Supporting Information

Acid-Catalyzed, Regioselective [3+3] Annulation of Enaminones and α-Substituted Cinnamic acids: Access to 3,4-Dihydropyridones and 2-Piperidinones

Sivanna Chithanna,[a] Animesh Roy,[a] and Ding-Yah Yang[a,b]*

[a]Department of Chemistry, Tunghai University

[b]Graduate Program for Biomedical and Materials Science, Tunghai University

No. 1727, Sec. 4, Taiwan Boulevard, Xitun District, Taichung 407224, Taiwan

*Corresponding author; Tel: 886-4-2359-7613; Fax: 886-4-2359-0426;

Email: yang@thu.edu.tw

Table of Contents

Instrumentation: Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. Infrared (IR) spectra were recorded using 1725XFT-IR spectrophotometer. High resolution mass spectra (HRMS) were obtained on a Thermo Fisher Scientific Finnigan MAT95XL spectrometer using magnetic sector analyzer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100) spectra were recorded on a Bruker 400 spectrometer. Chemical shifts were reported in parts per million on the scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Visualization was accomplished by using portable UV light, ninhydrin spray, or iodine chamber. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. Solvents, unless otherwise specified, were reagent grade and distilled once prior to use. All new compounds exhibited satisfactory spectroscopic and analytical data.

X-ray crystallographic data of compound **5a** (CCDC-2071541)

Single crystal of **5a** was obtained by slow evaporation from a mixture of dichloromethane and *n*-hexane at 25 ℃. Single-crystal X-ray data were collected at 150 K on a Bruker APEX-II CCD diffractometer using graphite-monochromated Mo KR radiation (λ = 0.71073A°). The crystal structures were solved by using SHELXS-97 and the structures were refined using SHELXL-97 2014. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at geometrically calculated positions and were refined using riding model.

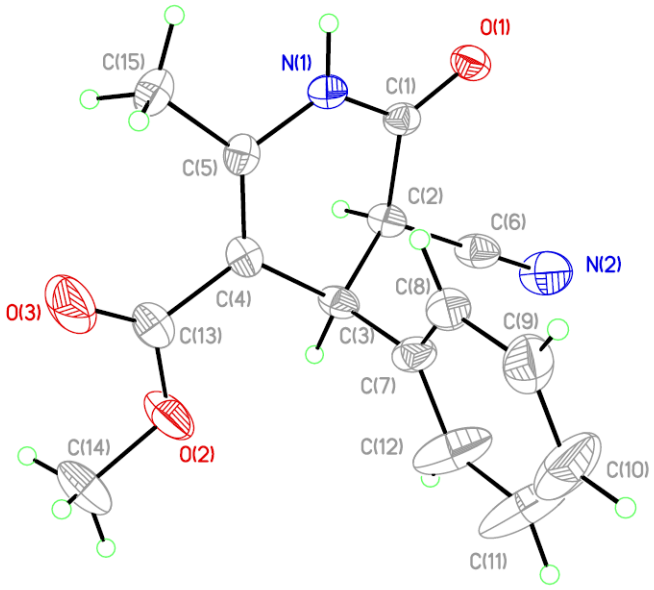


Figure S1: ORTEP diagram of compound **5a**. The ellipsoid contour probability levels: 50%

Table S1. Crystal data and structure refinement of compound **5a**.

Identification code	CS577	
Empirical formula	C15 H14 N2 O3	
Formula weight	270.28	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 13.4631(9) Å	a= 90°.
	b = 11.5917(7) Å	b= 90.303(3)°.
	c = 8.6603(6) Å	g = 90°.
Volume	1351.51(15) $Å^3$	
Z	4	
Density (calculated)	1.328 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	568	
Crystal size	0.370 x 0.330 x 0.180 mm^3	
Theta range for data collection	2.936 to 27.895°.	
Index ranges	-17<=h<=17, -15<=k<=15, -11<=l<=11	
Reflections collected	25167	
Independent reflections	3201 [R(int) = 0.0488]	
Completeness to theta = 25.242°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9281 and 0.8966	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3201 / 0 / 185	
Goodness-of-fit on F^2	1.008	
Final R indices [I>2sigma(I)]	R1 = 0.0587, wR2 = 0.1681	
R indices (all data)	R1 = 0.0659, wR2 = 0.1767	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.403 and -0.448 $e.Å^{-3}$	

X-ray crystallographic data of compound **5b** (CCDC-2071542)

Single crystal of **5b** was obtained by slow evaporation from a mixture of dichloromethane and *n*-hexane at 25 °C. Single-crystal X-ray data were collected at 150 K on a Bruker APEX-II CCD diffractometer using graphite-monochromated Mo KR radiation (λ = 0.71073A°). The crystal structures were solved by using SHELXS-97 and the structures were refined using SHELXL-97 2014. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at geometrically calculated positions and were refined using riding model.

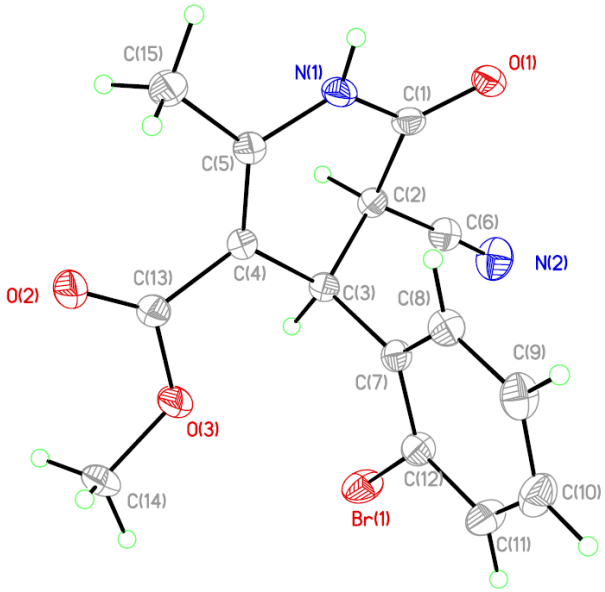


Figure S2: ORTEP diagram of compound **5b**. The ellipsoid contour probability levels: 50%

Table S2. Crystal data and structure refinement for compound **5b**.

Identification code	CS-607	
Empirical formula	$C_{15}H_{13}BrN_2O_3$	
Formula weight	349.18	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.7353(7) Å	a= 90°.
	b = 12.0789(8) Å	b= 104.410(2)°.
	c = 10.6288(6) Å	g = 90°.
Volume	1459.23(15) $Å^3$	
Z	4	
Density (calculated)	1.589 Mg/m^3	
Absorption coefficient	2.828 mm^{-1}	
F(000)	704	
Crystal size	0.410 x 0.170 x 0.120 mm^3	
Theta range for data collection	3.426 to 27.901°.	
Index ranges	-15<=h<=15, -15<=k<=15, -13<=l<=13	
Reflections collected	25829	
Independent reflections	3469 [R(int) = 0.0486]	
Completeness to theta = 25.242°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9281 and 0.7145	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3469 / 0 / 194	
Goodness-of-fit on F^2	1.012	
Final R indices [I>2sigma(I)]	R1 = 0.0273, wR2 = 0.0780	
R indices (all data)	R1 = 0.0333, wR2 = 0.0832	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.764 and -0.790 $e.Å^{-3}$	

X-ray crystallographic data of compound **8c** (CCDC-2071539)

Single crystal of **8c** was obtained by slow evaporation from a mixture of dichloromethane and *n*-hexane at 25 ℃. Single-crystal X-ray data were collected at 150 K on a Bruker APEX-II CCD diffractometer using graphite-monochromated Mo KR radiation (λ = 0.71073A°). The crystal structures were solved by using SHELXS-97 and the structures were refined using SHELXL-97 2014. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at geometrically calculated positions and were refined using riding model.

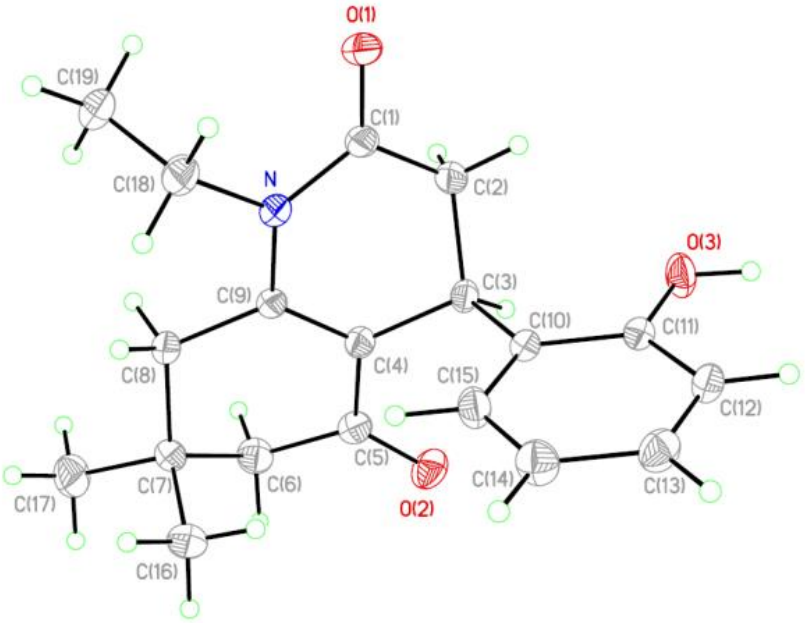


Figure S3: ORTEP diagram of compound **8c**. The ellipsoid contour probability levels: 50%

Table S3. Crystal data and structure refinement for compound **8c**.

Identification code	CS-538	
Empirical formula	$C_{19}H_{23}NO_3$	
Formula weight	313.38	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.8358(6) Å	a= 90°.
	b = 9.6075(6) Å	b= 115.331(2)°.
	c = 14.3495(8) Å	g = 90°.
Volume	1599.43(16) $Å^3$	
Z	4	
Density (calculated)	1.301 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	672	
Crystal size	0.340 x 0.330 x 0.240 mm^3	
Theta range for data collection	2.869 to 27.870°.	
Index ranges	-16<=h<=16, -12<=k<=12, -18<=l<=18	
Reflections collected	32456	
Independent reflections	3793 [R(int) = 0.0489]	
Completeness to theta = 25.242°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9281 and 0.8623	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3793 / 0 / 212	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0413, wR2 = 0.1108	
R indices (all data)	R1 = 0.0478, wR2 = 0.1186	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.357 and -0.197 $e.Å^{-3}$	

X-ray crystallographic data of compound **9a** (CCDC-2071540)

Single crystal of **9a** was obtained by slow evaporation from a mixture of methanol and dichloromethane at 25 ℃. Single-crystal X-ray data were collected at 150 K on a Bruker APEX-II CCD diffractometer using graphite-monochromated Mo KR radiation (λ = 0.71073A°). The crystal structures were solved by using SHELXS-97 and the structures were refined using SHELXL-97 2014. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at geometrically calculated positions and were refined using riding model.

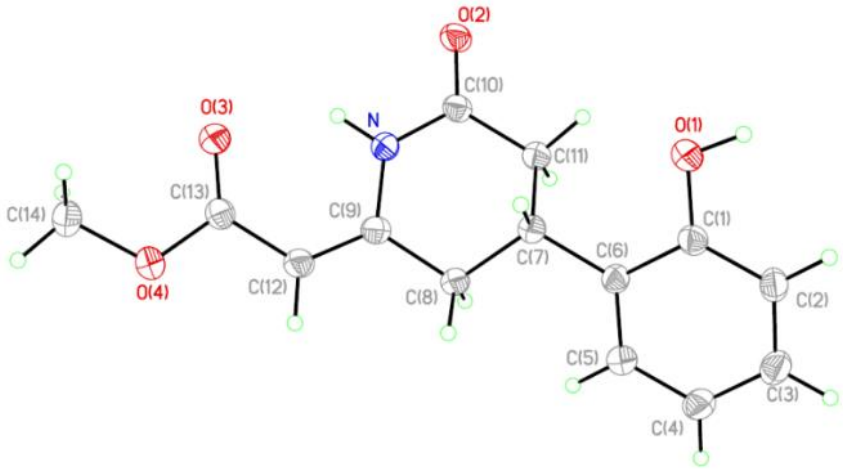


Figure S4: ORTEP diagram of compound **9a**. The ellipsoid contour probability levels: 50%

Table S4. Crystal data and structure refinement for compound **9a**.

Identification code	CS-547A	
Empirical formula	$C_{14}H_{15}NO_4$	
Formula weight	261.27	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 8.0107(5) Å	a= 90°.
	b = 14.7221(9) Å	b= 102.468(3)°.
	c = 10.7274(7) Å	g = 90°.
Volume	1235.29(14) $Å^3$	
Z	4	
Density (calculated)	1.405 Mg/m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	552	
Crystal size	0.470 x 0.260 x 0.230 mm^3	
Theta range for data collection	3.208 to 27.881°.	
Index ranges	-10<=h<=10, -19<=k<=19, -14<=l<=14	
Reflections collected	22665	
Independent reflections	2930 [R(int) = 0.0519]	
Completeness to theta = 25.242°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9281 and 0.8768	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2930 / 0 / 180	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0391, wR2 = 0.1117	
R indices (all data)	R1 = 0.0513, wR2 = 0.1295	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.292 and -0.184 $e.Å^{-3}$	

X-ray crystallographic data of compound **9e** (CCDC-2078427)

Single crystal of **9e** was obtained by slow evaporation from a mixture of methanol and dichloromethane at 25 °C. Single-crystal X-ray data were collected at 150 K on a Bruker APEX-II CCD diffractometer using graphite-monochromated Mo KR radiation (λ = 0.71073A°). The crystal structures were solved by using SHELXS-97 and the structures were refined using SHELXL-97 2014. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at geometrically calculated positions and were refined using riding model.

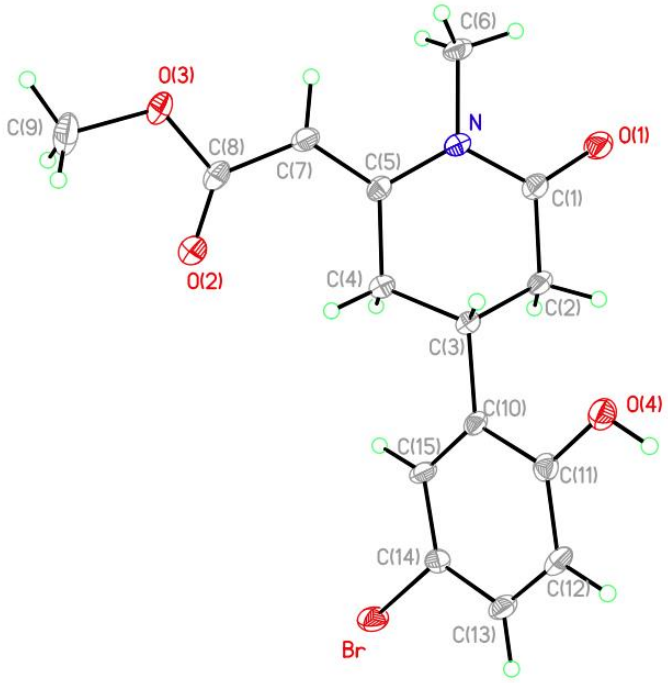


Figure S5: ORTEP diagram of compound **9a**. The ellipsoid contour probability levels: 50%

Table S5. Crystal data and structure refinement for compound **9e**.

Identification code	CS-619	
Empirical formula	$C_{15}H_{16}BrNO_4$	
Formula weight	354.20	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2/n	
Unit cell dimensions	a = 9.2266(7) Å	a= 90°.
	b = 8.5709(7) Å	b= 92.636(4)°.
	c = 18.4502(15) Å	g = 90°.
Volume	1457.5(2) $Å^3$	
Z	4	
Density (calculated)	1.614 Mg/m^3	
Absorption coefficient	2.836 mm^{-1}	
F(000)	720	
Crystal size	0.500 x 0.220 x 0.200 mm^3	
Theta range for data collection	3.246 to 28.108°.	
Index ranges	-12<=h<=12, -11<=k<=11, -24<=l<=24	
Reflections collected	27590	
Independent reflections	3525 [R(int) = 0.0715]	
Completeness to theta = 25.242°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.4626	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3525 / 0 / 206	
Goodness-of-fit on F^2	1.064	
Final R indices [I>2sigma(I)]	R1 = 0.0509, wR2 = 0.1410	
R indices (all data)	R1 = 0.0576, wR2 = 0.1483	
Extinction coefficient	n/a	
Largest diff. peak and hole	2.472 and -1.078 $e.Å^{-3}$	

X-ray crystallographic data of compound **25** (CCDC- 2077711)

Single crystal of **25** was obtained by slow evaporation from a mixture of dichloromethane and *n*-hexane at 25 °C. Single-crystal X-ray data were collected at 150 K on a Bruker APEX-II CCD diffractometer using graphite-monochromated Mo KR radiation (λ = 0.71073A°). The crystal structures were solved by using SHELXS-97 and the structures were refined using SHELXL-97 2014. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at geometrically calculated positions and were refined using riding model.

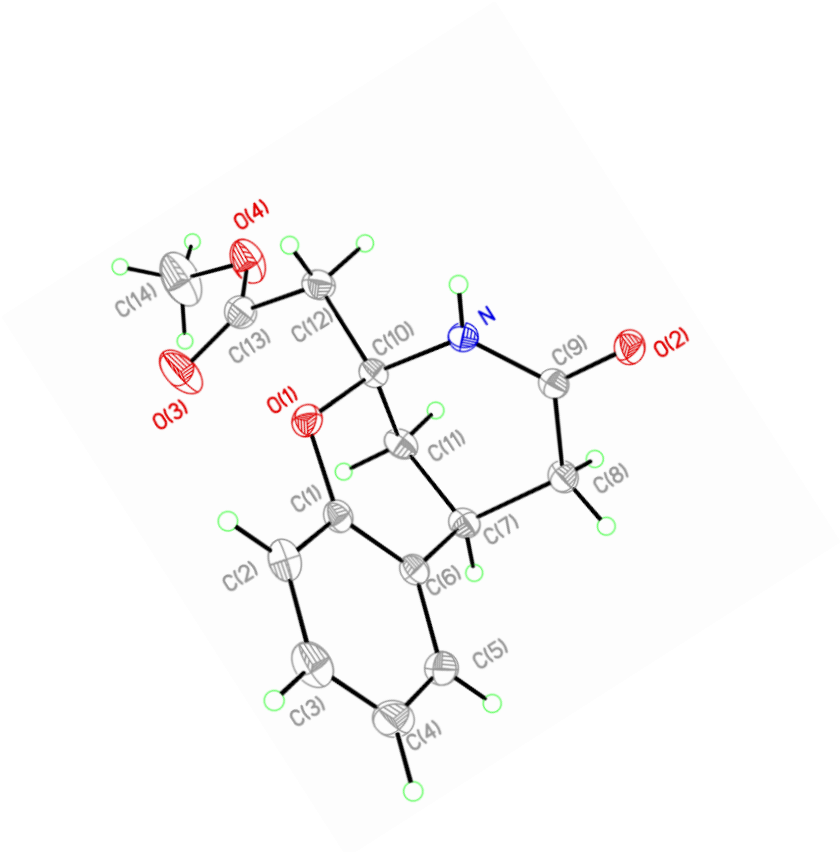


Figure S6: ORTEP diagram of compound **25**. The ellipsoid contour probability levels: 50%

Table S6. Crystal data and structure refinement for compound **25**.

Identification code	CS-547B	
Empirical formula	$C_{14}H_{15}NO_4$	
Formula weight	261.27	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 9.1578(6) Å	a= 90°.
	b = 8.0660(5) Å	b= 95.892(3)°.
	c = 17.2518(10) Å	g = 90°.
Volume	1267.60(14) $Å^3$	
Z	4	
Density (calculated)	1.369 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	552	
Crystal size	0.320 x 0.310 x 0.190 mm^3	
Theta range for data collection	3.374 to 27.925°.	
Index ranges	-12<=h<=12, -10<=k<=10, -22<=l<=22	
Reflections collected	23984	
Independent reflections	2997 [R(int) = 0.0478]	
Completeness to theta = 25.242°	98.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.6560	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2997 / 0 / 176	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0419, wR2 = 0.1230	
R indices (all data)	R1 = 0.0452, wR2 = 0.1273	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.405 and -0.182 $e.Å^{-3}$	

X-ray crystallographic data of compound **27** (CCDC-2088154)

Single crystal of **27** was obtained by slow evaporation from a mixture of dichloromethane and *n*-hexane at 25 °C. Single-crystal X-ray data were collected at 150 K on a Bruker APEX-II CCD diffractometer using graphite-monochromated Mo KR radiation (λ = 0.71073A°). The crystal structures were solved by using SHELXS-97 and the structures were refined using SHELXL-97 2014. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were fixed at geometrically calculated positions and were refined using riding model.

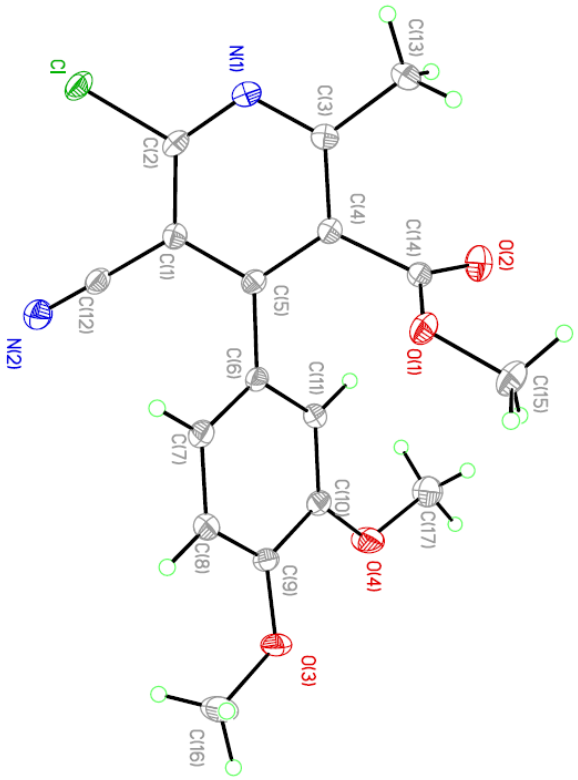


Figure S7: ORTEP diagram of compound **27**. The ellipsoid contour probability levels: 50%

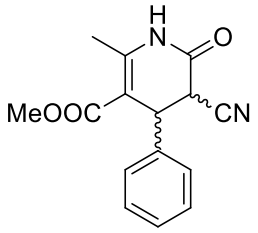
Table S7. Crystal data and structure refinement for compound **27**.

Identification code	CS-629	
Empirical formula	C_{17} H_{15} Cl N_2 O_4	
Formula weight	346.76	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 7.5619(5) Å	a= 90°.
	b = 7.8517(5) Å	b= 96.461(3)°.
	c = 26.9250(17) Å	g = 90°.
Volume	1588.49(18) $Å^3$	
Z	4	
Density (calculated)	1.450 Mg/m^3	
Absorption coefficient	0.265 mm^{-1}	
F(000)	720	
Crystal size	0.510 x 0.350 x 0.210 mm^3	
Theta range for data collection	2.704 to 27.894°.	
Index ranges	-9<=h<=9, -10<=k<=9, -35<=l<=35	
Reflections collected	28899	
Independent reflections	3767 [R(int) = 0.0457]	
Completeness to theta = 25.242°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7456 and 0.6291	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3767 / 0 / 229	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0341, wR2 = 0.0888	
R indices (all data)	R1 = 0.0357, wR2 = 0.0898	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.383 and -0.222 $e.Å^{-3}$	

General procedure A for preparation of compounds **5a**–**h**.

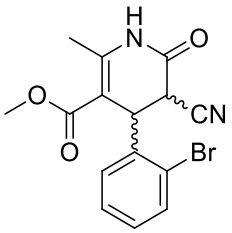
To a stirred solution of commercially available enamine **1** (0.5 mmol) and α,β-unsaturated carboxylic acid **4** (0.5 mmol) in dry toluene (5 mL) was added boric acid (5 mol%) at room temperature. The resulting mixture was refluxed for 3 h. After completion of the reaction, the solution was evaporated and the residue was diluted with ethyl acetate (100 mL), washed with water (30 mL) and brine (30 mL). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide the crude product which was further purified by column chromatography to obtain the desired compound.

Methyl 5-cyano-2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5a).



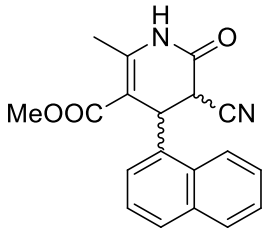
The title compound **5a** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*E*)-2-cyano-3-phenylacrylic acid (**4a**, 87 mg, 0.5 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (120 mg, 89% yield). R_f = 0.5 (50% EtOAc/hexanes). (*Cis* diastereomer) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.54 (s, 1H), 7.37–7.28 (m, 3H), 7.20–7.18 (m, 2H), 4.93 (d, J = 6.8 Hz, 1H), 4.34 (d, J = 6.8 Hz, 1H), 3.56 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 166.4, 163.5, 148.4, 138.0, 129.2 (2C), 128.4, 128.1 (2C), 116.1, 105.8, 51.8, 41.2, 41.1, 18.6. IR $_{vmax}$ (neat): 3130, 2230, 1628, 1416, 1279, 792, 635 cm^{-1}. (*Trans* diastereomer) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.65 (s, 1H), 7.37–7.28 (m, 3H), 7.25–7.23 (m, 2H), 4.50 (d, J = 3.2 Hz, 1H), 4.14 (d, J = 3.2 Hz, 1H), 3.56 (s, 3H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 166.7, 162.0, 148.3, 138.3, 129.3 (2C), 128.2, 127.5 (2C), 117.1, 104.3, 51.9, 42.1, 40.7, 18.4. HRMS (EI) m/z: [M$^+$] calcd for $C_{15}H_{14}N_2O_3$, 270.1004; found, 270.1006.

Methyl 4-(2-bromophenyl)-5-cyano-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5b).



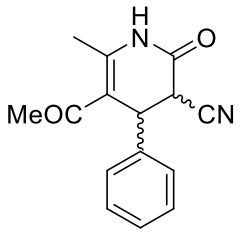
The title compound **5b** was synthesized by following general procedure A from enamine **1a** (58 mg, 0.5 mmol), (*E*)-3-(2-bromophenyl)-2-cyanoacrylic acid (**4b**, 126 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (30% EtOAc in hexanes) to give a white solid (162 mg, 93% yield). R_f = 0.5 (40% EtOAc/hexanes). (*Cis* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.04 (s, 1H), 7.65 (dd, J = 8.0, 1.2 Hz, 1H), 7.26 (td, J = 8.0, 1.2 Hz, 1H), 7.18 (td, J = 8.0, 2.0 Hz, 1H), 7.13 (dd, J = 8.0, 2.0 Hz, 1H), 5.24 (d, J = 8.0 Hz, 1H), 4.15 (d, J = 8.0 Hz, 1H), 3.65 (s, 3H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 166.3, 162.6, 148.1, 137.7, 133.1, 129.5, 128.1, 127.6, 125.0, 114.1, 106.0, 50.5, 47.6, 39.6, 17.0. IR $_{vmax}$ (neat): 3133, 2228, 1628, 1412, 1285, 792, 625 cm^{-1}. (*Trans* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.00 (s, 1H), 7.64 (dd, J = 8.0, 1.2 Hz, 1H), 7.26 (td, J = 8.0, 1.2 Hz, 1H), 7.16 (td, J = 8.0, 2.0 Hz, 1H), 6.99 (dd, J = 8.0, 2.0 Hz, 1H), 5.00 (d, J = 2.0 Hz, 1H), 3.77 (d, J = 2.0 Hz, 1H), 3.66 (s, 3H), 2.56 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 165.8, 161.1, 149.2, 135.9, 133.6, 129.8, 128.0, 127.4, 123.8, 115.2, 103.3, 50.8, 47.8, 42.5, 13.1. HRMS (EI) m/z: [M^+] calcd for $C_{15}H_{13}BrN_2O_3$, 348.0110; found, 348.0113.

Methyl 5-cyano-2-methyl-4-(naphthalen-1-yl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5c).



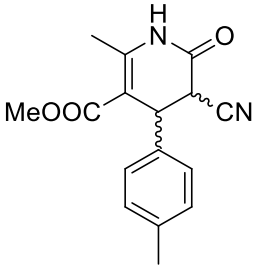
The title compound **5c** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*E*)-2-cyano-3-(naphthalen-1-yl)acrylic acid (**4c**, 112 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (50% EtOAc in hexanes) to give a white solid (120 mg, 87% yield). R_f = 0.5 (50% EtOAc/hexanes). (*Cis* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.60 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 7.63–7.57 (m, 1H), 7.54 (t, J = 6.8 Hz, 1H), 7.48–7.43 (m, 1H), 7.27 (d, J = 6.8 Hz, 1H), 5.49 (d, J = 7.2 Hz, 1H), 4.98 (d, J = 7.2 Hz, 1H), 3.41 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 166.6, 163.4, 148.6, 135.3, 134.0, 132.0, 128.9, 128.9, 126.5, 126.3, 126.0, 124.5, 124.4, 116.1, 104.6, 51.7, 41.2, 35.0, 18.7. IR $_{vmax}$ (neat): 2988, 2233, 1641, 1414, 1290, 789, 624 cm^{-1}. (*Trans* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.72 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 7.67 (td, J = 8.0, 1.2 Hz, 1H), 7.63–7.57 (m, 1H), 7.48–7.43 (m, 1H), 7.24 (d, J = 6.8 Hz, 1H), 5.34 (d, J = 3.2 Hz, 1H), 4.05 (d, J = 3.2 Hz, 1H), 3.41 (s, 3H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 166.6, 161.8, 148.9, 134.4, 133.0, 130.5, 129.5, 129.2, 127.5, 126.5, 125.9, 124.3, 123.5, 116.9, 104.6, 51.8, 38.5, 31.4, 18.5. HRMS (EI) m/z: [M^+] calcd for $C_{19}H_{16}N_2O_3$, 320.1161; found, 320.1163.

5-Acetyl-4-(2-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitrile (5d).



The title compound **5d** was synthesized by following general procedure A from enamine **1d** (58.0 mg, 0.5 mmol), (*E*)-3-(2-bromophenyl)-2-cyanoacrylic acid (**4a**, 92 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (120 mg, 72% yield). R_f = 0.5 (50% EtOAc/hexanes). (*Cis* diastereomer) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.58 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 4.95 (d, J = 5.2 Hz, 1H), 3.17 (d, J = 5.2 Hz, 1H), 2.31 (s, 3H), 2.06 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 196.4, 162.7, 147.5, 137.5, 133.8, 130.6, 129.3, 128.7, 125.2, 115.5, 114.8, 40.4, 40.2, 30.2, 19.2. IR $_{vmax}$ (neat): 3050, 2222, 1690, 1470, 1279, 778, 634 cm^{-1}. (*Trans* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.70 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 4.85 (d, J = 4.8 Hz, 1H), 4.06 (d, J = 4.8 Hz, 1H), 2.35 (s, 3H), 2.03 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 196.9, 161.3, 146.8, 136.7, 134.1, 130.7, 129.1, 128.7, 124.5, 116.3, 113.7, 42.6, 38.7, 30.3, 18.9. HRMS (EI) m/z: [M^+] calcd for $C_{15}H_{13}BrN_2O_2$, 332.0160; found, 332.0163.

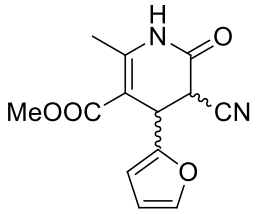
Methyl 5-cyano-2-methyl-6-oxo-4-(p-tolyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (5e).



The title compound **5e** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*E*)-2-cyano-3-(*p*-tolyl)acrylic acid (**4e**, 94 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (111 mg, 83% yield). R_f = 0.6 (50% EtOAc/hexanes). (*Cis* diastereomer) ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.51 (s, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 4.89 (d, J = 6.8 Hz, 1H), 4.31 (d, J = 6.8 Hz, 1H), 3.55 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 166.4, 163.5, 148.2, 137.6, 135.0, 129.7 (2C), 128.0 (2C), 116.2, 106.0,

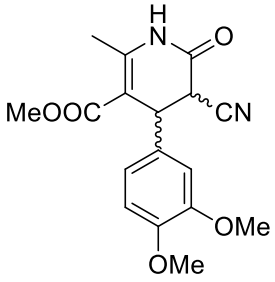
51.8, 41.3, 40.8, 21.1, 18.5. IR $_{vmax}$ (neat): 3023, 2223, 1701, 1471, 1268, 775, 630 cm^{-1}. (*Trans* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.62 (s, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 4.45 (d, J = 3.2 Hz, 1H), 4.08 (d, J = 3.2 Hz, 1H), 3.56 (s, 3H), 2.38 (s, 3H), 2.26 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 166.7, 162.1, 154.8, 131.3, 130.4, 129.9 (2C), 127.3 (2C), 117.1, 104.4, 51.9, 41.7, 40.4, 21.0, 18.4. HRMS (EI) m/z: [M^{+}] calcd for $C_{16}H_{16}N_2O_3$, 284.1161; found, 284.1163.

Methyl 5-cyano-4-(furan-2-yl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5f).



The title compound **5f** was synthesized by following general procedure A from enamine **1** (58.0 mg, 0.5 mmol), (*E*)-2-cyano-3-(furan-2-yl)acrylic acid (**4f**, 82 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (50% EtOAc in hexanes) to give a white solid (97 mg, 79% yield). R_f = 0.5 (60% EtOAc/hexanes). (*Cis* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.23 (s, 1H), 7.34 (s, 1H), 6.33–6.30 (m, 2H), 4.66 (d, J = 6.8 Hz, 1H), 4.04 (d, J = 6.8 Hz, 1H), 3.75 (s, 3H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 167.6, 164.6, 152.3, 149.6, 143.9, 116.0, 111.4, 108.9, 105.2, 52.0, 41.5 36.9, 18.5. IR $_{vmax}$ (neat): 3020, 2260, 1710, 1571, 1368, 789, 633 cm^{-1}. (*Trans* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.19 (s, 1H), 7.34 (s, 1H), 6.29–6.27 (m, 1H), 6.10 (d, J = 3.2 Hz, 1H), 4.66 (d, J = 1.2 Hz, 1H), 3.90 (d, J = 1.2 Hz, 1H), 3.77 (s, 3H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 167.3, 165.3, 151.6, 149.4, 144.1, 115.8, 111.5, 109.6, 108.2, 52.2, 41.6, 37.9, 18.4. IR $_{vmax}$ (neat): cm^{-1}. HRMS (EI) m/z: [M^{+}] calcd for $C_{13}H_{12}N_2O_4$, 260.0797; found, 260.0795.

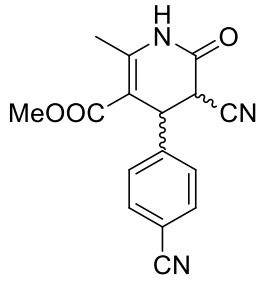
Methyl 5-cyano-4-(3,4-dimethoxyphenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5g).



