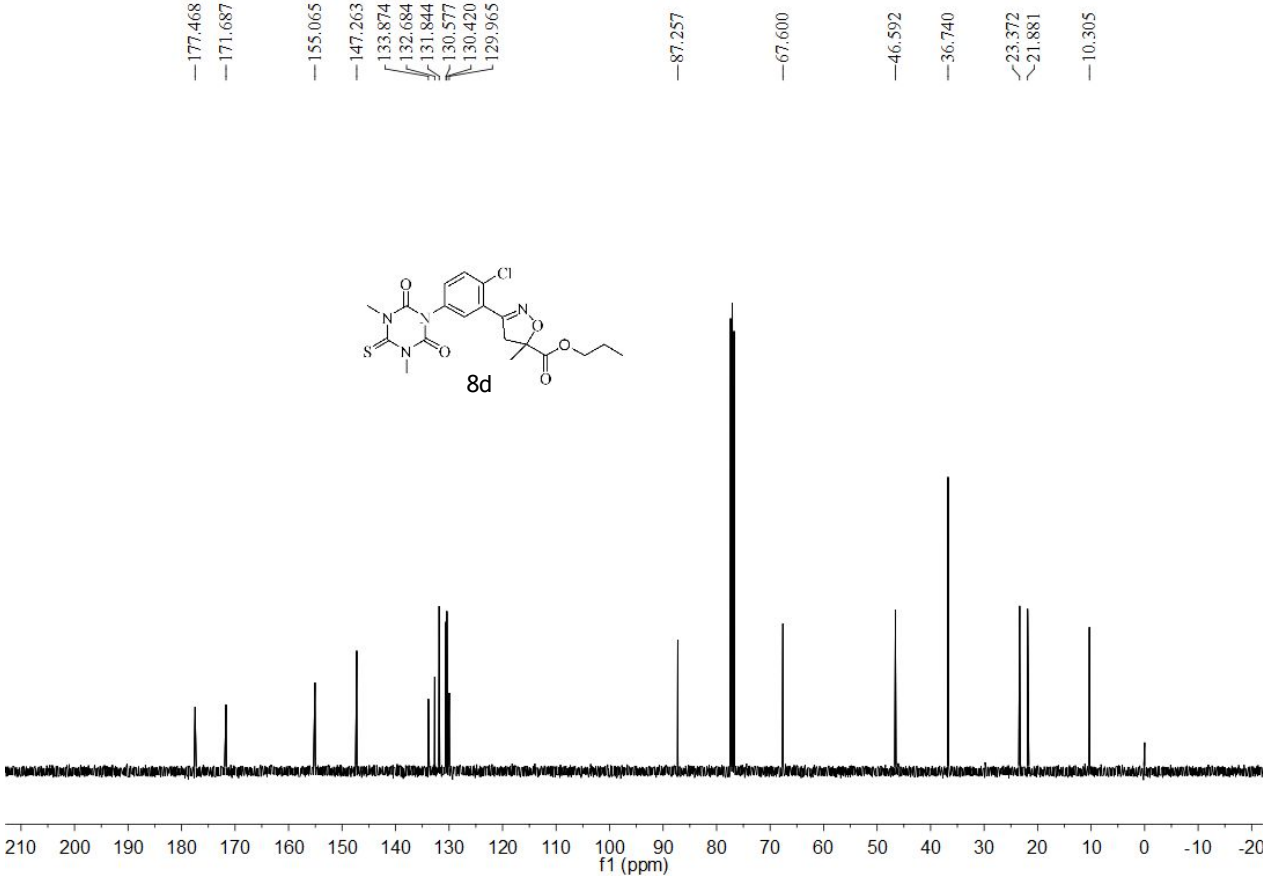
7.278
7.272
7.257
7.251
4.185
4.168
4.151
4.050
4.006
3.764
3.443
3.399
1.764
1.746
1.728
1.716
1.693
1.675
0.982
0.963
0.944
8d
0.93
1.00
0.56
0.50
2.11
1.09
6.39
1.12
5.21
3.19
f1 (ppm)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131.844
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130.420
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87.257
67.600
46.592
