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Tandem Copper Catalyzed Regioselective *N*-Arylation–Amidation: Synthesis of Angularly Fused Dihydroimidazoquinazolinones and Anticancer Agent TIC10/ONC201

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Table of Contents:-

1. General information S2
2. Synthesis of starting materials S3
3. General experimental procedure for optimization survey S6
4. Optimization survey (Tables T1 to T7) S7
5. General procedure for the synthesis of dihydroimidazoquinazolinone derivatives **3a-w** S13
6. Gram scale procedure for the synthesis of **3a** S14
7. Total Synthesis of Anticancer Clinical Agent TIC10/ONC201 S15
8. Control experiments and mechanistic studies S18
9. Spectral data of starting materials and products S22
10. Copies of spectra (^{1}H-NMR, ^{13}C{^{1}H}-NMR, ^{19}F-NMR) S39
11. Crystallographic data for compounds **3a**, **3n**, **3t**, **4** S106
12. References S114

1. General information

Oven dried glass wares and screw-capped vials were used for carrying out the reactions, Parr shaker apparatus was used for the hydrogenation reaction. Reported temperatures are the metal heating block surrounding temperature of the screw-cap reaction vial. Reactions were magnetically stirred and monitored by TLC using UV lamp.

Column chromatography was used for purifying the products by using 60-120, 100-200 silica mesh. Hexane & ethyl acetate, $CHCl_3$ & CH_3OH were used as eluents, solvents were concentrated under reduced pressure at 40-45 ^oC by using rotary evaporator.

All the commercially available catalysts, ligands, bases, reagents like imidazolinethione, substituted *ortho*-halo benzoic acids and solvents such as DMSO, THF *etc* were used without further purification.

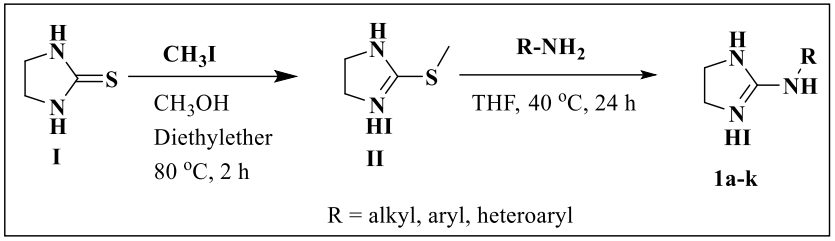
For characterization of synthesized compounds subsequently mentioned analytical tools were utilized. ^{1}H-NMR spectra were recorded on 300, 400 and 500 MHz instruments; $^{13}C\{^1H\}$-NMR spectra were recorded on 75, 100 and 125 MHz spectrometers. Chemical shifts are reported in ppm with the reference solvent TMS = 0 internal standard $CDCl_3$ = 7.26, DMSO-d_6 = 2.50 (^{1}H-NMR), CD_3OD = (^{1}H-NMR) $CDCl_3$ = 77.16 ($^{13}C\{^1H\}$-NMR), peaks which appears at 1.26, 0.86 in ^{1}H-NMR and 29.7 in $^{13}C\{^1H\}$-NMR corresponds to the residual grease present in the solvent.[1] Multiplicity of spectra was explained by using the following abbreviations (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet). With this the structure of the compounds were analyzed. Mass spectra were analysed by Electro Spray Ionization (ESI) method and was obtained on a Shimadzu LCMS-2020 mass spectrometer. High resolution mass spectra were recorded on a Thermo Scientific Exactive^{TM} Orbitrap mass spectrometer or Q STAR XL Hybrid MS/M which gave exact molecular weight of the synthesized compounds. Melting points (MP) were determined by using a digital melting point apparatus. MPs reported in this work are uncorrected. Infrared spectroscopy (IR-neat) was performed on a BRUKER FT-IR spectrophotometer in chloroform, and IR [KBr5pi8] spectra were recorded on a THERMO NICOLET NEXUS 670 FT-IR instrument which helps in analyzing the presence of functional groups. Along with these, crystal structures obtained from the crystallographer for few compounds, they collected single crystal X-ray data at room temperature on a Bruker D8 QUEST.

2. Synthesis of starting materials

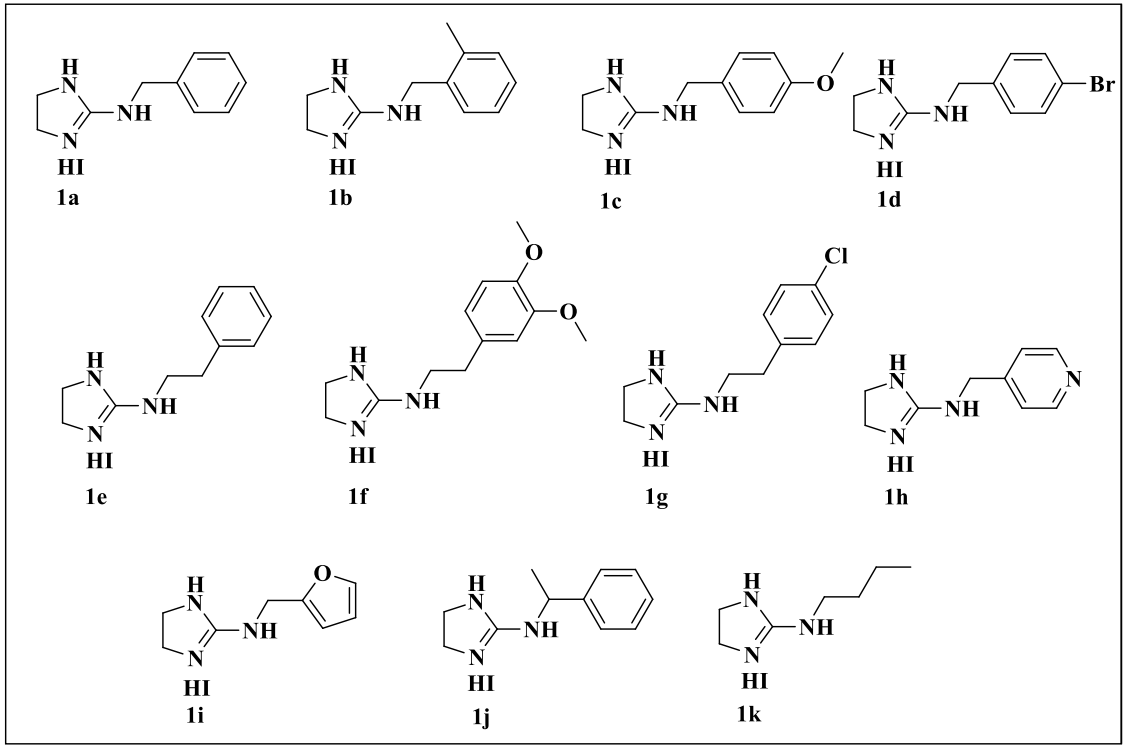
a. General experimental procedure for the synthesis of 2-aminoimidazoline:

To a two necked round bottom flask containing a stirred suspension of imidazolinethione (1 equiv, 94 mmol, 8.8 g) in methanol: diethyl ether (20:20 mL) methyl iodide (1.2 equiv, 112.8 mmol, 14.6 mL) was added and reaction mixture was refluxed at 80 ºC for 2 h. The reaction mixture was cooled to room temperature subsequently formed white precipitate was subjected to filter column on silica gel to afford desired *S*-methylisothiouronium hydroiodide **II**.[2]

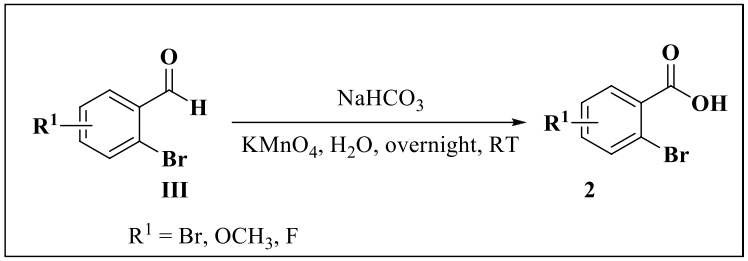
To a two necked round bottom flask containing a stirred suspension of *S*-methylisothiouronium hydroiodide **II** (1 equiv, 10 mmol, 2.44 g) in anhydrous THF (10 mL), at room temperature amine was added (1.1 equiv, 11 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 40 ºC for 24 h, reaction mixture was cooled to room temperature and concentrated under reduced pressure to obtain the crude which, was washed with EtOAc to afford precipitate. The precipitate was purified by flash column chromatography on silica gel to obtain products as hydroiodide salts form **1a-k**.

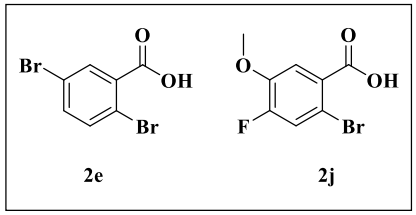


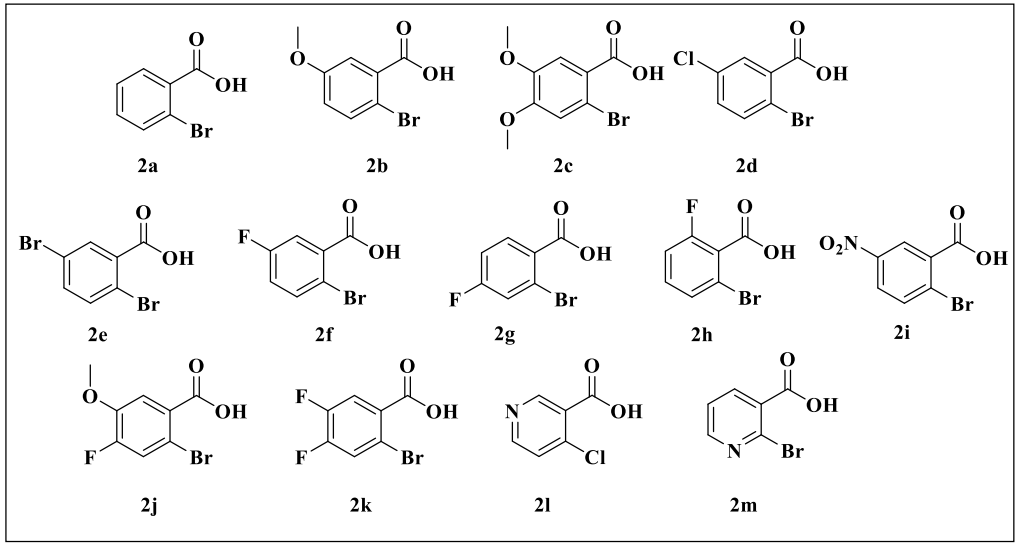
The substituted 2-aminoimidazolines **1a-k** were synthesised by using the above scheme/procedure reported in the literature.[3] The compounds **1a**, **1h**, **1i**, **1k** were reported by Aoyagi *et al.*[3] and **1e**, **1j** were reported by Chiaramonte *et al.*[4]



The spectral data of other substituted 2-aminoimidazolines were in good agreement with the reported data **1b**,[5] **1c**.[6] The spectral data for 2-aminoimidazolines **1d**, **1f** and **1g** are provided.

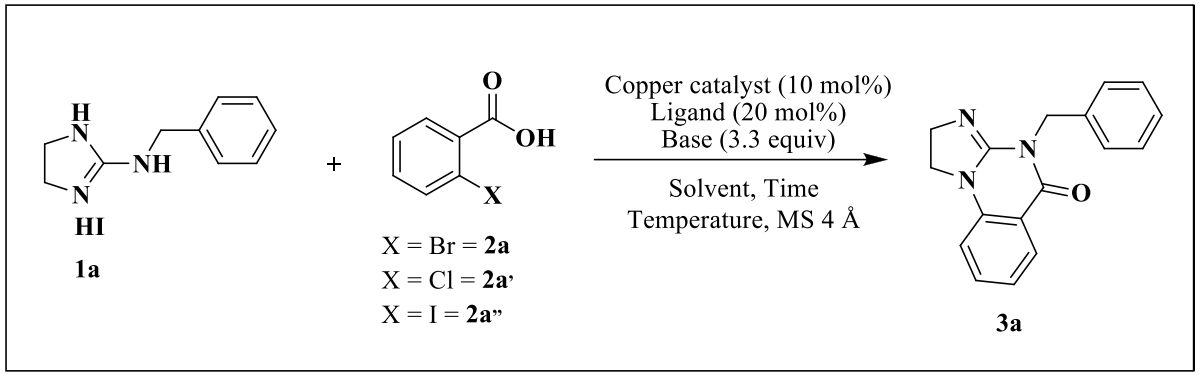






Other coupling partner 2-bromobenzoic acid **2a** and substituted 2-bromobenzoic acids **2b**, **2d**, **2f**, **2g**, **2h**, **2i**, **2k**, **2l**, **2m** were procured from commercially available sources. **2c** was prepared according to the literature report and data is in good agreement.[7] **2e**, **2j** were also prepared according to reported method,[7] the data is in good agreement with literature reports: **2e**,[8] **2j**.[9]

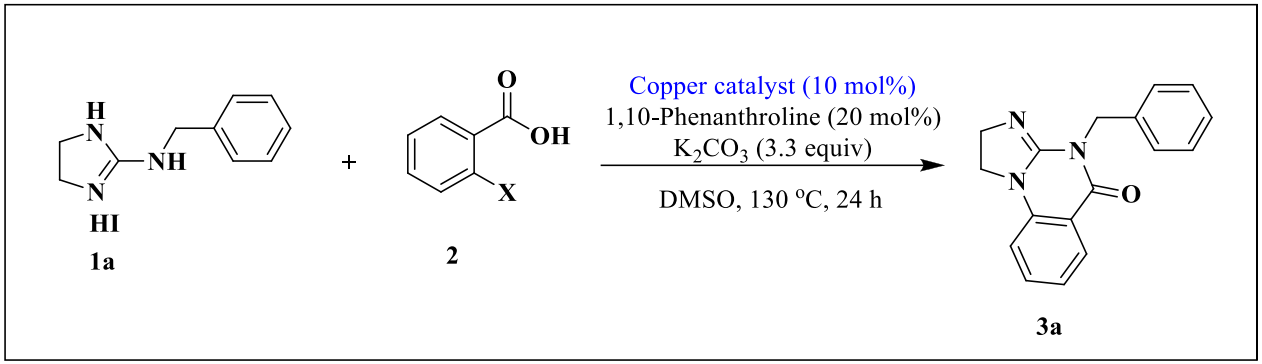
3. General experimental procedure for optimization survey



In a 15 mL screw-capped vial were added *ortho*-halobenzoic acid **2** (1 equiv, 1 mmol), copper catalyst (0.1 equiv, 0.1 mmol), ligand (0.2 equiv, 0.2 mmol), base (3.3 equiv, 3.3 mmol), and solvent (4 mL), MS 4 Å (700 mg) under atmospheric conditions. Then the reaction mixture was stirred for 1 min at room temperature followed by the addition of *N*-benzyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide **1a** (1 equiv, 1 mmol, 303 mg). The vial was closed under atmospheric conditions and the reaction mixture was allowed to stir at specified temperature and time. Completion of the reaction was monitored by TLC. Reaction mixture was cooled to room temperature then added water (10 mL) and the reaction mixture was extracted with dichloromethane (2 x 10 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered solvent was evaporated under reduced pressure to afford the crude residue which was purified by column chromatography (Ethyl acetate/Hexane, 40:60) on silica gel to obtain 4-benzyl-1,2-dihydroimidazo[1,2-*a*]quinazoline-5(4*H*)-one **3a**.

4. Optimization survey

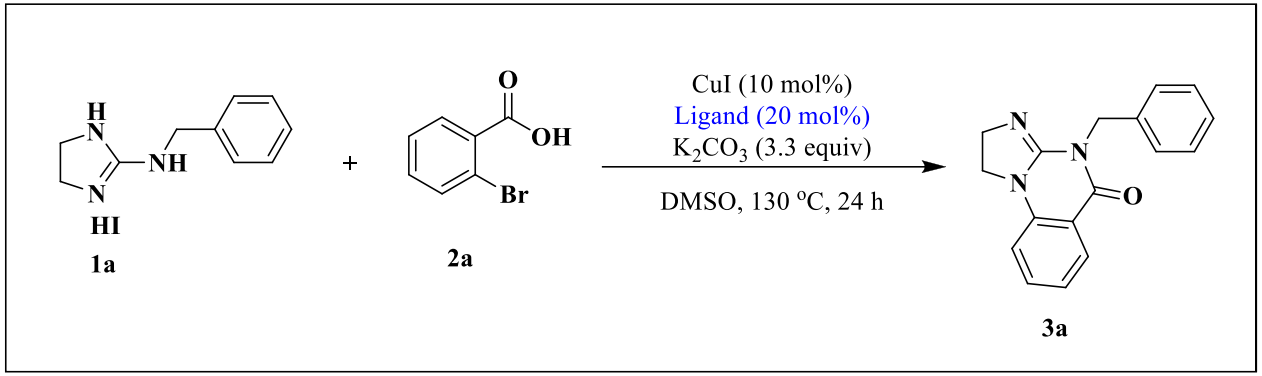
Table T1: Screening of various copper catalysts



Entry	X in 2a	Copper catalyst	Time (h)	% Yield of 3a[a]
1	Br	CuI	12	53
2	Br	CuI	24	70
3	Cl	CuI	24	69
4	I	CuI	24	51
5	Br	CuBr	24	69
6	Br	CuCl	24	62
7	Br	CuO	24	54
8	Br	$Cu(OAc)_2$	24	57
9	Br	CuTc	24	56
10	Br	Cu powder	24	57

a) Isolated yield of **3a**, CuTc:- Copper(I) thiophene-2- carboxylate

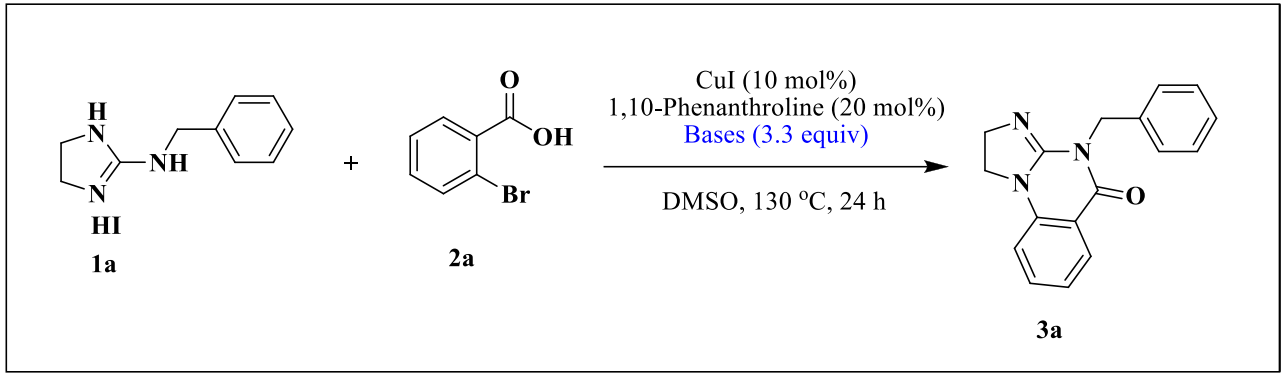
Table T2: Screening of various ligands



Entry	Ligands	% Yield of 3a[a]
1	1,10-Phenanthroline	70
2	Picolinic acid	49
3	8-Hydroxyquinoline	65
4	DMEDA	48
5	*trans*-Cyclohexane-1,2-diamine	55
6	(L)-Proline	69
7	Dimethyltriazolium iodide	59
8	(*S*)-BINOL	52

a) Isolated yield of **3a**

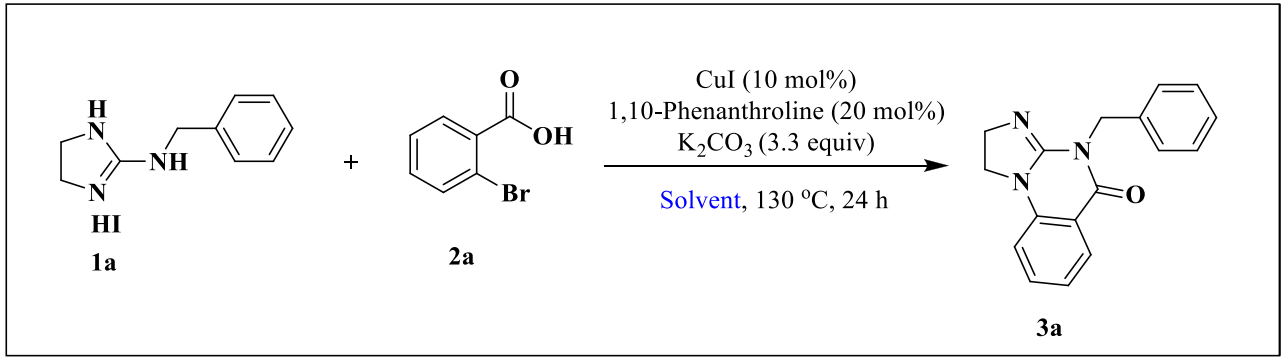
Table T3: Screening of various bases



Entry	Bases	% Yield of 3a[a]
1	K_2CO_3	70
2	$NaHCO_3$	60
3	K_3PO_4	53
4	NaOH	51
5	NaH	57
6	DBU	66
7	Cs_2CO_3	65%

a) Isolated yield of **3a**

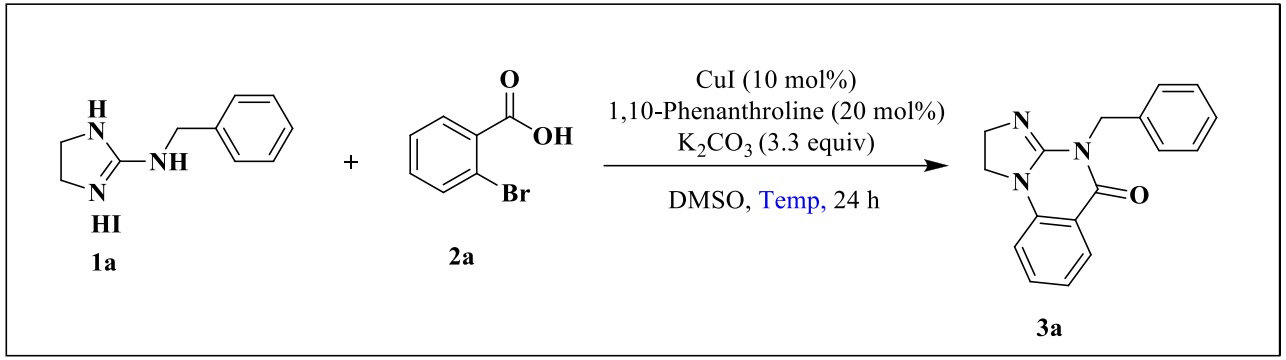
Table T4: Screening of various solvents



Entry	Solvents	% Yield of 3a[a]
1	DMSO	70
2	DMF	56
3	NMP	46
4	Toluene	19

a) Isolated yield of **3a**

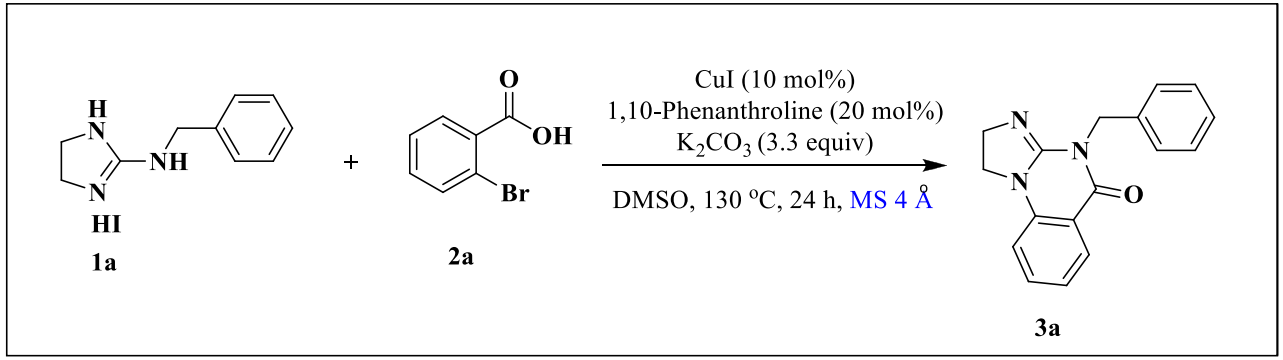
Table T5: Screening of temperature



Entry	Temp (°C)	% Yield of 3a[a]
1	130	70
2	100	61
3	150	50

a) Isolated yield of **3a**

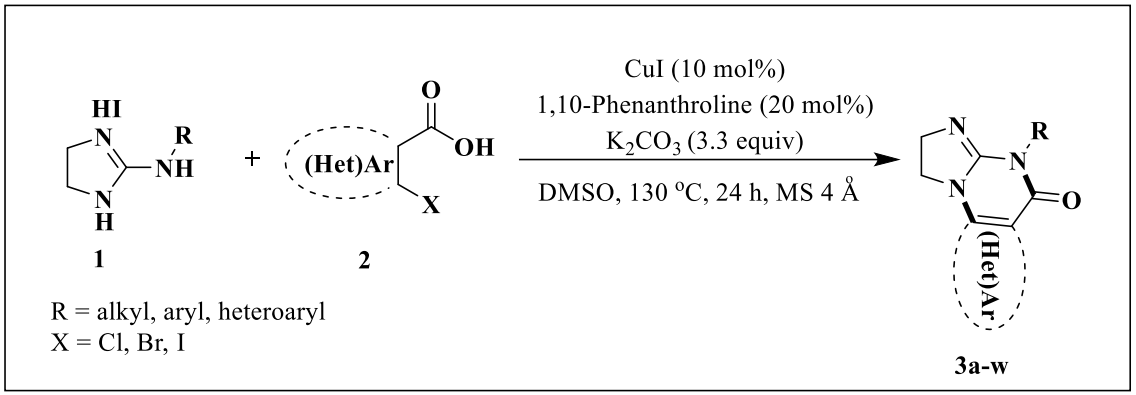
Table T6: Screening the essentiality of catalyst components/reagents



Entry	Catalyst	Ligand	Base	Additive	% Yield of 3a[a]
1	**CuI**	**1,10-Phenanthroline**	**K_2CO_3**	**MS 4 Å**	**77**
2	–	1,10-Phenanthroline	K_2CO_3	MS 4 Å	–
3	CuI	–	K_2CO_3	MS 4 Å	60
4	–	–	K_2CO_3	MS 4 Å	trace
5	CuI	1,10-Phenanthroline	–	MS 4 Å	–

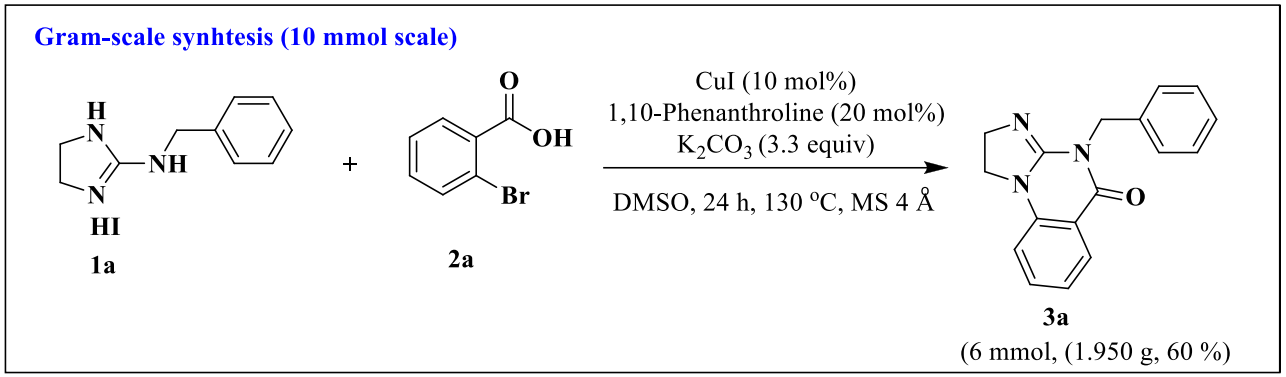
a) Isolated yield of **3a**

5. General procedure for the synthesis of dihydroimidazoquinazolinone 3a-w



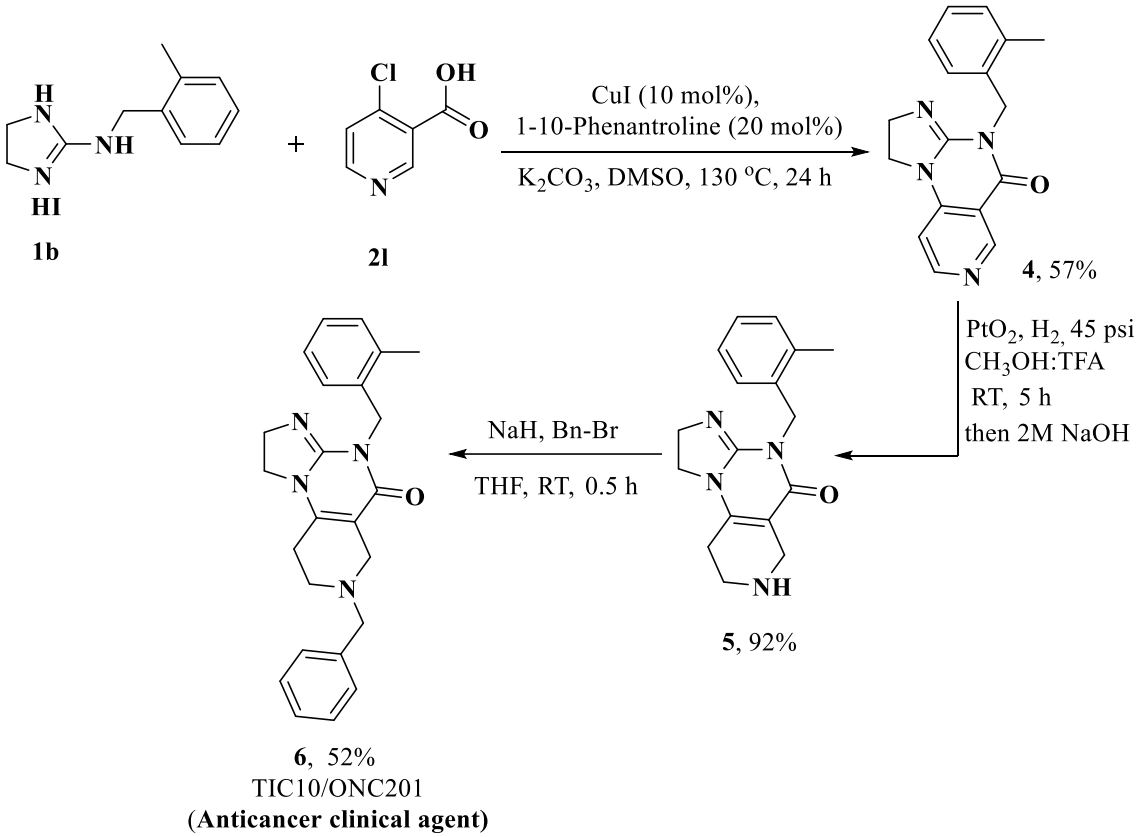
ortho-Bromobenzoic acid derivatives **2** (1 equiv, 1 mmol), copper iodide (0.1 equiv, 0.1 mmol, 19 mg), 1,10-phenanthroline (0.2 equiv, 0.2 mmol, 36 mg), K_2CO_3 (3.3 equiv, 3.3 mmol, 460 mg) and DMSO (4 mL), MS 4 Å (700 mg) were taken in a 15 mL screw-capped vial under atmospheric conditions. Then the reaction mixture was stirred for 1 min at room temperature followed by the addition of substituted 2-aminoimidazoline derivatives **1** (1 equiv, 1 mmol). The vial was closed under atmospheric conditions and the reaction vial was placed in a preheated metal block and stirred at 130 °C for 24 h (inside vial temperature was 120 °C). The reaction mixture was cooled to room temperature, diluted with water (10 mL) and the organic content was extracted with dichloromethane (2 x 15 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and solvent was evaporated under reduced pressure to afford crude residue which was purified by column chromatography (Ethyl acetate/Hexane) on silica gel to obtain dihydroimidazo[1,2-*a*]quinazoline-5(4*H*)-one derivatives **3a-w**.

6 Gram scale procedure for the synthesis of 3a

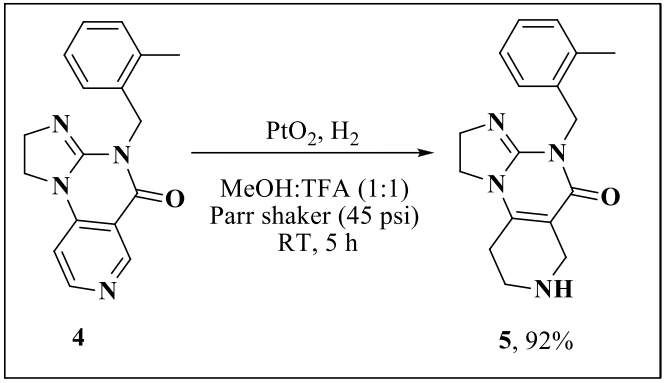


To a two necked round bottom flask were added *ortho*-bromobenzoic acid **2a** (1 equiv, 10 mmol, 2.55 g), CuI (0.1 equiv, 1 mmol, 191 mg), 1,10-phenanthroline (0.2 equiv, 2 mmol, 360 mg), K_2CO_3 (3.3 equiv, 33 mmol, 4.560 g), MS 4 Å (7 g), and dimethyl sulphoxide (40 mL) under atmospheric conditions. Then the reaction mixture was stirred for 1 min at room temperature followed by the addition of *N*-benzyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide **1a** (1.equiv, 10 mmol, 3.03 g) and reaction mixture was stirred at 130 ^{o}C for 24 h, under atmospheric conditions. The reaction mixture was cooled to room temperature diluted with ice cold water (50 mL) and organic content was extracted with dichloromethane (2 x 50 mL), washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and solvent was evaporated under reduced pressure to obtain the crude residue which was purified by column chromatography (EtOAc/Hexane, 40:60) on silica gel to afford the 4-benzyl-1,2-dihydroimidazo[1,2-*a*]quinazoline-5(4*H*)-one **3a** in 60 % yield (1.950 g).

7. Total Synthesis of Anticancer Clinical Agent TIC10/ONC201

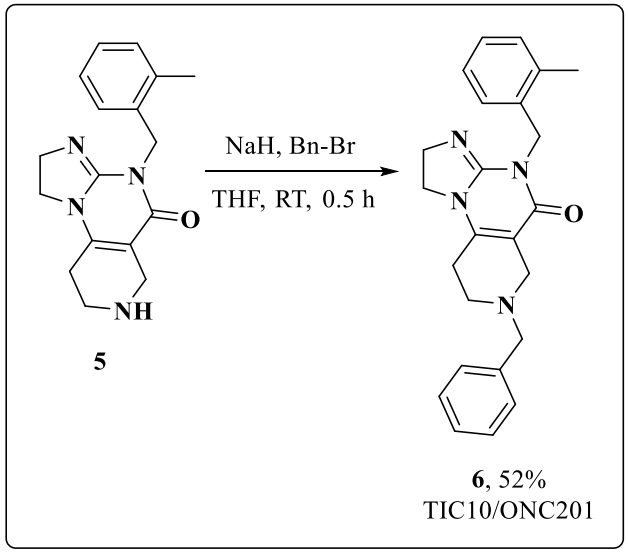


a. Experimental procedure for the reduction of 4-(2-Methylbenzyl)-1,2-dihydroimidazo[1,2-*a*]pyrido[3,4-*e*]pyrimidin-5(4*H*)-one (5)



A mixture of **4** (292 mg, 1 mmol), PtO_2 (60 mg), MeOH (3 mL), and TFA (3 mL) was subjected for hydrogenation (45 psi) in a Parr shaker for 5 h. The mixture was filtered through a Celite® pad and removed catalyst, then concentrated in vacuo, further it was dissolved in 1:1 EtOAc/H_2O (40 mL), made basic by addition of 2 M NaOH (10 mL) confirmed with litmus paper, and two layers were separated. The aqueous layer was extracted with EtOAc (40 mL). The organic layer was washed with brine (20 mL), dried over (Na_2SO_4), and concentrated in vacuo. Purification was done by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH, 19:1:0.1) to afford **5** in 92% of yield.

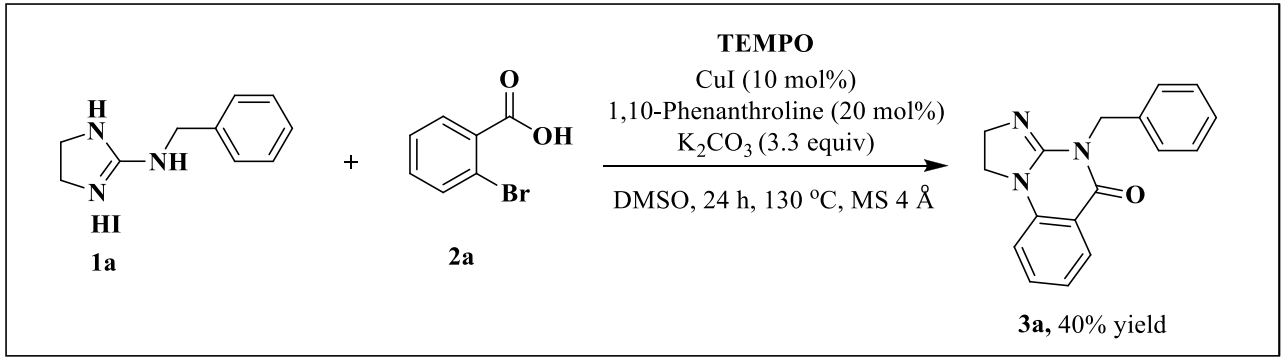
b. Experimental procedure for the benzylation of 5



In a 15 mL two necked RB flask starting material **5** (1 equiv, 0.5 mmol, 150 mg) was dissolved in dry DMF and reaction mixture was cooled to 0 ^{o}C followed by addition of NaH (1.1 equiv, 0.55 mmol, 22 mg) and suspension was allowed to stir at same temperature for half an hr. Further benzyl bromide was added drop wise to the reaction mixture and stirred it at room temperature for another half an hr. Reaction mixture was quenched with ammonium chloride and diluted with water and organic layer extracted with dichloromethane (2 x 15 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Solvent was concentrated under reduced pressure to afford the crude residue which was purified by column chromatography (CH_2Cl_2/MeOH, 19:1) to obtain benzylated product TIC10/ONC201 in 52% yield.

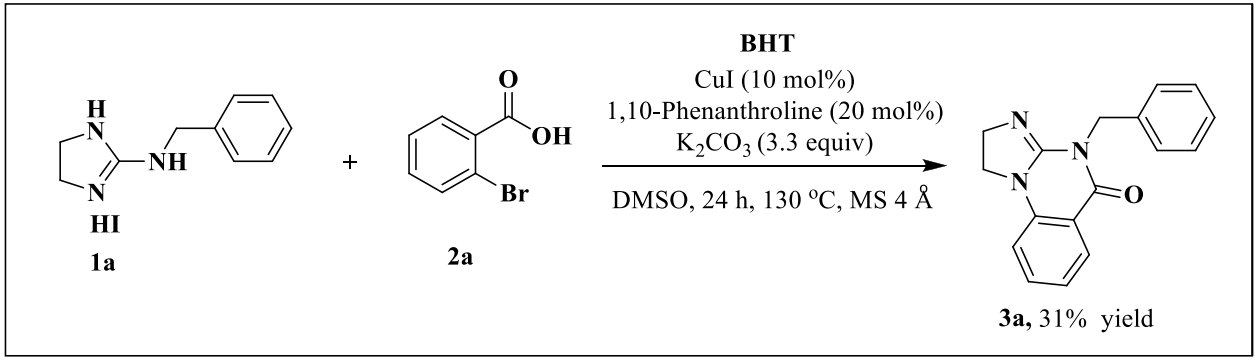
8. Control experiments and mechanistic studies

a. Experimental procedure for the copper catalyzed reaction of 1a and 2a in the presence of TEMPO:



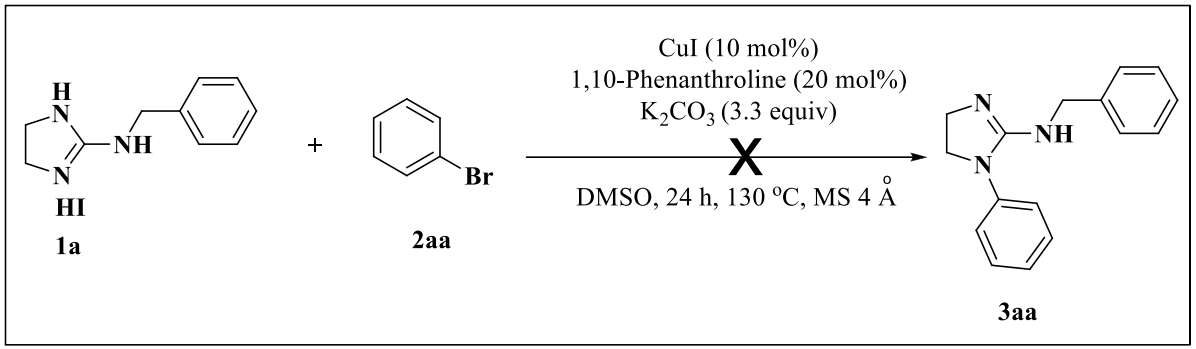
In a 15 mL screw-capped vial were added *ortho*-bromobenzoic acid **2a** (1 equiv, 1 mmol, 202 mg) CuI (0.1 equiv, 0.1 mmol, 19 mg), 1,10-phenanthroline (0.2 equiv, 0.2 mmol, 36 mg), K_2CO_3 (3 equiv, 3 mmol, 460 mg), 2,2,6,6-Tetramethylpiperidinyloxy (TEMPO) (1 equiv, 1 mmol, 156 mg), MS 4 Å (700 mg), and dimethyl sulphoxide (4 mL) under atmospheric conditions. Then the reaction mixture was stirred for 1 min at room temperature followed by the addition of *N*-benzyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide **1a** (1 equiv, 1 mmol, 303 mg). The reaction vial was closed under atmospheric conditions and the reaction mixture was stirred at 130 °C for 24 h. The reaction mixture was cooled to room temperature diluted with water (10 mL), and extracted with dichloromethane (2 x 15 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Solvent was evaporated under reduced pressure to afford the crude residue which was purified by column chromatography (EtOAc/Hexane, 40:60) on silica gel to obtain 4-benzyl-1,2-dihydroimidazo[1,2-*a*]quinazoline-5(4*H*)-one **3a** in 40% yield.

b. Experimental procedure for the copper catalyzed reaction of 1a and 2a in the presence of BHT



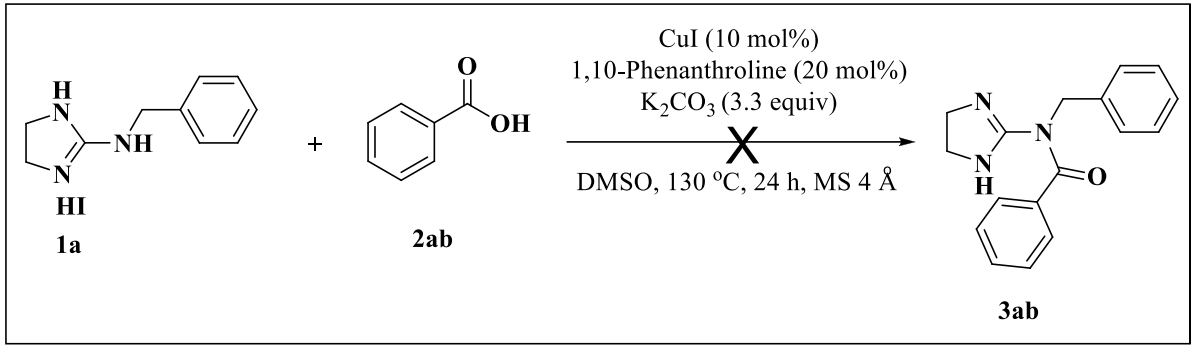
In a 15 mL screw-capped vial were added *ortho*-bromobenzoic acid **2a** (1 equiv, 1 mmol, 202 mg,) CuI (0.1 equiv, 0.1 mmol, 19 mg), 1,10-phenanthroline (0.2 equiv, 0.2 mmol, 36 mg), K_2CO_3 (3 equiv, 3 mmol, 460 mg), butylated hydroxy toluene (BHT) (1 equiv, 1 mmol, 220 mg), MS 4 Å (700 mg), and dimethyl sulphoxide (4 mL) under atmospheric conditions. Then the reaction mixture was stirred for 1 min at room temperature followed by the addition of *N*-benzyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide **1a** (1 equiv, 1 mmol, 303 mg). The reaction vial was closed under atmospheric conditions. The reaction mixture was stirred at 130 ^{o}C for 24 h. The reaction mixture was cooled to room temperature diluted with water (10 mL), and extracted with dichloromethane (2 x 15 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Solvent was evaporated under reduced pressure to afford the crude residue which was purified by column chromatography (EtOAc/Hexane, 40:60) on silica gel to obtain 4-benzyl-1,2-dihydroimidazo[1,2-*a*]quinazoline-5(4*H*)-one **3a** in 31% yield.

c. Experimental procedure for the copper catalyzed reaction of 1a and 2aa



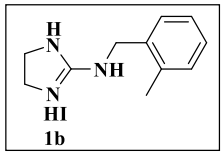
In a 15 mL screw-capped vial were added bromobenzene **2aa** (1 equiv, 1 mmol, 0.1 mL), CuI (0.1 equiv, 0.1 mmol, 19 mg), 1,10-phenanthroline (0.2 equiv, 0.2 mmol, 36 mg), K_2CO_3 (3.3 equiv, 3.3 mmol, 460 mg), MS 4 Å (700 mg), and dimethyl sulphoxide (4 mL) under atmospheric conditions. Then the reaction vial was stirred for 1 min at room temperature followed by the addition of *N*-benzyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide **1a** (1 equiv, 1 mmol, 303 mg). The reaction vial was closed under atmospheric conditions and the reaction mixture was stirred at 130 ºC for 24 h. The reaction mixture was cooled to room temperature and diluted with water (20 mL), and extracted with dichloromethane (2 x 15 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Solvent was concentrated under reduced pressure to afford the crude residue which was purified by column chromatography to recover the starting materials.

d. Experimental procedure for the copper catalyzed reaction of 1a and 2ab:

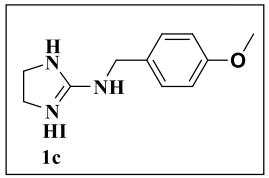


In a 15 mL screw-capped vial were added benzoic acid **2ab** (1 equiv, 1 mmol, 122 mg), CuI (0.1 equiv, 0.1 mmol, 19 mg), 1,10-phenanthroline (0.2 equiv, 0.2 mmol, 36 mg), K_2CO_3 (3.3 equiv, 3.3 mmol, 460 mg), MS 4 Å (700 mg), and dimethyl sulphoxide (4 mL) under atmospheric conditions. Then the reaction vial was stirred for 1 min at room temperature followed by the addition of *N*-benzyl-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide **1a** (1.2 equiv, 1.2 mmol, 175 mg). The reaction vial was closed under atmospheric conditions and the reaction mixture was stirred at 130 °C for 24 h. The reaction mixture was cooled to room temperature diluted with water (20 mL), and extracted with dichloromethane (2 x 15 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. Solvent was concentrated under reduced pressure to afford the crude residue which was purified by column chromatography to recover the starting materials.