The title compound **5g** was synthesized by following general procedure A from enamine **1** (58.0 mg, 0.5 mmol), (*E*)-2-cyano-3-(3,4-dimethoxyphenyl)acrylic acid (**4g**, 117 mg, 0.55 mmol),

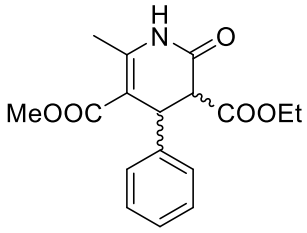
boric acid (5 mol%) and purified by flash column chromatography (30% EtOAc in hexanes) to give a white solid (107 mg, 68% yield). R_f = 0.5 (40% EtOAc/hexanes). (*Cis* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.72 (s, 1H), 6.83 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.76 (dd, J = 8.4, 2.0 Hz, 1H), 4.45 (d, J = 6.8 Hz, 1H), 4.15 (d, J = 6.8 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.68 (s, 3H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 166.0, 163.4, 149.2, 149.0, 146.2, 127.9, 119.5, 114.5, 111.9, 111.5, 107.6, 56.0, 55.8, 51.9, 41.5, 41.0, 18.8. IR $_{vmax}$ (neat): 3033, 2262, 1716, 1572, 1368, 789, 633 cm^{-1}. (*Trans* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.76 (s, 1H), 6.82 (s, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.69 (dd, J = 8.4, 2.0 Hz, 1H), 6.66 (d, J = 2.0 Hz, 1H), 4.55 (d, J = 2.8 Hz, 1H), 3.71 (d, J = 2.8 Hz, 1H), 3.84 (s, 6H), 3.69 (s, 3H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 166.3, 162.3, 149.5, 148.9, 146.1, 129.6, 118.5, 115.4, 111.6, 110.3, 105.9, 56.0, 55.9, 51.9, 42.4, 40.0, 18.8. HRMS (EI) m/z: [M$^+$] calcd for $C_{17}H_{18}N_2O_5$, 330.1216; found, 330.1217.

Methyl 5-cyano-4-(4-cyanophenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5h).



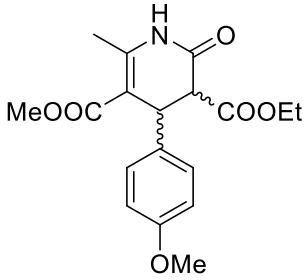
The title compound **5h** was synthesized by following general procedure A from enamine **1** (58.0 mg, 0.5 mmol), (*E*)-2-cyano-3-(4-cyanophenyl)acrylic acid (**4h**, 99 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (128 mg, 92% yield). R_f = 0.5 (50% EtOAc/hexanes). (*Cis* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.93 (bs, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 4.45 (d, J = 7.2 Hz, 1H), 4.18 (d, J = 7.2 Hz, 1H), 3.68 (s, 3H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 165.5, 162.0, 147.0, 141.1, 132.9 (2C), 128.8 (2C), 118.3, 113.5, 112.7, 106.4, 52.1, 41.5, 40.7, 19.2. IR $_{vmax}$ (neat): 3115, 2227, 1727, 1671, 1386, 790, 623 cm^{-1}. (*Trans* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.89 (bs, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.63 (d, J = 2.8 Hz, 1H), 3.67 (d, J = 2.8 Hz, 1H), 3.68 (s, 3H), 2.53 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 165.7, 160.8, 146.9, 142.8, 133.2 (2C), 127.8 (2C), 118.1, 114.6, 112.5, 104.7, 42.8, 39.3, 31.0, 29.3. HRMS (EI) m/z: [M$^+$] calcd for $C_{16}H_{13}N_3O_3$, 295.0957; found, 295.0960.

3-Ethyl 5-methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (5i).



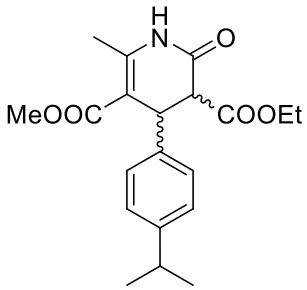
The title compound **5i** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*Z*)-2-(ethoxycarbonyl)-3-phenylacrylic acid (**4i**, 121 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (140 mg, 88% yield). R_f = 0.6 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.78 (s, 1H), 7.32–7.29 (m, 2H), 7.26–7.24 (m, 1H), 7.22–7.20 (m, 2H), 4.69 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 3.65 (s, 3H), 3.60 (d, J = 1.6 Hz, 1H), 2.41 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 168.0, 167.2, 166.9, 146.7, 139.8, 129.0, 127.4, 126.8, 105.6, 62.1, 54.8, 51.6, 42.0, 18.8, 14.1. IR $_{vmax}$ (neat): 2927, 1729, 1683, 1269, 1197, 1028, 702 cm^{-1}. HRMS (EI) m/z: [M^+] calcd for $C_{17}H_{19}NO_5$, 317.1263; found, 317.1260.

3-Ethyl 5-methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (5j).



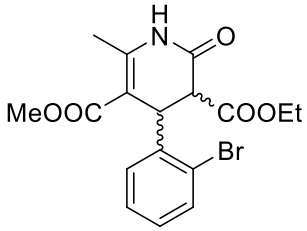
The title compound **5j** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*Z*)-2-(ethoxycarbonyl)-3-(4-methoxyphenyl)acrylic acid (**4j**, 138 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (142 mg, 82% yield). R_f = 0.5 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.46 (s, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.64 (s, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 3.56 (d, J = 1.6 Hz, 1H), 2.41 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 168.0, 167.1, 167.0, 158.8, 146.2, 131.7, 127.9, 114.3, 106.1, 62.1, 55.2, 55.0, 51.6, 41.2, 18.8, 14.1. IR $_{vmax}$ (neat): 2925, 1740, 1696, 1248, 1181, 1026, 841 cm^{-1}. HRMS (EI) m/z: [M^+] calcd for $C_{18}H_{21}NO_6$, 347.1369; found, 347.1374.

3-Ethyl 5-methyl 4-(4-isopropylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (5k).



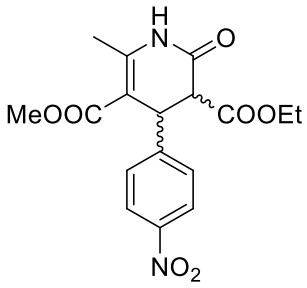
The title compound **5k** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*Z*)-2-(ethoxycarbonyl)-3-(4-isopropylphenyl)acrylic acid (**4k**, 138 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (131 mg, 73% yield). R_f = 0.6 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.40 (s, 1H), 7.17–7.11 (m, 4H), 4.67 (s, 1H), 4.24 (q, J = 7.0 Hz, 2H), 3.67 (s, 3H), 3.60 (d, J = 1.6 Hz, 1H), 2.91–2.84 (m, 1H), 2.41 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.23 (d, J = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 168.1, 167.1, 167.0, 147.9, 146.2, 137.0, 127.0, 126.7, 106.0, 62.1, 54.8, 51.6, 41.6, 33.7, 23.9, 18.9, 14.1. IR $_{vmax}$ (neat): 2957, 1737, 1702, 1198, 1089, 1021, 782 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{20}H_{25}NO_5$, 359.1733; found, 359.1731.

3-Ethyl 5-methyl 4-(2-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (5l).



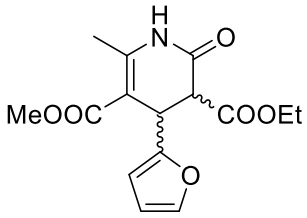
The title compound **5l** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*Z*)-3-(2-bromophenyl)-2-(ethoxycarbonyl)acrylic acid (**4l**, 165 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (168 mg, 85% yield). R_f = 0.5 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.83 (s, 1H), 7.62 (dd, J = 8.0, 1.2 Hz, 1H), 7.23–7.21 (m, 1H), 7.16–7.11 (m, 1H), 7.03 (dd, J = 7.8, 1.4 Hz), 5.13 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.68 (s, 1H), 3.65 (s, 3H), 2.49 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 167.5, 166.6, 166.3, 147.5, 137.5, 133.9, 129.2, 127.9, 127.6, 124.2, 105.0, 62.2, 52.7, 51.7, 41.5, 18.9, 14.1. IR $_{vmax}$ (neat): 2924, 1737, 1708, 1278, 1200, 1092, 760 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{17}H_{18}BrNO_5$, 395.0368; found, 395.0364.

3-Ethyl 5-methyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (5m).



The title compound **5m** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*Z*)-2-(ethoxycarbonyl)-3-(4-nitrophenyl)acrylic acid (**4m**, 146 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (50% EtOAc in hexanes) to give a pale yellow solid (147 mg, 81% yield). R_f = 0.4 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.81 (s, 1H), 8.15 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 4.77 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 3.65 (s, 3H), 3.56 (d, J = 1.6 Hz, 1H), 2.42 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 167.4, 166.5, 147.5, 147.4, 147.3, 128.0, 124.3, 104.6, 62.6, 54.1, 51.8, 41.8, 18.9, 14.0. IR $_{vmax}$ (neat): 2927, 1735, 1691, 1348, 1182, 1091, 856 cm^{-1}. HRMS (EI) m/z: [M^+] calcd for $C_{17}H_{18}N_2O_7$, 362.1114; found, 362.1119.

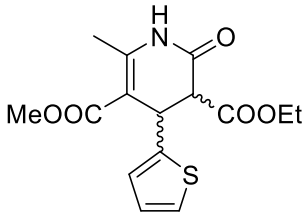
3-Ethyl 5-methyl 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (5n).



The title compound **5n** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*Z*)-2-(ethoxycarbonyl)-3-(furan-2-yl)acrylic acid (**4n**, 116 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (106 mg, 69% yield). R_f = 0.5 (50% EtOAc/hexanes). (*Major* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.47 (s, 1H), 7.31 (d, J = 1.6 Hz, 1H), 6.25 (dd, J = 2.8, 1.6 Hz, 1H), 6.05 (d, J = 2.8 Hz, 1H), 4.77 (s, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.78 (d, J = 1.2 Hz, 1H), 3.73 (s, 3H), 2.37 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 167.4, 166.8, 166.6, 152.5, 147.2, 142.4, 110.3, 106.1, 103.6, 62.2, 51.6, 51.4, 36.0, 18.9, 14.0. IR $_{vmax}$ (neat): 2952, 1737, 1702, 1279, 1183, 1090, 734 cm^{-1}. (*Minor* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22 (d, J = 1.2 Hz, 1H), 6.21 (dd, J = 3.2, 1.2 Hz, 1H), 6.10 (s, 1H), 5.93 (d, J = 3.2 Hz, 1H), 5.20 (s, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.72 (s, 1H), 3.71 (s, 3H), 2.33 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 167.9, 167.4, 166.8, 158.5, 145.7, 141.0,

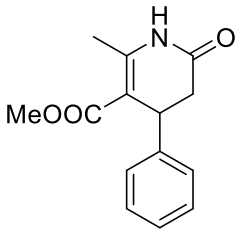
110.0, 104.3, 100.4, 60.4, 51.4, 51.1, 33.2, 19.4, 14.2. HRMS (EI) m/z: [M^+] calcd for $C_{15}H_{17}NO_6$, 307.1056; found, 307.1054.

3-Ethyl 5-methyl 6-methyl-2-oxo-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyridine-3,5-dicarboxylate (5o).



The title compound **5o** was synthesized by following general procedure A from enamine **1a** (58.0 mg, 0.5 mmol), (*Z*)-2-(ethoxycarbonyl)-3-(thiophen-2-yl)acrylic acid (**4o**, 124 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (126 mg, 78% yield). R_f = 0.5 (50% EtOAc/hexanes). (*Major* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.66 (s, 1H), 7.15 (dd, J = 5.0, 1.0 Hz, 1H), 6.91–6.89 (m, 1H), 6.87–6.85 (m, 1H), 4.94 (s, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.74 (s, 4H), 2.37 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 167.3, 167.0, 166.6, 146.8, 143.3, 126.9, 124.5, 124.3, 106.5, 62.3, 54.5, 51.6, 37.3, 18.8, 14.0. IR $_{vmax}$ (neat): 2950, 1737, 1698, 1434, 1183, 1094, 716 cm^{-1}. (*Minor* diastereomer) ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.05 (dd, J = 5.0, 1.0 Hz, 1H), 6.87–6.85 (m, 1H), 6.78 (d, J = 3.6 Hz, 1H), 6.29 (s, 1H), 5.34 (s, 1H), 4.13 (q, J = 7.0 Hz, 2H), 3.721 (s, 1H), 3.720 (s, 3H), 2.33 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 167.8, 167.3, 167.0, 151.5, 145.2, 126.5, 123.2, 122.9, 103.1, 62.3, 54.5, 51.1, 34.3, 19.3, 14.0. HRMS (EI) m/z: [M^+] calcd for $C_{15}H_{17}NO_5S$, 323.0827; found, 323.0829.

Methyl 2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (3).



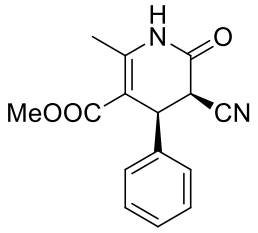
To a stirred solution of commercially available enamine **1a** (58.0 mg, 0.5 mmol) and (*Z*)-2-(ethoxycarbonyl)-3-phenylacrylic acid (**4i**, 121 mg, 0.55 mmol) in dry toluene (5 mL) was added boric acid (5 mol%) at room temperature. The resulting mixture was refluxed for overnight. After completion of the reaction, the solution was evaporated and the residue was diluted with ethyl acetate (100 mL), washed with water (30 mL) and brine (30 mL). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide the crude product which was further purified by column chromatography (40% EtOAc in hexanes) to obtain the desired compound **3** as a white solid (102 mg, 83% yield). R_f = 0.5 (50%

EtOAc/hexanes). mp 191–193 °C (Lit.[1] 191–193 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.46 (s, 1H), 7.31–7.28 (m, 2H), 7.25–7.18 (m, 3H), 4.27 (d, J = 7.6 Hz, 1H), 3.67 (s, 3H), 2.95 (ABdq, J = 16.4, 8.4, Hz, 1H), 2.72 (d, J = 15.6 Hz, 1H), 2.42 (s, 3H).

Procedure for preparation of *Cis* diastereomer of compound **5a**.

To a stirred solution of commercially available enamine **1a** (58.0 mg, 0.5 mmol) and (*E*)-2-cyano-3-phenylacrylic acid (**4a**, 87 mg, 0.5 mmol) in dry toluene (5 mL) was added (+)-camphorsulfonic acid (5 mol%) at room temperature. The resulting mixture was refluxed for 3 h. After completion of the reaction, the solution was evaporated and the residue was diluted with ethyl acetate (100 mL), washed with water (30 mL) and brine (30 mL). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide the crude product which was further purified by column chromatography (40% EtOAc in hexanes) to obtain the desired *Cis* diastereomer of compound **5a**.

(4*S*,5*R*)-Methyl 5-cyano-2-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (5a).

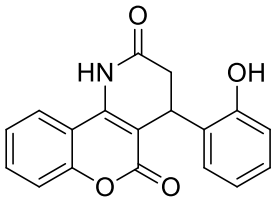


White solid (116 mg, 86% yield). R_f = 0.5 (50% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.54 (s, 1H), 7.37–7.30 (m, 3H), 7.20–7.18 (m, 2H), 4.93 (d, J = 6.8 Hz, 1H), 4.34 (d, J = 6.8 Hz, 1H), 3.56 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 166.4, 163.5, 148.4, 138.0, 129.2 (2C), 128.4, 128.1 (2C), 116.2, 105.8, 51.8, 41.2, 41.1, 18.6. IR $_{vmax}$ (neat): 3133, 2228, 1630, 1415, 1280, 790, 636 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{15}H_{14}N_2O_3$, 270.1004; found, 270.1006.

General procedure B for preparation of compounds **8a**–**e**.

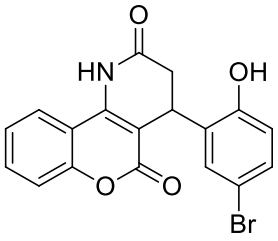
To a stirred solution of commercially available enamine **6** (0.5 mmol) and carboxylic acid **7** (0.5 mmol) in dry toluene (5 mL) was added boric acid (5 mol%) at room temperature. The resulting mixture was refluxed for 3 h in an oil bath. After completion of the reaction, the solution was evaporated and the residue was diluted with ethyl acetate (100 mL), washed with water (30 mL) and brine (30 mL). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide the crude product which was further purified by column chromatography to obtain the desired compound.

4-(2-Hydroxyphenyl)-3,4-dihydro-1H-chromeno[4,3-*b*]pyridine-2,5-dione (**8a**).



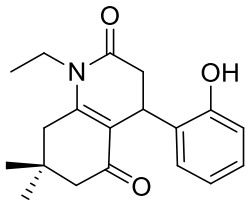
The title compound **8a** was synthesized by following general procedure B from enamine **6a** (81 mg, 0.5 mmol), 2-oxo-2*H*-chromene-3-carboxylic acid (**7a**, 95 mg, 0.5 mmol), boric acid (5 mol%) and purified by flash column chromatography (60% EtOAc in hexanes) to give a white solid (126 mg, 82% yield). R_f = 0.4 (60% EtOAc/hexanes). mp 234–236 °C. ^{1}H NMR (CD_3OD, 400 MHz) δ: 8.06 (dd, J = 8.4, 1.2 Hz, 1H), 7.71 (td, J = 8.4, 1.2 Hz, 1H), 7.48–7.45 (m, 2H), 7.07 (td, J = 8.4, 1.2 Hz, 1H), 6.85–6.82 (m, 2H), 6.70 (t, J = 7.2 Hz, 1H), 4.76 (dd, J = 8.4, 1.2 Hz, 1H), 3.14 (dd, J = 16.4, 8.4 Hz, 1H), 2.90 (dd, J = 16.4, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ: 171.0, 160.5, 155.3, 153.3, 146.8, 132.8, 128.5, 126.8, 126.7, 124.7, 123.5, 119.4, 117.3, 115.9, 113.6, 103.1, 36.8, 31.1. IR ν_{max} (neat): 3254, 2928, 1741, 1646, 1237, 1036, 947, 759 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{18}H_{13}NO_4$, 307.0845; found, 307.0843.

4-(5-Bromo-2-hydroxyphenyl)-3,4-dihydro-1H-chromeno[4,3-b]pyridine-2,5-dione (**8b**).



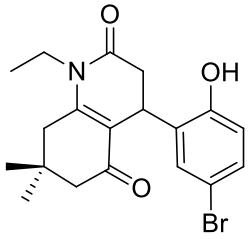
The title compound **8b** was synthesized by following general procedure A from enamine **6a** (81.0 mg, 0.5 mmol), 6-bromo-2-oxo-2*H*-chromene-3-carboxylic acid (**7b**, 92 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (50% EtOAc in hexanes) to give a white solid (176 mg, 91% yield). R_f = 0.4 (50% EtOAc/hexanes). mp 228–230 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.99 (s, 1H), 10.18 (s, 1H), 8.25 (dd, J = 8.0, 1.2 Hz, 1H), 7.71 (td, J = 8.0, 1.2 Hz, 1H), 7.48 (dd, J = 8.0, 0.4 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.25 (dd, J = 8.0, 2.0 Hz, 1H), 6.85–6.83 (m, 2H), 4.52 (d, J = 8.4 Hz, 1H), 3.17 (dd, J = 16.4, 8.4 Hz, 1H), 2.58 (d, J = 16.4 Hz, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 170.8, 160.5, 154.8, 153.3, 147.0, 133.0, 131.3, 129.8, 129.4, 124.7, 123.6, 118.1, 117.4, 113.5, 110.5, 102.4, 36.6, 31.3. IR ν_{max} (neat): 3244, 2930, 1747, 1655, 1238, 1040, 943, 755 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{18}H_{12}BrNO_4$, 384.9950; found, 384.9953.

1-Ethyl-4-(2-hydroxyphenyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (**8c**).



The title compound **8c** was synthesized by following general procedure B from enamine **6b** (84.0 mg, 0.5 mmol), 2-oxo-2*H*-chromene-3-carboxylic acid (**7a**, 95 mg, 0.5 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (144 mg, 92% yield). R_f = 0.5 (50% EtOAc/hexanes). mp 238–240 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.57 (s, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.10 (t, J = 7.6 Hz, 1H), 4.36 (d, J = 7.2 Hz, 1H), 3.90–3.81 (m, 1H), 3.62–3.54 (m, 1H), 2.88, 2.55 (ABq, J = 15.2 Hz, 1H each), 2.79 (dd, J = 15.2, 8.0 Hz, 1H), 2.60 (d, J = 15.2 Hz, 1H), 2.32, 2.17 (ABq, J = 15.2 Hz, 1H each), 1.14 (s, 3H), 1.10 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 195.3, 169.7, 155.3, 155.1, 128.0, 127.0, 126.6, 119.0, 115.9, 115.8, 49.9, 39.3, 37.3, 36.6, 33.0, 29.3, 27.8, 27.7, 14.9. IR $_{vmax}$ (neat): 3248, 2927, 1733, 1635, 1236, 803, 738, 699 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{19}H_{23}NO_3$, 313.1678; found, 313.1675.

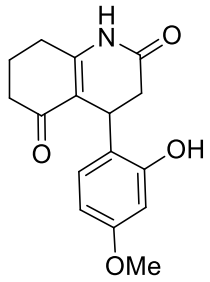
4-(5-Bromo-2-hydroxyphenyl)-1-ethyl-7,7-dimethyl-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (**8d**).



The title compound **8d** was synthesized by following general procedure B from enamine **6b** (84.0 mg, 0.5 mmol), 6-bromo-2-oxo-2*H*-chromene-3-carboxylic acid (**7b**, 135 mg, 0.5 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (189 mg, 96% yield). R_f = 0.5 (50% EtOAc/hexanes). mp 232–234 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.20 (s, 1H), 7.16 (dd, J = 8.8, 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 4.32 (dd, J = 6.8, 2.0 Hz, 1H), 4.13–4.04 (m, 1H), 3.76–3.67 (m, 1H), 2.96–2.85 (m, 2H), 2.60, 2.47 (ABq, J = 17.2 Hz, 1H each), 2.34, 2.33 (ABq, J = 17.2 Hz, 1H each), 1.24 (t, J = 7.2 Hz, 3H), 1.14 (s, 3H), 1.07 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 195.3, 169.4, 155.4, 154.7, 130.7, 129.7, 129.3, 117.9, 115.7, 110.3, 49.7, 39.3, 37.0, 36.4,

33.0, 28.8, 27.94, 27.90, 14.9. IR $_{vmax}$ (neat): 3250, 2930, 1735, 1638, 1237, 803, 740, 691 cm^{-1}. HRMS (EI) m/z: [M^+] calcd for $C_{19}H_{22}BrNO_3$, 391.0783; found, 391.0785.

4-(2-Hydroxy-4-methoxyphenyl)-3,4,7,8-tetrahydroquinoline-2,5(1*H*,6*H*)-dione (**8e**).

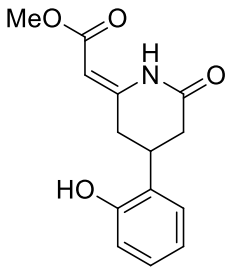


The title compound **8e** was synthesized by following general procedure B from enamine **6c** (56.0 mg, 0.5 mmol), 7-methoxy-2-oxo-2*H*-chromene-3-carboxylic acid (**7c**, 110 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (60% EtOAc in hexanes) to give a white solid (105 mg, 73% yield). R_f = 0.3 (50% EtOAc/hexanes). mp 226–228 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.02 (s, 1H), 9.59 (s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 6.23 (dd, J = 8.4, 2.4 Hz, 1H), 4.26 (d, J = 8.0 Hz, 1H), 3.64 (s, 3H), 2.73 (dd, J = 16.4, 8.0 Hz, 1H), 2.58–2.54 (m, 2H), 2.43 (d, J = 16.4 Hz, 1H), 2.29 (t, J = 6.0 Hz, 2H), 2.04–1.95 (m, 2H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 195.2, 171.0, 159.4, 156.0, 156.9, 127.1, 120.3, 113.1, 104.2, 102.1, 55.3, 37.5, 37.0, 28.0, 27.0, 21.6. IR $_{vmax}$ (neat): 3246, 2956, 1716, 1623, 1236, 819, 753, 684 cm^{-1}. HRMS (EI) m/z: [M^+] calcd for $C_{16}H_{17}NO_4$, 287.1158; found, 287.1155.

General procedure C for preparation of compounds **9a**–**e**.

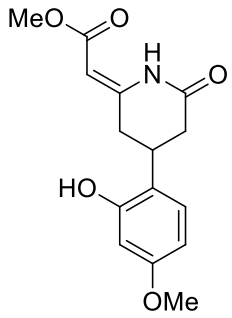
To a stirred solution of commercially available enamine **1** (0.5 mmol) and carboxylic acid **7** (0.5 mmol) in dry toluene (5 mL) was added boric acid (5 mol%) at room temperature. The resulting mixture stirred at 90 °C for 10 h in an oil bath. After completion of the reaction, the solution was evaporated and the residue was diluted with ethyl acetate (100 mL), washed with water (30 mL) and brine (30 mL). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide the crude product which was further purified by column chromatography to obtain the desired compound.

(*Z*)-Methyl 2-(4-(2-hydroxyphenyl)-6-oxopiperidin-2-ylidene)acetate (**9a**).



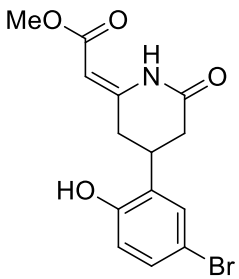
The title compound **9a** was synthesized by following general procedure C from enamine **1** (58.0 mg, 0.5 mmol), 2-oxo-2*H*-chromene-3-carboxylic acid (**7a**, 92 mg, 0.5 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (96 mg, 73% yield). R_f = 0.4 (30% EtOAc/hexanes). mp 188–190 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.53 (s, 1H), 9.61 (s, 1H), 7.12 (dd, J = 7.6, 1.2 Hz, 1H), 7.08 (td, J = 7.6, 1.2 Hz, 1H), 6.83 (dd, J = 7.6, 1.2 Hz, 1H), 6.78 (td, J = 7.6, 1.2 Hz, 1H), 5.05 (s, 1H), 3.65 (s, 3H), 3.52–3.45 (m, 1H), 2.90–2.84 (m, 1H), 2.84–2.77 (m, 1H), 2.76–2.70 (m, 1H), 2.68–2.62 (m, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 170.5, 169.0, 155.6, 155.2, 128.3, 128.2, 127.0, 119.7, 115.7, 91.3, 51.4, 37.5, 33.6, 30.5. IR $_{vmax}$ (neat): 3243, 2931, 1715, 1635, 1295, 1190, 1036, 863, 738 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{14}H_{15}NO_4$, 261.1001; found, 261.1005.

(*Z*)-Methyl 2-(4-(2-hydroxy-4-methoxyphenyl)-6-oxopiperidin-2-ylidene)acetate (**9b**).



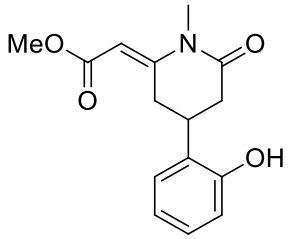
The title compound **9b** was synthesized by following general procedure C from enamine **1** (58.0 mg, 0.5 mmol), 7-methoxy-2-oxo-2*H*-chromene-3-carboxylic acid (**7c**, 110 mg, 0.5 mmol), boric acid (5 mol%) and purified by flash column chromatography (35% EtOAc in hexanes) to give a white solid (99 mg, 68% yield). R_f = 0.5 (40% EtOAc/hexanes). mp 188–190 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.8 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.61 (bs, 1H), 6.43 (dd, J = 8.4, 2.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 4.94 (s, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.52–3.44 (m, 1H), 2.93–2.82 (m, 2H), 2.77–2.67 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 169.5, 168.5, 160.1, 159.7, 154.9, 153.6, 151.4, 129.5, 127.3, 92.6, 55.4, 55.3, 52.4, 51.1, 44.2. IR $_{vmax}$ (neat): 3248, 2930, 1720, 1645, 1291, 1188, 1033, 863, 736 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{15}H_{17}NO_5$, 353.0263; found, 353.0266.

(*Z*)-Methyl 2-(4-(5-bromo-2-hydroxyphenyl)-6-oxopiperidin-2-ylidene)acetate (**9c**).



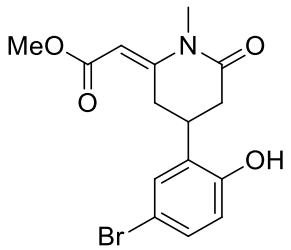
The title compound **9c** was synthesized by following general procedure C from enamine **1** (58.0 mg, 0.5 mmol), 6-bromo-2-oxo-2*H*-chromene-3-carboxylic acid (**7b**, 135 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (30% EtOAc in hexanes) to give a white solid (150 mg, 88% yield). R_f = 0.5 (50% EtOAc/hexanes). mp 184–186 °C. ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.26 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 8.4, 2.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.05 (s, 1H), 3.71 (s, 3H), 3.57–3.50 (m, 1H), 2.99-2.91 (m, 1H), 2.98–2.91 (m, 1H), 2.79–2.75 (m, 2H). ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ: 171.6, 168.8, 154.3, 153.7, 130.5, 130.2, 129.3, 116.7, 111.0, 92.1, 50.2, 36.5, 32.9, 31.2. IR ν_{max} (neat): 3245, 2948, 1706, 1636, 1361, 1091, 734, 700 cm^{-1}. HRMS (EI) m/z: [M^+] calcd for $C_{14}H_{14}BrNO_4$, 339.0106; found, 339.0106.

(*E*)-Methyl 2-(4-(2-hydroxyphenyl)-1-methyl-6-oxopiperidin-2-ylidene)acetate (**9d**).



The title compound **9d** was synthesized by following general procedure C from enamine **1b** (65.0 mg, 0.5 mmol), 2-oxo-2*H*-chromene-3-carboxylic acid (**7a**, 95 mg, 0.5 mmol), boric acid (5 mol%) and purified by flash column chromatography (40% EtOAc in hexanes) to give a white solid (105 mg, 76% yield). R_f = 0.5 (50% EtOAc/hexanes). mp 178–180 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.59 (s, 1H), 7.12–7.06 (m, 2H), 6.84–6.79 (m, 2H), 5.34 (s, 1H), 3.89 (d, J = 16.4 Hz, 1H), 3.58 (s, 3H), 3.41–3.36 (m, 1H), 3.14 (s, 3H), 2.86 (t, J = 16.4 Hz, 2H), 2.70 (d, J = 16.4 Hz, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 170.6, 167.5, 157.2, 155.2, 128.8, 128.1, 126.9, 119.7, 115.6, 95.9, 51.1, 38.3, 31.5, 30.0, 29.7. IR ν_{max} (neat): 2928, 1719, 1680, 1547, 1455, 1261, 801, 740 cm^{-1}. HRMS (EI) m/z: [M^+] calcd for $C_{15}H_{17}NO_4$, 275.1158; found, 275.1155.

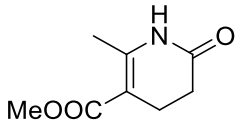
(*E*)-Methyl 2-(4-(5-bromo-2-hydroxyphenyl)-1-methyl-6-oxopiperidin-2-ylidene)acetate (**9e**).



The title compound **9e** was synthesized by following general procedure C from enamine **1** (65.0 mg, 0.5 mmol), 6-bromo-2-oxo-2*H*-chromene-3-carboxylic acid (**7b**, 135 mg, 0.55 mmol), boric

acid (5 mol%) and purified by flash column chromatography (25% EtOAc in hexanes) to give a white solid (140 mg, 79% yield). R_f = 0.5 (30% EtOAc/hexanes). mp 170–172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.20–7.18 (m, 2H), 6.67–6.64 (m, 1H), 5.41 (s, 1H), 4.17 (dt, J = 6.0, 3.2 Hz, 1H), 3.71 (s, 3H), 3.39 (tt, J = 7.2, 3.6 Hz, 1H), 3.25 (s, 3H), 3.02 (dt, J = 6.0, 3.2 Hz, 1H), 2.90–2.83 (m, 1H), 2.70 (dd, J = 16.8, 12.0 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 171.7, 168.1, 156.2, 153.4, 130.9, 130.2, 129.8, 117.3, 112.5, 97.7, 51.4, 38.2, 30.8, 30.6, 30.4. IR $_{vmax}$ (neat): 2921, 1716, 1683, 1540, 1457, 1265, 801, 737 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{15}H_{16}BrNO_4$, 353.0263; found, 353.0266.

Methyl 2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**14**).

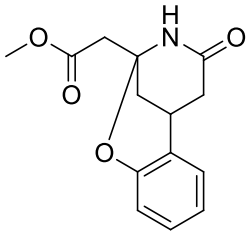


The title compound **14** was synthesized by following general procedure A from enamine **1** (65.0 mg, 0.5 mmol), acrylic acid (**13**, 36.0 mg, 0.55 mmol), boric acid (5 mol%) and purified by flash column chromatography (30% EtOAc in hexanes) to give a white solid (78 mg, 92% yield). R_f = 0.5 (50% EtOAc/hexanes). mp 60–62 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.05 (s, 1H), 3.74 (s, 3H), 2.66 (t, J = 8.4 Hz, 2H), 2.48 (t, J = 8.4 Hz, 2H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 172.7, 167.6, 146.0, 103.4, 51.3, 30.1, 21.3, 18.6. IR $_{vmax}$ (neat): 2922, 1716, 1653, 1540, 1265, 1077, 739, 702 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_8H_{11}NO_3$, 169.0739; found, 169.0741.

Procedure for the preparation of compound **25**.

To a stirred solution of compound **9a** (0.5 mmol) in dry toluene (5 mL) was added boric acid (5 mol%) at room temperature. The resulting mixture was refluxed for 10 h in an oil bath. After completion of the reaction, the solution was evaporated and the residue was diluted with ethyl acetate (100 mL), washed with water (30 mL) and brine (30 mL). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide the crude product which was further purified by column chromatography (60% EtOAc in hexanes) to obtain the compound **25**.

Methyl 2-(4-oxo-3,4,5,6-tetrahydro-2*H*-2,6-methanobenzo[*g*][1,3]oxazocin-2-yl)acetate (**25**).

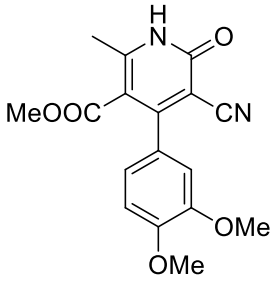


White solid (49.5 mg, 99% yield). R_f = 0.3 (50% EtOAc/hexanes). mp 118–120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (bs, 1H), 7.15 (td, J = 7.2, 1.6 Hz, 1H), 7.10 (dd, J = 7.2, 1.6 Hz, 1H), 6.94 (td, J = 7.2, 1.6 Hz, 1H), 6.78 (dd, J = 8.4, 0.8 Hz, 1H), 3.80 (s, 3H), 3.28–3.25 (m, 1H), 3.00, 2.87 (ABq, J = 15.2 Hz, 1H each), 2.71 (dd, J = 17.2, 4.8 Hz, 1H), 2.64–2.60 (m, 1H), 2.22 (d, J = 3.2 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ: 170.8, 169.5, 150.7, 129.1, 128.7, 124.4, 121.8, 117.7, 82.3, 52.3, 44.3, 40.6, 32.0, 29.1. IR $_{vmax}$ (neat): 3239, 2943, 1711, 1629, 1292, 1195, 1036, 867, 732 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{14}H_{15}NO_4$, 261.1001; found, 261.1003.

Procedure for the preparation of compound **26**.

To a stirred solution of compound **5g** (100 mg, 0.3 mmol) in dry toluene (5 mL) was added DDQ (69 mg, 0.3 mmol) at room temperature. The resulting mixture was stirred at 90 °C for 1 h in an oil bath. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (100 mL), washed with saturated $NaHCO_3$ solution (3 x 30 mL) and brine (30 mL). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide the crude product which was further purified by column chromatography (60% EtOAc in hexanes) to obtain the compound **26**.

Methyl 5-cyano-4-(3,4-dimethoxyphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (**26**).