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23.372
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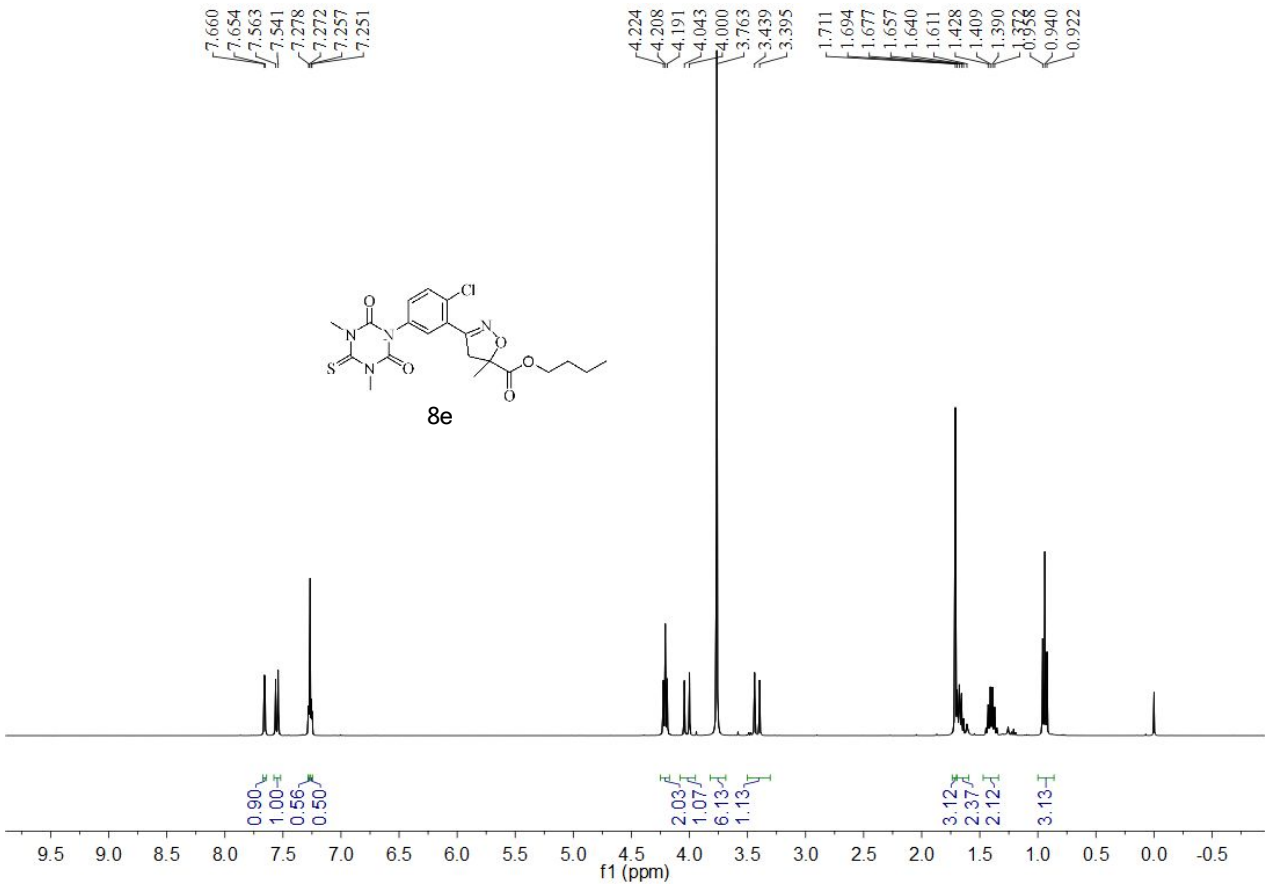
10.305
8d
f1 (ppm)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7.278
7.272
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7.251
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3.395
1.711
1.694
1.677
1.657
1.640
1.611
1.428
1.409
1.390
0.958
0.940
0.922
8e
