Supporting Information

Novel deazaflavin analogues potently inhibited tyrosyl DNA phosphodiesterase 2 (TDP2) and strongly sensitized cancer cells toward treatment with topoisomerase II (TOP2) poison etoposide

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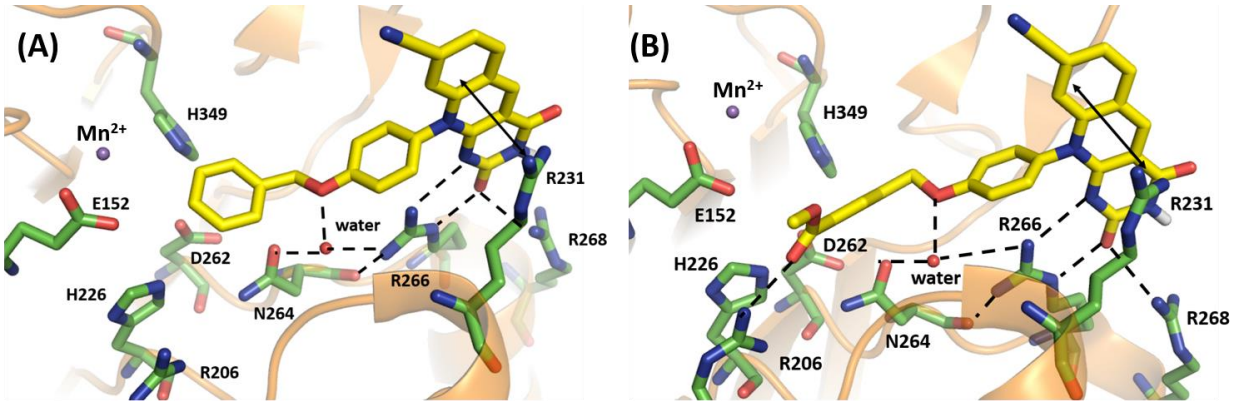
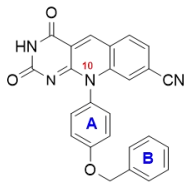
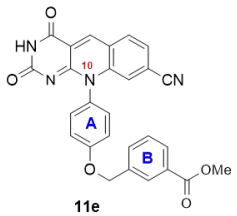




11a

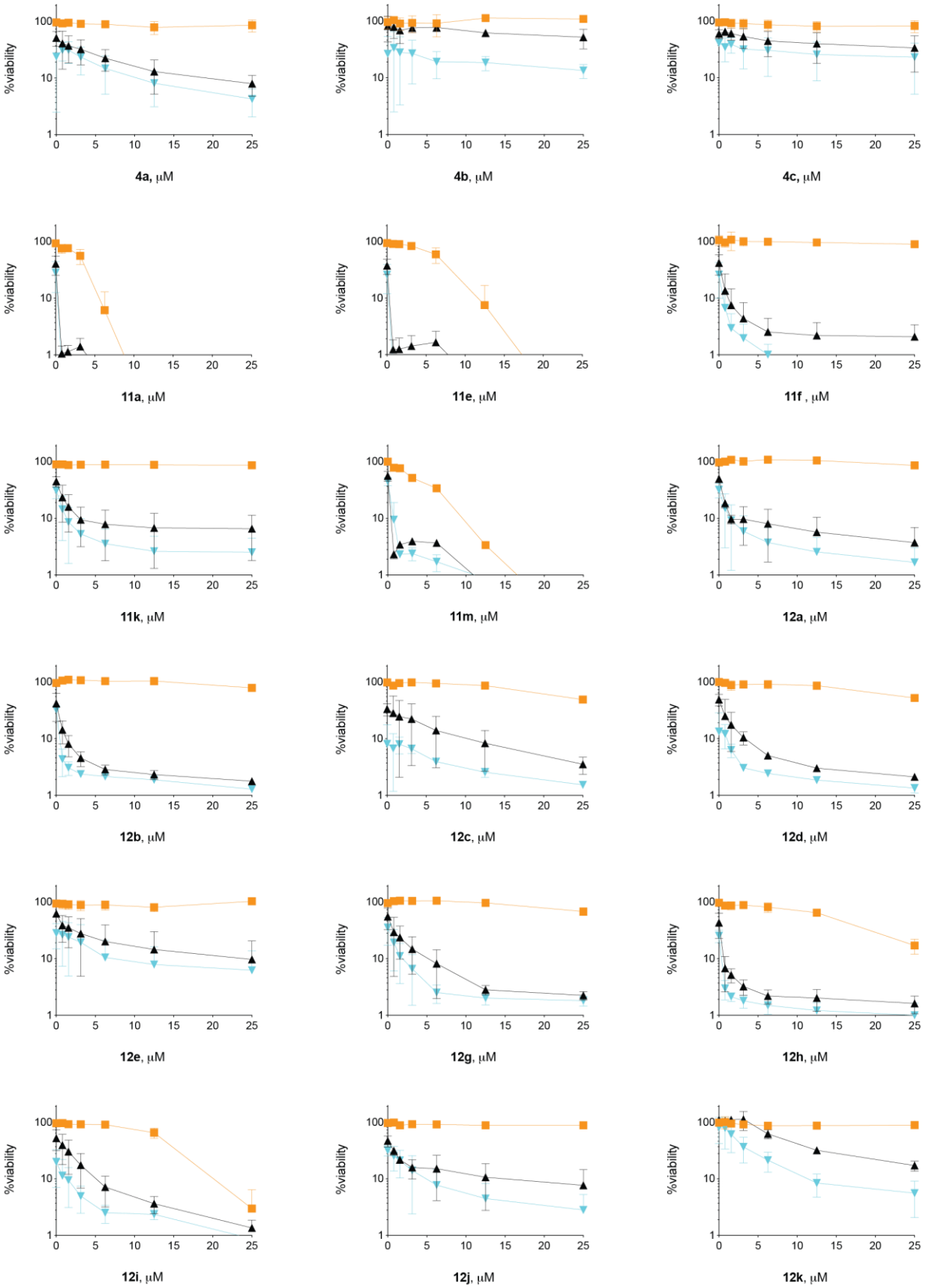


11e

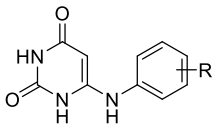
(C)

Compd	Glide score
4c	-8.21
11a	-7.99
11e	-8.56
11k	-9.01
12b	-9.85

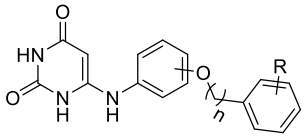
Figure S1. Molecular modeling of **11a** and **11e** and docking scores. (A) Predicted binding mode of **11a** within the catalytic domain of humanized mouse TDP2 (PDB code: 5J42). (B) Predicted binding mode of **11e** within the catalytic domain of humanized mouse TDP2 (PDB code: 5J42). Key residues are highlighted in green sticks. H-bond interactions are depicted as black dotted lines. Cation-π interaction is represented as double headed arrow in black. Water molecule and magnesium ion were represented as red and blue non-bonded sphere. All the residue numberings are based on the human TDP2. (C) Docking scores of selected TDP2 inhibitors using Glide.


%viability
100
10
1
0 5 10 15 20 25
4a, μM
4b, μM
4c, μM
11a, μM
11e, μM
11f , μM
11k, μM
11m, μM
12a, μM
12b, μM
12c, μM
12d, μM
12e, μM
12g, μM
12h, μM
12i, μM
12j, μM
12k, μM
No Etoposide
0.1 μM Etoposide
0.15 μM Etoposide

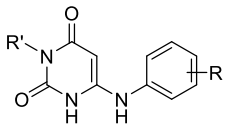
General procedure for the synthesis of 6-amination derivatives 15, 25, and 30.



15



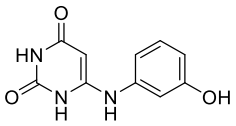
25



30

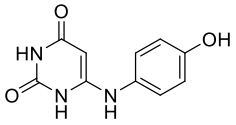
To a suspension of 6-chlorouracil **13** or **29** (0.50 g, 1.0 eq) and aniline derivative **14**, **20** or **21** (1.3 eq) in ethanol (5 mL) was irradiated at 150 °C for 30 minutes under microwave conditions. The reaction mixture was cooled and the precipitated solid was filtered, washed with cold methanol and ether and air dried to furnish the desired product **15**, **25** or **30.** Compounds **30c** (R'= 4-ClPh, R= *p*-$NHSO_2Me$), and **30d** (R'= 4-ClPh, R= *m*-$NHSO_2Me$) were oils and observed to slightly decompose on drying, and therefore they were taken directly to the next step after purification by column chromatography.

6-((3-Hydroxyphenyl)amino)pyrimidine-2,4(1H,3H)-dione (15b).



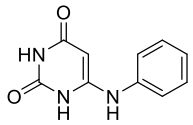
Compound **15b** was synthesized using 6-chlorouracil (**13**) and 3-hydroxyaniline (**14b**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.45 (s, 1H), 10.04 (s, 1H), 9.57 (s, 1H), 8.17 (s, 1H), 7.15 (t, J = 8.1 Hz, 1H), 6.63 – 6.59 (m, 2H), 6.54 (dd, J = 8.1, 1.5 Hz, 1H), 4.76 (s, 1H).

6-((4-Hydroxyphenyl)amino)pyrimidine-2,4(1*H*,3*H*)-dione (15c).



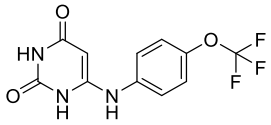
Compound **15c** was synthesized using 6-chlorouracil (**13**) and 4-hydroxyaniline (**14c**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.31 (s, 1H), 10.06 (s, 1H), 9.50 (s, 1H), 7.82 (s, 1H), 7.02 (d, J = 8.1 Hz, 2H), 6.77 (d, J = 8.1 Hz, 2H), 4.35 (s, 1H).

6-(Phenylamino)pyrimidine-2,4(1*H*,3*H*)-dione (15d).



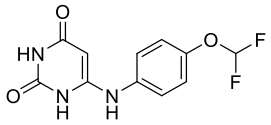
Compound **15d** was synthesized using 6-chlorouracil (**13**) and aniline (**14d**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 10.20 (s, 1H), 8.28 (s, 1H), 7.41 (t, 2H, J = 7.8 Hz), 7.15–7.23 (m, 3H), 4.70 (s, 1H).

6-((4-(Trifluoromethoxy)phenyl)amino)pyrimidine-2,4(1H,3H)-dione (15e).



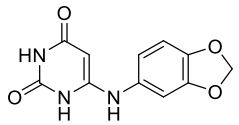
Compound **15e** was synthesized using 6-chlorouracil (**13**) and 4-(trifluoromethoxy)aniline (**14e**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.50 (s, 1H), 10.29 (s, 1H), 8.43 (s, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.33 – 7.27 (m, 2H), 4.71 (s, 1H).

6-((4-(Difluoromethoxy)phenyl)amino)pyrimidine-2,4(1H,3H)-dione (15f).



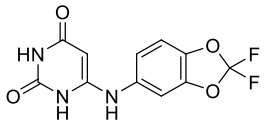
Compound **15f** was synthesized using 6-chlorouracil (**13**) and 4-(difluoromethoxy)aniline (**14f**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.43 (s, 1H), 10.20 (s, 1H), 8.23 (s, 1H), 7.30 (t, J = 78 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.19 – 7.16 (m, 2H), 4.58 (s, 1H).

6-(Benzo[d][1,3]dioxol-5-ylamino)pyrimidine-2,4(1H,3H)-dione (15g).



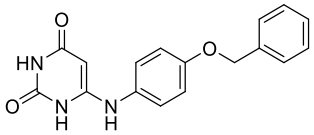
Compound **15g** was synthesized using 6-chlorouracil (**13**) and benzo[*d*][1,3]dioxol-5-amine (**14g**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.36 (s, 1H), 10.12 (s, 1H), 7.98 (s, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.67 (dd, J = 8.2, 2.1 Hz, 1H), 6.03 (s, 2H), 4.46 (s, 1H).

6-((2,2-Difluorobenzo[d][1,3]dioxol-5-yl)amino)pyrimidine-2,4(1H,3H)-dione (15h).



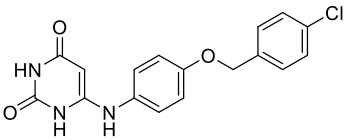
Compound **15h** was synthesized using 6-chlorouracil (**13**) and 2,2-difluorobenzo[*d*][1,3]dioxol-5-amine (**14h**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.46 (s, 1H), 10.29 (s, 1H), 8.35 (s, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.02 (dd, J = 8.6, 2.1 Hz, 1H), 4.60 (s, 1H).

6-((4-(Benzyloxy)phenyl)amino)pyrimidine-2,4(1H,3H)-dione (25a).



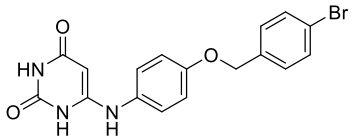
Compound **25a** was synthesized using 6-chlorouracil (**13**) and 4-(benzyloxy)aniline (**20a**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.35 (s, 1H), 10.11 (s, 1H), 7.96 (s, 1H), 7.44 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 1H), 7.16 – 7.11 (m, 2H), 7.05 – 6.99 (m, 2H), 5.10 (s, 2H), 4.42 (s, 1H).

6-((4-((4-Chlorobenzyl)oxy)phenyl)amino)pyrimidine-2,4(1H,3H)-dione (25b).



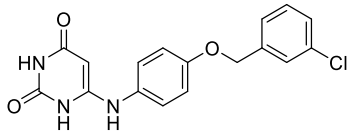
Compound **25b** was synthesized using 6-chlorouracil (**13**) and 4-((4-chlorobenzyl)oxy)aniline **(20b)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.36 (s, 1H), 10.12 (s, 1H), 7.97 (s, 1H), 7.49-7.45 (m, 4H), 7.15 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 5.10 (s, 2H), 4.43 (s, 1H).

6-((4-((4-Bromobenzyl)oxy)phenyl)amino)pyrimidine-2,4(1H,3H)-dione (25c).



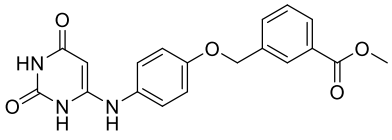
Compound **25c** was synthesized using 6-chlorouracil (**13**) and 4-((4-bromobenzyl)oxy)aniline **(20c)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.35 (s, 1H), 10.12 (s, 1H), 7.97 (s, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 5.09 (s, 2H), 4.42 (s, 1H).

6-((4-((3-Chlorobenzyl)oxy)phenyl)amino)pyrimidine-2,4(1H,3H)-dione (25d).



Compound **25d** was synthesized using 6-chlorouracil (**13**) and 4-((3-chlorobenzyl)oxy)aniline **(20d)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.36 (s, 1H), 10.12 (s, 1H), 7.97 (s, 1H), 7.52 (s, 1H), 7.47 – 7.35 (m, 3H), 7.15 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H), 5.12 (s, 2H), 4.43 (s, 1H).

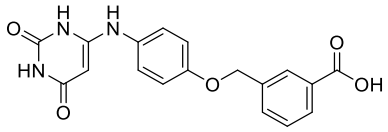
Methyl 3-((4-((2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)amino)phenoxy)-methyl)benzoate (25e).



Compound **25e** was synthesized using 6-chlorouracil (**13**) and methyl 3-((4-aminophenoxy)methyl)benzoate (**20e**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.35 (s, 1H), 10.12 (s,

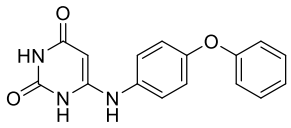
1H), 8.05 (s, 1H), 7.97 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 8.9 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 2H), 5.19 (s, 2H), 4.43 (s, 1H), 3.86 (s, 3H).

3-((4-((2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)amino)phenoxy) methyl)-benzoic acid (25f).



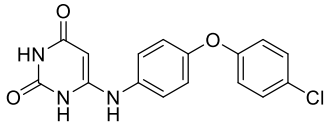
To a solution of **25e** (0.3 g, 1.0 eq) in ethanol (5 mL), was added NaOH (1N, 5 mL) and heated to reflux for 3 h. The reaction mixture was cooled, and ethanol was evaporated *in vacuo*. Water (5 mL) was added to it and acidified to a pH of 3-4 with 1N HCl. The resultant precipitate was filtered and washed with excess water and air dried to leave the desired acid **25f** as colorless solid (85%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.02 (s, 1H), 10.36 (s, 1H), 10.16 (s, 1H), 8.07 (s, 1H), 8.03 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 5.18 (s, 2H), 4.44 (s, 1H).

6-((4-Phenoxyphenyl)amino)pyrimidine-2,4(1H,3H)-dione (25g).



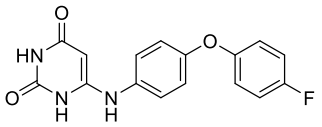
Compound **25g** was synthesized using 6-chlorouracil (**13**) and 4-phenoxyaniline (**21a**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.42 (s, 1H), 10.18 (s, 1H), 8.17 (s, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.05-7.01 (m, 4H), 4.58 (s, 1H).

6-((4-(4-Chlorophenoxy)phenyl)amino)pyrimidine-2,4(1H,3H)-dione (25h).



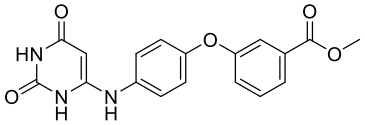
Compound **25h** was synthesized using 6-chlorouracil (**13**) and 4-(4-chlorophenoxy)aniline (**21b**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.43 (s, 1H), 10.20 (s, 1H), 8.20 (s, 1H), 7.50 – 7.36 (m, 2H), 7.30 – 7.19 (m, 2H), 7.09 – 7.03 (m, 4H), 4.60 (s, 1H).

6-((4-(4-Fluorophenoxy)phenyl)amino)pyrimidine-2,4(1H,3H)-dione (25i).



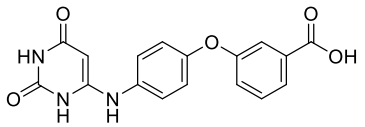
Compound **25i** was synthesized using 6-chlorouracil (**13**) and 4-(4-fluorophenoxy)aniline (**21c**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.41 (s, 1H), 10.17 (s, 1H), 8.16 (s, 1H), 7.24 – 7.20 (m, 4H), 7.09 – 7.06 (m, 2H), 7.02 – 6.99 (m, 2H), 4.56 (s, 1H).

Methyl 3-(4-((2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)amino)phenoxy)-benzoate (25j).



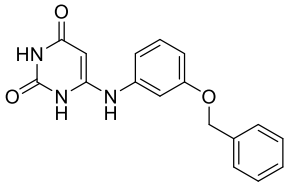
Compound **25j** was synthesized using 6-chlorouracil (**13**) and methyl 3-(4-aminophenoxy)benzoate (**21d**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.43 (s, 1H), 10.22 (s, 1H), 8.22 (s, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.46 (s, 1H), 7.34 (dd, J = 8.2, 2.5 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 4.61 (s, 1H), 3.83 (s, 3H).

3-(4-((2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)amino)phenoxy)benzoic acid (25k).



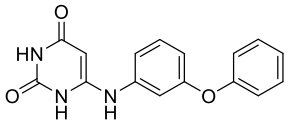
Compound **25k** was synthesized using the same procedure as **25f**, using **25j** as starting material. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.11 (s, 1H), 10.43 (s, 1H), 10.24 (s, 1H), 8.29 (s, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.32 – 7.28 (m, 1H), 7.26-7.22 (m, 2H), 7.11 – 7.08 (m, 2H), 4.61 (s, 1H).

6-((3-(Benzyloxy)phenyl)amino)pyrimidine-2,4(1H,3H)-dione (25l).



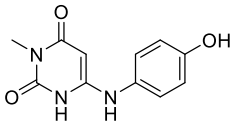
Compound **25l** was synthesized using 6-chlorouracil (**13**) and 3-(benzyloxy)aniline (**19f**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.46 (s, 1H), 10.13 (s, 1H), 8.23 (s, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 6.82-6.80 (m, 3H), 5.09 (s, 2H), 4.73 (s, 1H).

6-((3-Phenoxyphenyl)amino)pyrimidine-2,4(1H,3H)-dione (25m).



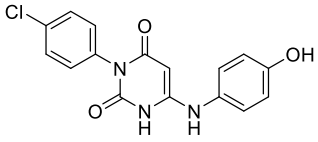
Compound **25m** was synthesized using 6-chlorouracil (**13**) and 3-phenoxyaniline (**21e**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.48 (s, 1H), 10.19 (s, 1H), 8.38 (s, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.78 (s, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 4.76 (s, 1H).

6-((4-Hydroxyphenyl)amino)-3-methylpyrimidine-2,4(1H,3H)-dione (30a).



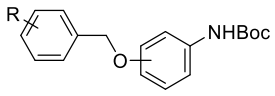
Compound **30a** was synthesized using 6-chloro-3-methyluracil (**29b**) and 4-aminophenol (**14a**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.39 (s, 1H), 9.49 (s, 1H), 7.82 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.50 (s, 1H), 3.04 (s, 3H).

3-(4-chlorophenyl)-6-((4-hydroxyphenyl)amino)pyrimidine-2,4(1H,3H)-dione (30b).



Compound **30b** was synthesis using **29a** and 4-aminophenol (**14a**). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.73 (s, 1H), 9.55 (s, 1H), 8.22 (s, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.55 (s, 1H).

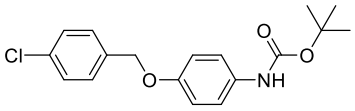
General procedure for the synthesis of 19



19

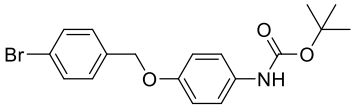
To a solution of *N*-Boc protected aminophenol derivative **17** (1.0 g, 1.0 eq) in DMF (15 mL) was added K_2CO_3 (2.0 eq) and stirred for 15 min followed by the addition of benzyl bromide derivative **18** (1.2 eq) over 15 min and stirred at r.t for 12 h. Water was added, and the aqueous solution was extracted with EtOAc (3 x 25 mL) followed by brine, dried over Na_2SO_4 and evaporated in vacuo. The crude compound was triturated with ether to furnish **19** which was sufficiently pure for the next step.

Tert-butyl (4-((4-chlorobenzyl)oxy)phenyl)carbamate (19b).



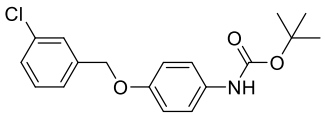
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.49 – 7.40 (m, 4H), 7.33 (d, *J* = 7.9 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 5.03 (s, 2H), 1.45 (s, 9H).

Tert-butyl (4-((4-bromobenzyl)oxy)phenyl)carbamate (19c).



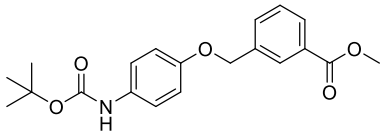
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 5.02 (s, 2H), 1.45 (s, 9H).

Tert-butyl (4-((3-chlorobenzyl)oxy)phenyl)carbamate (19d).



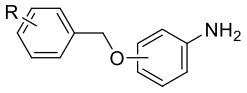
^{1}H NMR (600 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.48 (s, 1H), 7.43 – 7.36 (m, 3H), 7.34 (d, J = 8.0 Hz, 2H), 6.92 – 6.89 (m, 2H), 5.05 (s, 2H), 1.45 (s, 9H).

Methyl 3-((4-((tert-butoxycarbonyl)amino)phenoxy)methyl)benzoate (19e).



^{1}H NMR (600 MHz, DMSO-d6) δ 9.14 (s, 1H), 8.02 (s, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.54 (*t*, J = 7.7 Hz, 1H), 7.35 (d, J = 7.5 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 5.13 (s, 2H), 3.86 (s, 3H), 1.46 (s, 9H).

General procedure for the synthesis of 20

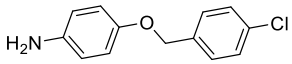


20

To a solution of TFA in DCM (4:1, 15 mL) was added *N*-Boc protected phenoxy aniline **19** and stirred at r.t for 6 h. The solvent was evaporated in vacuo and neutralized the solution with 2N NaOH (pH = 7 - 9) and extracted with EtOAc (2x 20 mL). The combined organic solution was washed with brine, dried over Na_2SO_4 and evaporated in vacuo. Compounds **20d** (*p*, R= 3-Cl), and

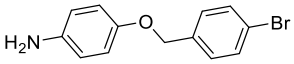
20e (*p*, R= 3-COOMe) were oils and observed to slightly decompose on drying, so they were taken to the next step without any further purification.

4-((4-Chlorobenzyl)oxy)aniline (20b).



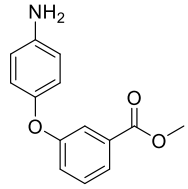
Colorless solid, 75% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.42-7.40 (m, 4H), 6.70 (d, J = 8.6 Hz, 2H), 6.49 (d, J = 8.6 Hz, 2H), 4.94 (s, 2H), 4.62 (s, 2H).

4-((4-Bromobenzyl)oxy)aniline (20c).



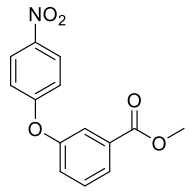
^{1}H NMR (600 MHz, DMSO-d_6) δ 7.56 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 6.71 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 8.7 Hz, 2H), 4.92 (s, 2H).