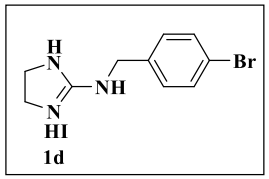
9. Spectral data of starting materials and products



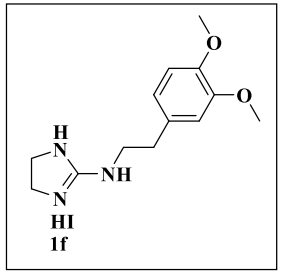
***N*-(2-Methylbenzyl)-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide (1b): ^{1}H-NMR** (400 MHz, CD_3OD) δ = 2.35 (s, 3H), 3.74 (s, 4H), 4.42 (s, 2H), 7.19-7.28 (m, 4H).



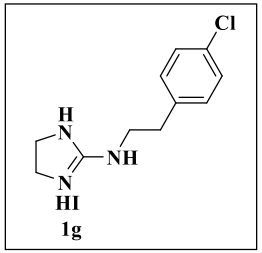
***N*-(4-Methoxybenzyl)-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide (1c): ^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 3.64-3.78 (7H), 4.47 (s, 2H), 6.81-6.88 (m, 2H), 7.28-7.32 (m, 2H).



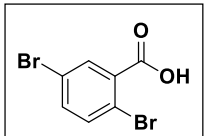
***N*-(4-Bromobenzyl)-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide (1d): 1H-NMR** (400 MHz, DMSO) δ = 3.62 (d, *J* = 8.2 Hz, 4H), 4.32 (t, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 8.3 Hz, 2H), 7.41 (dd, *J* = 11.6, 5.0 Hz, 2H); **^{13}C{^{1}H}-NMR** (101 MHz, DMSO) δ = 43.0, 45.2, 121.2, 129.95, 131.9, 136.96, 159.8.



***N*-(3,4-Dimethoxyphenethyl)-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide (1f):** Orange semisolid, 3.11 g (8.20 mmol); 82%, R_f = 0.1 (MeOH/$CHCl_3$, 10:90); **IR** 1462, 1515, 1668, 2943, 3190 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 2.89 (t, *J* = 7.1 Hz, 2H), 3.66-3.59 (m, 6H), 3.81 (s, 3H), 3.90 (s, 3H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.92 (d, *J* = 1.9 Hz, 1H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$) δ = 35.1, 42.6, 45.5, 56.1, 56.6, 159.7, 111.5, 112.7, 121.2, 130.0, 147.8, 148.9. **MS** (ESI, *m/z*): $[M+H]^+$ 250; **HRMS** (ESI, *m/z*): calcd for $C_{13}H_{21}IN_3O_2$ $[M+H]^+$ 250.1546 found 250.155

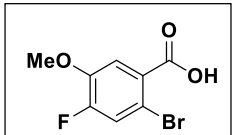


***N*-(4-Chlorophenethyl)-4,5-dihydro-1*H*-imidazol-2-amine hydroiodide (1g):** Brown solid, 1.124 g (5.00 mmol); 50%, R_f = 0.22 (MeOH/$CHCl_3$, 10:90) **MP** 126-131 ºC; **IR** 1492, 1597, 1670, 3199 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 2.93 (t, *J* = 7.1 Hz, 2H), 3.62-3.66 (m, 6H), 7.24-7.30 (m, 4H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ=34.7, 42.6, 45.15, 128.8, 130.7, 132.7, 135.8, 159.6. **MS** (ESI, *m/z*): $[M+H]^+$ 224; **HRMS** (ESI, *m/z*): calcd for $C_{11}H_{16}ClIN_3$ $[M+H]^+$ 224.0948 found 224.0949.



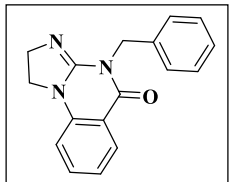
2e

2,5-Dibromobenzoic acid (2e): Off white solid**, ^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.51 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 2.4 Hz, 1H).



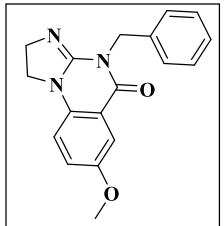
2j

2-Bromo-5-fluoro-4-methoxybenzoic acid (2j): Off white solid, **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 3.94 (s, 3H), 7.44 (d, *J* = 10.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H).



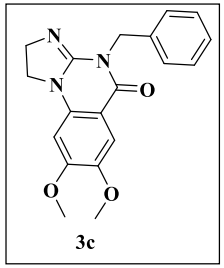
3a

4-Benzyl-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3a): White solid, 199 mg (0.770 mmol), 77%, R_f = 0.26 (EtOAc/Hexane, 50:50); **MP** 131-135 ^oC; **IR** 1493, 1630, 1681, 2926 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 3.95-3.99 (m, 2H), 4.0-4.05 (m, 2H), 5.24 (s, 2H), 6.68 (d, *J* = 8.1 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.23-7.31 (m, 3H), 7.51-7.53 (m, 3H), 8.06 (d, *J* = 7.8 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 46.0, 46.8, 50.7, 111.5, 113.9, 120.8, 127.5, 128.4, 128.6, 129.25, 135.1, 136.8, 139.9, 152.3, 161.4; **MS** (ESI, *m/z*): $[M+H]^+$ 278; **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{16}N_3O$ $[M+H]^+$ 278.1287, found 278.1291.



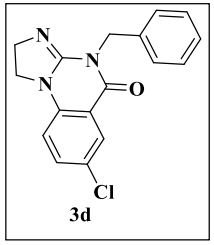
3b

4-Benzyl-7-methoxy-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3b): Pale yellow solid, 221 mg (0.754 mmol), 75%, R_f = 0.21 (EtOAc/Hexane 50:50); **MP** 162-165 ^oC; **IR** 1492, 1622, 1678, 2922, cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 3.82 (s, 3H), 3.93-4.04 (m, 4H), 5.24 (s, 2H), 6.63 (d, *J* = 8.8 Hz, 1H), 7.13 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.22-7.32 (m, 3H), 7.53 (dd, *J* = 12.5, 5.0 Hz, 3H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 46.2, 47.1, 50.2, 55.9, 110.9, 113.2, 114.3, 123.9, 127.55, 128.4, 128.6, 134.5, 136.65, 152.5, 154.2, 161.3; **MS** (ESI, *m/z*): $[M+H]^+$ 308; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{18}N_3O_2$ $[M+H]^+$ 308.1393, found 308.1400.



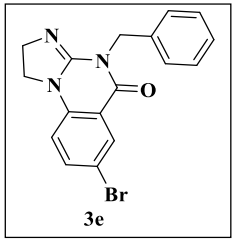
3c

4-Benzyl-7,8-dimethoxy-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3c): Pale Brown solid**,** 225 mg (0.667 mmol), 67%, R_f = 0.19 (EtOAc/Hexane 50:50); **MP** 189-193 ºC; **IR** 1500, 1621, 1667, 2925 cm^{-1}; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 3.89 (s, 3H), 3.96 (s, 3H), 4.00-4.03 (m, 4H), 5.23 (s, 2H), 6.15 (s, 1H), 7.23-7.31 (m, 3H), 7.52 (d, *J* = 5.2 Hz, 3H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 46.0, 47.1, 50.2, 56.35, 94.8, 105.7, 110.2, 127.5, 128.4, 128.55, 135.9, 136.8, 144.2, 152.7, 155.4, 161.1; **MS** (ESI, *m/z*): $[M+H]^+$ 338; **HRMS** (ESI, *m/z*): calcd for $C_{19}H_{20}N_3O_3$ $[M+H]^+$ 338.1499, found 338.1508.



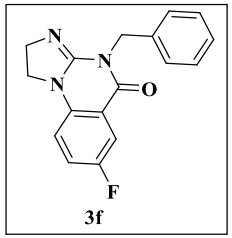
3d

4-Benzyl-7-chloro-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3d): Off-white solid, 164 mg (0.528 mmol), 53%, R_f = 0.34 (EtOAc/Hexane 50:50); **MP** 155-160 ºC; **IR** 1482, 1638, 1686, 2941 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 3.92-3.95 (m, 2H), 4.02-4.05 (m, 2H), 5.21 (s, 2H), 6.67 (s, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.23-7.31 (m, 3H), 7.50-7.51 (m, 2H), 7.96 (d, *J* = 8.4 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 46.1, 46.8, 50.7, 111.5, 112.4, 121,15, 127.6, 128.4, 128.7, 130.7, 136.5, 140.7, 141.3, 151.8, 160.7, **MS** (ESI, *m/z*): $[M+H]^+$ 312, **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{15}{}^{35}ClN_3O$ $[M+H]^+$ 312.0896, found 312.0904.



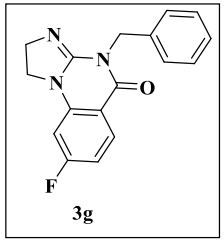
3e

4-Benzyl-7-bromo-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3e): Brown solid, 279 mg (0.785 mmol), 79%, R_f = 0.26 (EtOAc/Hexane, 50:50); **MP** 157-162 ºC; **IR** 1483, 1631, 1684, 2926 cm^{-1}; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 3.90-3.97 (m, 2H), 4.00-4.07 (m, 2H), 5.22 (s, 2H), 6.56 (d, *J* = 8.6 Hz, 1H), 7.25-7.33 (m, 3H), 7.51 (d, *J* = 6.5 Hz, 2H), 7.58 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.15 (d, *J* = 2.2 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 46.2, 46.8, 50.7, 113.1, 113.3, 115.4, 127.7, 128.4, 128.8, 131.7, 136.5, 137.7, 138.8, 151.75, 160.2; **MS** (ESI, *m/z*): $[M+H]^+$ 356; **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{15}{}^{79}BrN_3O$ $[M+H]^+$ 356.0393, found 356.0406.



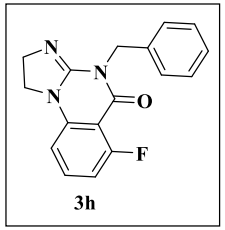
3f

4-Benzyl-7-fluoro-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3f): Pale yellow solid, 251 mg (0.847 mmol), 85%, R_f = 0.23 (EtOAc/Hexane 50:50); **MP** 189-195 ºC; **IR** 1490, 1681, 1628, 2928 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 3.93-3.97 (m, 2H), 4.01-4.05 (m, 2H), 5.22 (s, 2H), 6.64 (dd, *J* = 8.9, 4.0 Hz, 1H), 7.23-7.32 (m, 4H), 7.50-7.52 (m, 2H), 7.74 (dd, *J* = 8.5, 2.9 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 46.2, 47.1, 50.6, 112.9 (d, $J_{C\text{-}F}$ = 7.1 Hz), 114.9 (d, $J_{C\text{-}F}$ = 10.1 Hz), 115.2, 122.4, 122.7, 127.6, 128.4, 128.7, 136.6 (d, $J_{C\text{-}F}$ = 9.1 Hz), 152.1, 157.1 (d, $J_{C\text{-}F}$ = 242 Hz), 160.6; **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -121.8 (s); **MS** (ESI, *m/z*): $[M+H]^+$ 296; **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{15}FN_3O$ $[M+H]^+$ 296.1193, found 296.1199.



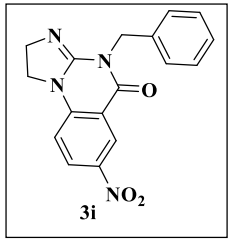
3g

4-benzyl-8-fluoro-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3g): Off-white solid, 188 mg (0.640 mmol), 64%, R_f = 0.24 (EtOAc/Hexane 50:50); **MP** 159-162 ºC; **IR** 1492, 1633, 1684, 2924 cm^{-1}; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 3.90-3.96 (m, 2H), 4.02-4.08(m, 2H), 5.21 (s, 2H), 6.36 (dd, *J* = 9.5, 2.2 Hz, 1H), 6.68-6.74 (m, *J* = 8.6, 2.2 Hz, 1H), 7.24-7.33 (m, *J* = 10.0, 6.7, 3.4 Hz, 3H), 7.51 (d, *J* = 6.7 Hz, 2H), 8.05 (dd, *J* = 8.7, 6.1 Hz, 1H), **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$) δ = 46.0, 46.8, 50.65, 98.6 (d, J_{C-F} = 26.46 Hz), 108.4 (d, J_{C-F} = 18.18 Hz), 110.4, 127.6, 128.4, 128.7, 132.13 (d, J_{C-F} = 11.3 Hz), 136.6, 141.70 (d, J_{C-F} = 12.6 Hz), 151.9, 160.6, 167.14 (d, J_{C-F} = 11.3 Hz); **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -101.6 (s); **MS** (ESI, *m/z*): $[M+H]^+$ 296 **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{15}FN_3O$ $[M+H]^+$ 296.1194, found 296.1199.



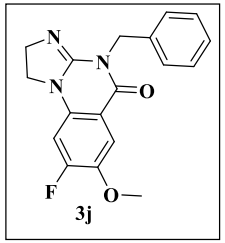
3h

4-Benzyl-6-fluoro-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3h): Pale brown solid, 136 mg (0.462 mmol), 46%, R_f = 0.17 (EtOAc/Hexane 50:50); **MP** 170-178 ºC; **IR** 1498, 1619, 1688, 2924 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 3.94-3.98 (m, 2H), 4.01-4.05 (m, 2H), 5.20 (s, 2H), 6.44 (d, *J* = 8.3 Hz, 1H), 6.66-6.71 (m, 1H), 7.23-7.32 (m, 3H), 7.40-7.45 (m, 1H), 7.54 (d, *J* = 6.9 Hz, 2H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 45.8, 47.4, 50.55, 107.41 (d, J_{C-F} = 3.6 Hz), 108.6, 108.8, 127.6, 128.4, 128.9, 135.88 (d, J_{C-F} = 11.7 Hz), 136.6, 141.4, 151.70, 160.1 (d, J_{C-F} = 330 Hz), 164.4; **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -110.2 (s); **MS** (ESI, *m/z*): $[M+H]^+$ 296 **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{15}FN_3O$ $[M+H]^+$ 296.1186, found 296.1193.



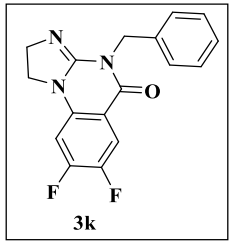
3i

4-Benzyl-7-nitro-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3i): Yellow solid, 241 mg (0.748 mmol), 75%, R_f = 0.21 (EtOAc/Hexane 50:50); **MP** 150-158 ºC; **IR** 1483, 1640, 1690, 2924 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 4.02-4.14 (m, 4H), 5.23 (s, 2H), 6.74 (d, *J* = 9.0 Hz, 1H), 7.27-7.33 (m, 3H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 2H), 8.37 (dd, *J* = 9.0, 2.6 Hz, 1H), 8.91 (d, *J* = 2.6 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 46.4, 46.9, 50.9, 111.9, 113.9, 125.9, 127.9, 128.5, 129.0, 130.35, 136.0, 141.2, 143.6, 150.8, 159.6, **MS** (ESI, *m/z*): $[M+H]^+$ 323; **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{15}N_4O_3$ $[M+H]^+$ 323.1138, found 323.1147.



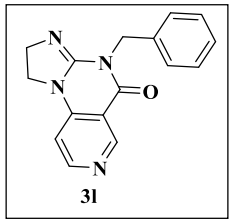
3j

4-Benzyl-8-fluoro-7-methoxy-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3j): Off-white solid, 159 mg (0.490 mmol), 49%, R_f = 0.3 (EtOAc/Hexane 50:50); **MP** 180-185 ºC; **IR** 1499, 1625, 1684, 2925 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 3.89 (s, 3H), 3.92-3.95 (m, 2H), 4.00-4.05 (m, 2H), 5.22 (s, 2H), 6.47 (d, *J* = 11.1 Hz, 1H), 7.27-7.32 (m, 3H), 7.49-7.52 (m, 2H), 7.65 (d, 1H), **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 46.2. 47.2, 50.5, 56.7, 100.31 (d, J_{C-F} = 23.7 Hz), 109.6, 113.35 (d, J_{C-F} = 4.04 Hz), 127.6, 128.4, 128.7, 135.28 (d, J_{C-F} = 10.9 Hz), 136.6, 142.63 (d, J_{C-F} = 11.3 Hz), 152.3, 157.2 (d, J_{C-F} = 257 Hz), 160.7; **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -122.2 (s); **MS** (ESI, *m/z*): $[M+H]^+$ 326; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{17}FN_3O_2$ $[M+H]^+$ 326.1299, found 326.1308.



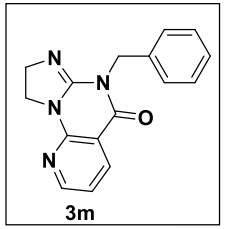
3k

4-Benzyl-7,8-difluoro-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3k): pale yellow solid, 160 mg (0.512 mmol), 51%, R_f = 0.2 (EtOAc/Hexane 50:50); **MP** 95-97 ºC; **IR** 1432, 1499, 1640, 1683, 2960 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 3.91-3.94 (m, 2H), 4.02- 4.05 (m, 2H), 5.20 (s, 2H), 6.48 (dd, *J* = 10.5, 6.1 Hz, 1H), 7.24-7.32 (m, 3H), 7.50 (d, *J* = 7.2 Hz, 2H),7.86 (dd, *J* = 9.8, 8.7 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 46.0, 46.8, 50.6, 98.6 (d, J_{C-F} = 26.2 Hz), 108.5 (d, J_{C-F} = 22.7 Hz), 110.4, 127.6, 128.4, 128.7, 132.15 (d, J_{C-F} = 11.3 Hz), 136.6, 141.7 (d, J_{C-F} = 12.6 Hz), 151.9, 160.6, 167.1 (d, J_{C-F} = 255.5 Hz); **^{19}F-NMR** (377 MHz, $CDCl_3$) δ = -125.3 (s), -146.1 (s); **MS** (ESI, *m/z*): $[M+H]^+$314; **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{14}F_2N_3O$ $[M+H]^+$ 314.1095, found 314.1099.



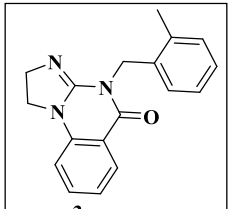
3l

4-Benzyl-1,2-dihydroimidazo[1,2-*a*]pyrido[3,4-*e*]pyrimidin-5(4*H*)-one (3l): Pale brown solid, 0.114 mg (0.0425 mmol), 42%, R_f = 0.08 (EtOAc); **MP** 156-159 ºC; **IR** 1454, 1633, 1690, 2924 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 3.94-3.98 (m, 2H), 4.06-4.11 (m, 2H), 5.22 (s, 2H), 6.57 (d, *J* = 5.7 Hz, 1H), 7.25-7.33 (m, 4H), 7.51-7.53 (m, 2H), 8.54 (d, *J* = 5.7 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 45.9, 51.1, 105.9, 109.9, 127.8, 128.45, 128.9, 136.3, 144.8, 150.85, 151.2, 154.4, 160.3; **MS** (ESI, *m/z*): $[M+H]^+$279; **HRMS** (ESI, *m/z*): calcd for $C_{16}H_{15}N_4O$ $[M+H]^+$ 279.1240, found 279.1244.



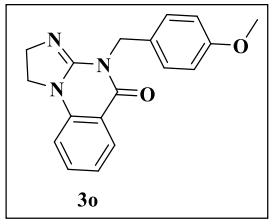
3m

6-Benzyl-8,9-dihydroimidazo[1,2-*a*]pyrido[3,2-*e*]pyrimidin-5(6*H*)-one (3m): Off white solid, 196 mg (0.706 mmol), 70%, R_f = 0.25 (EtOAc/Hexane, 60:40); **MP** 145-150 ºC; **IR** 1497, 1639, 1690, 2926 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 4.01-4.05 (m, 2H), 4.16-4.20 (m, 2H), 5.22 (s, 2H), 6.96 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.24-7.32 (m, 4H), 7.51-7.53 (m, 2H), 8.26 (dd, *J* = 7.7, 1.9 Hz, 1H), 8.43 (dd, *J* = 4.9, 1.9 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 45.9, 46.2, 50.7, 109.75, 116.8, 127.7, 128.4, 128.7, 136.4, 137.6, 150.6, 151.5, 154.1, 161.2. **MS** (ESI, *m/z*): $[M+H]^+$ 279; **HRMS** (ESI, *m/z*): calcd for $C_{16}H_{15}N_4O$ $[M+H]^+$ 279.1212 found 279.1245.



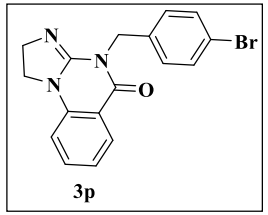
3n

4-(2-Methylbenzyl)-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3n): Brown solid, 172 mg (0.592 mmol), 59%, R_f = 0.17 (EtOAc/Hexane 50:50); **MP** 182-185 ºC; **IR** 1492, 1629, 1682, 2927 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 2.45 (s, 3H), 4.01 (s, 4H), 5.23 (s, 2H), 6.74 (d, *J* = 8.2 Hz, 1H), 7.03-7.16 (m, 5H), 7.56 (dd, *J* = 12.0, 4.8 Hz, 1H), 8.07 (dd, *J* = 7.9, 1.4 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 19.3, 43.9, 46.9, 50.7, 111.6, 113.9, 120.9, 125.1, 125.9, 126.9, 129.3, 130.3, 134.1, 135.2, 135.6, 140.1, 152.4, 161.4; **MS** (ESI, *m/z*): $[M+H]^+$ 292; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{18}N_3O$ $[M+H]^+$ 292.1444, found 292.1447.



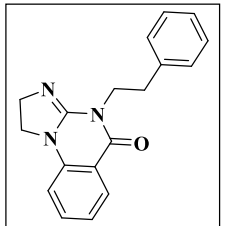
3o

4-(4-Methoxybenzyl)-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3o): Off white solid, 231 mg (0.753 mmol), 75%, R_f = 0.15 (EtOAc/Hexane 50:50); **MP** 135-138 ºC; **IR** 1493, 1627, 1680, 2927 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 3.76 (s, 3H). 3.95-3.99 (m, 2H), 4.03-4.08 (m, 2H), 5.18 (s, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.81-6.84 (m, 2H), 7.01-7.04 (m, 1H), 7.49-7.53 (m, 3H), 8.05 (dd, *J* = 7.9, 1.4 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 45.5, 46.7, 50.3, 55.3, 111.6, 113.7, 113.9, 120.9, 128.9, 129.2, 130.4, 135.1, 139.8, 152.3, 159.1, 161.3 **MS** (ESI, *m/z*): $[M+H]^+$ 308; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{18}N_3O_2$ $[M+H]^+$ 308.1393, found 308.1394.



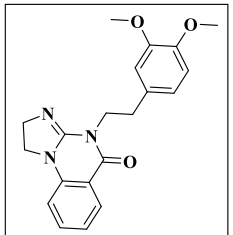
3p

4-(4-Bromobenzyl)-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3p): Brown solid, 299 mg (0.840 mmol), 84%, R_f = 0.21 (EtOAc/Hexane 50:50); **MP** 178-182 ºC; **IR** 1488, 1610, 1674, 2869 cm^{-1}; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ = 3.96-4.06 (m, 4H), 5.17 (s, 2H), 6.70 (d, *J* = 8.1 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 7.41 (s, 4H), 7.54 (t, *J* = 7.7 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 45.4, 46.8, 50.6, 111.6, 113.8, 120.9, 121.5, 129.2, 130.6, 131.5, 135.2, 135.8, 139.9, 152.1, 161.4; **MS** (ESI, *m/z*): $[M+H]^+$ 357; **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{15}{}^{79}BrN_3O$ $[M+H]^+$ 356.0393, found. 356.0387



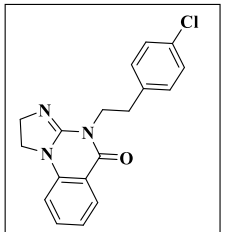
3q

4-Phenethyl-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3q): Brown solid, 167 mg (0.574 mmol), 57%, R_f =0.16 (EtOAc/Hexane 50:50); **MP** 150-155 ^oC; **IR** 1493, 1627, 1681, 2925 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 3.01-3.05 (m, 2H), 3.95-4.06 (m, 4H), 4.24-4.28 (m, 2H), 6.70 (d, *J* = 8.1 Hz, 1H), 7.03-7.07 (m, 1H), 7.16-7.23 (m, 1H), 7.27-7.36 (m, *J* = 13.0, 8.1, 3.9 Hz, 4H), 7.51-7.56 (m, 1H), 8.06 (dd, *J* = 7.9, 1.4 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 33.4, 44.3, 46.65, 50.7, 111.5, 113.9, 120.8, 126.4, 128.4, 128.7, 129.1, 135.0, 138.7, 139.95, 152.0, 161.25; **MS** (ESI, *m/z*): $[M+H]^+$ 292; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{18}N_3O$ $[M+H]^+$ 292.1444, found 292.1445.



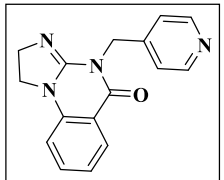
3r

4-(3,4-Dimethoxyphenethyl)-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3r): Off white solid, 262 mg (0.749 mmol), 75%, R_f = 0.04 (EtOAc/Hexane 60:40); **MP** 150-156 ^oC; **IR** 1494, 1629, 1681, 2925 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 2.96-3.00 (m, 2H), 3.86 (d, *J* = 2.5 Hz, 6H), 3.96-4.08 (m, 4H), 4.23-4.27 (m, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.81 (t, *J* = 5.5 Hz, 1H), 6.87-6.90 (m, 2H), 7.04-7.09 (m, 1H), 7.55 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 8.06 (dd, *J* = 7.9, 1.4 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 32.95, 44.45, 46.6, 50.5, 55.9, 111.2, 111.6, 112.3, 114.0, 120.9, 121.0, 129.1, 131.2, 135.1, 139.9, 147.6, 148.8, 152.1, 161.2; **MS** (ESI, *m/z*): $[M+H]^+$ 352; **HRMS** (ESI, *m/z*): calcd for $C_{20}H_{22}N_3O_3$ $[M+H]^+$ 352.1645, found 352.1655.



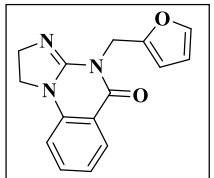
3s

4-(4-Chlorophenethyl)-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3s): brown solid, 218 mg (0.672 mmol), 67%, R_f = 0.16 (EtOAc/Hexane 50:50); **MP** 170-175 ºC; **IR** 1489, 1610, 1680, 2952 cm^{-1}, **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 2.98-3.02 (m, 2H). 3.95-4.06 (m, 4H), 4.21-4.25 (m, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 7.03-7.07 (m, 1H), 7.23-7.29 (m, 4H), 7.54 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 8.05 (dd, *J* = 7.9, 1.4 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 32.7, 43.9, 46.65, 50.6, 111.6, 113.9, 120.9, 128.5, 129.1, 130.4, 132.2, 135.1, 137.1, 139.9, 152.0, 161.2; **MS** (ESI, *m/z*): $[M+H]^+$ 326; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{17}{}^{35}ClN_3O$ $[M+H]^+$ 326.1054, found 326.1060.



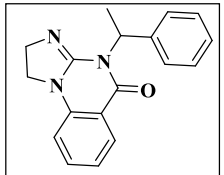
3t

4-(Pyridin-4-ylmethyl)-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3t): Brown solid, 76 mg (0.274 mmol), 27%, R_f = 0.05 (EtOAc); **MP** 190-195 ºC; **IR** 1493, 1629, 1681, 2950 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 4.02 (s, 4H), 5.24 (s, 2H), 6.73 (d, *J* = 8.2 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 5.9 Hz, 2H), 7.55-7.57 (m, 1H), 8.06 (dd, *J* = 7.8, 0.9 Hz, 1H), 8.54 (d, *J* = 5.9 Hz, 2H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 45.0, 46.9, 50.6, 111.7, 113.55, 121.1, 122.9, 129.3, 135.5 , 139.9, 145.6, 149.8, 152.1, 161.3; **MS** (ESI, *m/z*): $[M+H]^+$ 279; **HRMS** (ESI, *m/z*): calcd for $C_{16}H_{15}N_4O$ $[M+H]^+$ 279.1240, found 279.1246.



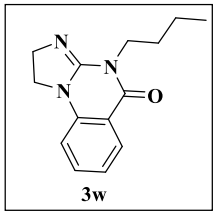
3u

4-(Furan-2-ylmethyl)-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3u): White solid, 201 mg (0.755 mmol), 75%, R_f = 0.16 (EtOAc/Hexane 50:50); **MP** 165-170 ºC; **IR** 1495, 1629, 1682, 2924 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 3.97-4.00 (m, 2H), 4.05-4.09 (m, 2H), 5.24 (s, 2H), 6.31 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.43 (d, *J* = 3.1 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 1.1 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 8.07 (d, *J* = 7.9 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 39.0. 46.8, 50.7, 109.3, 110.4, 111.6, 113.8, 120.9, 129.30, 135.2, 139.9, 142.1, 150.0, 151.9, 161.1; **MS** (ESI, *m/z*): $[M+H]^+$ 268; **HRMS** (ESI, *m/z*): calcd for $C_{15}H_{14}N_3O_2$ $[M+H]^+$ 268.1076, found 268.1080.



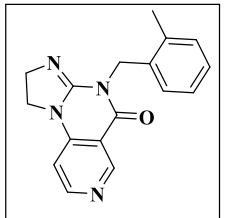
3v

4-(1-Phenylethyl)-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3v): Brown solid, 152 mg (0.523 mmol), 52%, R_f = 0.26 (EtOAc/Hexane 50:50); **MP** 97-100 ºC; **IR** 1489, 1610, 1679, 2875 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 1.96 (d, *J* = 7.2 Hz, 3H). 3.94-4.08 (m, 4H), 6.25 (q, *J* = 7.1 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.98-7.00 (m, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.29-7.32(m, 2H), 7.48-7.52 (m, 3H), 7.96 (dd, *J* = 7.9, 1.4 Hz, 1H); **^{13}C{^{1}H}-NMR** (126 MHz, $CDCl_3$) δ = 15.9. 46.7, 50.5, 53.6, 111.4, 114.6, 120.8, 127.0, 127.1, 128.1, 129.1, 134.9, 139.9, 140.3, 152.6, 161.1; **MS** (ESI, *m/z*): $[M+H]^+$ 292; **HRMS** (ESI, *m/z*): calcd for $C_{18}H_{18}N_3O$ $[M+H]^+$ 292.1444, found 292.1447.



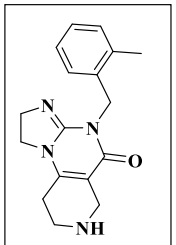
3w

4-Butyl-1,2-dihydroimidazo[1,2-*a*]quinazolin-5(4*H*)-one (3w): Pale brown solid, 124 mg (0.513 mmol), 51%, R_f = 0.10 (EtOAc/Hexane 50:50); **MP** 102-105 °C; **IR** 1483, 1637, 1686, 2954 cm^{-1}, **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 0.96 (t, *J* = 7.4 Hz, 3H), 1.38-1. 45 (m, 2H), 1.75-1.69 (m, 2H), 3.96-4.06 (m, 6H), 6.70 (d, *J* = 8.1 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ =13.9, 20.25, 29.4, 42.9, 46.6, 50.4, 111.5, 114.1, 120.9, 129.1, 134.9, 139.8, 152.2, 161.3; **MS** (ESI, *m/z*): $[M+H]^+$244; **HRMS** (ESI, *m/z*): calcd for $C_{14}H_{18}N_3O$ $[M+H]^+$ 244.1445, found 244.1450.



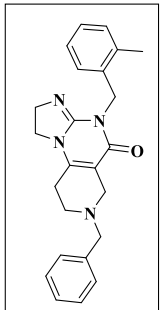
4

4-(2-Methylbenzyl)-1,2-dihydroimidazo[1,2-*a*]pyrido[3,4-*e*]pyrimidin-5(4*H*)-one (4): Brown solid, 166 mg (0.568 mmol), 57%, R_f = 0.08 (EtOAc); **MP** 210-215 °C; **IR** 1458, 1645, 1689, 2956 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 2.45 (s, 3H), 3.95-4.06 (m, 4H), 5.21 (s, 2H), 6.60 (d, *J* = 5.7 Hz, 1H), 7.08-7.15 (m, 4H), 8.56 (d, *J* = 5.7 Hz, 1H), 9.07 (s, 1H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 19.4, 43.73, 46.1, 51.1, 106.0, 109.8, 125.4, 126.0, 127.2, 130.45, 133.7, 135.8, 144.9, 151.0, 151.4, 154.55, 160.4; **MS** (ESI, *m/z*): $[M+H]^+$ 293, **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{17}N_4O$ 293.1396, found 293.1400.



5

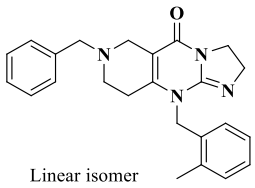
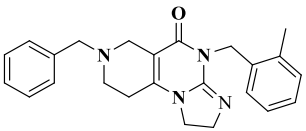
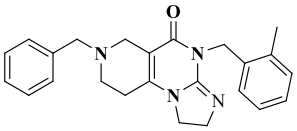
4-(2-Methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-*a*]pyrido[3,4-e]pyrimidin-5(4*H*)-one (5): Pale green semi-solid, 272 mg (0.918 mmol), 92 %. R_f= 0.12 (MeOH/DCM/NH_3 5:95:0.5); **IR** 1491, 1607, 1641, 2853, 2922 3328 cm^{-1}; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 2.47 (dd, *J* = 10.5, 5.2 Hz, 2H), 2.81 (br, 1H), 3.14 (t, *J* = 5.7 Hz, 2H), 3.66 (s, 2H), 3.82-3.96 (m, 4H), 5.05 (s, 2H), 7.00-7.07 (m, 1H), 7.06-7.14 (m, 3H); **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 19.3, 25.5, 29.7, 41.57 (d, *J* = 25.1 Hz), 43.2, 46.9, 50.5, 101.7, 125.1, 125.9, 126.9, 130.3, 134.1, 135.6, 145.7, 153.1, 161.4; **MS** (ESI, *m/z*): $[M+H]^+$297; **HRMS** (ESI, *m/z*): calcd for $C_{17}H_{21}N_4O$ $[M+H]^+$ 297.1705, found 297.1709.



6
TIC10/ONC201

7-Benzyl-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-*a*]pyrido[3,4-e]pyrimidin-5(4*H*)-one (6): Pale orange semi-solid, 202 mg (0.521 mmol), 52 % R_f = 0.25 ($CH_3OH/CHCl_3$ 5:95); **IR** 1490, 1610, 1644, 2882, 2922 cm^{-1}; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 2.54 (t, *J* = 5.5 Hz, 2H), 2.72 (t, *J* = 5.7 Hz, 2H), 3.31 (s, 2H), 3.67 (s, 2H), 3.84-3.91 (m, 4H), 5.04 (s, 2H), 7.02-7.04 (m, 1H), 7.08-7.12 (m, 3H), 7.26-7.34 (m, 5H). **^{13}C{^{1}H}-NMR** (101 MHz, $CDCl_3$) δ = 19.3, 26.8, 43.4, 46.9, 48.2, 49.6, 50.45, 62.3, 102.1, 125.2, 125.9, 126.8, 127.4, 128.45, 129.2, 130.2, 134.2, 135.6, 137.9, 145.7, 153.3, 161.4; **MS** (ESI, *m/z*): $[M+H]^+$387; **HRMS** (ESI, *m/z*): calcd for $C_{24}H_{27}N_4O$ $[M+H]^+$ found 387.2183.