0.90
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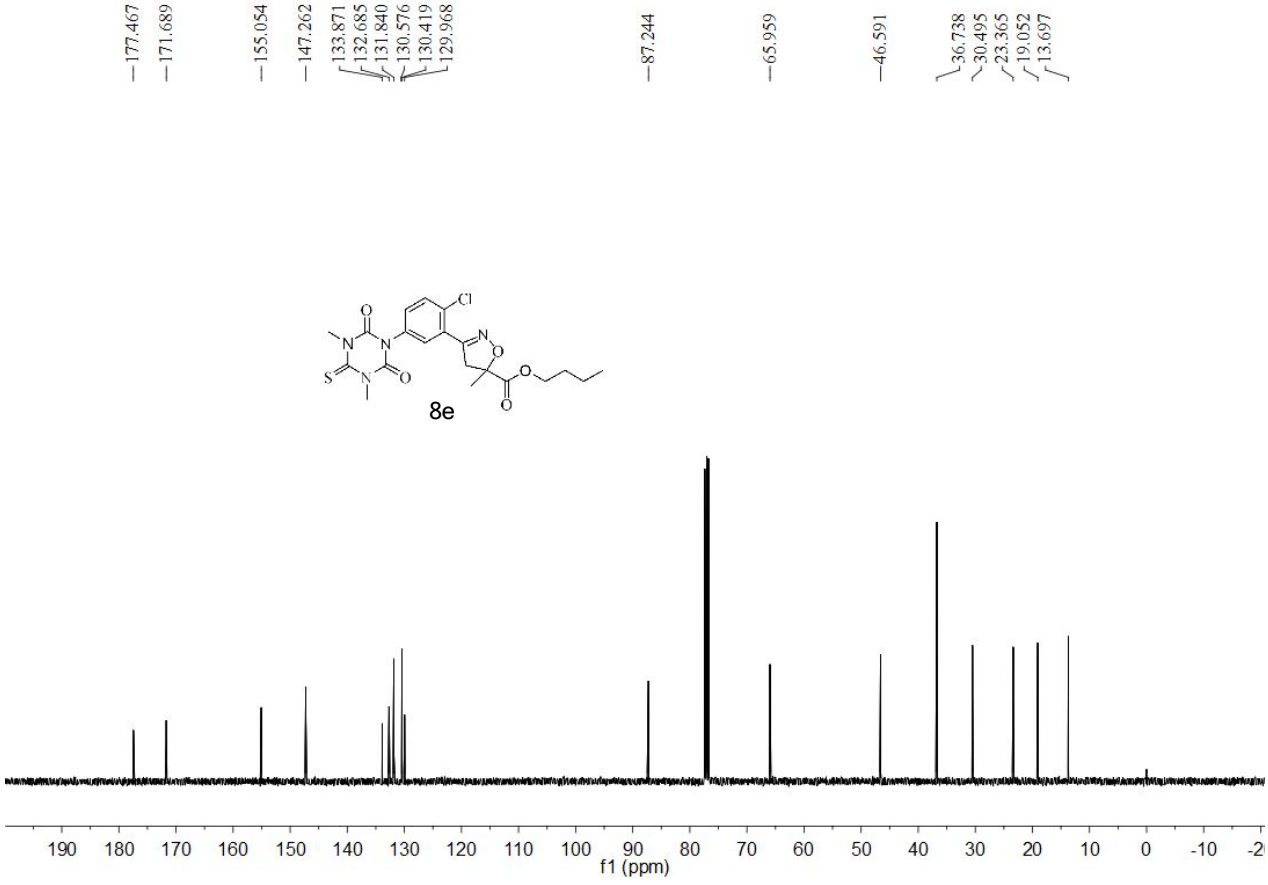
0.56
0.50
2.03
1.07
6.13
1.13
3.12
2.37
2.12
3.13
f1 (ppm)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36.738
30.495
23.365
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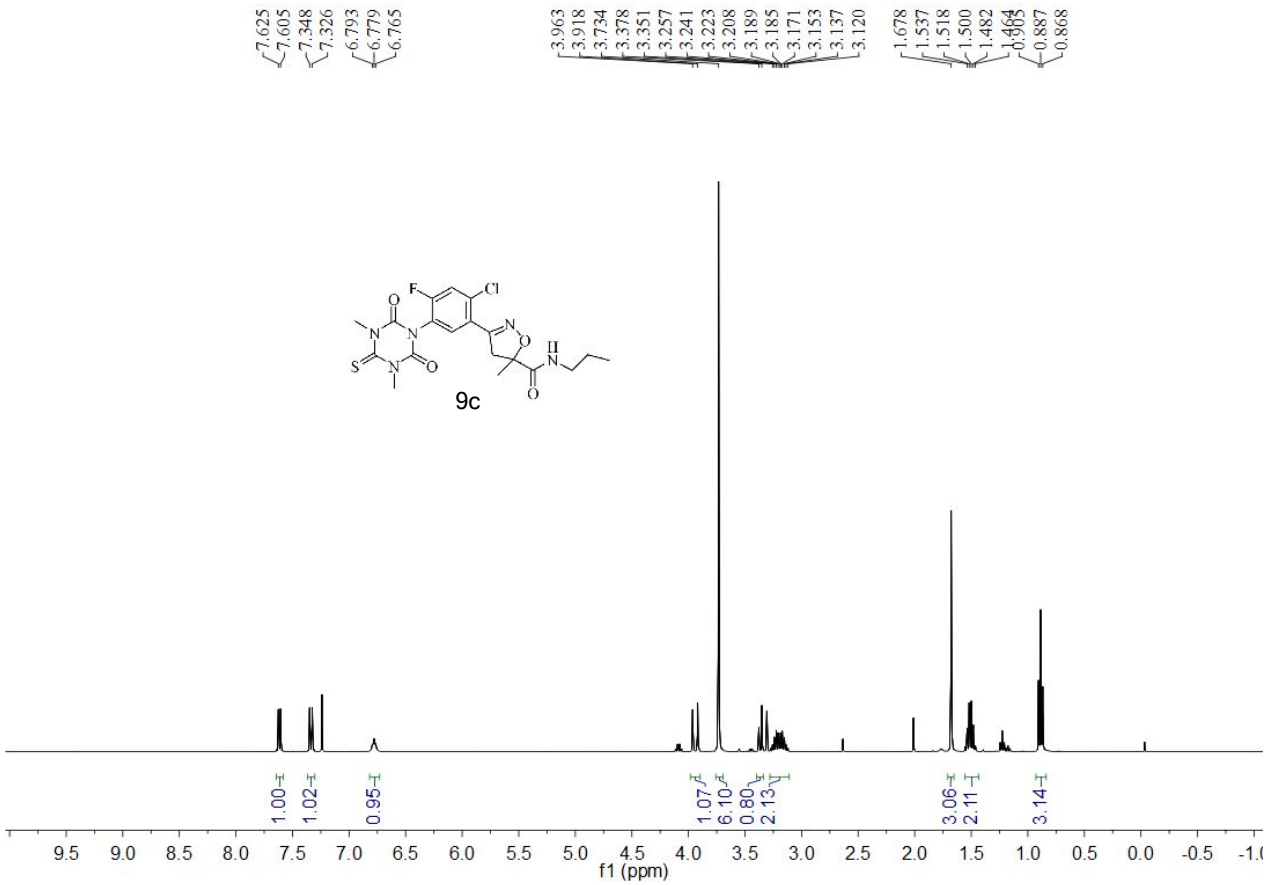
8e
f1 (ppm)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7.326