Synthesis of methyl 3-(4-aminophenoxy)benzoate (21d)



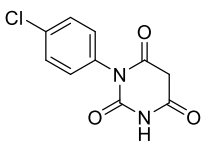
To a solution of **24a** (0.60 g, 2.19 mmol, 1.0 eq) in EtOAc (10 mL) was added 10% Pd/C (100 mg) and the reaction mixture was stirred at room temperature under a hydrogen environment (balloon) overnight. TLC indicated the disappearance of starting material and the product mass is confirmed by MS. The reaction mixture was filtered through celite, washed with EtOAc and dried under vacuo. The crude product was purified using CombiFlash with 0-30% EtOAc in hexane as an eluent to produce the desired product as colorless oil (0.46 g, 87%). The compound was observed to slightly decompose on drying, so it was taken to the next step without any further purification.

Synthesis of methyl 3-(4-nitrophenoxy)benzoate (24a)



To a solution of Methyl-3-hydroxybenzoate (1.29 g, 8.50 mmol, 1.2 eq) in DMF (15 mL) was added K_2CO_3 (1.96 g, 14.17 mmol, 2.0 eq) and stirred at room temperature for 15 min. 1-Fluoro-4-nitrobenzene (1.0 g, 7.09 mmol, 1.0 eq) was added and the reaction mixture was heated at 110 °C for 12 h and the TLC indicated the consumption of starting material. The reaction mixture was cooled, water (20 mL) was added and extracted with EtOAc (2 x 20 mL). The combined organic layers were extracted with water (2 x 20 mL), brine (2 x 15 mL), dried over Na_2SO_4, evaporated solution under vacuo and the trituration of the crude compound with ether furnished the desired compound as a colorless solid (1.14 g, 59%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.40 – 8.17 (m, 2H), 7.88 (d, J = 7.7 Hz, 1H), 7.67-7.64 (m, 2H), 7.52 (dd, J = 8.1, 1.8 Hz, 1H), 7.25 – 7.12 (m, 2H), 3.86 (s, 3H).

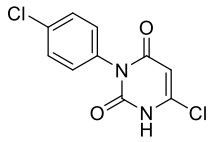
Synthesis of 1-(4-Chlorophenyl)pyrimidine-2,4,6(1H,3H,5H)-trione (28).



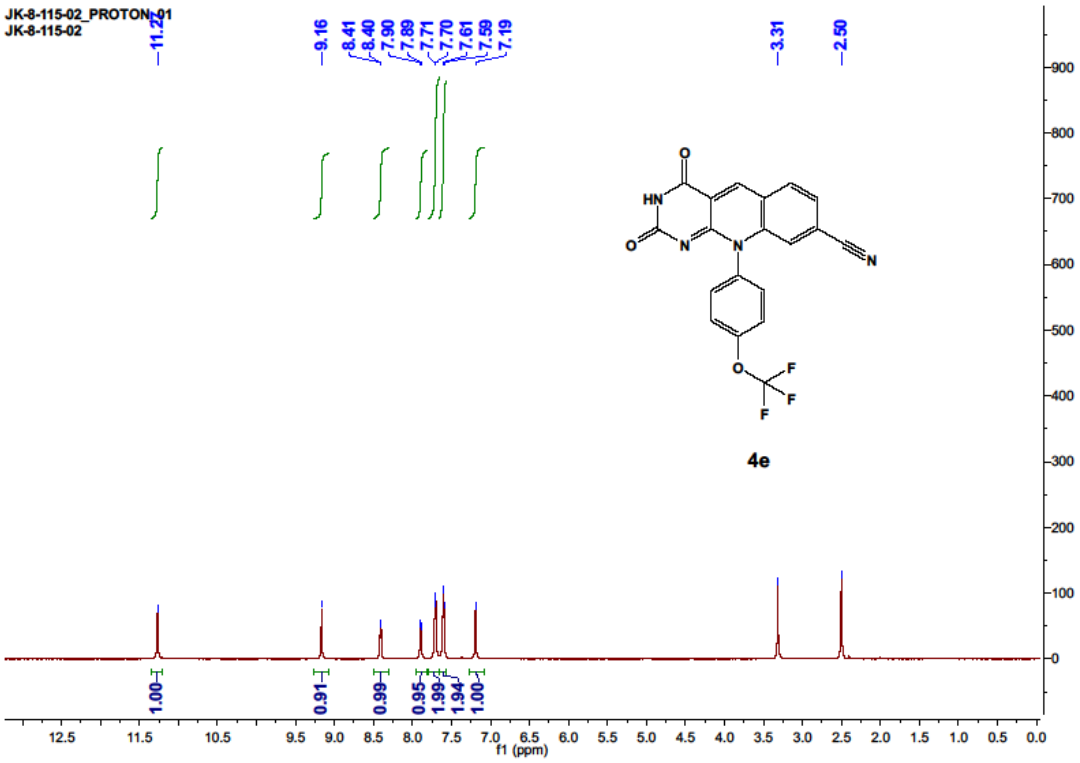
To a freshly made sodium ethoxide (17.58 mmol, 1.5 eq) in 17.6 mL of anhydrous ethanol, 1-(4-chlorophenyl)urea (2.0 g, 11.72 mmol, 1.0 eq) and diethyl malonate (1.79 mL, 17.56 mmol, 1.0

eq) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was cooled and solvent was removed under reduced pressure. The residue was dissolved in water, then treated with 1 N aqueous HCl to adjust the pH 4~5. The precipitate was filtered off, washed with small amount of cold methanol and diethyl ether, dried in vacuo to give compound **28** as a colorless solid in 85% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.52 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 3.71 (s, 2H).

Synthesis of 6-Chloro-3-(4-chlorophenyl)pyrimidine-2,4(1H,3H)-dione (29a).



To a solution of **28** (1.50 g, 6.29 mmol, 1.0 eq) in $POCl_3$ (6 mL) was added $BnEt_3NCl$ (2.86 g, 12.57 mmol, 2.0 equiv.) and the mixture was stirred at 50 °C temperature for 6 h. The reaction mixture was cool down to room temperature and then pour it onto the ice dropwise. The precipitate was filtered off, washed with excess water followed by cold ether and dried in vacuo furnished the desired compound 6-Chloro-3-(4-chlorophenyl)pyrimidine-2,4(1H,3H)-dione **(29a)** as light yellow solid in 85% yield. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.52 (s, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H), 6.02 (s, 2H).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JK-8-115-02
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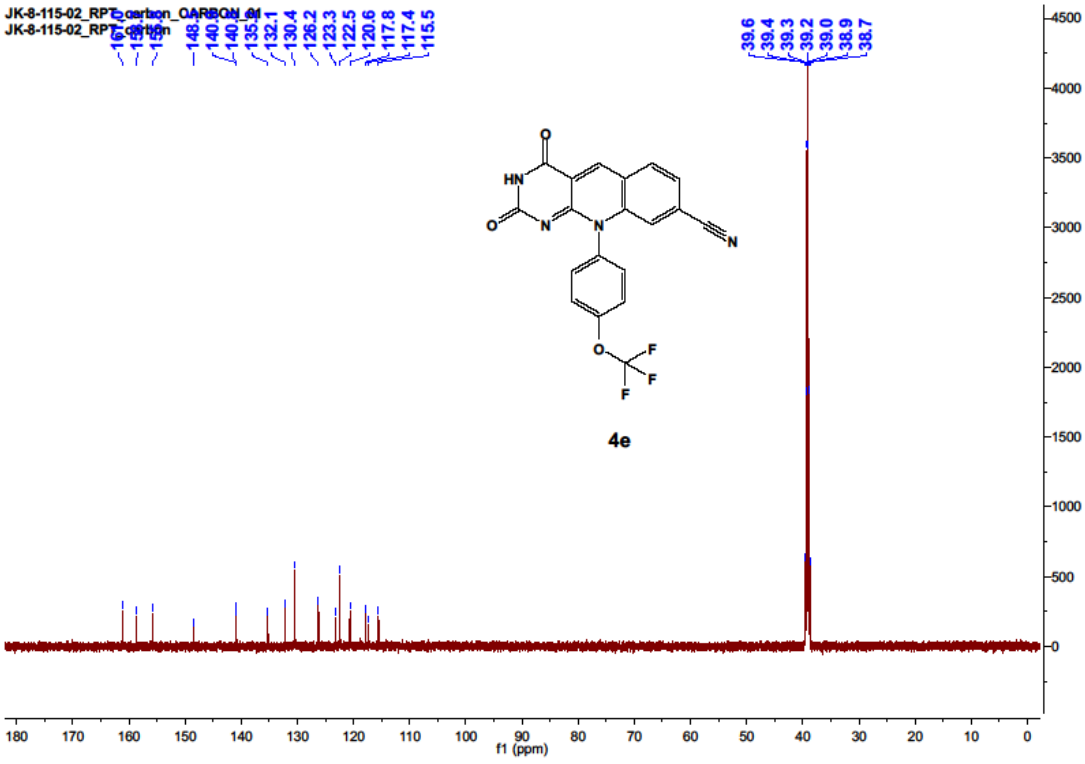
8.41
8.40
7.90
7.89
7.71
7.70
7.61
7.59
7.19
3.31
2.50
4e
1.00
0.91
0.99
0.95
1.99
1.94
1.00
f1 (ppm)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JK-8-115-02_RPT_carbon
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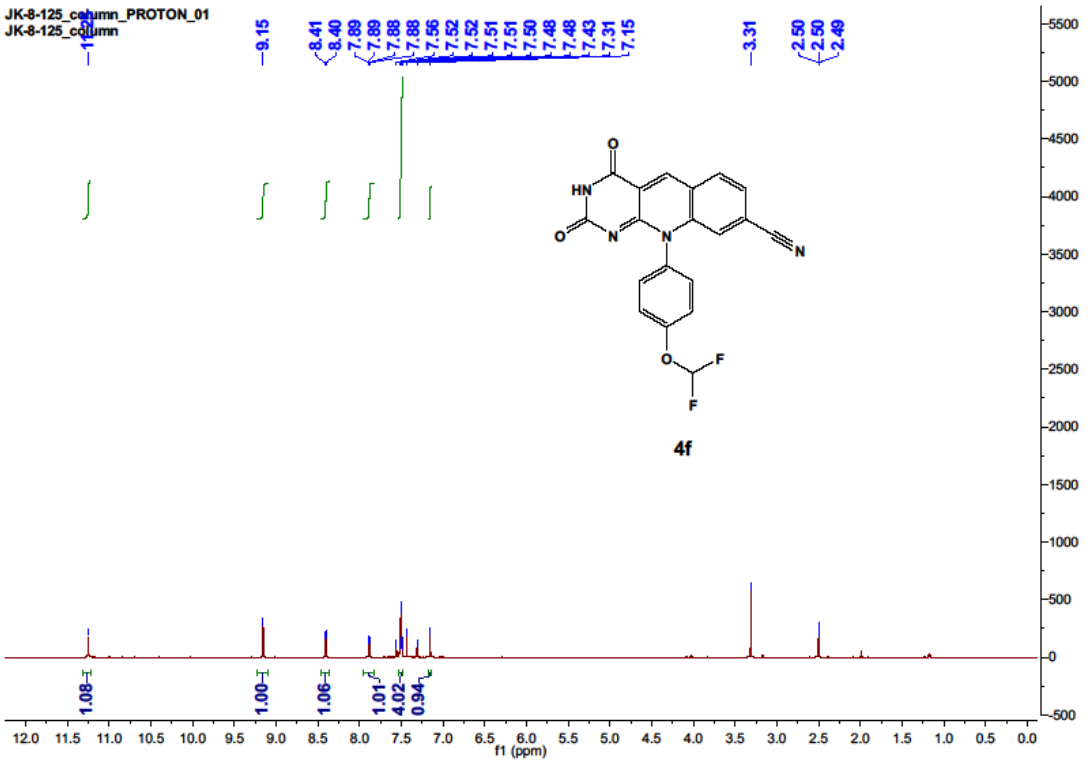
140.4
135.1
132.1
130.4
126.2
123.3
122.5
120.6
117.8
117.4
115.5
39.6
39.4
39.3
39.2
39.0
38.9
38.7
4e
f1 (ppm)


JK-8-125_column_PROTON_01
JK-8-125_column
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7.51
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7.48
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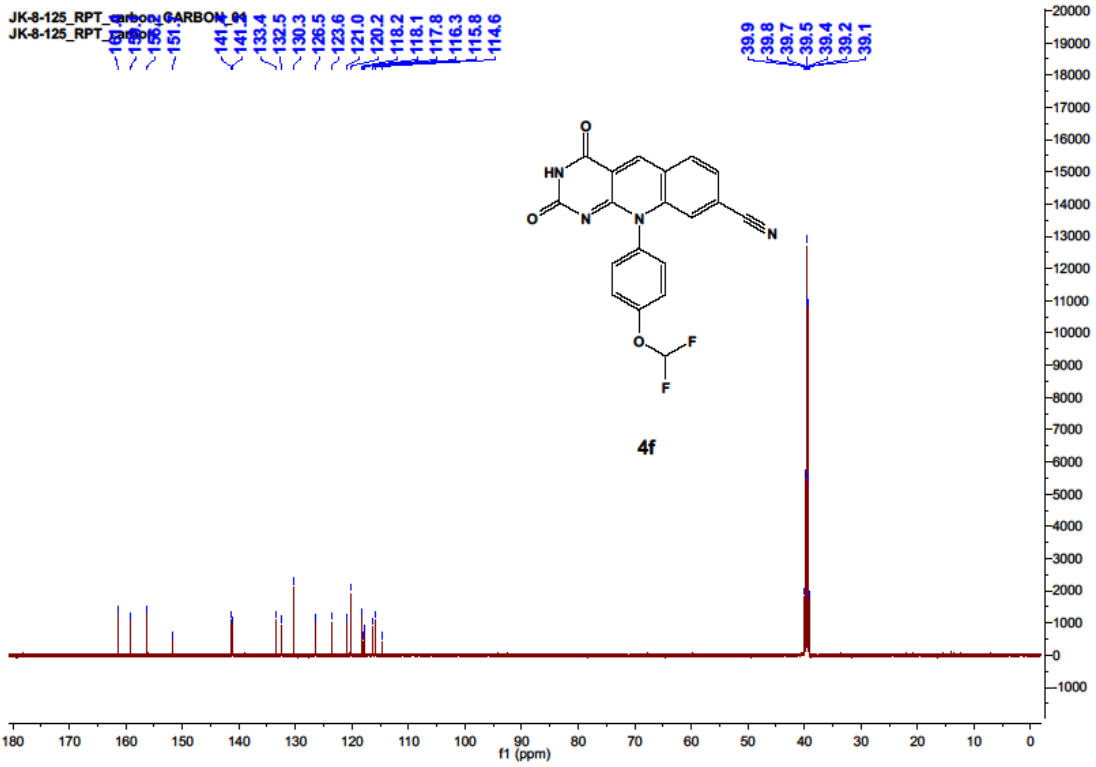
7.43
7.31
7.15
3.31
2.50
2.50
2.49
4f
1.08
1.00
1.06
1.01
4.02
0.94
f1 (ppm)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JK-8-125_RPT_carbon
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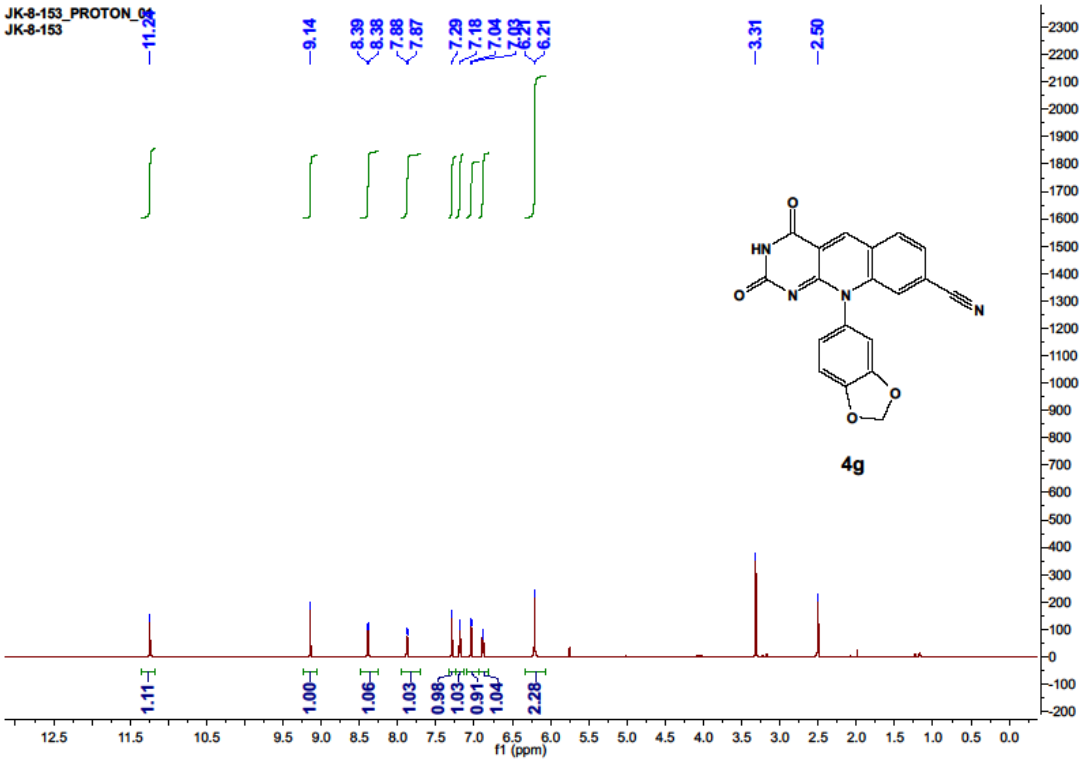
114.6
39.9
39.8
39.7
39.5
39.4
39.2
39.1
4f
f1 (ppm)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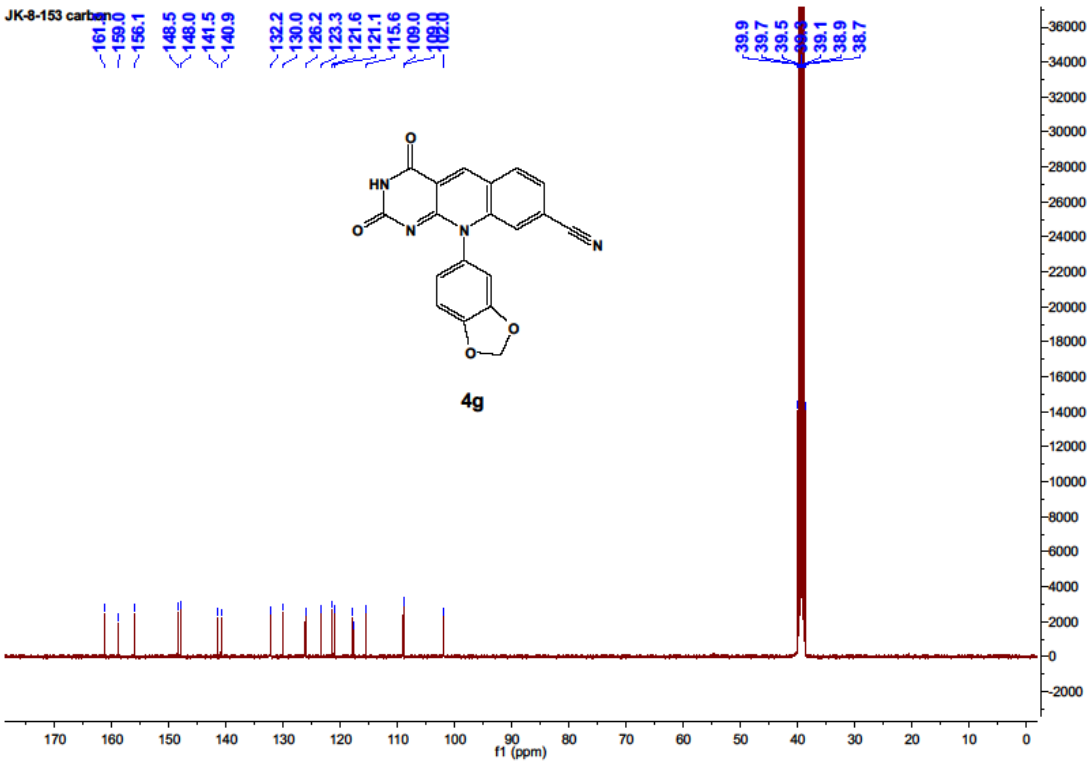
7.03
6.21
6.21
3.31
2.50
4g
1.11
1.00
1.06
1.03
0.98
1.03
0.91
1.04
2.28
f1 (ppm)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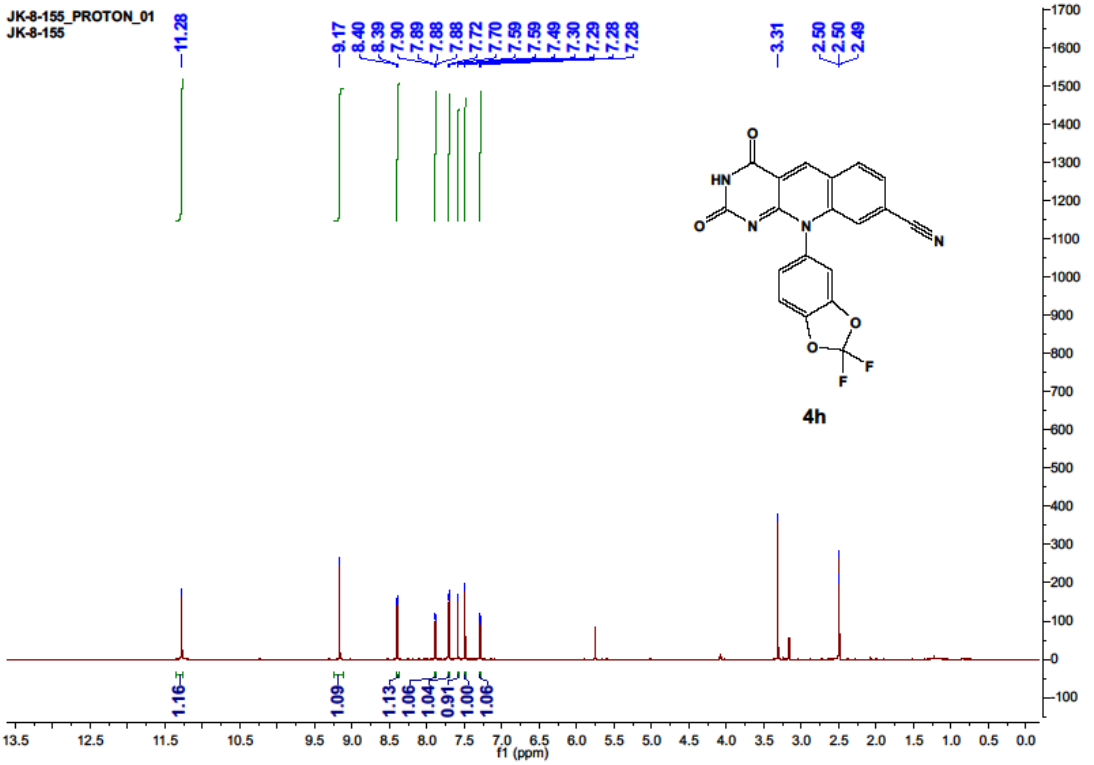
39.7
39.5
39.3
39.1
38.9
38.7
4g
f1 (ppm)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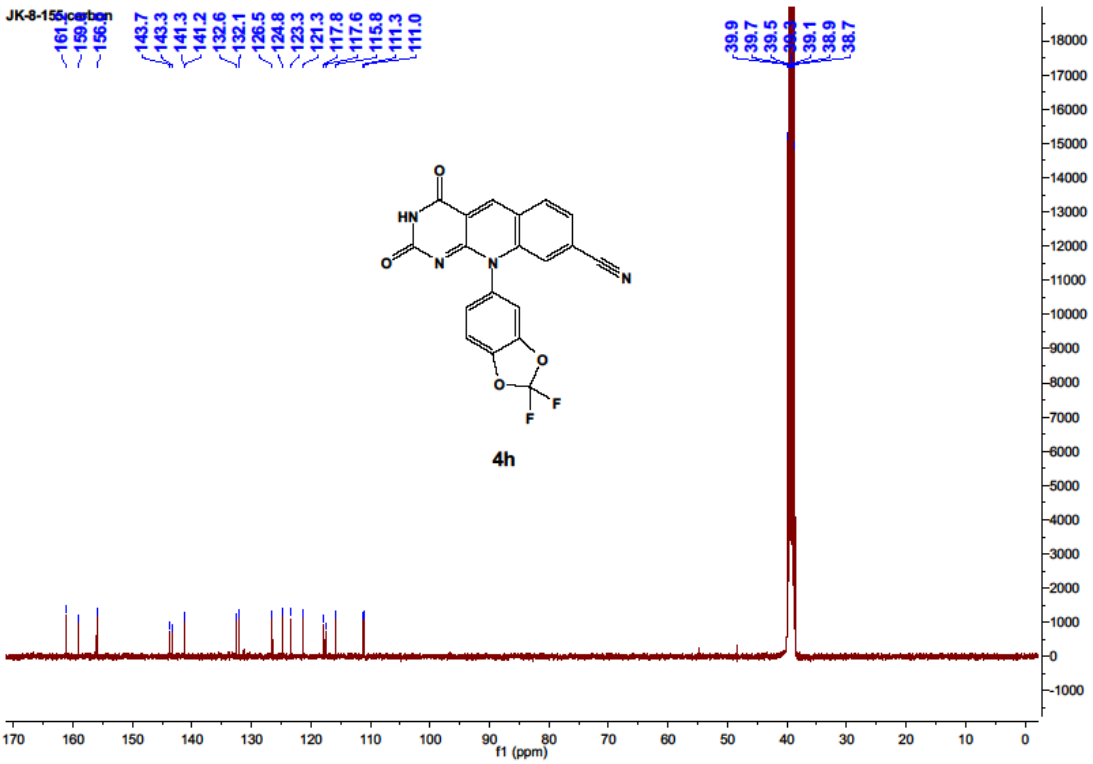
7.59
7.49
7.30
7.29
7.28
7.28
3.31
2.50
2.50
2.49
4h
1.16
1.09
1.13
1.06
1.04
0.91
1.00
1.06
f1 (ppm)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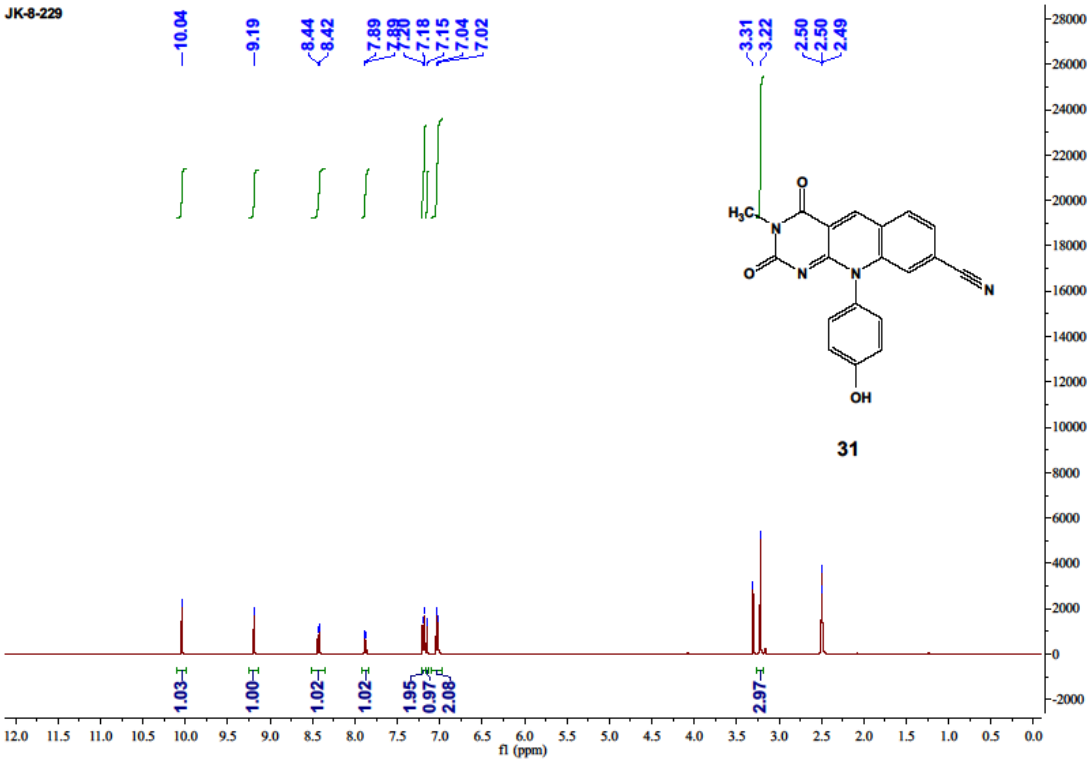
124.8
123.3
121.3
117.8
117.6
115.8
111.3
111.0
39.9
39.7
39.5
39.3
39.1
38.9
38.7
4h
f1 (ppm)