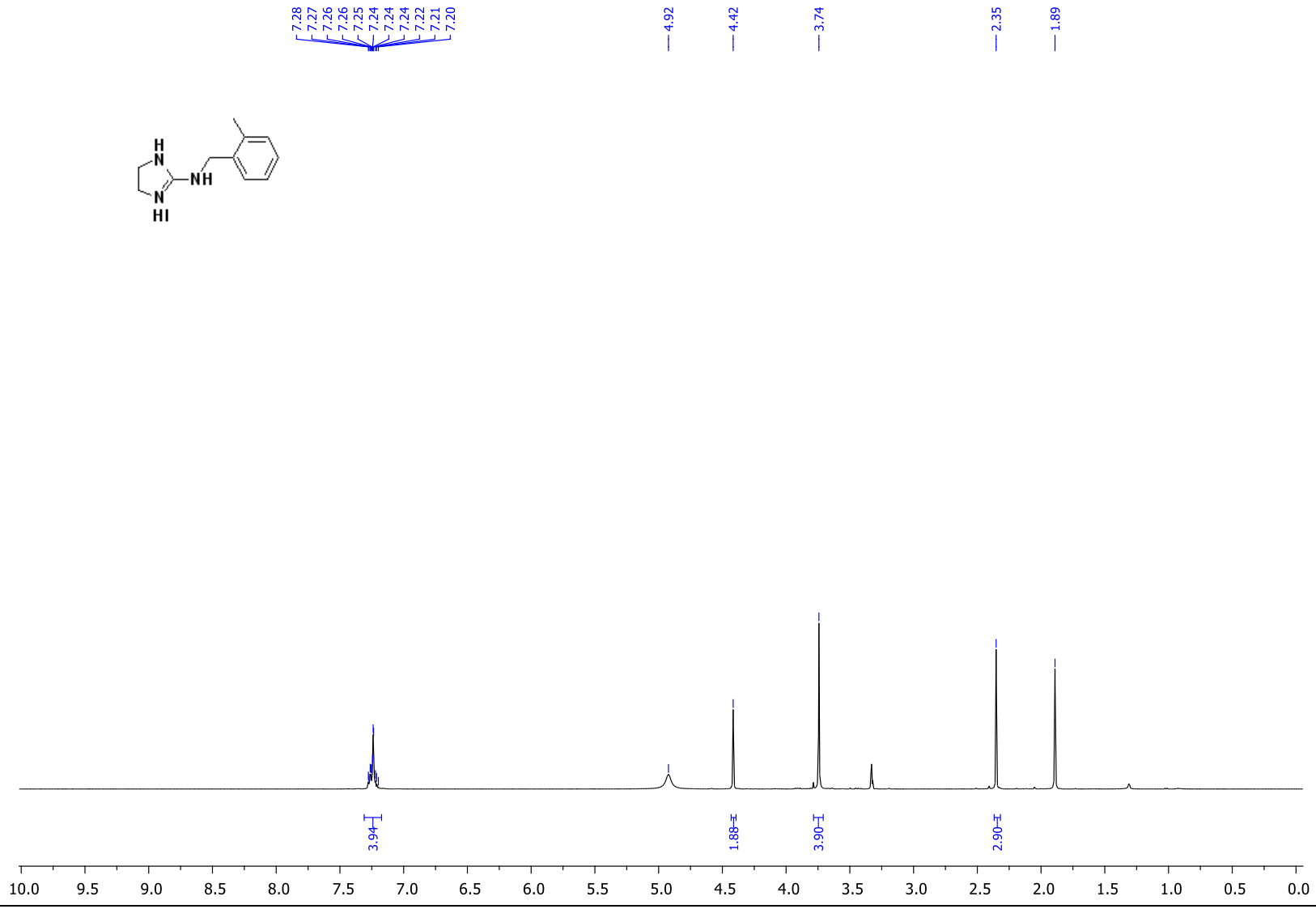
Comparison of $^{13}C\{^{1}H\}$-NMR chemical shifts for

JWL-1[5]	JWL-2[5]	Structure of-6
		This work
 Linear isomer	 Angular isomer (TIC10)	 **6**. Angular isomer (TIC10)
159.8	161.6	161.4
152.9	153.4	153.3
147.1	145.8	145.7
137.6	137.7	137.9
134.6	135.7	135.6
133.7	134.4	134.2
130.7	130.4	130.2
129.2	129.3	129.2
128.5	128.6	128.4
127.5	127.5	127.4
127.4	127.0	126.8
126.8	126.0	125.9
123.7	125.4	125.2
105.7	102.1	102.1
62.1	62.5	62.3
49.9	50.7	50.4
49.6	49.7	49.6
48.6	48.3	48.2
46.4	47.1	47.0
45.3	43.3	43.2
26.1	27.0	26.8
19.1	19.4	19.3

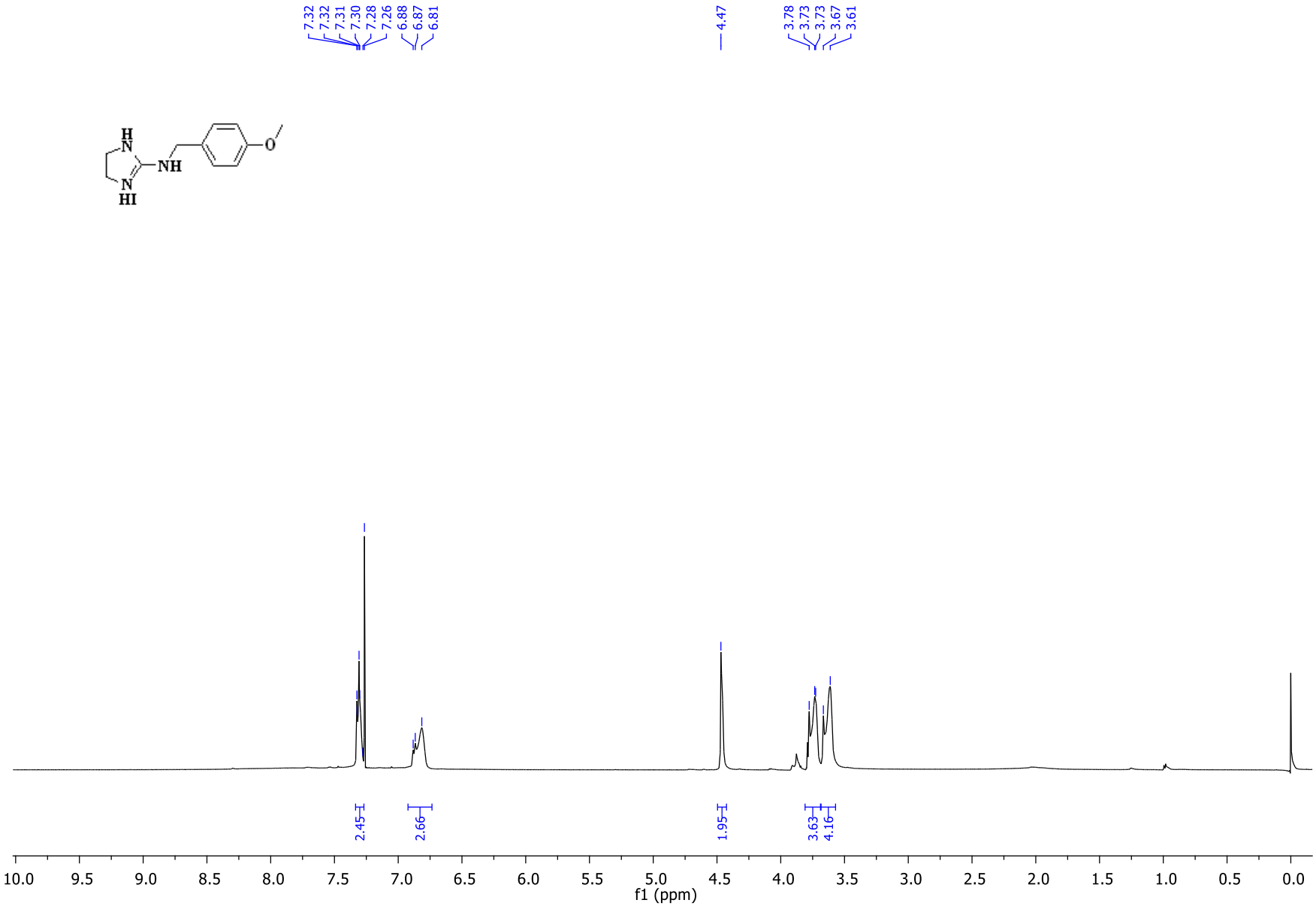
Spectral data of compound **6** were in good agreement with the cited reference.[5] (**JWL** is a notation in reference 5, **1** and **2** are the corresponding compound numbers)

10 Copies of ^{1}H and $^{13}C\{^{1}H\}$-NMR spectra of the starting materials and products

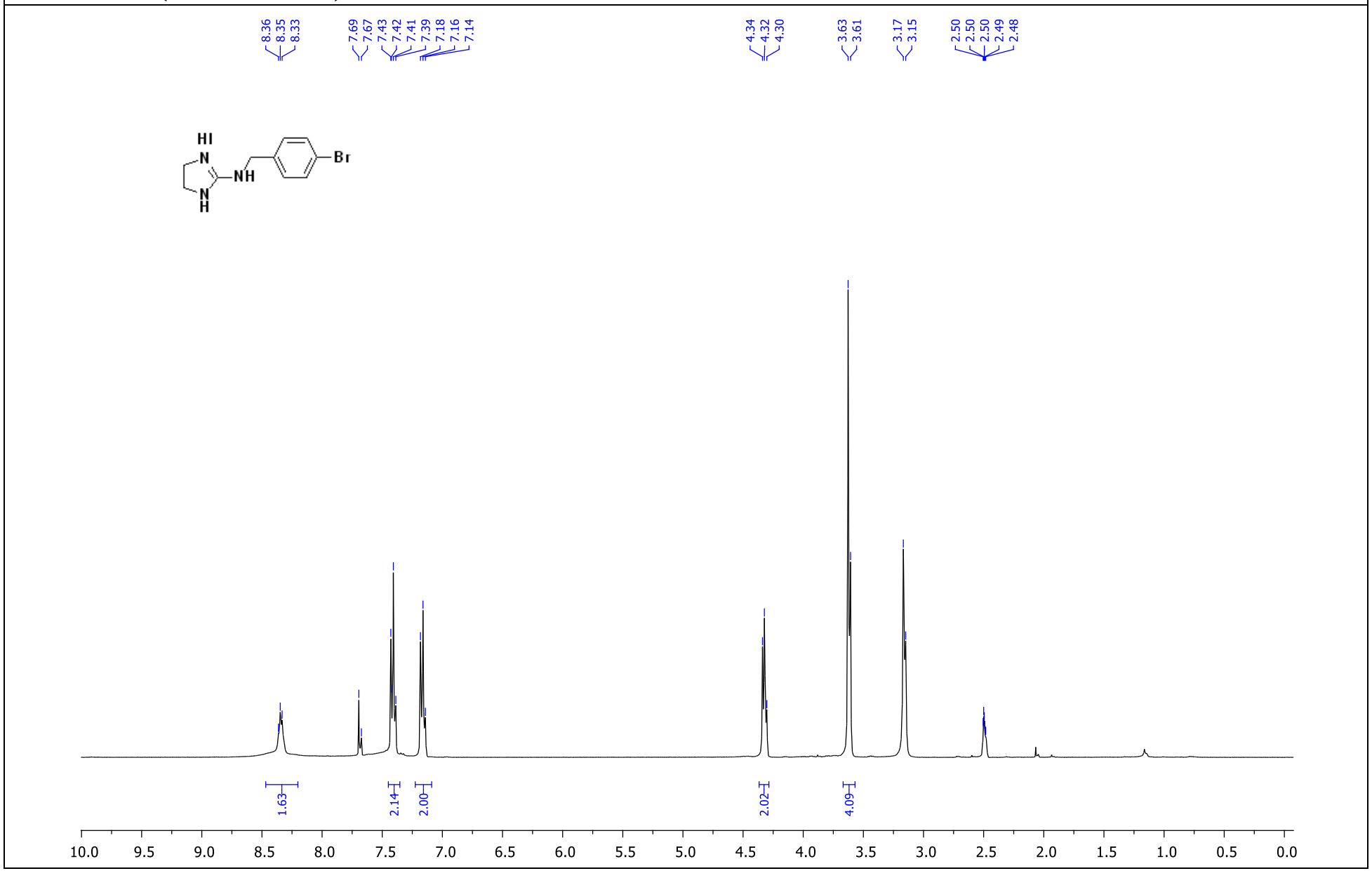
^{1}H-NMR of 1b (400 MHz, CD_3OD)



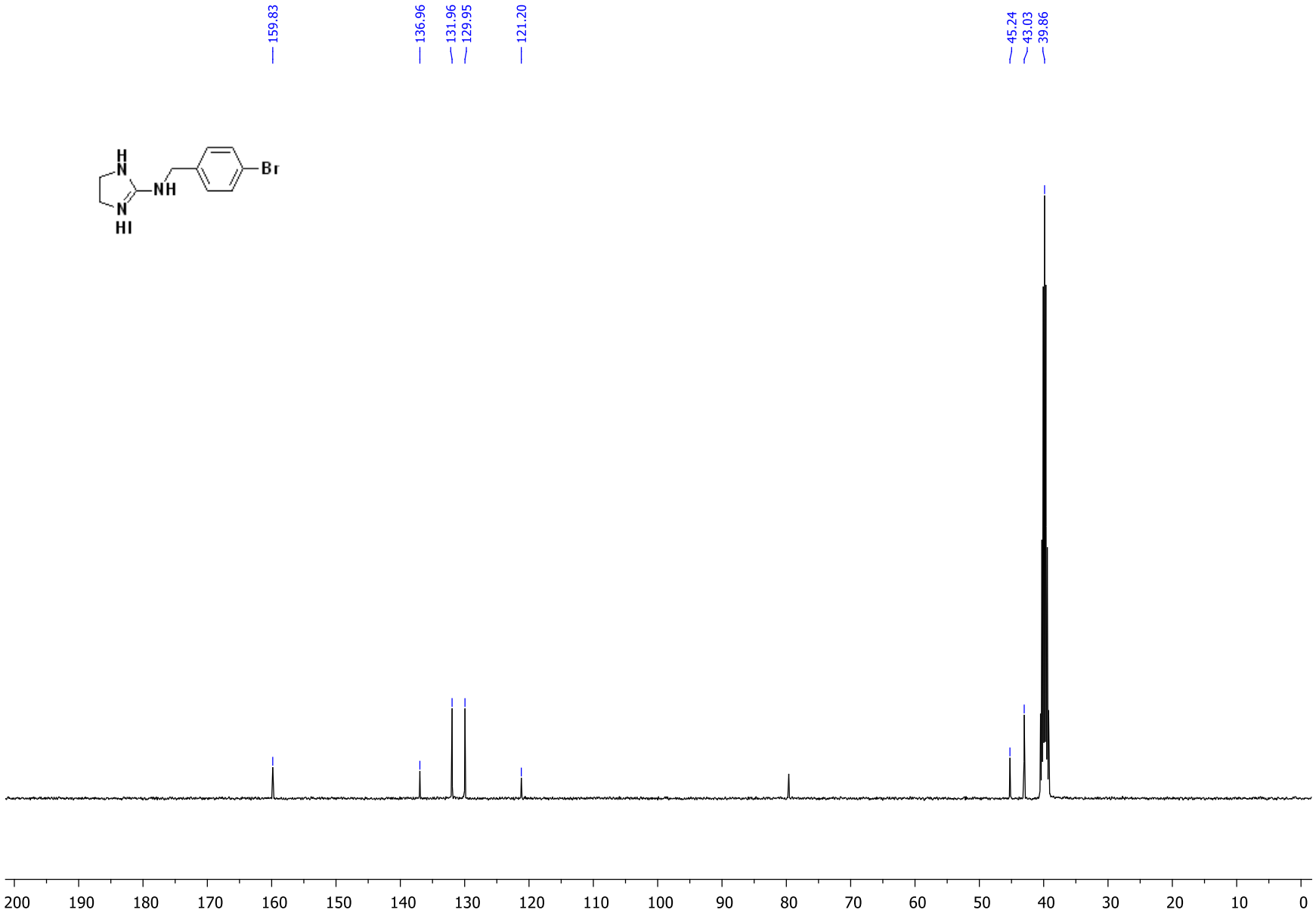
^{1}H-NMR of 1c (500 MHz, $CDCl_3$)



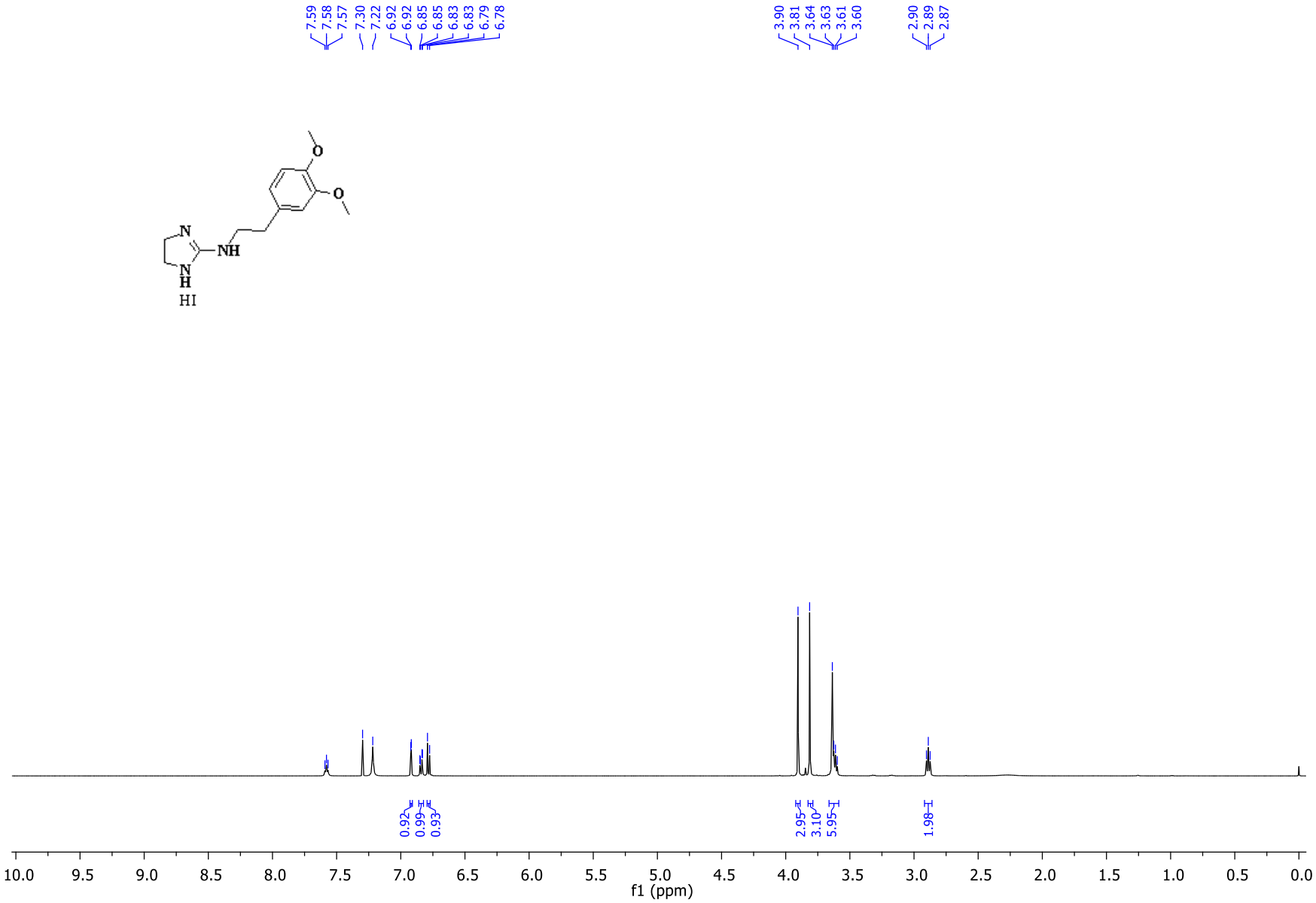
^{1}H-NMR of 1d (500 MHz, DMSO)



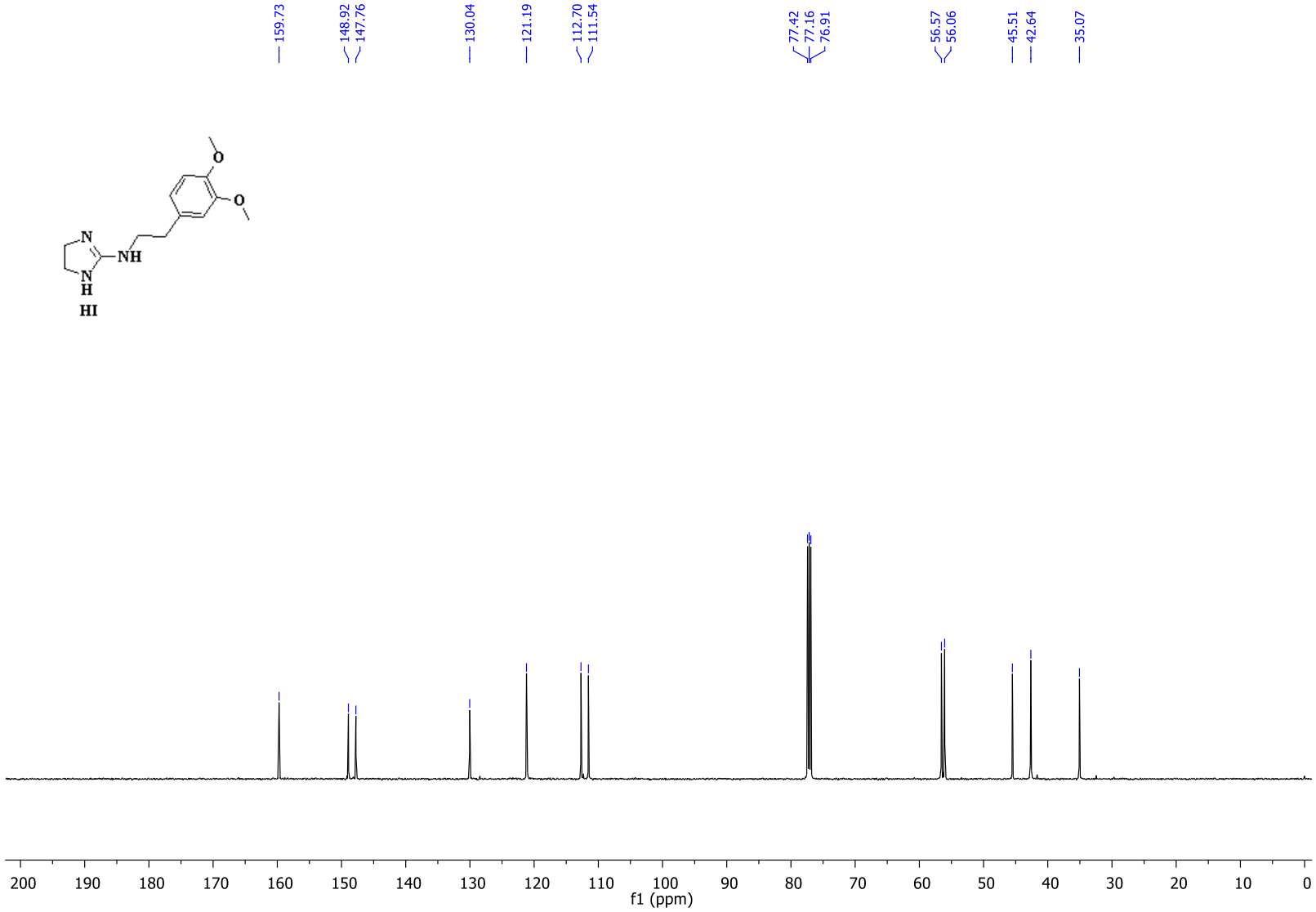
$^{13}C\{^{1}H\}$-NMR of 1d (101 MHz, DMSO)



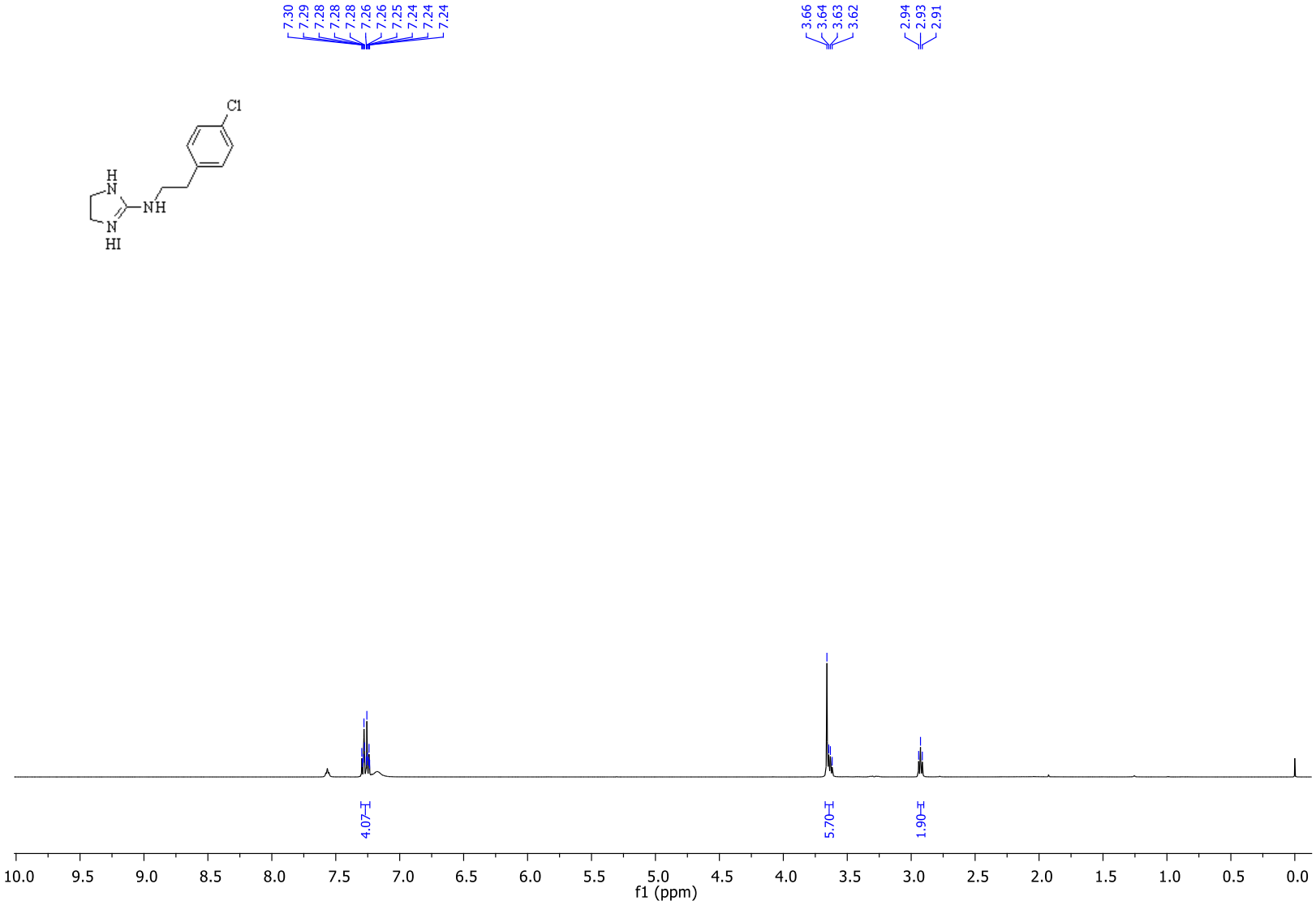
^{1}H-NMR of 1f (500 MHz, $CDCl_3$)



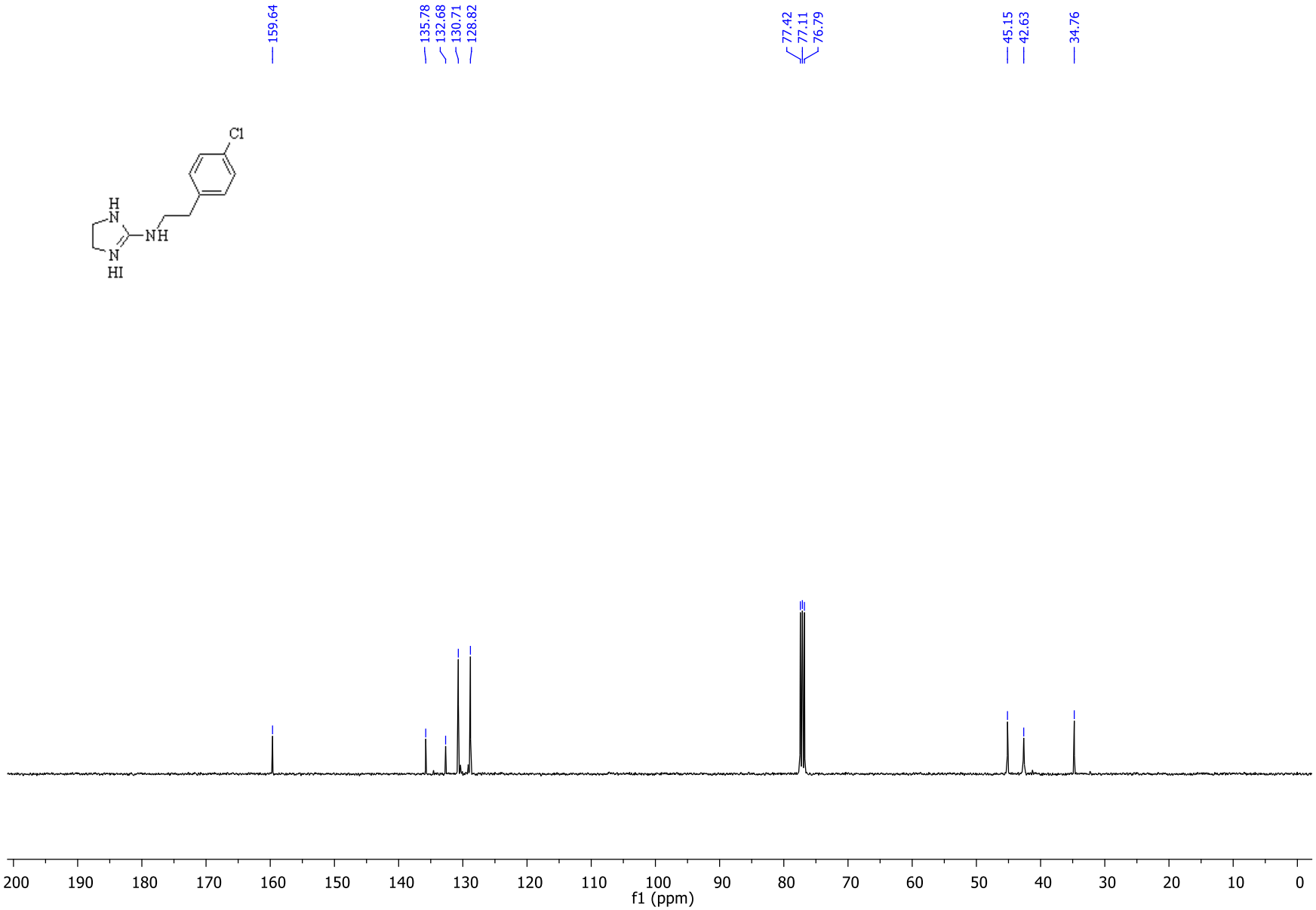
$^{13}C\{^{1}H\}$-NMR of 1f (126 MHz, $CDCl_3$)



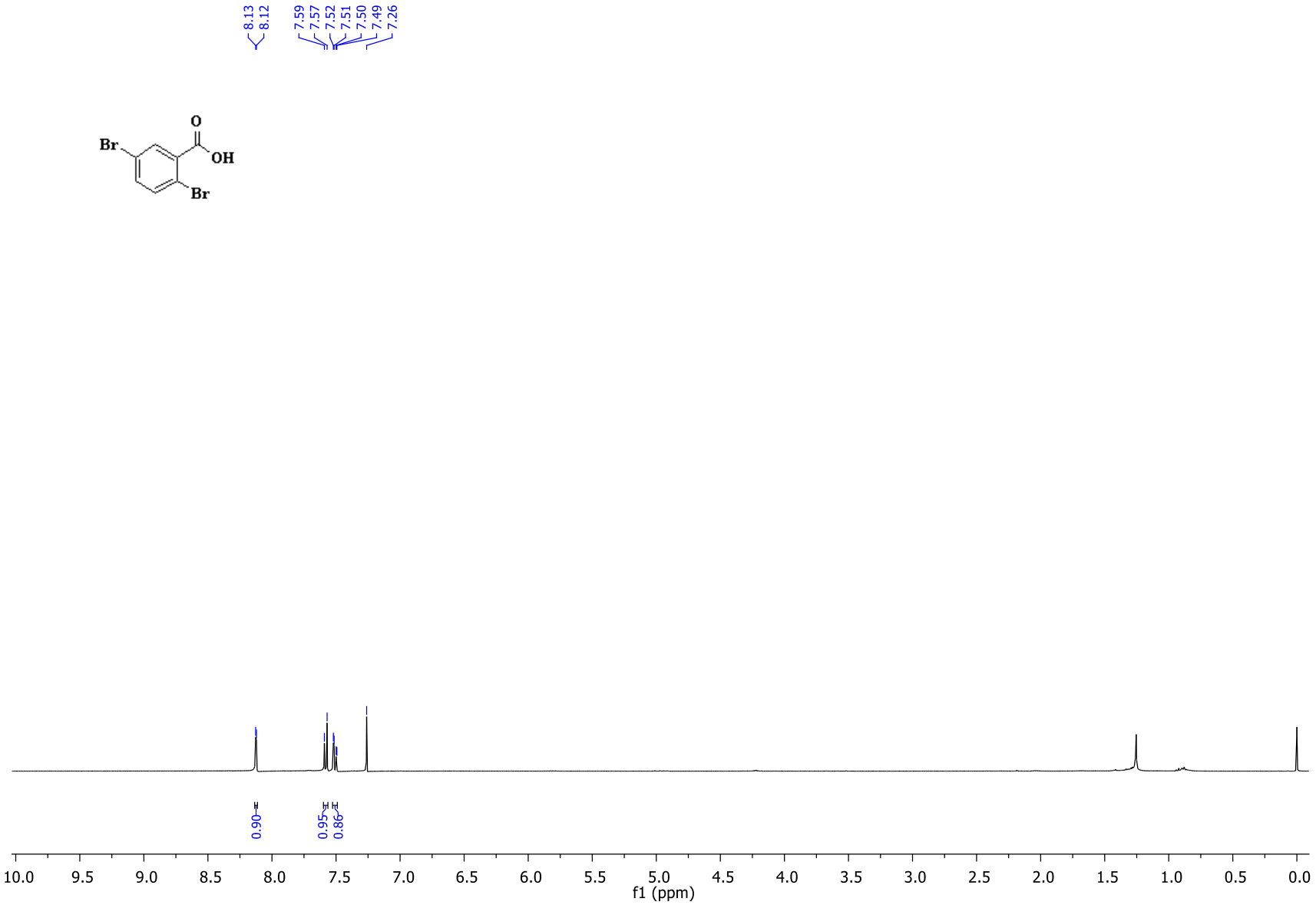
^{1}H-NMR of 1g (500 MHz, $CDCl_3$)



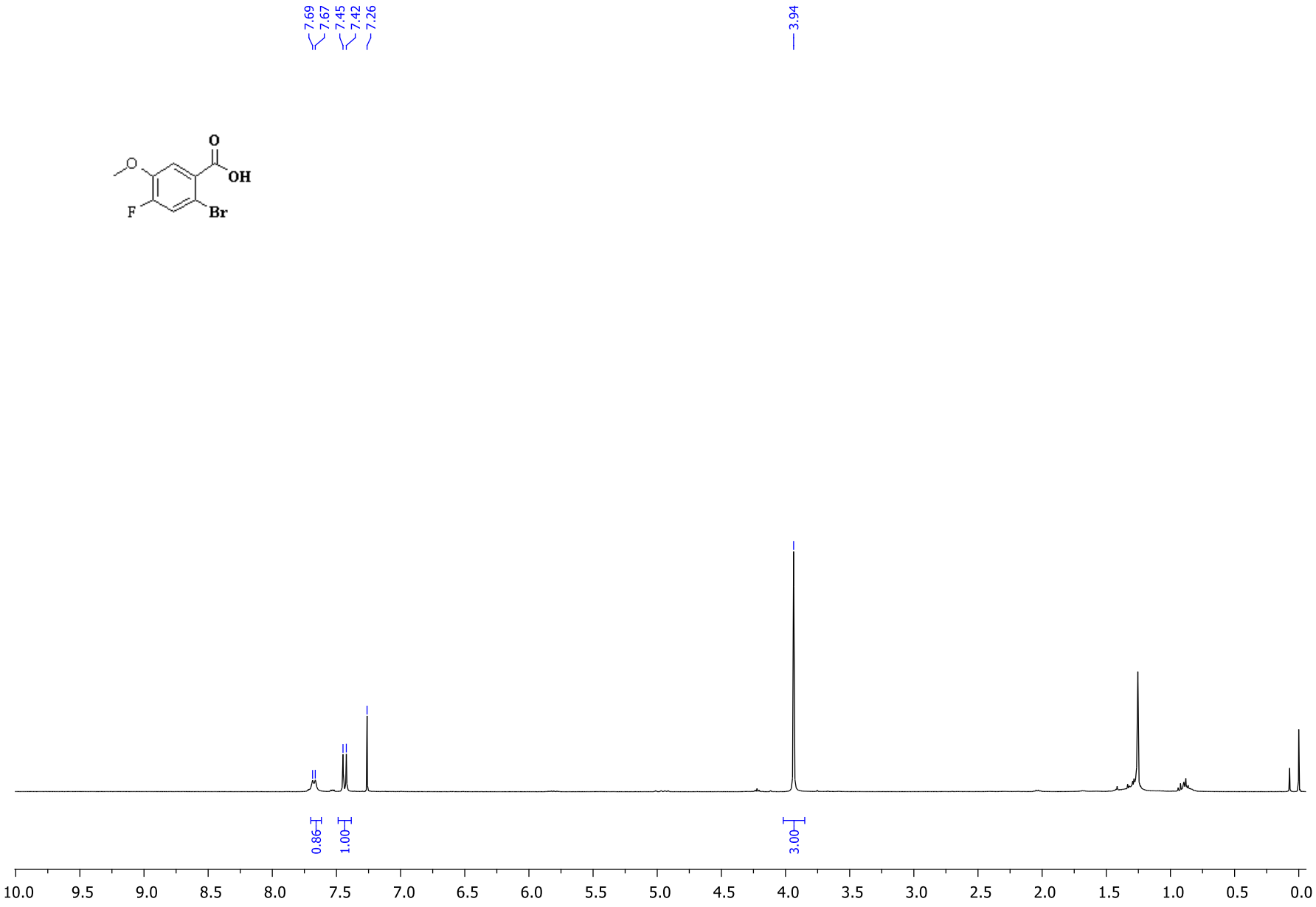
$^{13}C\{^{1}H\}$-NMR of 1g (101 MHz, $CDCl_3$)



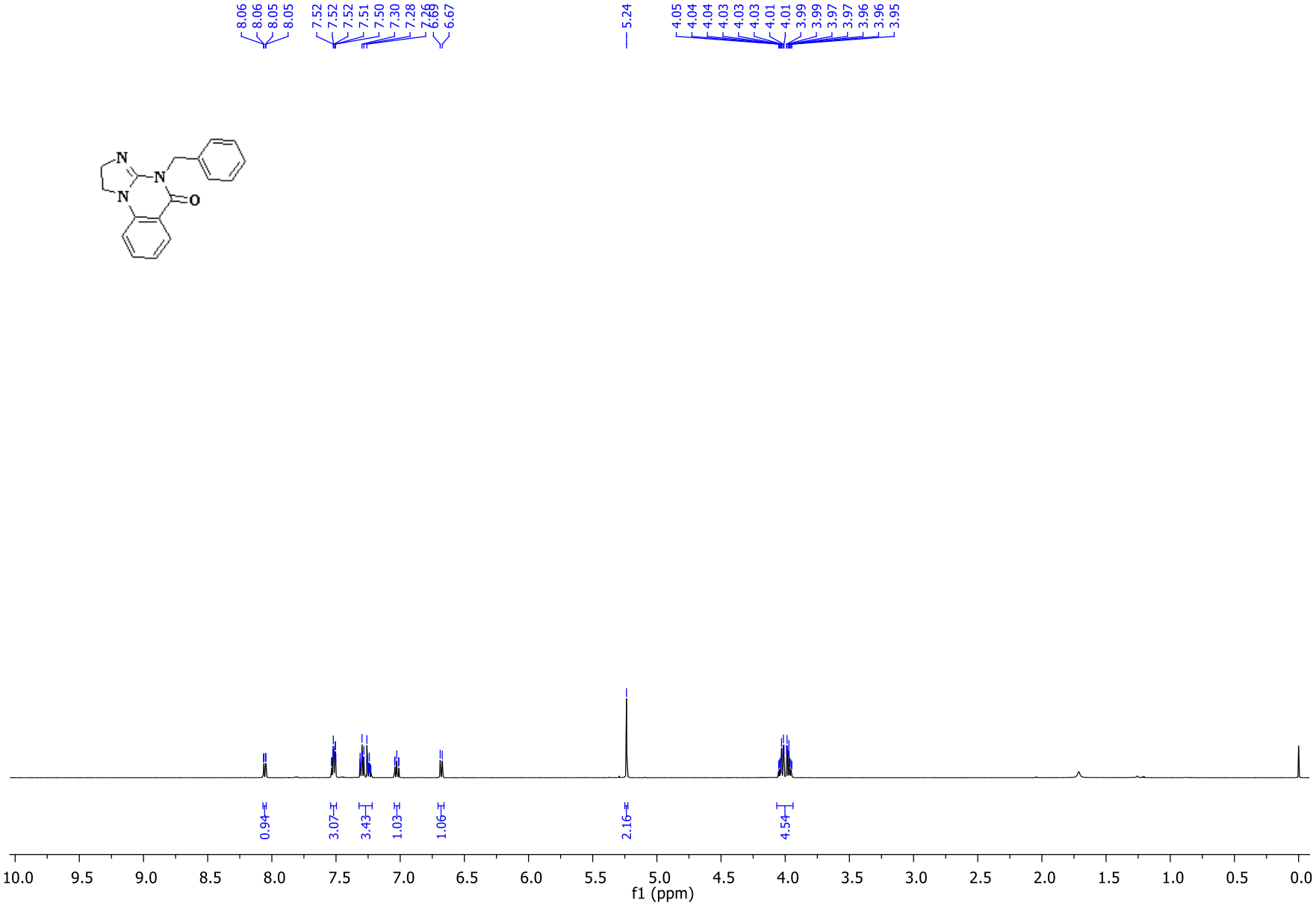
^{1}H-NMR of 2e (400 MHz, $CDCl_3$)



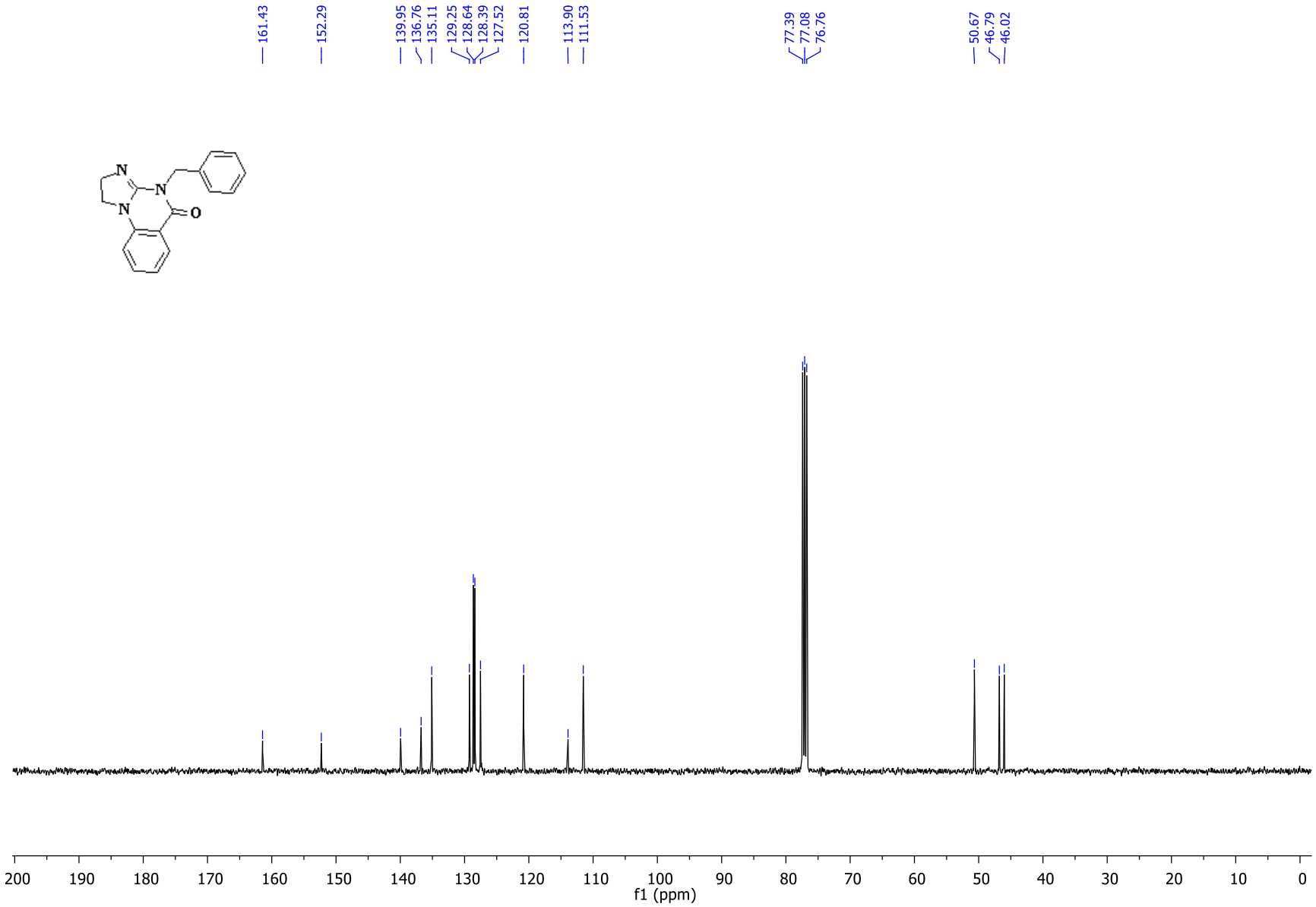
^{1}H-NMR of 2j (400 MHz, $CDCl_3$)



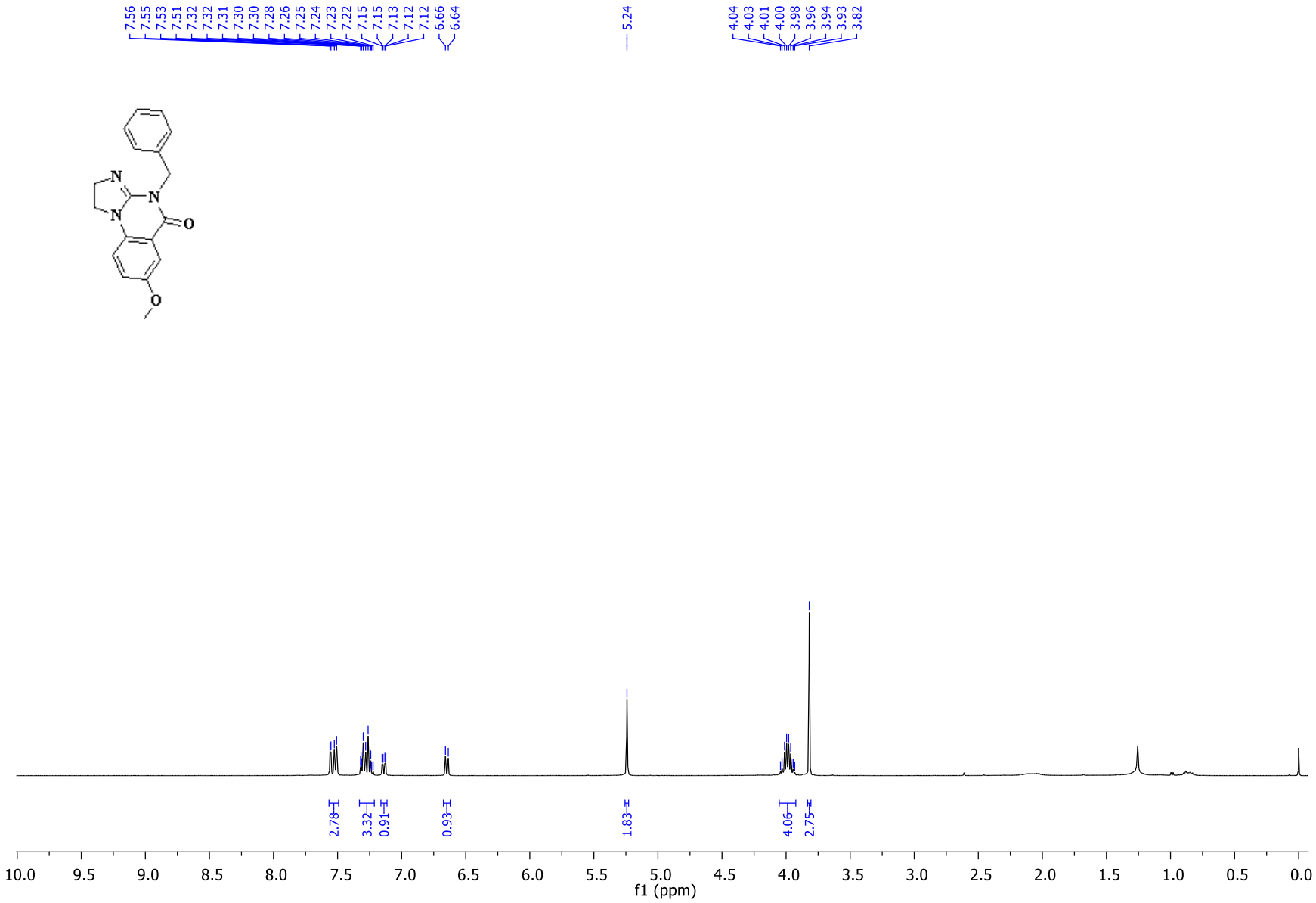
^{1}H-NMR of 3a (500 MHz, $CDCl_3$)