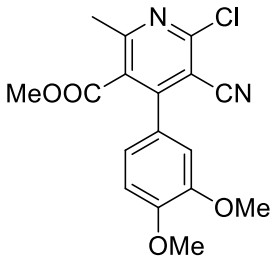
White solid (96 mg, 97% yield). R_f = 0.3 (50% EtOAc/hexanes). mp 182–184 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 13.59 (s, 1H), 7.00 (dd, J = 8.4, 2.0 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.53 (s, 3H), 2.59 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz) δ: 166.4, 160.5, 159.4, 152.5, 150.4, 148.8, 128.0, 120.8, 116.3, 112.8, 112.0, 111.1, 100.7, 56.1, 56.0, 52.7, 18.6. IR $_{vmax}$ (neat): 2992, 2242, 1740, 1632, 1414, 1270, 795, 630 cm^{-1}. HRMS (EI) m/z: [M$^+$] calcd for $C_{17}H_{16}N_2O_5$, 328.1059; found, 328.1057.

Procedure for the preparation of compound **27**.

To a compound **26** (50.0 mg, 0.15 mmol) was added $POCl_3$ (3 mL) at 0 °C. The resulting mixture was stirred at 90 °C for 3 h in an oil bath. After completion of the reaction, $POCl_3$ was removed from the reaction mixture under vacuum. Ice cold water (50 mL) was added to the residue. The resulting solution was basified with aqueous NaOH (1N) solution and then extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with brine (30 mL),

dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to provide the crude product which was further purified by column chromatography (15% EtOAc in hexanes) to obtain the desired compound **27**.

Methyl 6-chloro-5-cyano-4-(3,4-dimethoxyphenyl)-2-methylnicotinate (**27**).

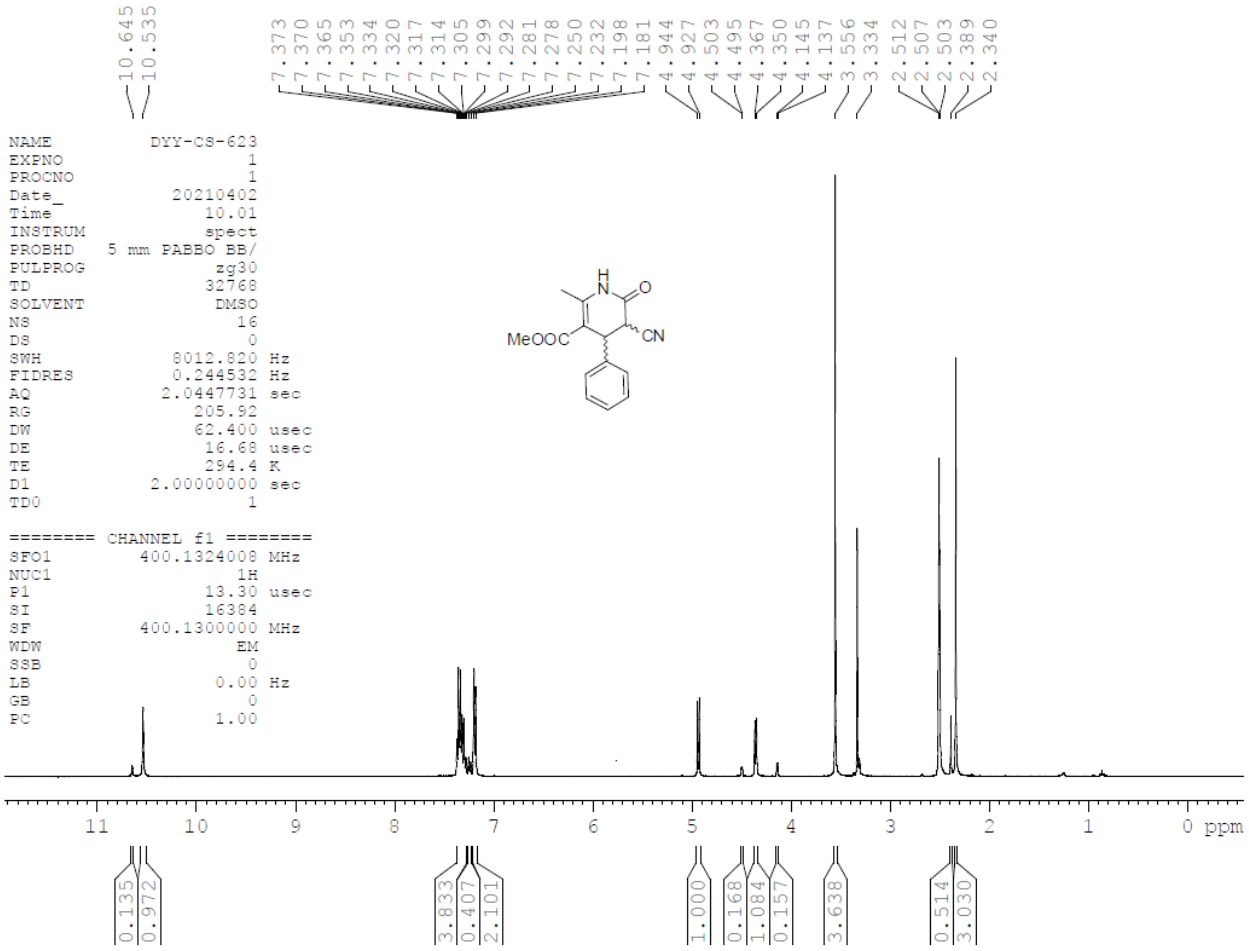


Yellow solid (47.0 mg, 88% yield). R_f = 0.5 (50% EtOAc/hexanes). mp 176–178 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.00–6.95 (m, 2H), 6.90 (d, J = 1.2 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.65 (s, 3H), 2.64 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ: 166.9, 159.8, 153.9, 153.2, 150.7, 149.1, 128.6, 125.9, 121.3, 114.3, 111.2 (2C), 108.2, 56.1, 56.0, 53.0, 23.2. IR $_{vmax}$ (neat): 2992, 2250, 1740, 1632, 1414, 1270, 795, 630 cm^{-1}. HRMS (EI) m/z: [M^+] calcd for $C_{17}H_{15}ClN_2O_4$, 346.0720; found, 346.0723.

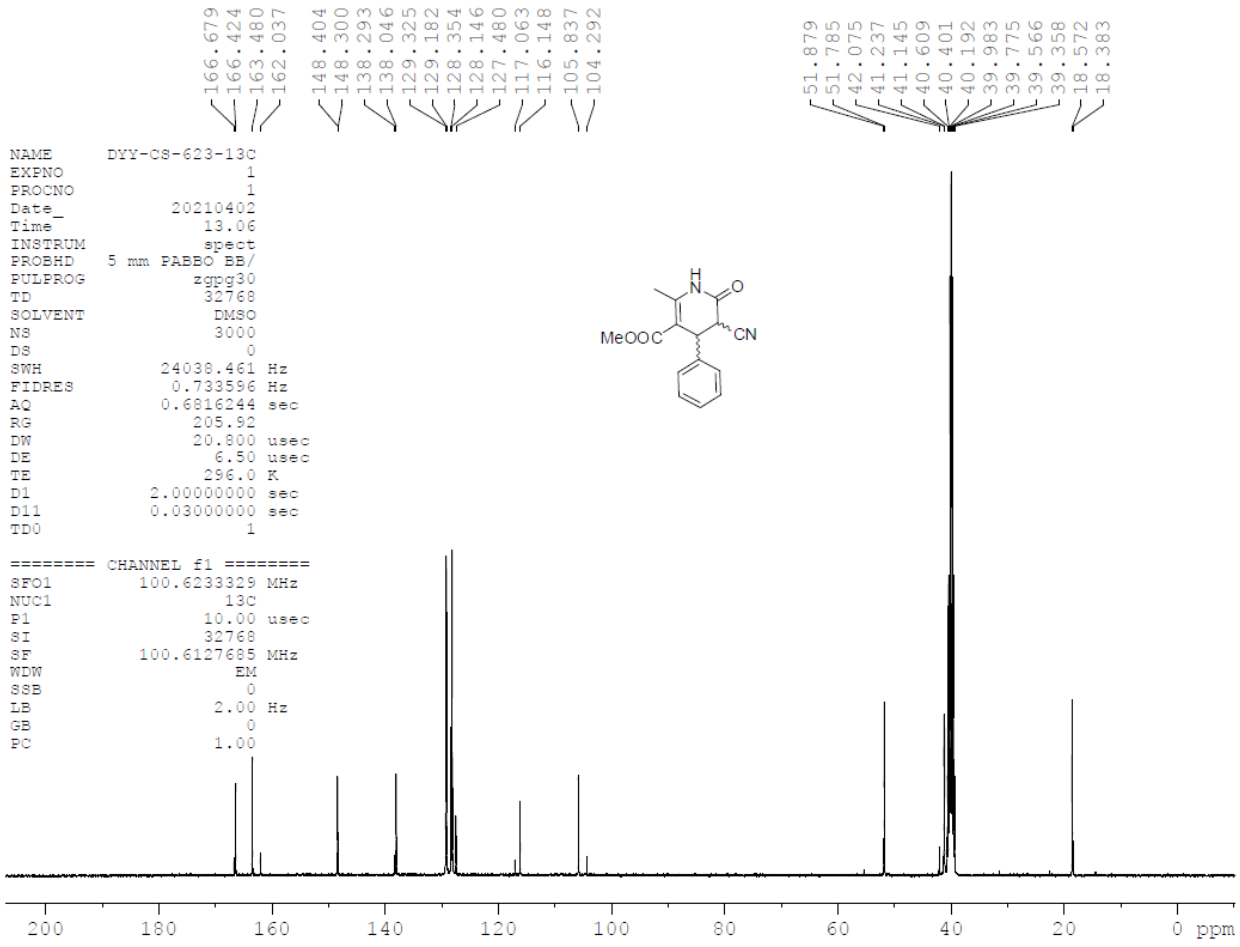
Reference:

1. B. Wanner, J. Mahatthananchai and J. W. Bode, *Org. Lett.*, 2011, **13**, 5378–5381.

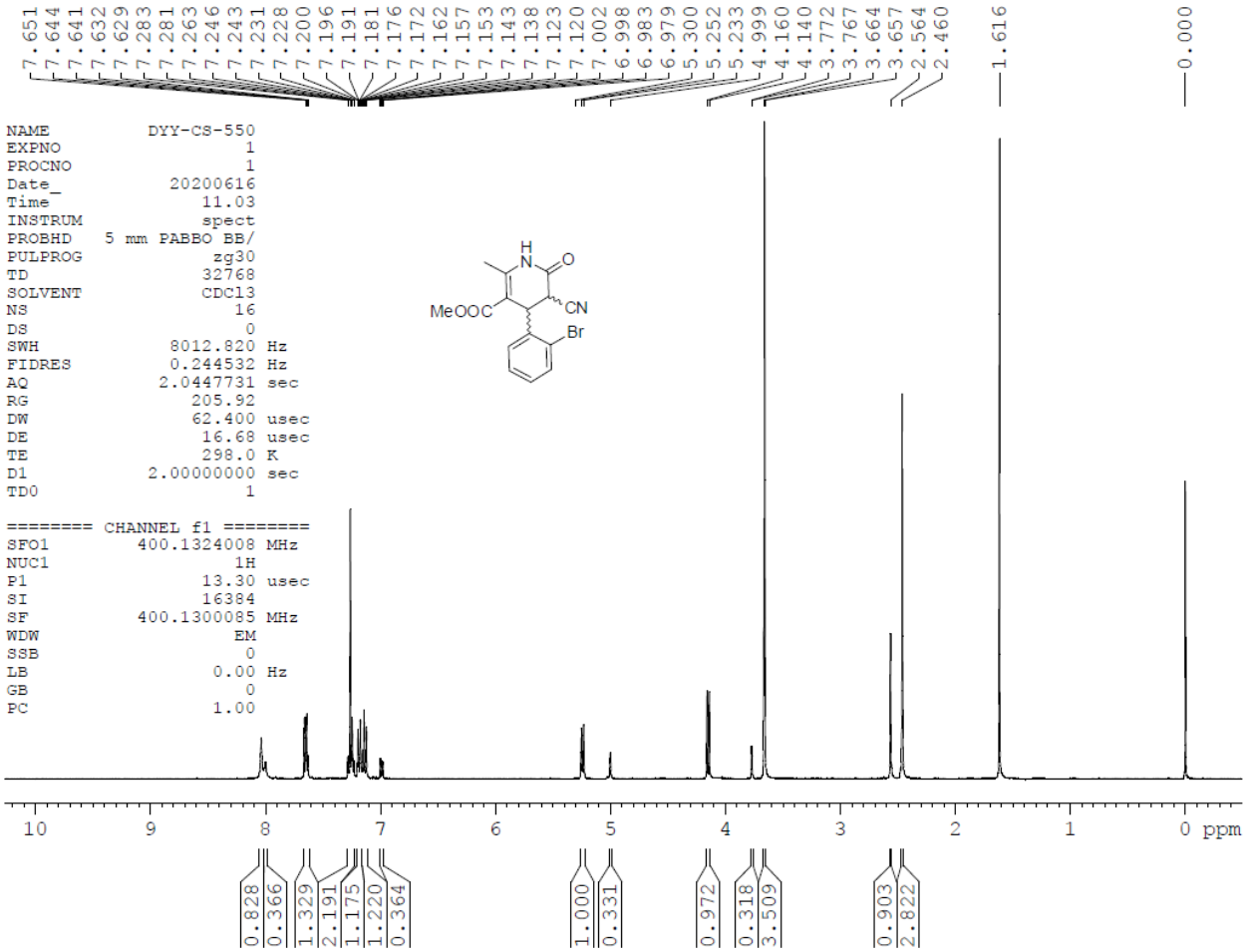
^{1}H NMR of compound **5a** (DMSO-d_6)



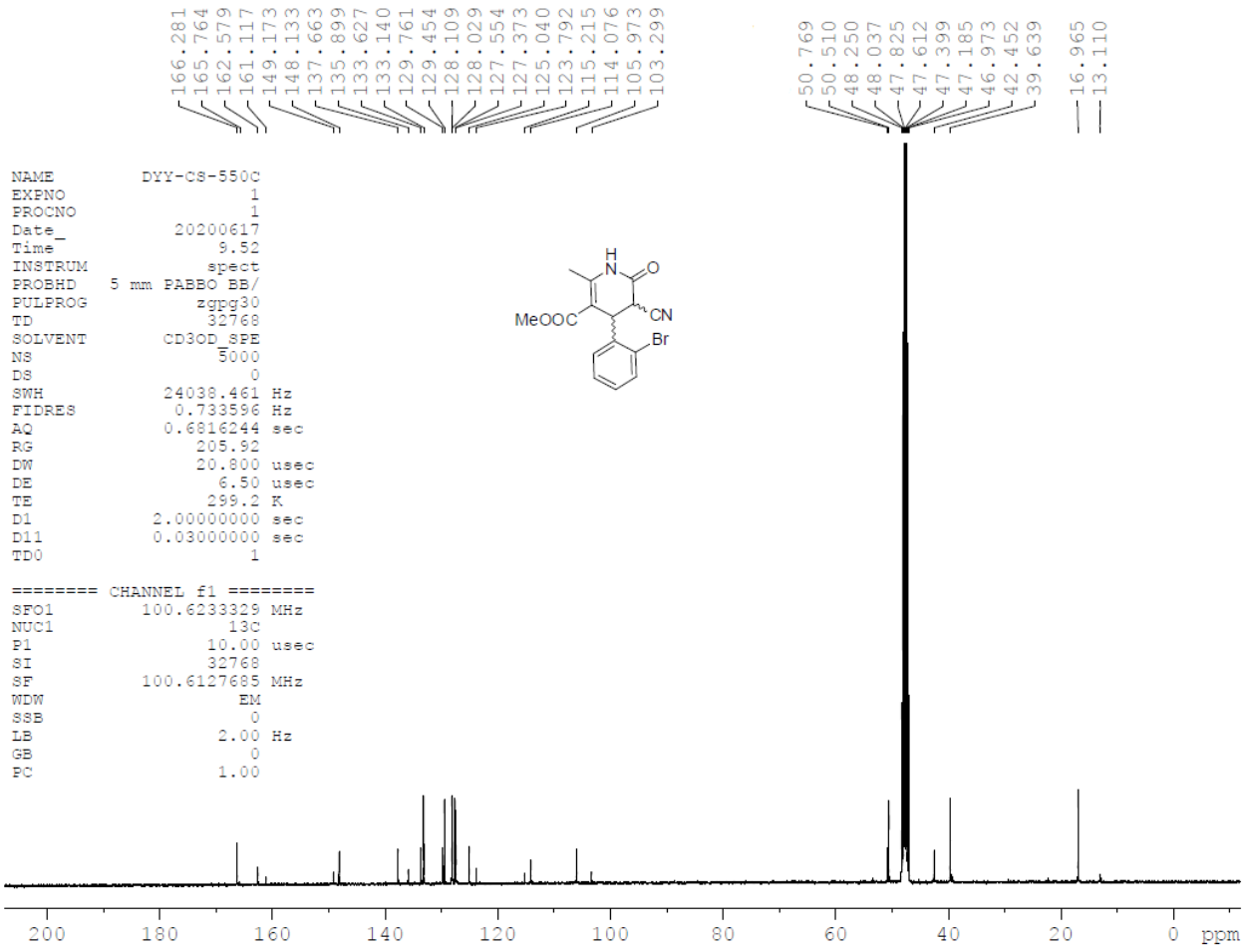
^{13}C NMR of compound **5a** (DMSO-d_6)



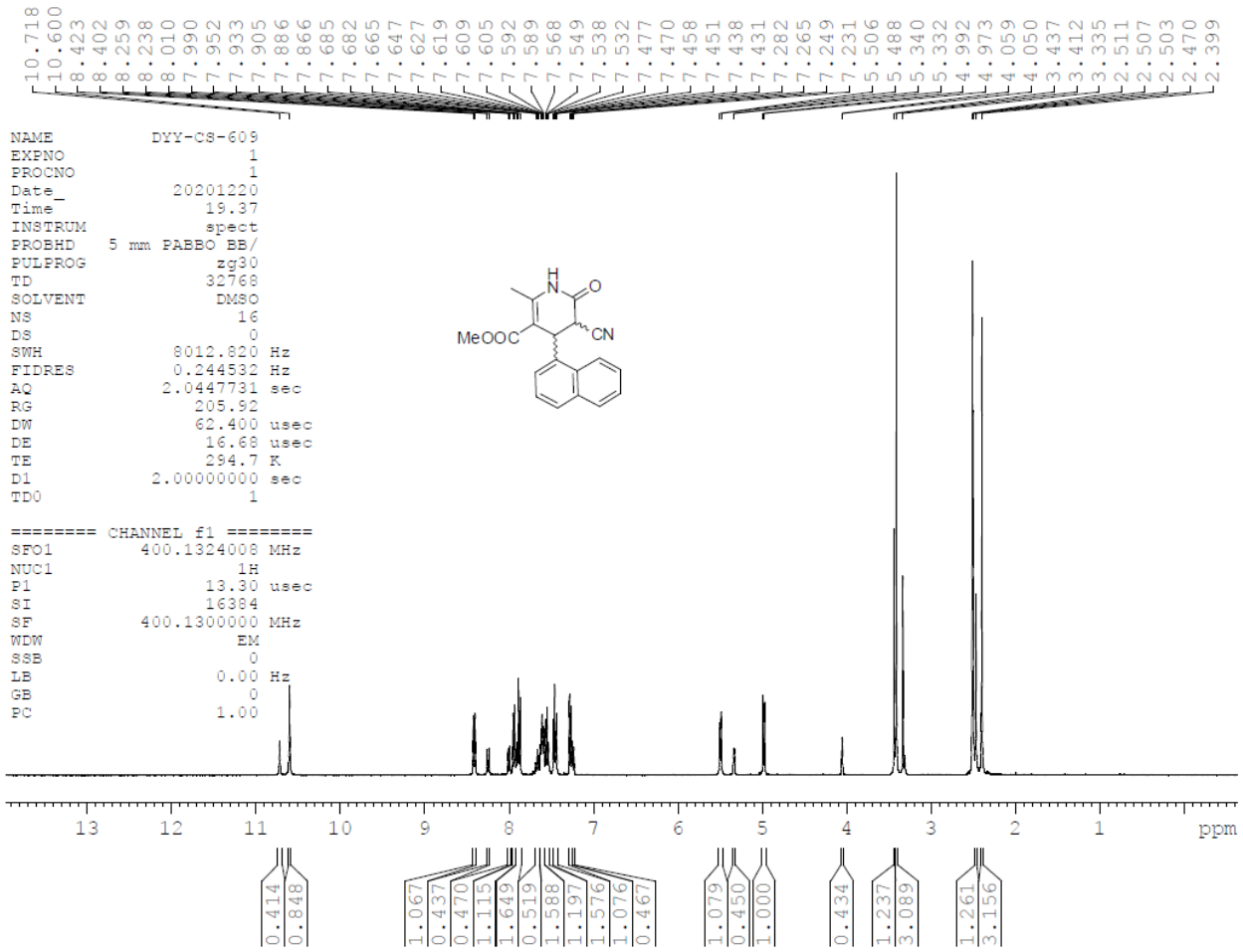
^{1}H NMR of compound **5b** ($CDCl_3$)



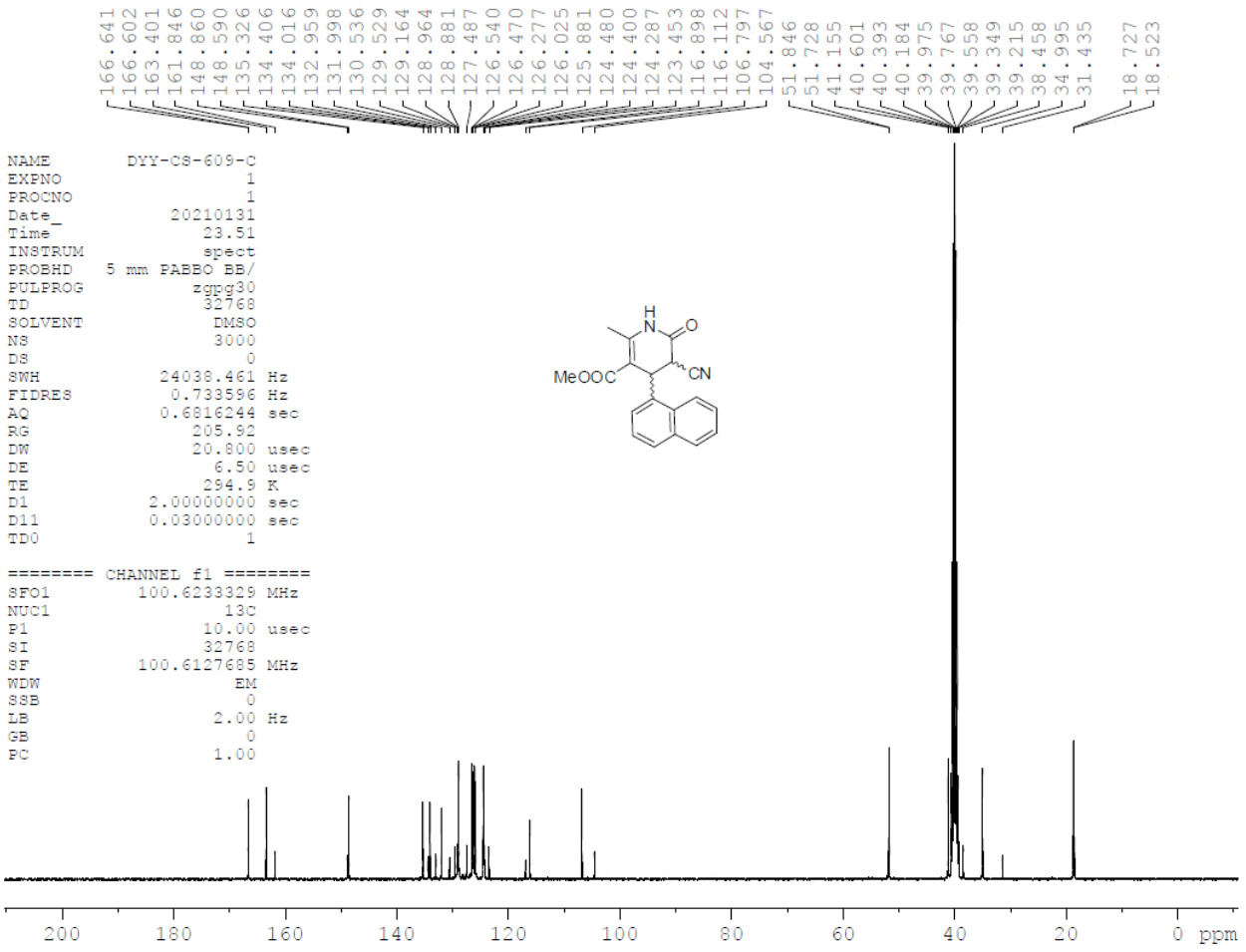
^{13}C NMR of compound **5b** (CD_3OD)



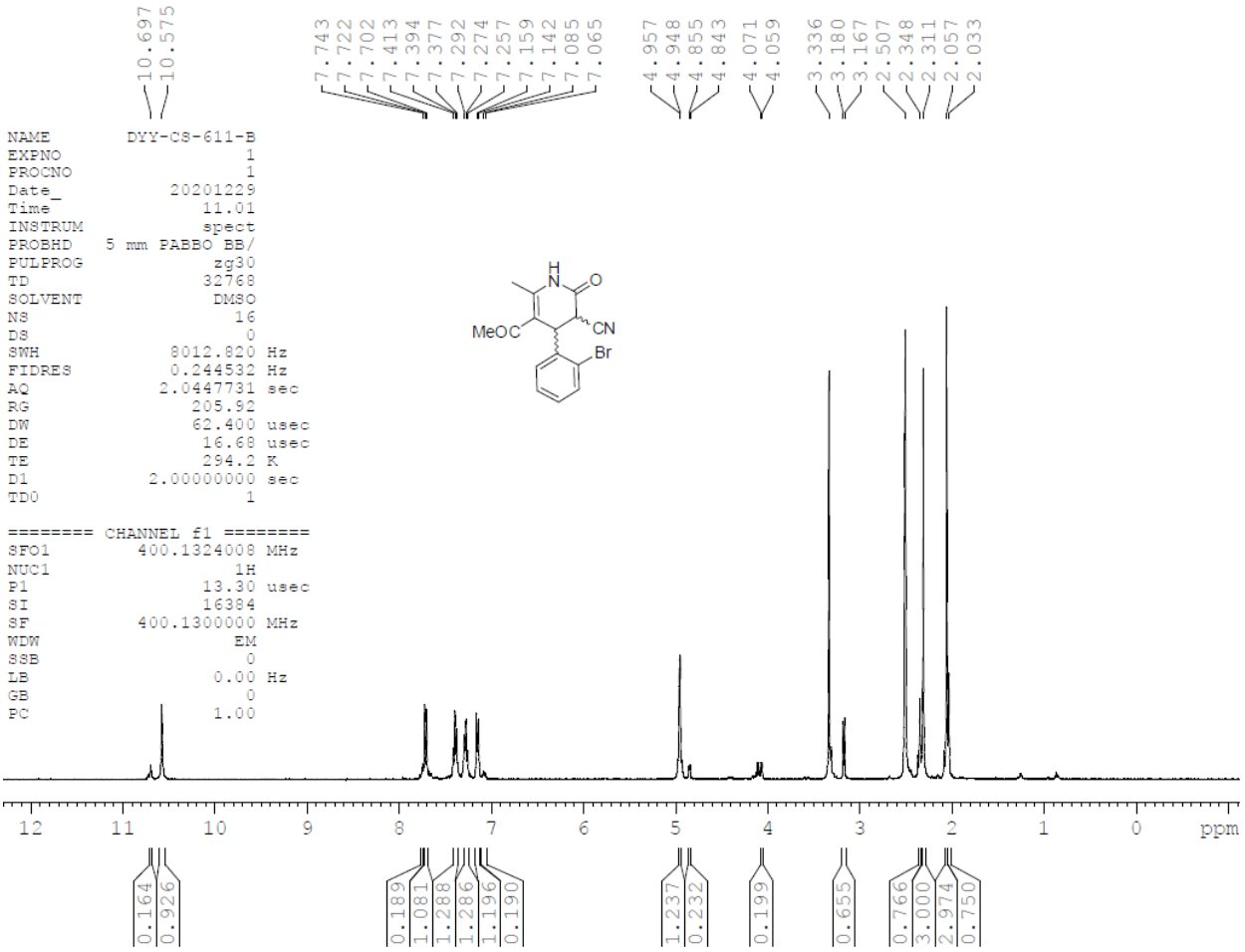
^{1}H NMR of compound **5c** (DMSO-d_6)



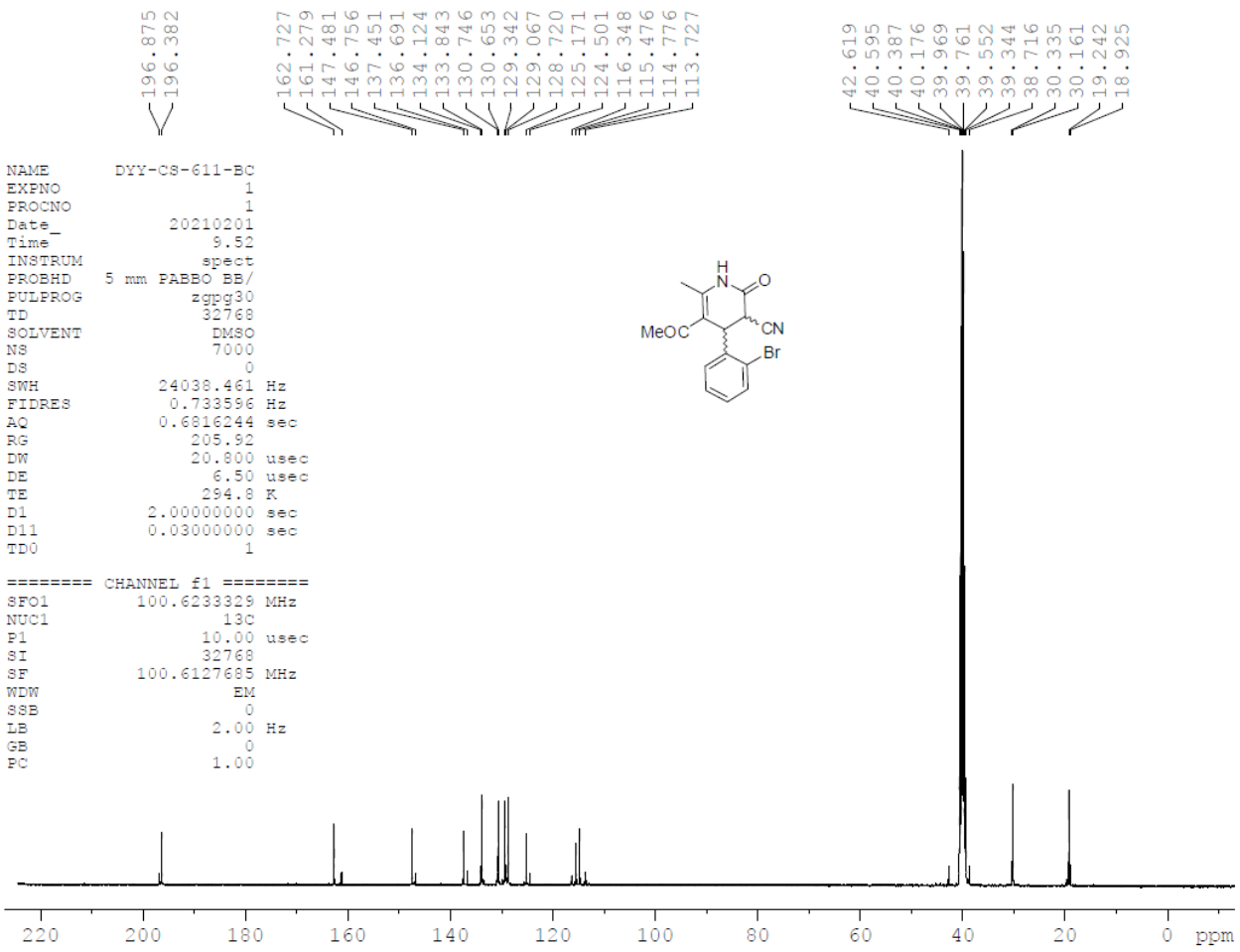
^{13}C NMR of compound **5c** (DMSO-d_6)



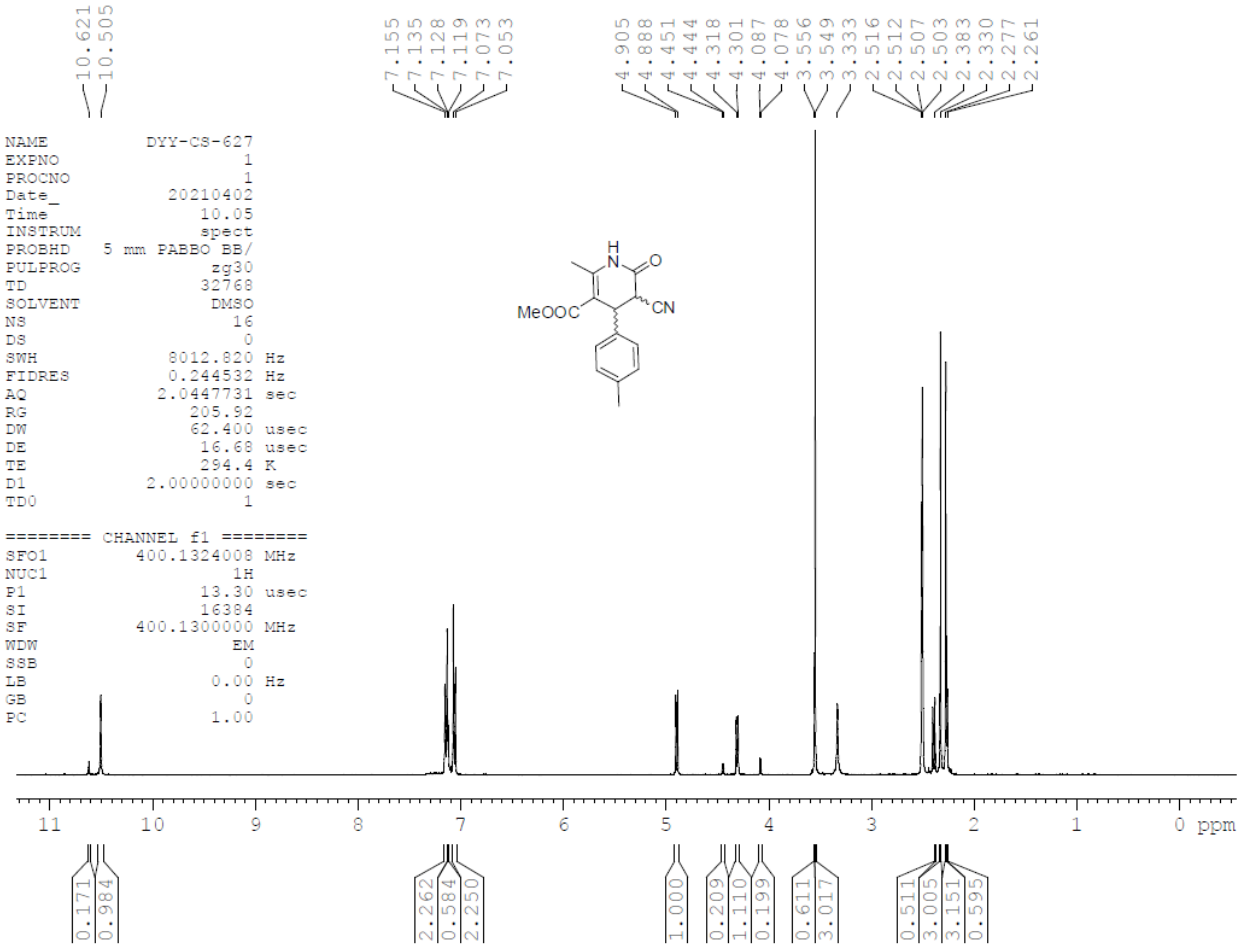
^{1}H NMR of compound **5d** (DMSO-d_6)