JK-8-229
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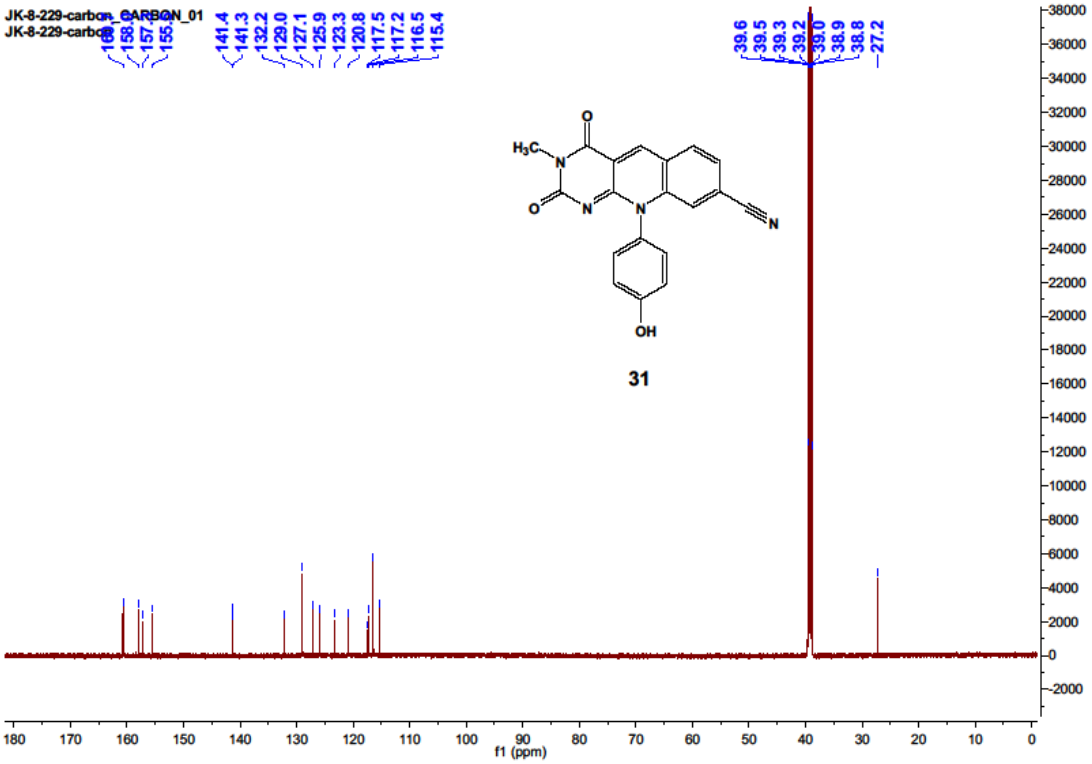
8.42
7.89
7.88
7.20
7.18
7.15
7.04
7.02
3.31
3.22
2.50
2.50
2.49
1.03
1.00
1.02
1.02
1.95
0.97
2.08
2.97
f1 (ppm)

31


JK-8-229-carbon_CARBON_01
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141.3
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120.8
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117.2
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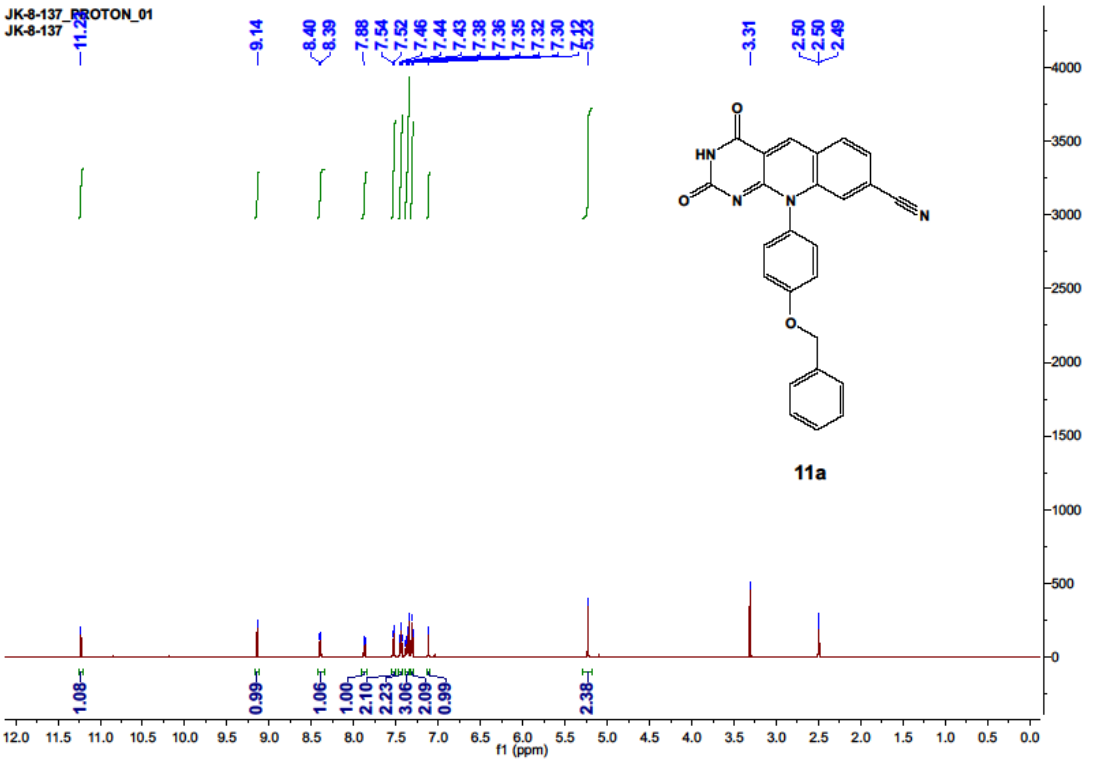
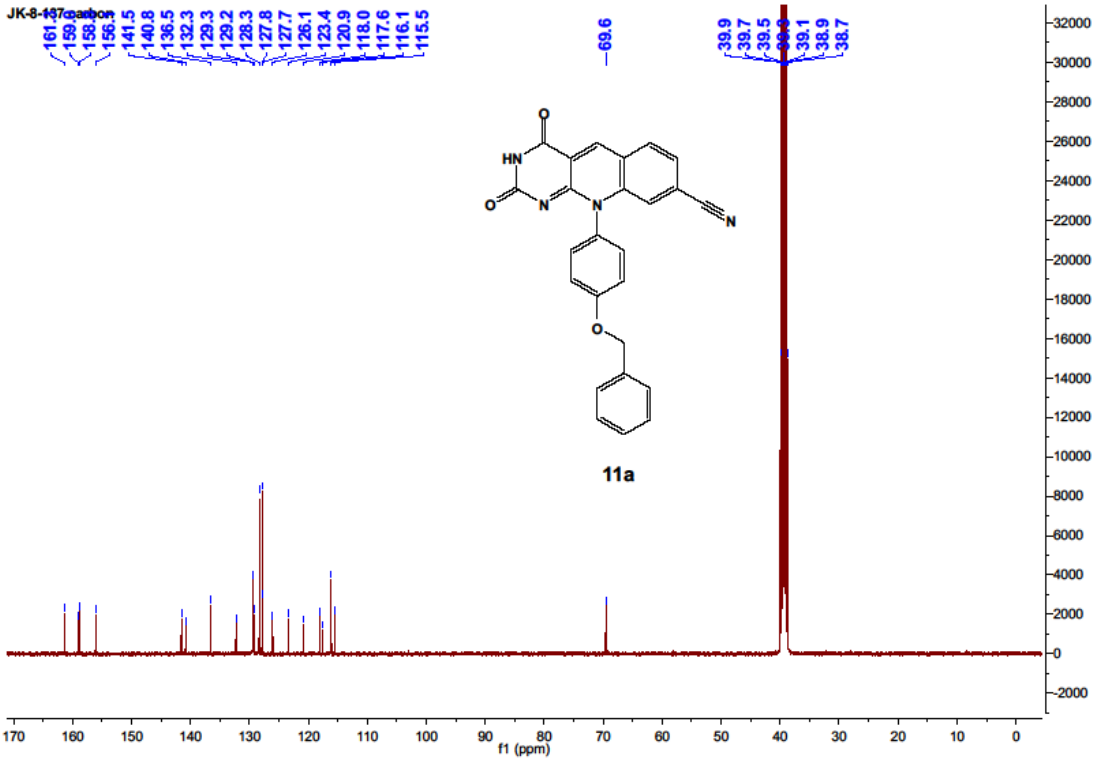
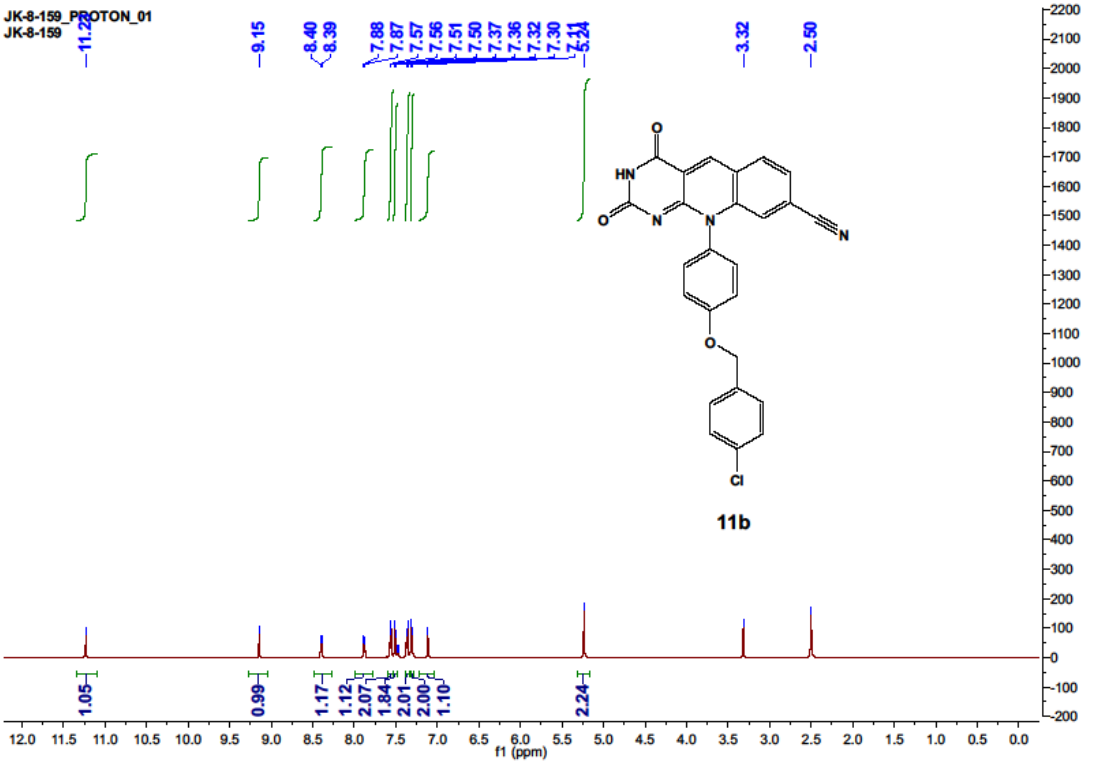
39.6
39.5
39.3
39.2
39.0
38.9
38.8
27.2
f1 (ppm)

31


JK-8-137_PROTON_01
JK-8-137
11a


JK-8-137carbon
11a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JK-8-159
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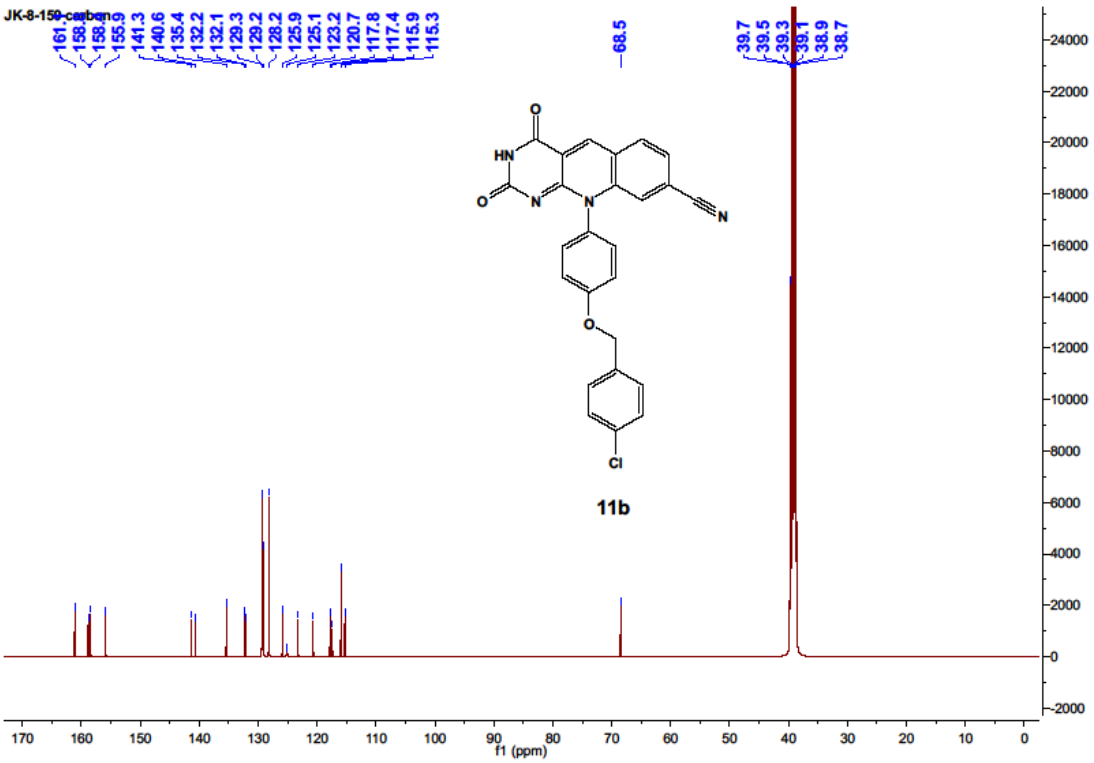
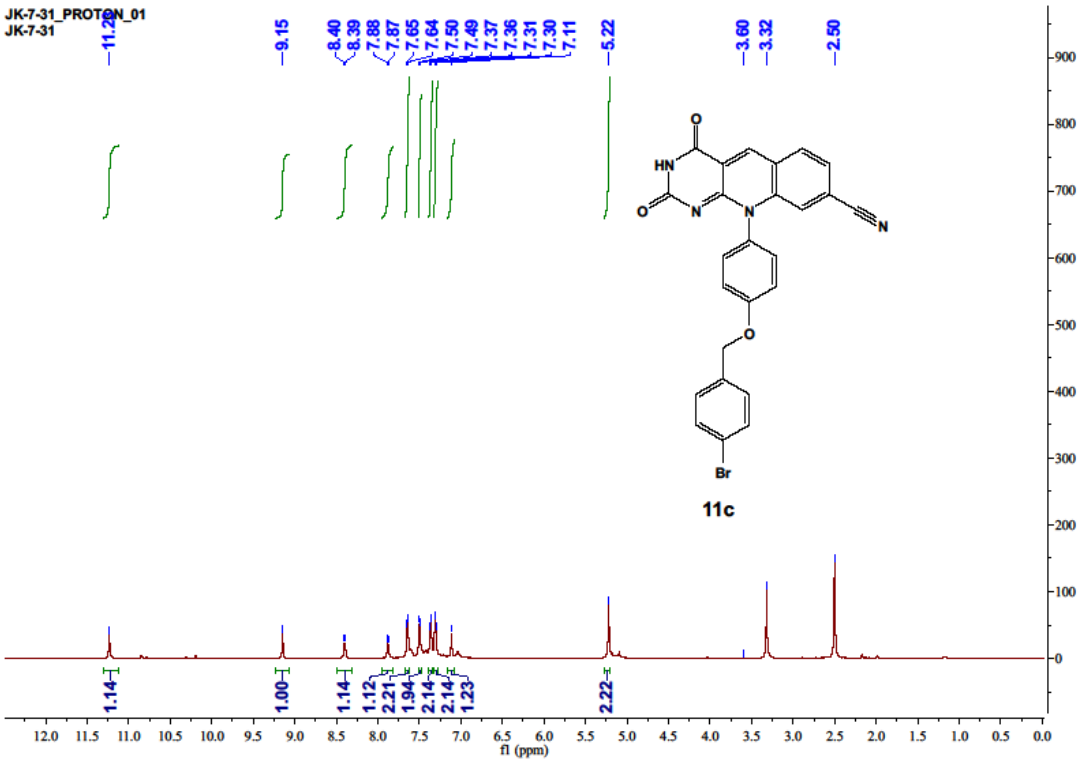
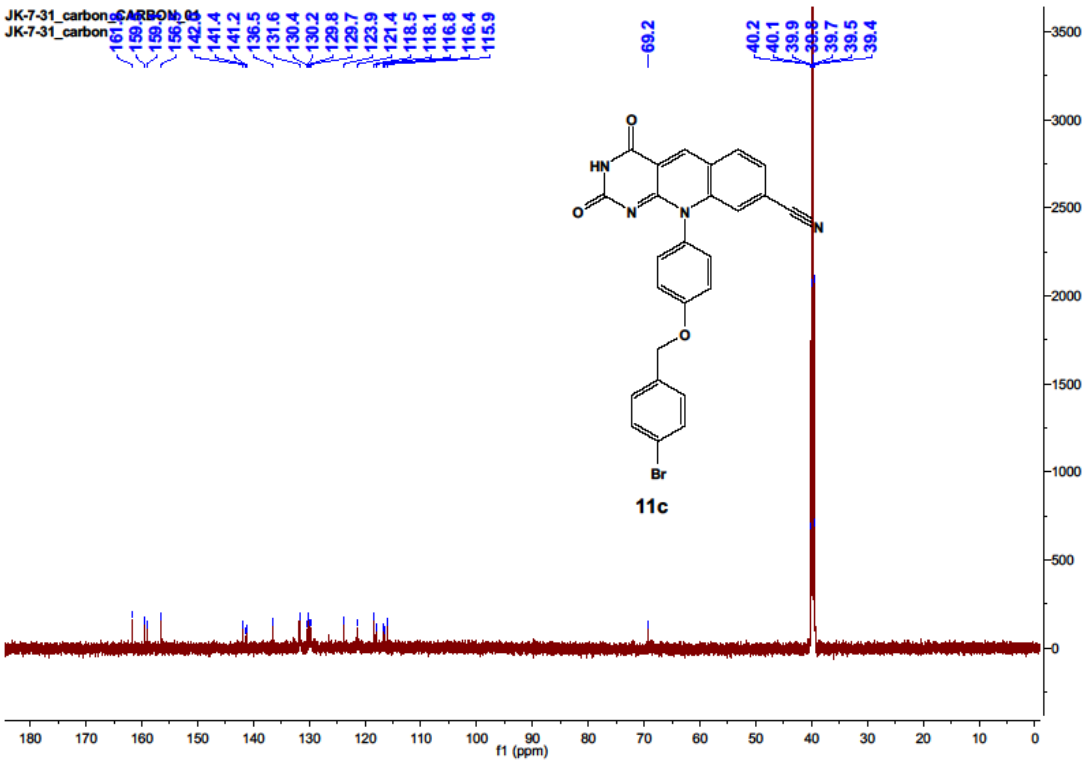
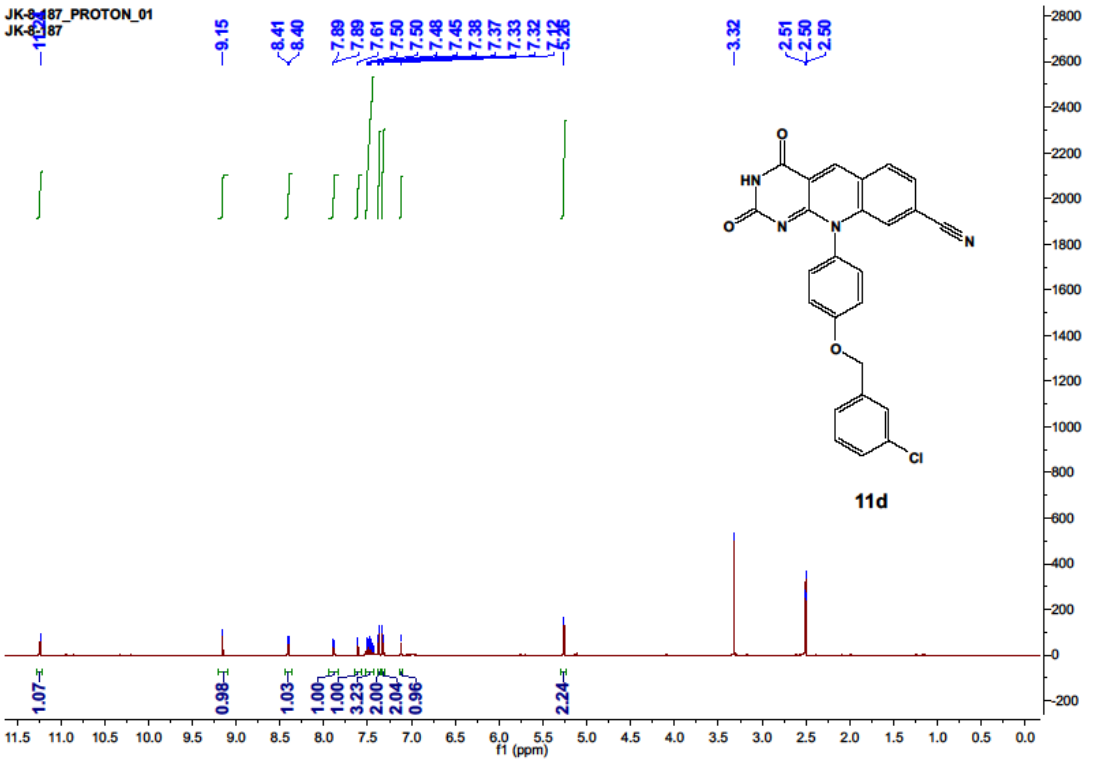
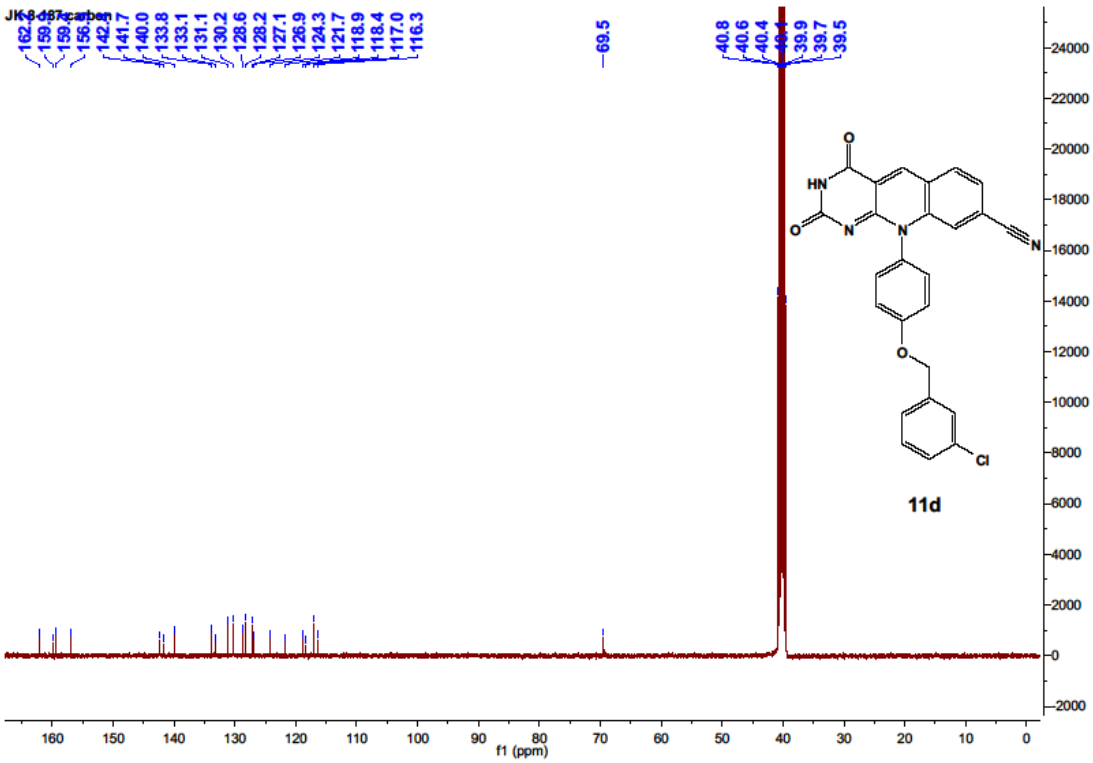
7.87
7.57
7.56
7.51
7.50
7.37
7.36
7.32
7.30
7.11
3.32
2.50
11b
1.05
0.99
1.17
1.12
2.07
1.84
2.01
2.00
1.10
2.24
f1 (ppm)