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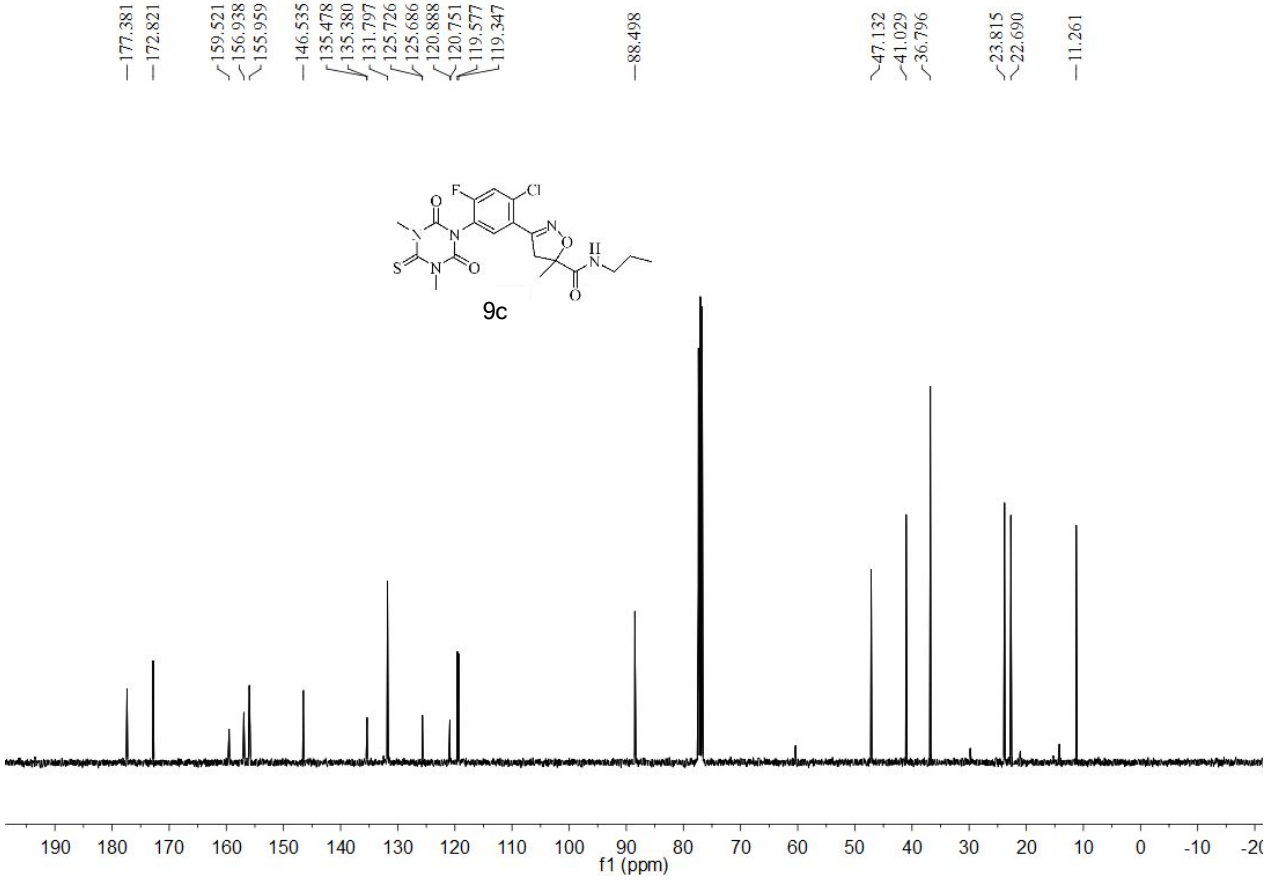
6.779
6.765
3.963
3.918
3.734
3.378
3.351
3.257
3.241
3.223
3.208
3.189
3.185
3.171
3.153
3.137
3.120
1.678
1.537
1.518
1.500
1.482
1.464
0.905
0.887
0.868
9c
1.00
1.02
0.95
1.07
6.10
0.80
2.13
3.06
2.11
3.14
f1 (ppm)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88.498
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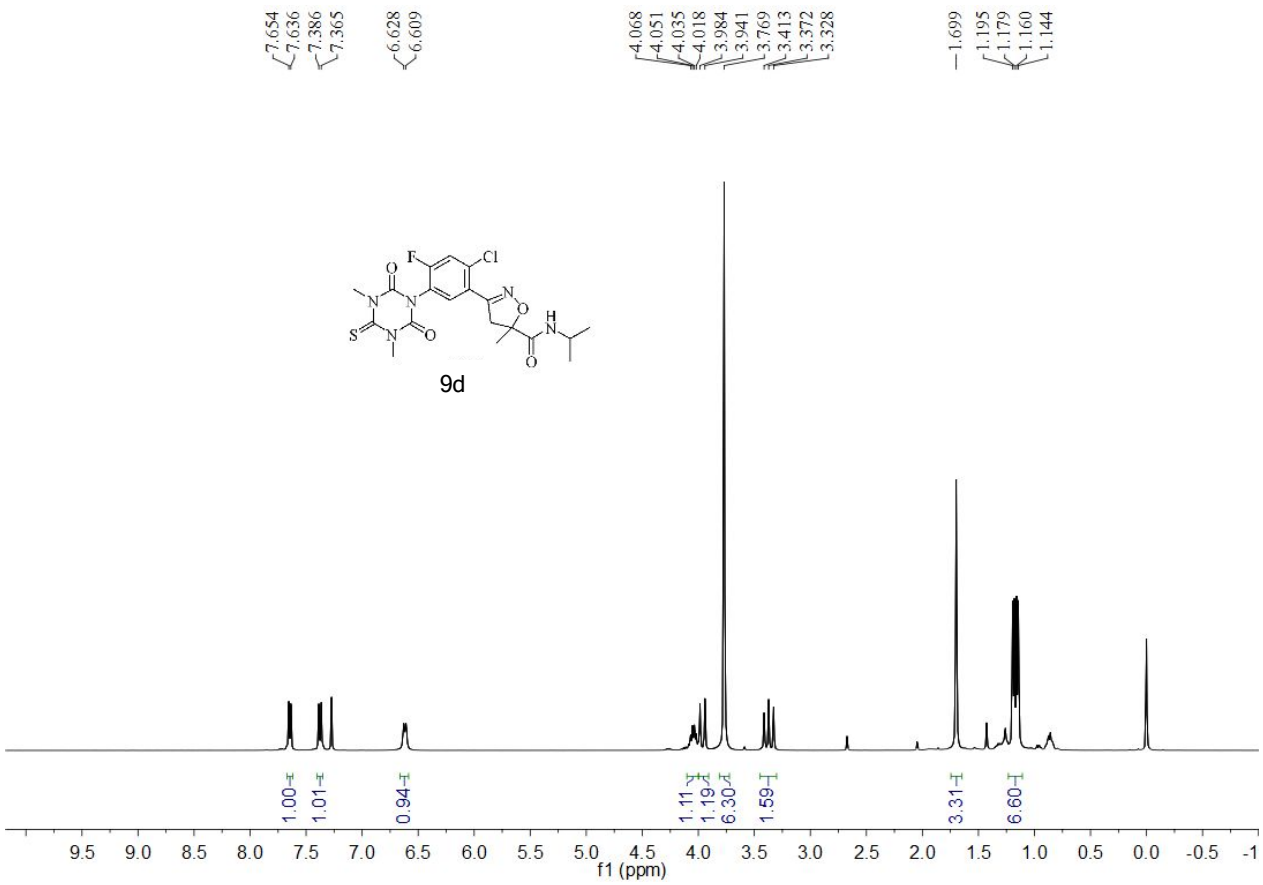