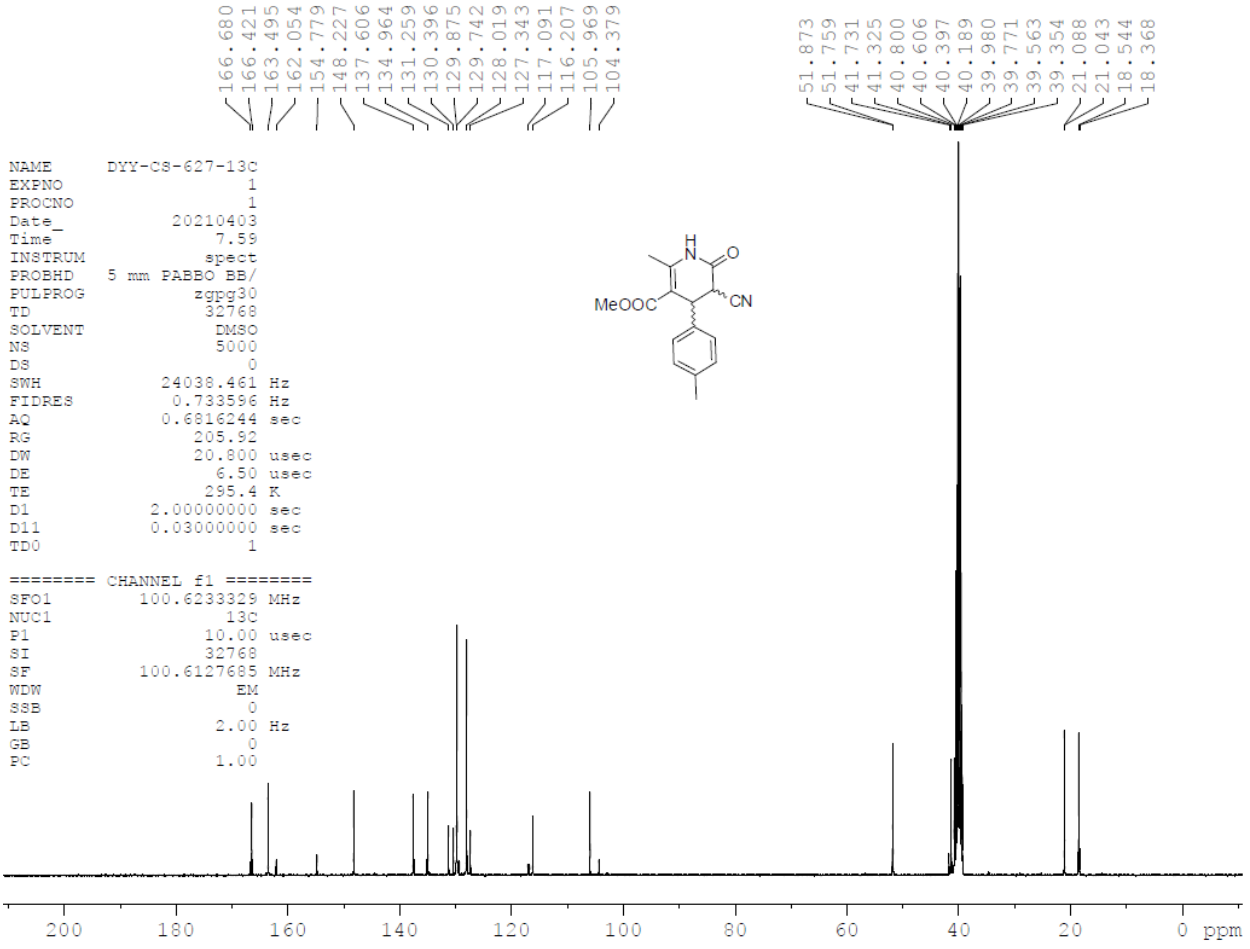
^{13}C NMR of compound **5d** (DMSO-d_6)



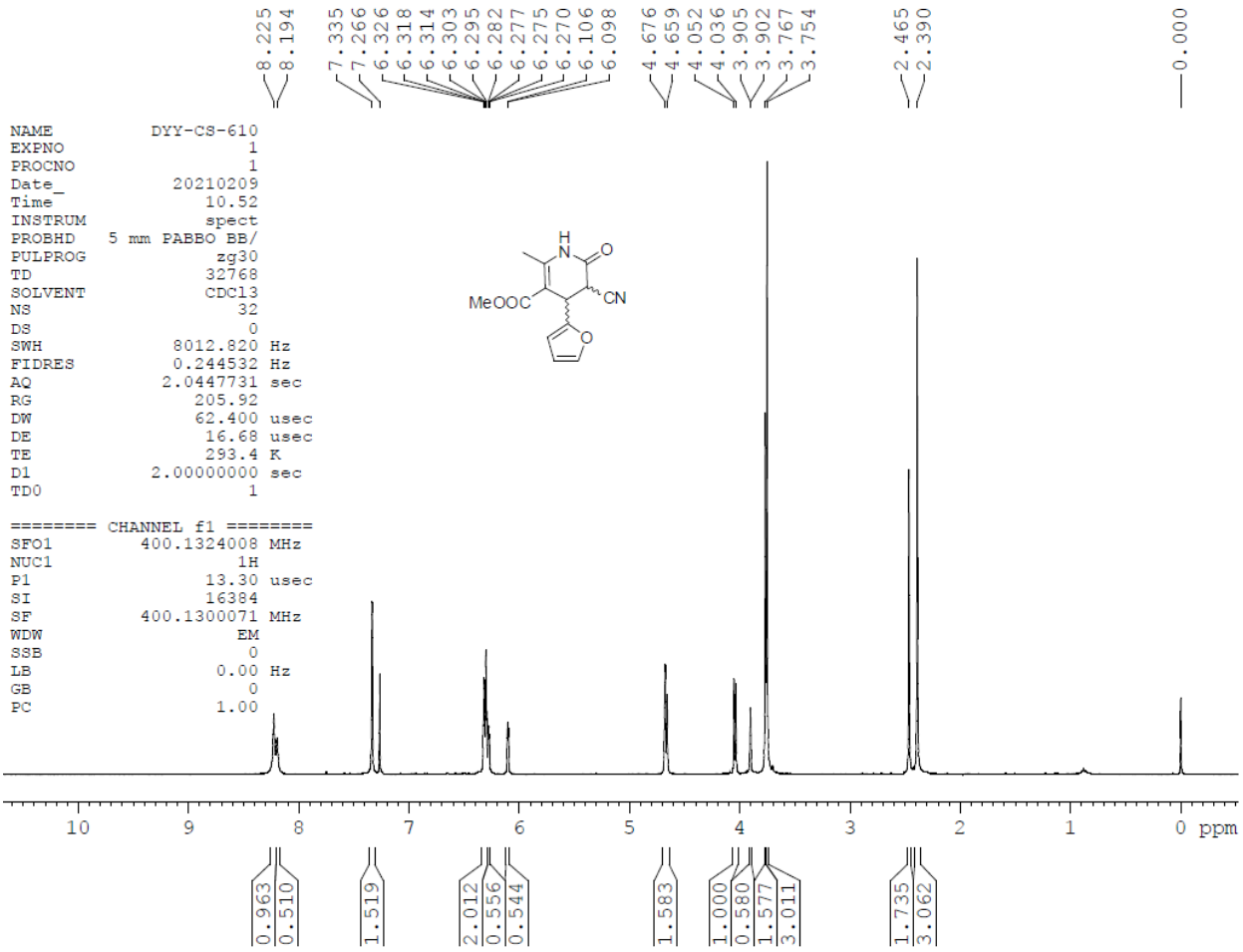
^{1}H NMR of compound **5e** ($CDCl_3$)



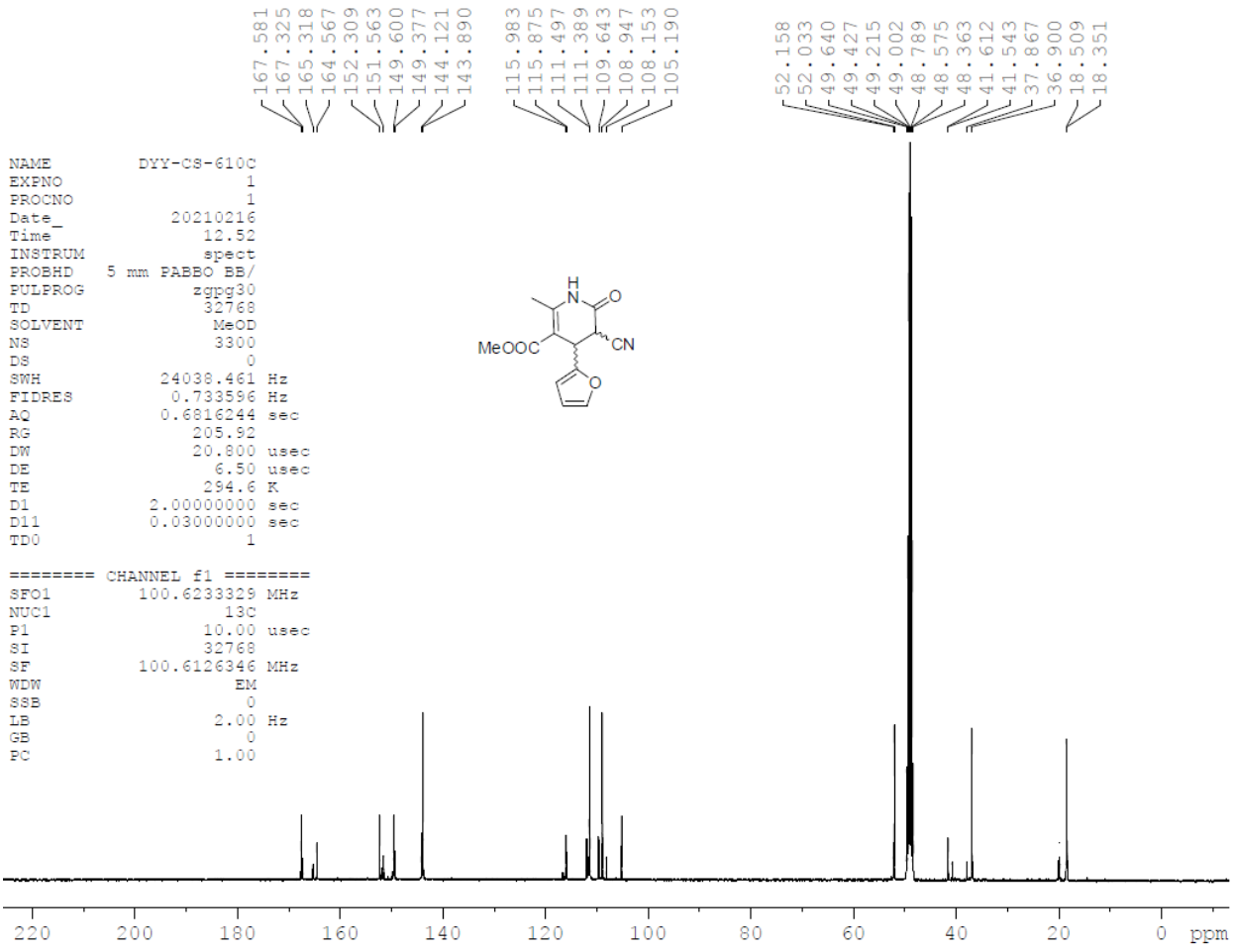
^{13}C NMR of compound **5e** (DMSO-d_6)



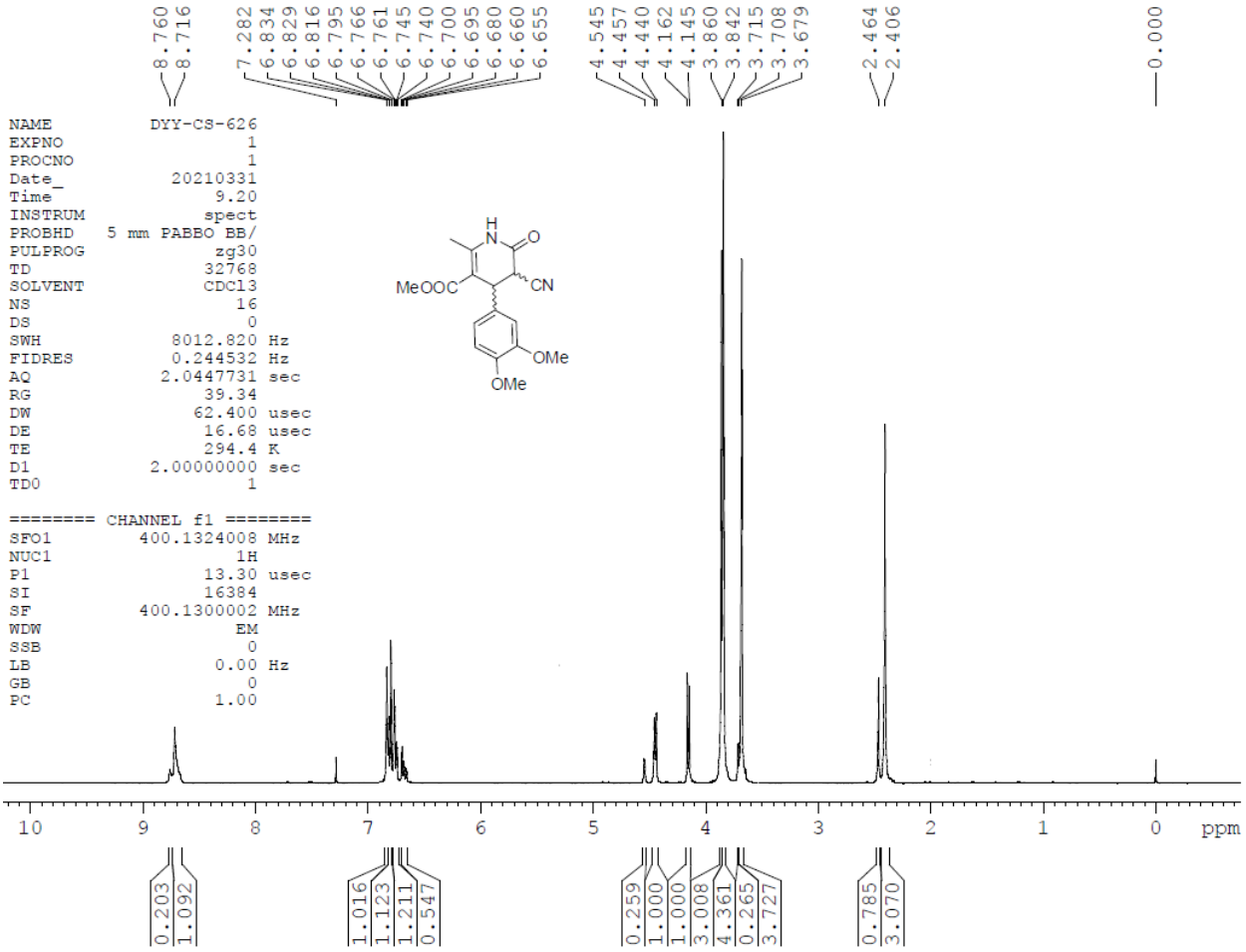
^{1}H NMR of compound **5f** ($CDCl_3$)



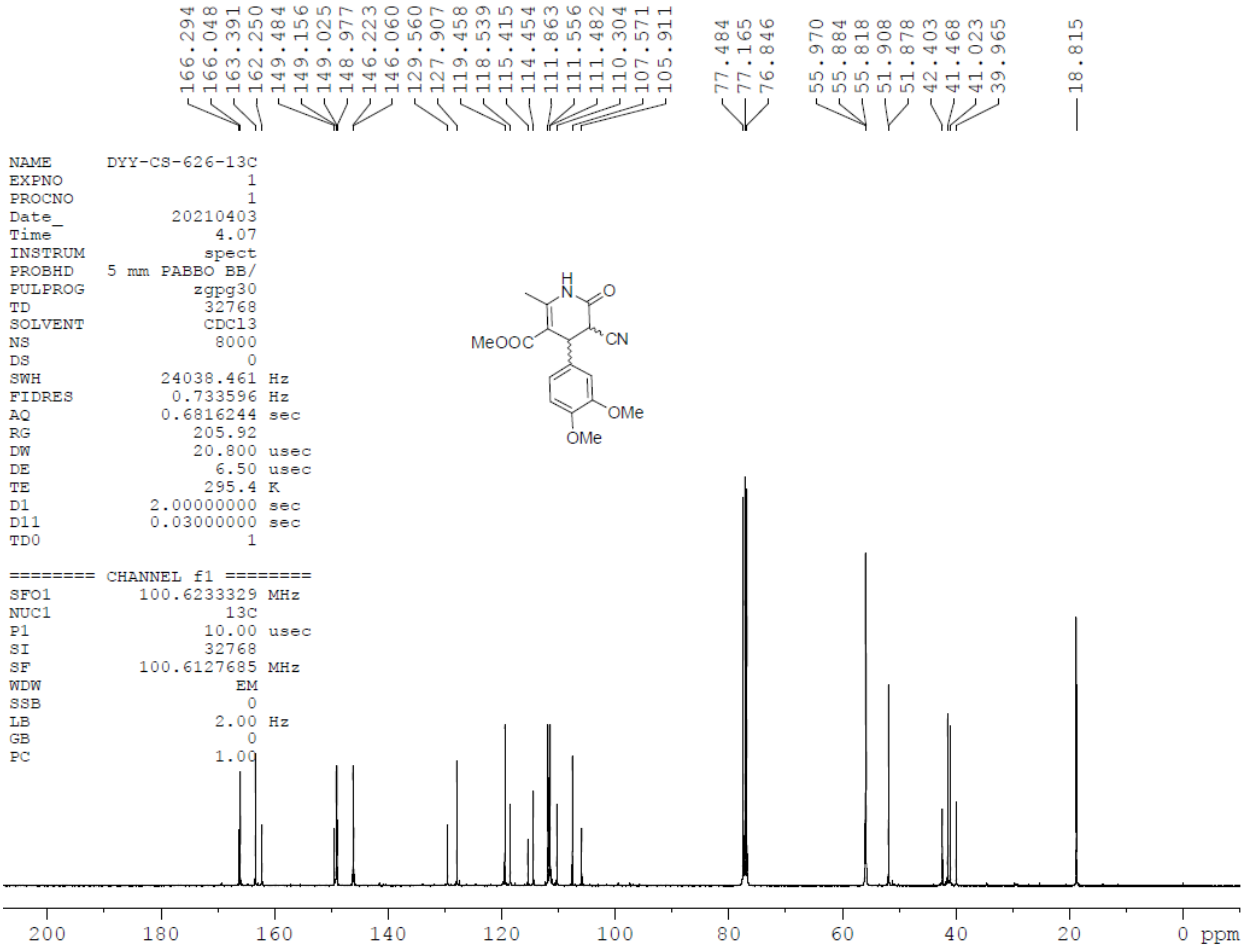
^{13}C NMR of compound **5f** (CD_3OD)



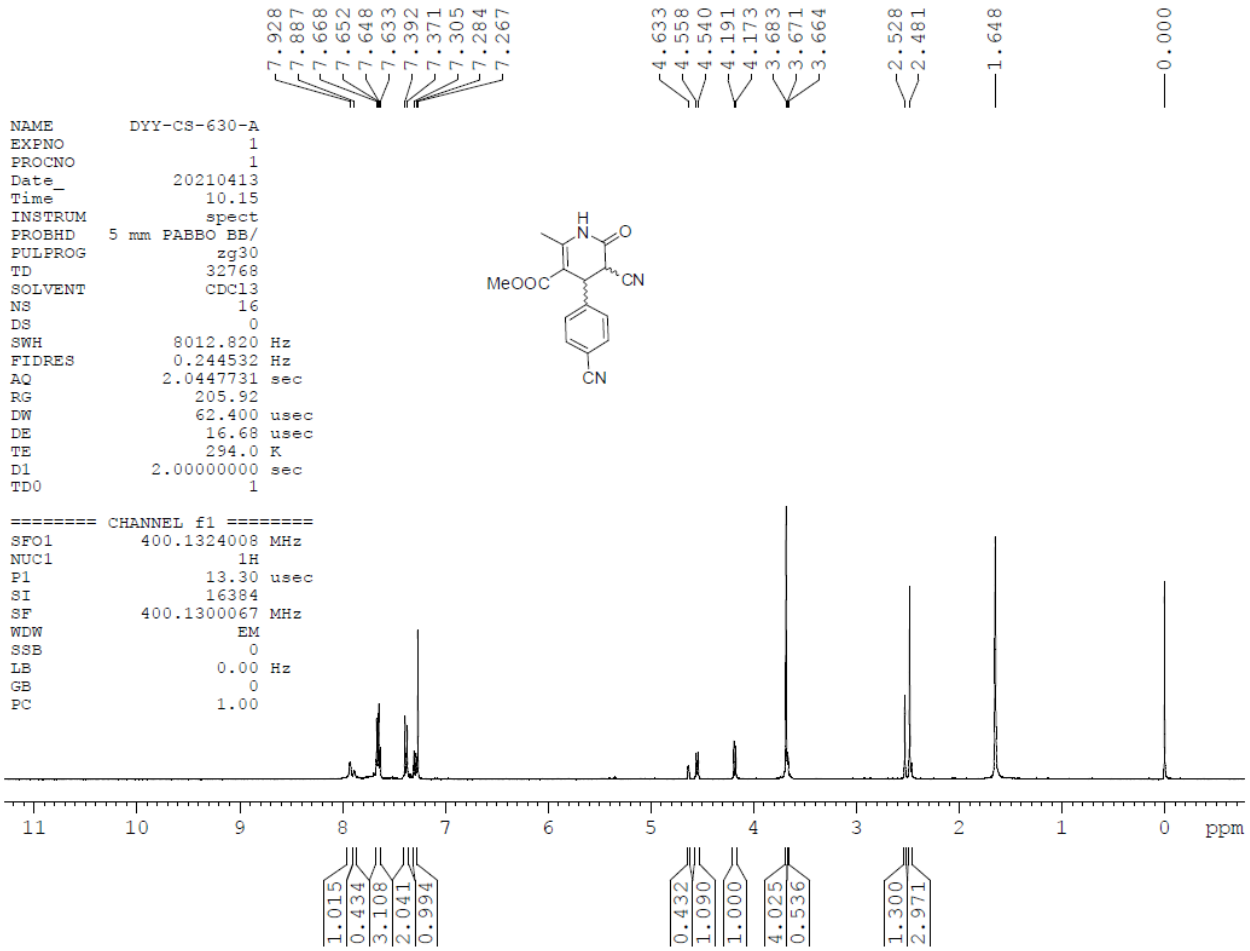
^{1}H NMR of compound **5g** ($CDCl_3$)



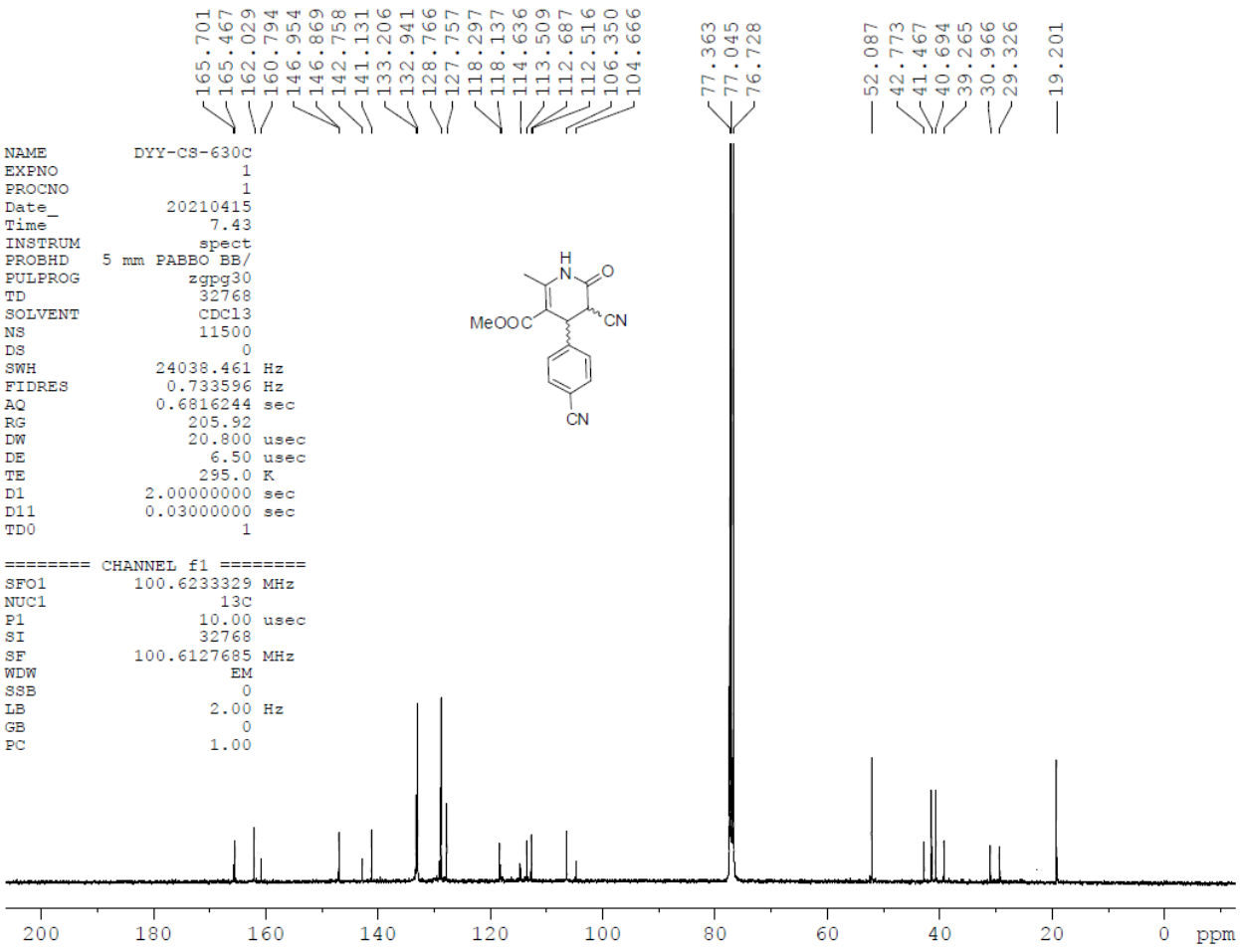
^{13}C NMR of compound **5g** ($CDCl_3$)



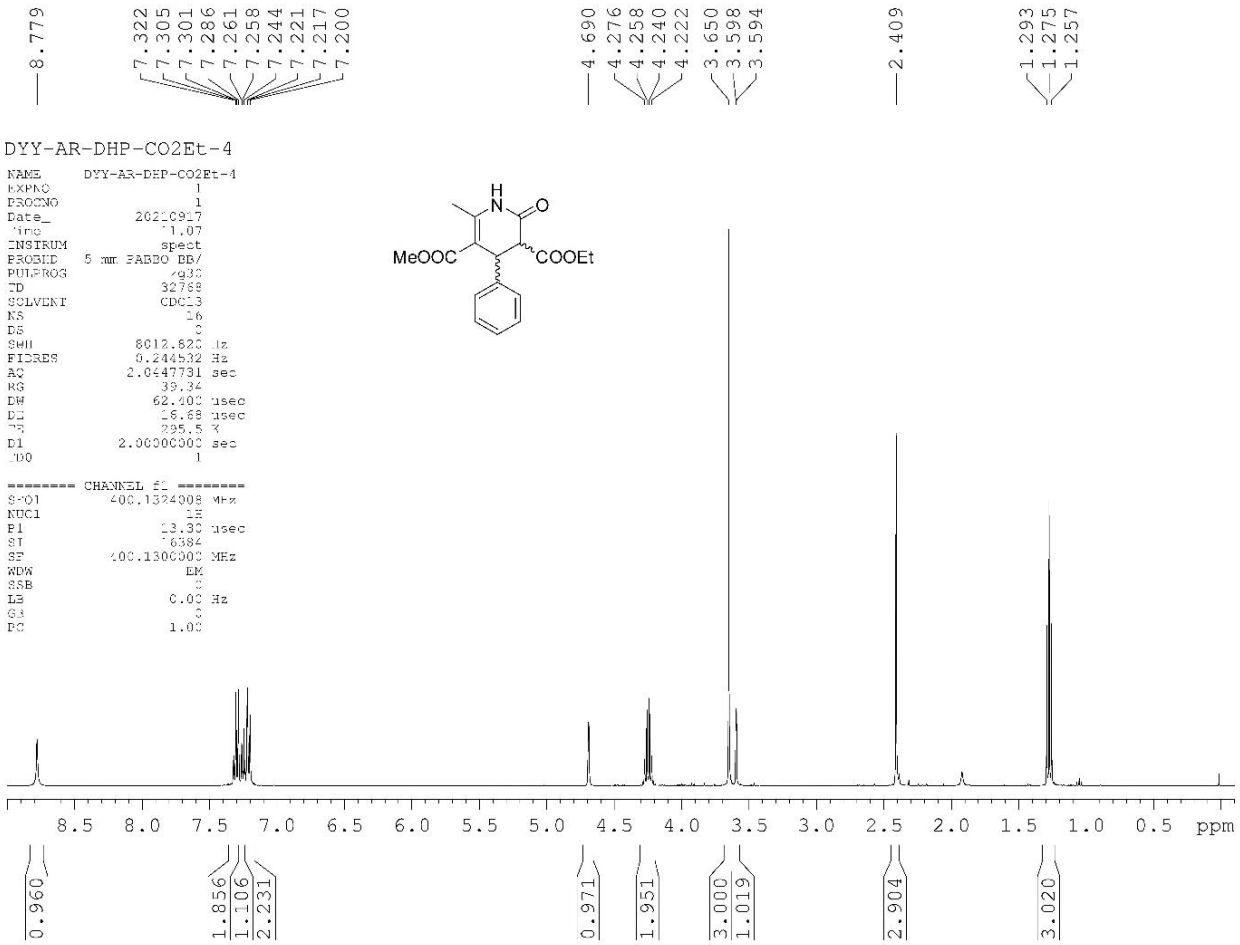
^{1}H NMR of compound **5h** ($CDCl_3$)



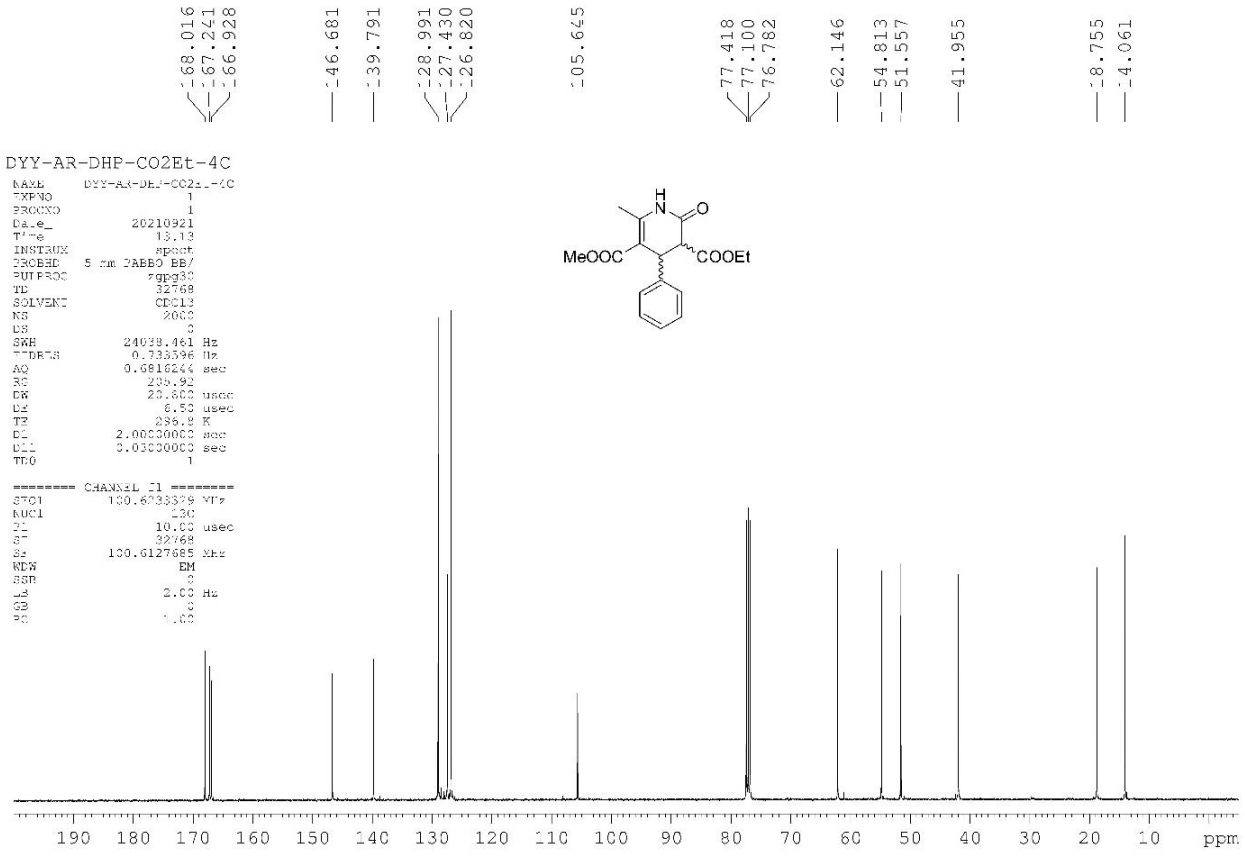
^{13}C NMR of compound **5h** ($CDCl_3$)



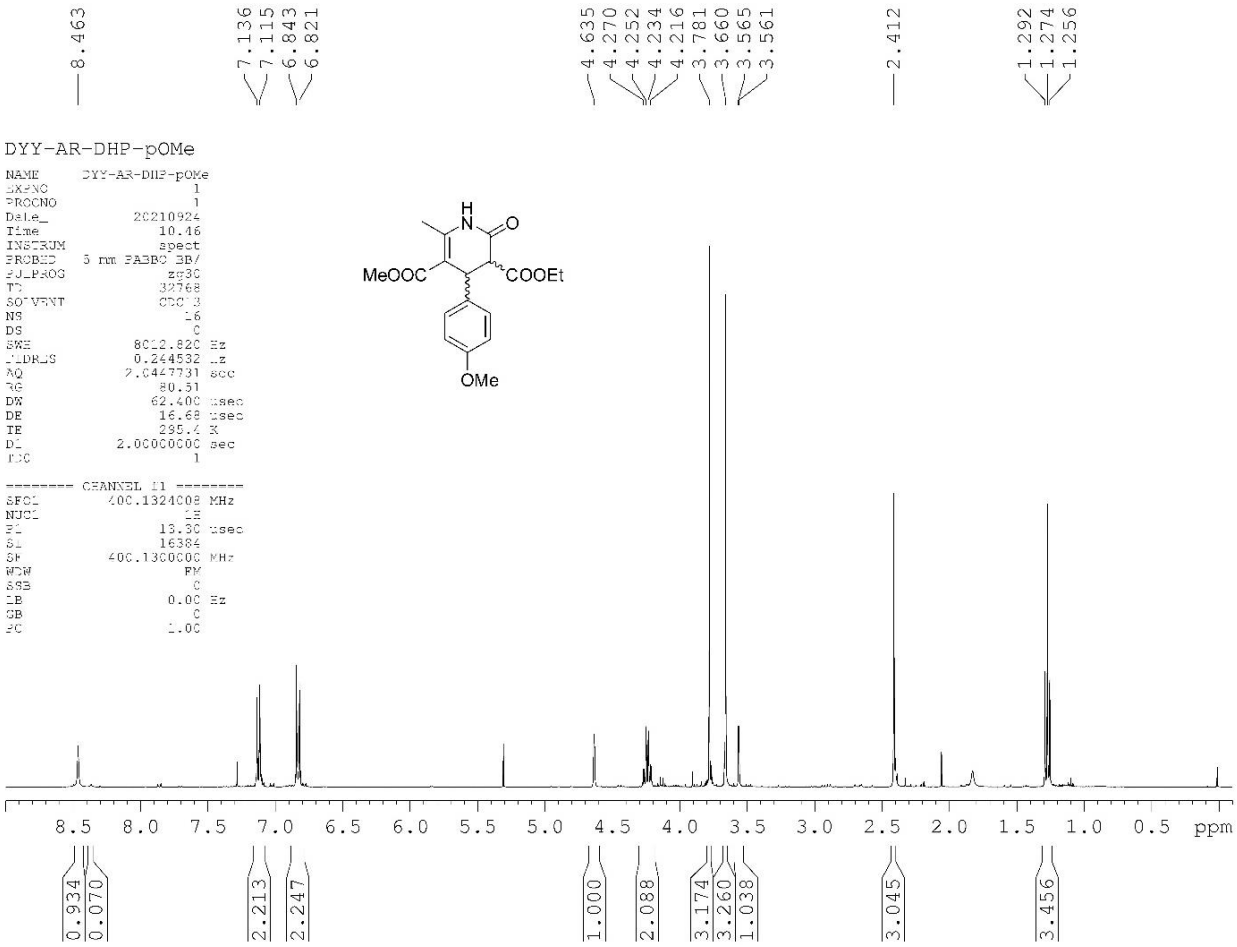
^{1}H NMR of compound **5i** ($CDCl_3$)