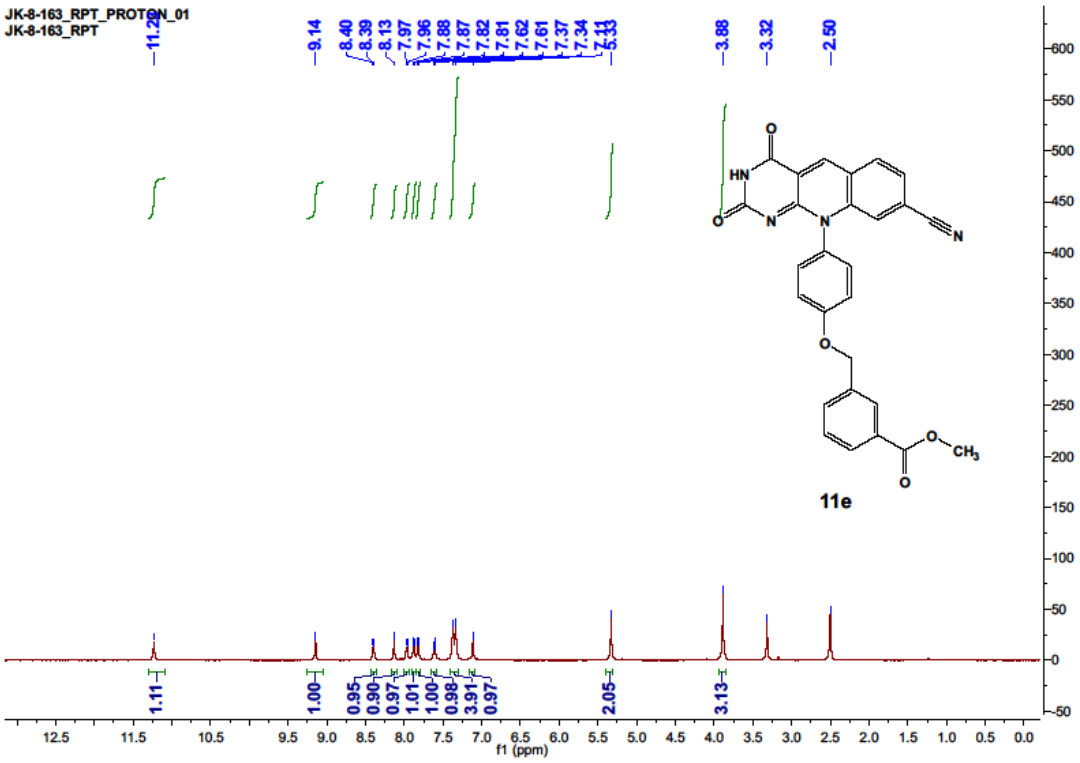

JK-8-159-carbon
161.1
158.8
158.3
155.9
141.3
140.6
135.4
132.2
132.1
129.3
129.2
128.2
125.9
125.1
123.2
120.7
117.8
117.4
115.9
115.3
68.5
39.7
39.5
39.3
39.1
38.9
38.7
11b
f1 (ppm)

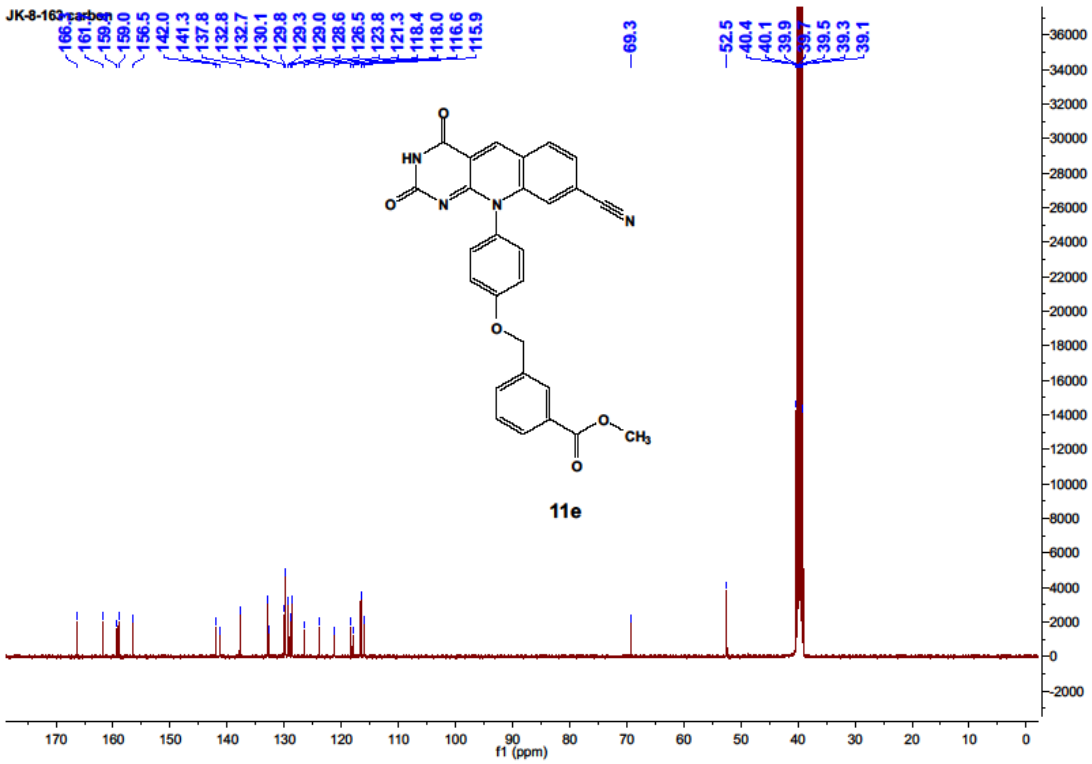

JK-7-31_PROTON_01
JK-7-31
11.22
9.15
8.40
8.39
7.88
7.87
7.65
7.64
7.50
7.49
7.37
7.36
7.31
7.30
7.11
5.22
3.60
3.32
2.50
HN
O
N
Br
11c
1.14
1.00
1.14
1.12
2.21
1.94
2.14
2.14
1.23
2.22
f1 (ppm)

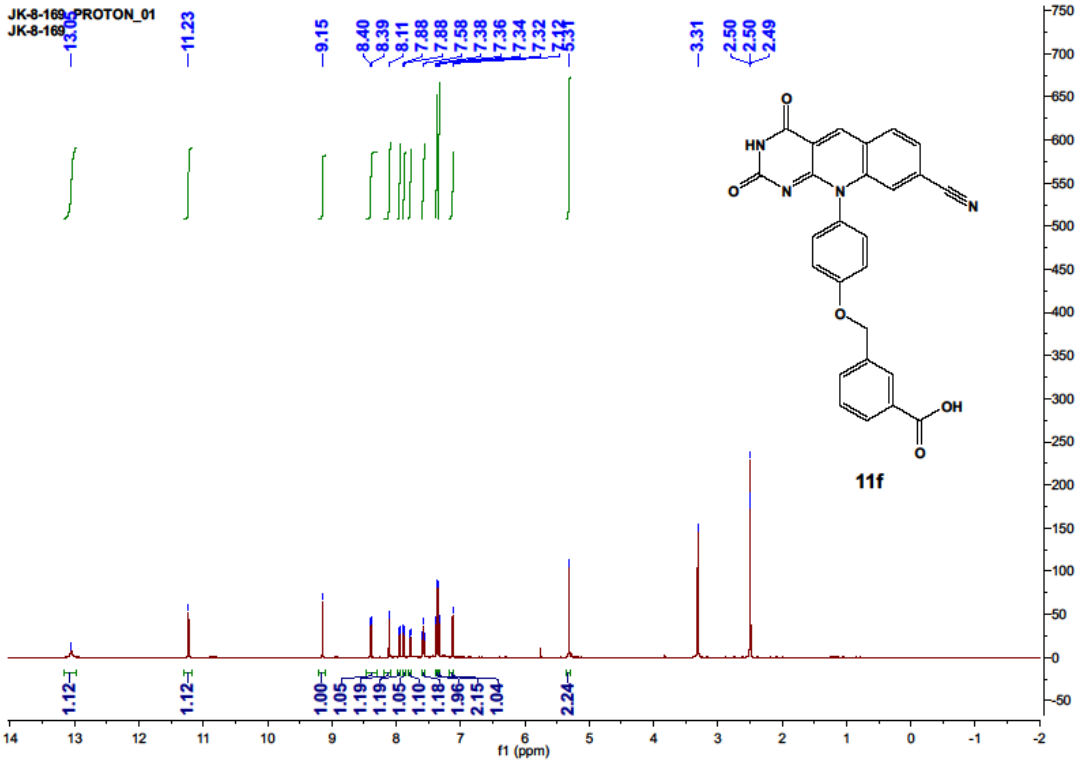

JK-7-31_carbon_CARBON_01
JK-7-31_carbon
161.8
159.7
159.2
156.6
142.4
141.4
141.2
136.5
131.6
130.4
130.2
129.8
129.7
123.9
121.4
118.5
118.1
116.8
116.4
115.9
69.2
40.2
40.1
39.9
39.8
39.7
39.5
39.4
HN
O
N
Br
11c
f1 (ppm)

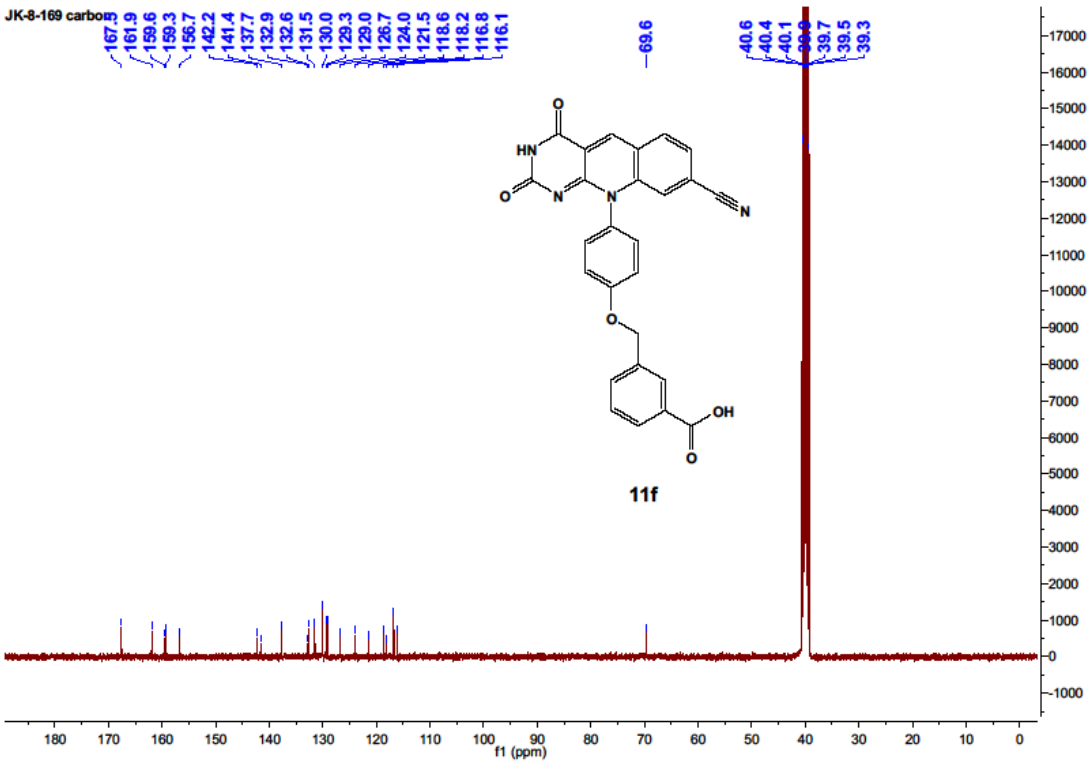

JK-8-187_PROTON_01
JK-8-187
11d
f1 (ppm)

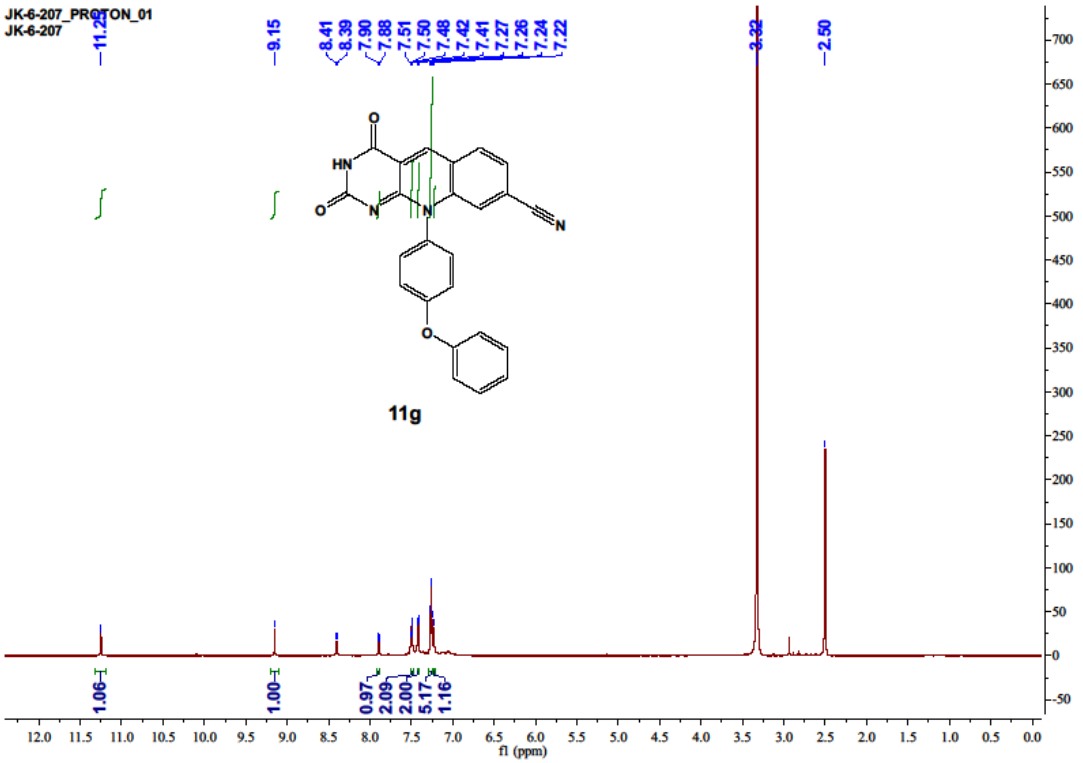

JK-8-187-carben
11d
f1 (ppm)

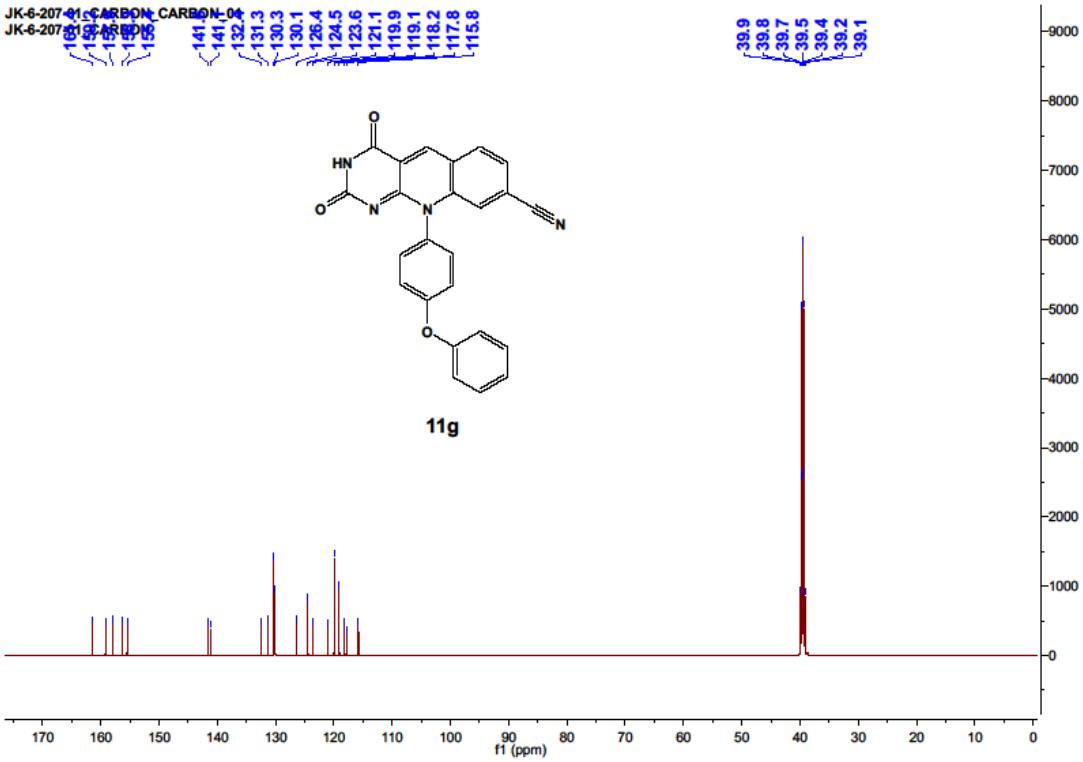

JK-8-163_RPT_PROTON_01
JK-8-163_RPT
11e
f1 (ppm)

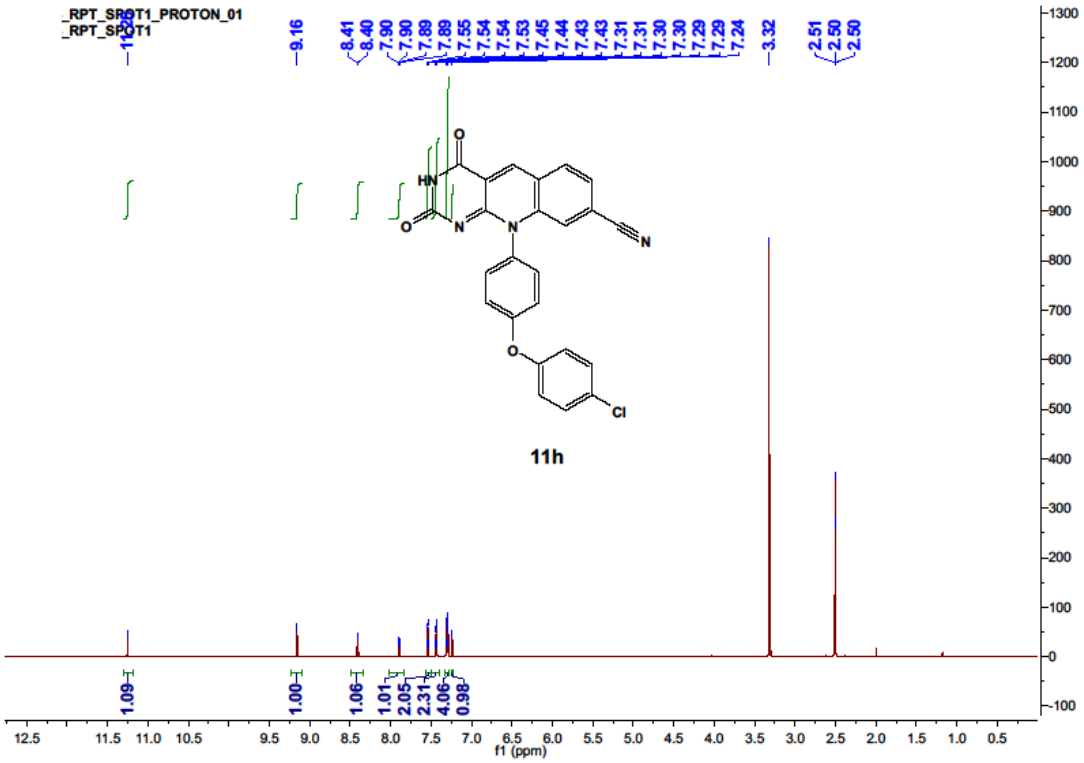

JK-8-163 carbon
11e
f1 (ppm)