41.029
36.796
23.815
22.690
11.261
9c
f1 (ppm)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6.609
4.068
4.051
4.035
4.018
3.984
3.941
3.769
3.413
3.372
3.328
1.699
1.195
1.179
1.160
1.144
9d
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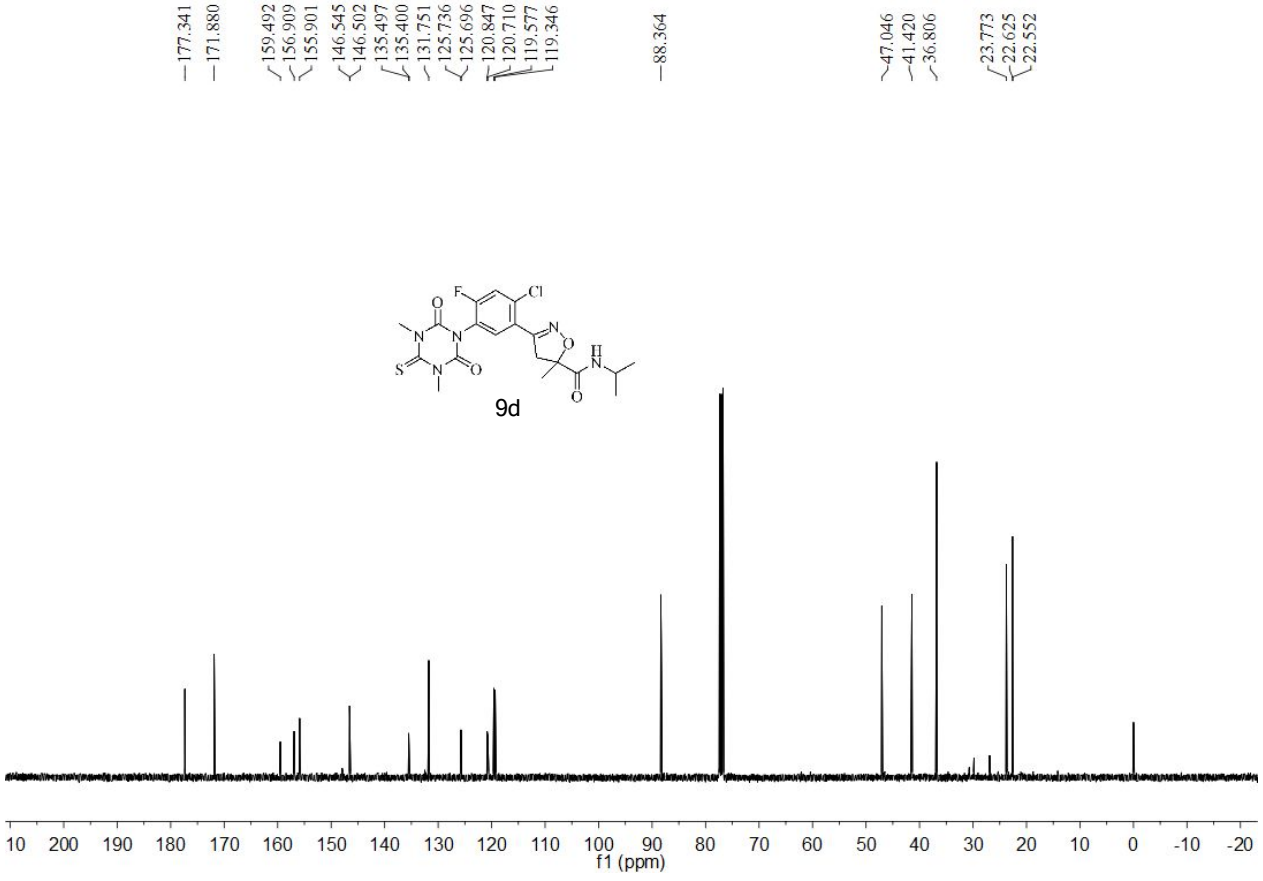
1.01
0.94
1.11
1.19
6.30
1.59
3.31
6.60
f1 (ppm)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135.400
131.751
125.736