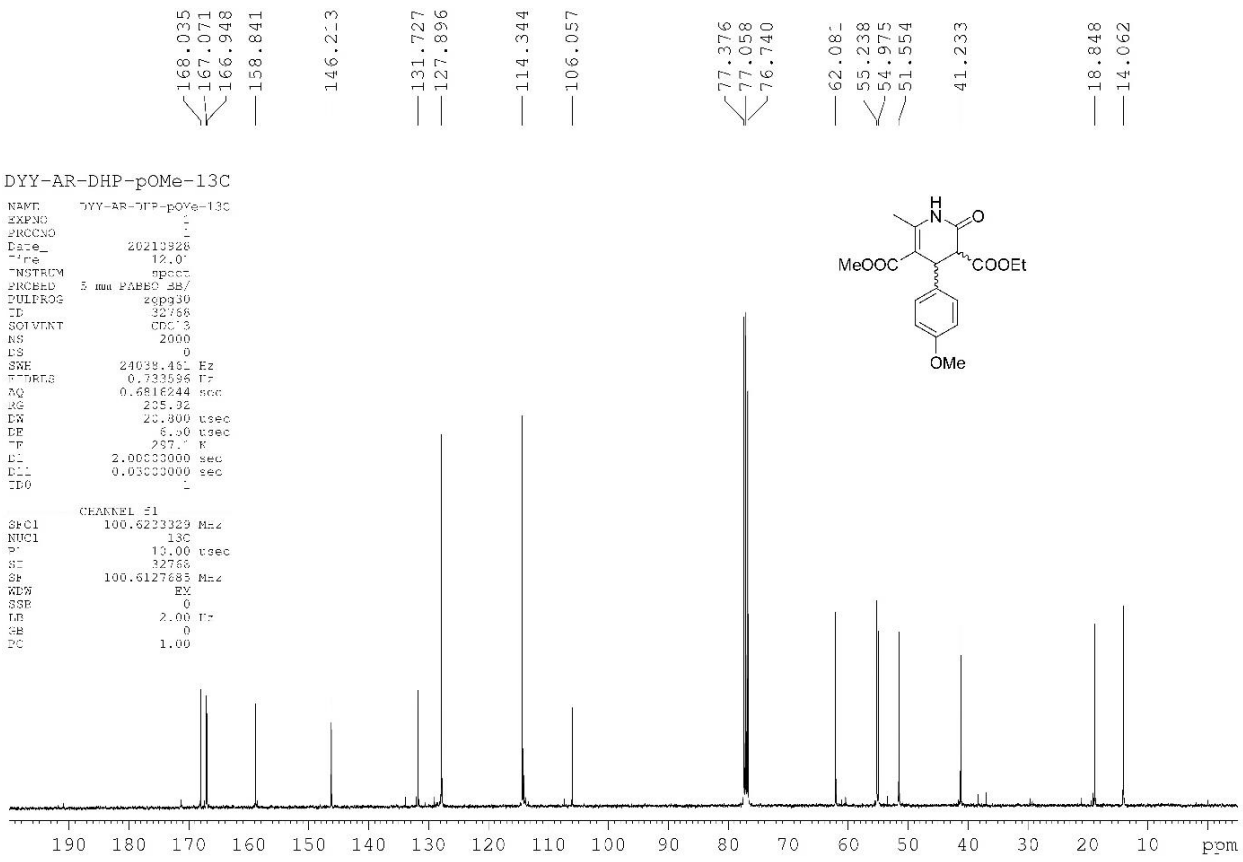
^{13}C NMR of compound **5i** ($CDCl_3$)



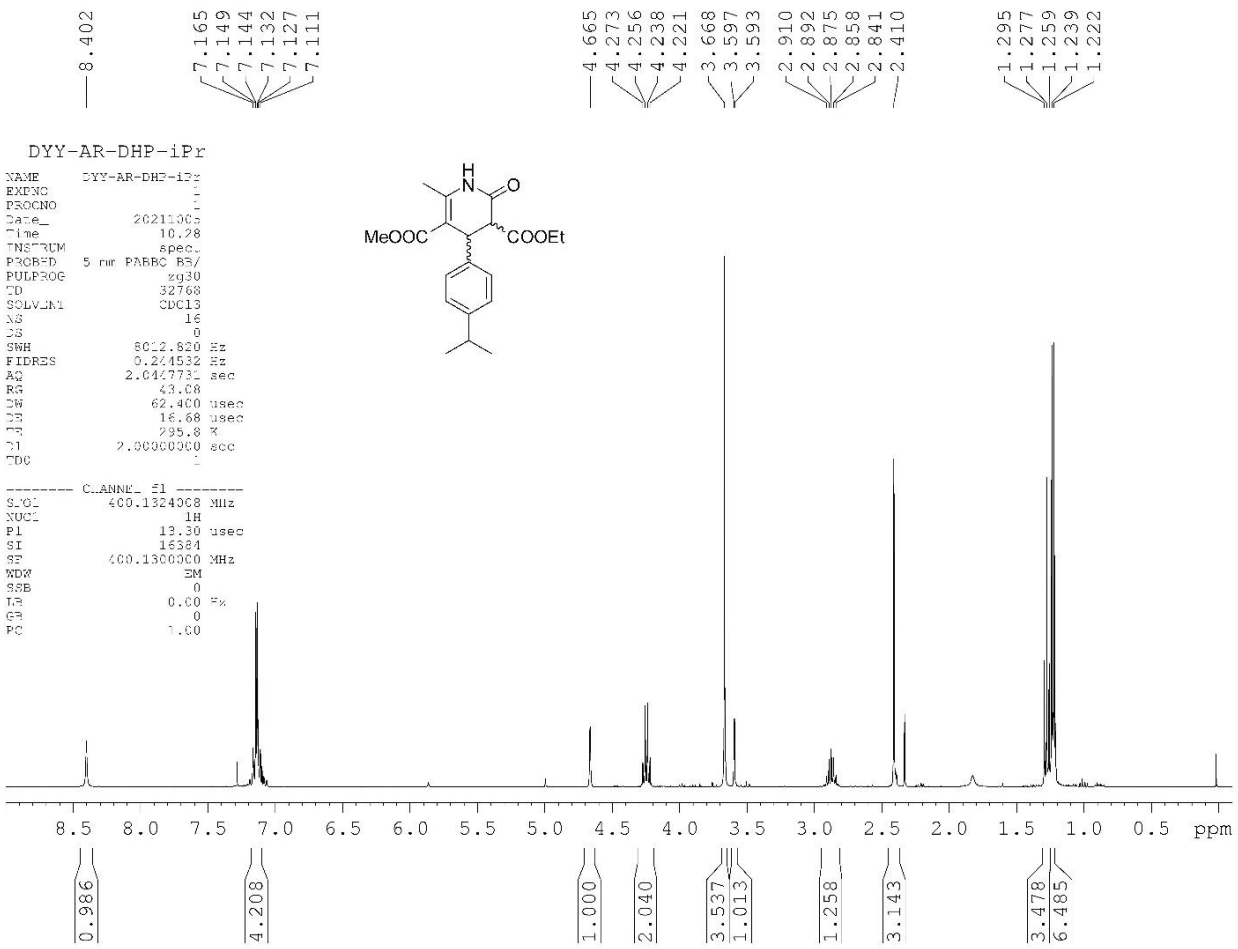
^{1}H NMR of compound **5j** ($CDCl_3$)



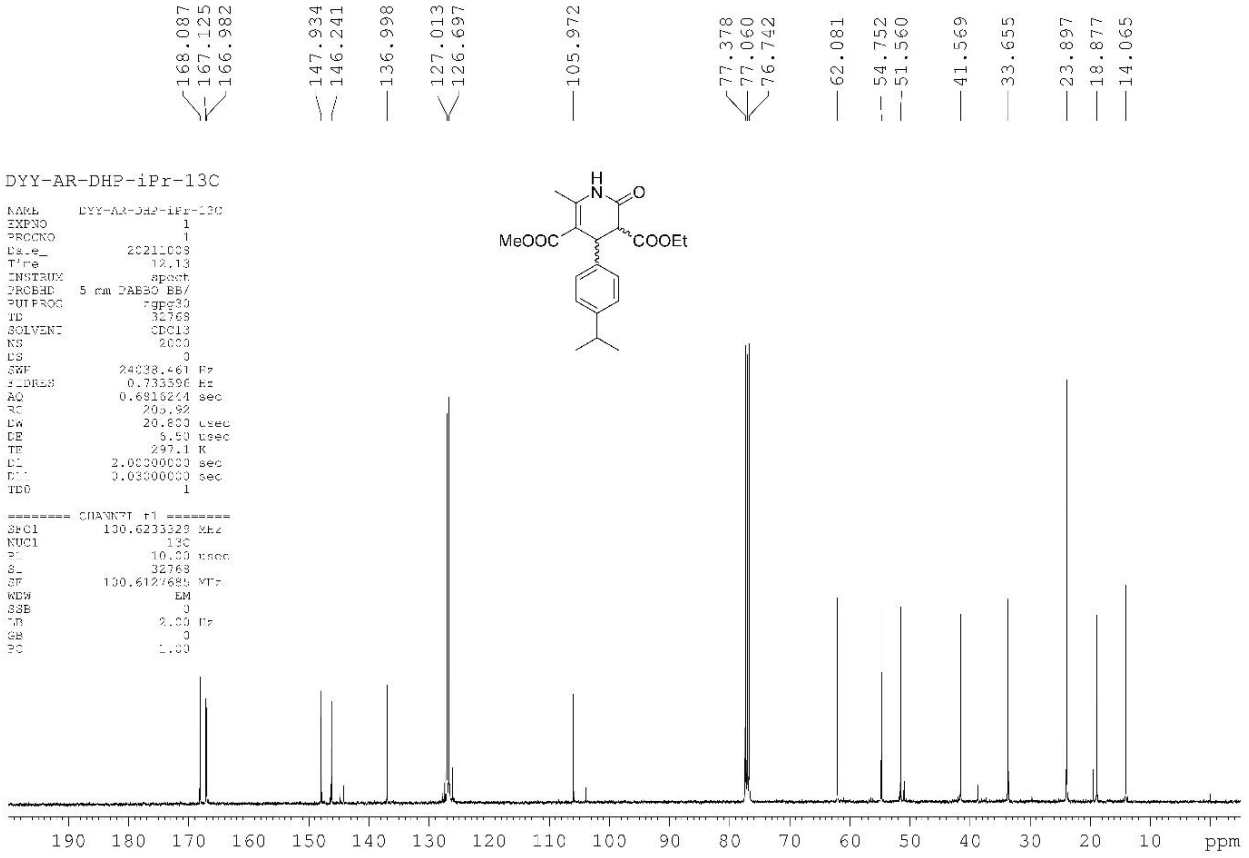
^{13}C NMR of compound **5j** ($CDCl_3$)



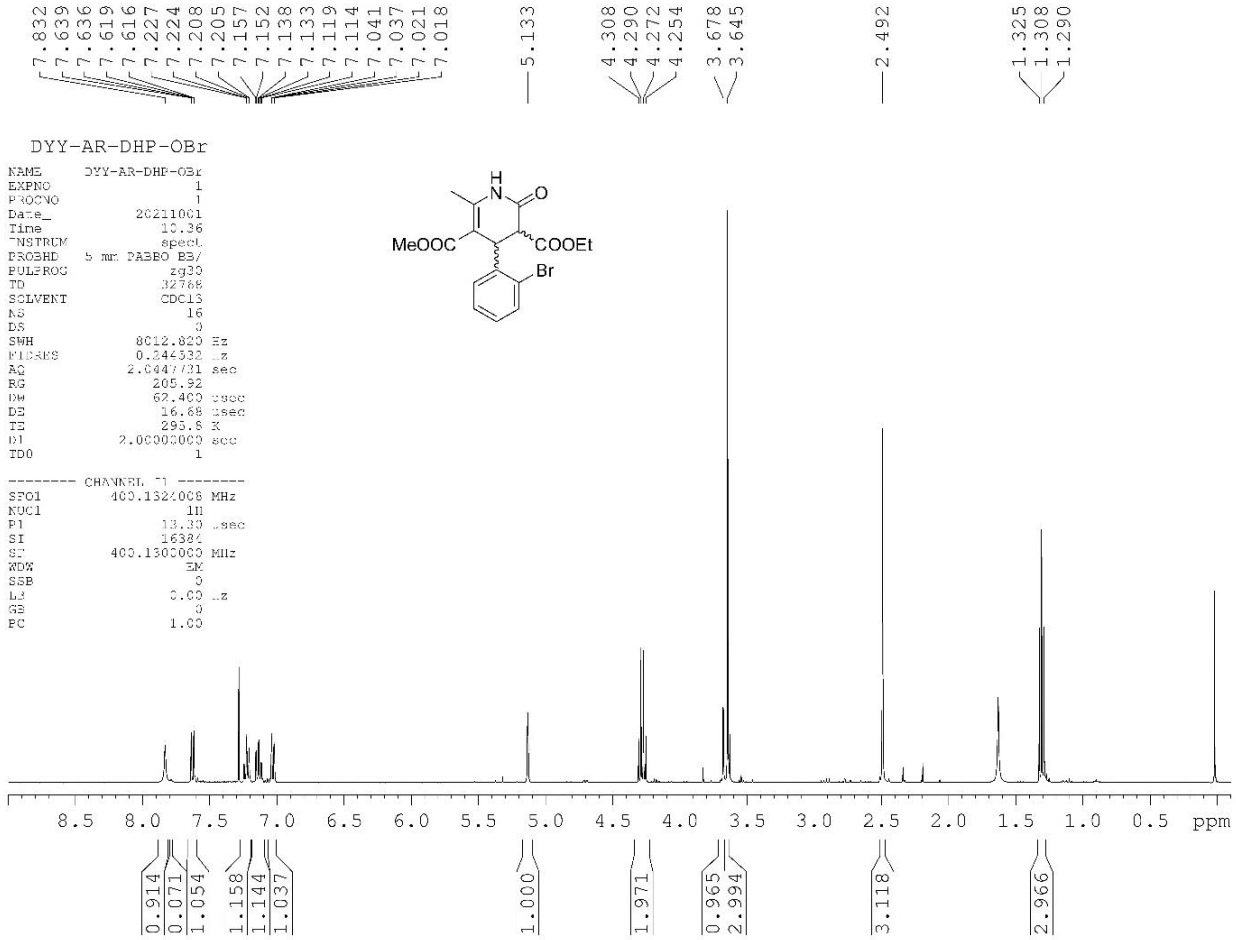
^{1}H NMR of compound **5k** ($CDCl_3$)



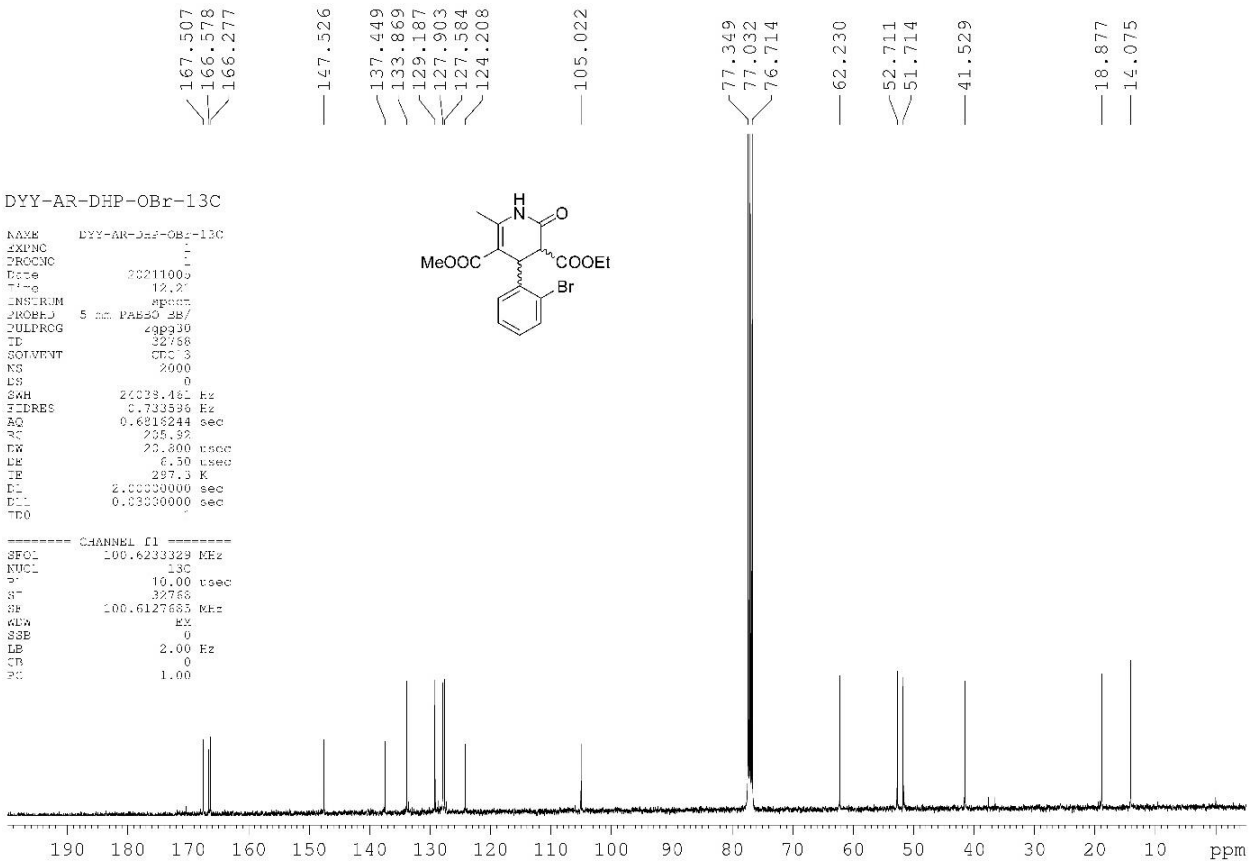
^{13}C NMR of compound **5k** ($CDCl_3$)



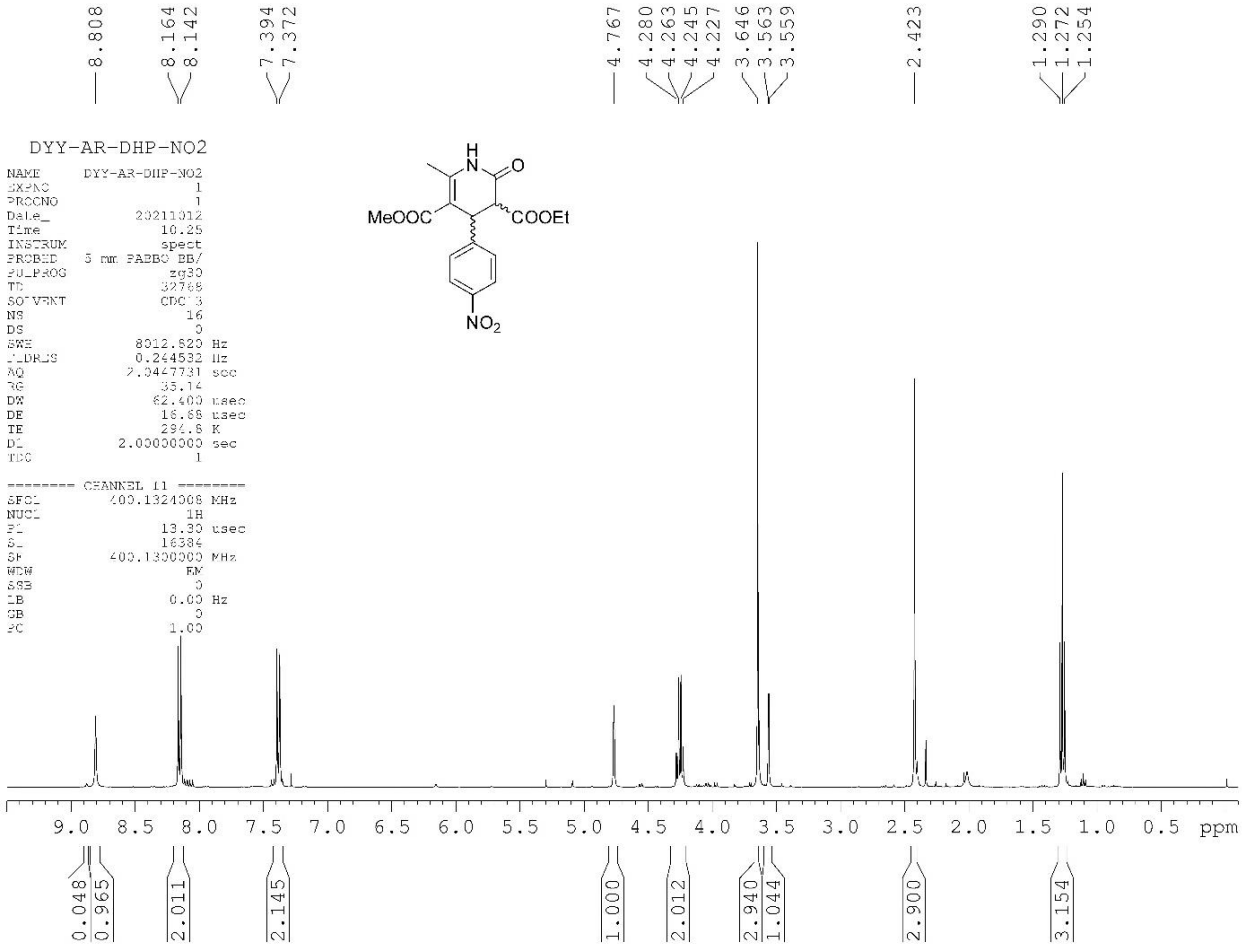
^{1}H NMR of compound **5l** ($CDCl_3$)



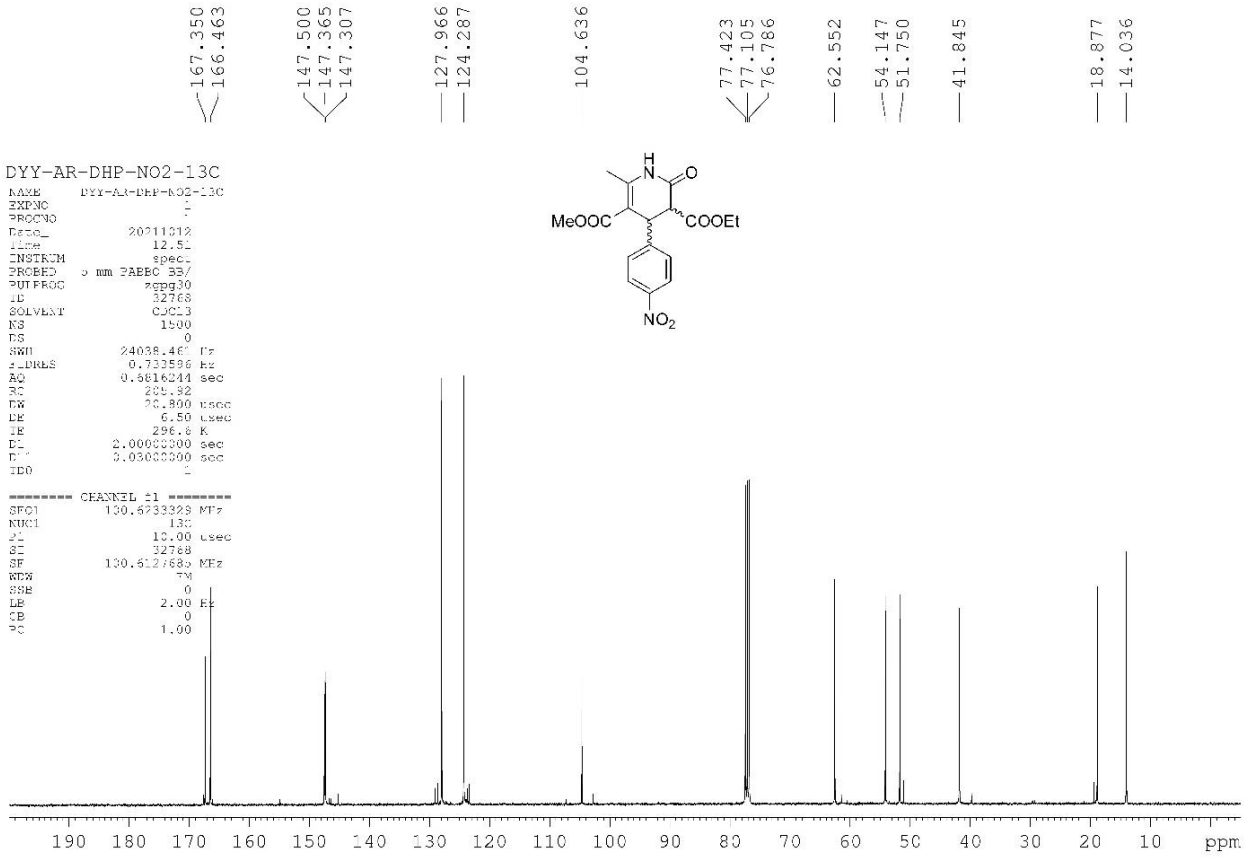
^{13}C NMR of compound **5l** ($CDCl_3$)



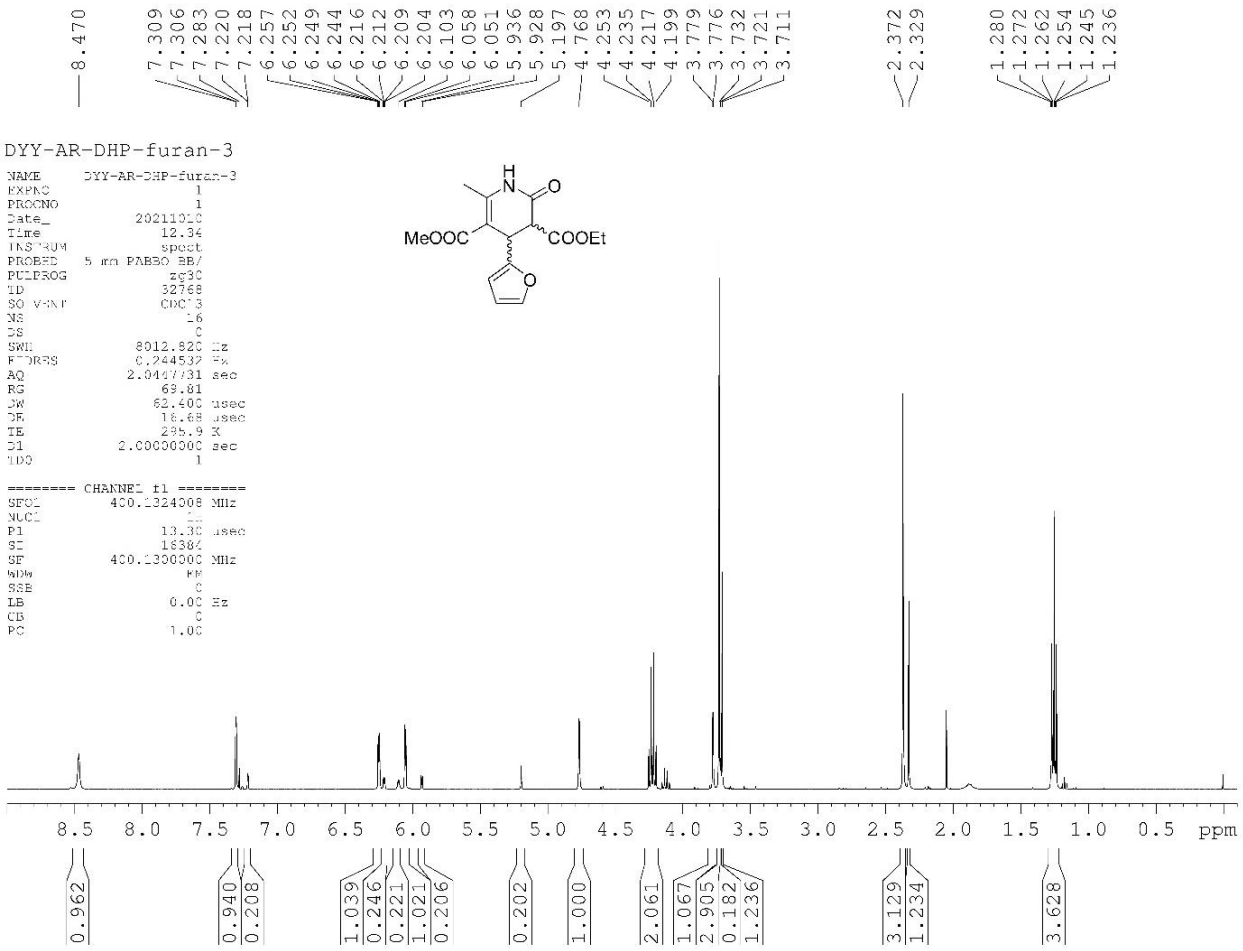
^{1}H NMR of compound **5m** ($CDCl_3$)



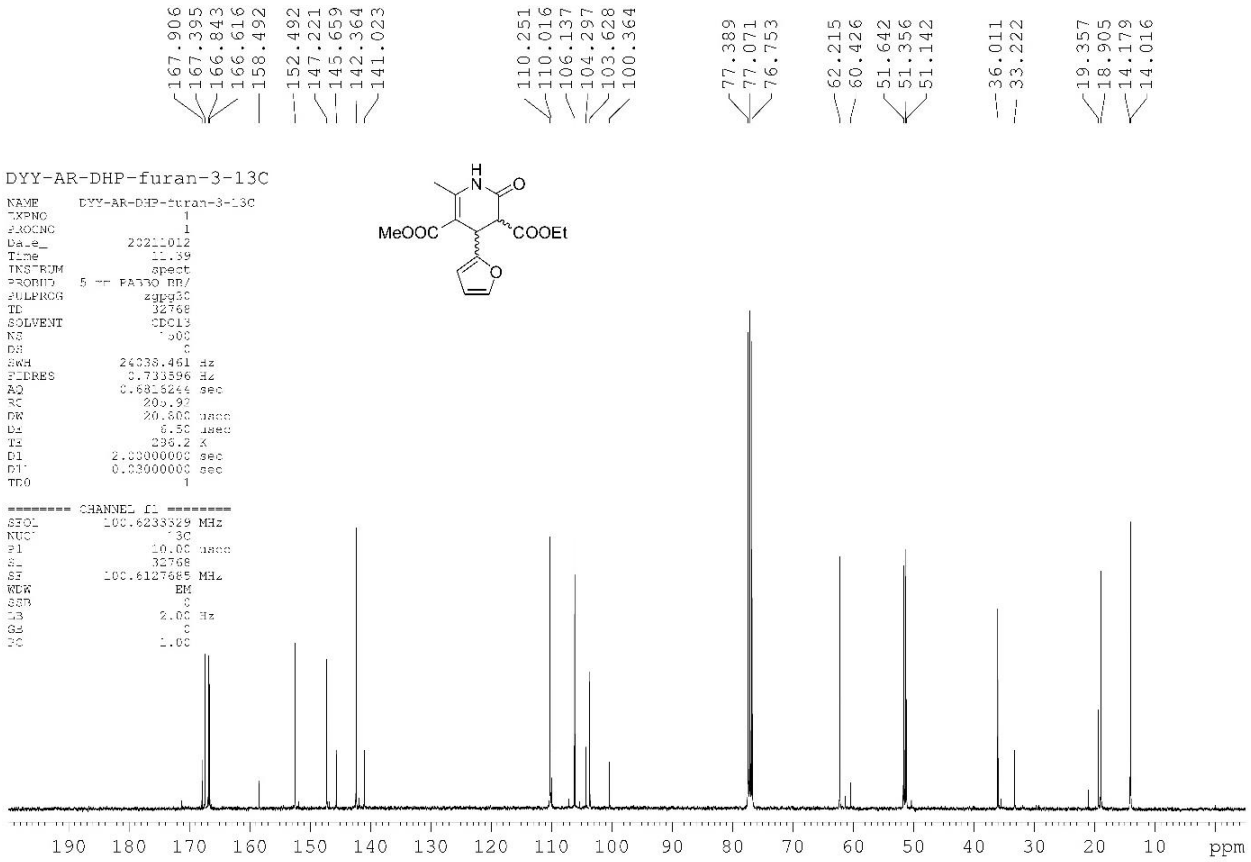
^{13}C NMR of compound **5m** ($CDCl_3$)