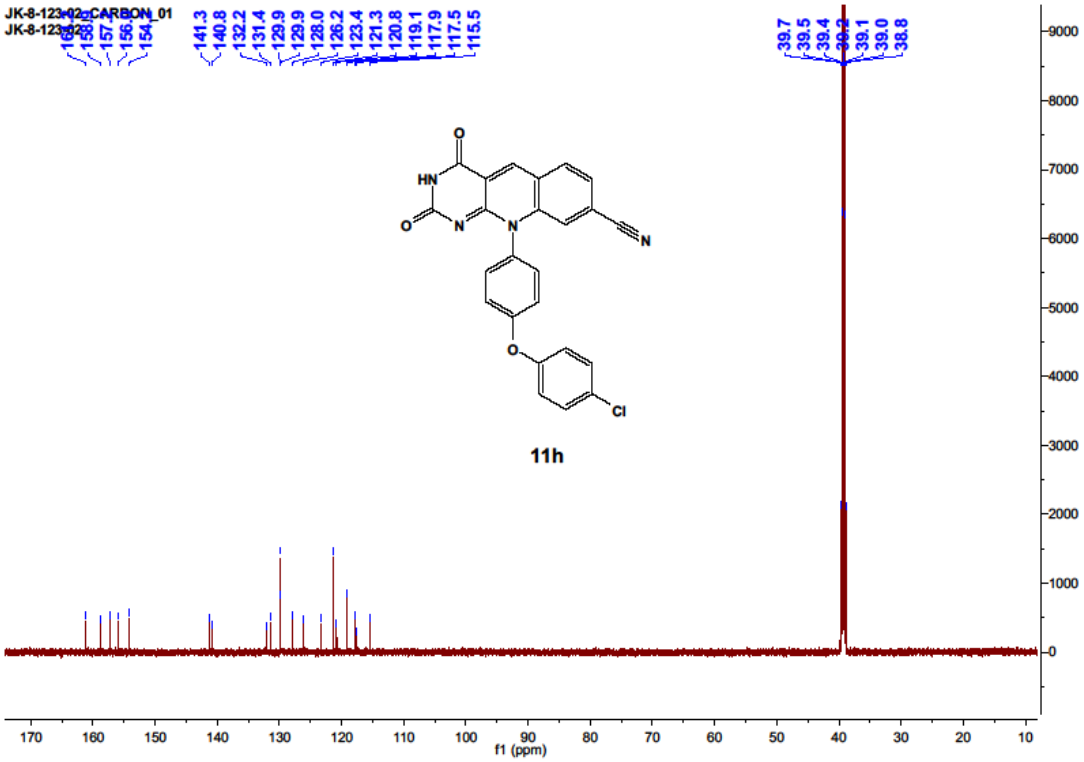

JK-8-169_PROTON_01
JK-8-169
13.04
11.23
9.15
8.40
8.39
8.11
7.88
7.88
7.58
7.38
7.36
7.34
7.32
7.12
5.31
3.31
2.50
2.50
2.49
HN
O
O
N
N
N
O
OH
O
11f
1.12
1.12
1.00
1.05
1.19
1.19
1.05
1.10
1.18
1.96
2.15
1.04
2.24
f1 (ppm)

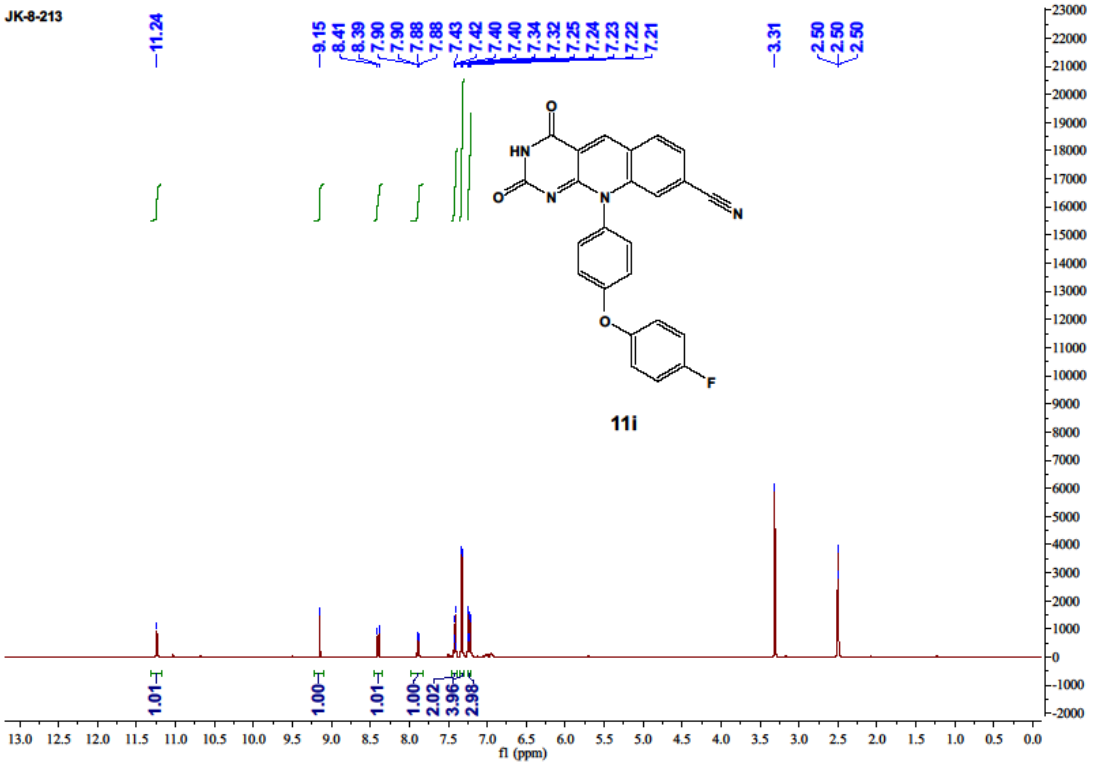

JK-8-169 carbon
167.9
161.9
159.6
159.3
156.7
142.2
141.4
137.7
132.9
132.6
131.5
130.0
129.3
129.0
126.7
124.0
121.5
118.6
118.2
116.8
116.1
69.6
40.6
40.4
40.1
39.9
39.7
39.5
39.3
HN
O
O
N
N
N
O
OH
O
11f
f1 (ppm)

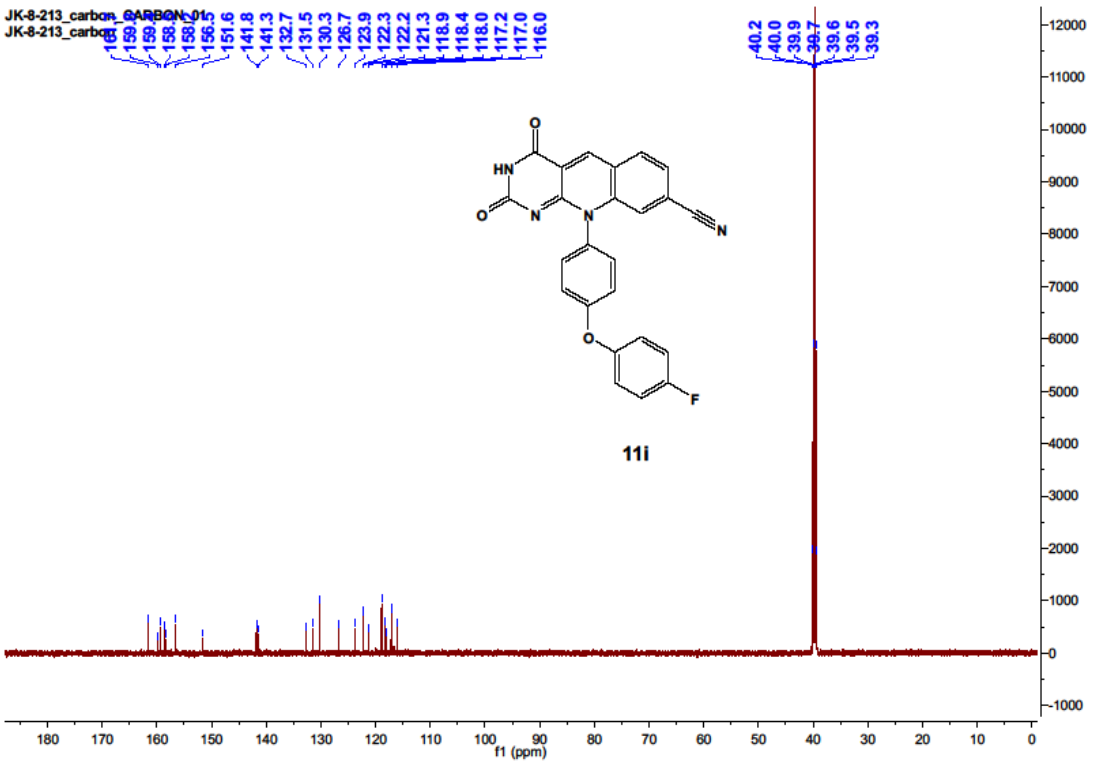

JK-6-207_PROTON_01
JK-6-207
11.22
9.15
8.41
8.39
7.90
7.88
7.51
7.50
7.48
7.42
7.41
7.27
7.26
7.24
7.22
3.32
2.50
11g
1.06
1.00
0.97
2.09
2.00
5.17
1.16
f1 (ppm)

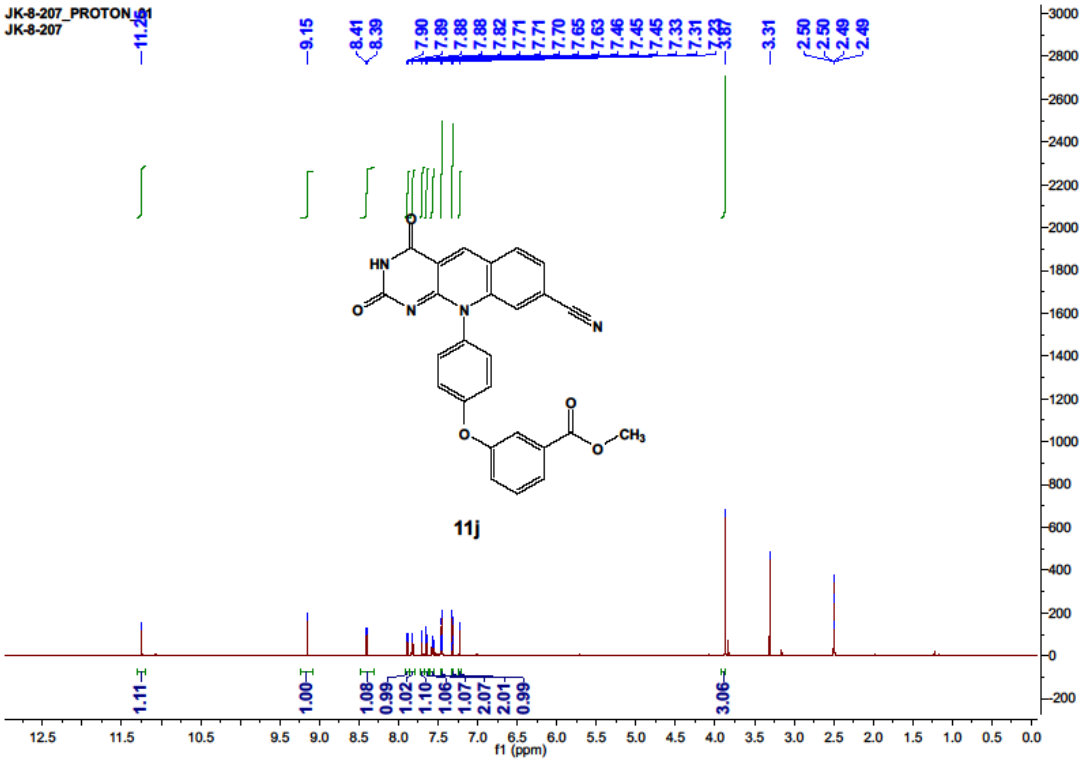

JK-6-207-01_CARBON_CARBON_04
JK-6-207-01_CARBON
141.8
141.7
132.4
131.3
130.3
130.1
126.4
124.5
123.6
121.1
119.9
119.1
118.2
117.8
115.8
39.9
39.8
39.7
39.5
39.4
39.2
39.1
11g
f1 (ppm)

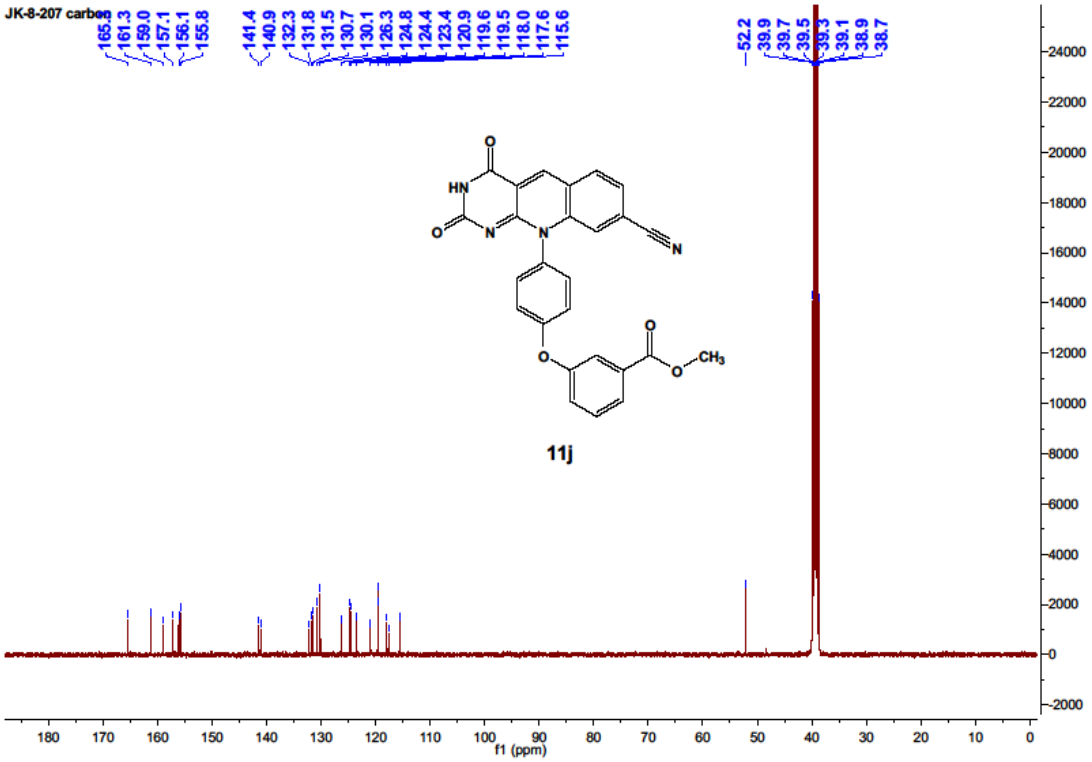

_RPT_SPOT1_PROTON_01
_RPT_SPOT1
11h
f1 (ppm)

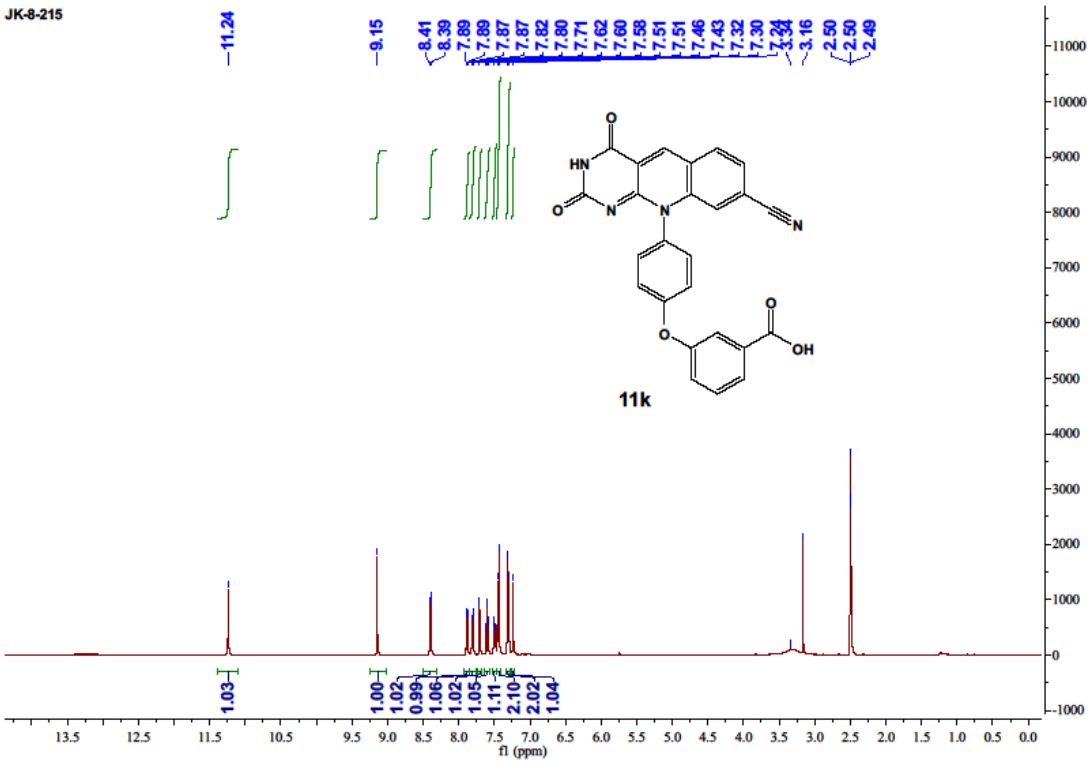

JK-8-123-h2_CARBON_01
11h
f1 (ppm)

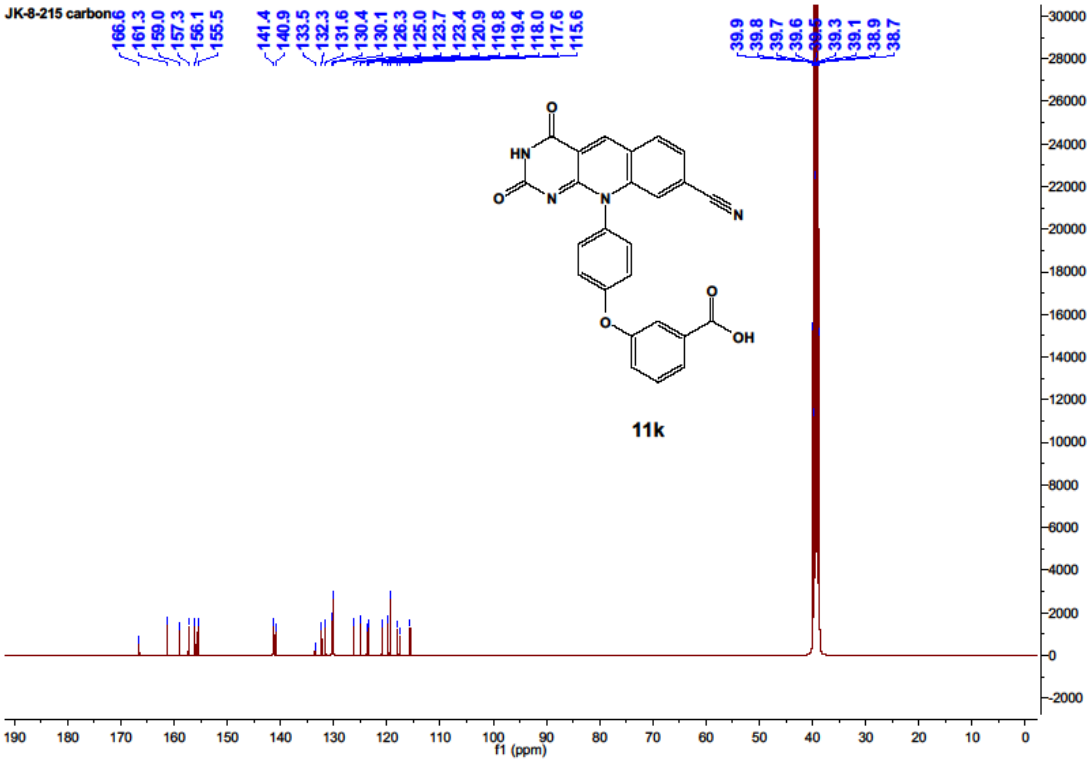

JK-8-213
11.24
9.15
8.41
8.39
7.90
7.90
7.88
7.43
7.42
7.40
7.40
7.34
7.32
7.25
7.24
7.23
7.22
7.21
3.31
2.50
2.50
2.50
HN
O
N
N
O
N
O
F
11i
1.01
1.00
1.01
1.00
2.02
3.96
2.98
f1 (ppm)

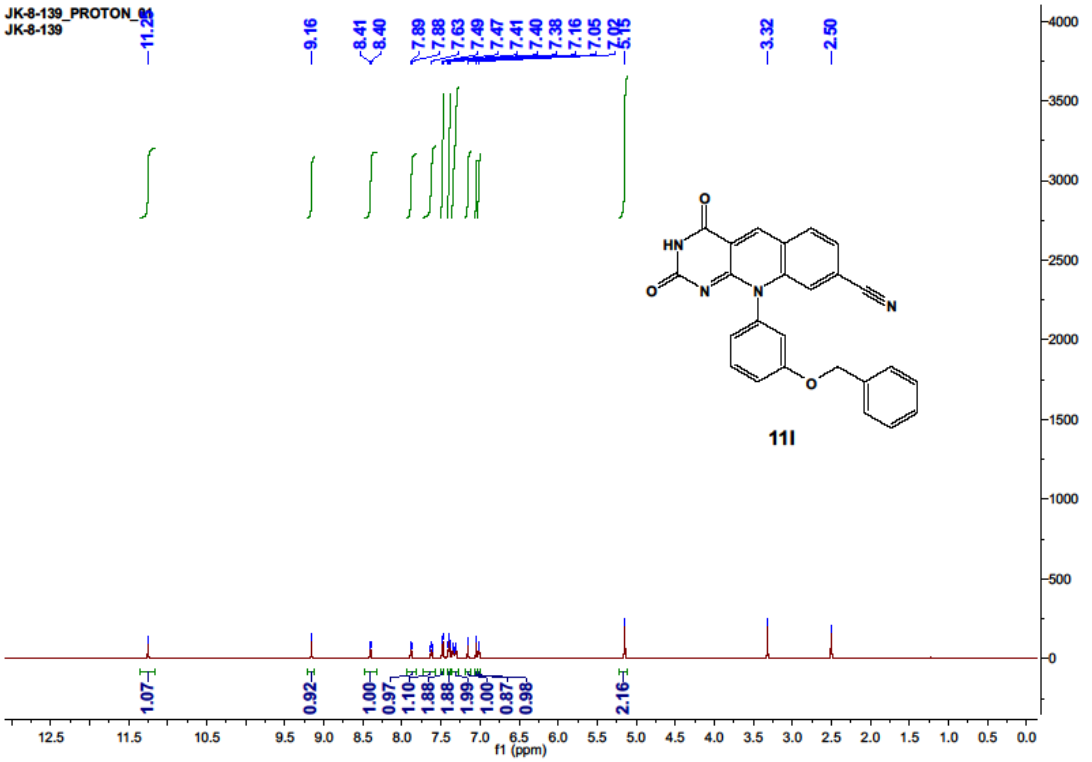

JK-8-213_carbon_CARBON_01
JK-8-213_carbon
156.5
151.6
141.8
141.3
132.7
131.5
130.3
126.7
123.9
122.3
122.2
121.3
118.9
118.4
118.0
117.2
117.0
116.0
40.2
40.0
39.9
39.7
39.6
39.5
39.3
HN
O
N
N
O
N
O
F
11i
f1 (ppm)


JK-8-207_PROTON_01
JK-8-207
11j
f1 (ppm)

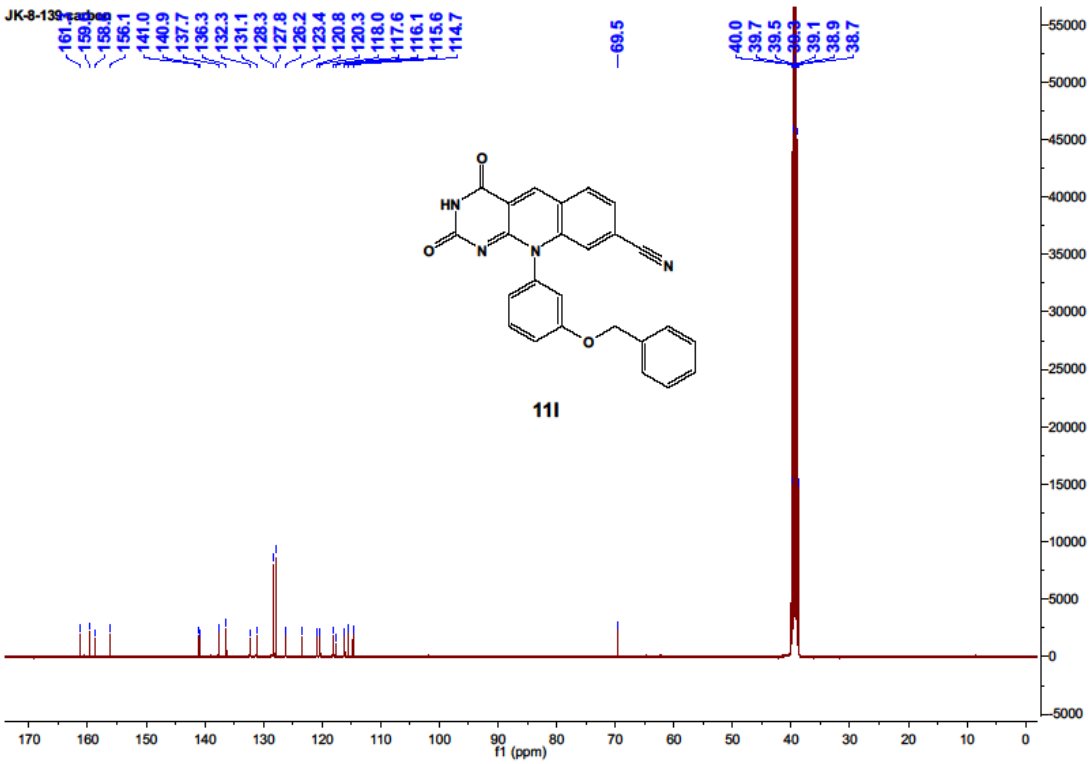

JK-8-207 carbon
11j
f1 (ppm)