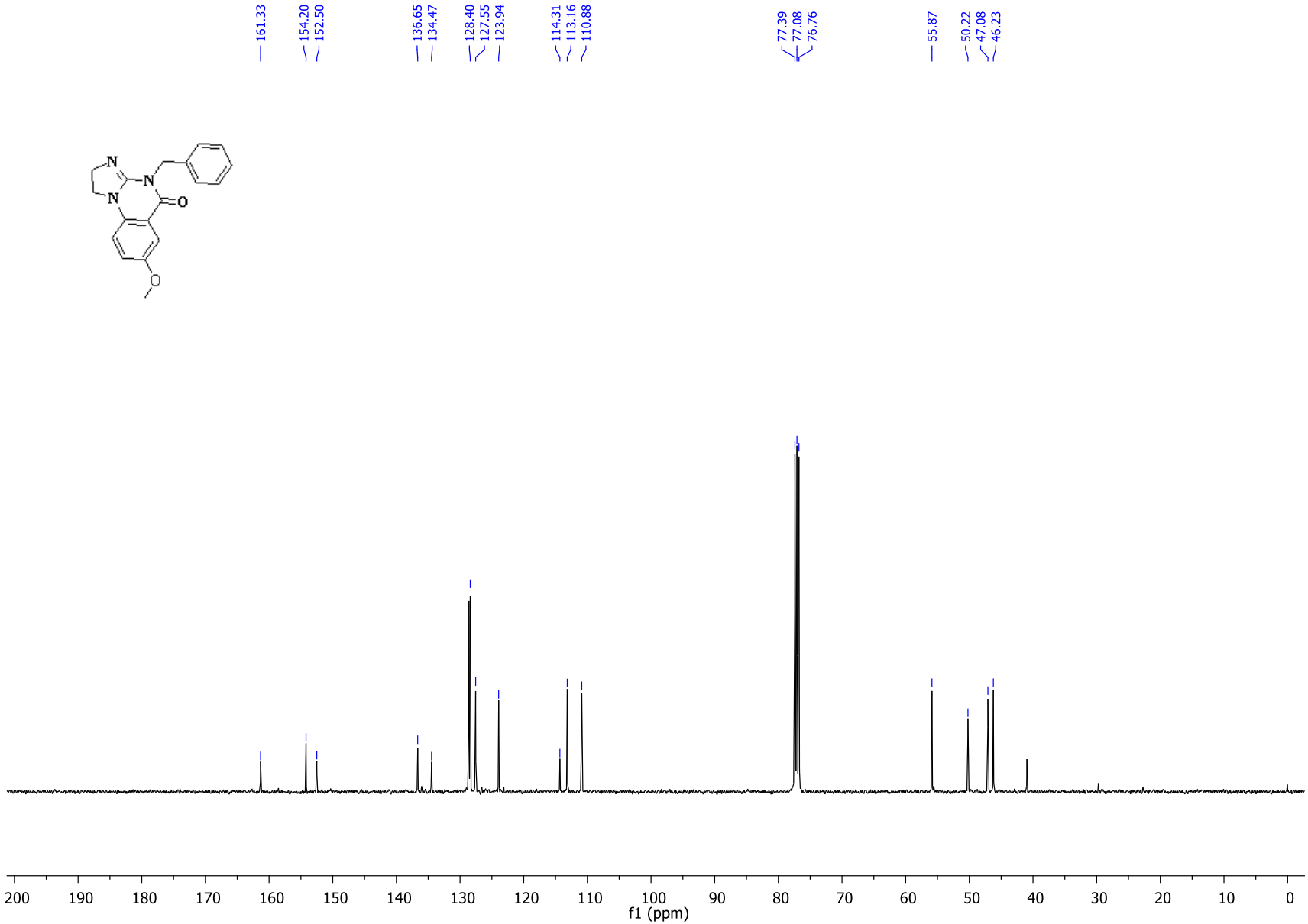
$^{13}C\{^{1}H\}$-NMR of 3a (101 MHz, $CDCl_3$)



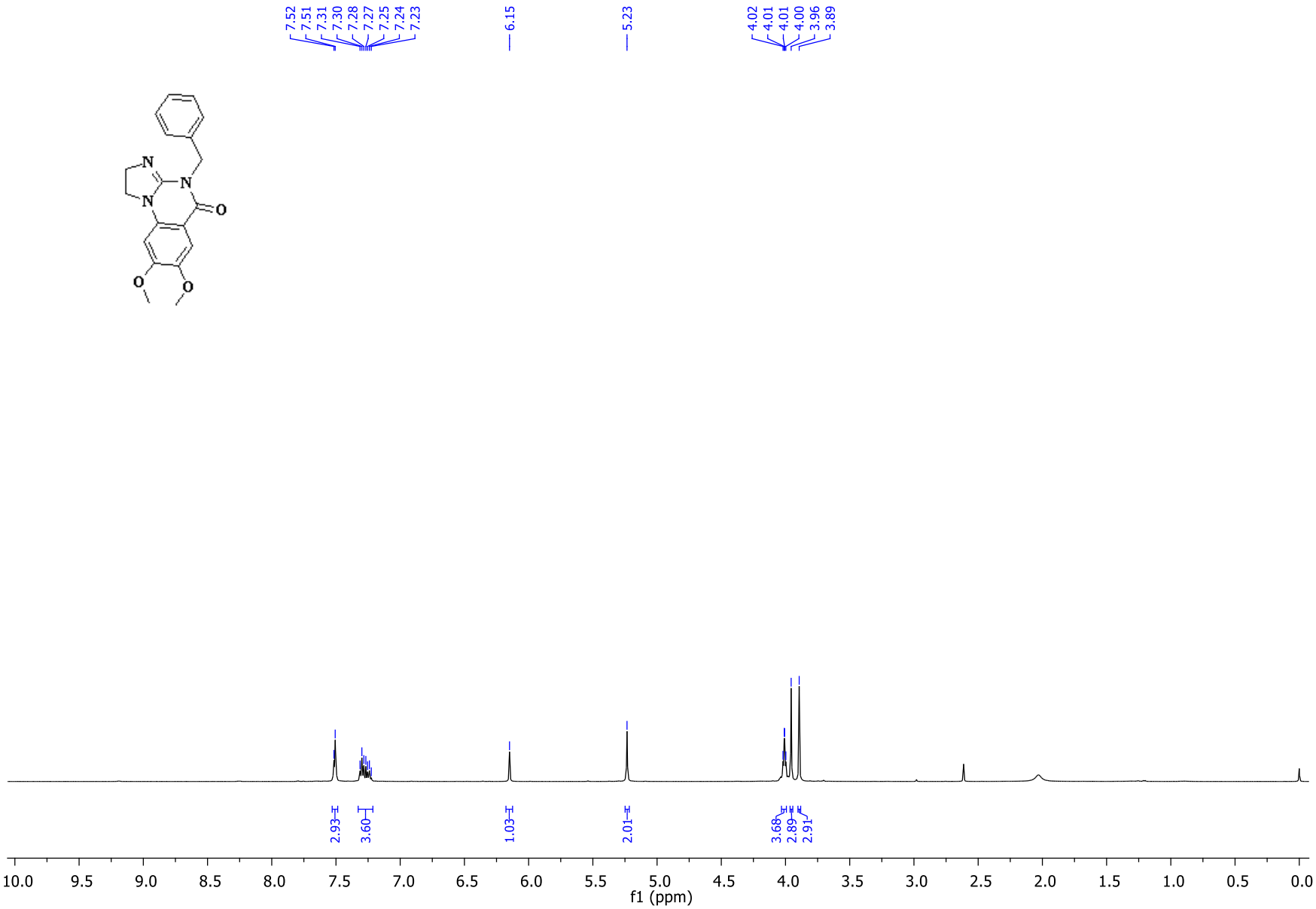
^{1}H-NMR of 3b (400 MHz, $CDCl_3$)



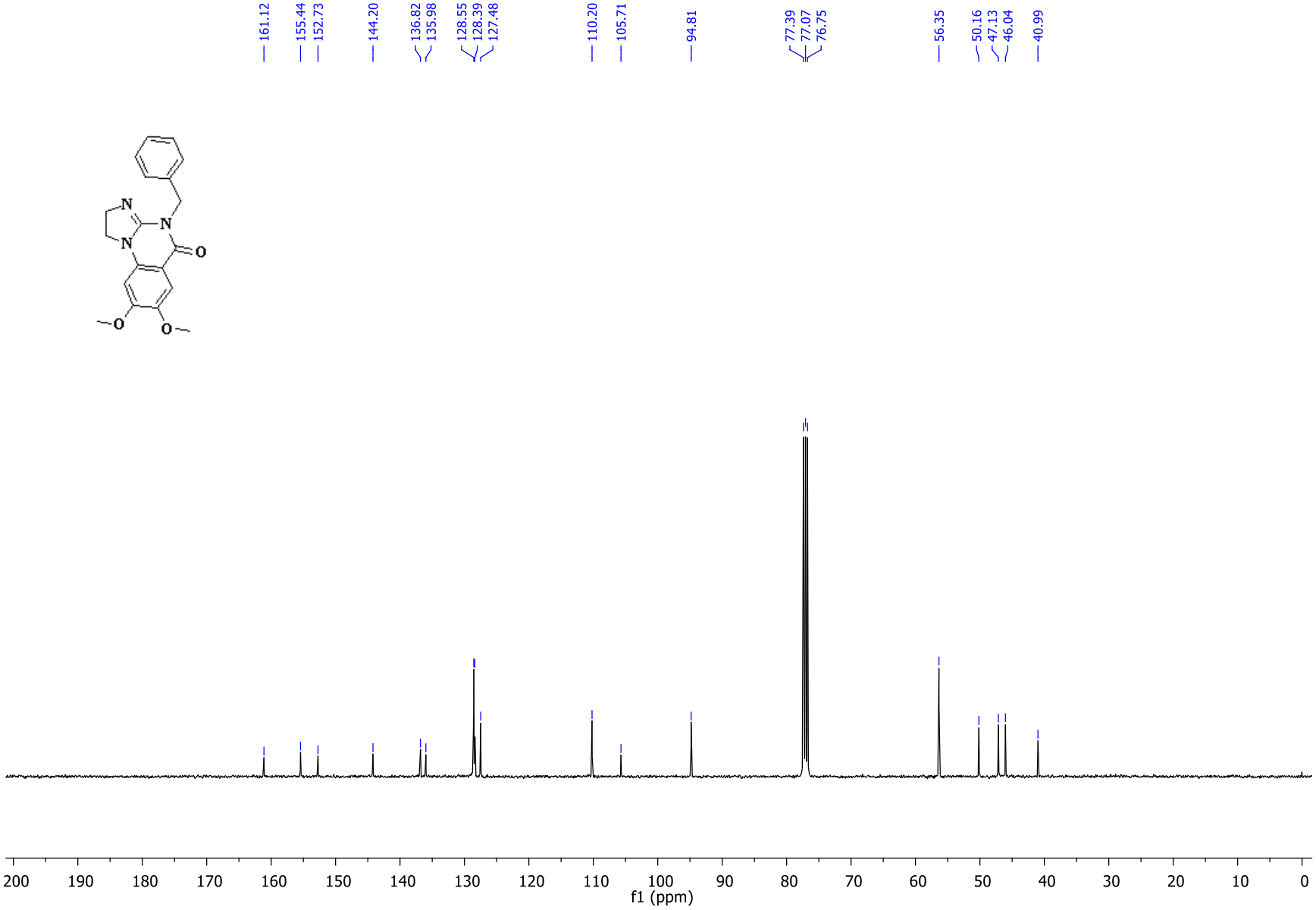
$^{13}C\{^{1}H\}$-NMR of 3b (101 MHz, $CDCl_3$)



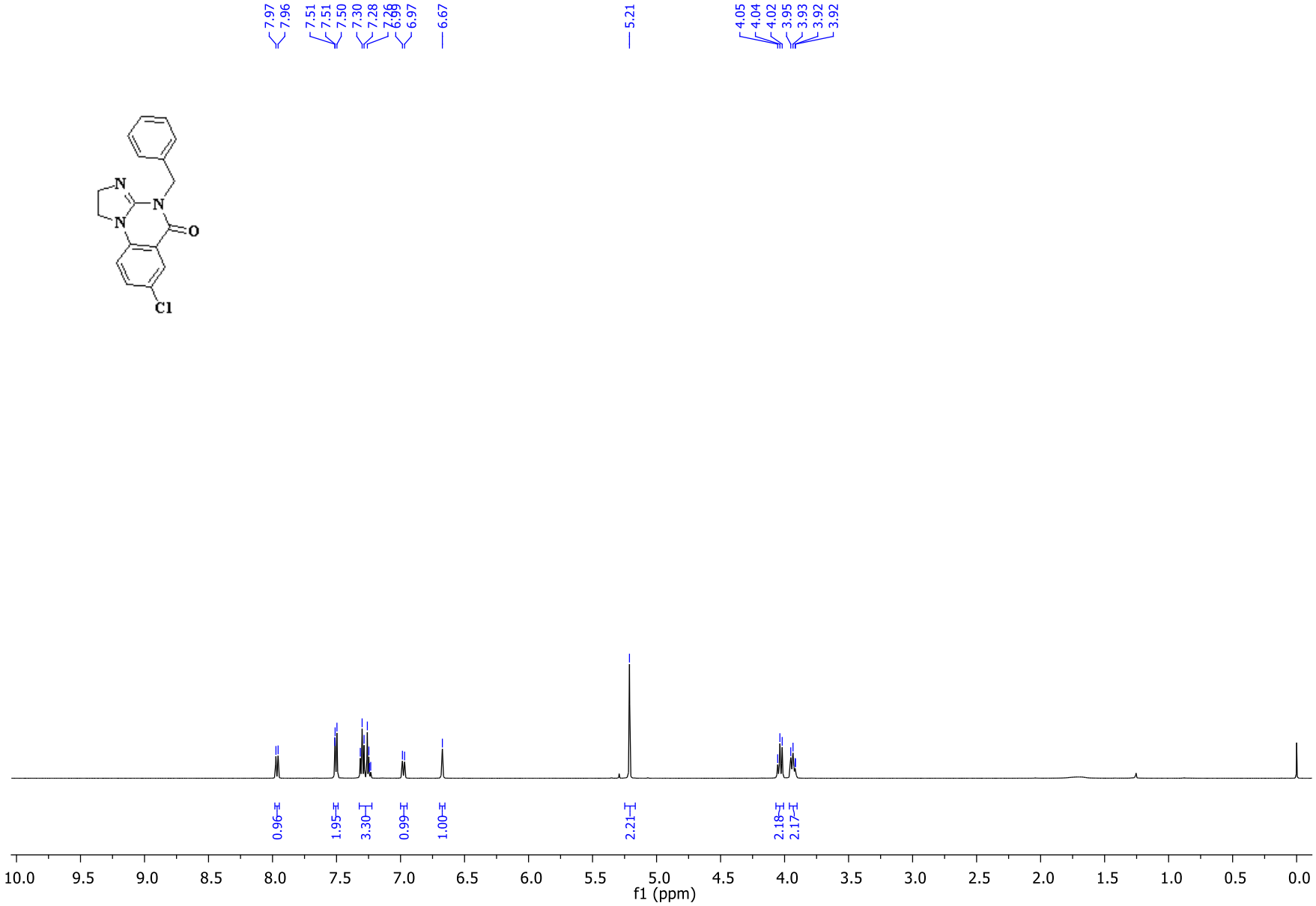
^{1}H-NMR of 3c (300 MHz, $CDCl_3$)



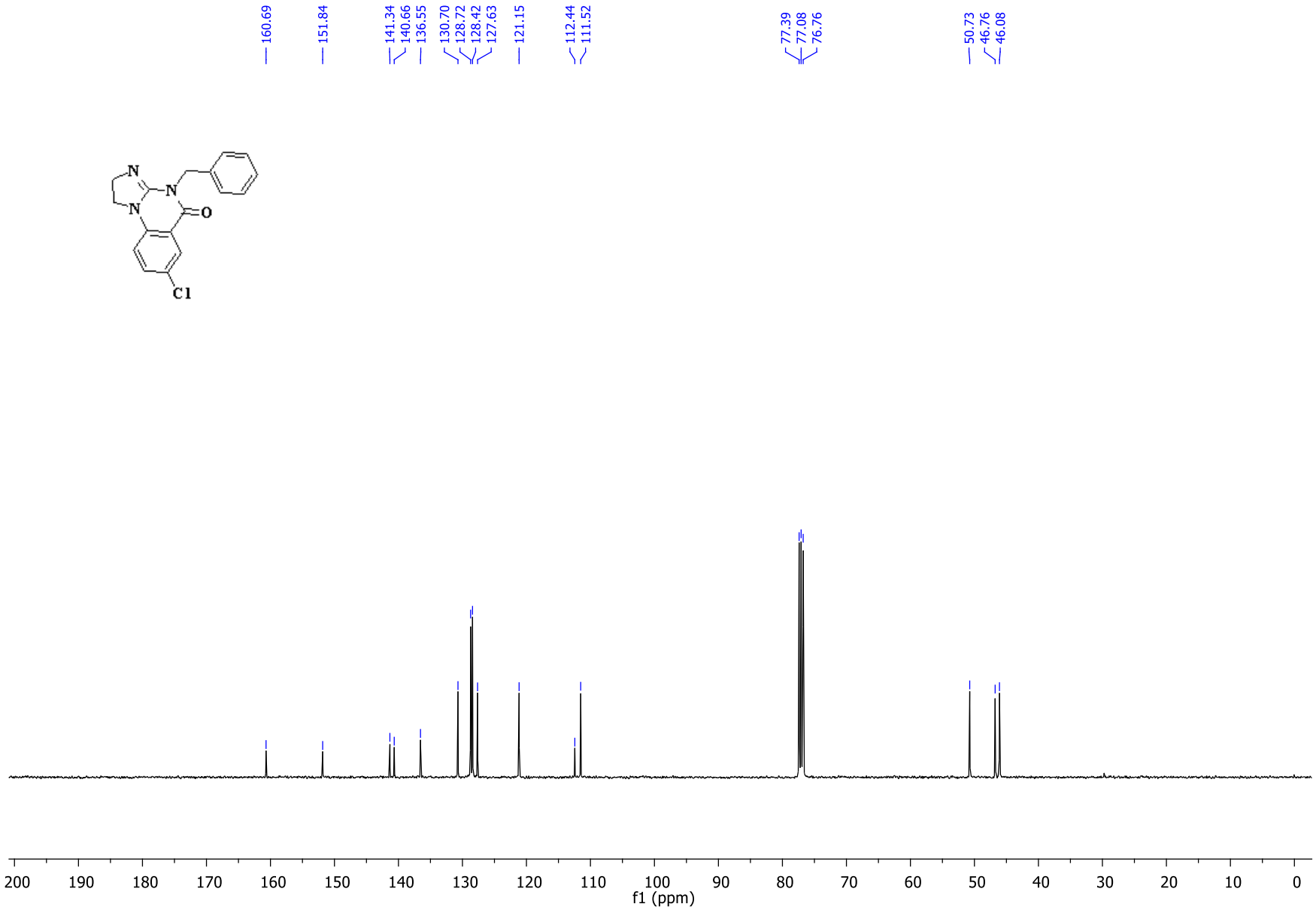
$^{13}C\{^{1}H\}$-NMR of 3c (101 MHz, $CDCl_3$)



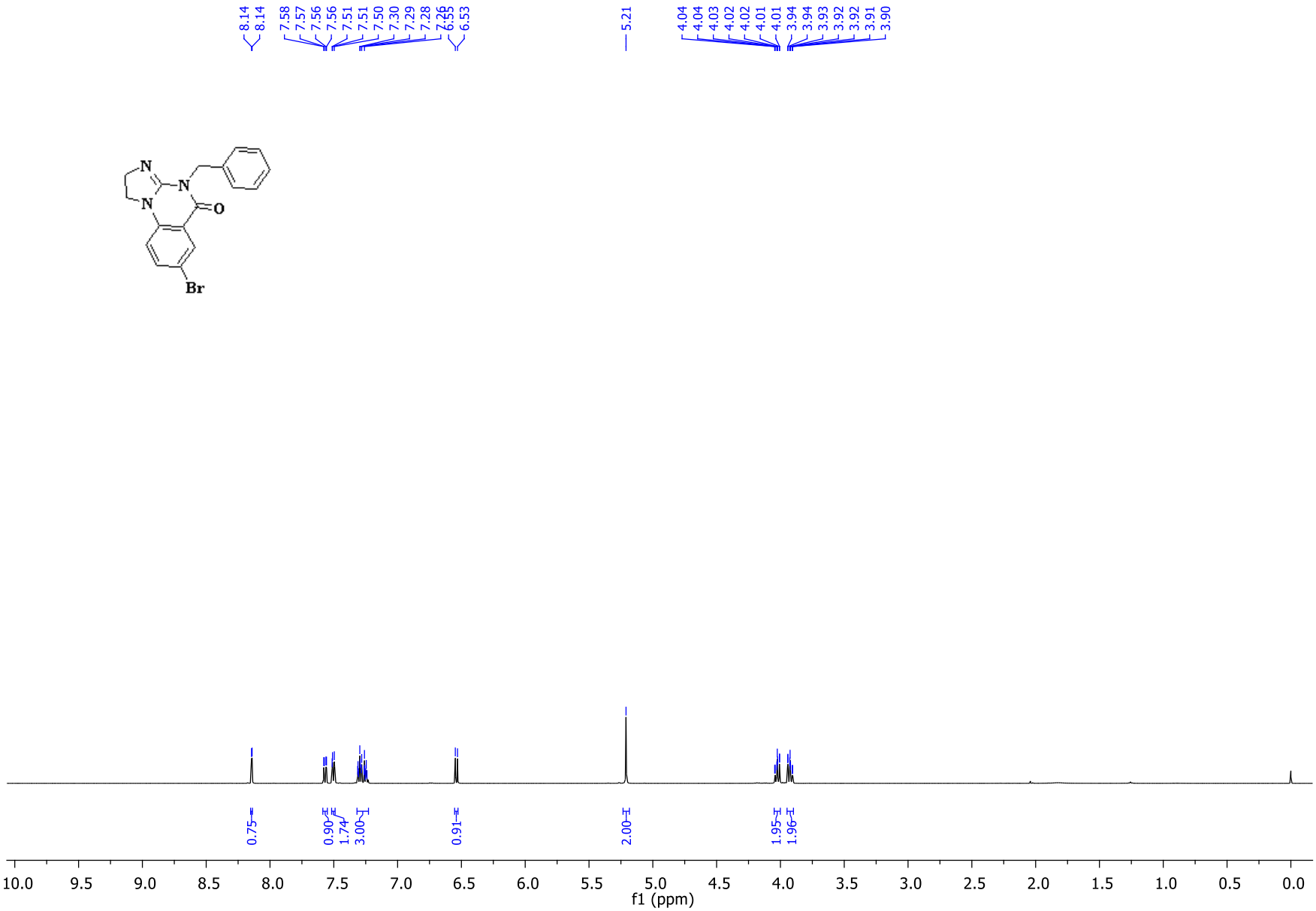
^{1}H-NMR of 3d (500 MHz, $CDCl_3$)



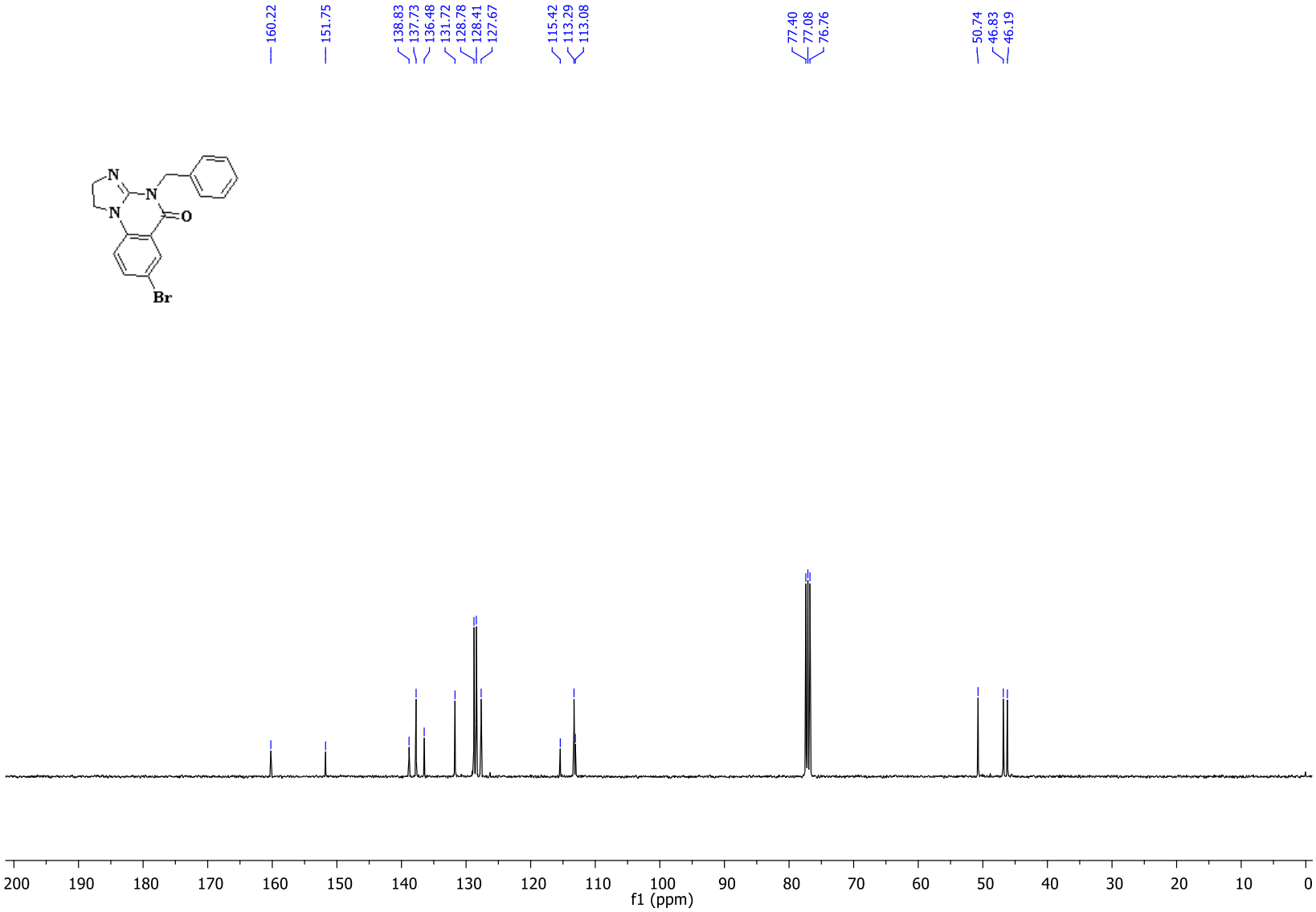
$^{13}C\{^{1}H\}$-NMR of 3d (101 MHz, $CDCl_3$)



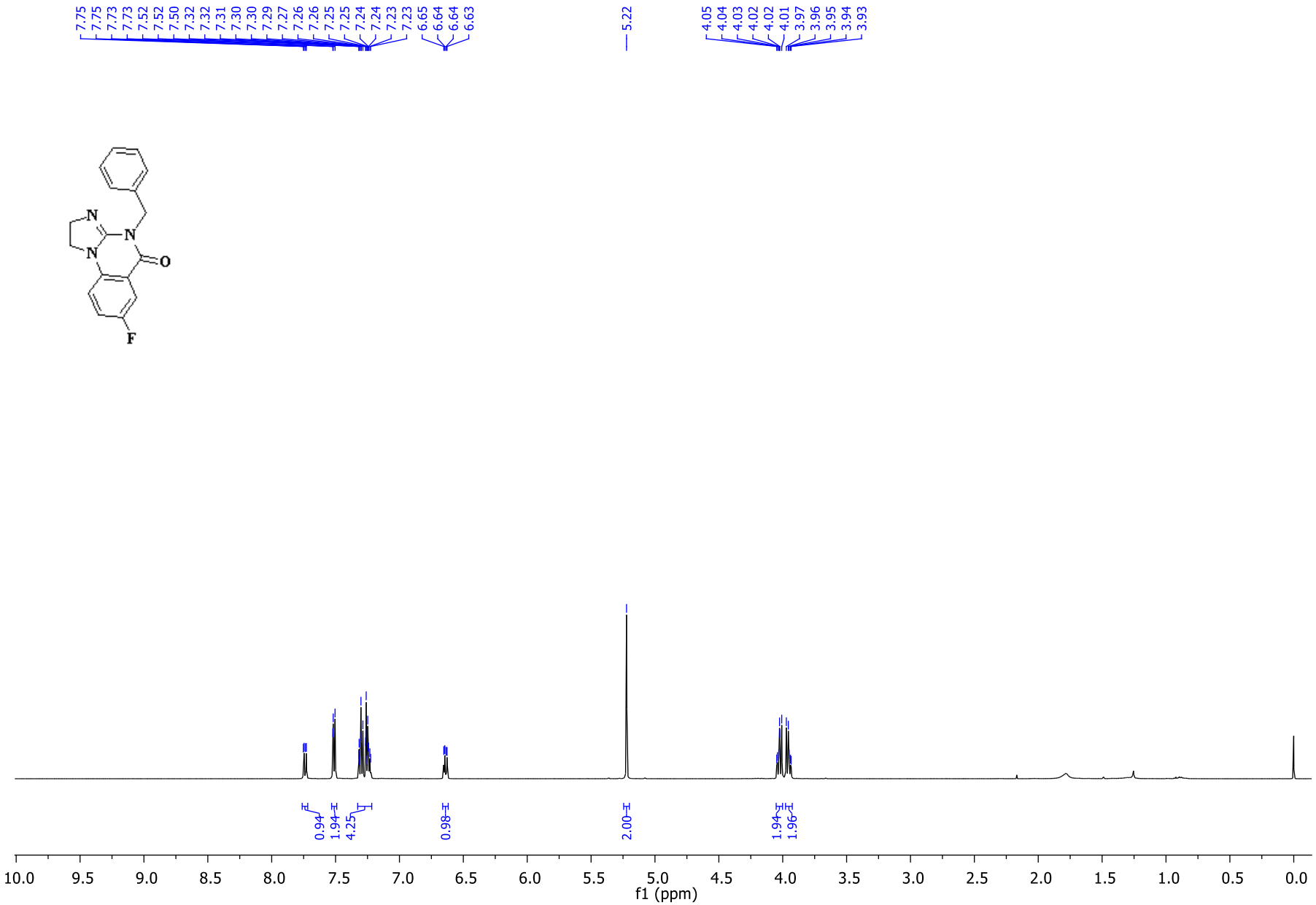
^{1}H-NMR of 3e (300 MHz, $CDCl_3$)



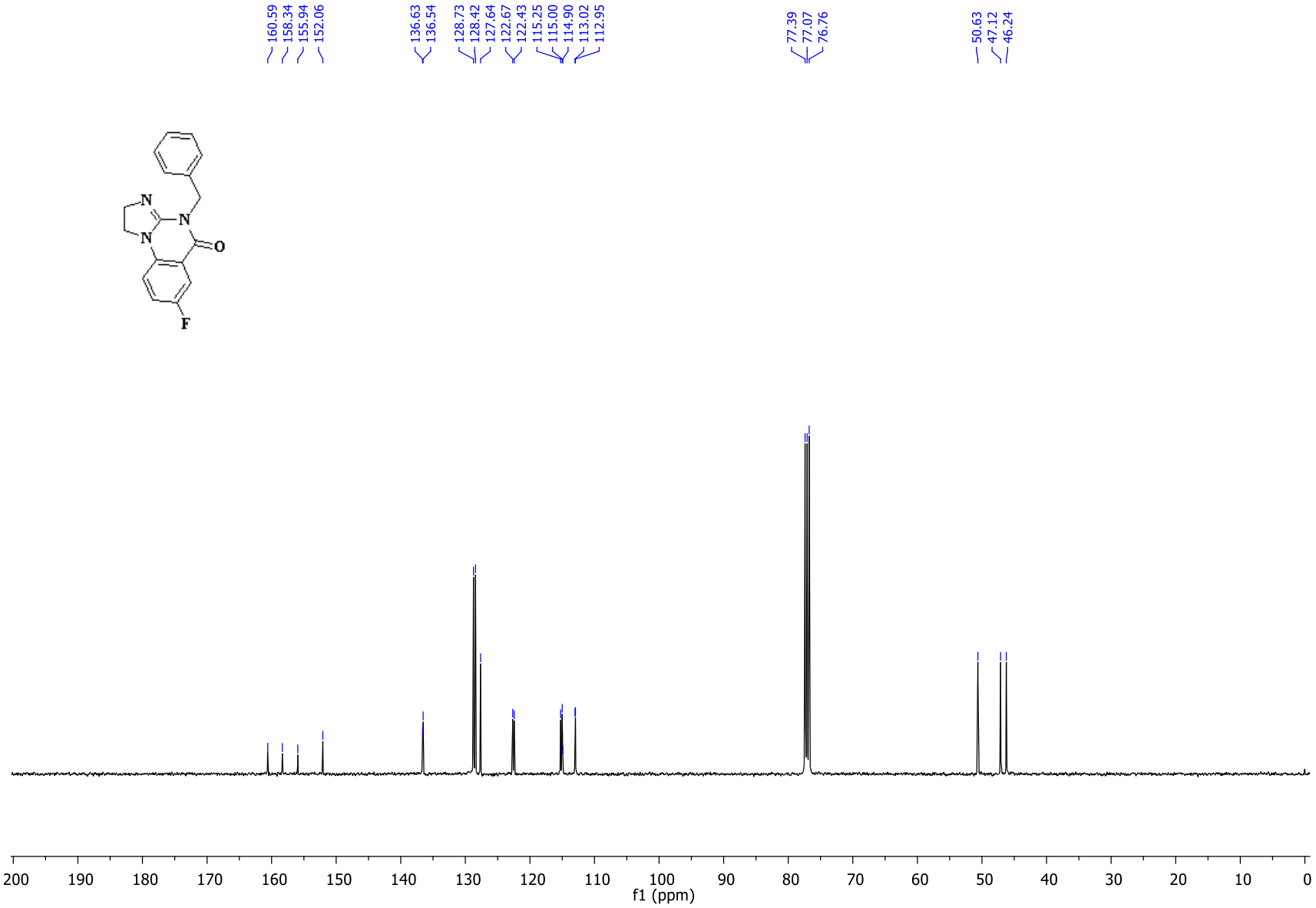
$^{13}C\{^{1}H\}$-NMR of 3e (101 MHz, $CDCl_3$)



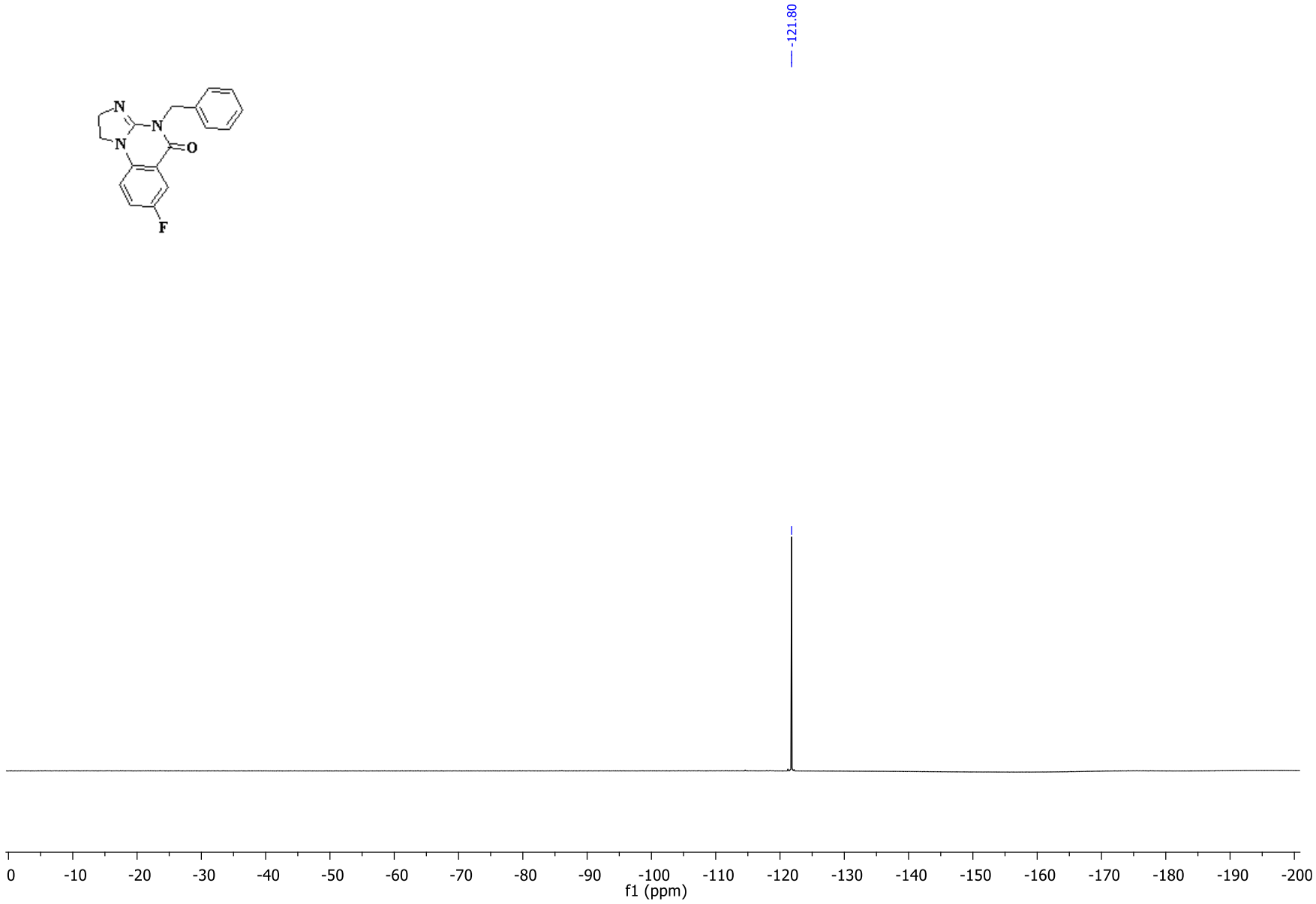
^{1}H-NMR of 3f (500 MHz, $CDCl_3$)



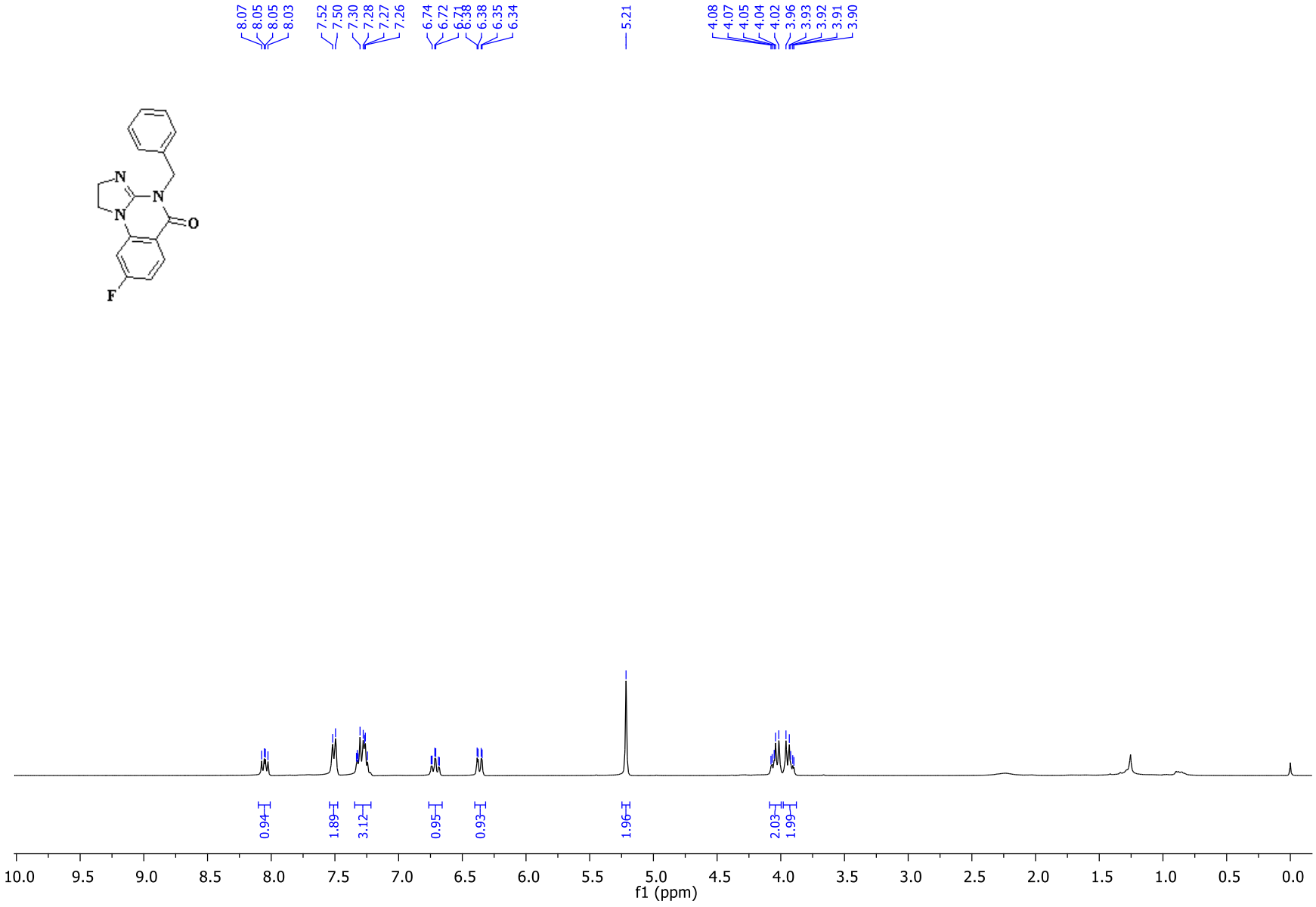
$^{13}C\{^{1}H\}$-NMR of 3f (101 MHz, $CDCl_3$)