125.696
120.847
120.710
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119.346
88.364
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36.806
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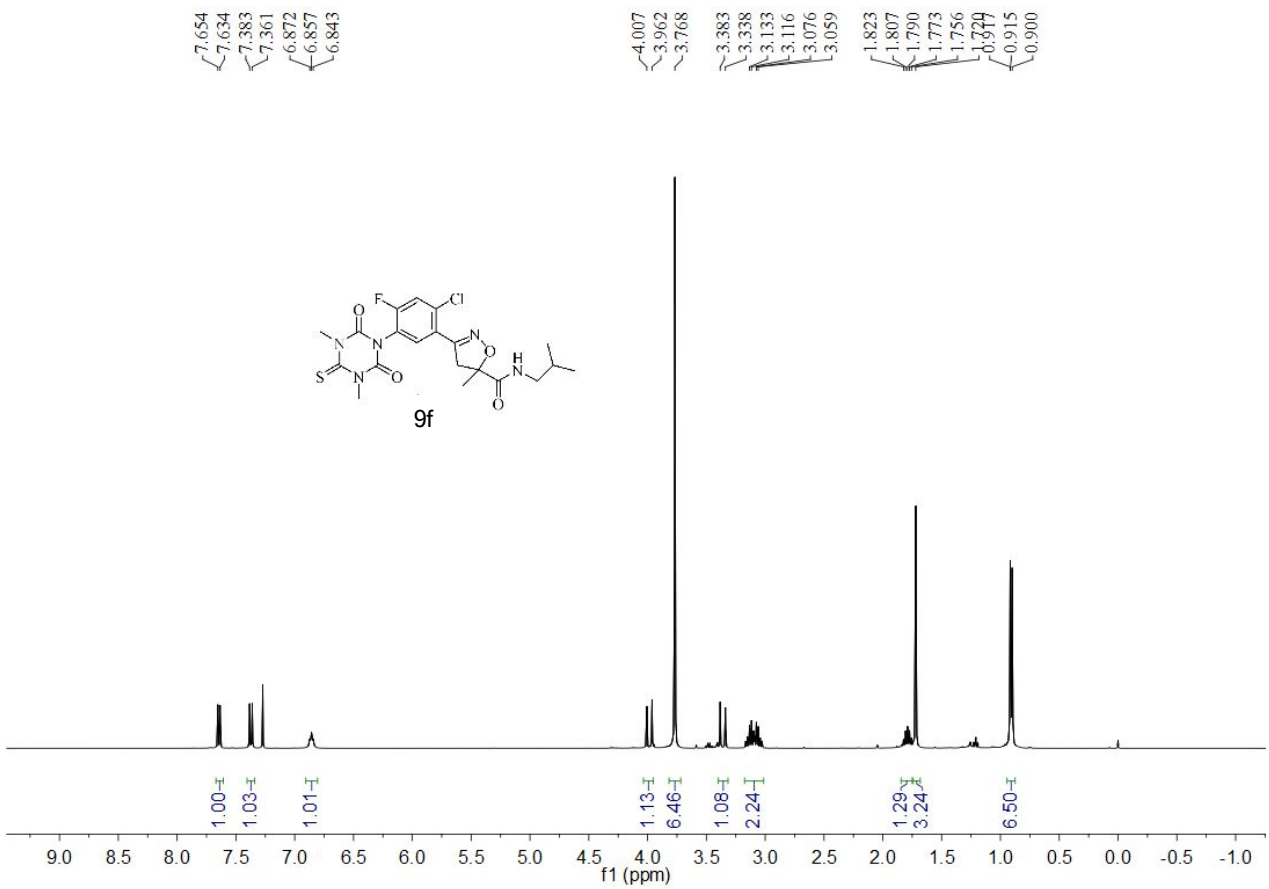
22.625
22.552
9d
f1 (ppm)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4.007
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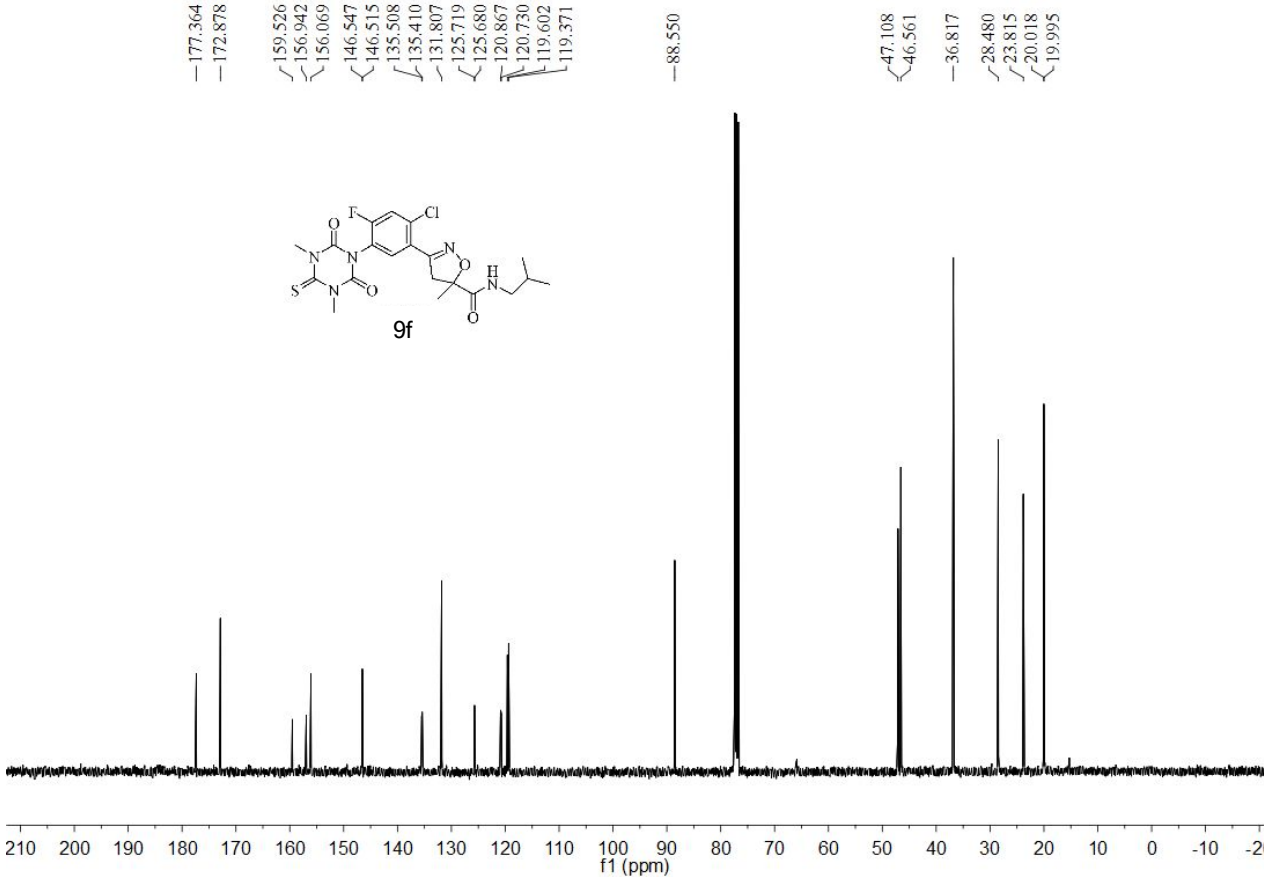
3.383