JK-8-215
11.24
9.15
8.41
8.39
7.89
7.89
7.87
7.87
7.82
7.80
7.71
7.62
7.60
7.58
7.51
7.51
7.46
7.43
7.32
7.30
7.24
3.34
3.16
2.50
2.50
2.49
HN
O
N
N
O
O
OH
11k
1.03
1.00
1.02
0.99
1.06
1.02
1.05
1.11
2.10
2.02
1.04
f1 (ppm)

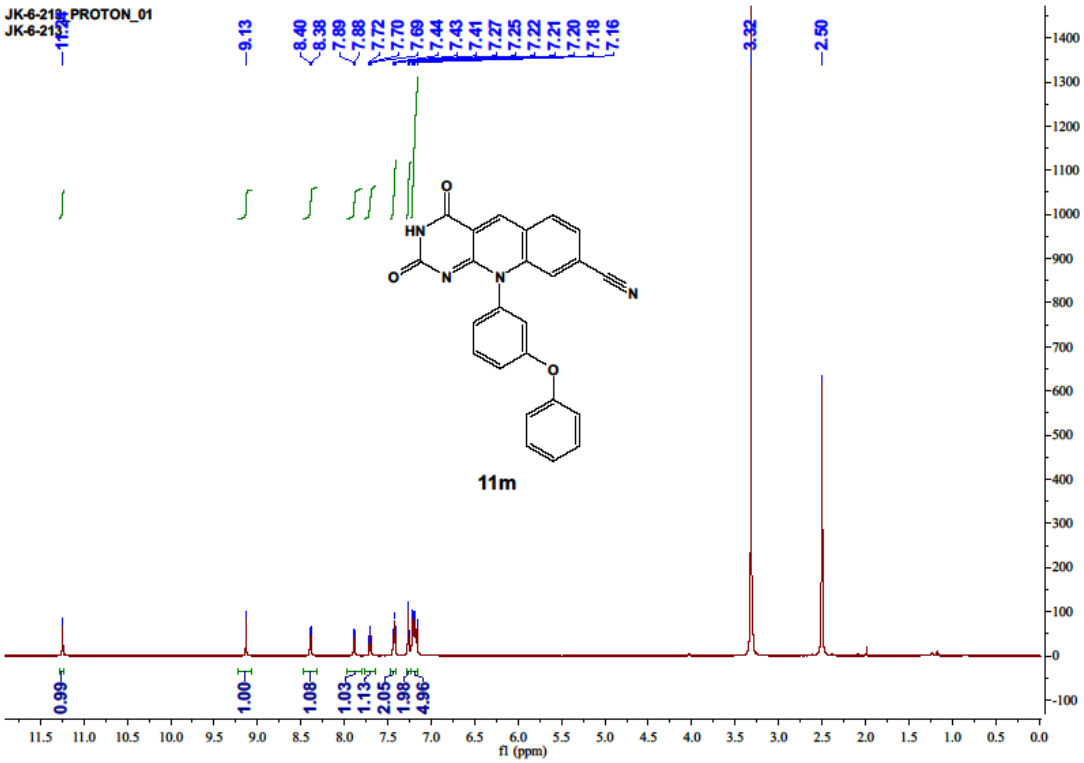

JK-8-215 carbon
166.6
161.3
159.0
157.3
156.1
155.5
141.4
140.9
133.5
132.3
131.6
130.4
130.1
126.3
125.0
123.7
123.4
120.9
119.8
119.4
118.0
117.6
115.6
39.9
39.8
39.7
39.6
39.5
39.3
39.1
38.9
38.7
HN
O
N
N
O
O
OH
11k
f1 (ppm)

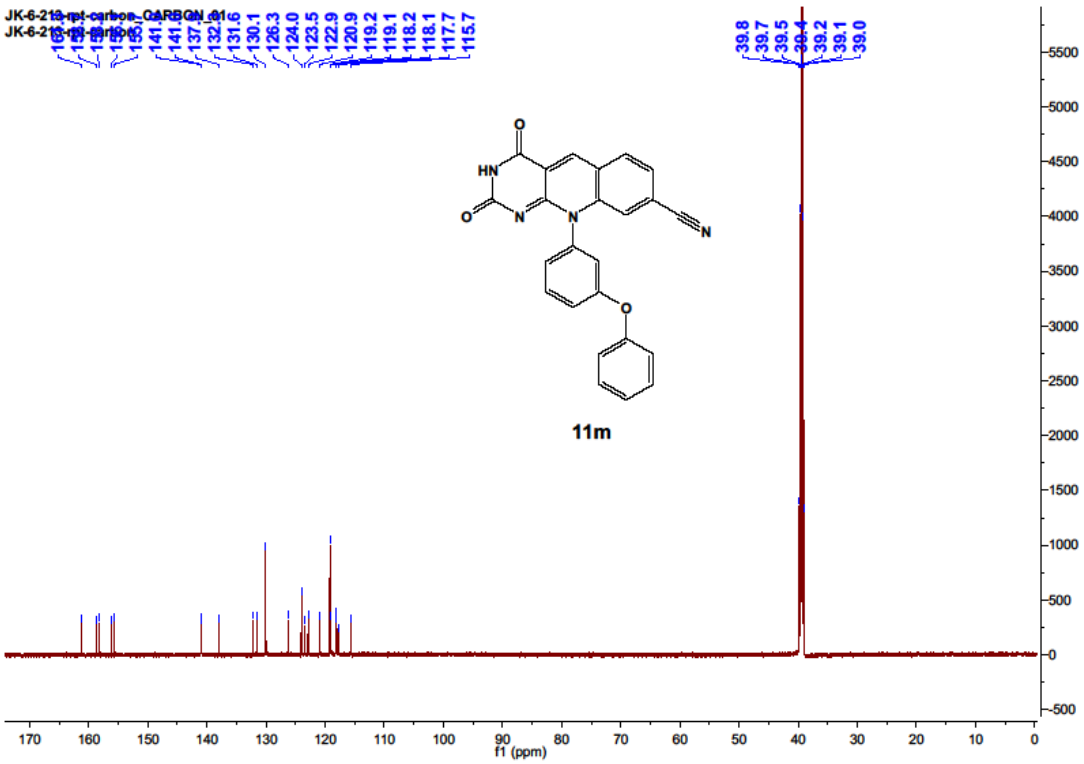

JK-8-139_PROTON_01
JK-8-139
11.24
9.16
8.41
8.40
7.89
7.88
7.63
7.49
7.47
7.41
7.40
7.38
7.16
7.05
7.02
5.15
3.32
2.50
1.07
0.92
1.00
0.97
1.10
1.88
1.88
1.99
1.00
0.87
0.98
2.16
f1 (ppm)

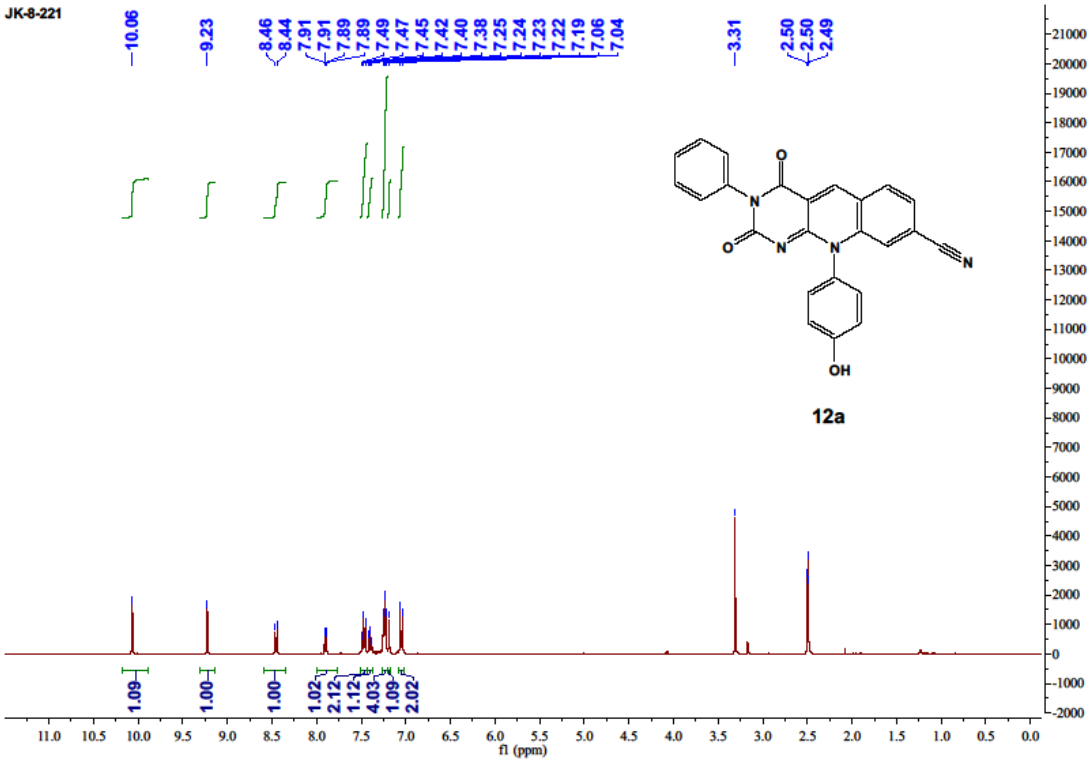
11l


JK-8-139-carbon
161.4
159.8
158.8
156.1
141.0
140.9
137.7
136.3
132.3
131.1
128.3
127.8
126.2
123.4
120.8
120.3
118.0
117.6
116.1
115.6
114.7
69.5
40.0
39.7
39.5
39.3
39.1
38.9
38.7
f1 (ppm)

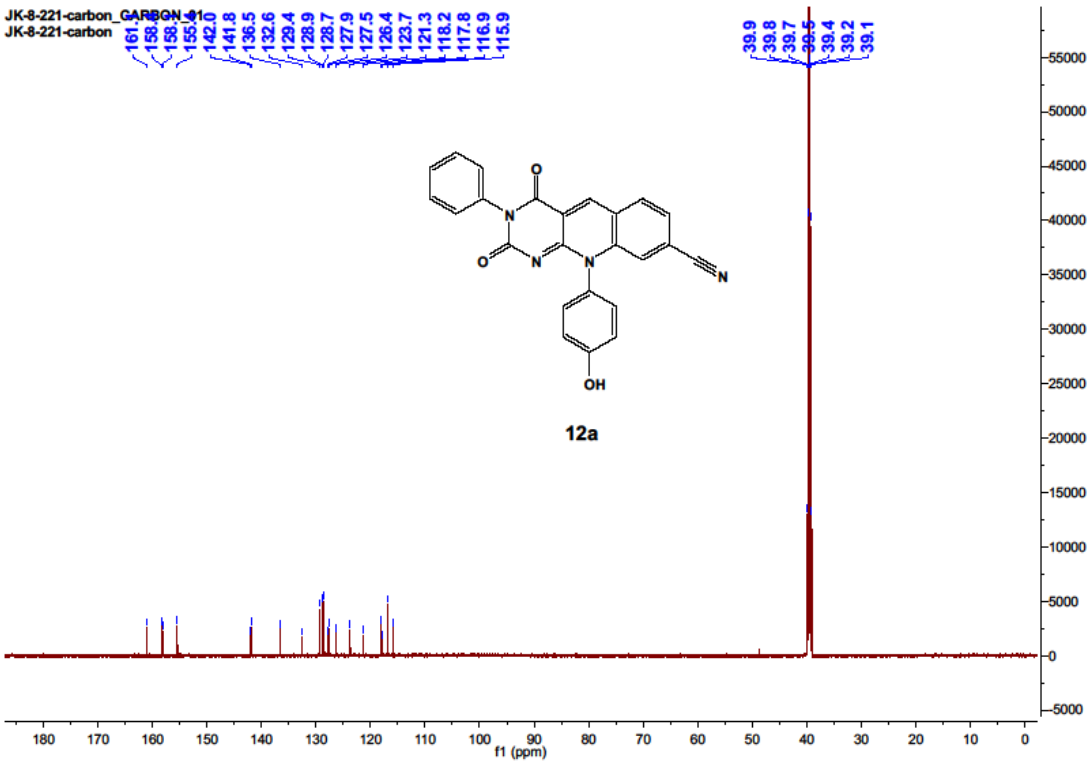
11l


JK-6-213-PROTON_01
11.54
9.13
8.40
8.38
7.89
7.88
7.72
7.70
7.69
7.44
7.43
7.41
7.27
7.25
7.22
7.21
7.20
7.18
7.16
3.32
2.50
11m
0.99
1.00
1.08
1.03
1.13
2.05
1.98
4.96
f1 (ppm)

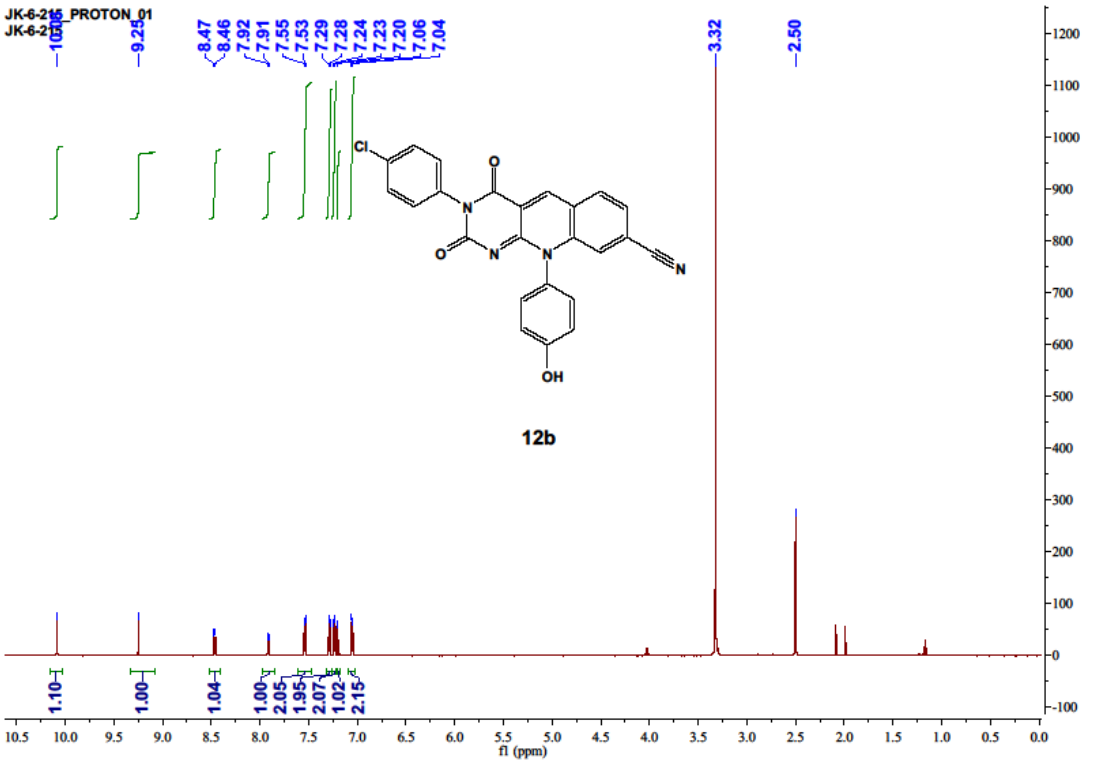

JK-6-213-pt-carbon_CARBON_01
39.8
39.7
39.5
39.4
39.2
39.1
39.0
11m
f1 (ppm)

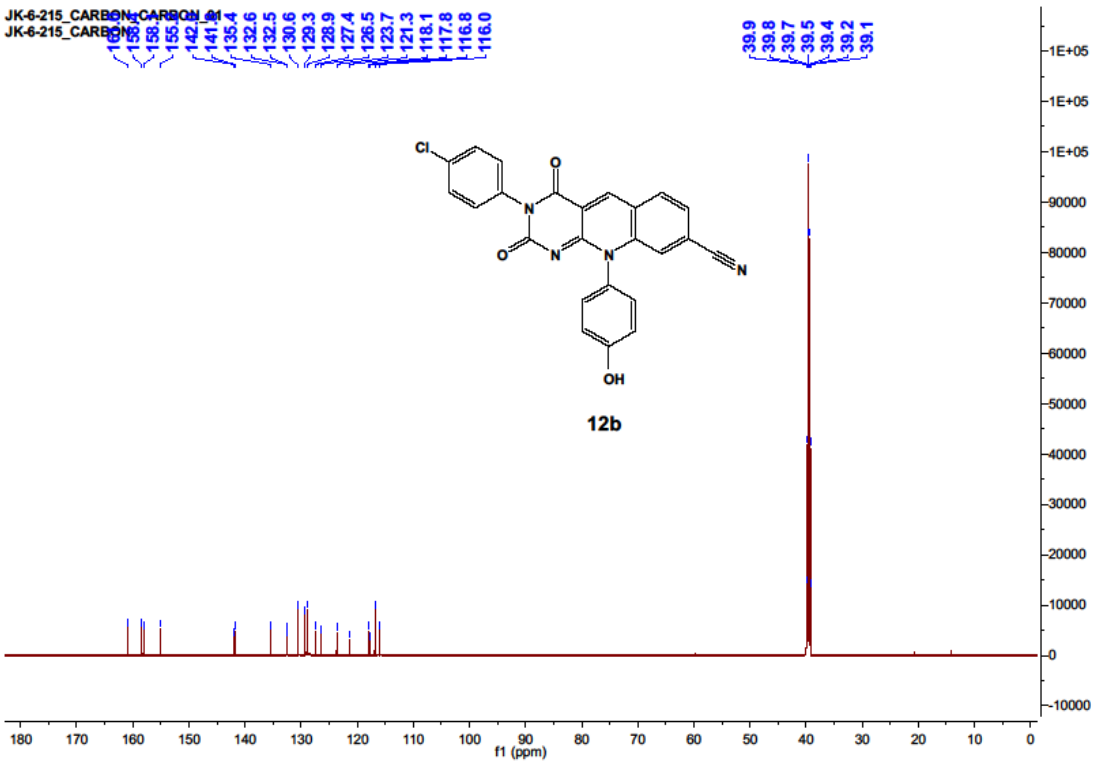

JK-8-221
10.06
9.23
8.46
8.44
7.91
7.91
7.89
7.89
7.49
7.47
7.45
7.42
7.40
7.38
7.25
7.24
7.23
7.22
7.19
7.06
7.04
3.31
2.50
2.50
2.49
1.09
1.00
1.00
1.02
2.12
1.12
4.03
1.09
2.02
f1 (ppm)

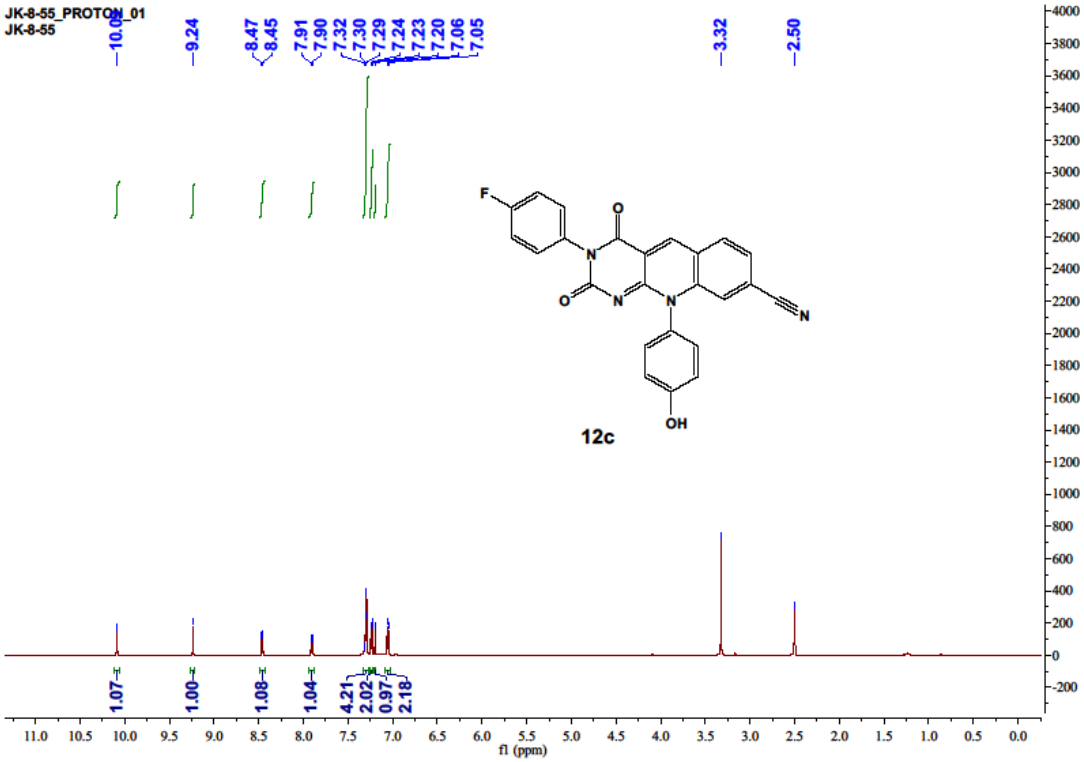
12a

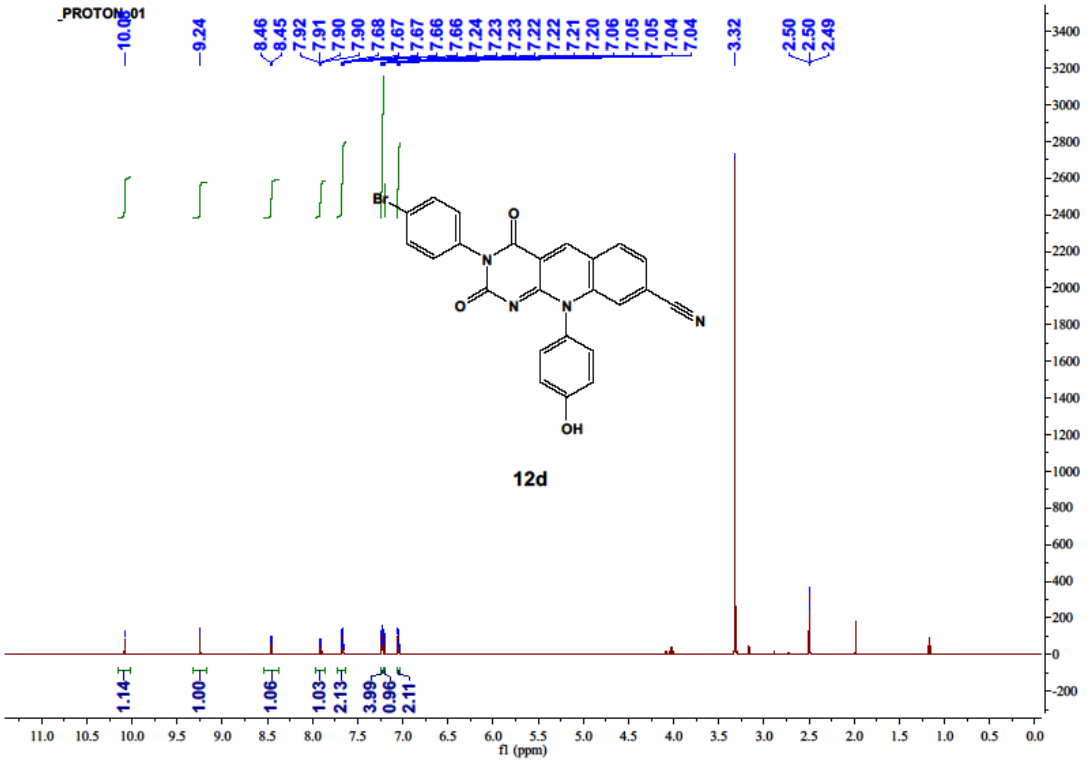

JK-8-221-carbon_CARBON_01
JK-8-221-carbon
161.3
158.8
158.2
155.4
142.0
141.8
136.5
132.6
129.4
128.9
128.7
127.9
127.5
126.4
123.7
121.3
118.2
117.8
116.9
115.9
39.9
39.8
39.7
39.5
39.4
39.2
39.1
f1 (ppm)