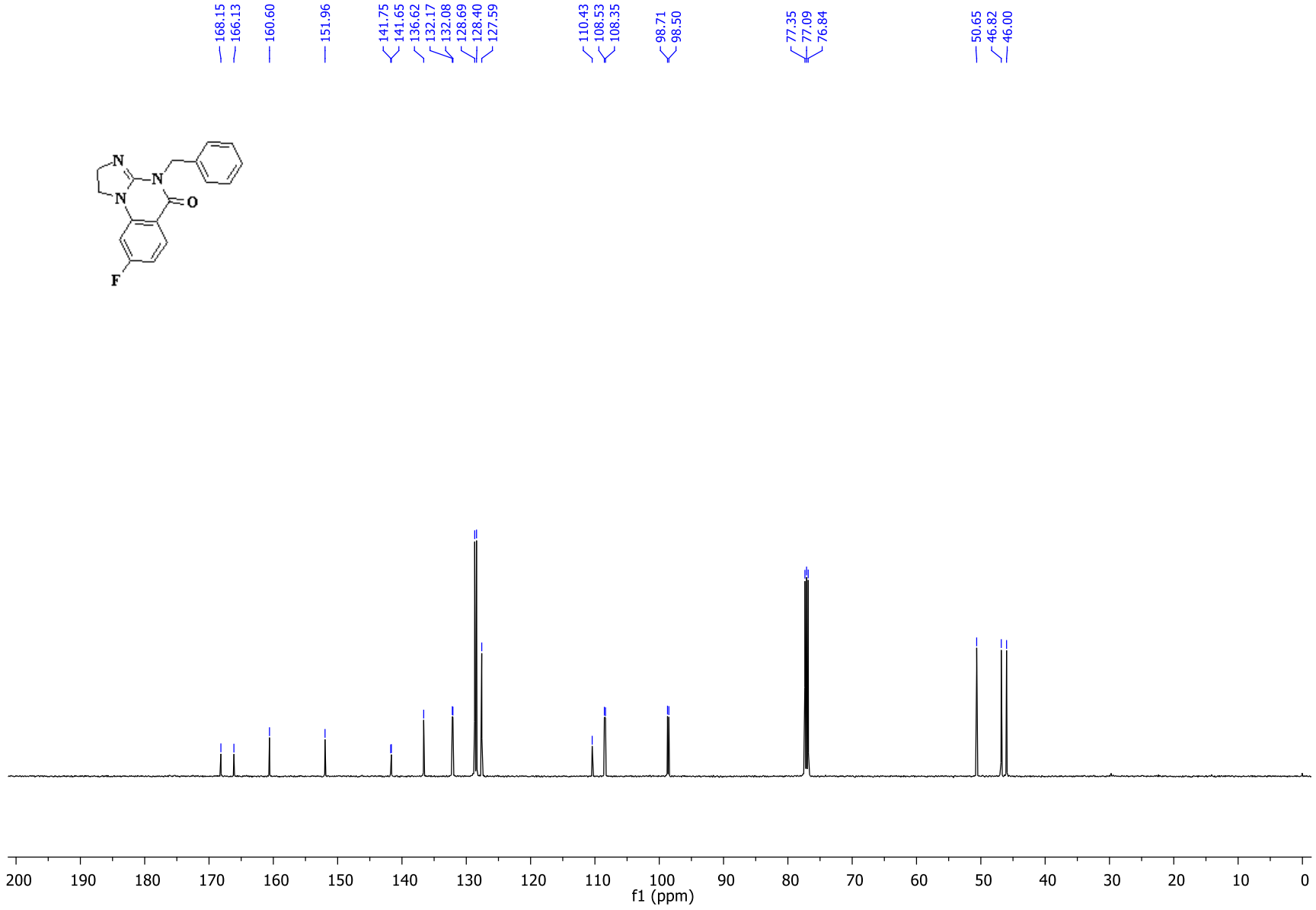
^{19}F-NMR of 3f (377 MHz, $CDCl_3$)



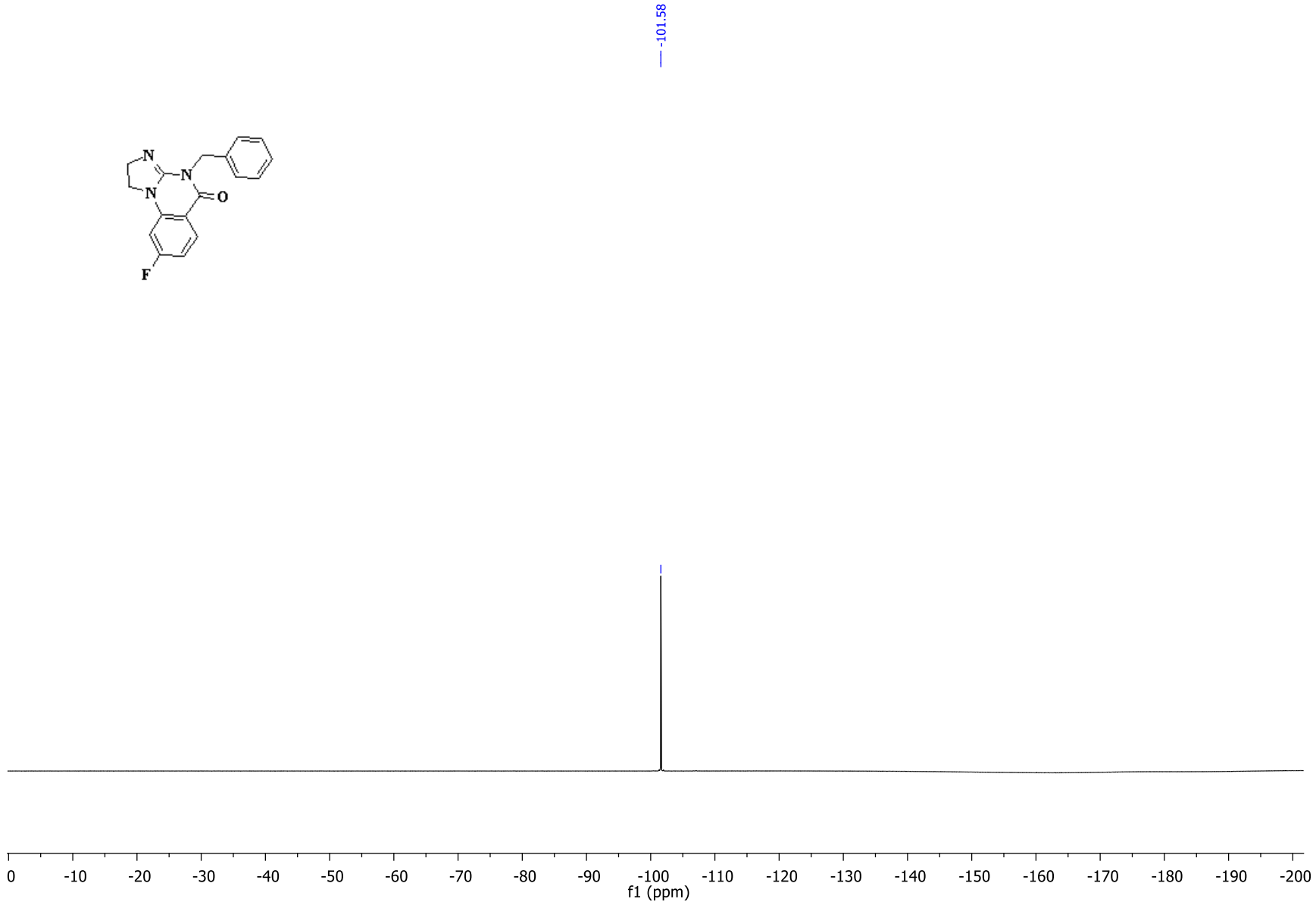
^{1}H-NMR of 3g (300 MHz, $CDCl_3$)



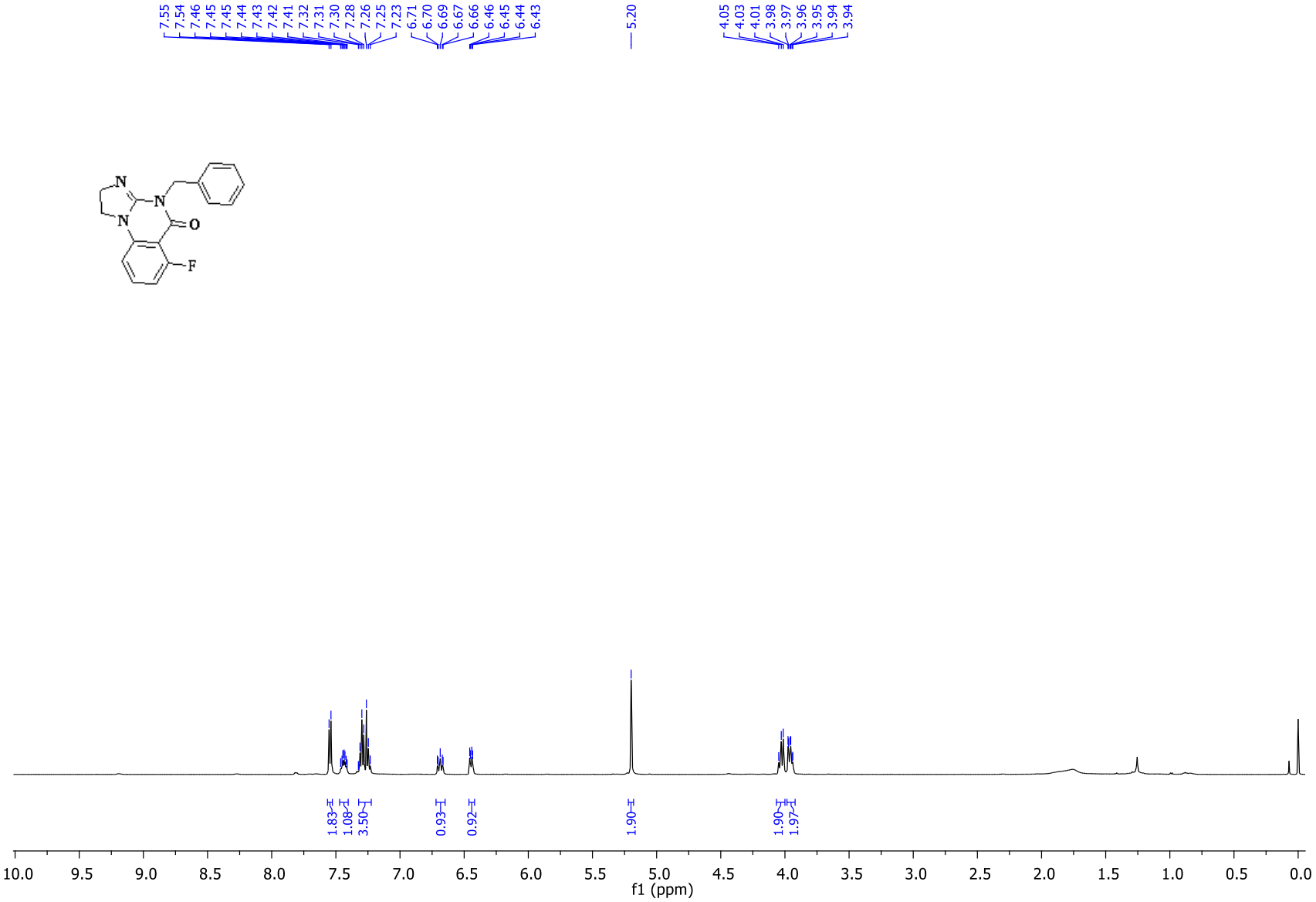
$^{13}C\{^{1}H\}$-NMR of 3g (126 MHz, $CDCl_3$)



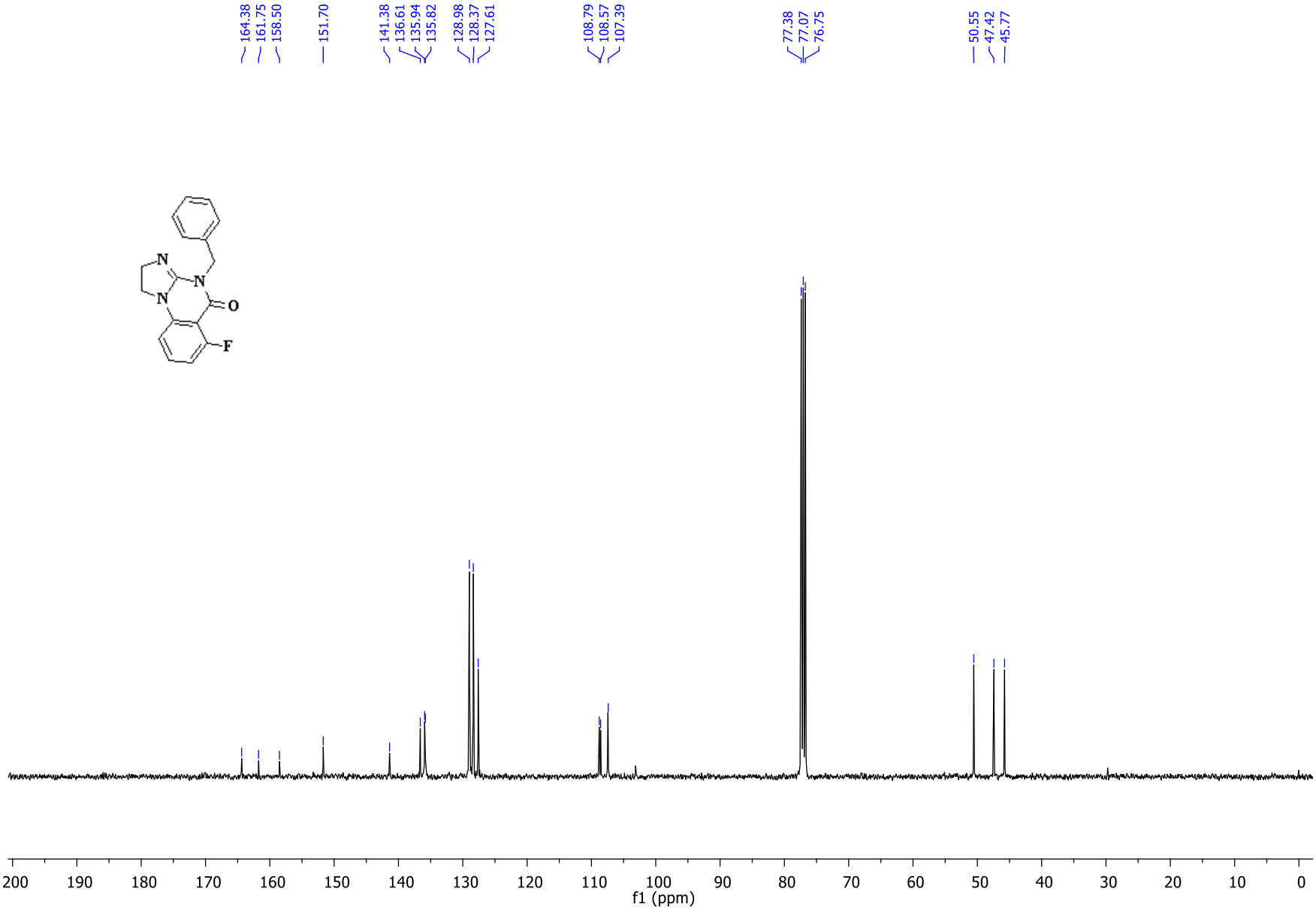
^{19}F-NMR of 3g (377 MHz, $CDCl_3$)



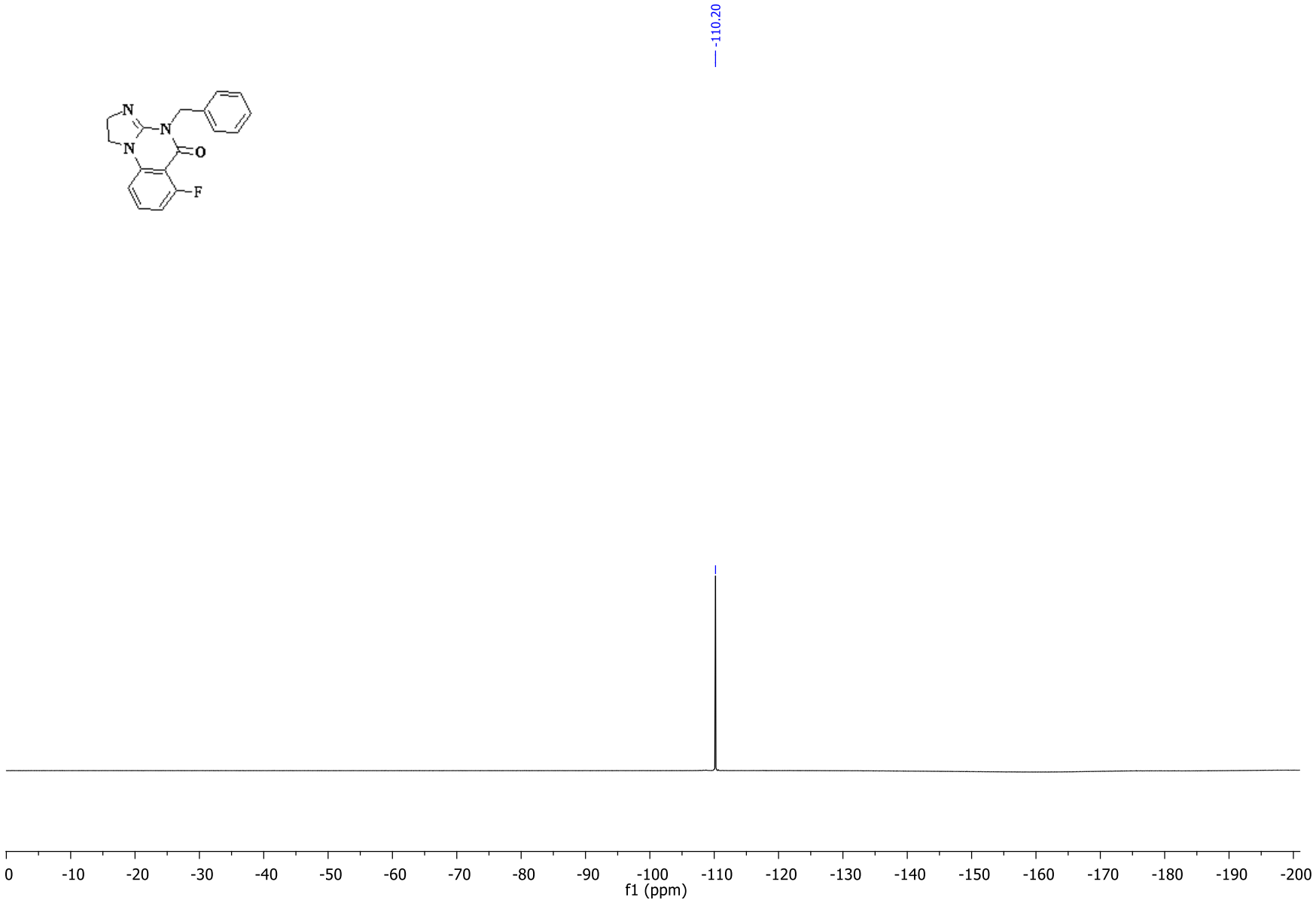
^{1}H-NMR of 3h (400 MHz, $CDCl_3$)



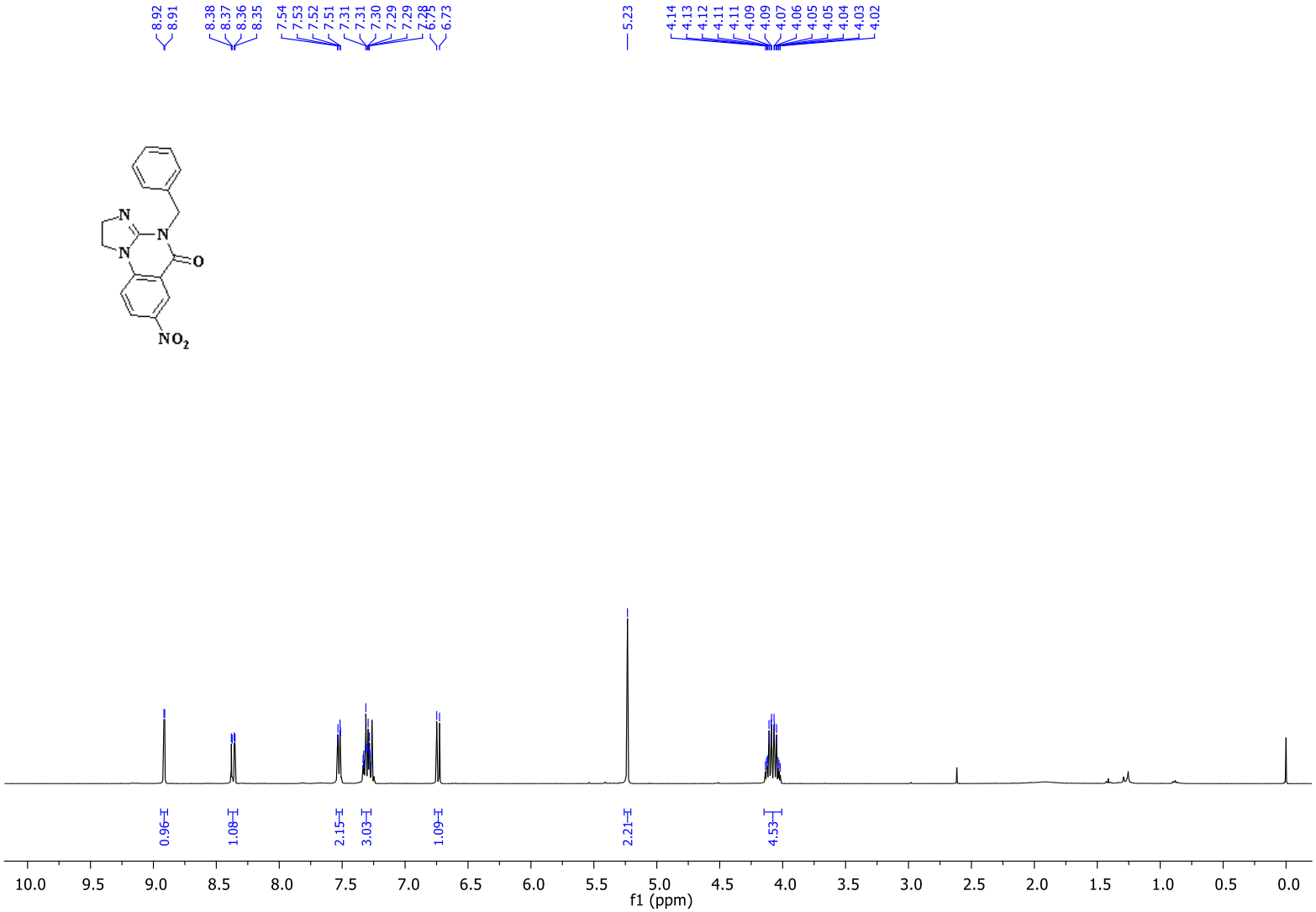
$^{13}C\{^{1}H\}$-NMR of 3h (101 MHz, $CDCl_3$)



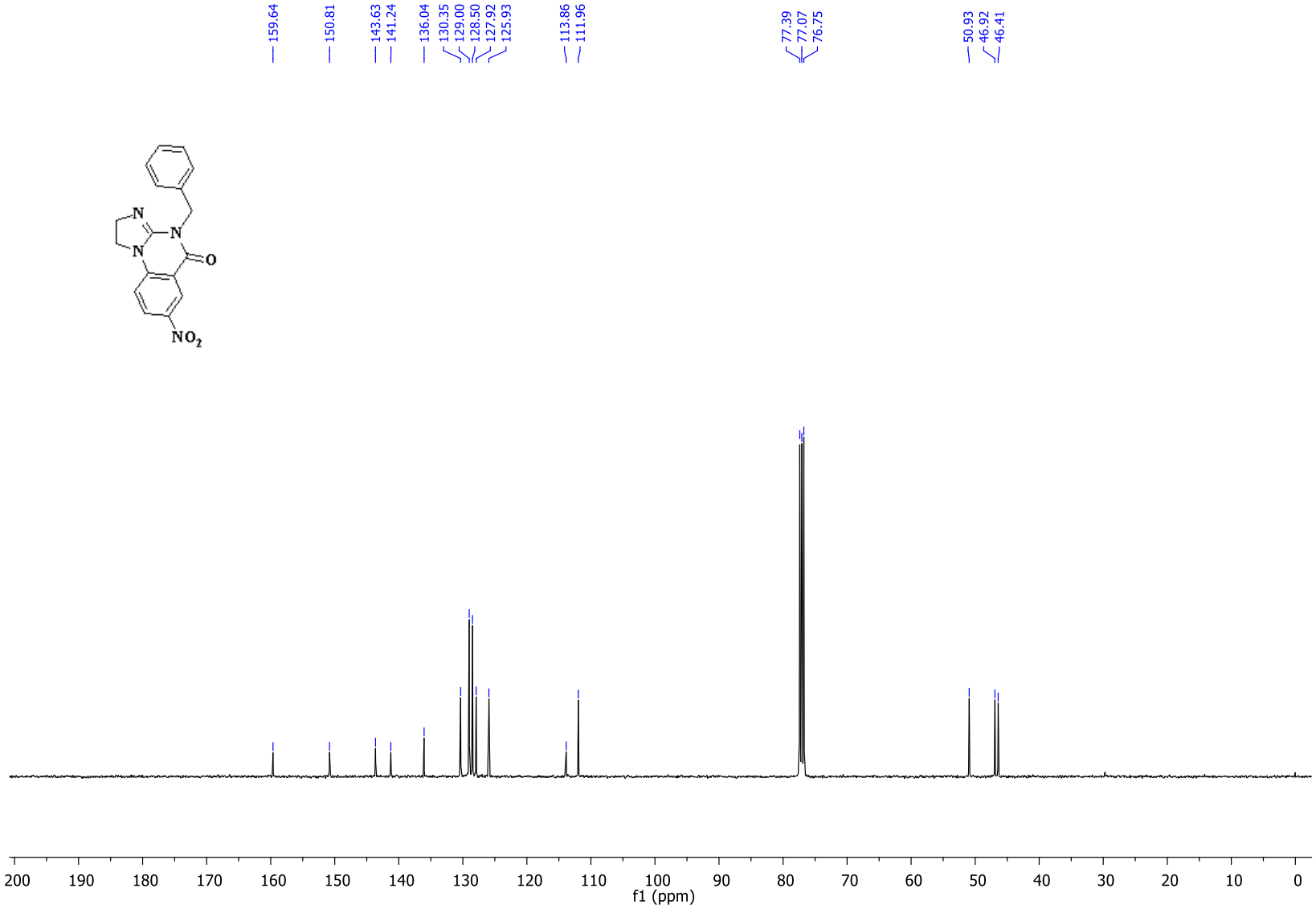
^{19}F-NMR of 3h (377 MHz, $CDCl_3$)



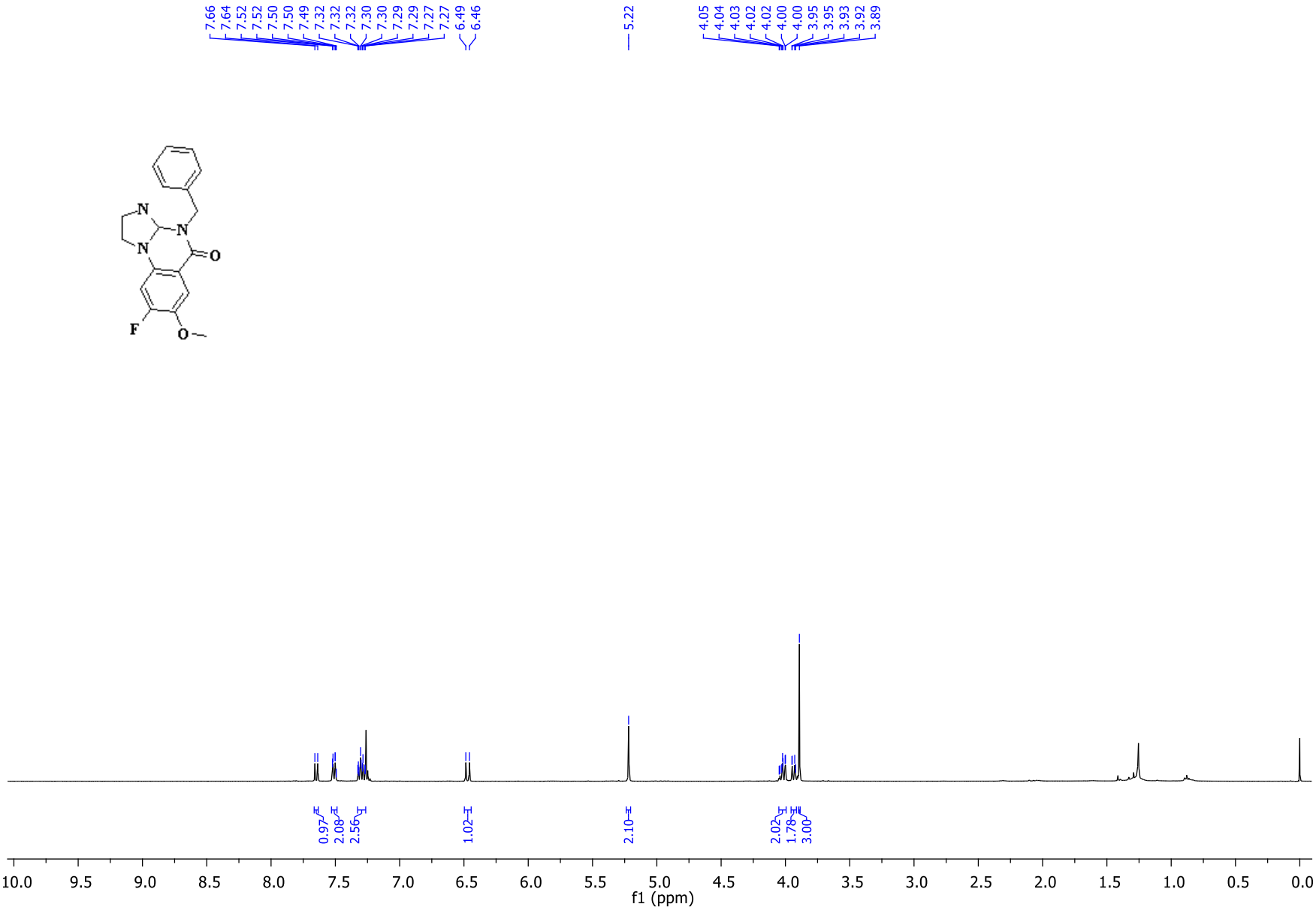
^{1}H-NMR of 3i (400 MHz, $CDCl_3$)



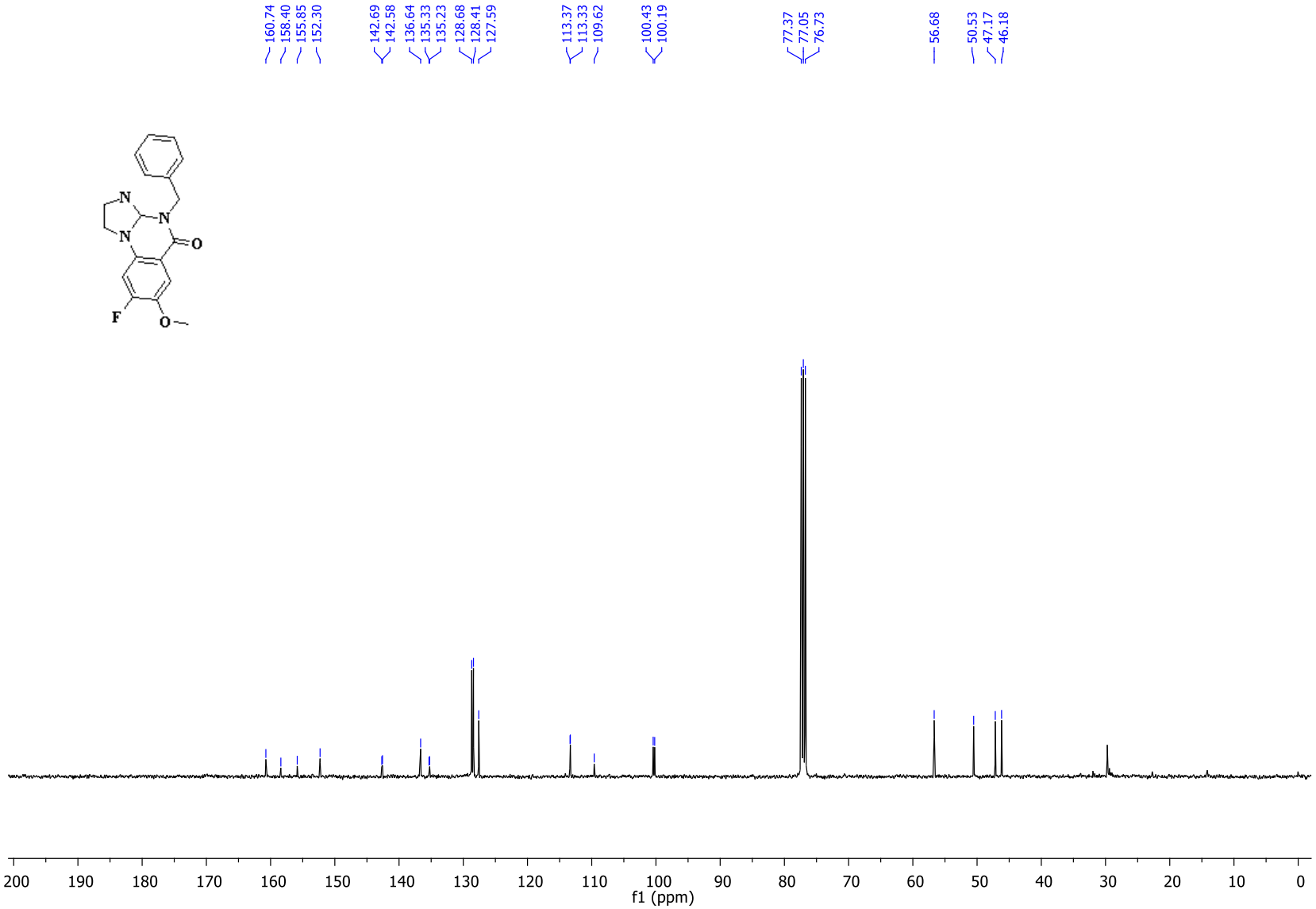
$^{13}C\{^{1}H\}$-NMR of 3i (101 MHz, $CDCl_3$)



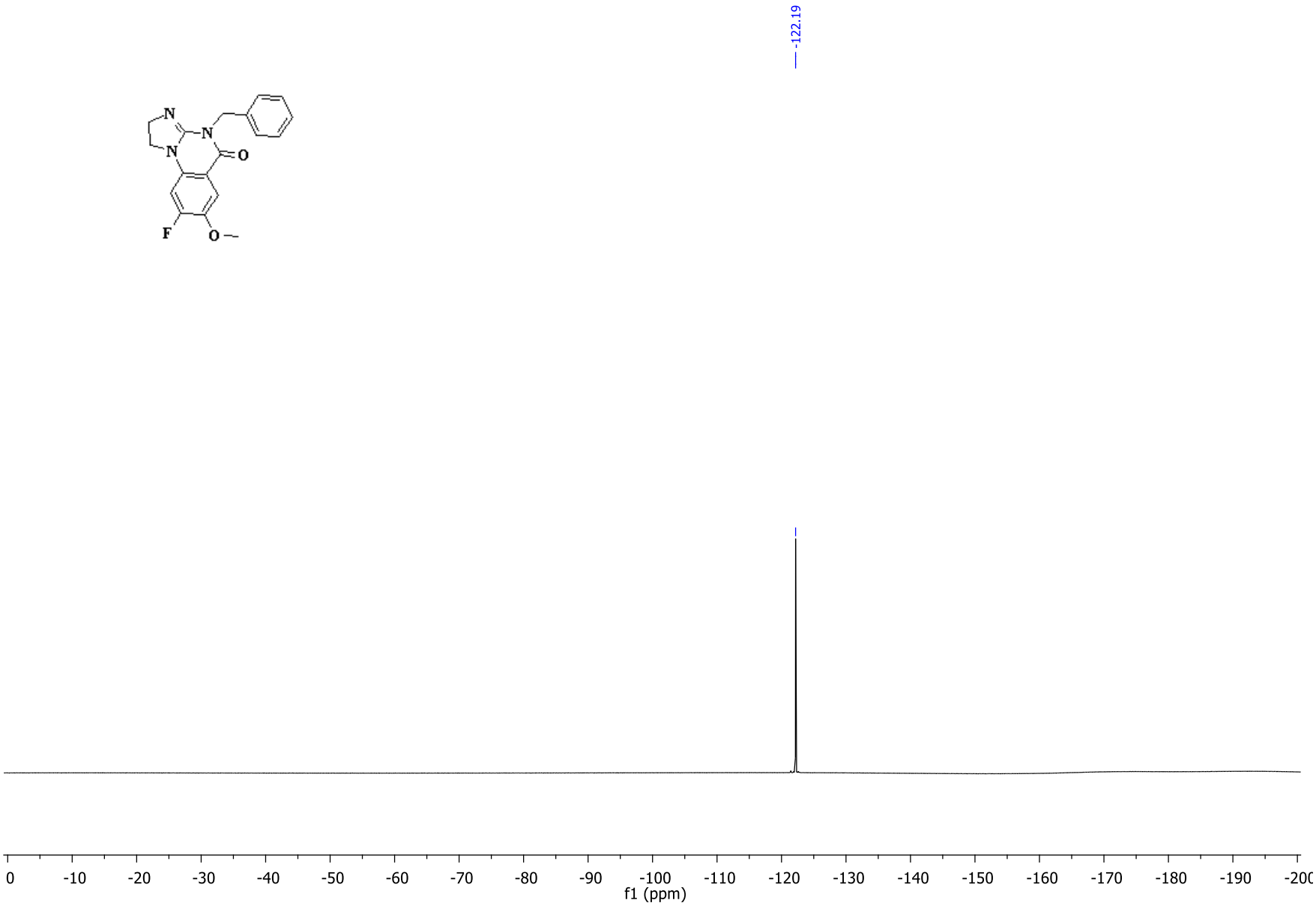
^{1}H-NMR of 3j (400 MHz, $CDCl_3$)



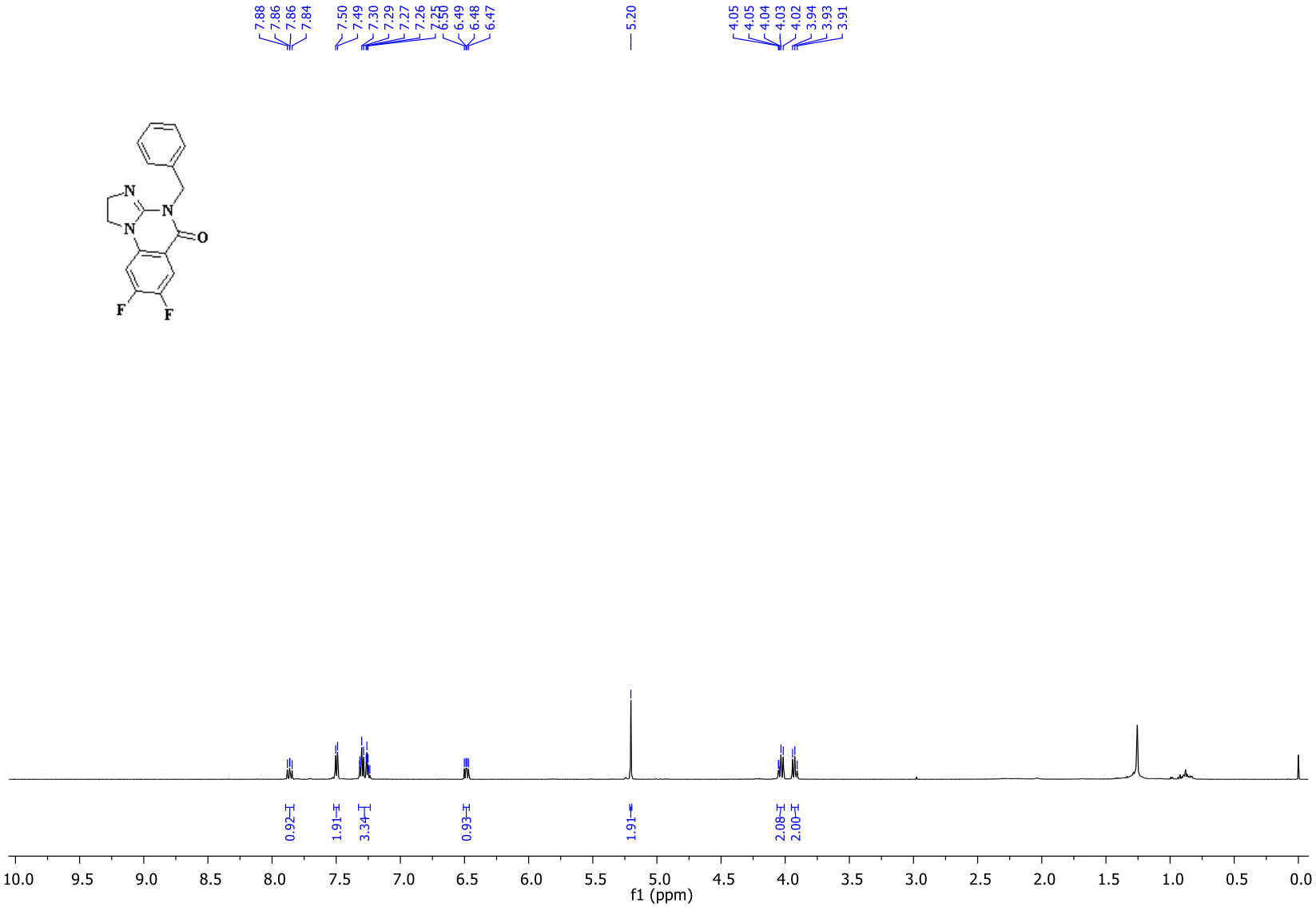
$^{13}C\{^{1}H\}$-NMR of 3j (101 MHz, $CDCl_3$)



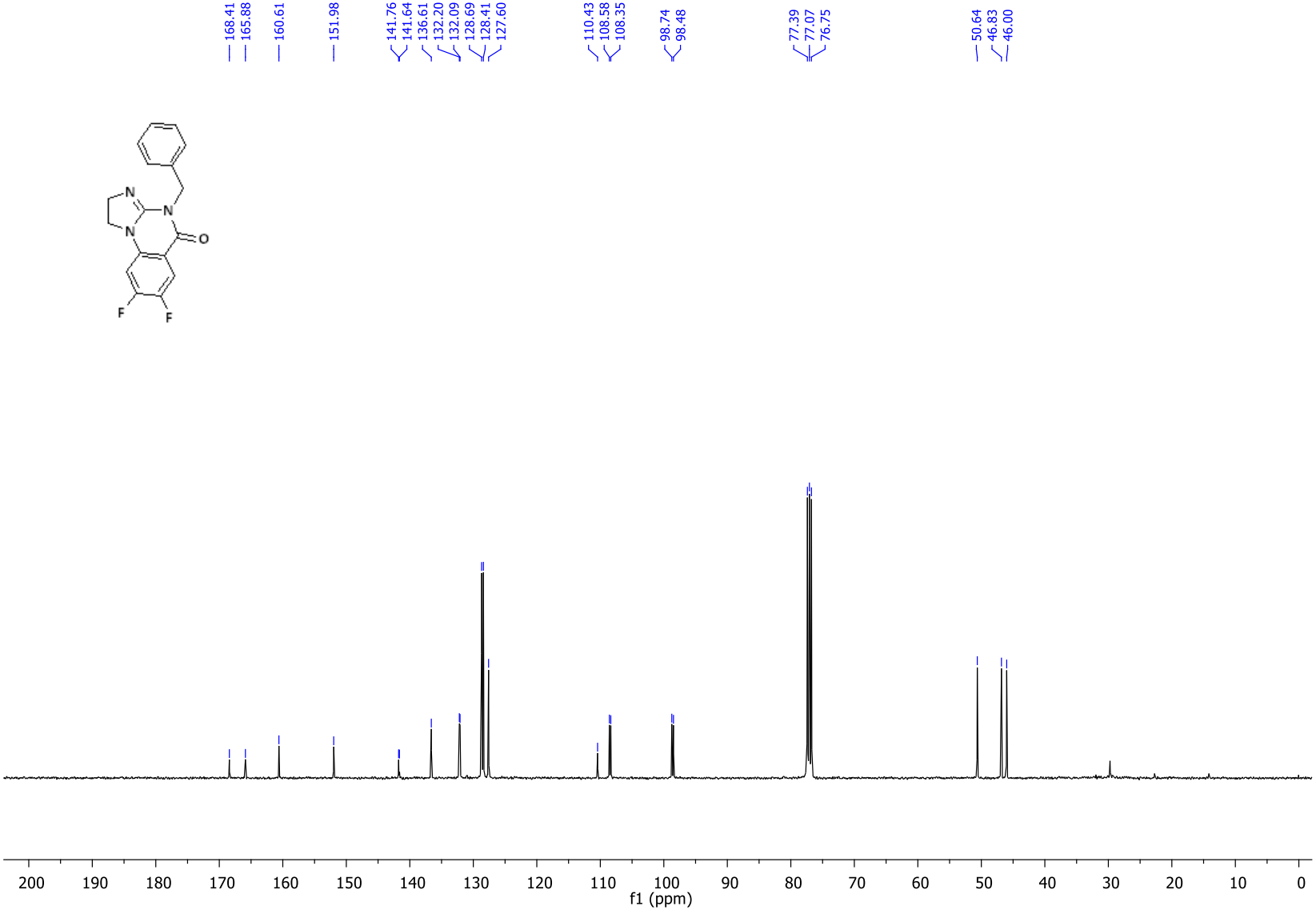
^{19}F-NMR of 3j (377 MHz, $CDCl_3$)