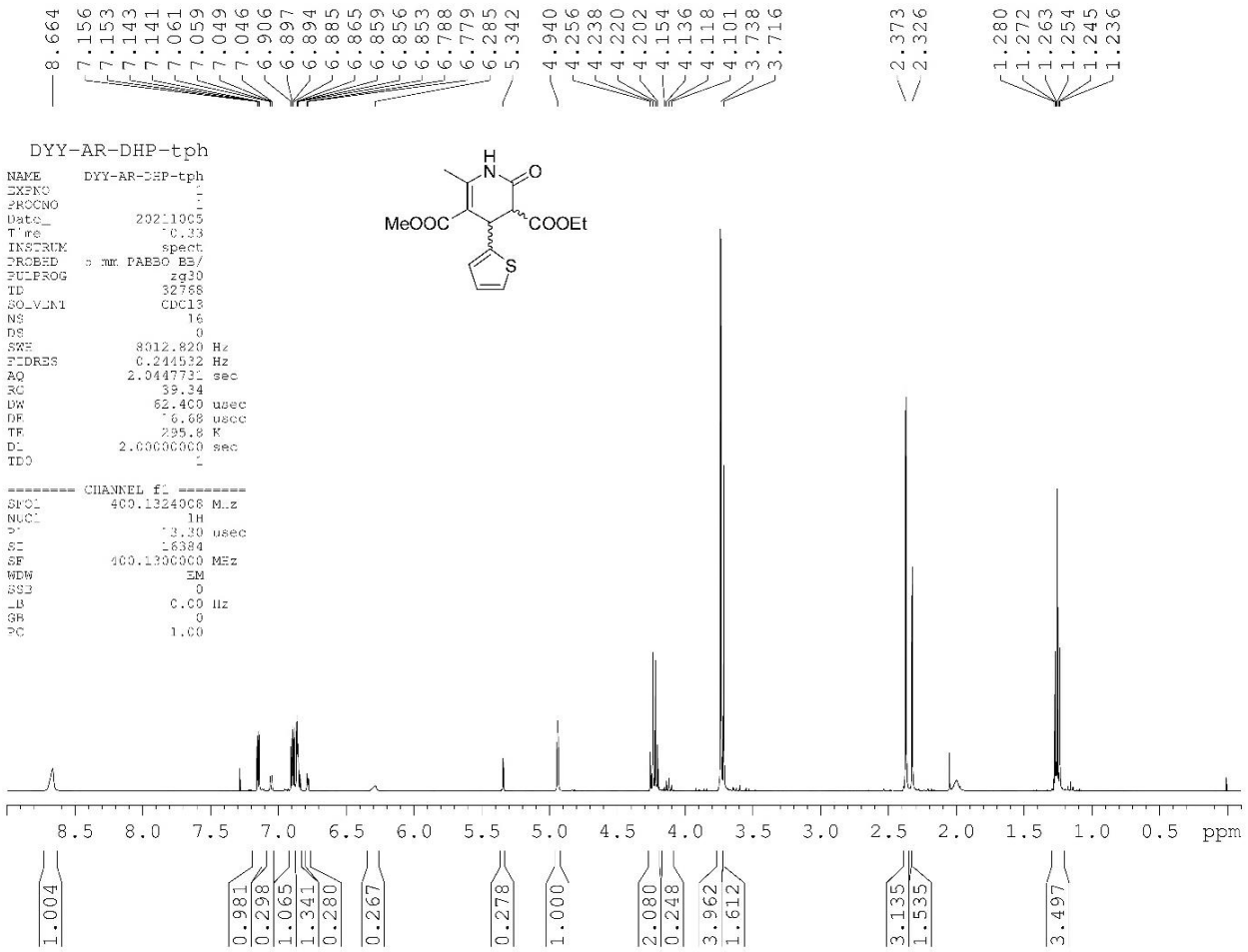
^{1}H NMR of compound **5n** ($CDCl_3$)



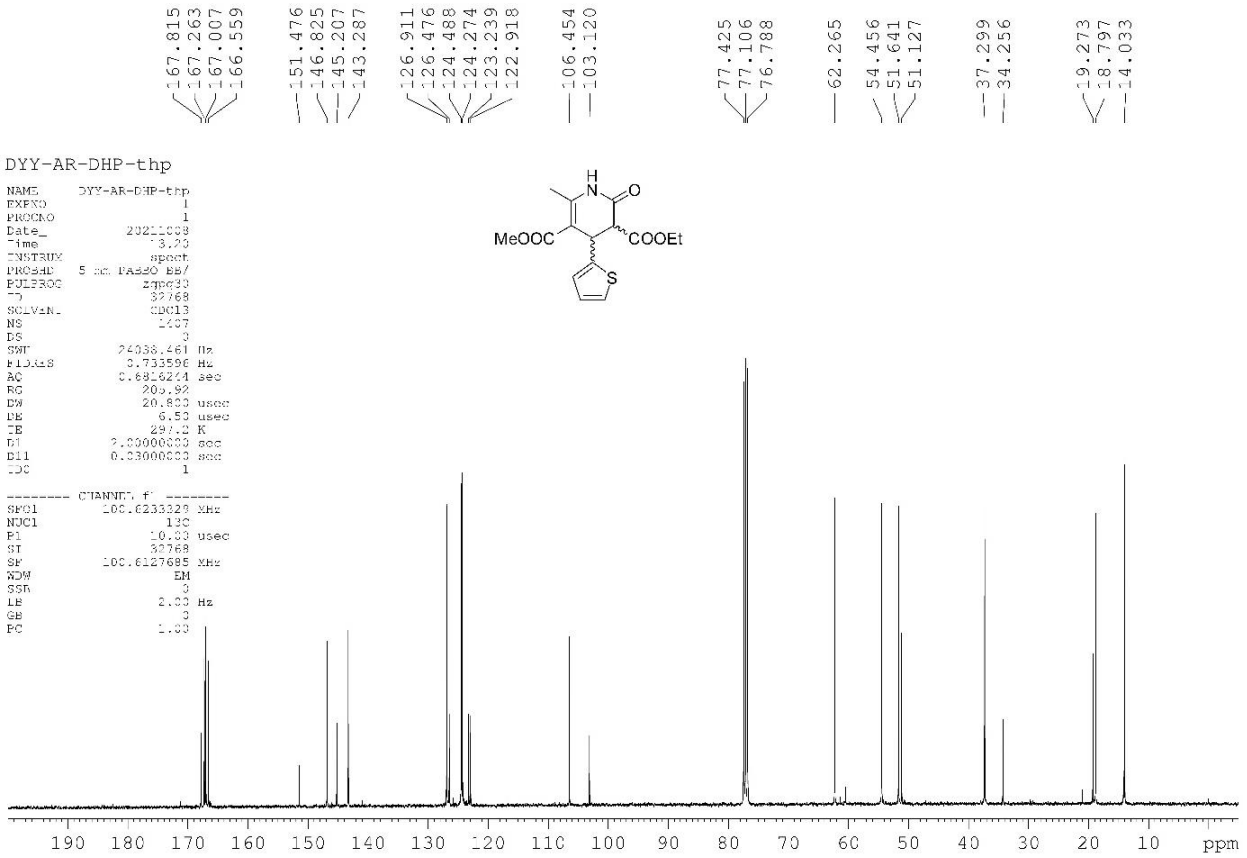
^{13}C NMR of compound **5n** ($CDCl_3$)



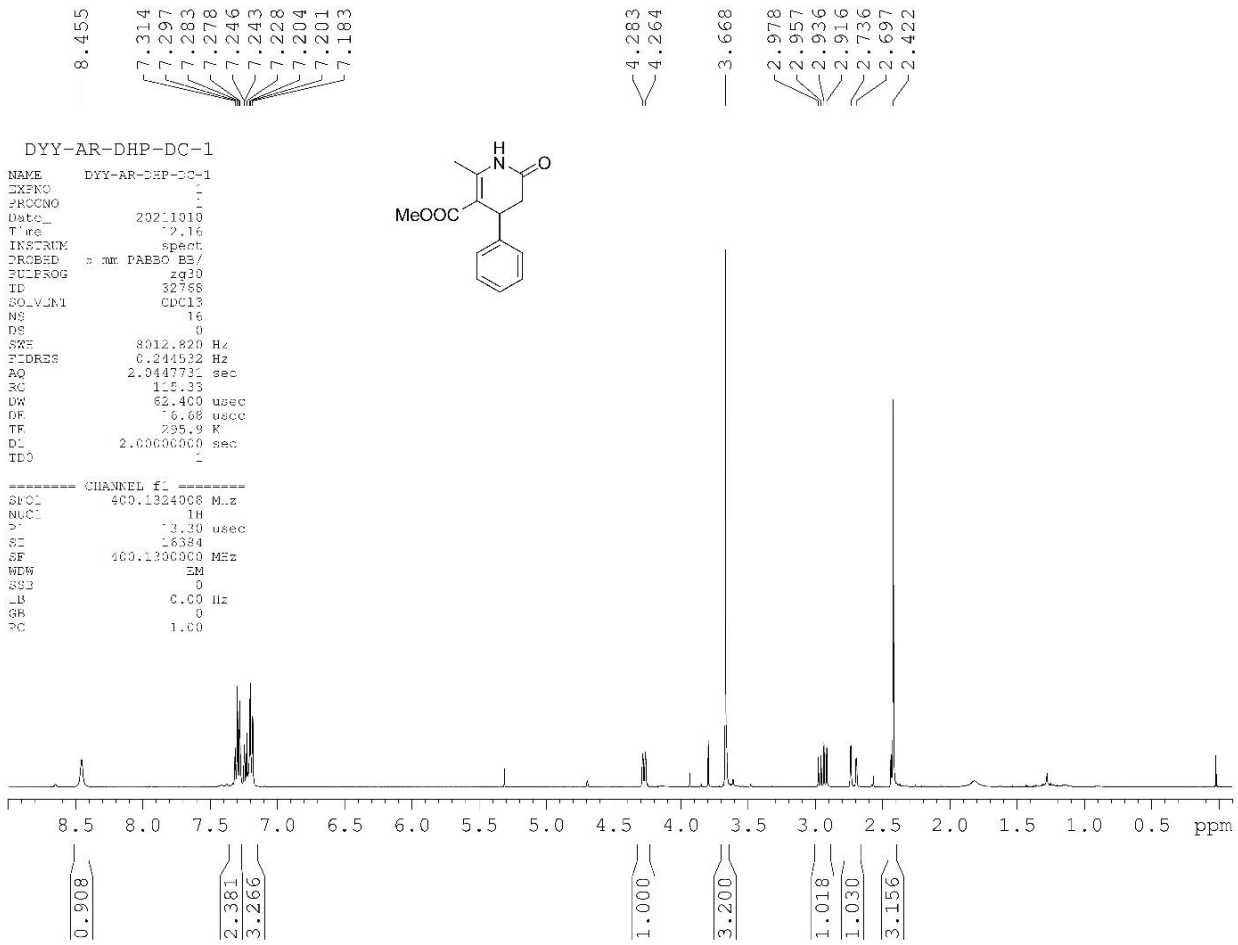
^{1}H NMR of compound **5o** ($CDCl_3$)



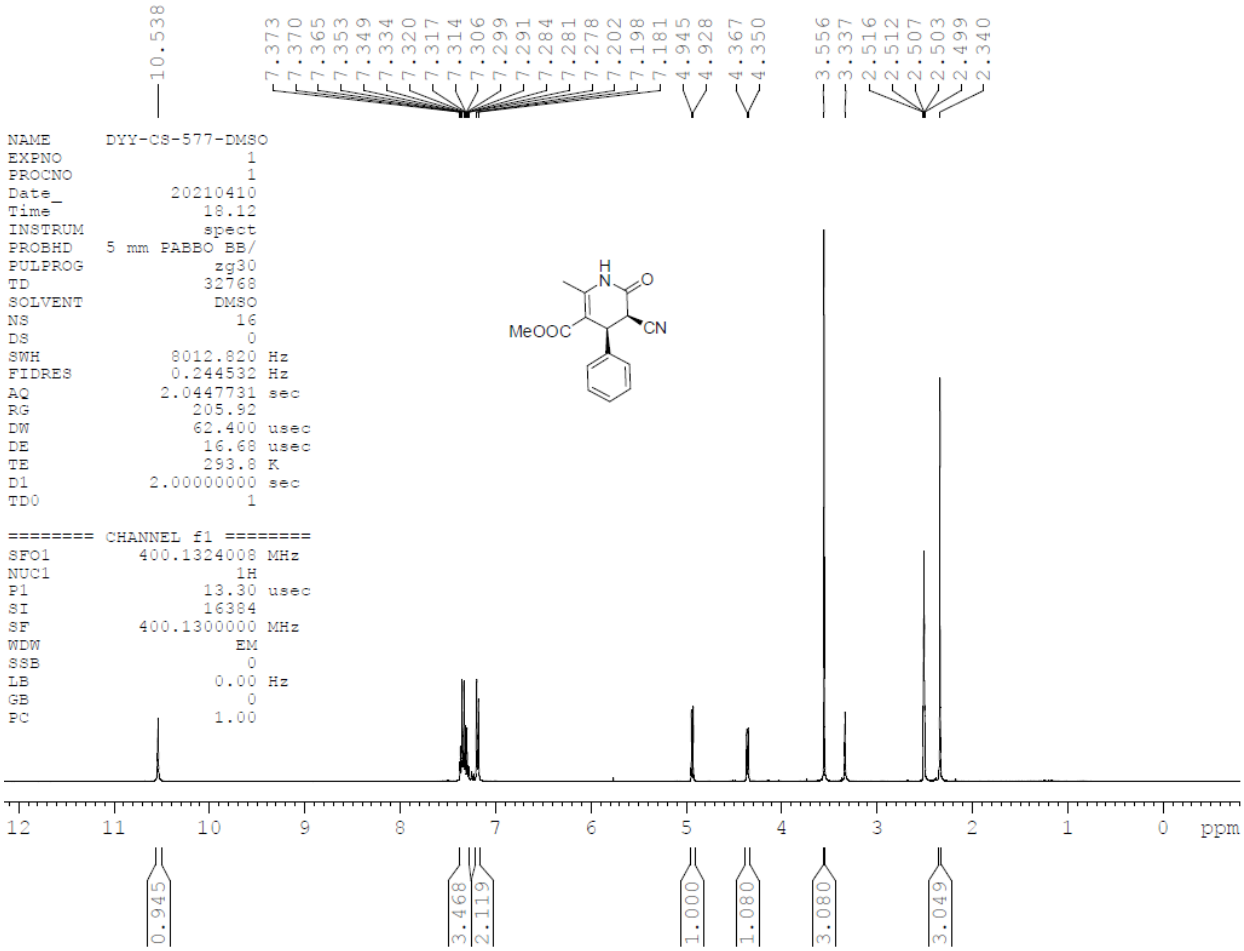
^{13}C NMR of compound **5o** ($CDCl_3$)



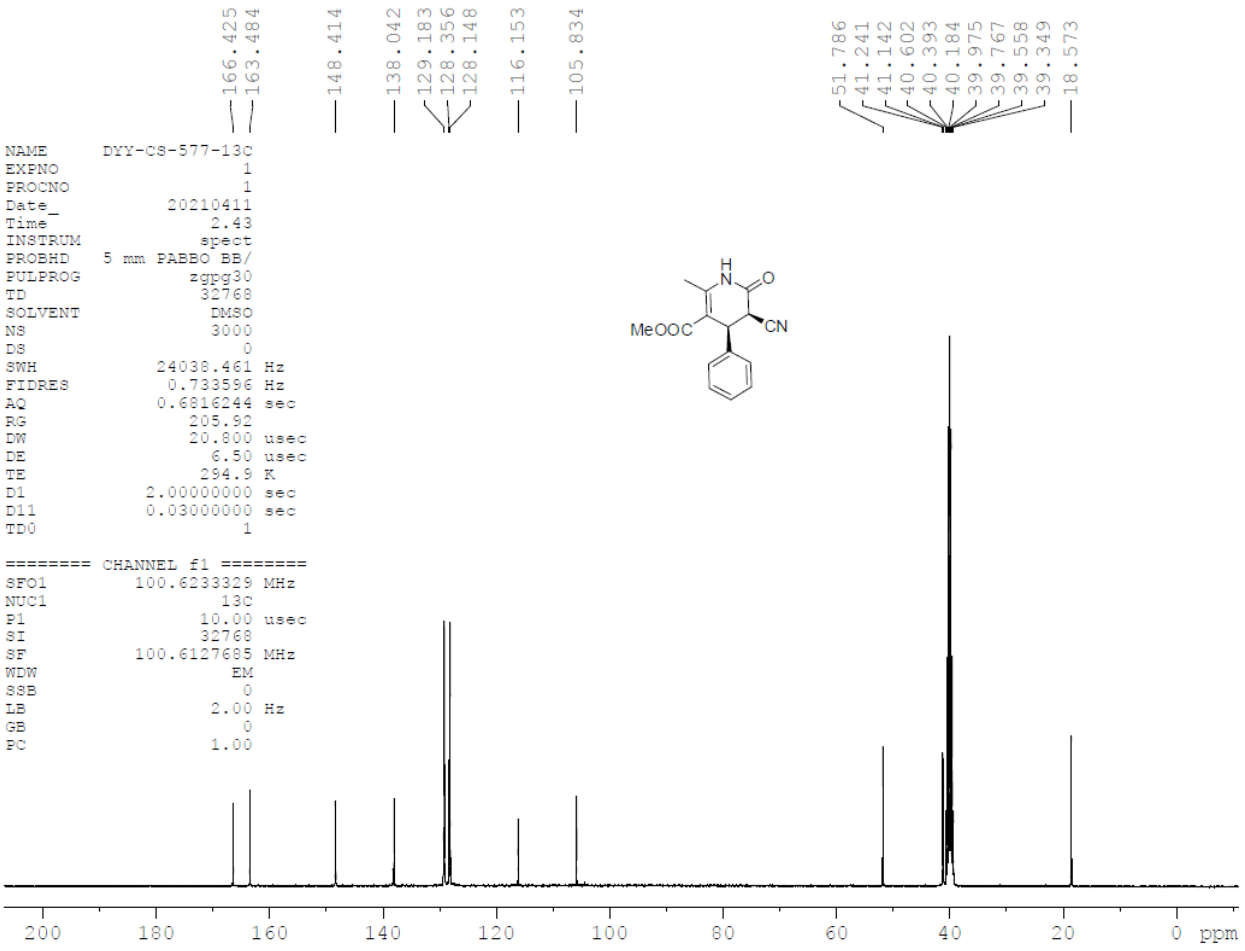
^{1}H NMR of compound **3** ($CDCl_3$)



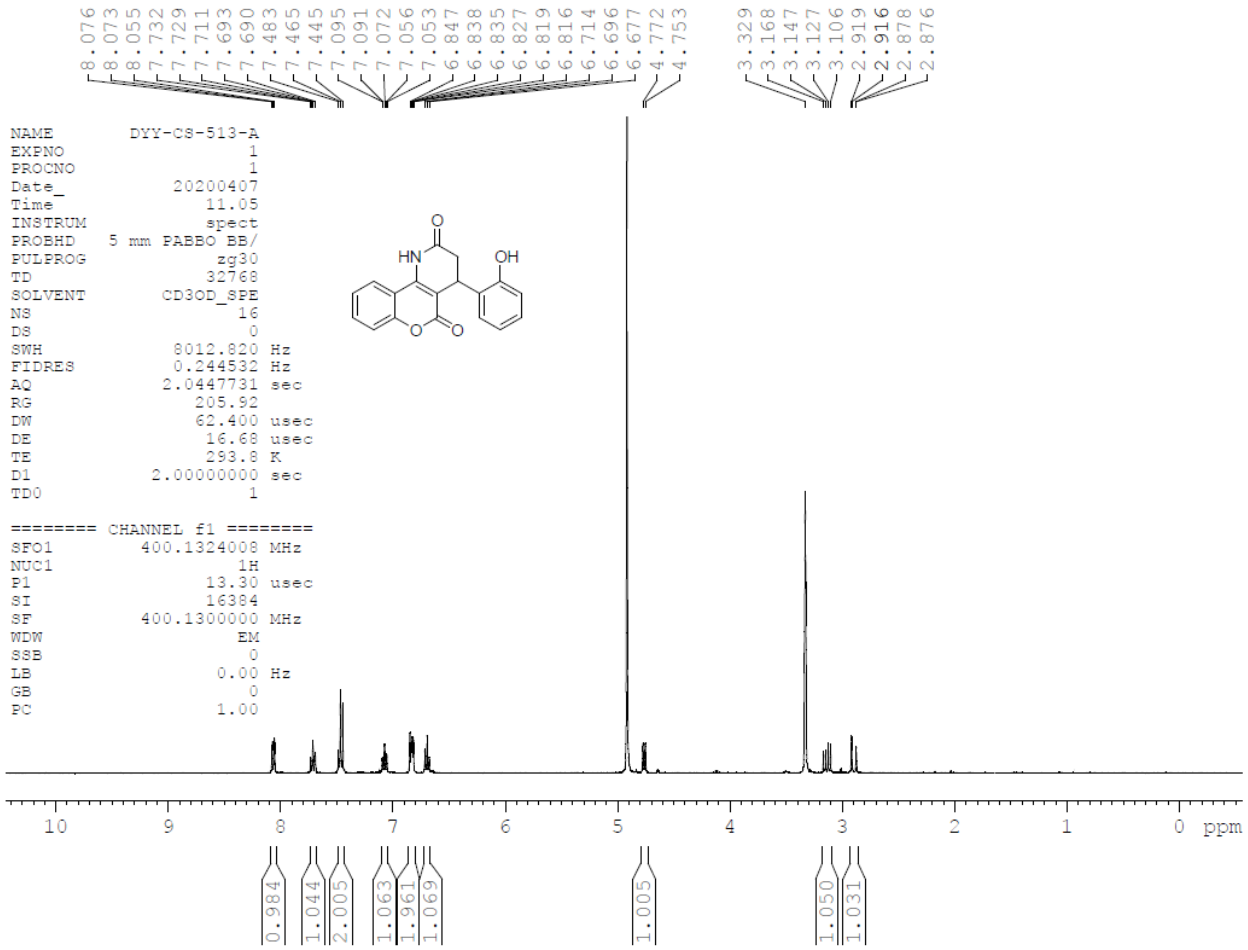
^{1}H NMR of *Cis* diastereomer of compound **5a** (DMSO-d_6)



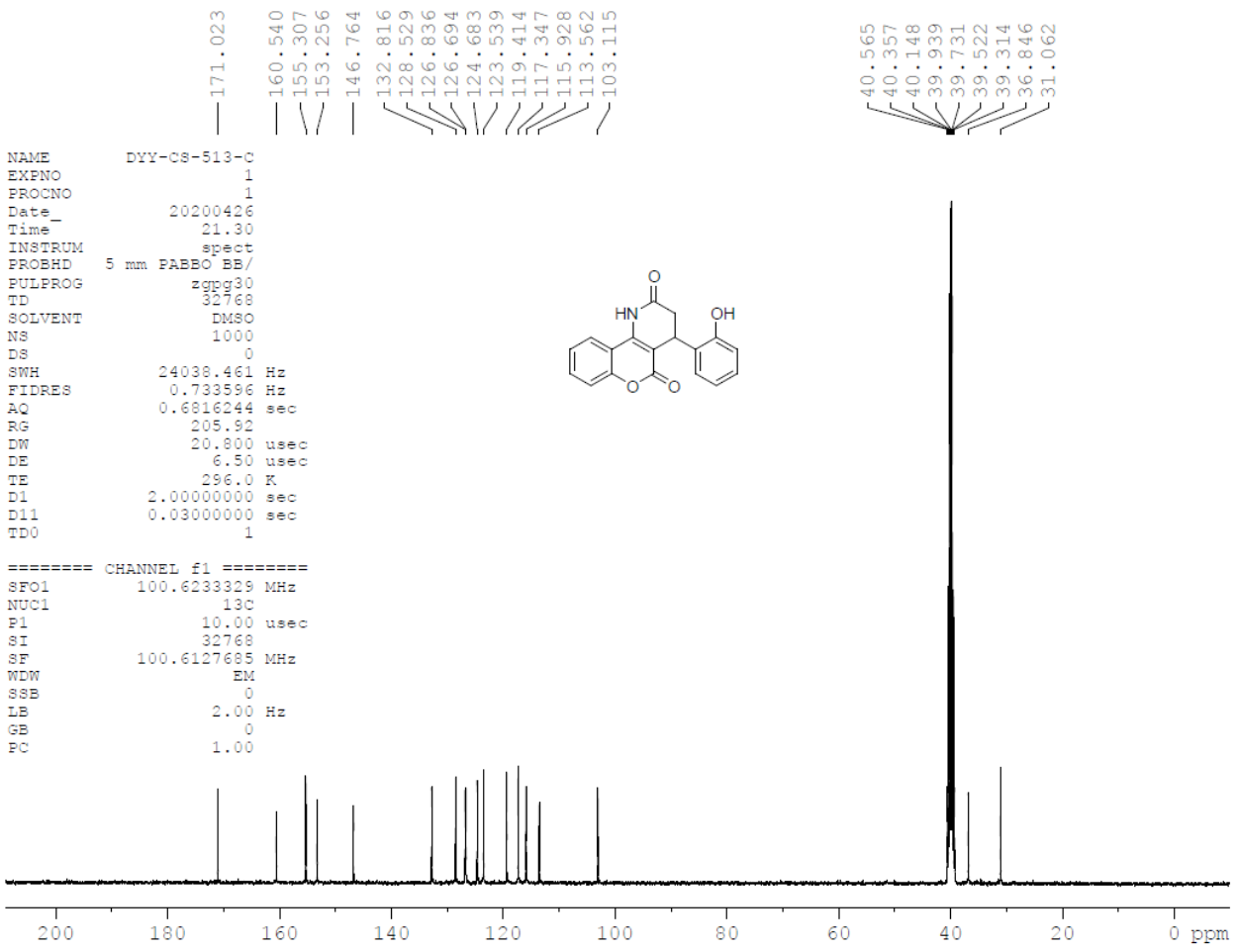
^{13}C NMR of *Cis* diastereomer of compound **5a** (DMSO-d_6)



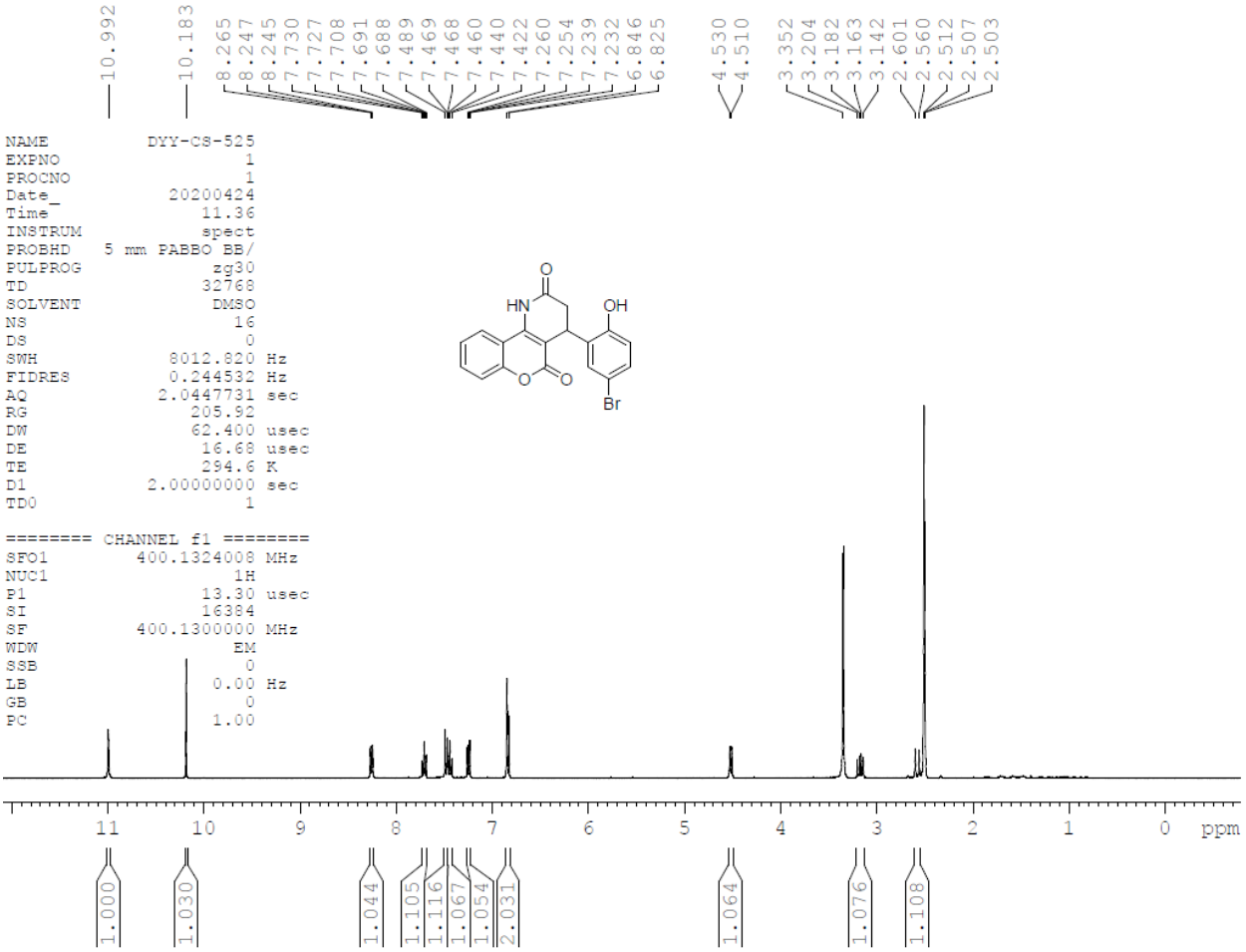
^{1}H NMR of compound **8a** (CD_3OD)



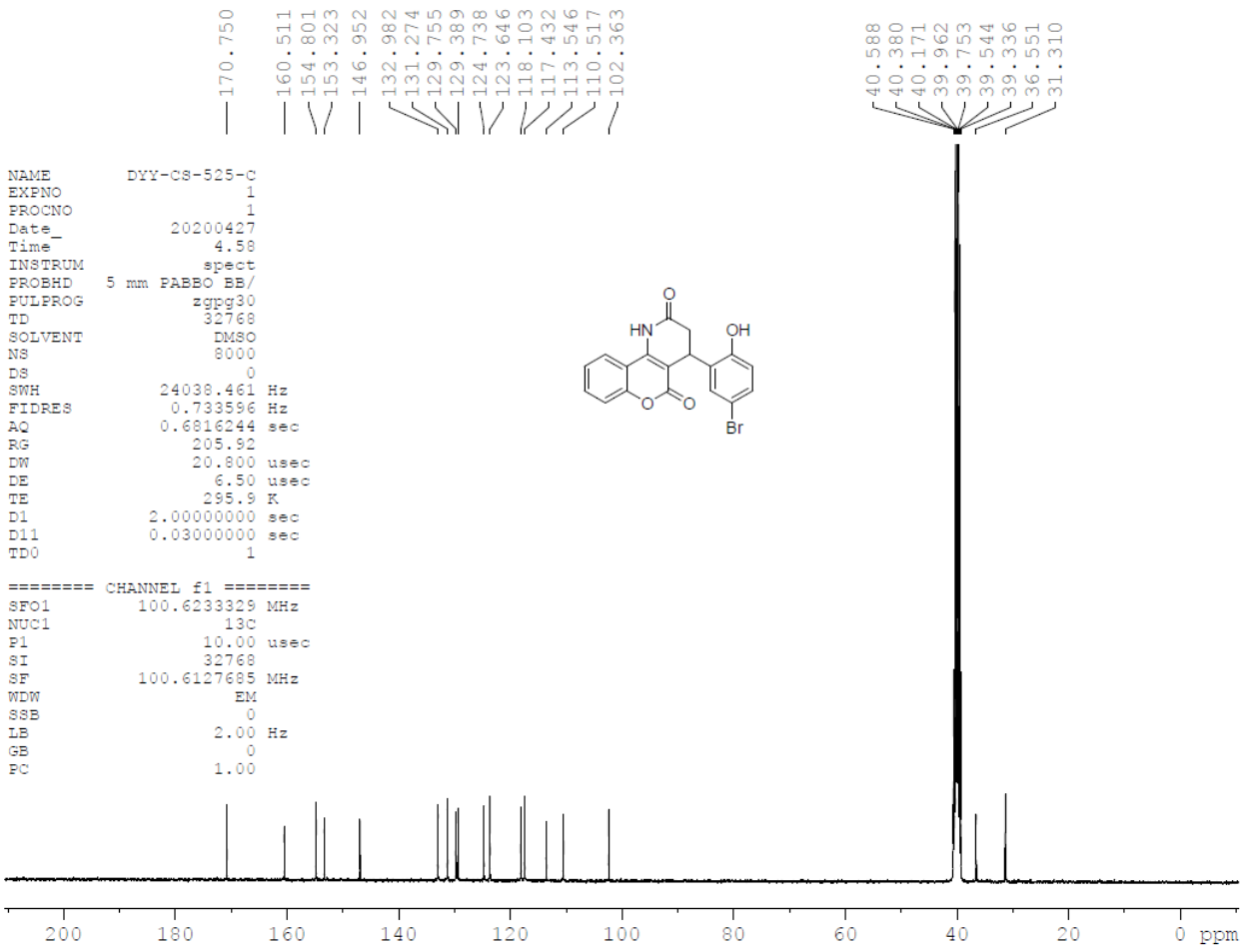
^{13}C NMR of compound **8a** (DMSO-d_6)



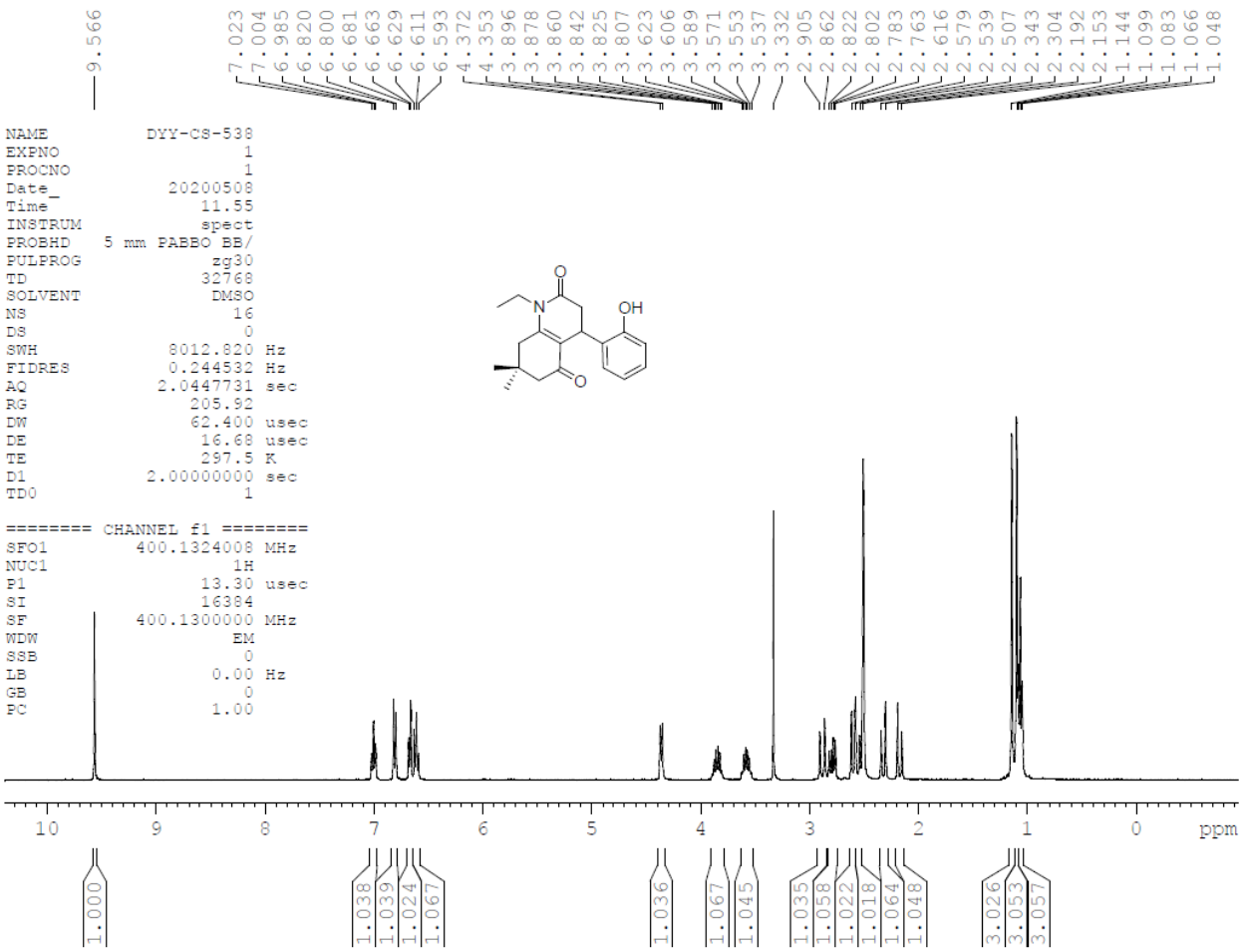
^{1}H NMR of compound **8b** (DMSO-d_6)