3.338
3.133
3.116
3.076
3.059
1.823
1.807
1.790
1.773
1.756
0.917
0.915
0.900
9f
1.00
1.03
1.01
1.13
6.46
1.08
2.24
1.29
3.24
6.50
f1 (ppm)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125.680
120.867
120.730
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119.371
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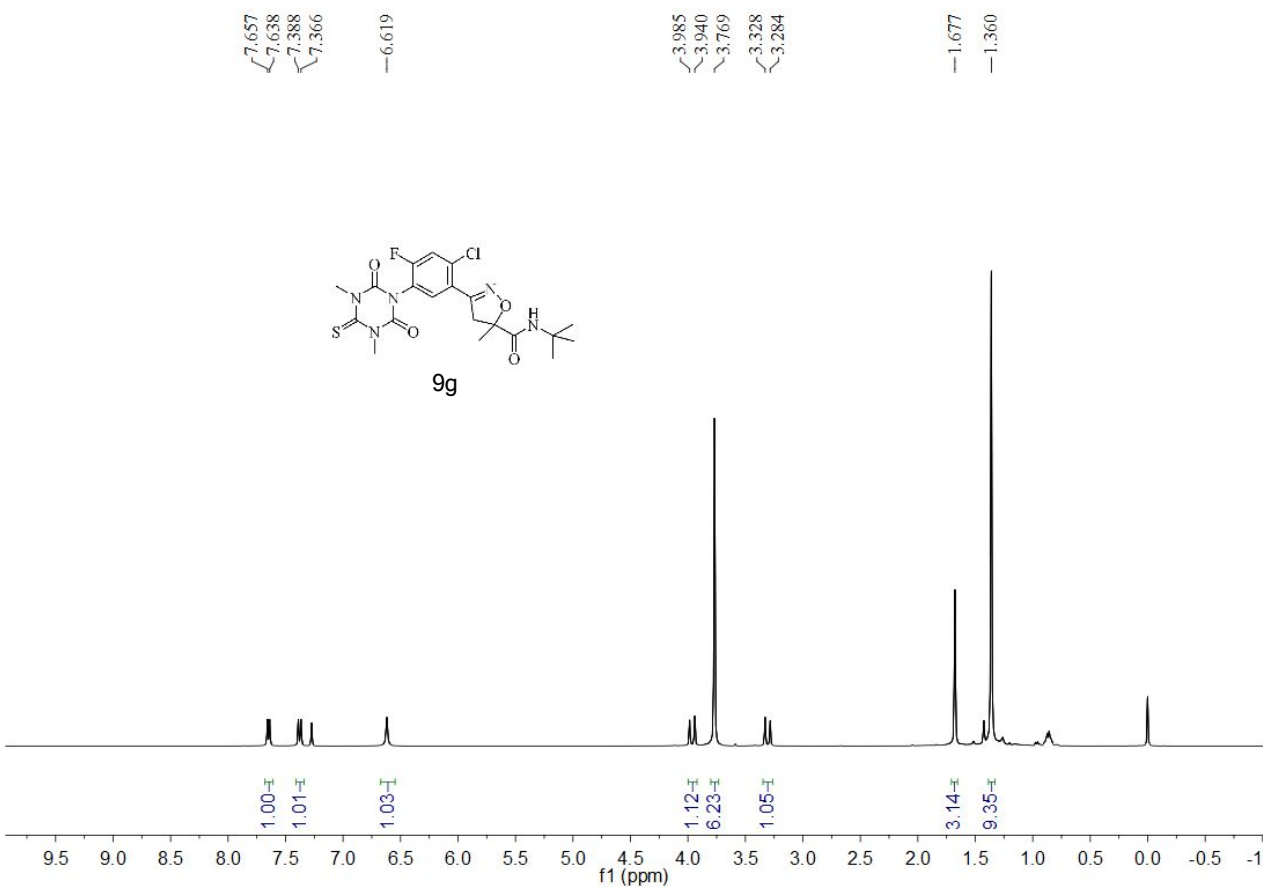
47.108
46.561
36.817
28.480
23.815
20.018
19.995
9f