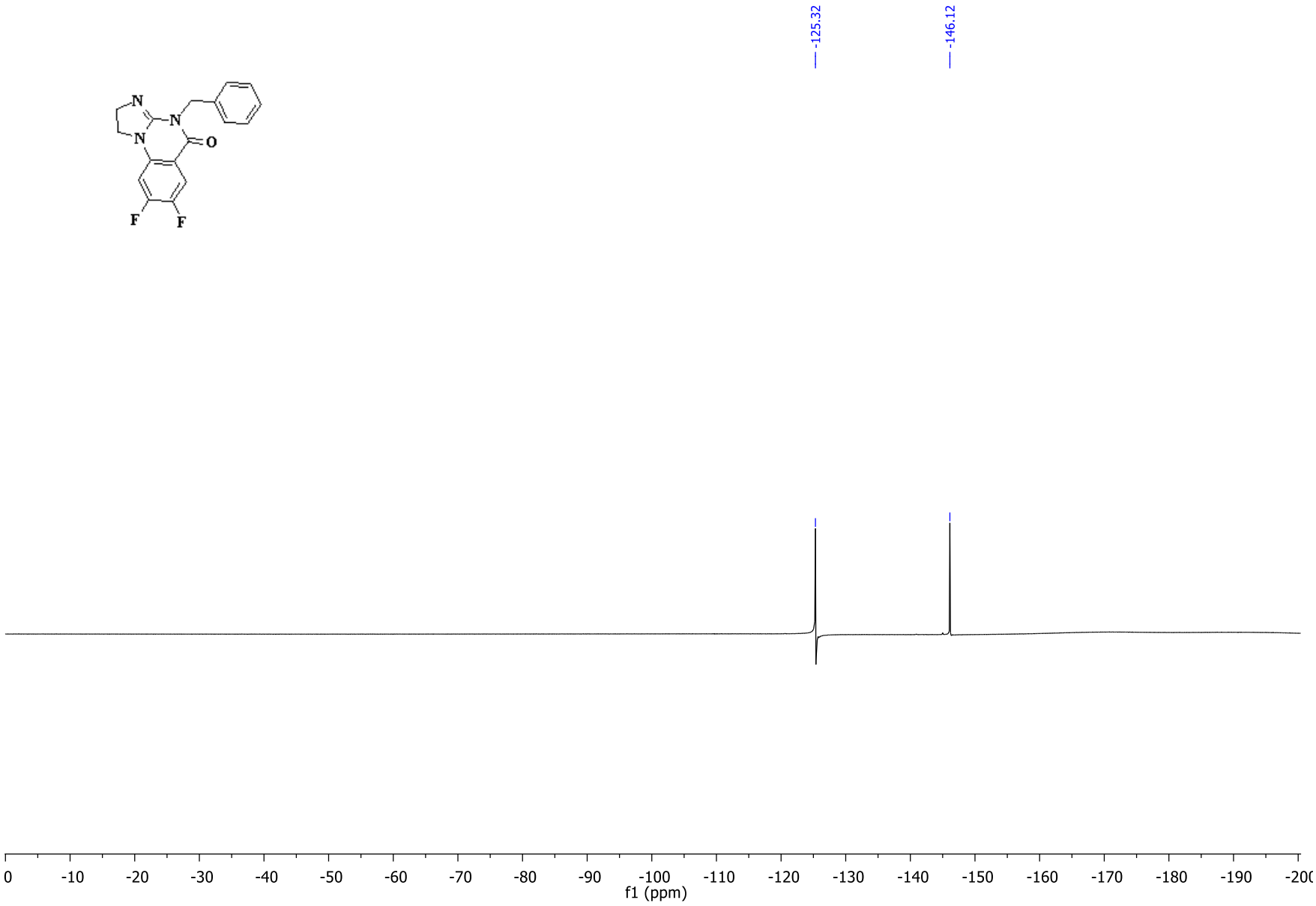
^{1}H-NMR of 3k (500 MHz, $CDCl_3$)



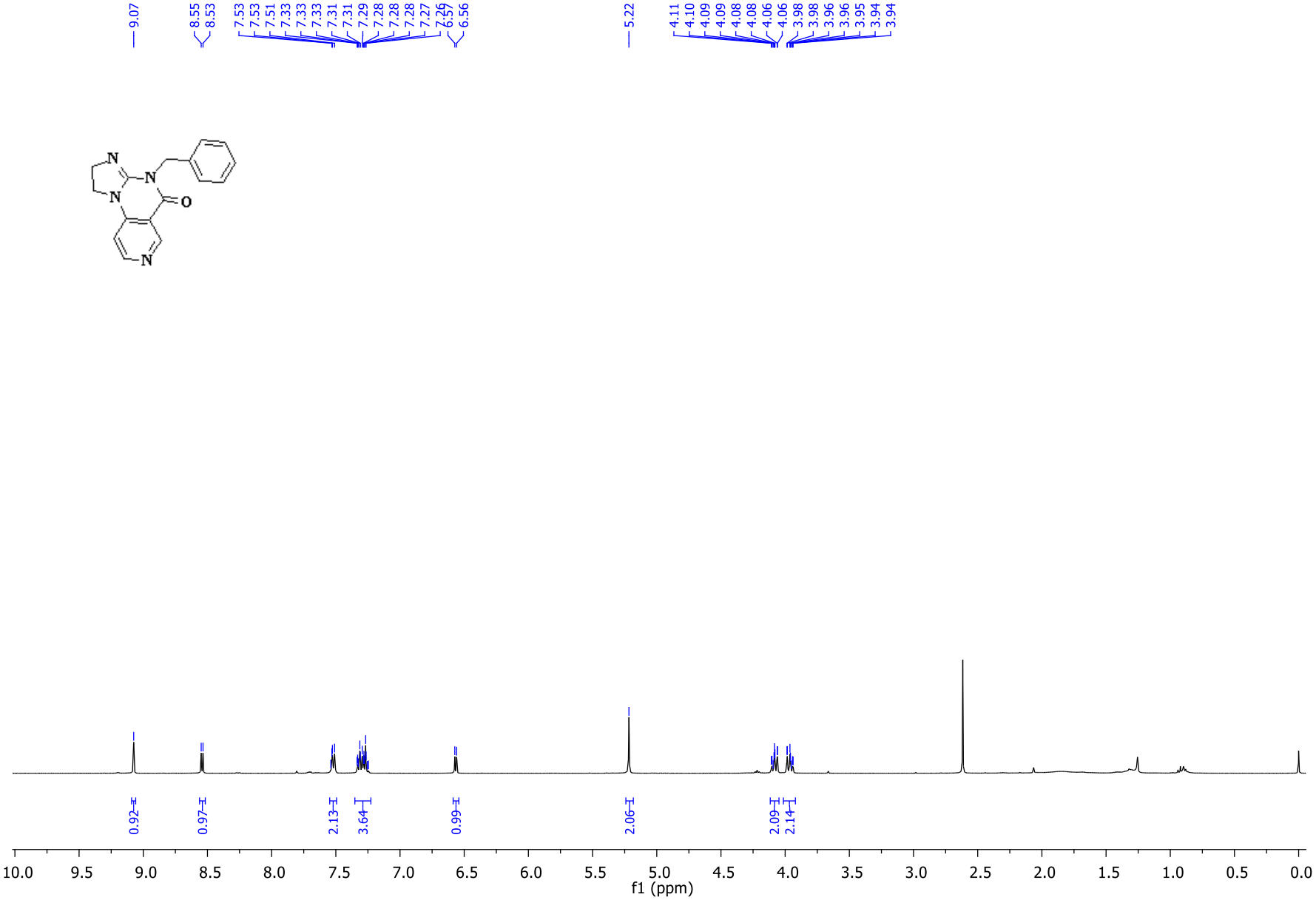
$^{13}C\{^{1}H\}$-NMR of 3k (101 MHz, $CDCl_3$)



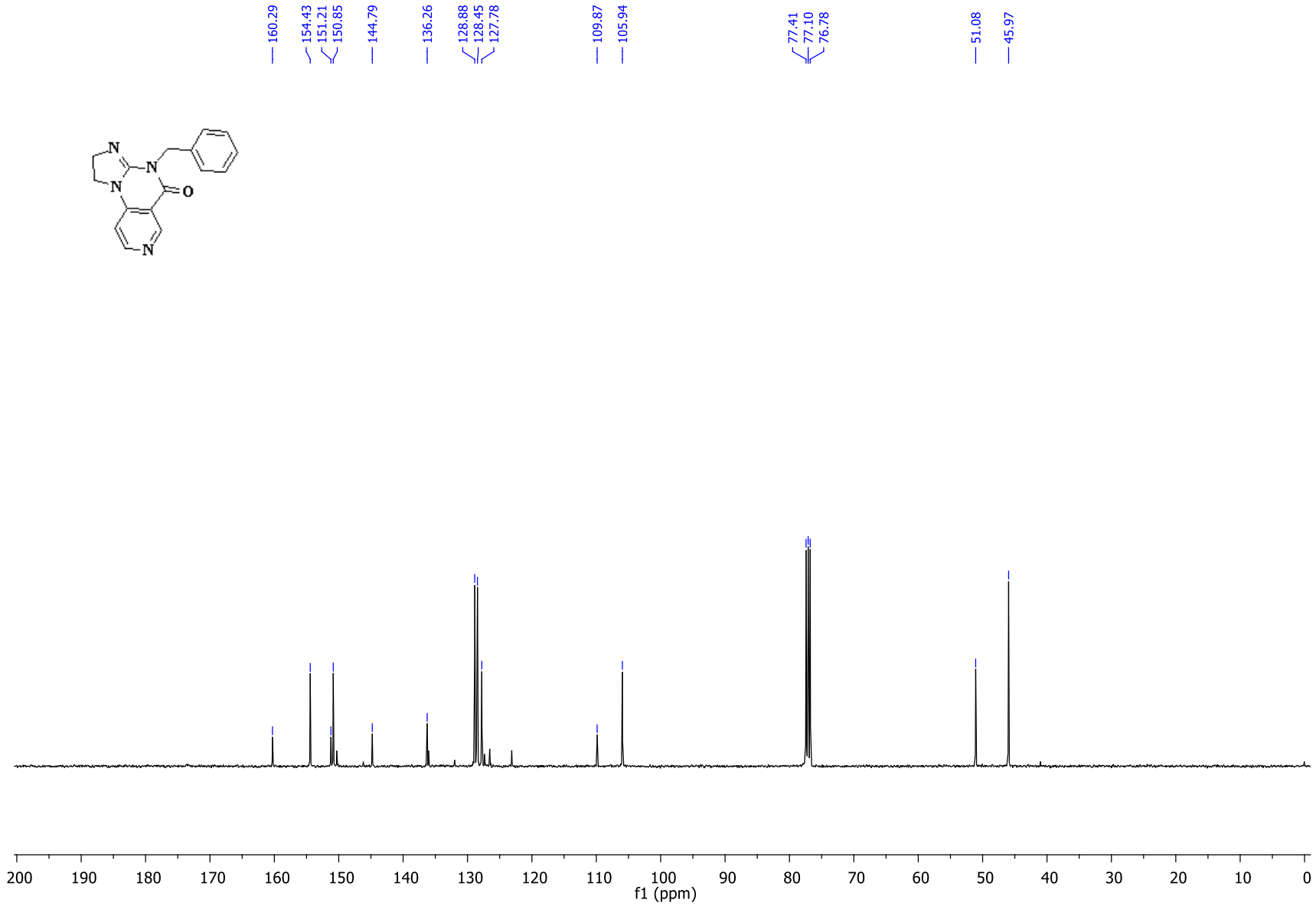
^{19}F-NMR of 3k (377 MHz, $CDCl_3$)



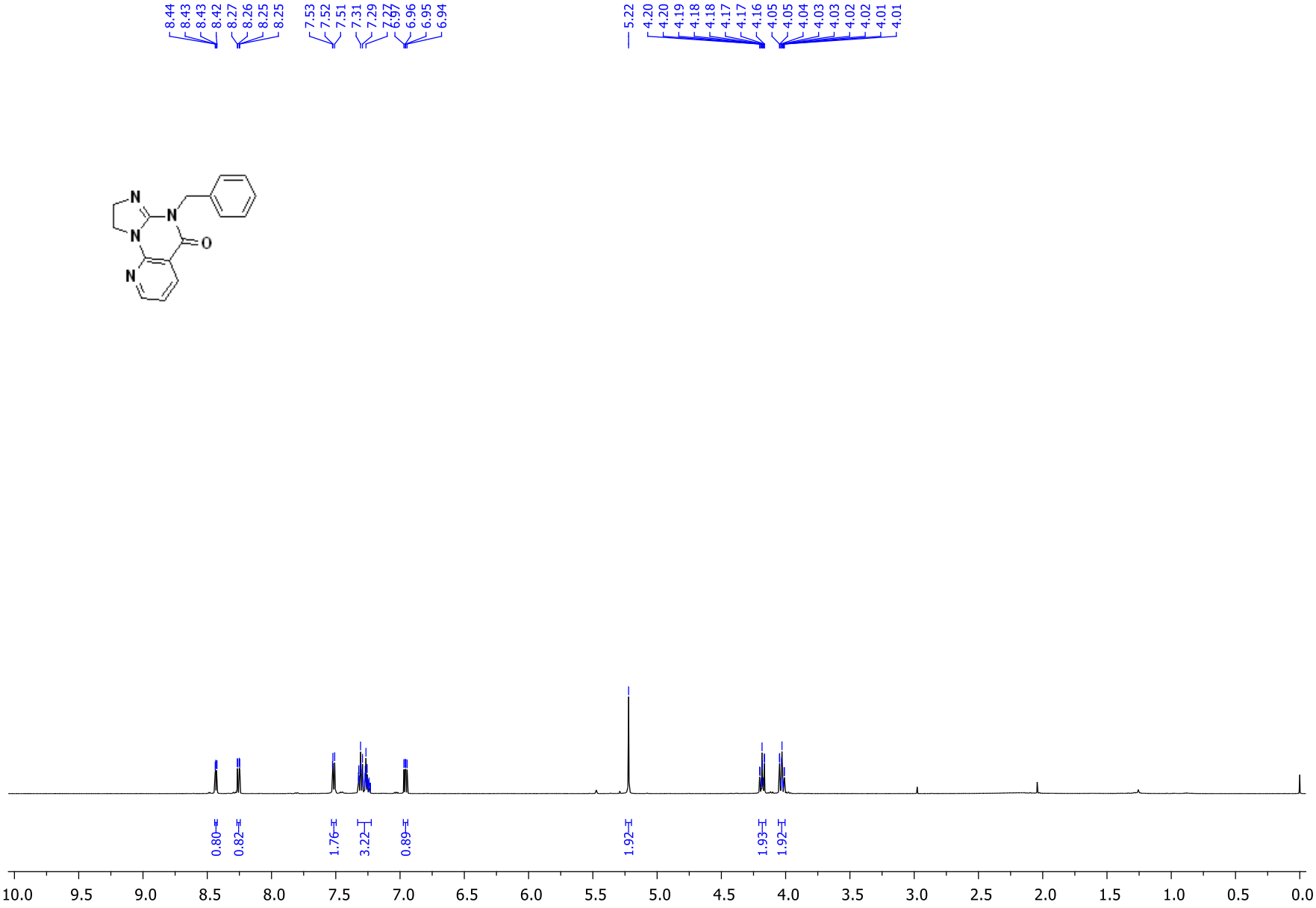
^{1}H-NMR of 3l (400 MHz, $CDCl_3$)



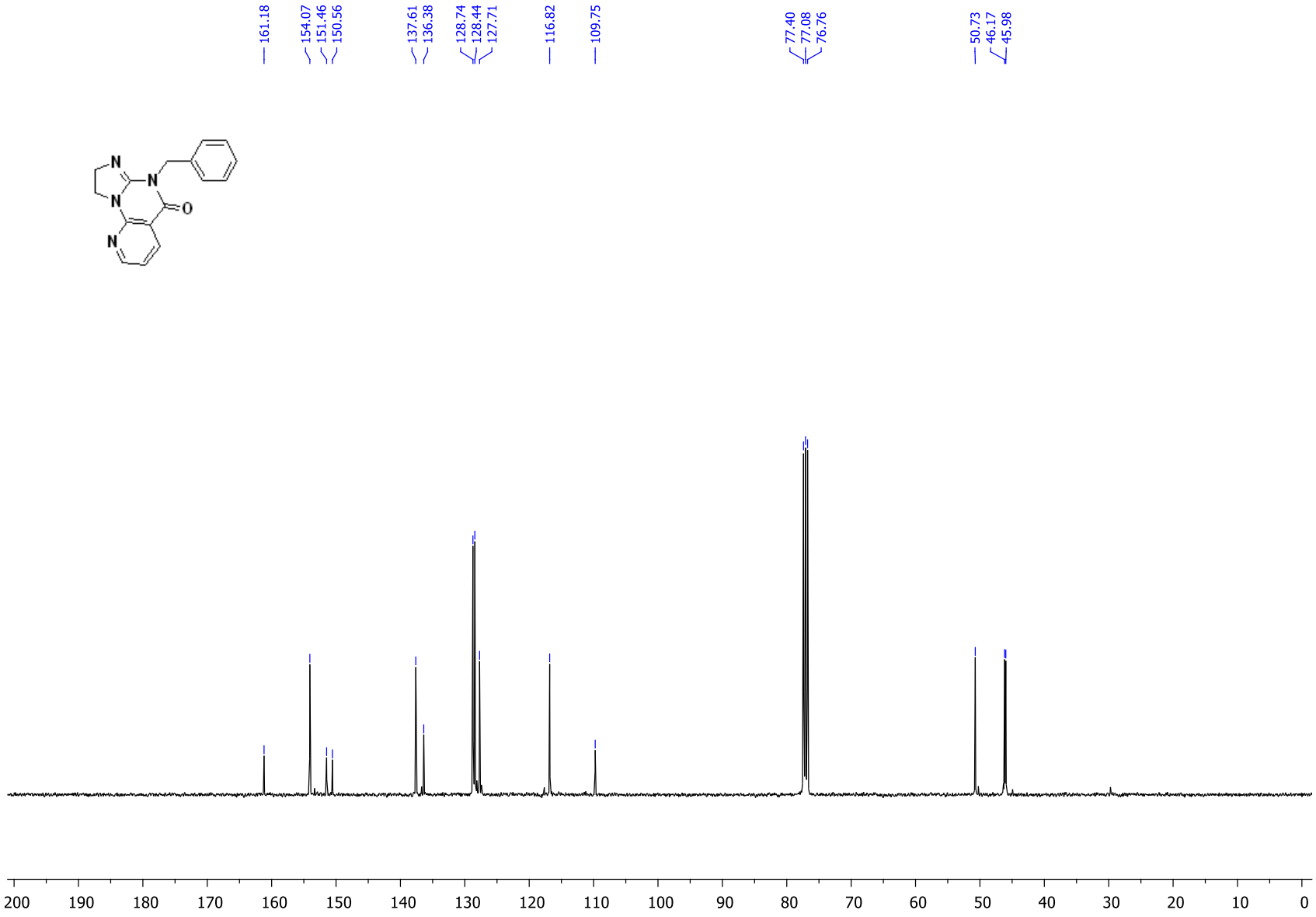
$^{13}C\{^{1}H\}$-NMR of 3l (101 MHz, $CDCl_3$)



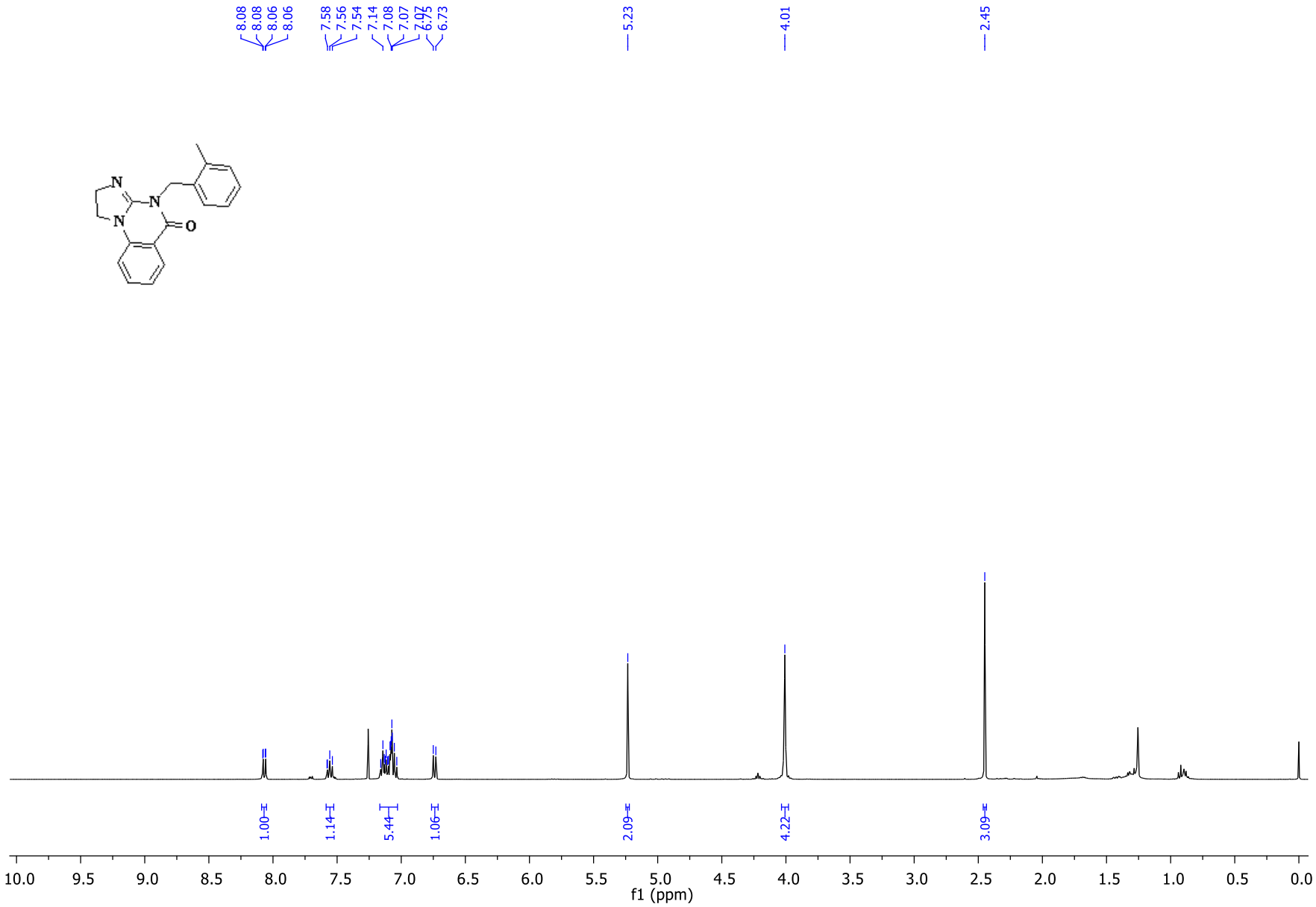
^{1}H-NMR of 3m (500 MHz, $CDCl_3$)



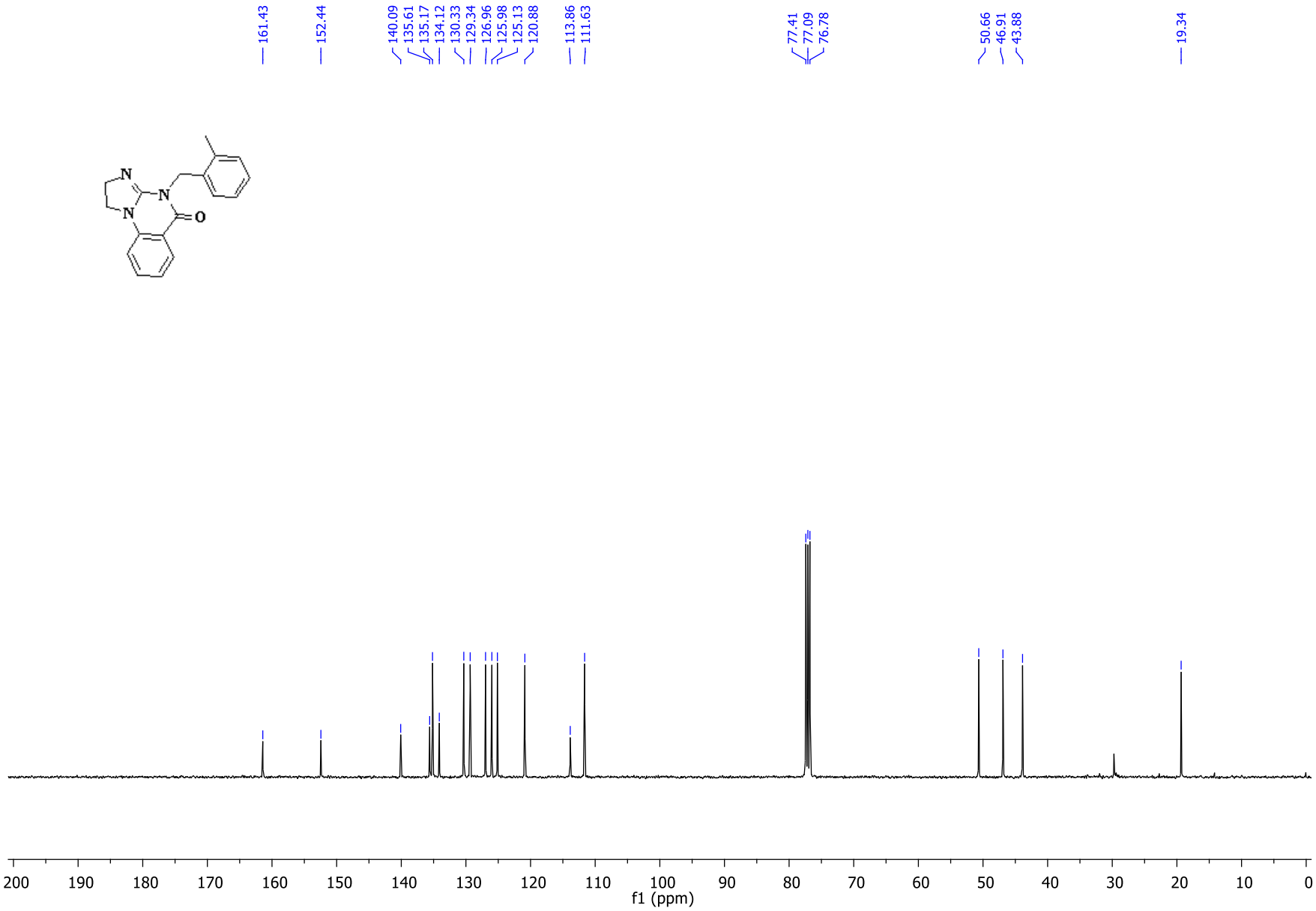
$^{13}C\{^{1}H\}$-NMR of 3m (101 MHz, $CDCl_3$)



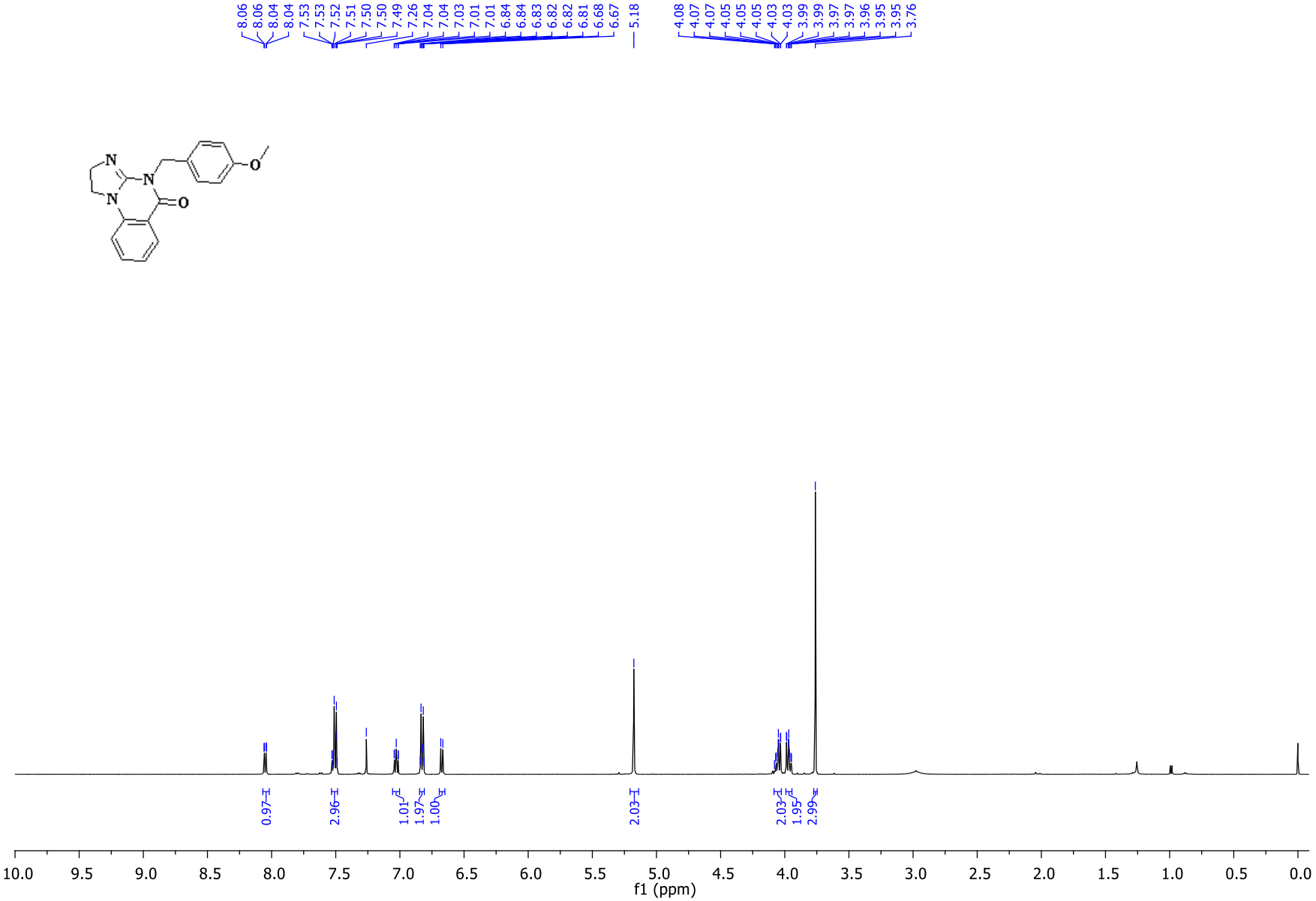
^{1}H-NMR 3n (400 MHz, $CDCl_3$)



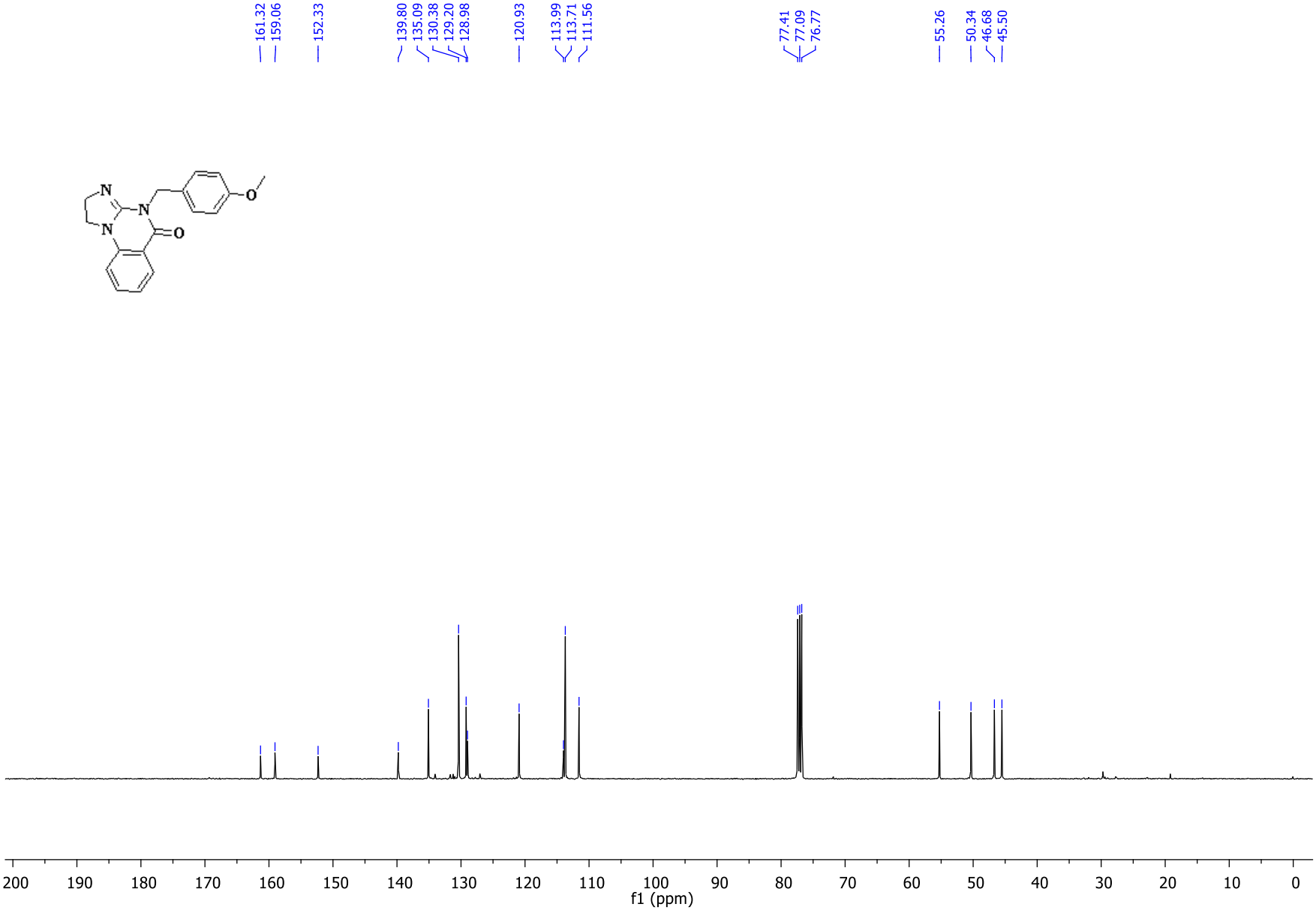
$^{13}C\{^{1}H\}$-NMR of 3n (101 MHz, $CDCl_3$)



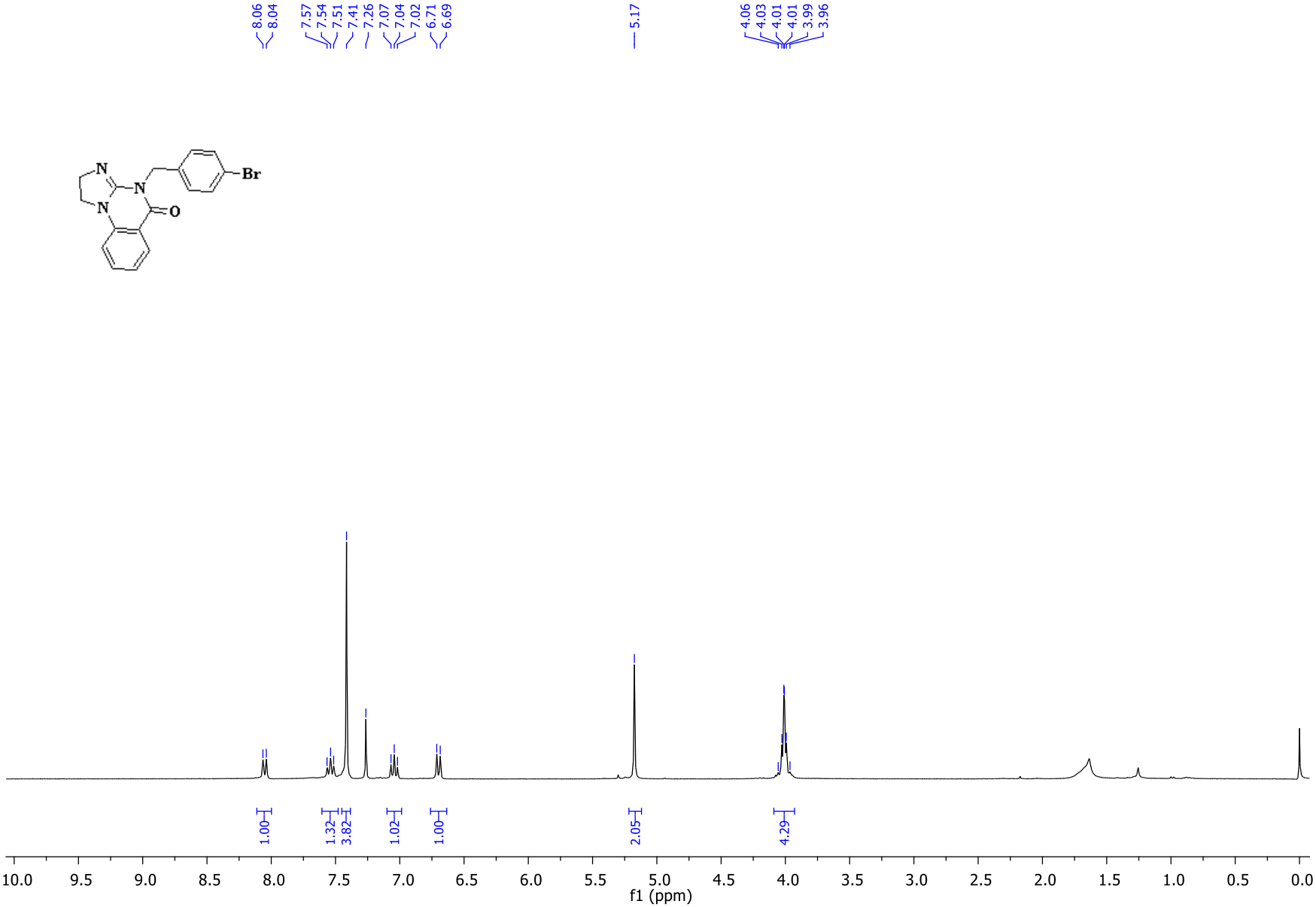
^{1}H-NMR 3o (500 MHz, $CDCl_3$)



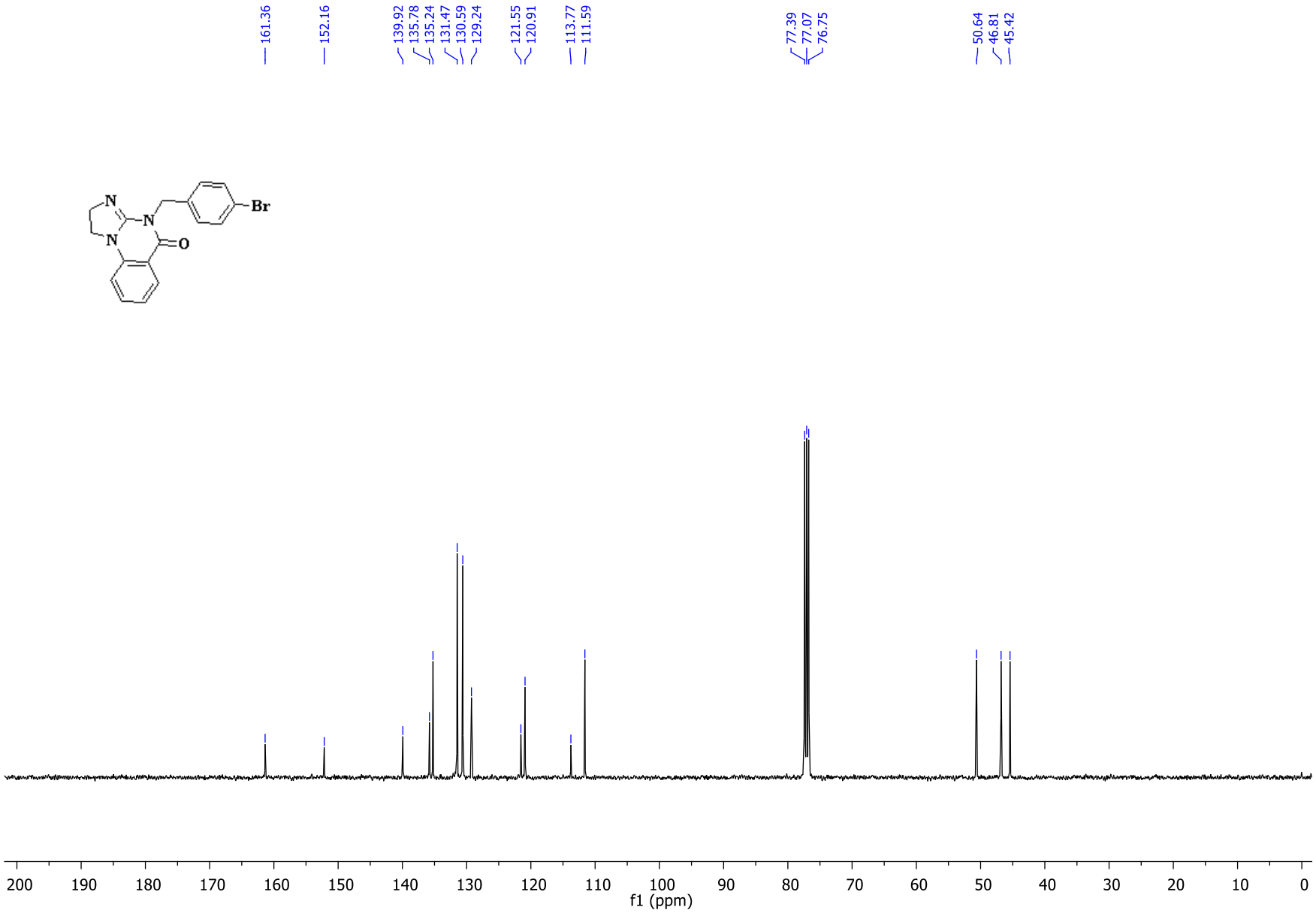
$^{13}C\{^{1}H\}$-NMR of 3o (101 MHz, $CDCl_3$)



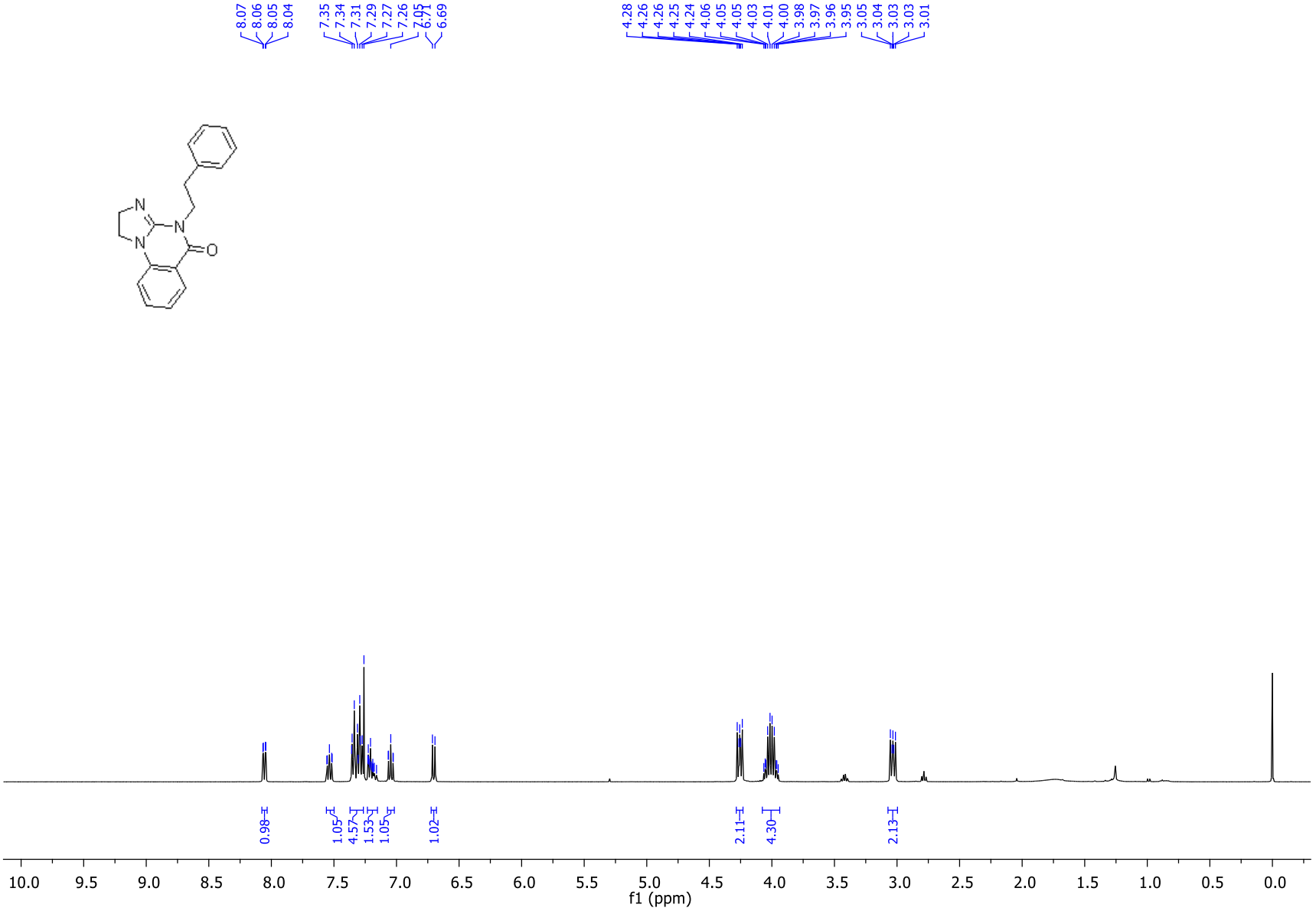
^{1}H-NMR of 3p (300 MHz, $CDCl_3$)