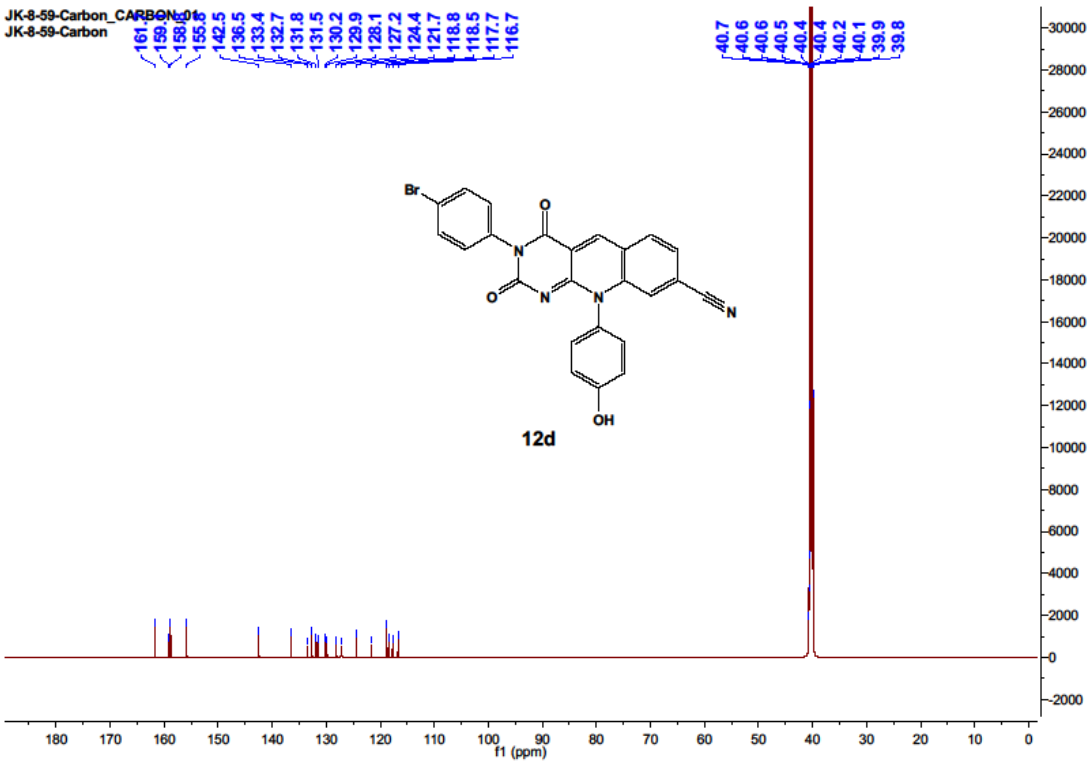
12a

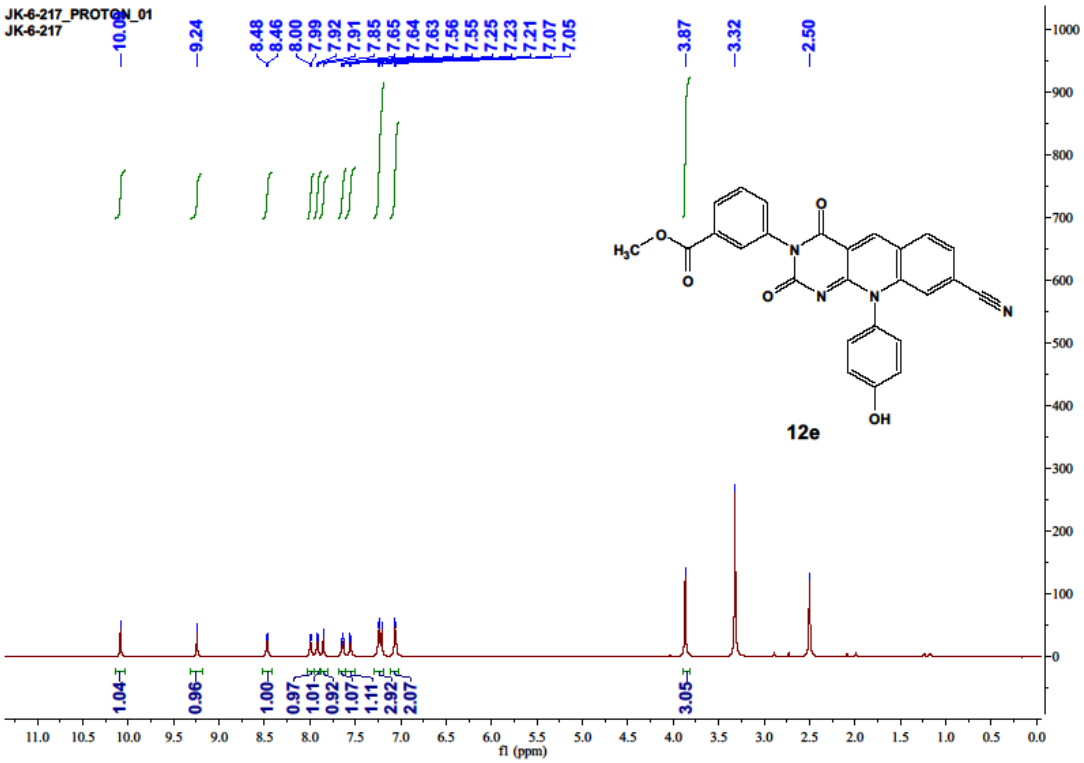

JK-6-215_PROTON_01
10.45
9.25
8.47
8.46
7.92
7.91
7.55
7.53
7.29
7.28
7.24
7.23
7.20
7.06
7.04
3.32
2.50
Cl
O
N
N
O
N
N
OH
12b
1.10
1.00
1.04
1.00
2.05
1.95
2.07
1.02
2.15
f1 (ppm)

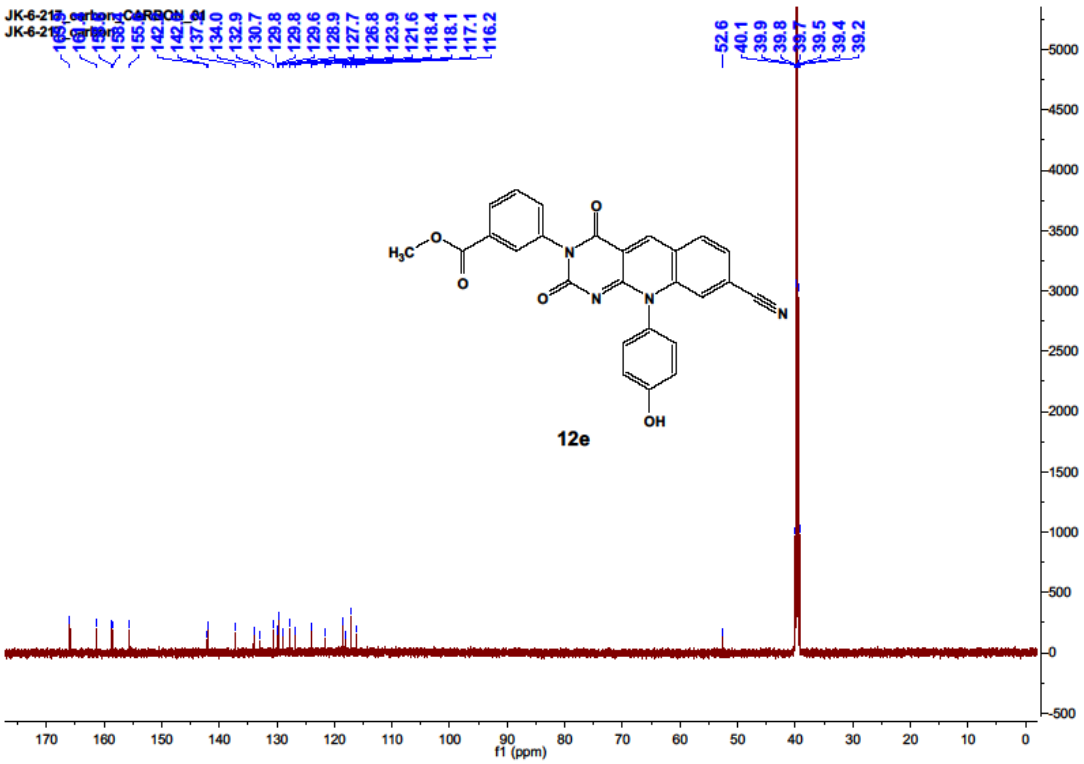

JK-6-215_CARBON_CARBON_01
JK-6-215_CARBON
158.4
155.2
142.1
141.4
135.4
132.6
132.5
130.6
129.3
128.9
127.4
126.5
123.7
121.3
118.1
117.8
116.8
116.0
39.9
39.8
39.7
39.5
39.4
39.2
39.1
Cl
O
N
N
O
N
N
OH
12b
f1 (ppm)

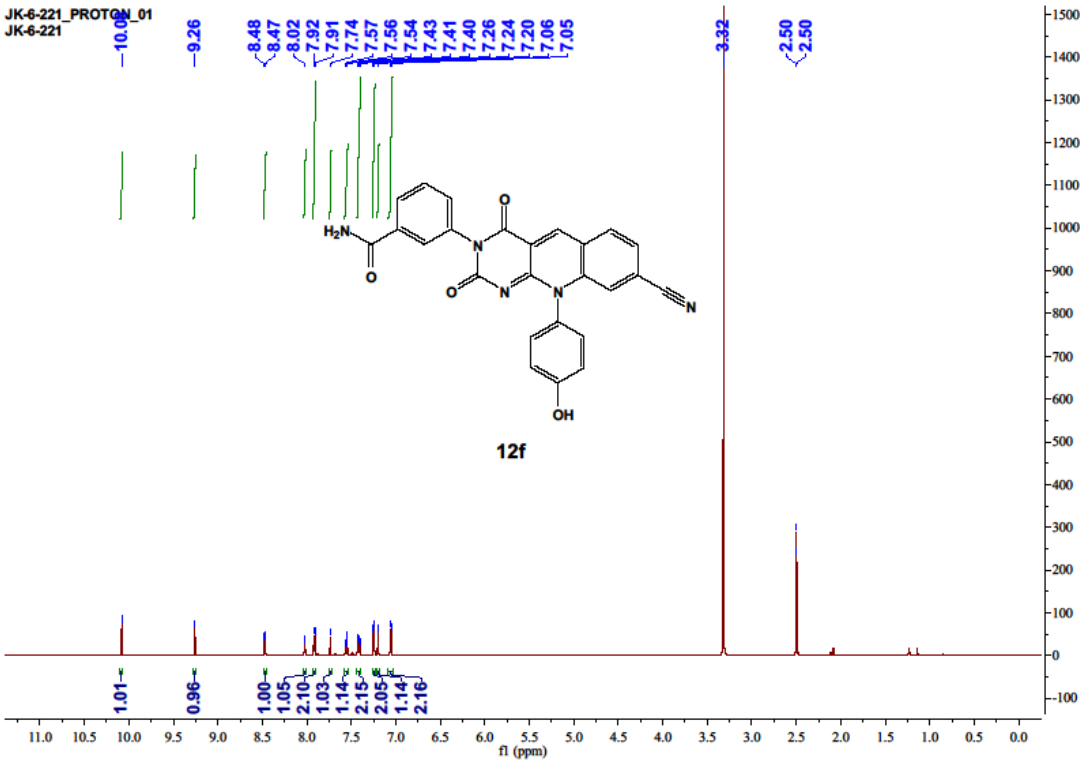

JK-8-55_PROTON_01
JK-8-55
10.07
9.24
8.47
8.45
7.91
7.90
7.32
7.30
7.29
7.24
7.23
7.20
7.06
7.05
3.32
2.50
F
O
N
O
N
N
N
OH
12c
1.07
1.00
1.08
1.04
4.21
2.02
0.97
2.18
f1 (ppm)


_PROTON_01
10.06
9.24
8.46
8.45
7.92
7.91
7.90
7.90
7.68
7.67
7.67
7.66
7.66
7.24
7.23
7.23
7.22
7.22
7.21
7.20
7.06
7.05
7.05
7.04
7.04
3.32
2.50
2.50
2.49
Br
O
N
O
N
N
N
OH
12d
1.14
1.00
1.06
1.03
2.13
3.99
0.96
2.11
f1 (ppm)

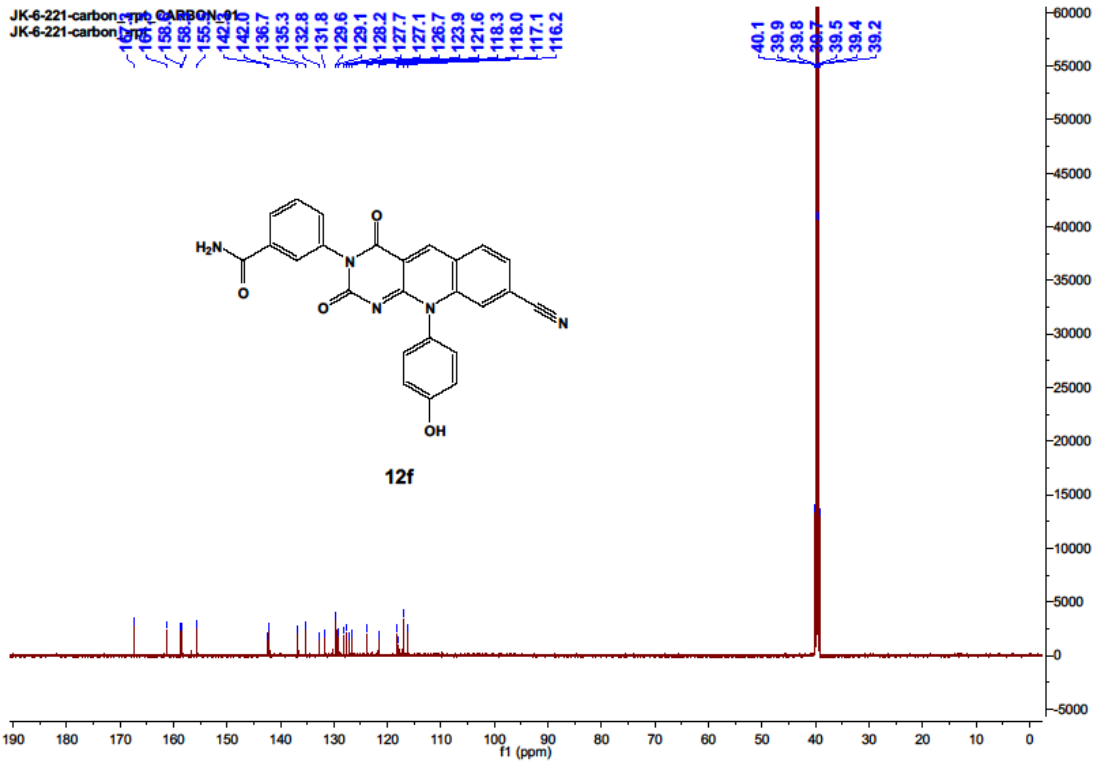

JK-8-59-Carbon_CARBON_01
JK-8-59-Carbon
161.2
159.4
158.6
155.8
142.5
136.5
133.4
132.7
131.8
131.5
130.2
129.9
128.1
127.2
124.4
121.7
118.8
118.5
117.7
116.7
40.7
40.6
40.6
40.5
40.4
40.4
40.2
40.1
39.9
39.8
Br
O
N
O
N
N
N
OH
12d
f1 (ppm)


JK-6-217_PROTON_01
JK-6-217
10.04
9.24
8.48
8.46
8.00
7.99
7.92
7.91
7.85
7.65
7.64
7.63
7.56
7.55
7.25
7.23
7.21
7.07
7.05
3.87
3.32
2.50
12e
1.04
0.96
1.00
0.97
1.01
0.92
1.07
1.11
2.92
2.07
3.05
f1 (ppm)

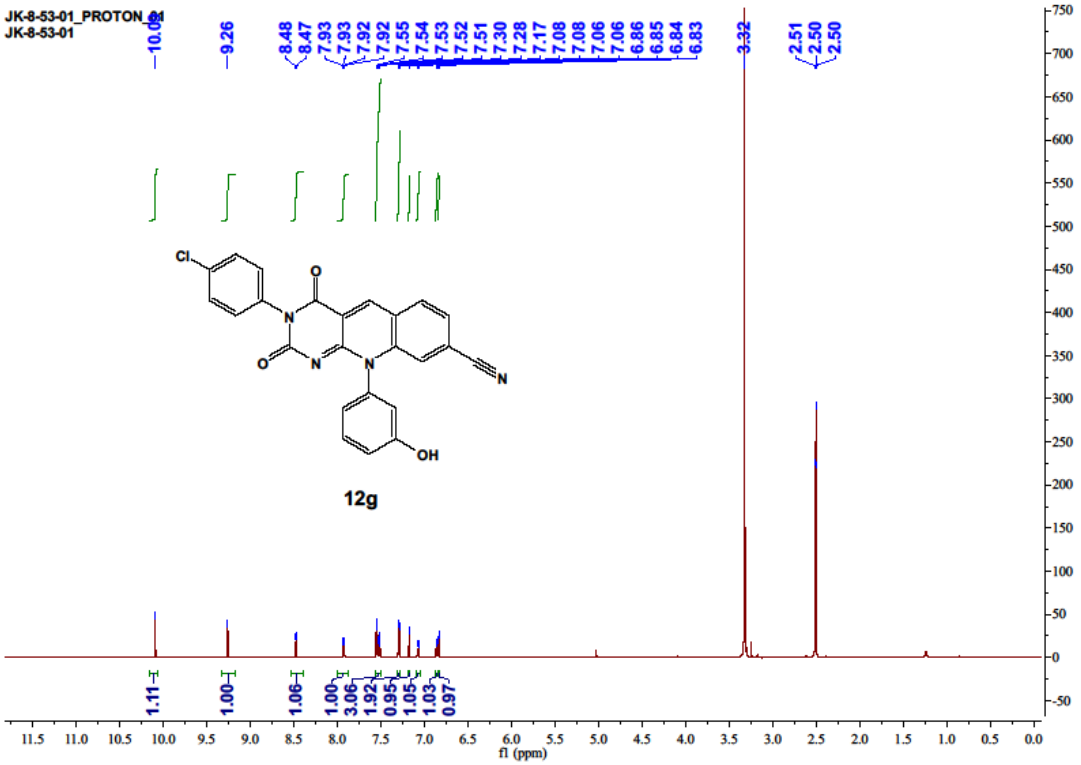

JK-6-217_carbon_CARBON_01
JK-6-217
52.6
40.1
39.9
39.8
39.7
39.5
39.4
39.2
12e
f1 (ppm)

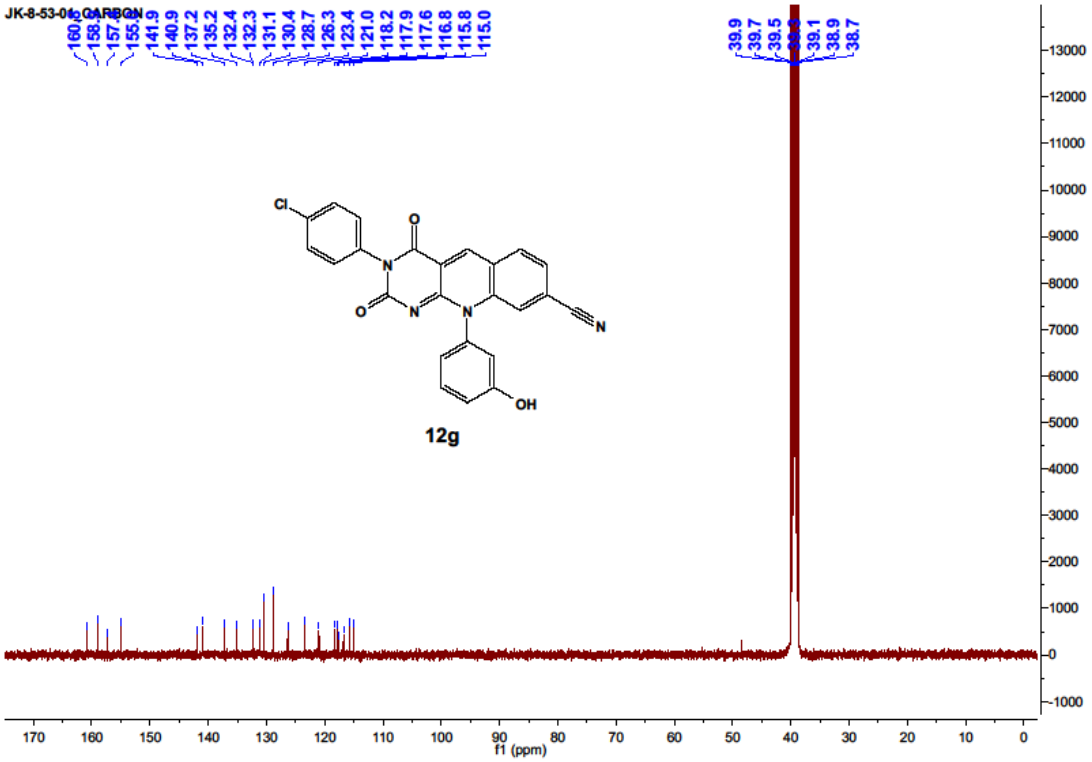

JK-6-221_PROTON_01
JK-6-221
10.08
9.26
8.48
8.47
8.02
7.92
7.91
7.74
7.57
7.56
7.54
7.43
7.41
7.40
7.26
7.24
7.20
7.06
7.05
3.32
2.50
2.50
1.01
0.96
1.00
1.05
2.10
1.03
1.14
2.15
2.05
1.14
2.16
f1 (ppm)

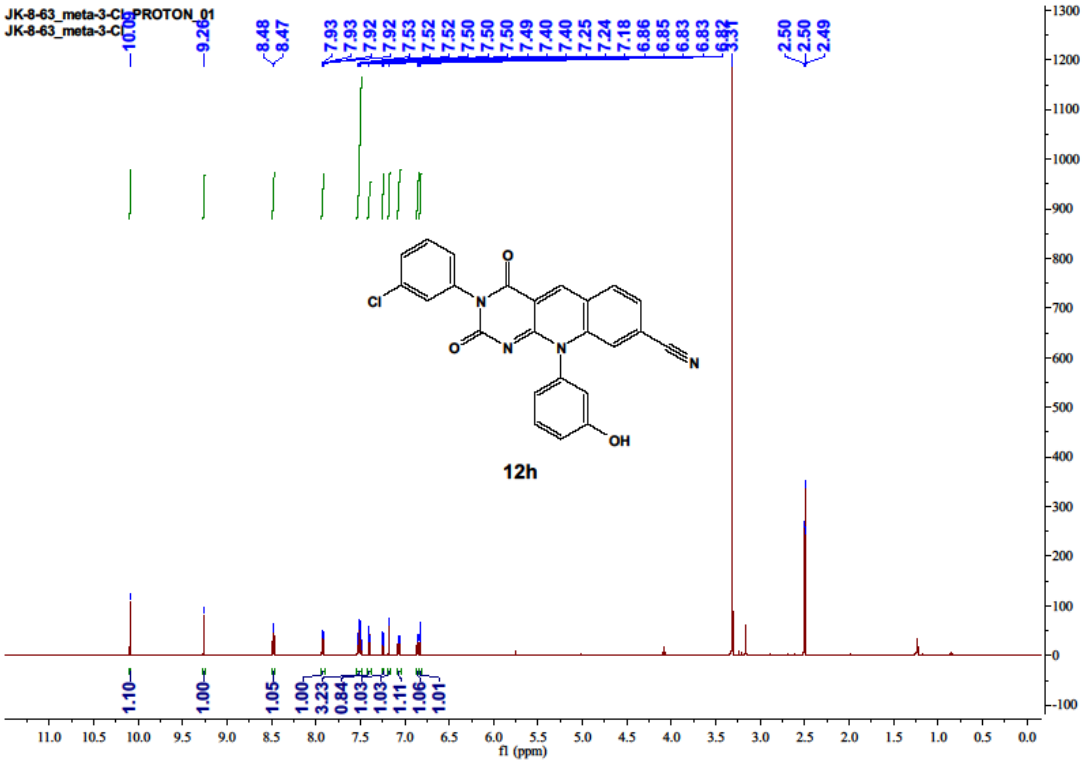
12f


JK-6-221-carbon
CARBON_01
40.1
39.9
39.8
39.5
39.4
39.2
f1 (ppm)