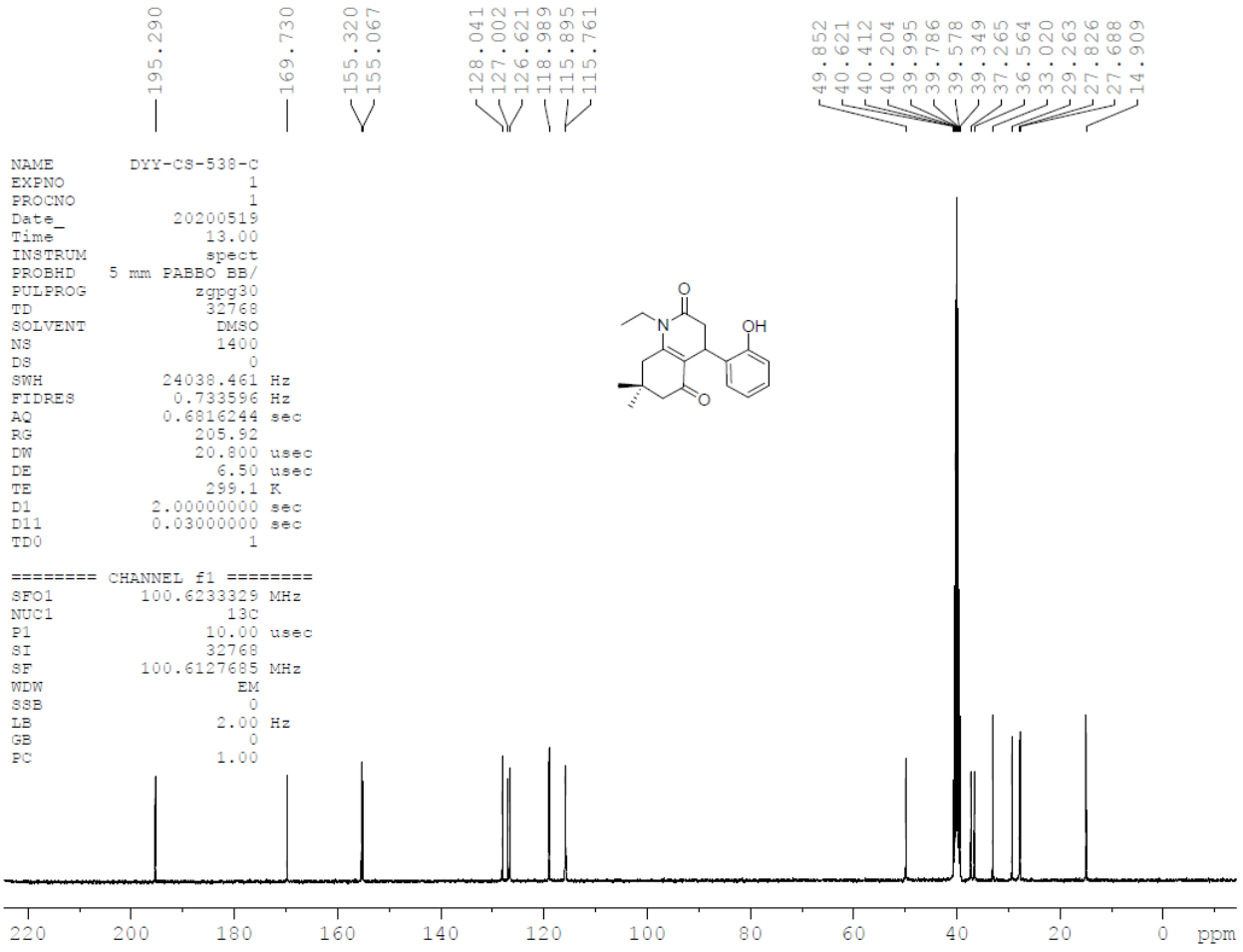
^{13}C NMR of compound **8b** (DMSO-d_6)



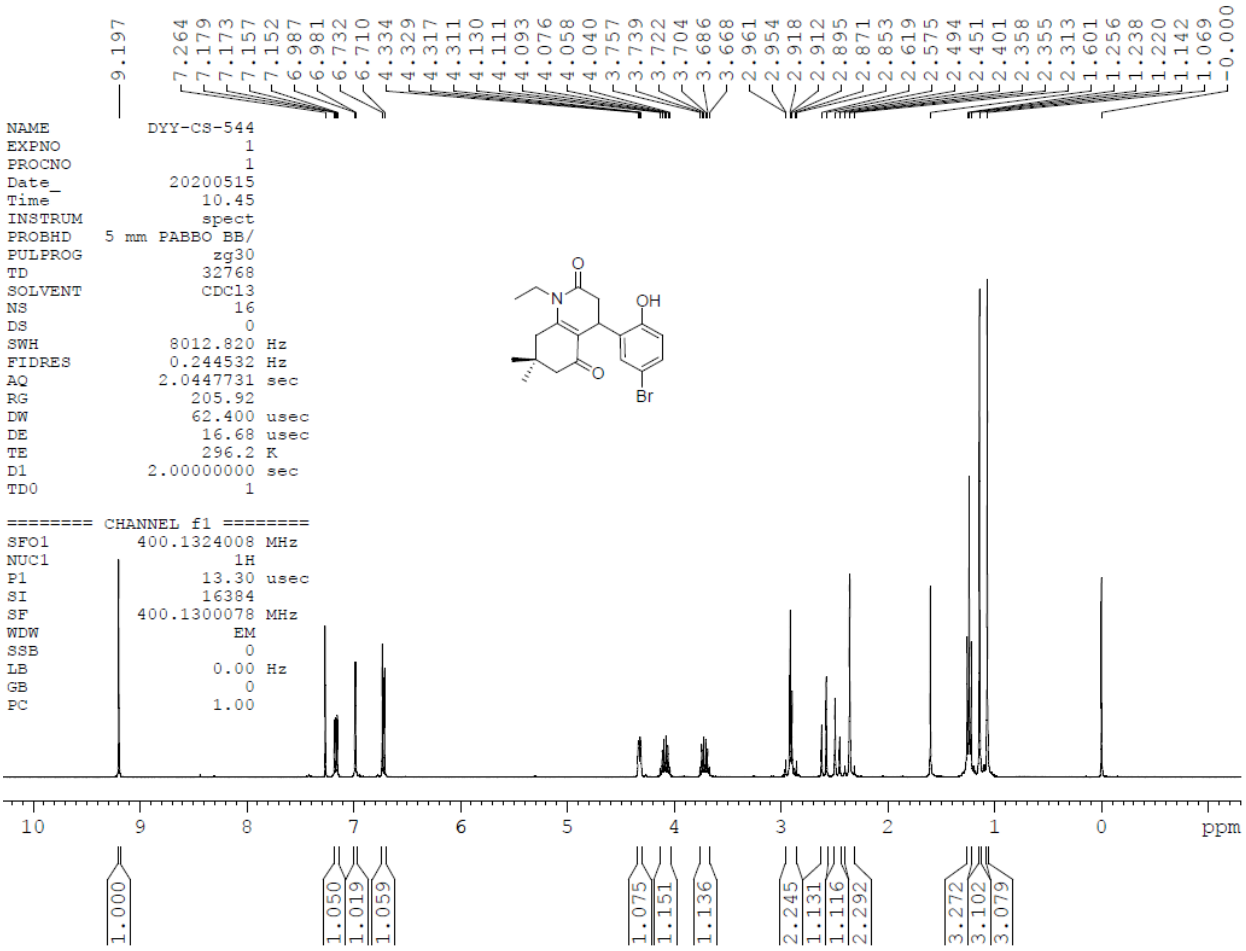
^{1}H NMR of compound **8c** (DMSO-d_6)



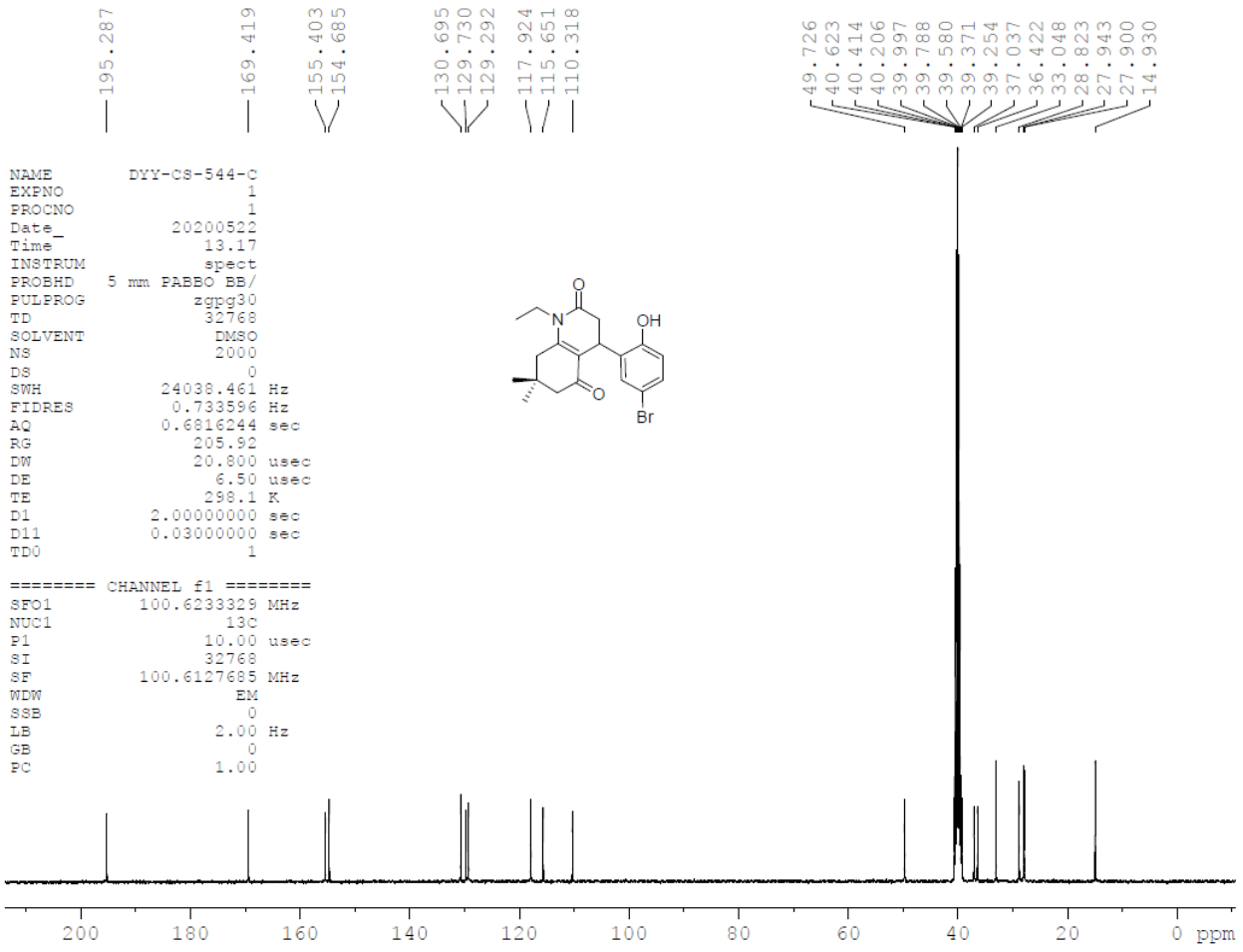
^{13}C NMR of compound **8c** (DMSO-d_6)



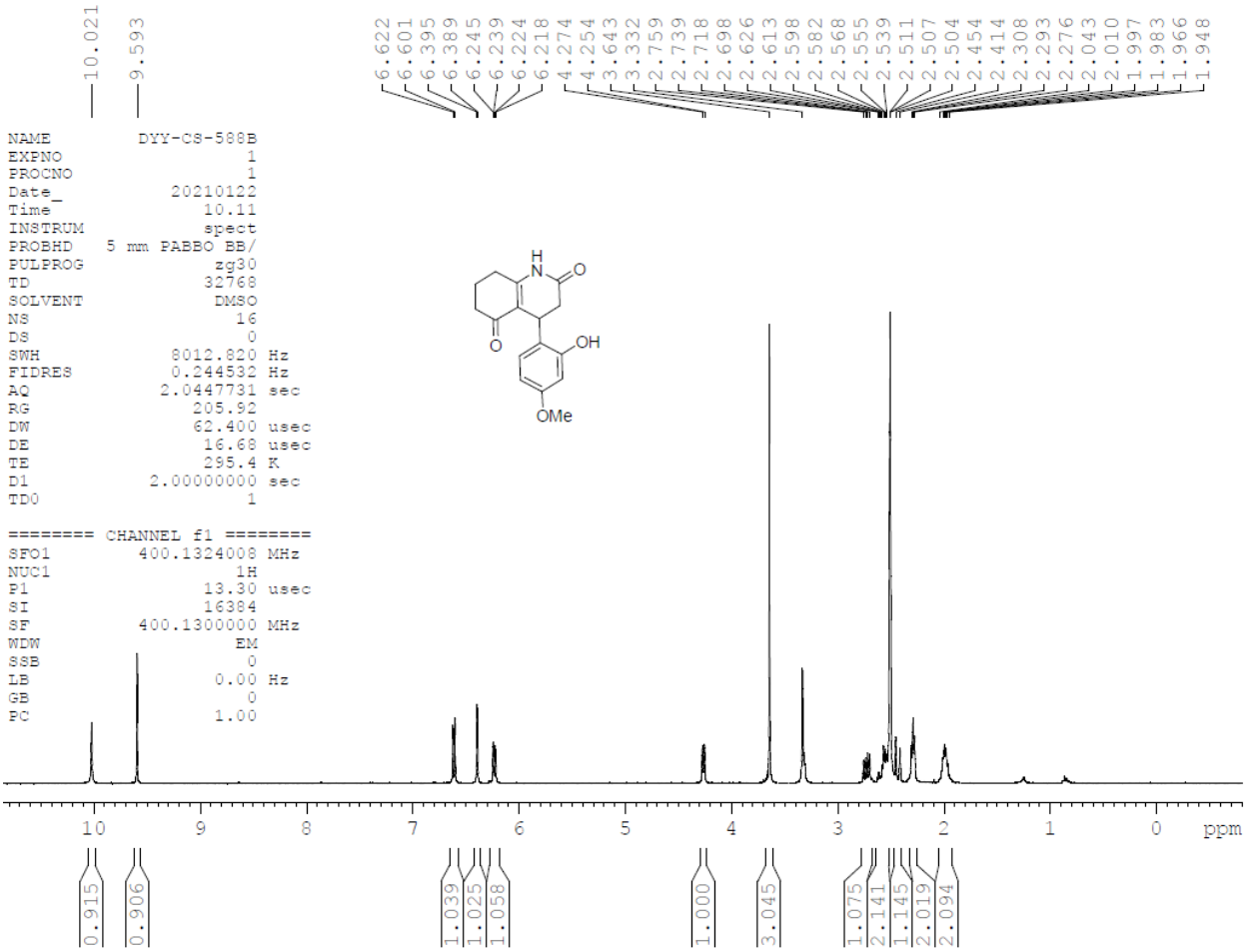
^{1}H NMR of compound **8d** ($CDCl_3$)



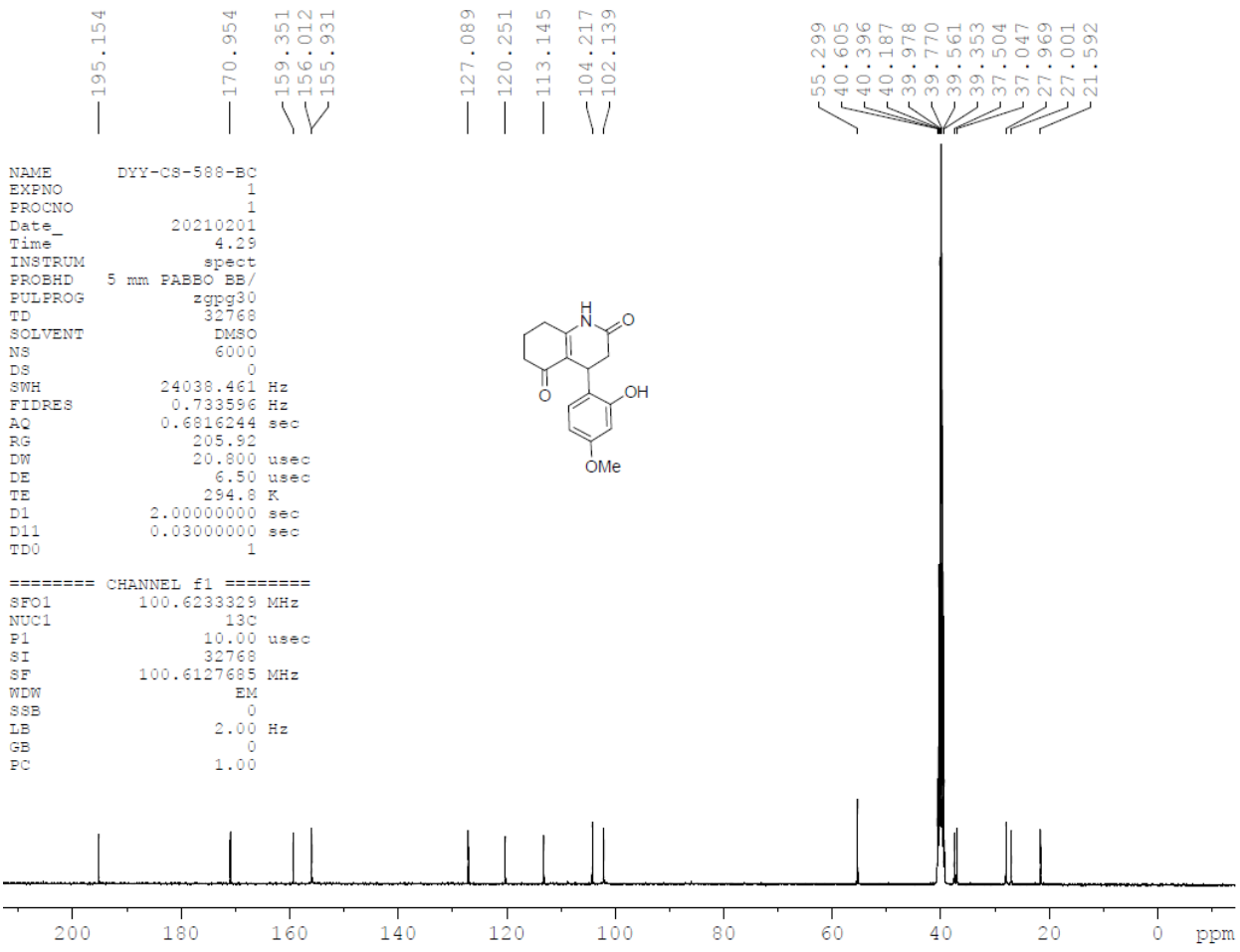
^{13}C NMR of compound **8d** (DMSO-d_6)



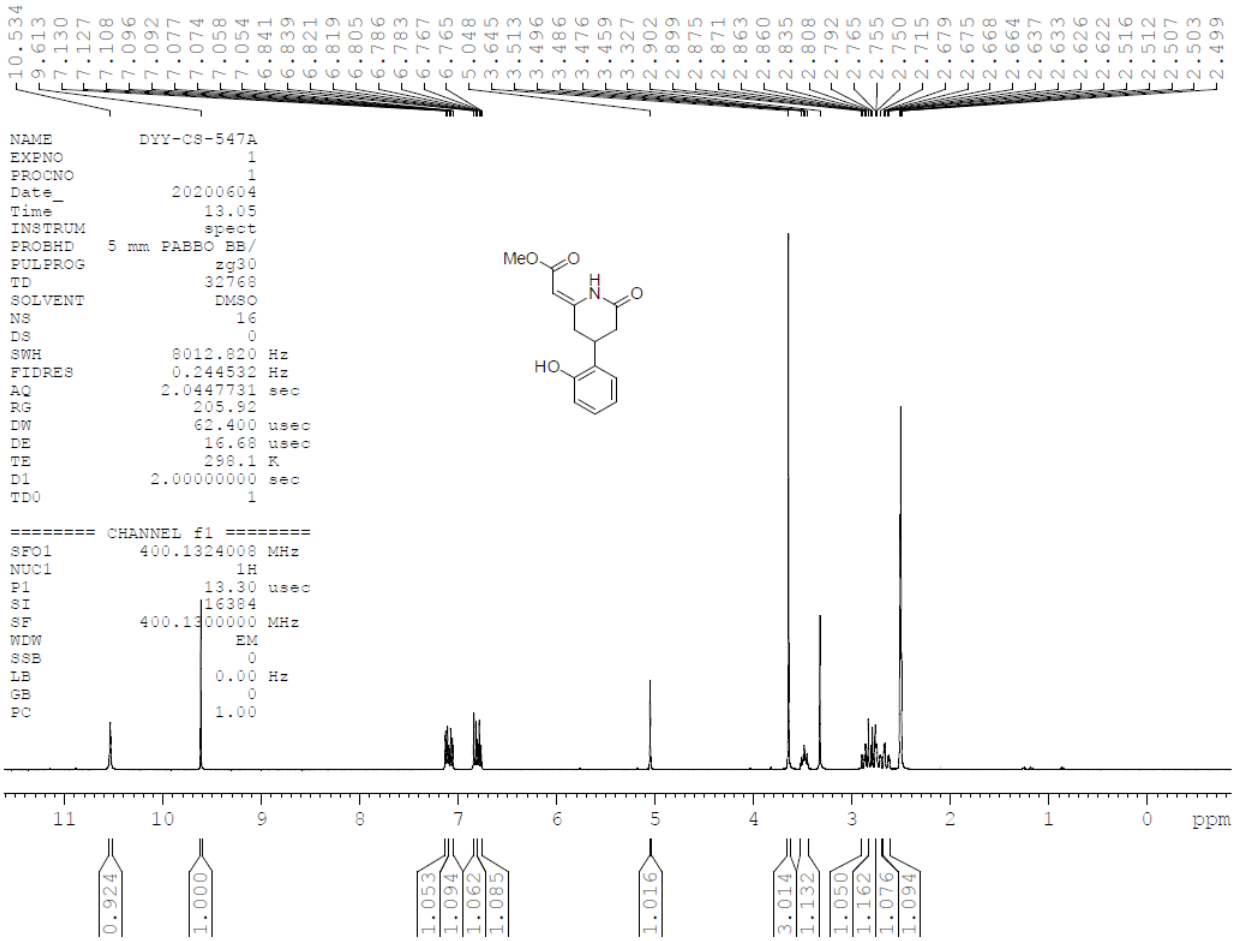
^{1}H NMR of compound **8e** (DMSO-d_6)



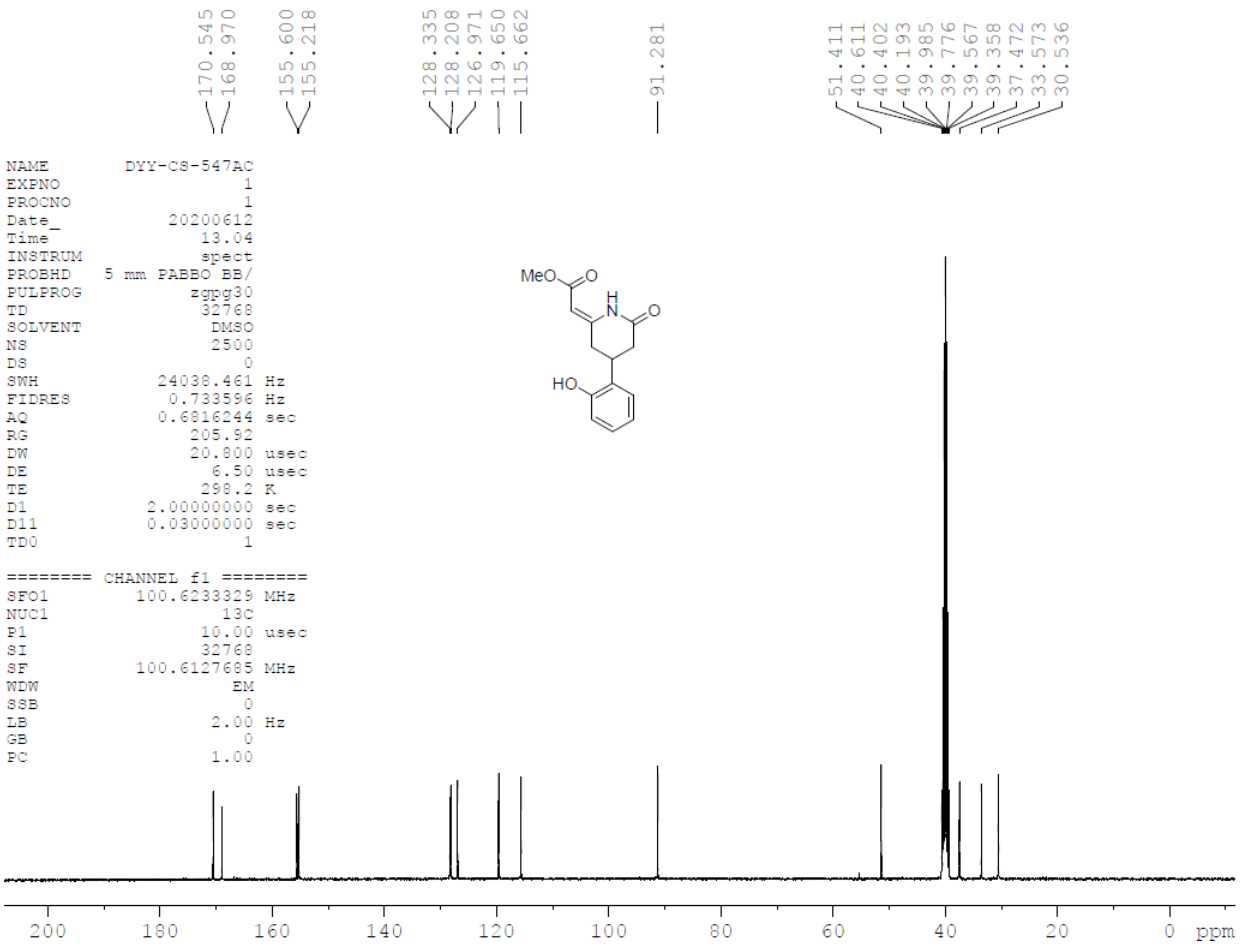
^{13}C NMR of compound **8e** (DMSO-d_6)



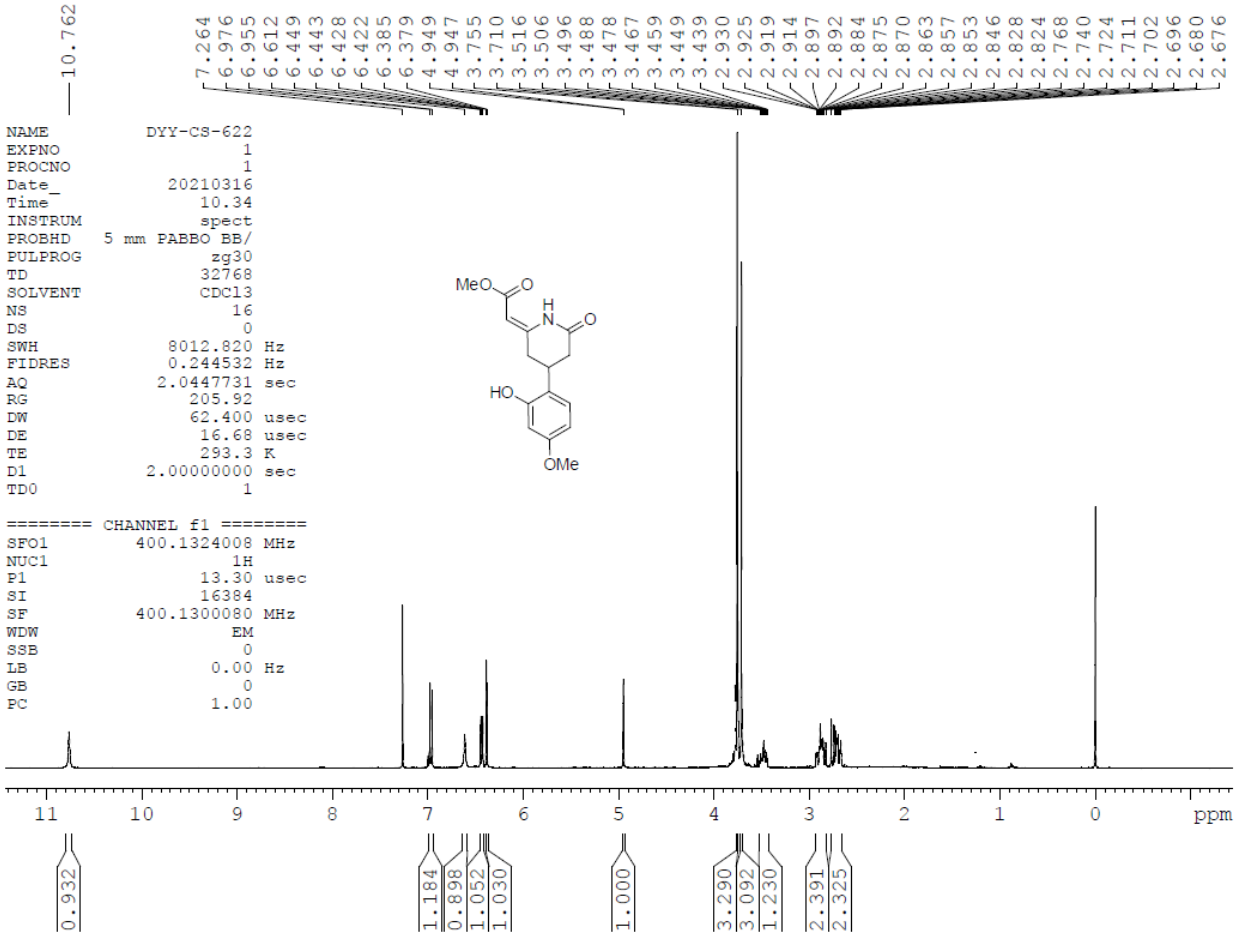
^{1}H NMR of compound **9a** (DMSO-d_6)



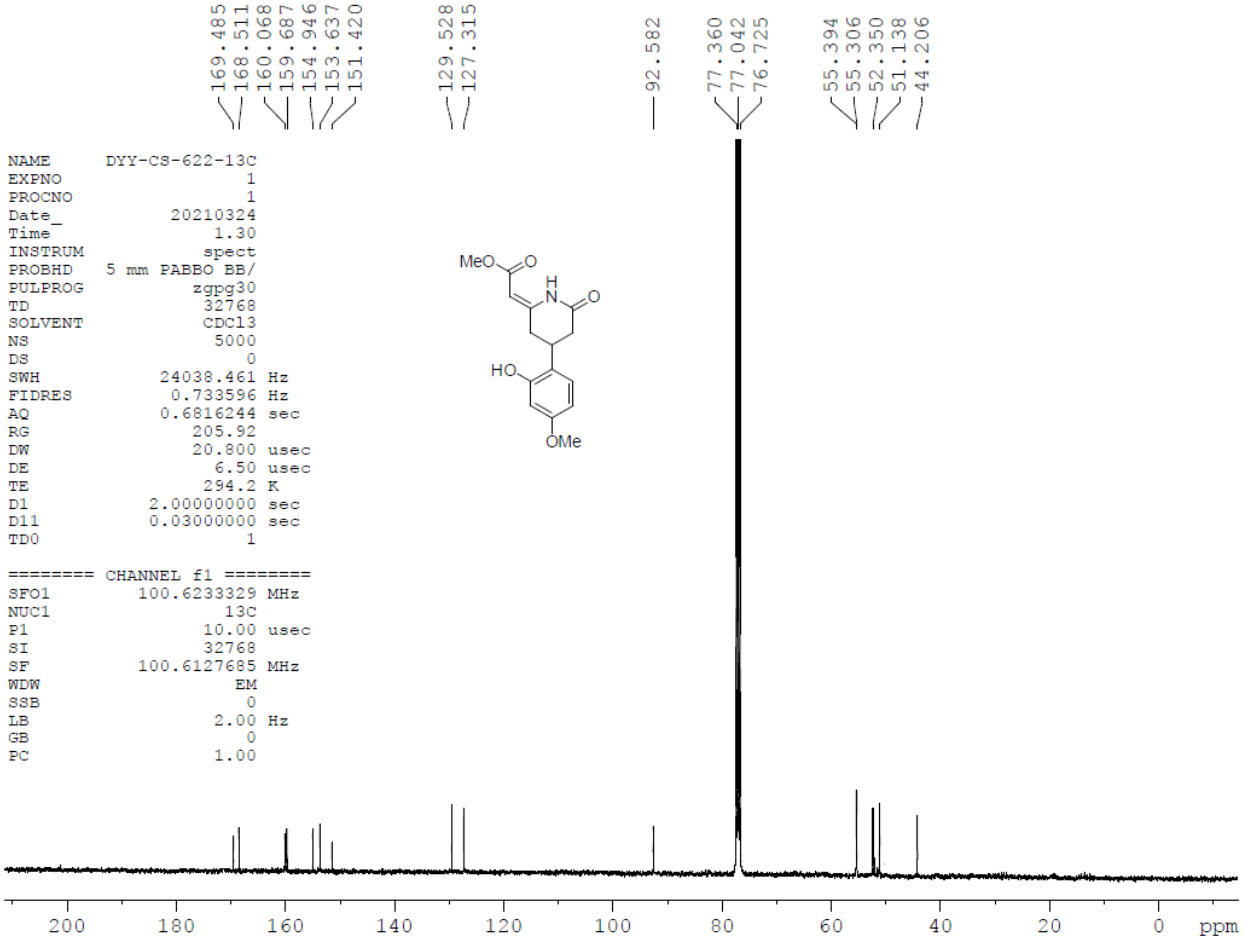
^{13}C NMR of compound **9a** (DMSO-d_6)