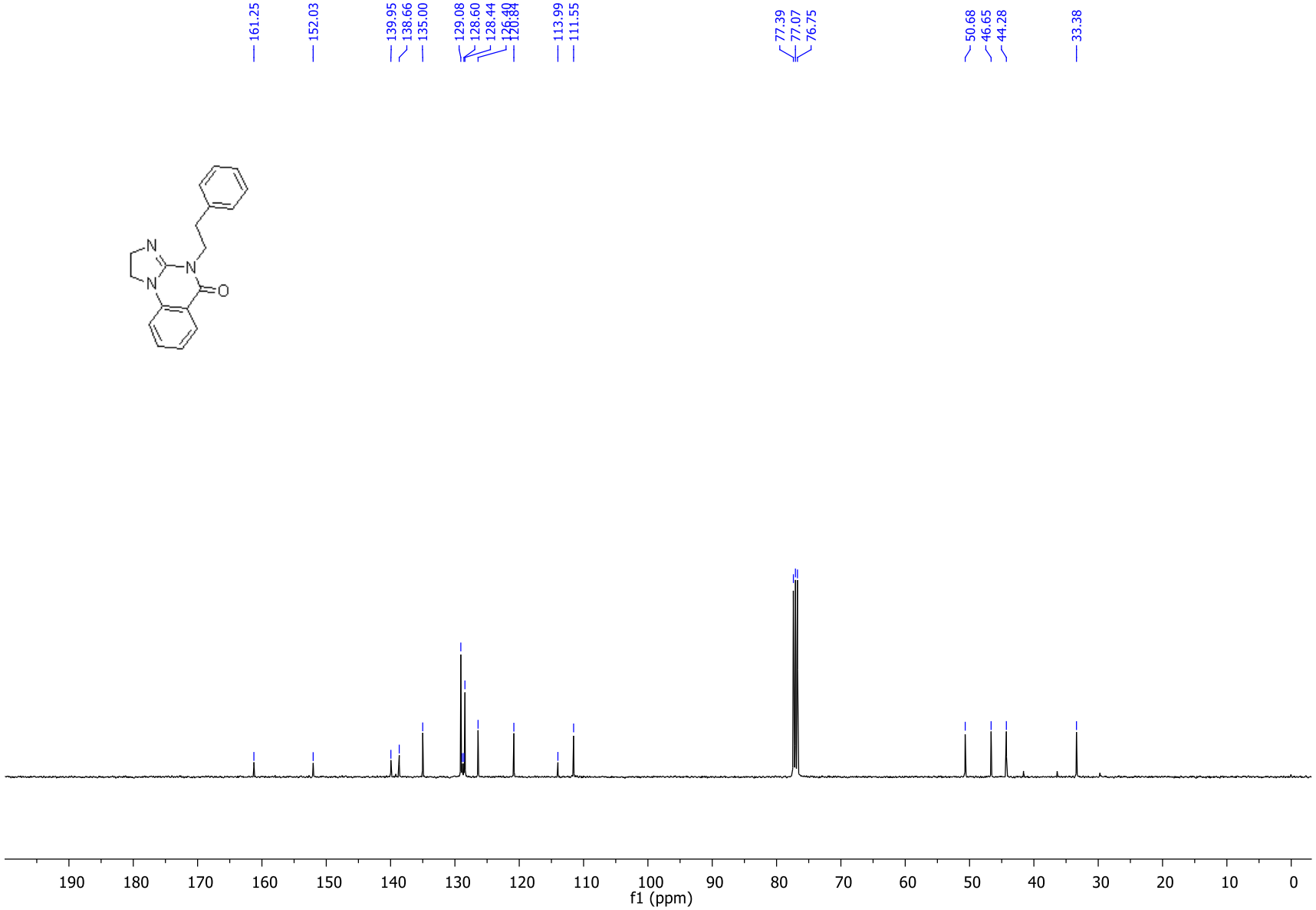
$^{13}C\{^{1}H\}$-NMR of 3p (101 MHz, $CDCl_3$)



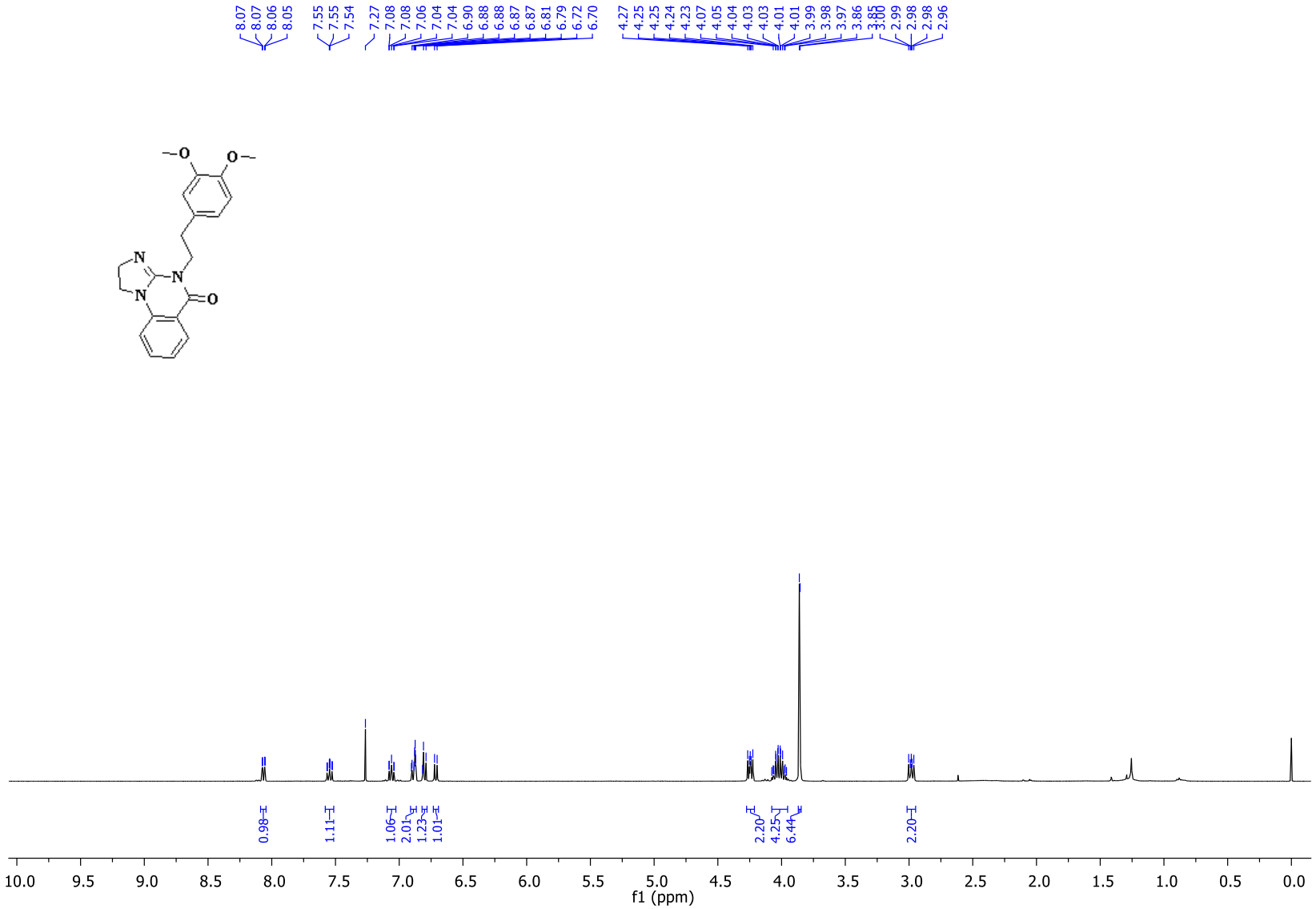
^{1}H-NMR of 3q (400 MHz, $CDCl_3$)



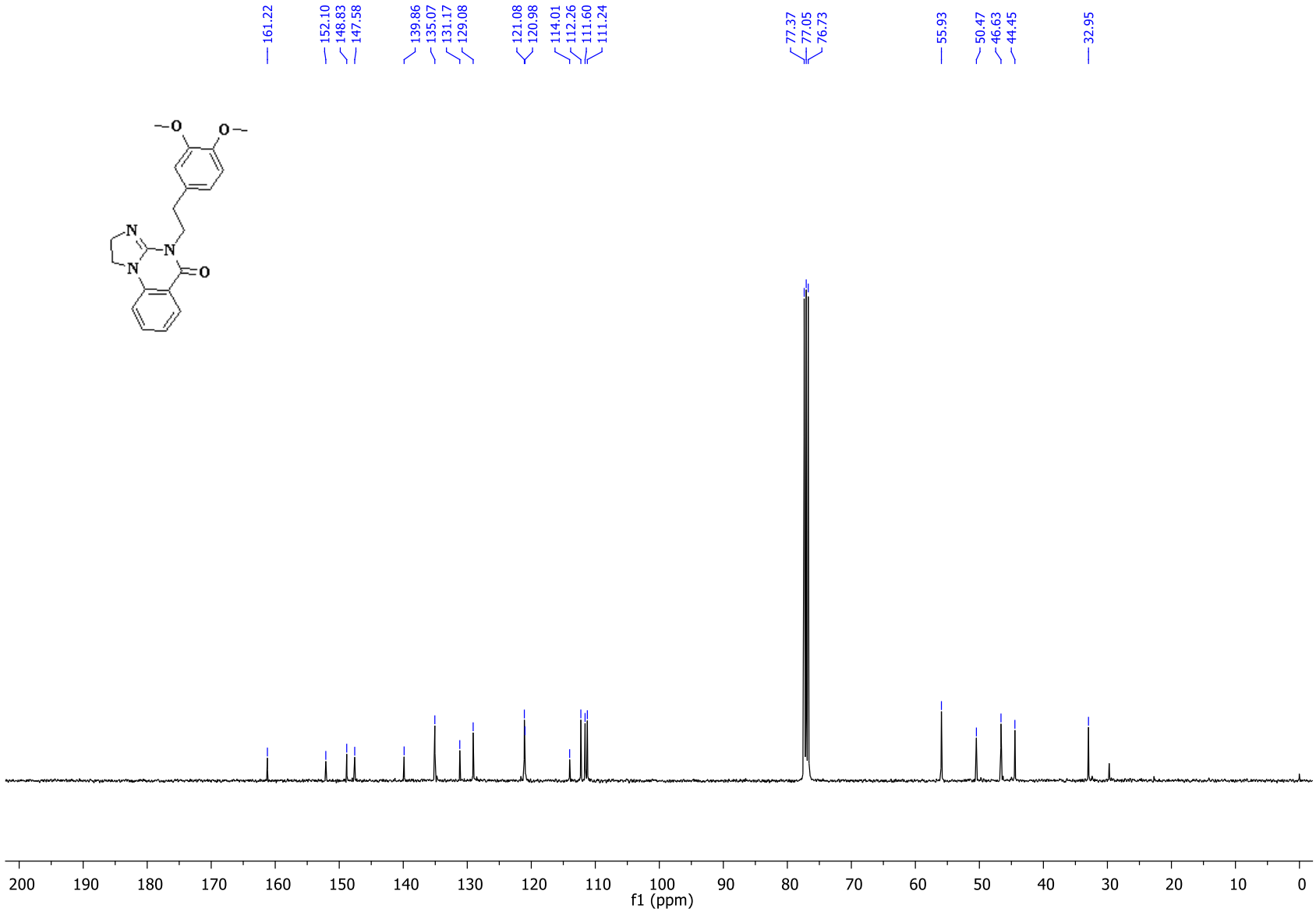
$^{13}C\{^{1}H\}$-NMR of 3q (101 MHz, $CDCl_3$)



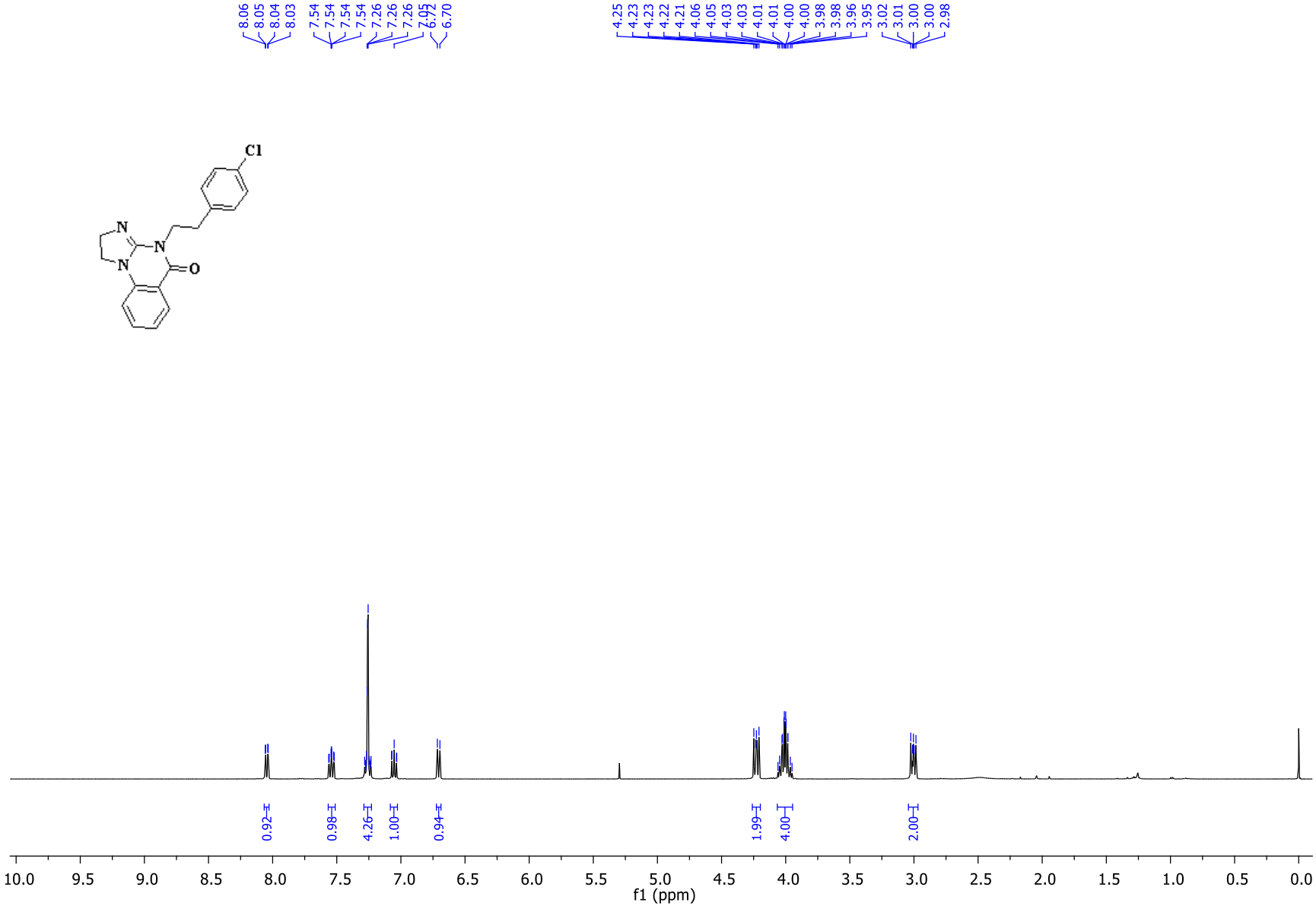
^{1}H-NMR of 3r (400 MHz, $CDCl_3$)



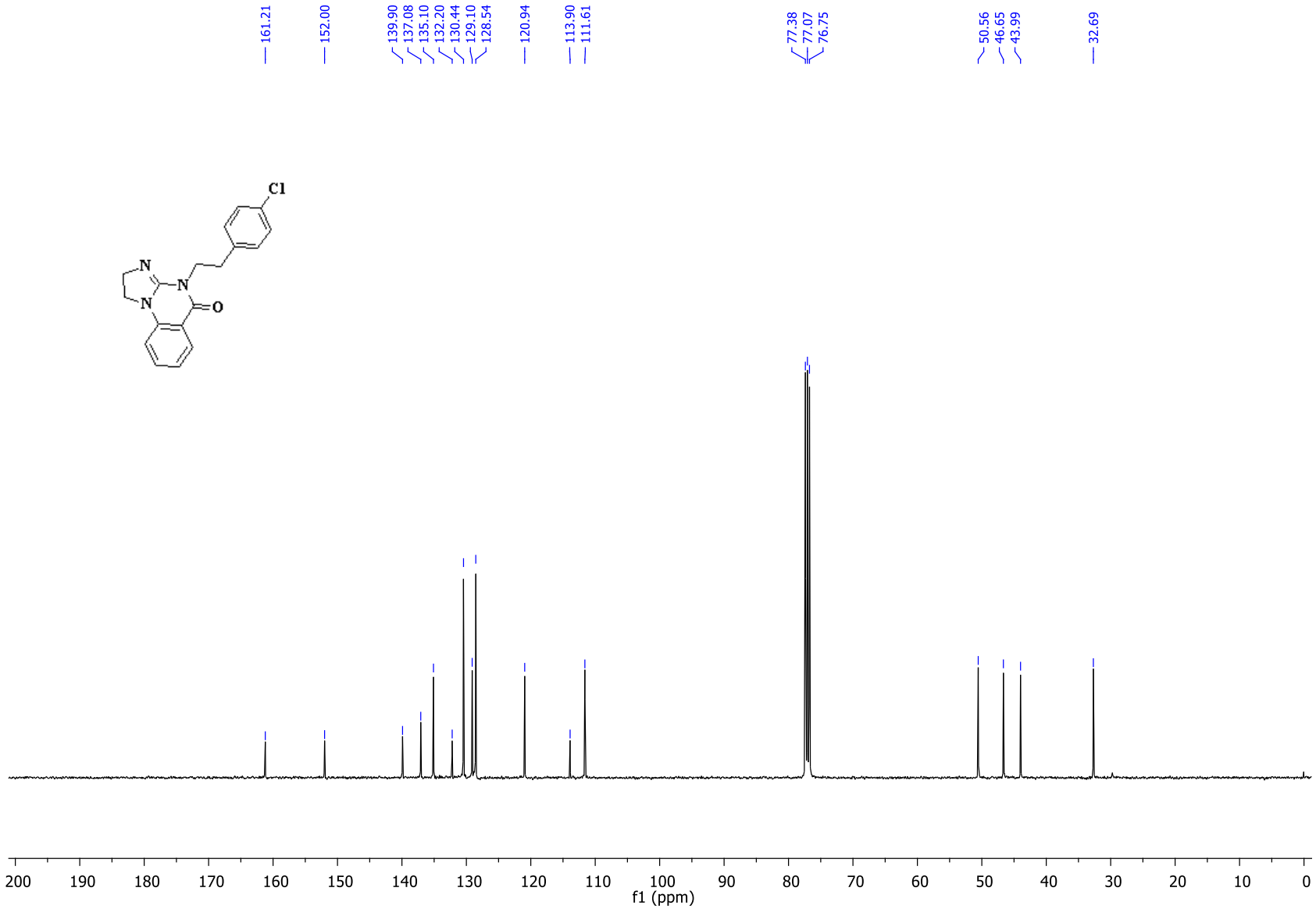
$^{13}C\{^{1}H\}$-NMR of 3r (101 MHz, $CDCl_3$)



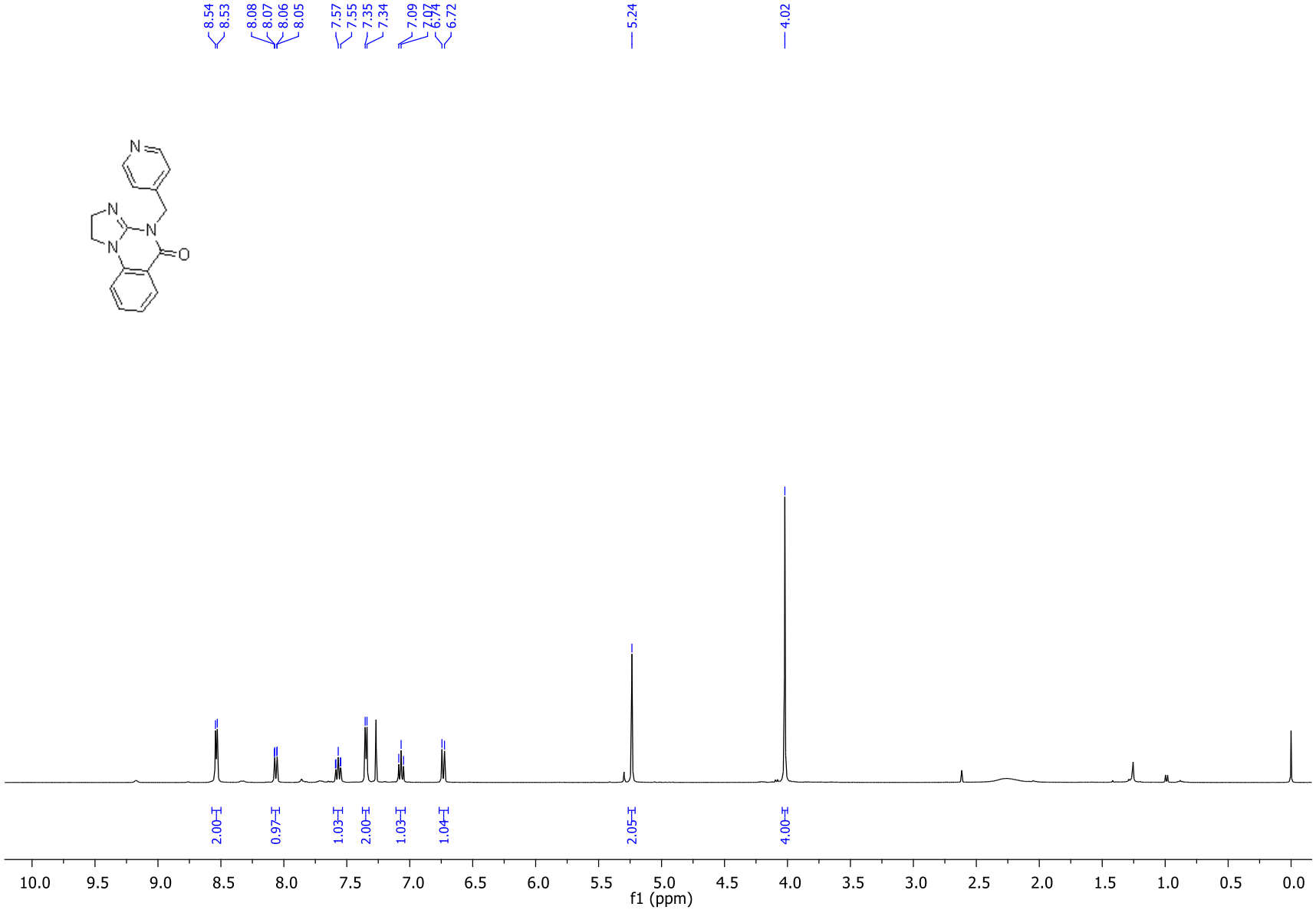
^{1}H-NMR of 3s (400 MHz, $CDCl_3$)



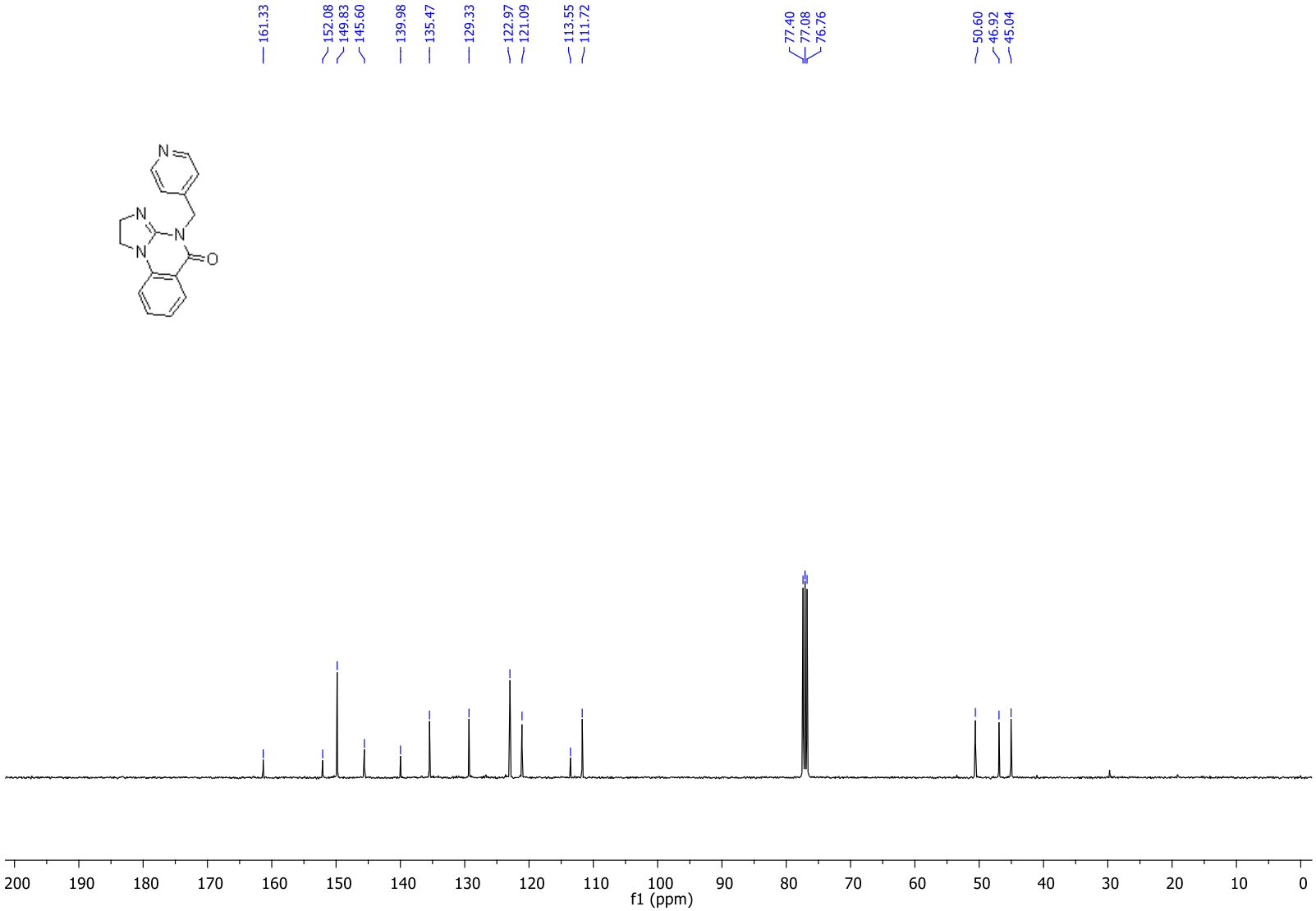
$^{13}C\{^{1}H\}$-NMR of 3s (101 MHz, $CDCl_3$)



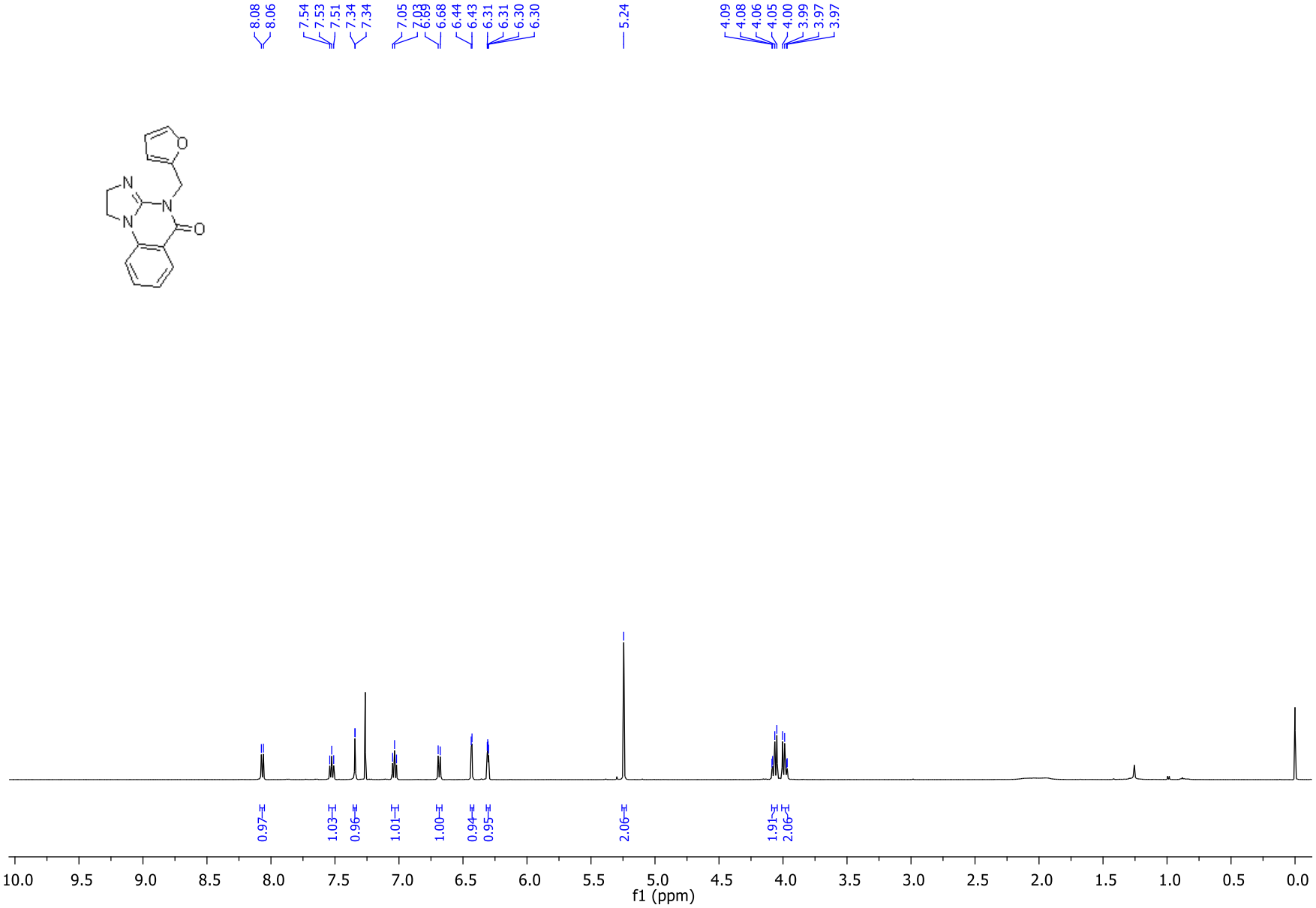
^{1}H-NMR of 3t (400 MHz, $CDCl_3$)



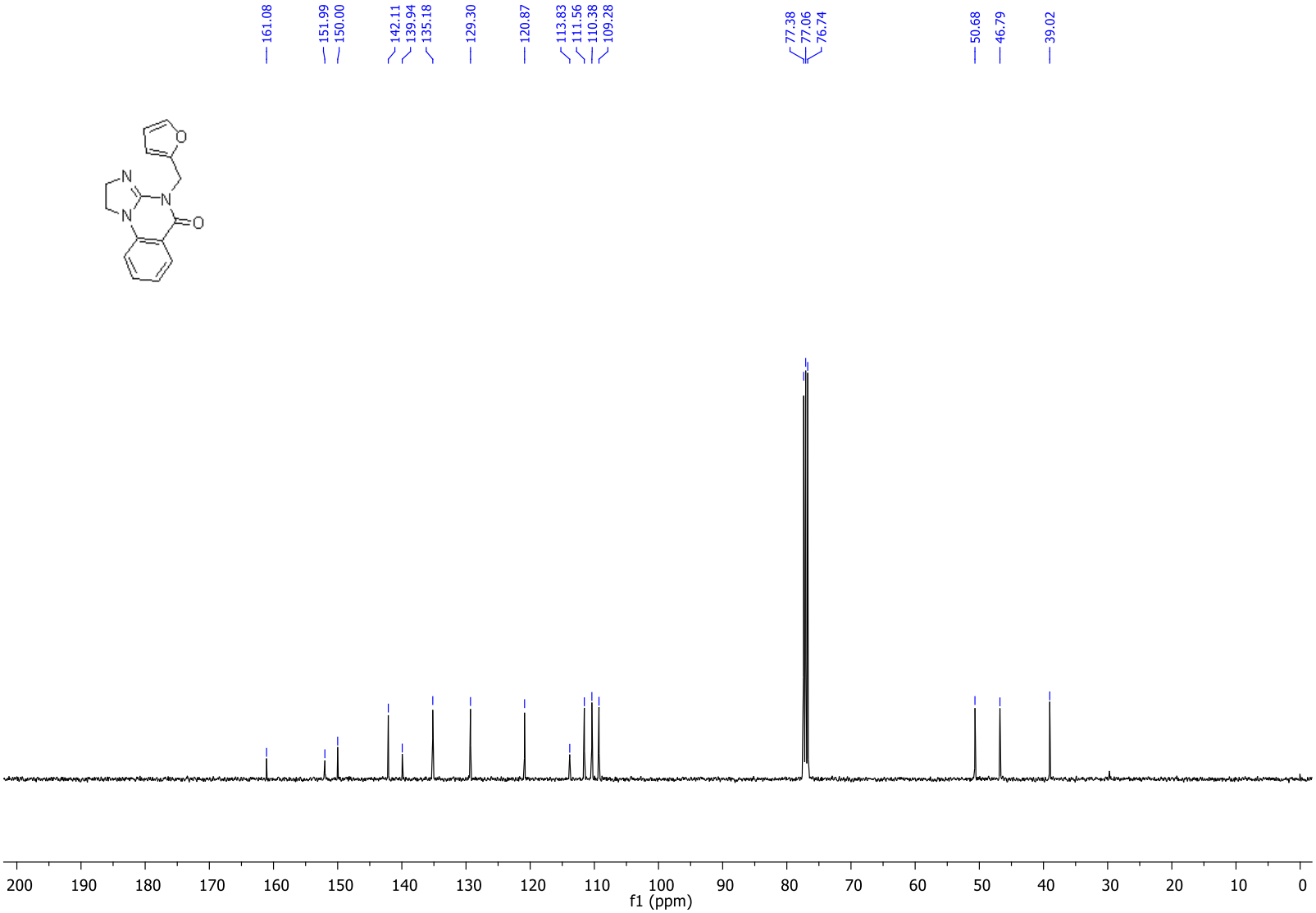
$^{13}C\{^{1}H\}$-NMR of 3t (101 MHz, $CDCl_3$)



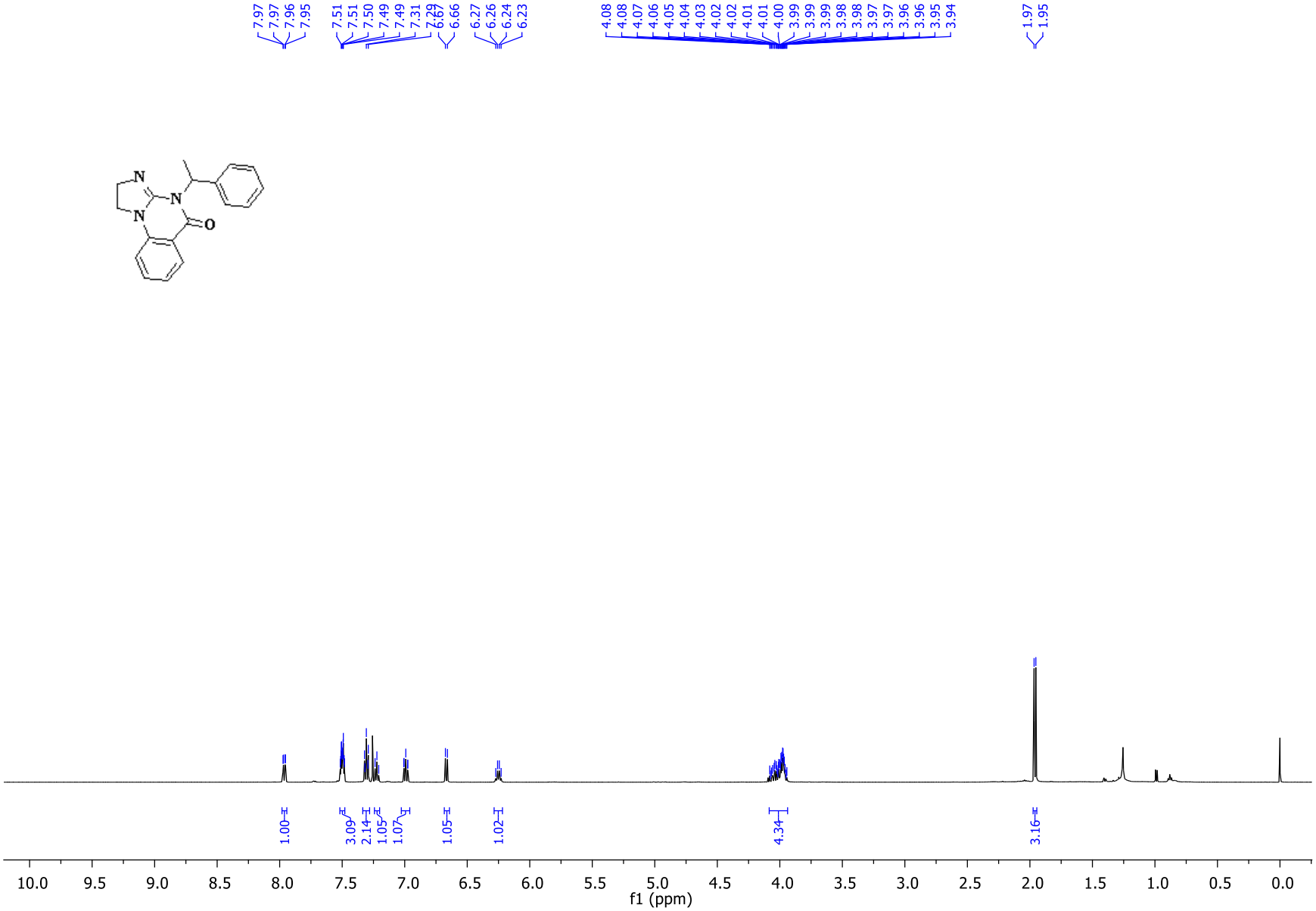
^{1}H-NMR of 3u (500 MHz, $CDCl_3$)



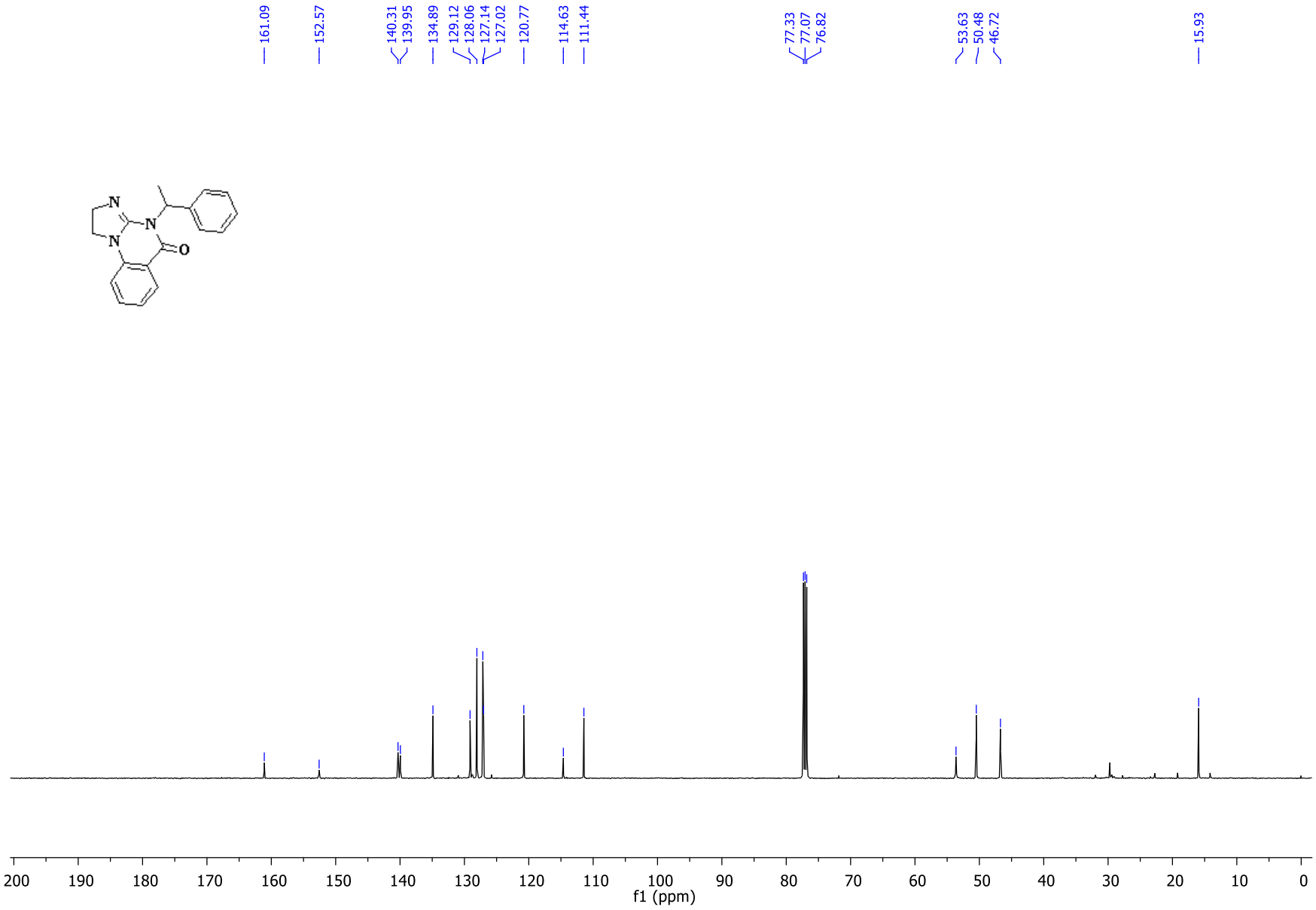
$^{13}C\{^{1}H\}$-NMR of 3u (101 MHz, $CDCl_3$)