f1 (ppm)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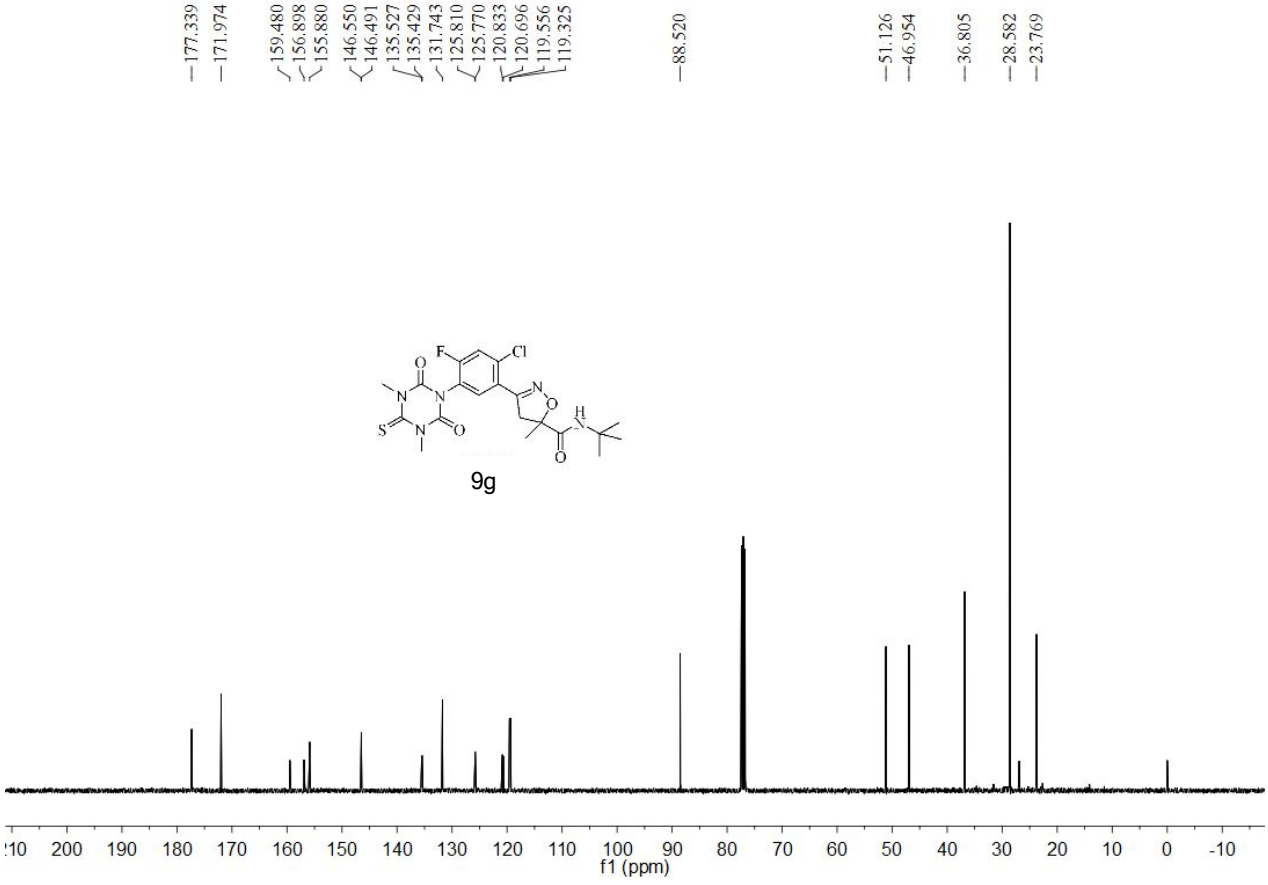
7.388
7.366
6.619
3.985
3.940
3.769
3.328
3.284
1.677
1.360
1.00
1.01
1.03
1.12
6.23
1.05
3.14
9.35
f1 (ppm)

9g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135.429
131.743
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125.770
120.833
120.696
119.556
119.325
88.520
51.126
46.954
36.805
28.582
23.769
f1 (ppm)

9g