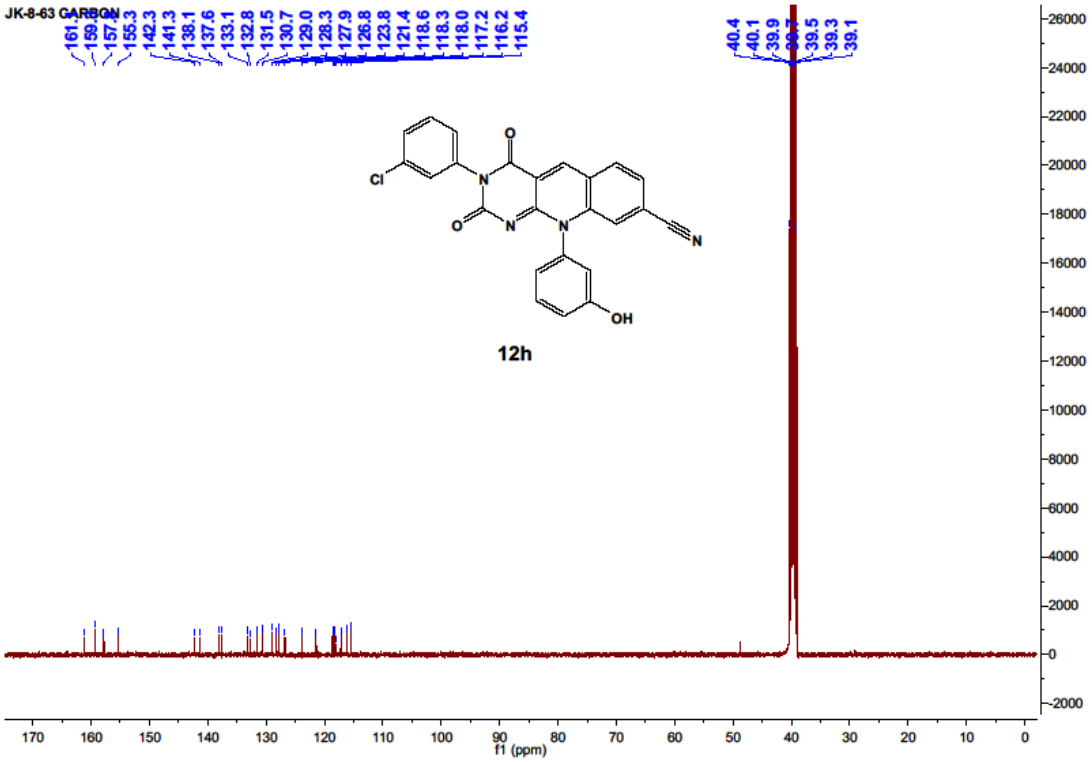
12f


JK-8-53-01_PROTON_01
JK-8-53-01
12g
f1 (ppm)

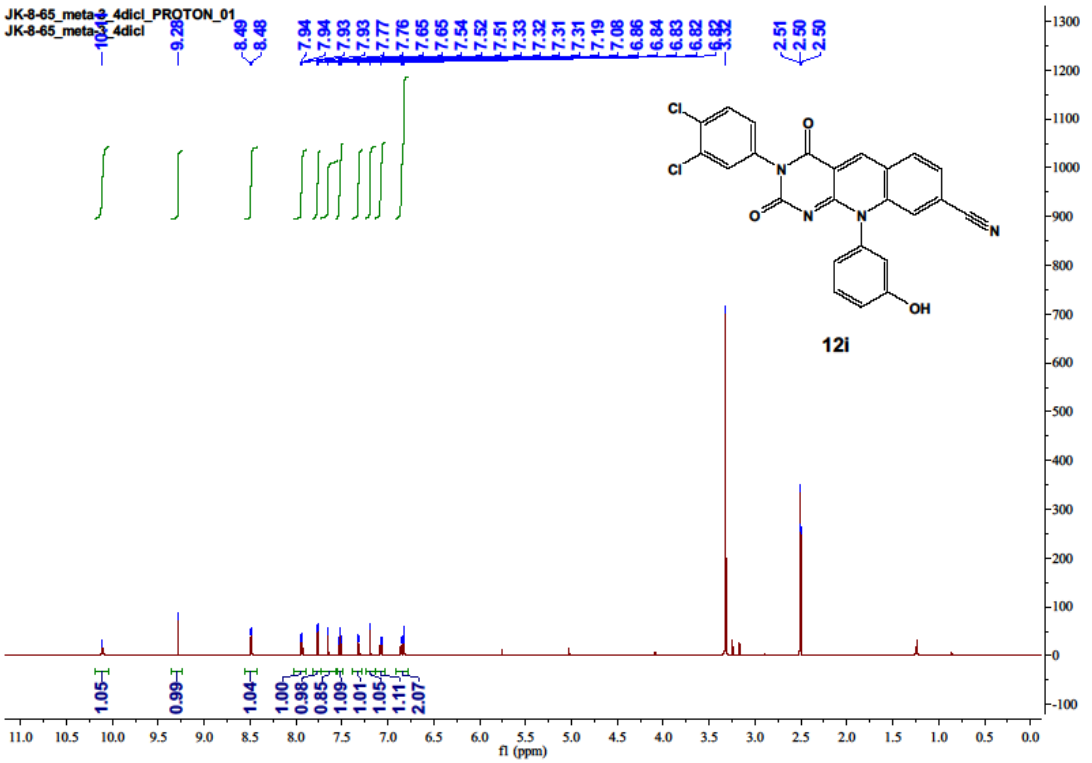

JK-8-53-01_CARBON
12g
f1 (ppm)

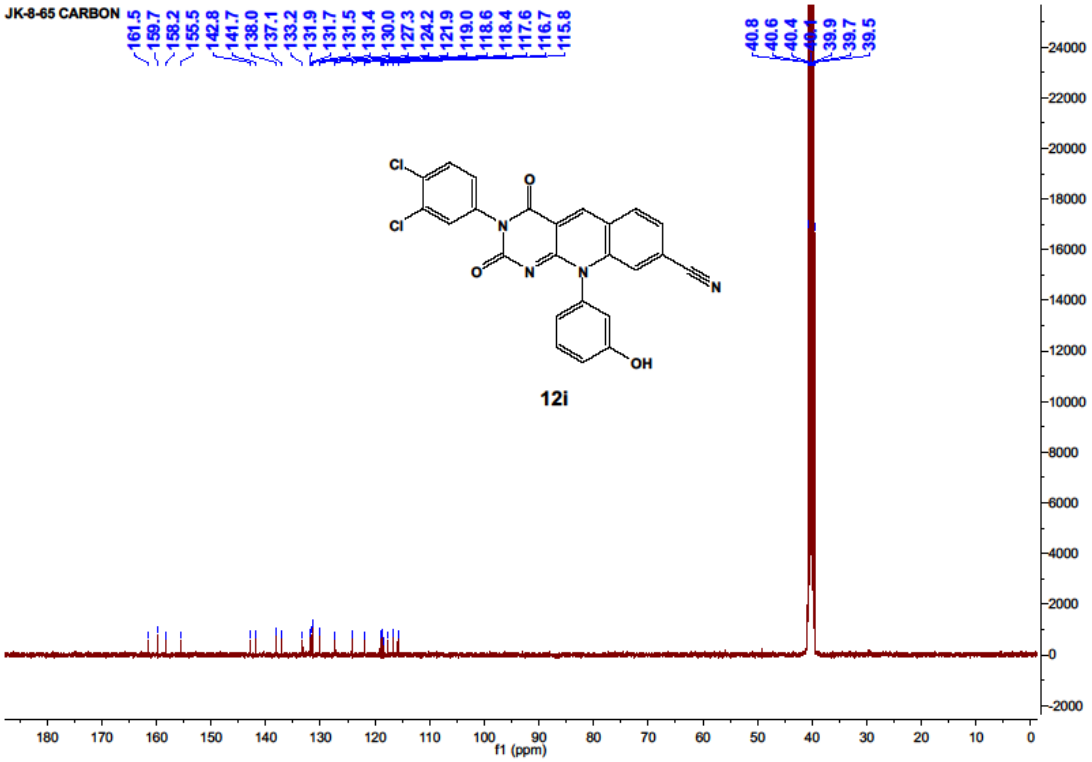

JK-8-63_meta-3-Cl-PROTON_01
JK-8-63_meta-3-Cl
10.06
9.26
8.48
8.47
7.93
7.93
7.92
7.92
7.53
7.52
7.52
7.50
7.50
7.50
7.49
7.40
7.40
7.25
7.24
7.18
6.86
6.85
6.83
6.83
6.82
3.31
2.50
2.50
2.49
1.10
1.00
1.05
1.00
3.23
0.84
1.03
1.03
1.11
1.06
1.01
f1 (ppm)

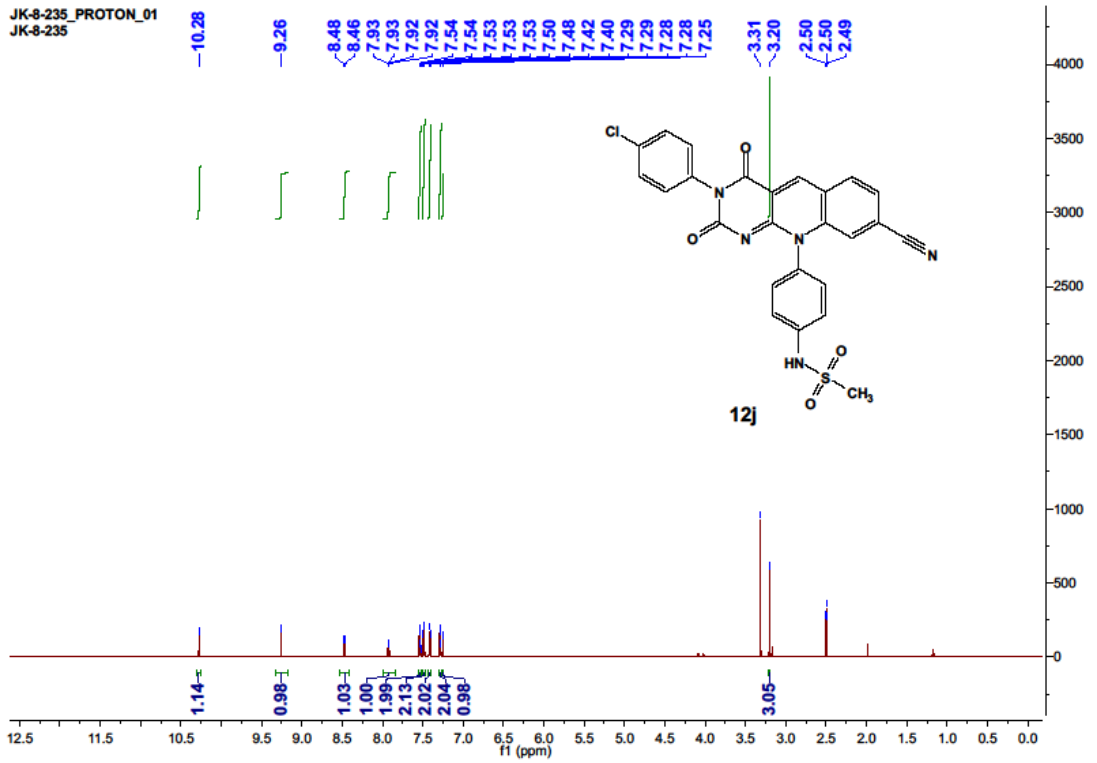
12h

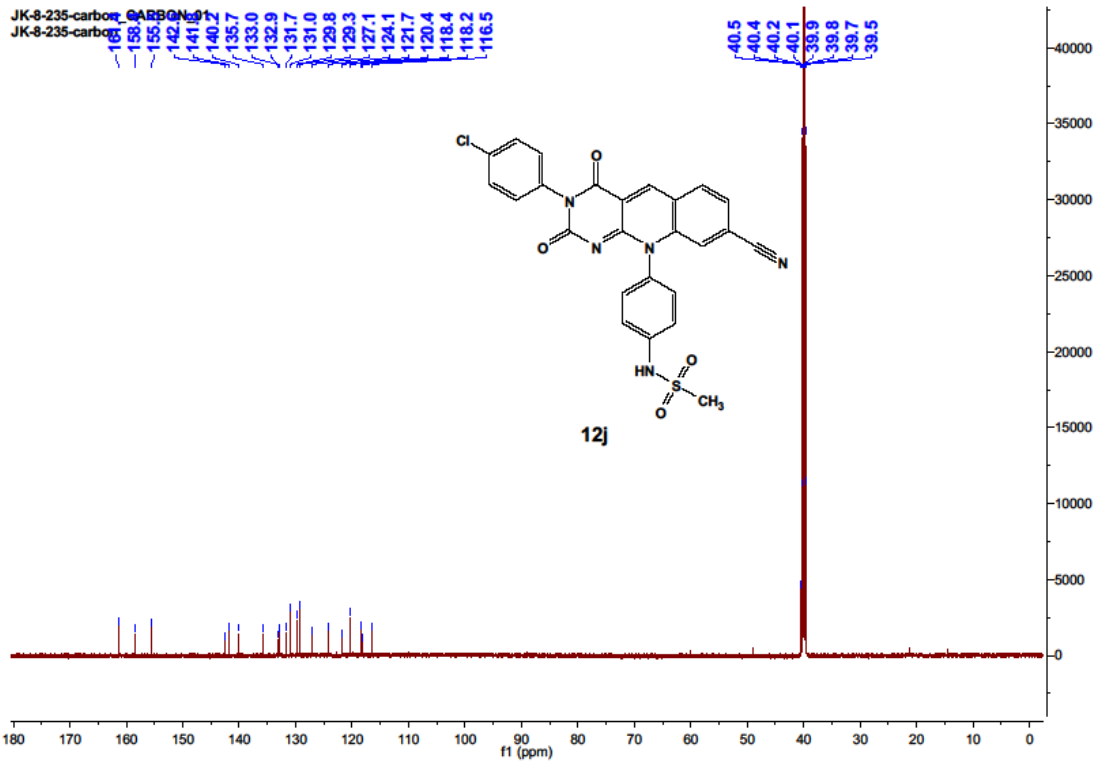

JK-8-63 CARBON
161.8
159.8
157.8
155.3
142.3
141.3
138.1
137.6
133.1
132.8
131.5
130.7
129.0
128.3
127.9
126.8
123.8
121.4
118.6
118.3
118.0
117.2
116.2
115.4
40.4
40.1
39.9
39.7
39.5
39.3
39.1
f1 (ppm)

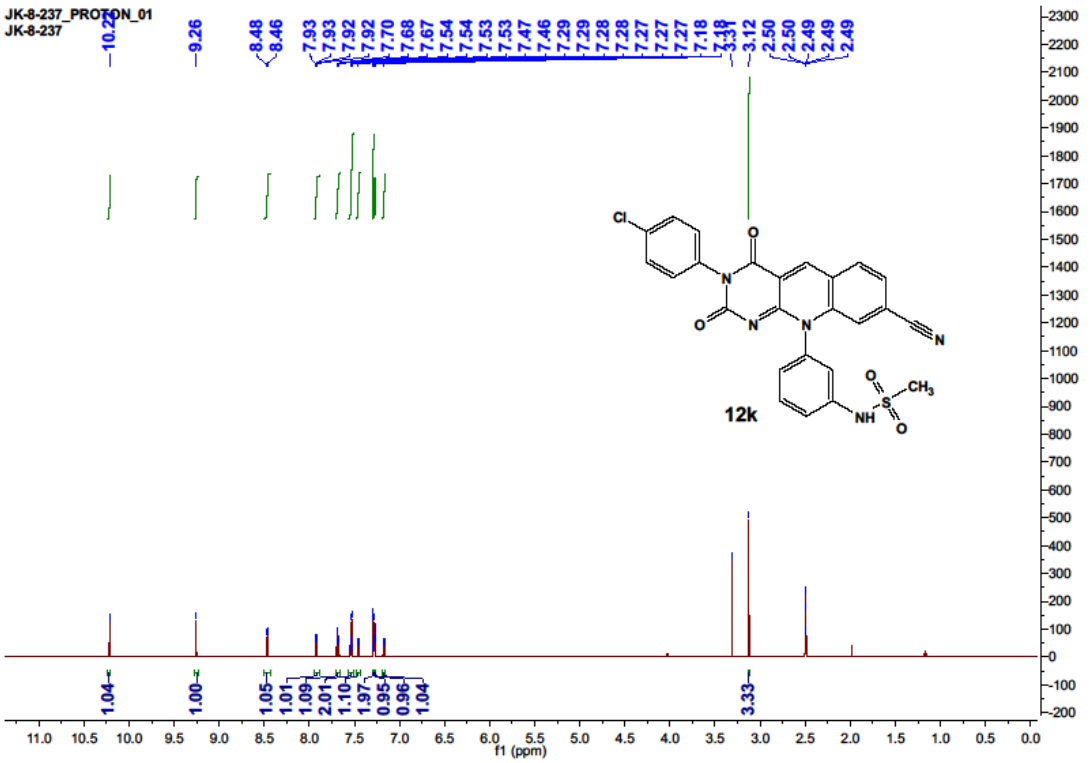
12h

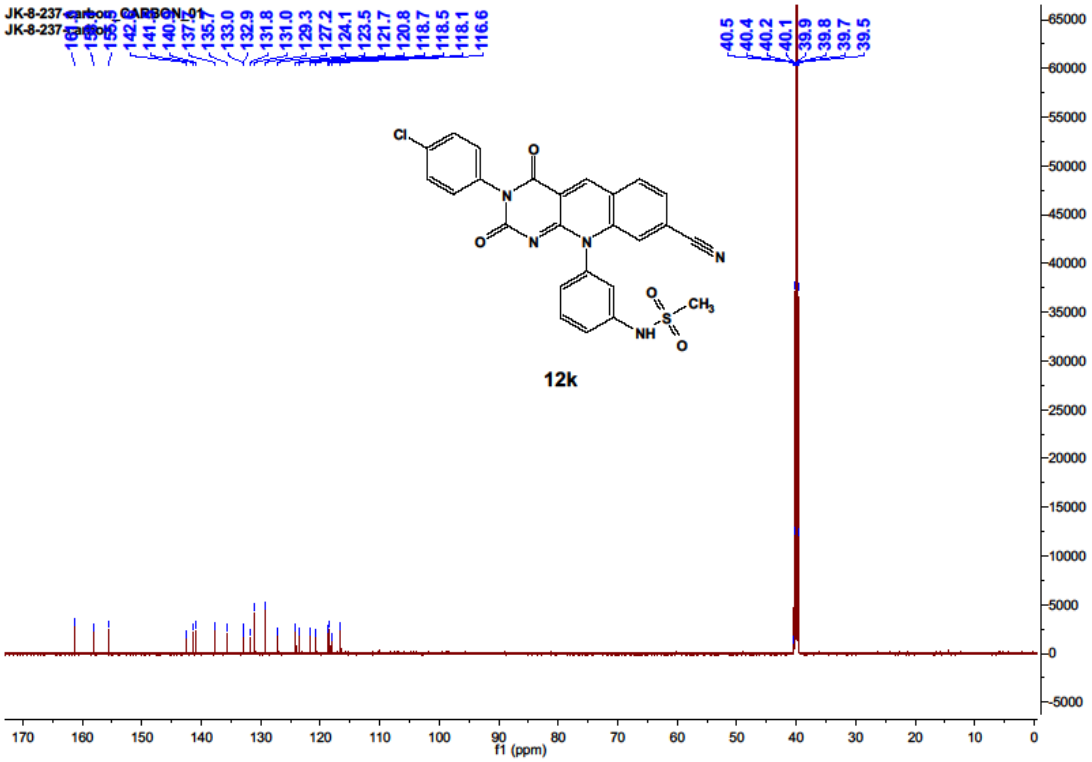

JK-8-65_meta-3_4dicl_PROTON_01
JK-8-65_meta-3_4dicl
10.17
9.28
8.49
8.48
7.94
7.94
7.93
7.93
7.77
7.76
7.65
7.65
7.54
7.52
7.51
7.33
7.32
7.31
7.31
7.19
7.08
6.86
6.84
6.83
6.82
3.32
2.51
2.50
2.50
Cl
Cl
O
N
O
N
N
OH
12i
1.05
0.99
1.04
1.00
0.98
0.85
1.09
1.01
1.05
1.11
2.07
f1 (ppm)

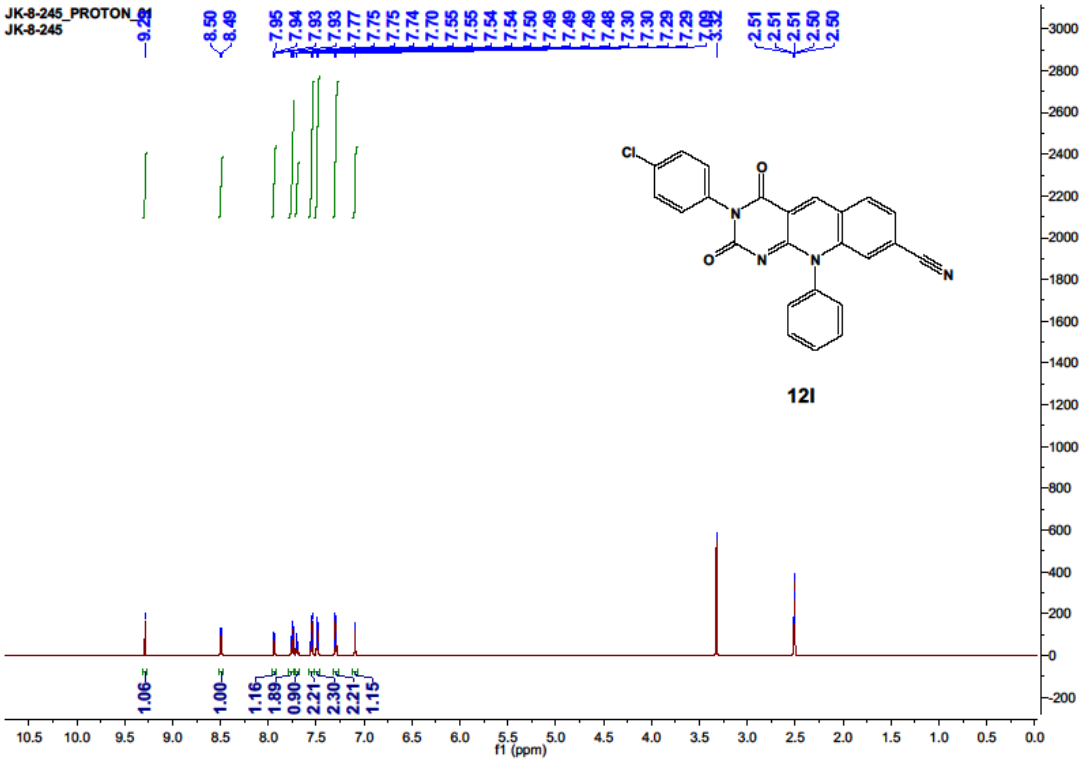

JK-8-65 CARBON
161.5
159.7
158.2
155.5
142.8
141.7
138.0
137.1
133.2
131.9
131.7
131.5
131.4
130.0
127.3
124.2
121.9
119.0
118.6
118.4
117.6
116.7
115.8
40.8
40.6
40.4
40.1
39.9
39.7
39.5
Cl
Cl
O
N
O
N
N
OH
12i
f1 (ppm)

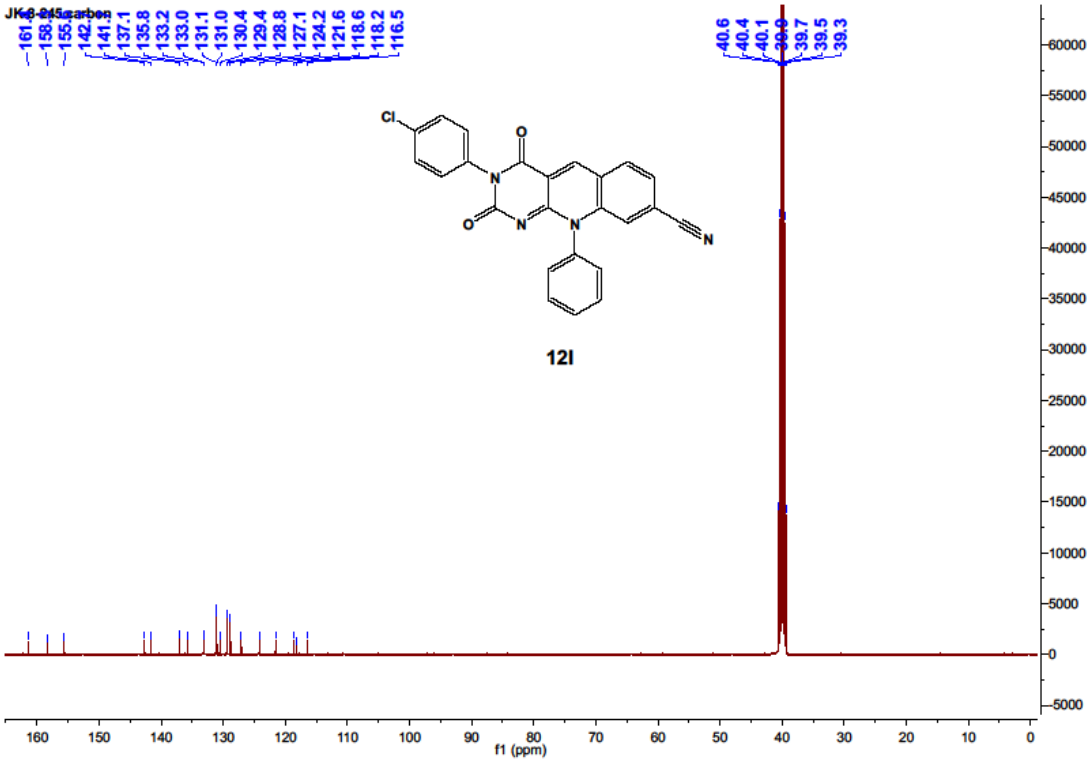

JK-8-235_PROTON_01
JK-8-235
12j
f1 (ppm)


JK-8-235-carbon_CARBON_01
JK-8-235-carbon
12j
f1 (ppm)


JK-8-237_PROTON_01
JK-8-237
12k
f1 (ppm)


JK-8-237_carbon_CARBON_01
JK-8-237
12k
f1 (ppm)


JK-8-245_PROTON_01
JK-8-245
12l
f1 (ppm)


JK-8-245carbon
12l
f1 (ppm)