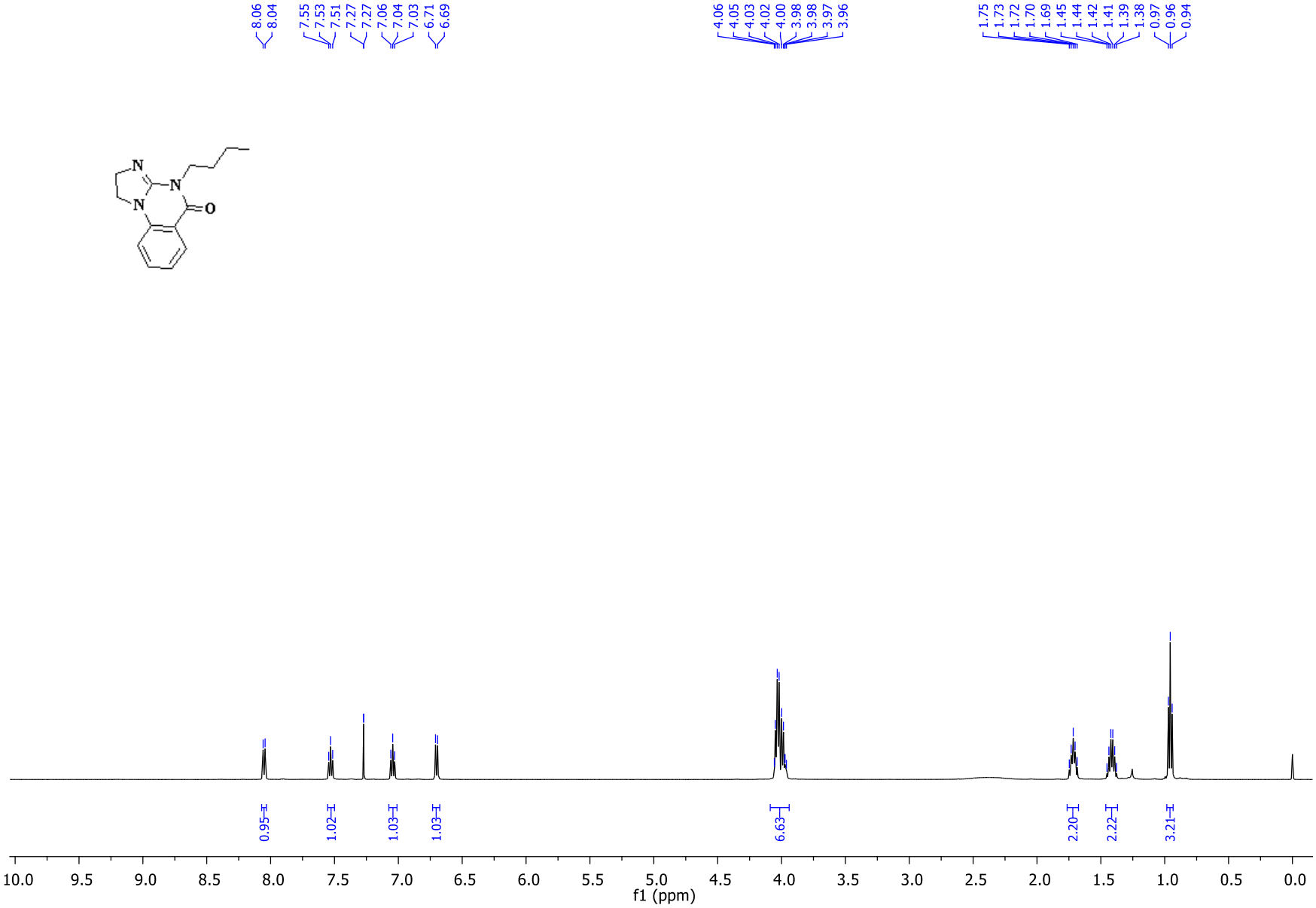
^{1}H-NMR of 3v (500 MHz, $CDCl_3$)



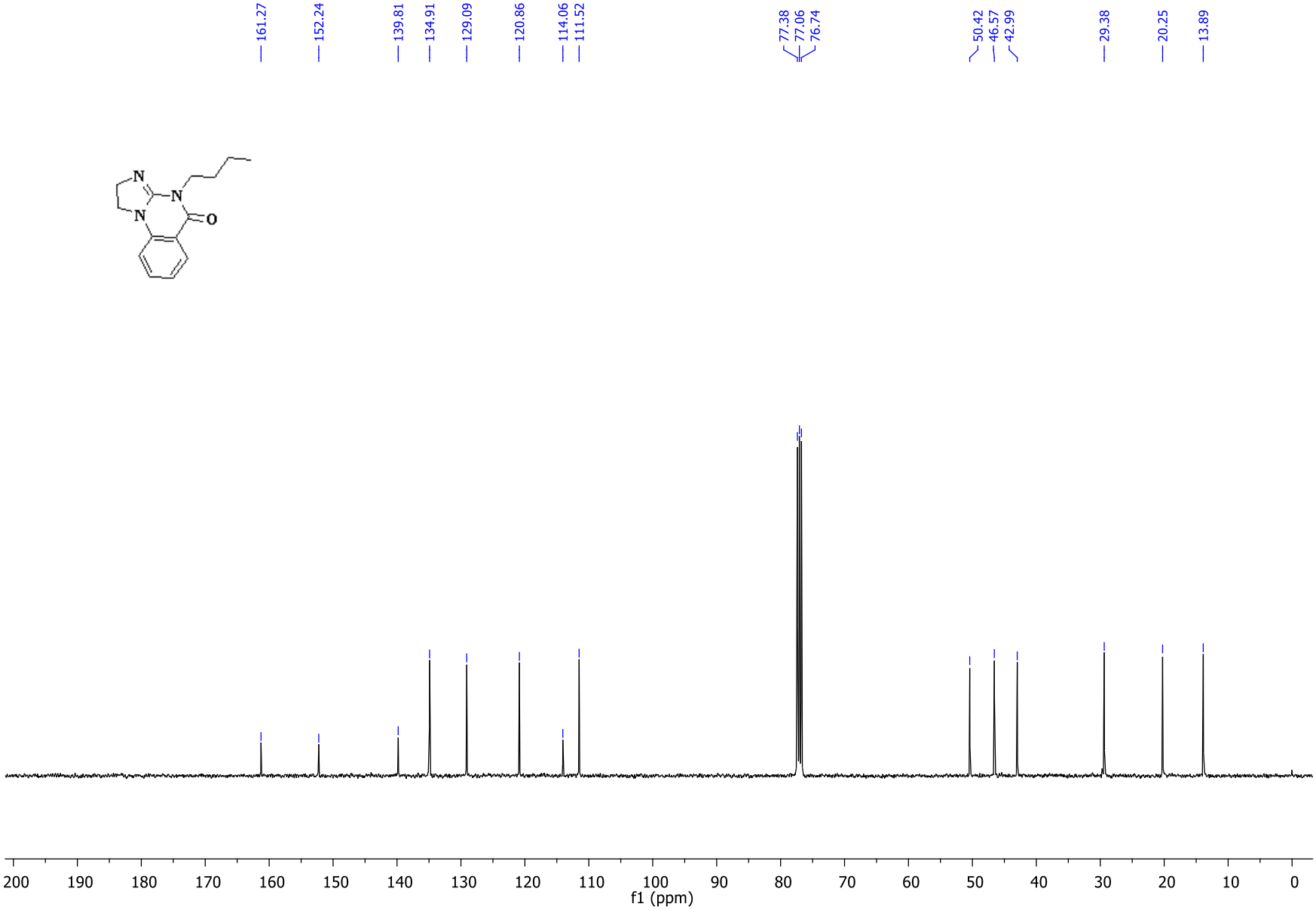
$^{13}C\{^{1}H\}$-NMR of 3v (126 MHz, $CDCl_3$)



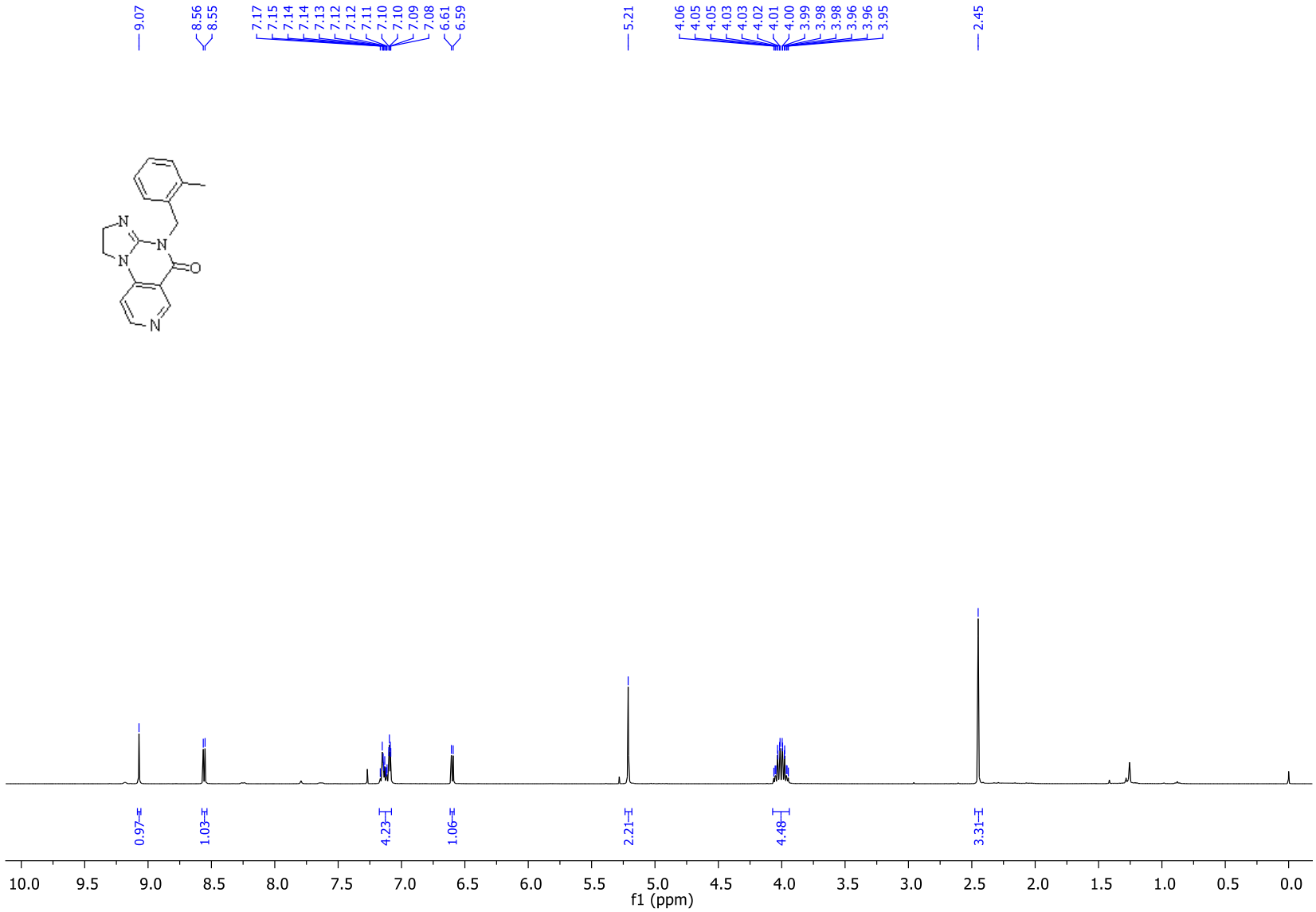
^{1}H-NMR of 3w (500 MHz, $CDCl_3$)



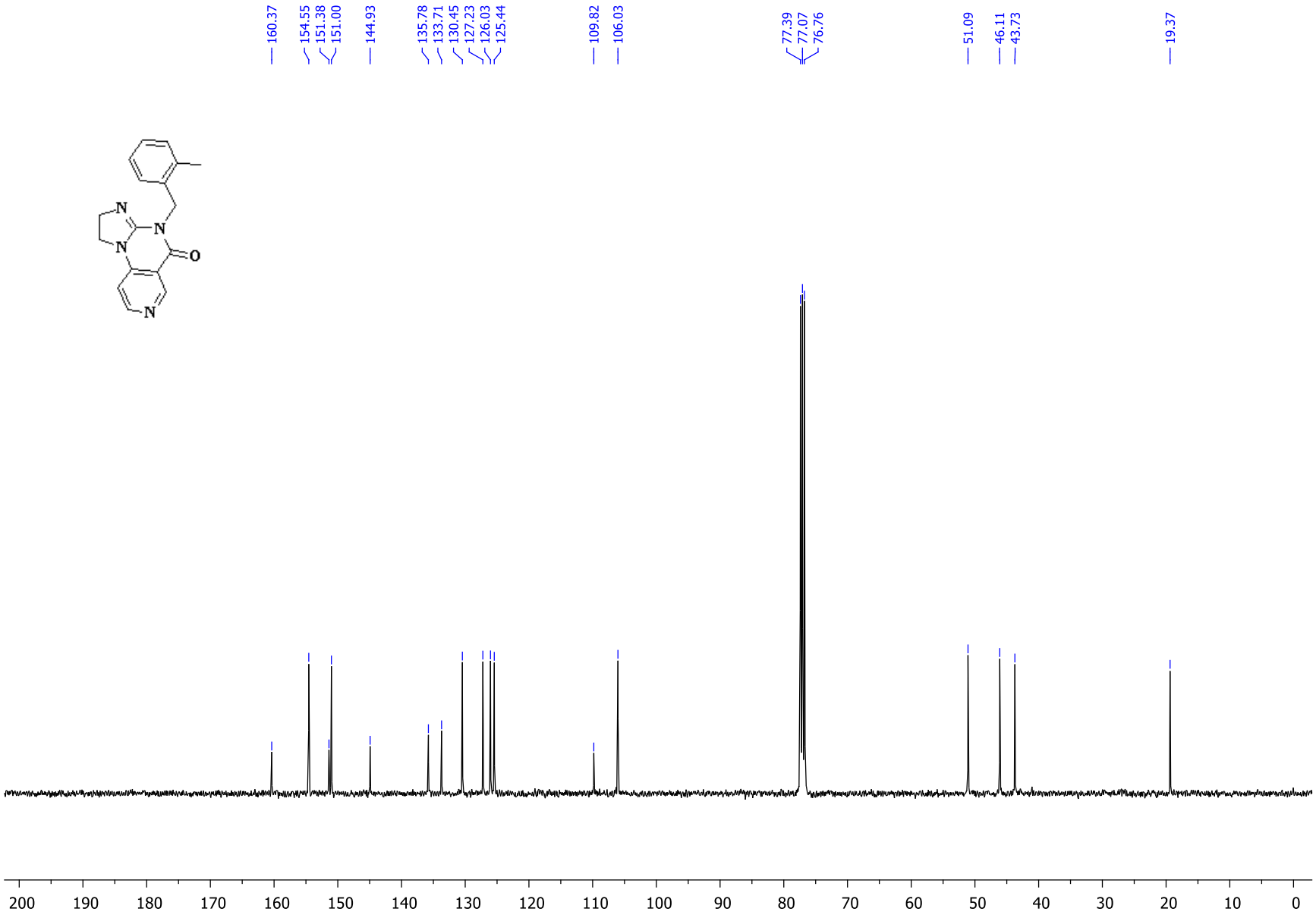
$^{13}C\{^{1}H\}$-NMR of 3w (101 MHz, $CDCl_3$)



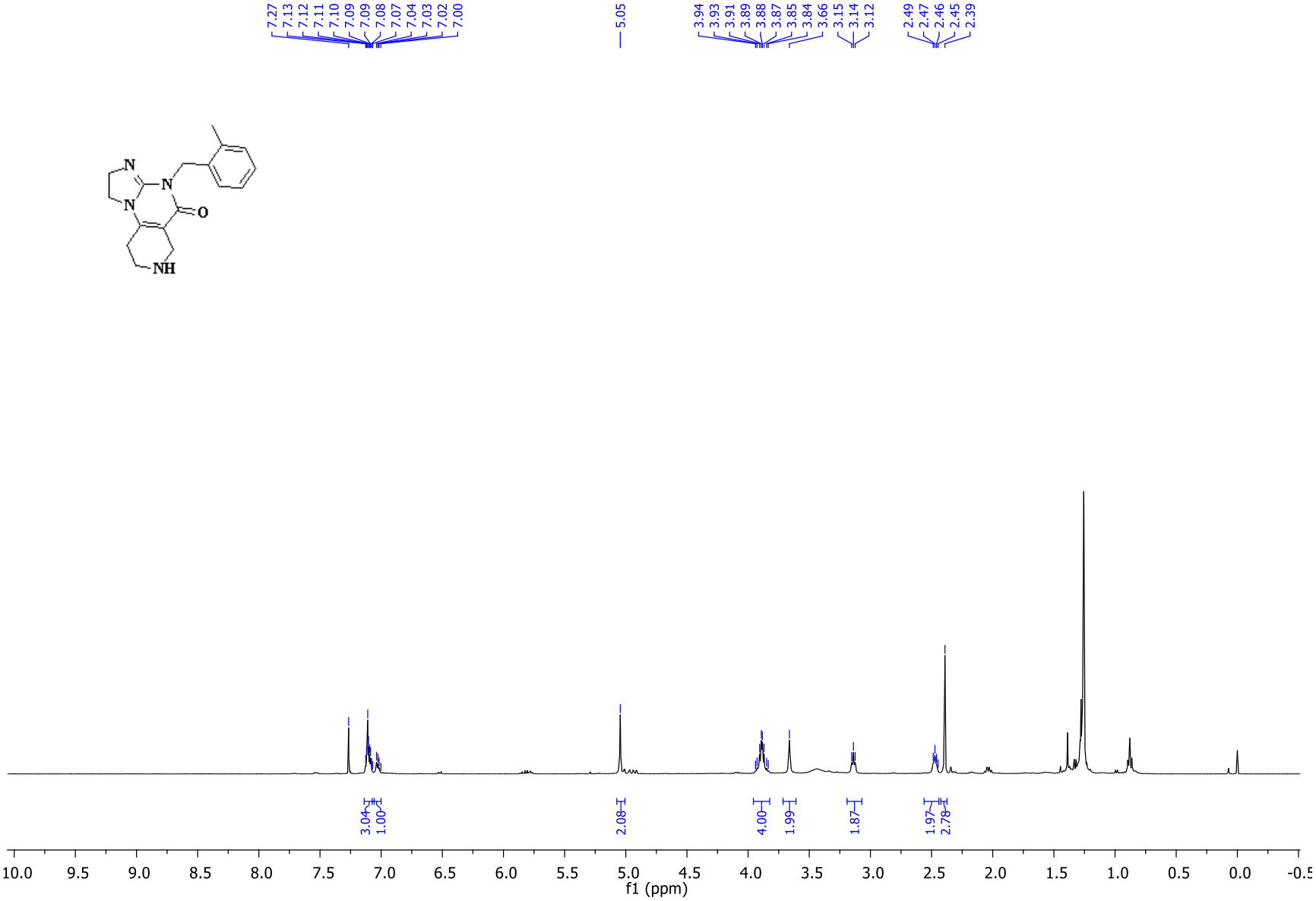
^{1}H-NMR 4 (400 MHz, $CDCl_3$)



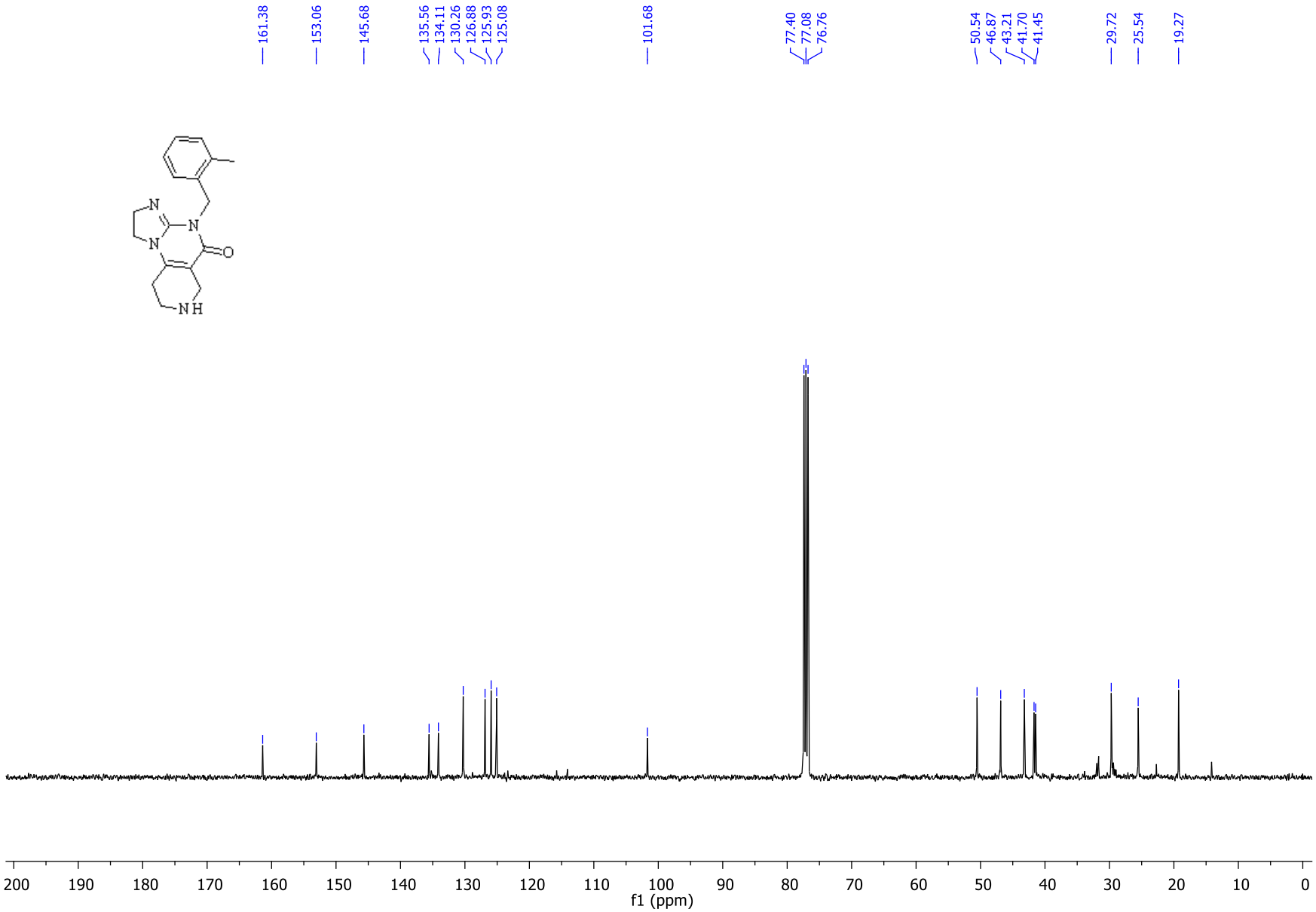
$^{13}C\{^{1}H\}$-NMR of 4 (101 MHz, $CDCl_3$)



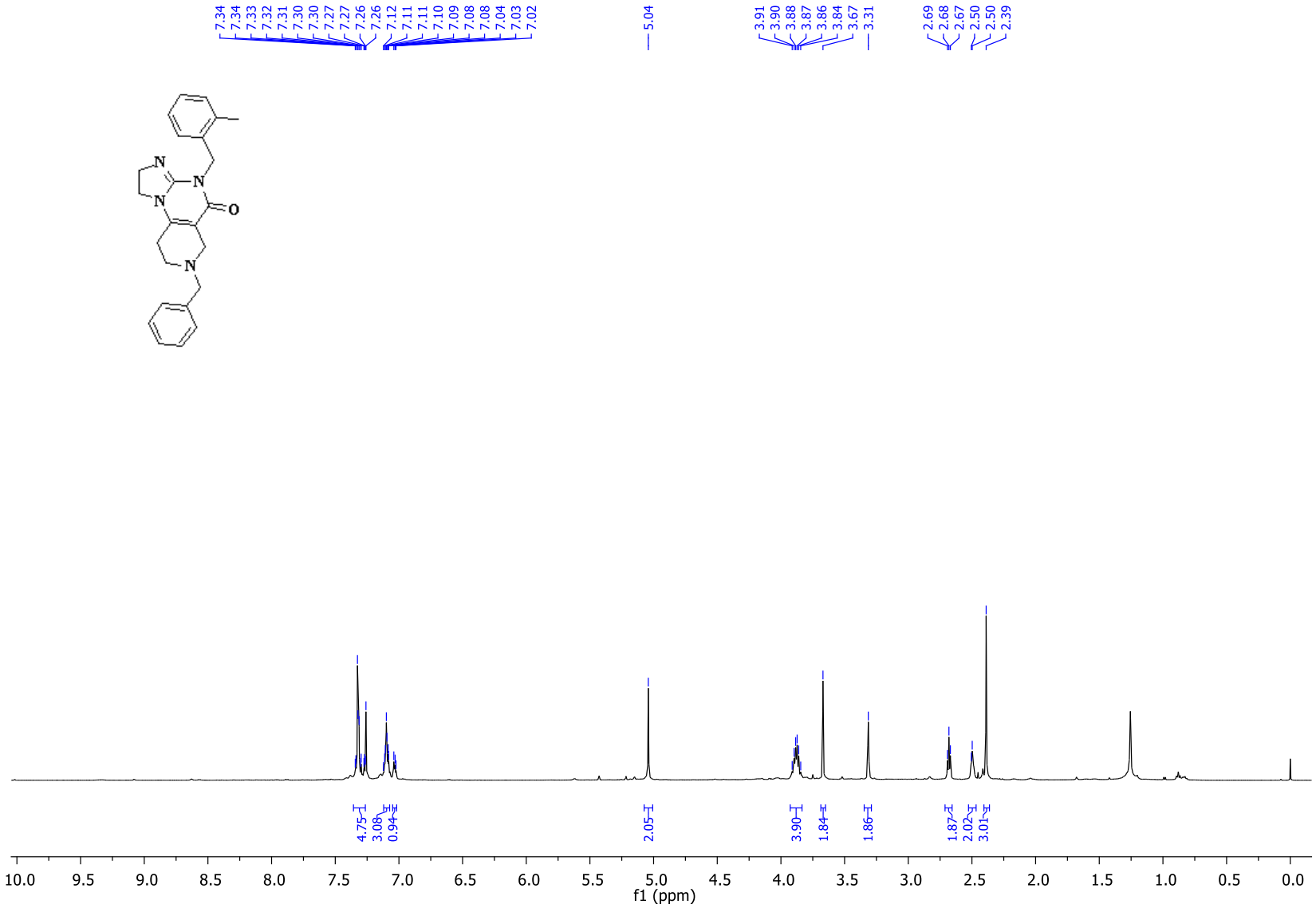
^{1}H-NMR of 5 (400 MHz, $CDCl_3$)



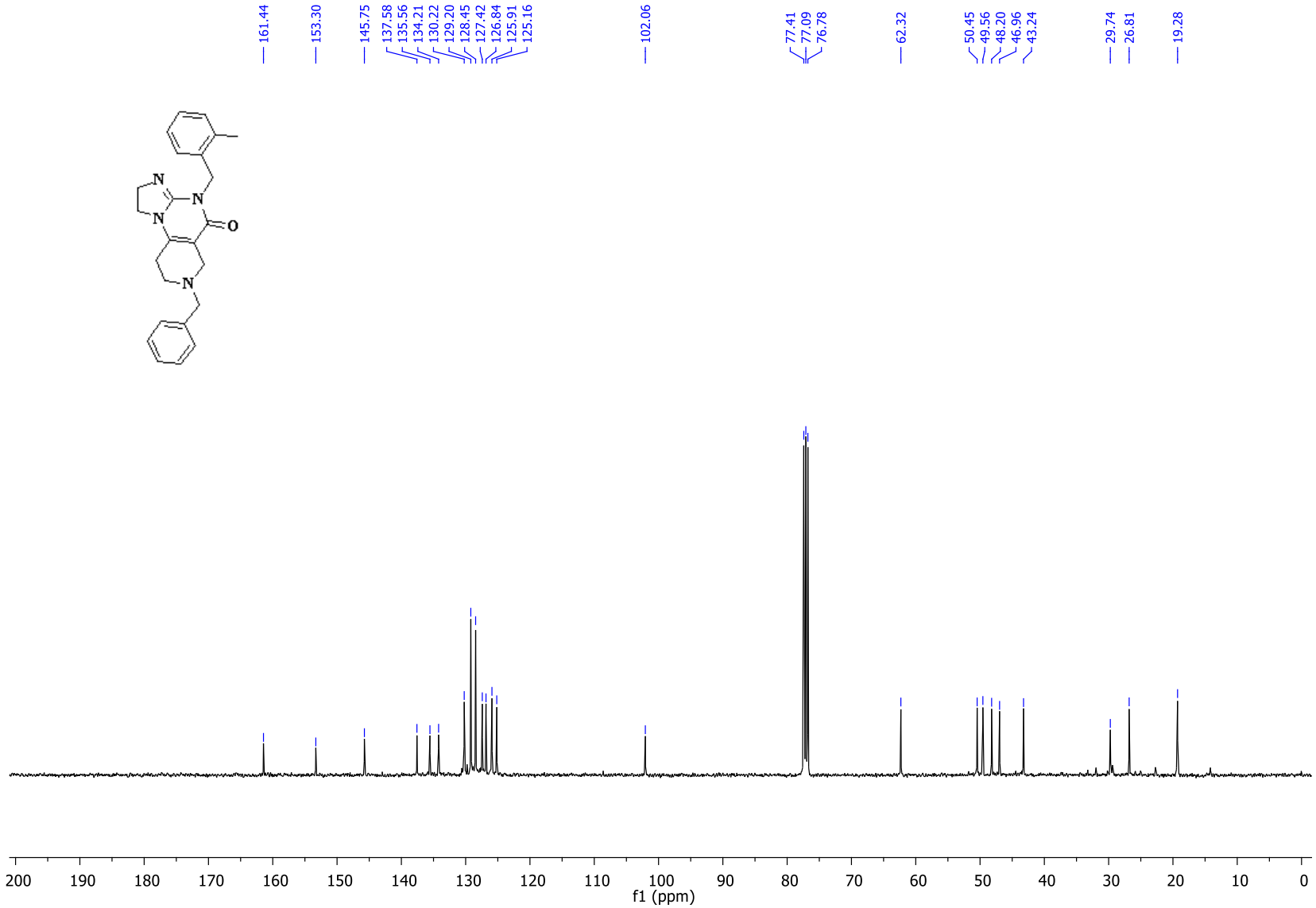
$^{13}C\{^{1}H\}$-NMR of 5 (101 MHz, $CDCl_3$)



^{1}H-NMR of 6 (500 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$-NMR of 6 (101 MHz, $CDCl_3$)



11. Crystallographic data for compounds

Crystallographic data for 3a

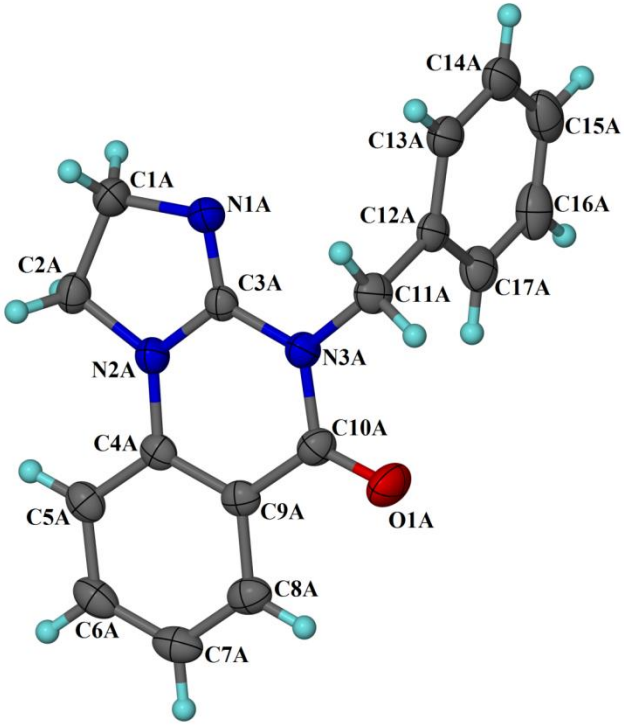


Figure caption: ORTEP diagram of **3a** compound with the atom-numbering. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radius. The asymmetric unit contains three molecules of **3a** compound (Z′=3). Only one molecule is shown in figure for clarity purpose.

Crystallization method: Compound **3a** was crystallized by using chloroform. Approximately 50 mg of **3a** was dissolved in 1 mL of solvent in a glass sample vial, which was covered with aluminium foil containing few holes, slow evaporation of the solvent allowed the formation of respective compound crystals **3a.**

Crystal data for 3a: $C_{17}H_{15}N_3O_1$, M = 277.32, Triclinic, space group *P-1* (No.2), a = 7.061(3)Å, b = 16.611(8)Å, c = 19.595(9)Å, α = 65.759(10)°, β = 87.399(11)°, γ = 80.205(10)°, V = 2064.5(16)Å^3, Z = 6, D_c = 1.338 g/cm^3, F_{000} = 876, Bruker D8 QUEST PHOTON-100, Mo-Kα radiation, λ = 0.71073 Å, T = 293(2)K, $2\theta_{max}$ = 55º, μ= 0.086 mm^{-1}, 48775 reflections collected, 9470 unique (R_{int} = 0.0495), 569 parameters, *R1* = 0.0510, *wR2* =0.1176, *R* indices based on 6216 reflections with I > 2σ(I) (refinement on F^2), Final *GooF* = 1.037, largest difference hole and peak = -0.206 and 0.246 e.Å^{-3}. **CCDC 2047921** deposition number contains the supplementary crystallographic data for this paper which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

Crystallographic data for 3n

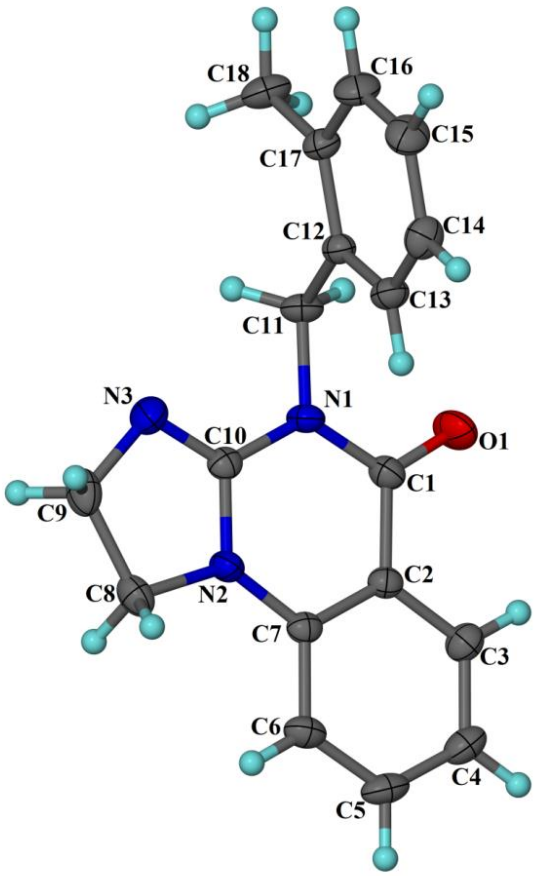


Figure caption: ORTEP diagram of **3n** compound with the atom-numbering. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radius.

Crystallization method: Compound **3n** was crystallized by using chloroform. Approximately 50 mg of **3n** was dissolved in 1 mL of solvent in a glass sample vial, which was covered with aluminium foil containing few holes, slow evaporation of the solvent allowed the formation of respective compound crystals **3n.**

Crystal data for 3n: $C_{18}H_{17}N_3O$, M = 291.34, Monoclinic, Space group $P2_1/c$ (No. 14), a = 7.6364(12)Å, b = 24.214(4)Å, c = 8.2875(13)Å, α = 90°, β = 108.818(7)°, γ = 90°, V = 1450.5(4)Å^3, Z = 4, D_c = 1.334 g/cm^3, F_{000} = 616, Bruker D8 QUEST PHOTON-100, Mo-Kα radiation, λ = 0.71073 Å, T = 293(2)K, $2\theta_{max}$ = 55º, μ= 0.085 mm^{-1}, 18774 reflections collected, 3322 unique (R_{int} = 0.0792), 201 parameters, *R1* = 0.0549, *wR2* =0.1033, *R* indices based on 1952 reflections with I > 2σ(I) (refinement on F^2), Final *GooF* = 1.034, largest difference hole and peak = -0.168 and 0.203 e.Å^{-3}. **CCDC 2076652** deposition number contain the supplementary crystallographic data for this paper which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

Crystallographic data for 3t

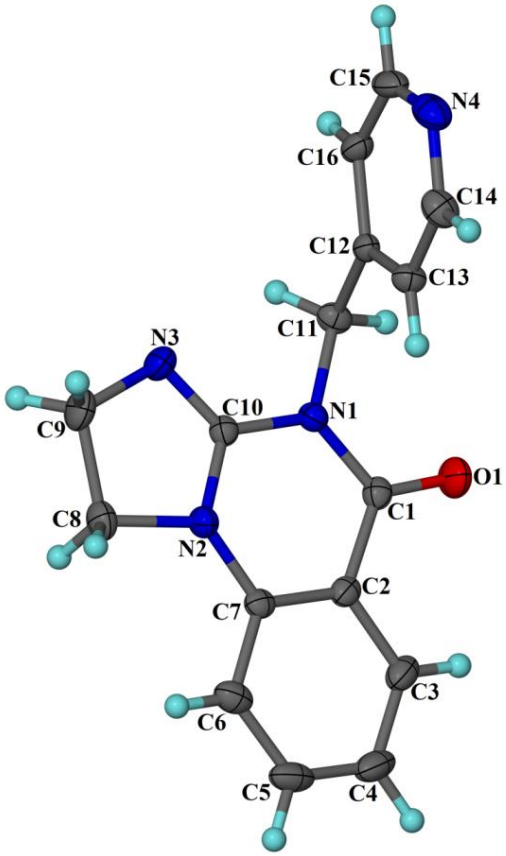


Figure caption: ORTEP diagram of **3t** compound with the atom-numbering. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radius.

Crystallization method: Compound **3t** was crystallized by using chloroform. Approximately 50 mg of **3t** was dissolved in 1 mL of solvent in a glass sample vial, which was covered with aluminium foil containing few holes, slow evaporation of the solvent allowed the formation of respective compound crystals **3t.**

Crystal data for 3t: $C_{16}H_{14}N_4O$, M = 278.31, Orthorhombic, Space group $P2_12_12_1$ (No.19), a = 8.275(6)Å, b = 9.736(6)Å, c = 16.380(15)Å, α = 90°, β = 90°, γ = 90°, V = 1320(2)Å^3, Z = 4, D_c = 1.401 g/cm^3, F_{000} = 584, Bruker D8 QUEST PHOTON-100, Mo-Kα radiation, λ = 0.71073 Å, T = 293(2)K, $2\theta_{max}$ = 55º, μ= 0.092 mm^{-1}, 15367 reflections collected, 3027 unique (R_{int} = 0.0378), 191 parameters, $R1$ = 0.0338, $wR2$ =0.0897, R indices based on 2797 reflections with I > 2σ(I) (refinement on F^2), Final $GooF$ = 1.077, largest difference hole and peak = -0.131 and 0.193 e.Å^{-3}. **CCDC 2076651** deposition number contain the supplementary crystallographic data for this paper which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

Crystallographic data for 4

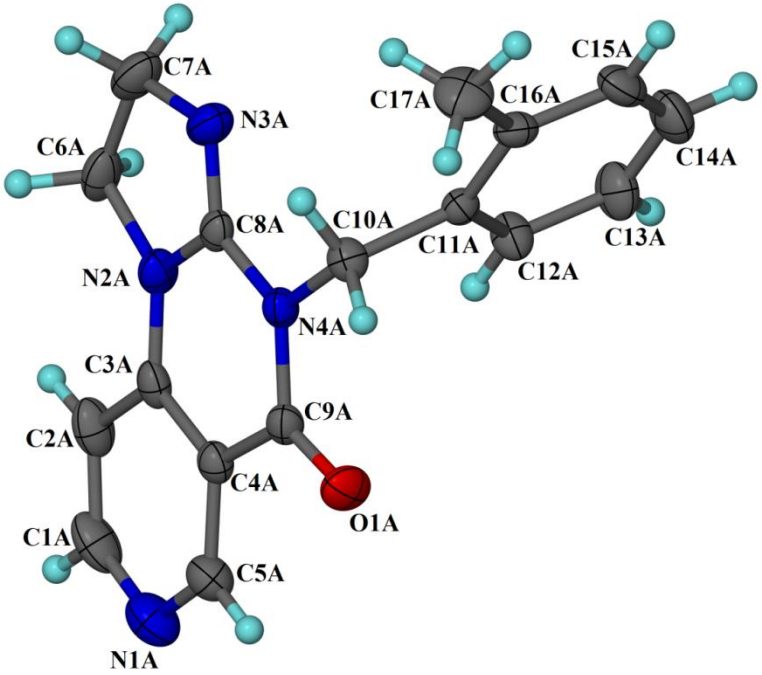


Figure caption: ORTEP diagram of **4** compound with the atom-numbering. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radius. The asymmetric unit contains two molecules of **4** compound (Z′=2). Only one molecule is shown in figure for clarity purpose.

Crystallization method: Compound **4** was crystallized by using chloroform. Approximately 50 mg of **4** was dissolved in 1 mL of solvent in a glass sample vial, which was covered with aluminium foil containing few holes, slow evaporation of the solvent allowed the formation of respective compound crystals **4.**

Crystal data for 4: $C_{17}H_{16}N_4O$, M = 292.34, Triclinic, space group *P-1* (No.2), a = 8.1289(7)Å, b = 10.9783(11)Å, c = 17.3875(16)Å, α = 82.153(3)°, β = 79.194(3)°, γ = 71.829(3)°, V = 1443.1(2)Å^3, Z = 4, D_c = 1.346 g/cm^3, F_{000} = 616, Bruker D8 QUEST PHOTON-100, Mo-Kα radiation, λ = 0.71073 Å, T = 293(2)K, $2\theta_{max}$ = 50º, μ= 0.088 mm^{-1}, 27376 reflections collected, 5081 unique (R_{int} = 0.0473), 400 parameters, *R1* = 0.0452, *wR2* =0.1072, *R* indices based on 3927 reflections with I > 2σ(I) (refinement on F^2), Final *GooF* = 1.035, largest difference hole and peak = -0.161 and 0.216 e.Å^{-3}. **CCDC 2047920** deposition number contains the supplementary crystallographic data for this paper which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

Data collection and Structure solution details: Single crystal X-ray data were collected at room temperature on a Bruker D8 QUEST equipped with a four-circle kappa diffractometer and Photon 100 detector. An Iμs microfocus Mo source (λ=0.71073Å) supplied the multi-mirror monochromated incident beam. A combination of Phi and Omega scans were used to collect the necessary data. Integration and scaling of intensity data were accomplished using SAINT program.[10] The structures were solved by Direct Methods using SHELXS97[11] and refinement was carried out by full-matrix least-squares technique using SHELXL-2014/7.[11-12] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms, with C-H distances of 0.93--0.97 Å, and with U_{iso}(H) = 1.2U_{eq} (C) or 1.5U_{eq} for methyl atoms. **CCDC 2076651-CCDC 2076652, CCDC 2047920-2047921** deposition numbers contain the supplementary crystallographic data for this paper which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

12. References

1. H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512–7515.

2. A. Gómez-SanJuan, J. M. Botija, A. Méndez, N. Sotomayor and E. Lete, *ARKIVOC*, 2014, **2**, 44–56.

3. N. Aoyagi and T. Endo, *Synth. Commun.*, 2017, **47**, 442–448.

4. N. Chiaramonte, S. Maach, C. Biliotti, A. Angeli, G. Bartolucci, L. Braconi, S. Dei, E. Teodori, C. T. Supuran and M. N. Romanelli, *J. Enzyme. Inhib. Med. Chem.*, 2020, **35**, 1003–1010.

5. N. T. Jacob, J. W. Lockner, V. V. Kravchenko and K. D. Janda, *Angew. Chem. Int. Ed.*, 2014, **126**, 6746–6749.

6. M. Genc and S. Servi, *Synth. Commun.*, 2009, **39**, 3263–3277.

7. S. Lulinski, J. Serwatowski and M. Szczerbinska, *Eur. J. Org. Chem.*, 2008, 1797–1801.

8. C-X. Jing, J-Y. Cai, Y. Zhang, D-Z. Chen, and X-J. Hao, *J. Chem. Res.*, 2015, **39**, 247–250.

9. ARBUTUS BIOPHARMA INC, Patent WO 2019/222238 A2.

10. SMART & SAINT. Software Reference manuals. Versions 6.28a & 5.625, Bruker Analytical X-ray Systems Inc., Madison, Wisconsin, U.S.A., 2001.

11. G. M. Sheldrick, SHELXS97 and SHELXL Version 2014/7, http://shelx.uni-ac.gwdg.de/SHELX/index.php

12. P. Muller, R. Herbst-Imer, A. L. Spek, T. R. Schneider and M. R. Sawaya, Crystal Structure Refinement: A Crystallographer's Guide to SHELXL. Muller, P. Ed. 2006 Oxford University Press: Oxford, New York, pp. 57–91.

13 A. L. Spek, *Acta Cryst.*, 2009, **D65**, 148-155.