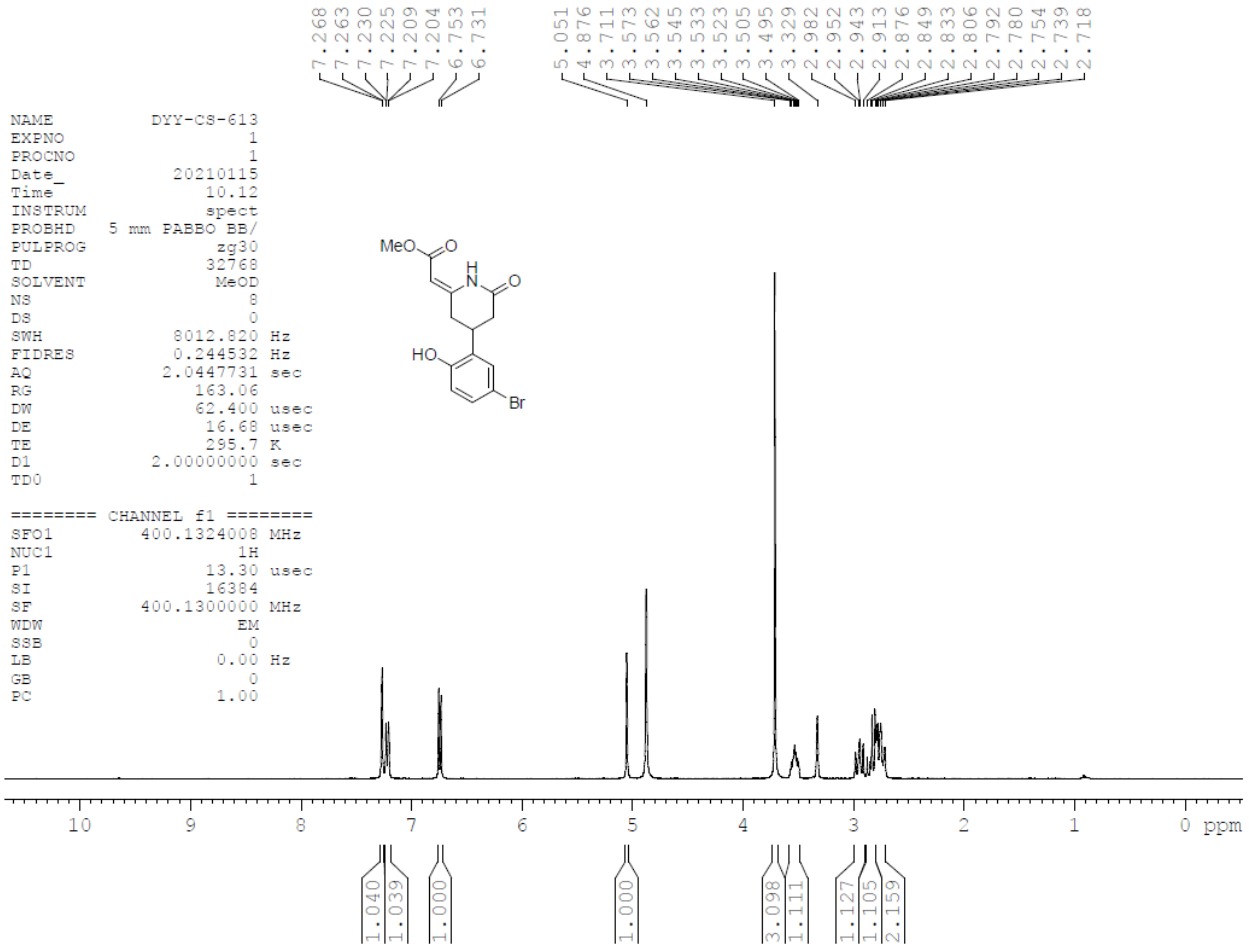
^{1}H NMR of compound **9b** ($CDCl_3$)



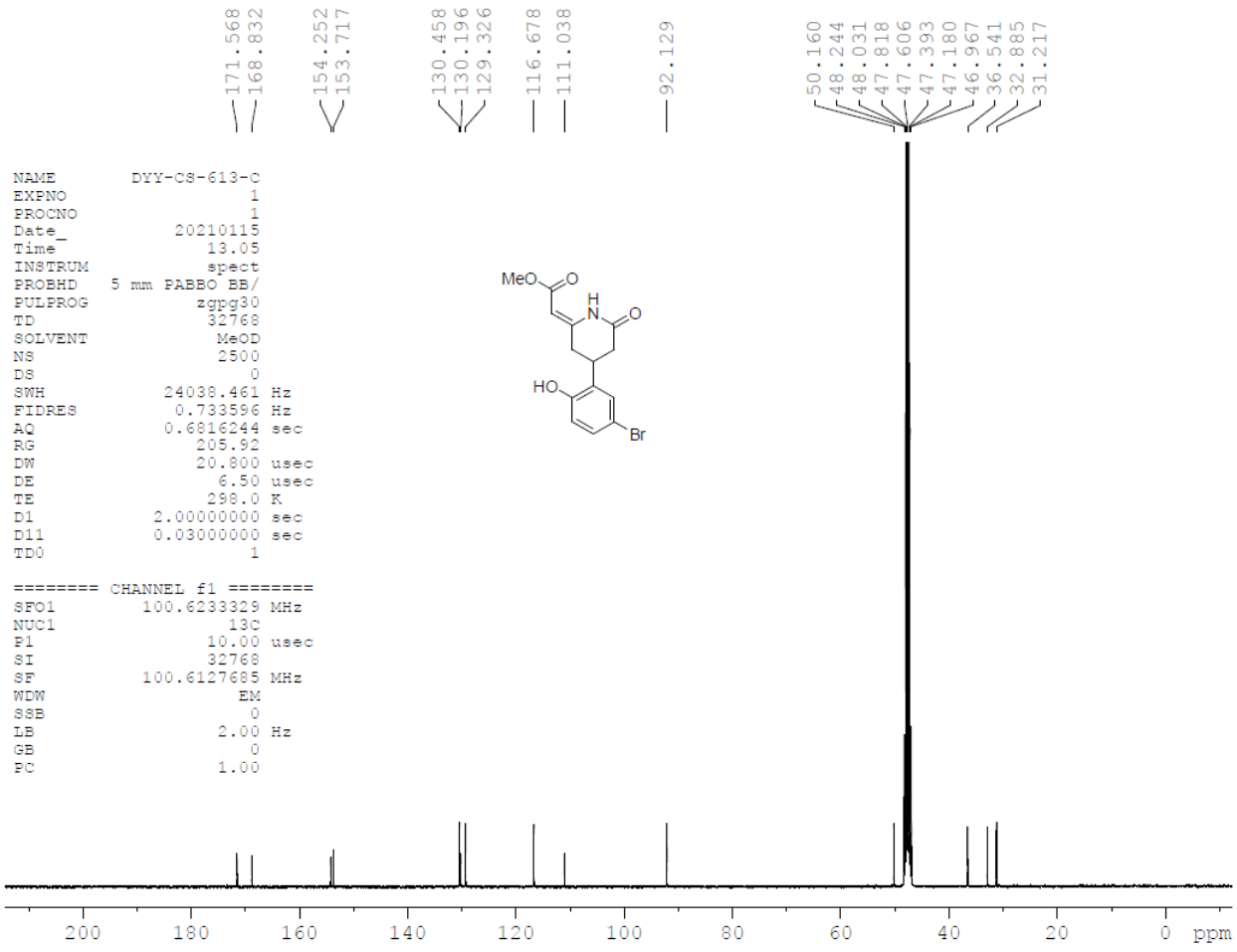
^{13}C NMR of compound **9b** ($CDCl_3$)



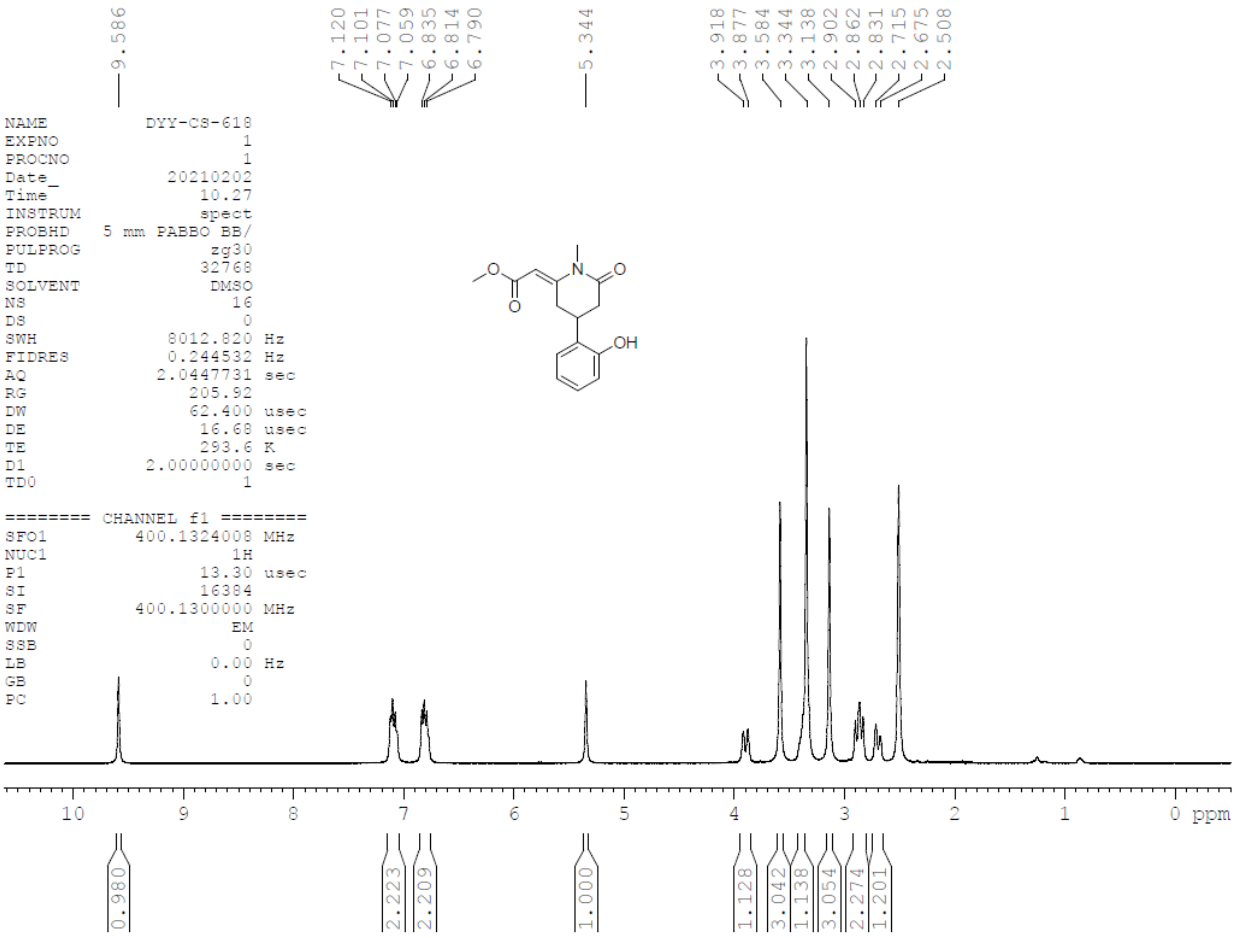
^{1}H NMR of compound **9c** ($CDCl_3$)



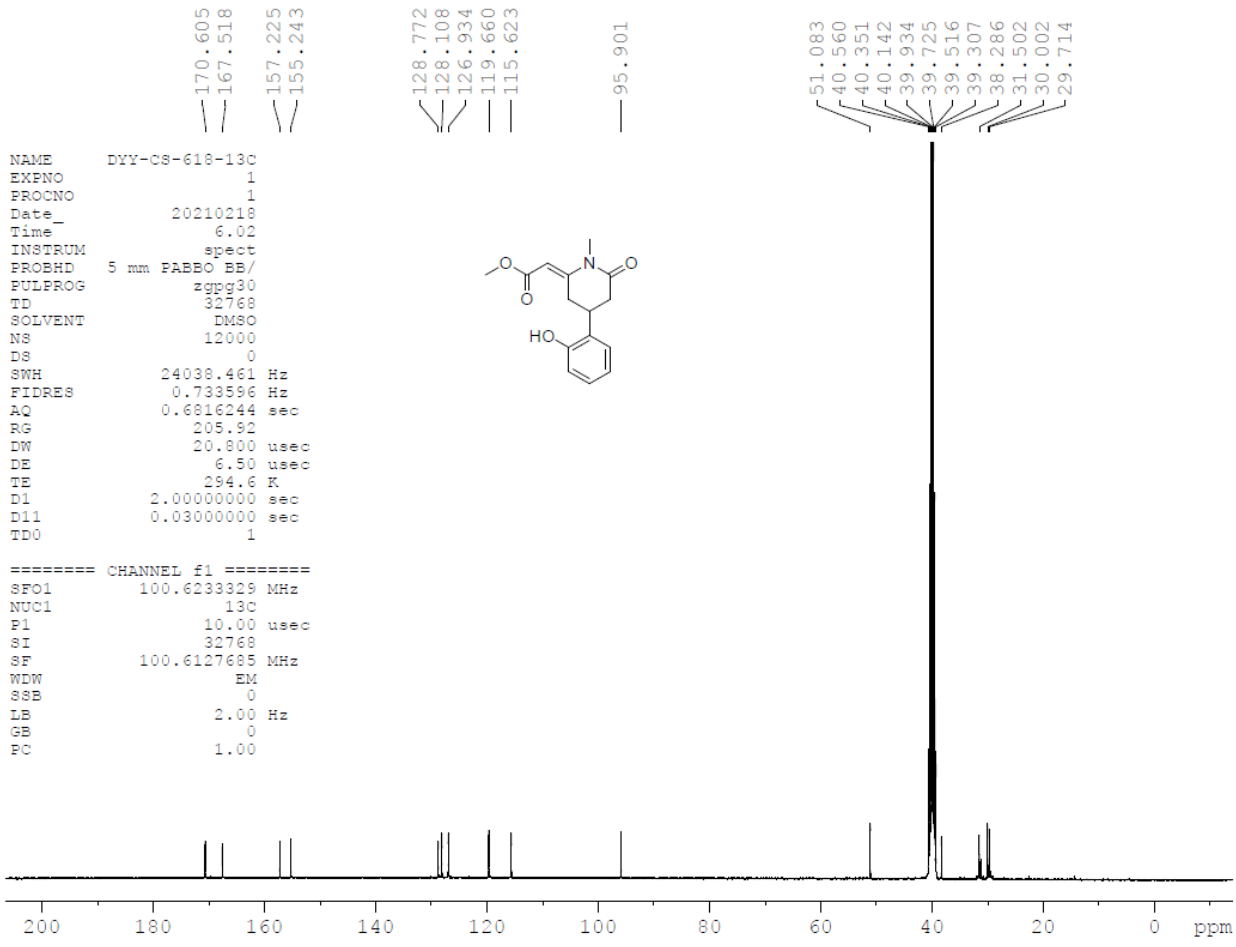
^{13}C NMR of compound **9c** ($CDCl_3$)



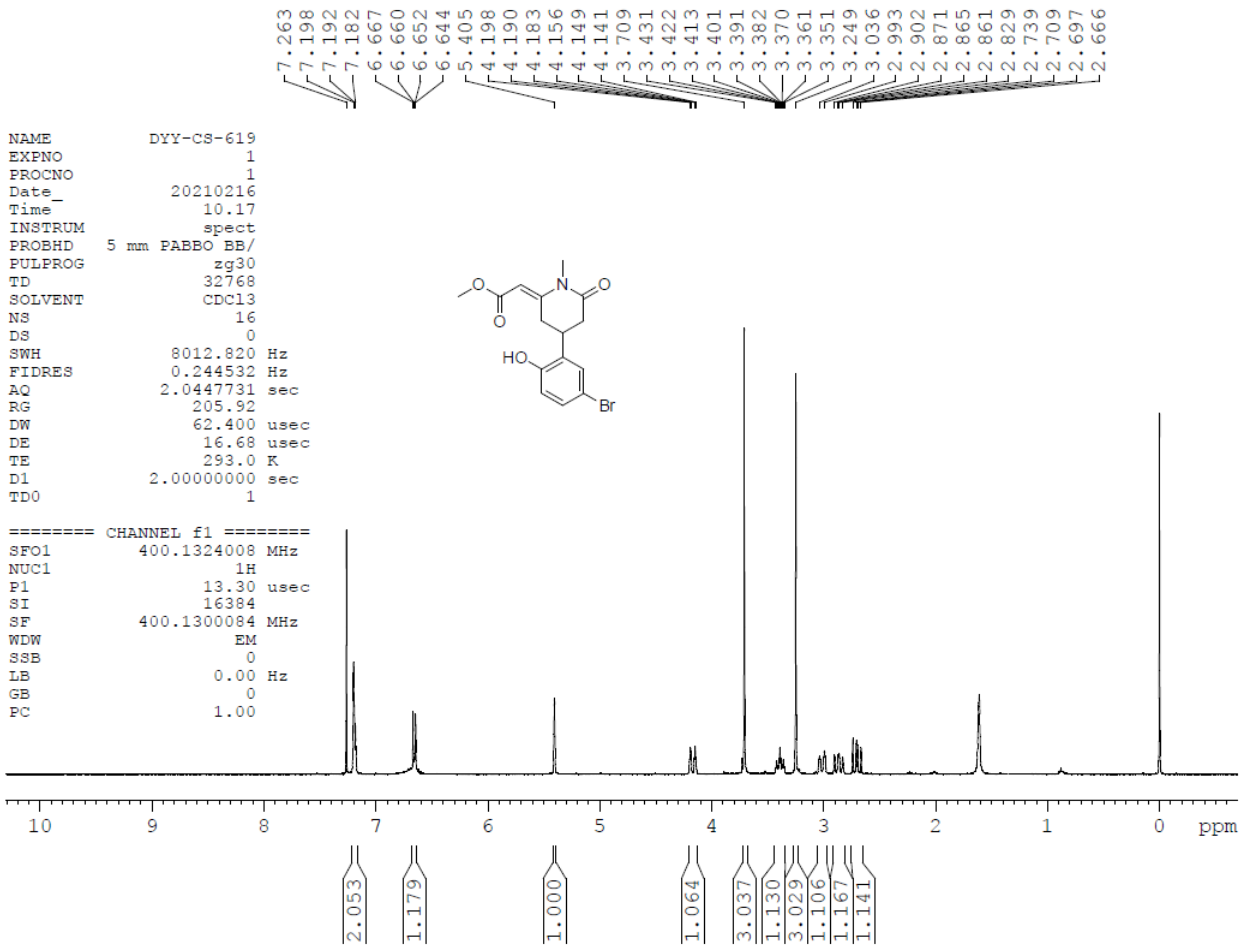
^{1}H NMR of compound **9d** ($CDCl_3$)



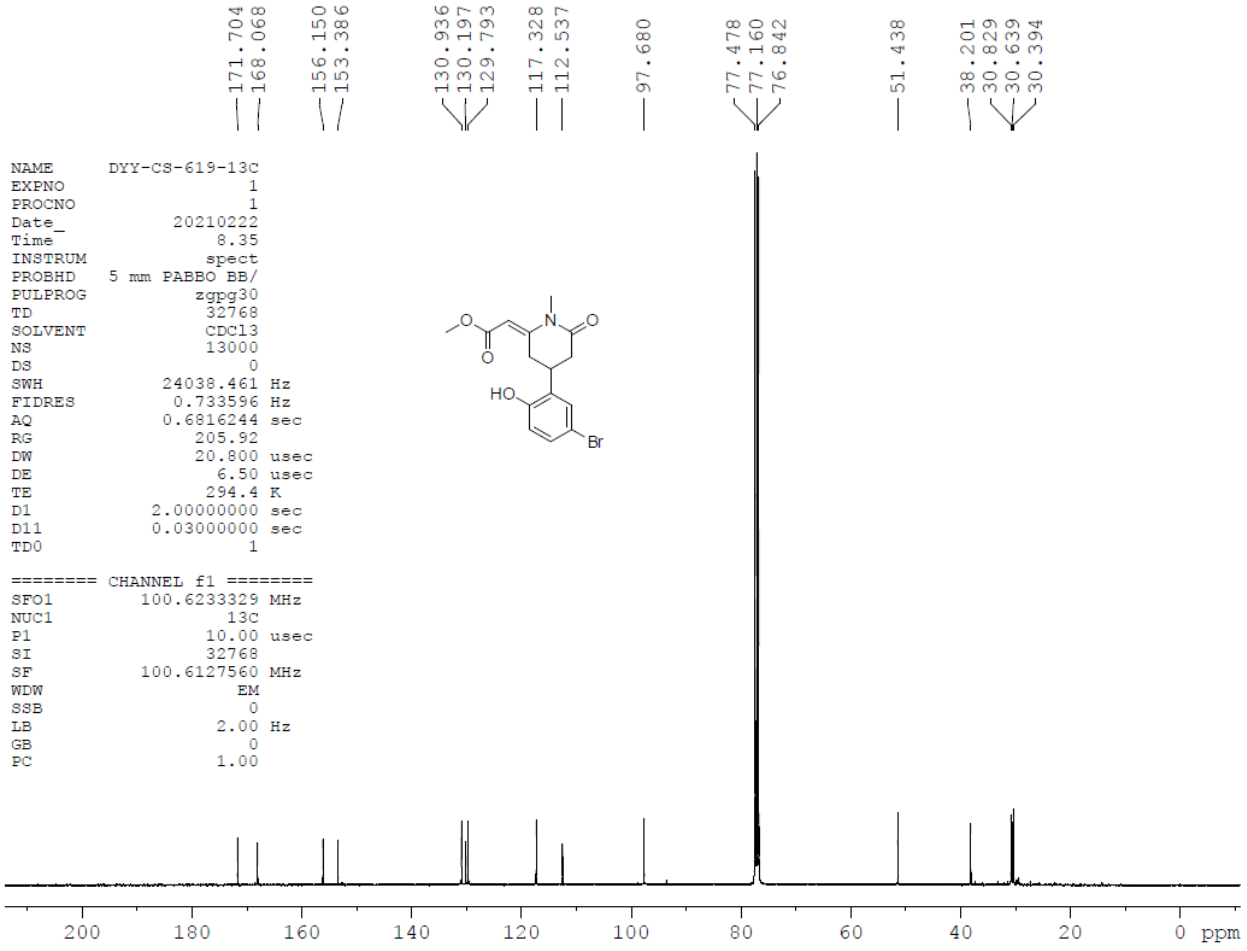
^{13}C NMR of compound **9d** (DMSO-d_6)



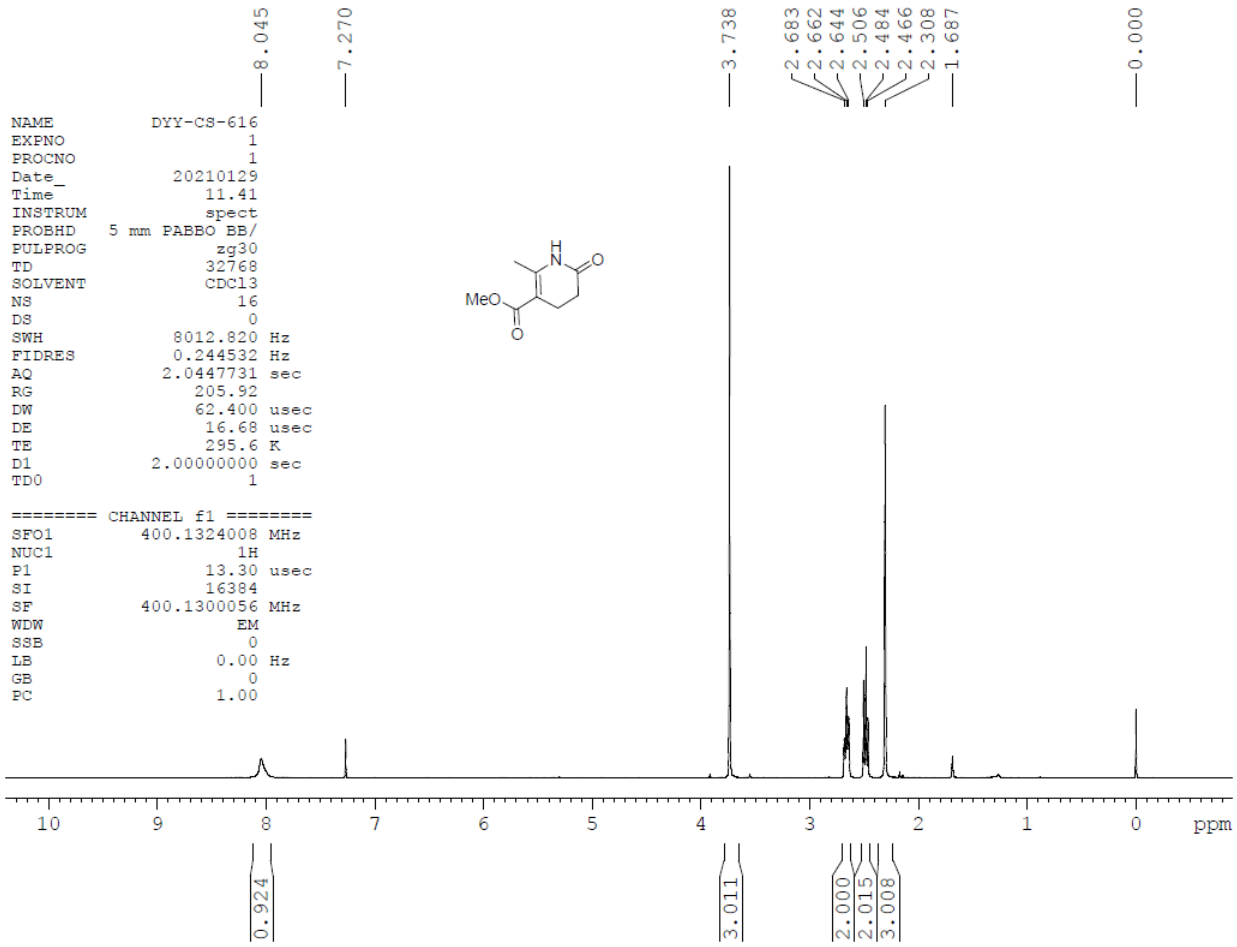
^{1}H NMR of compound **9e** ($CDCl_3$)



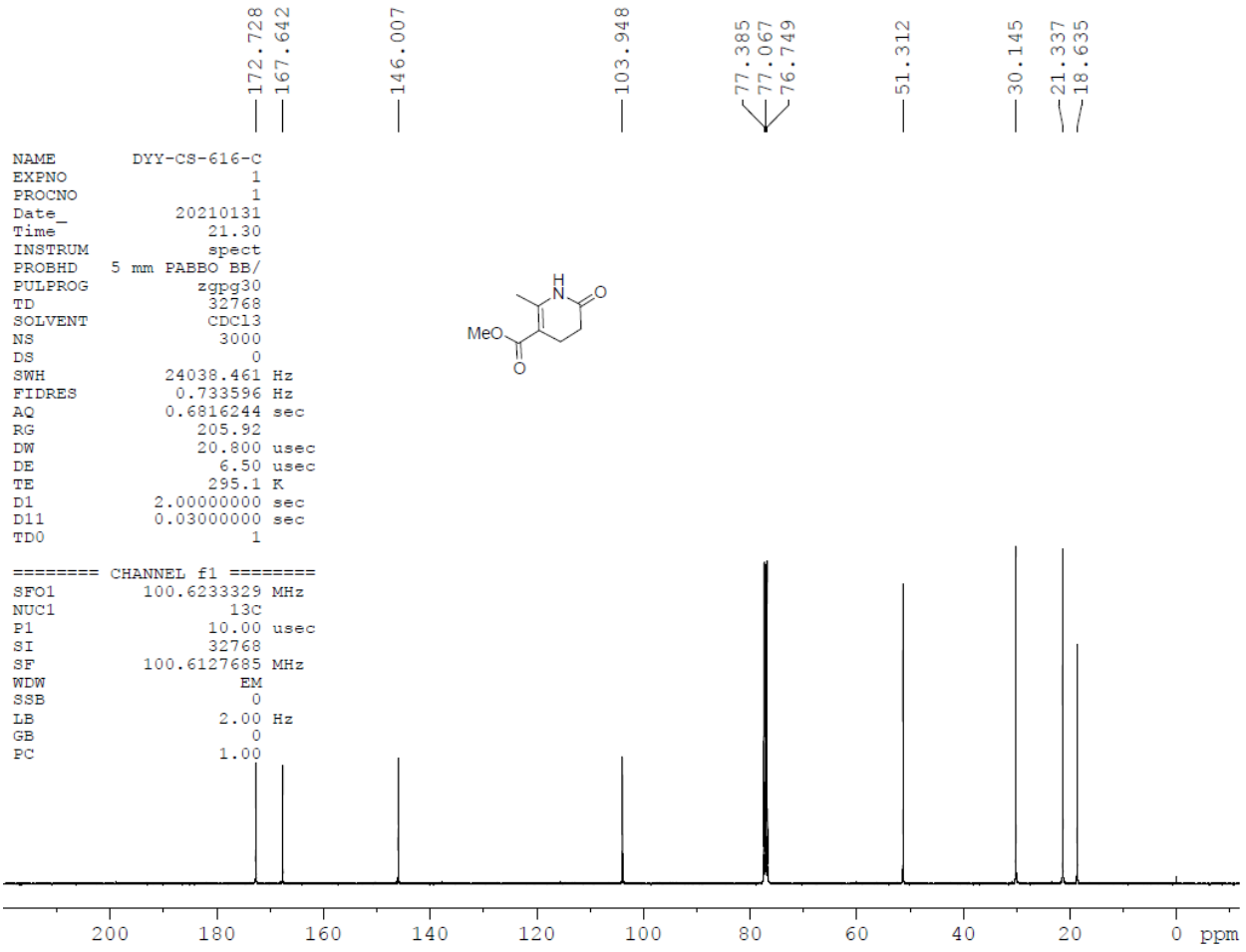
^{13}C NMR of compound **9e** ($CDCl_3$)



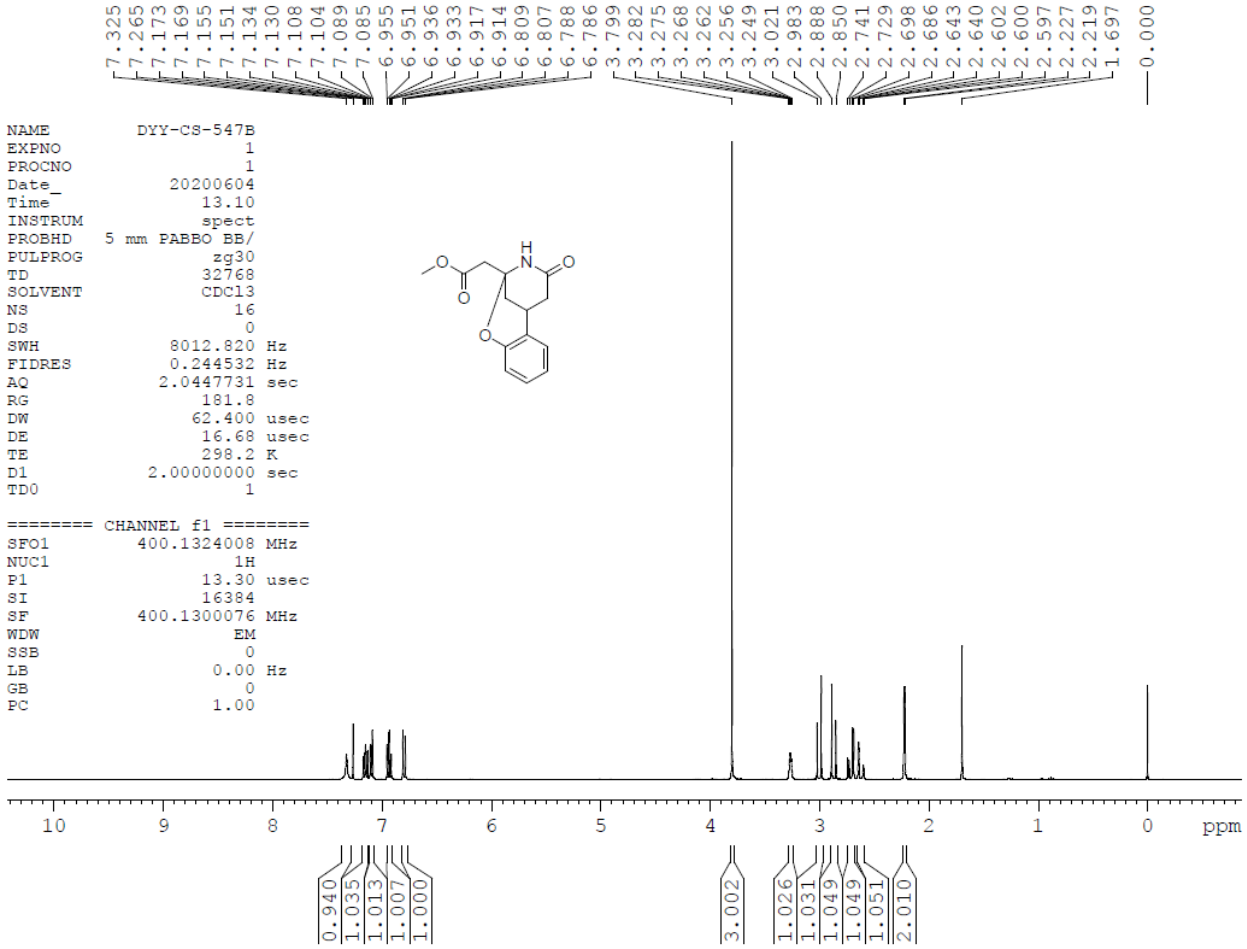
^{1}H NMR of compound **14** ($CDCl_3$)



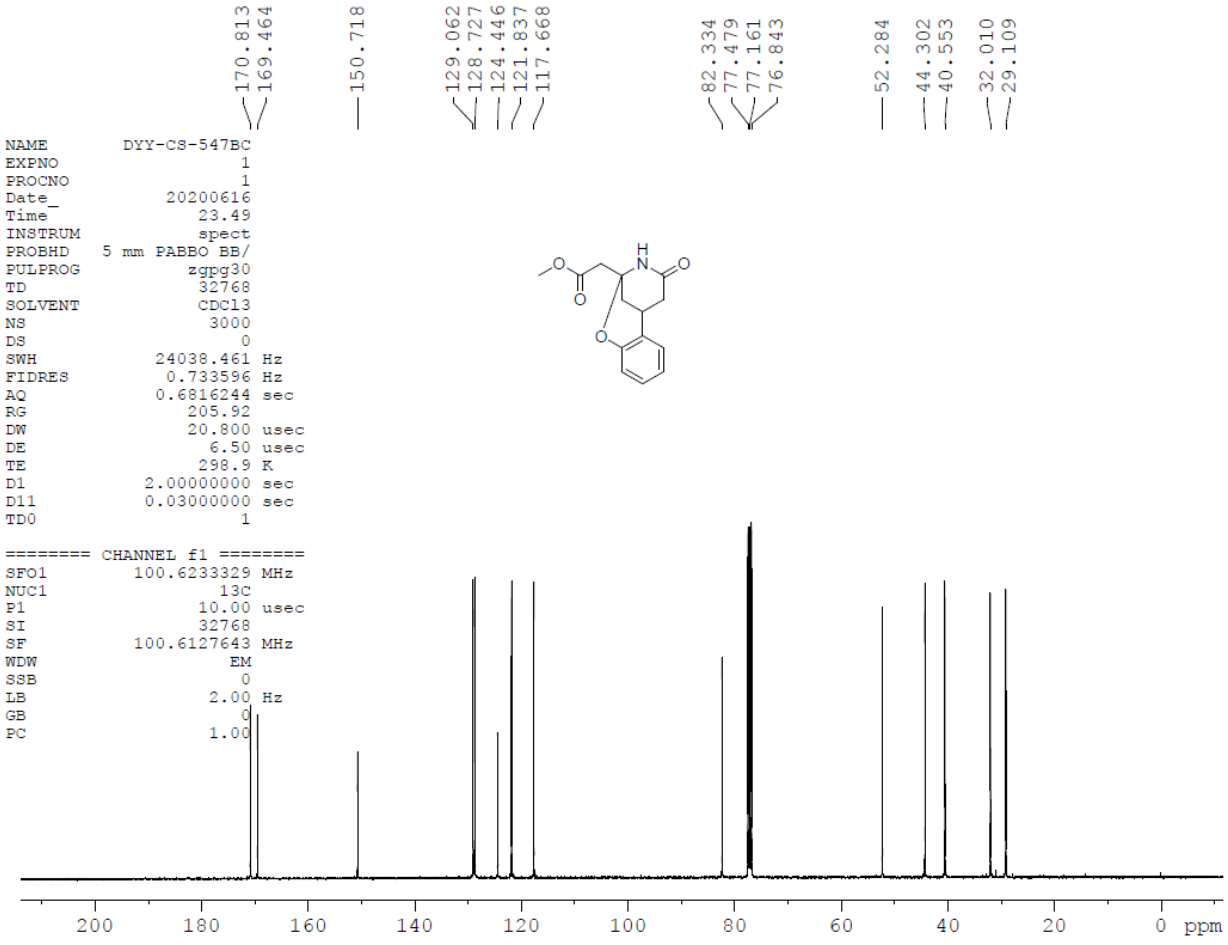
^{13}C NMR of compound **14** ($CDCl_3$)



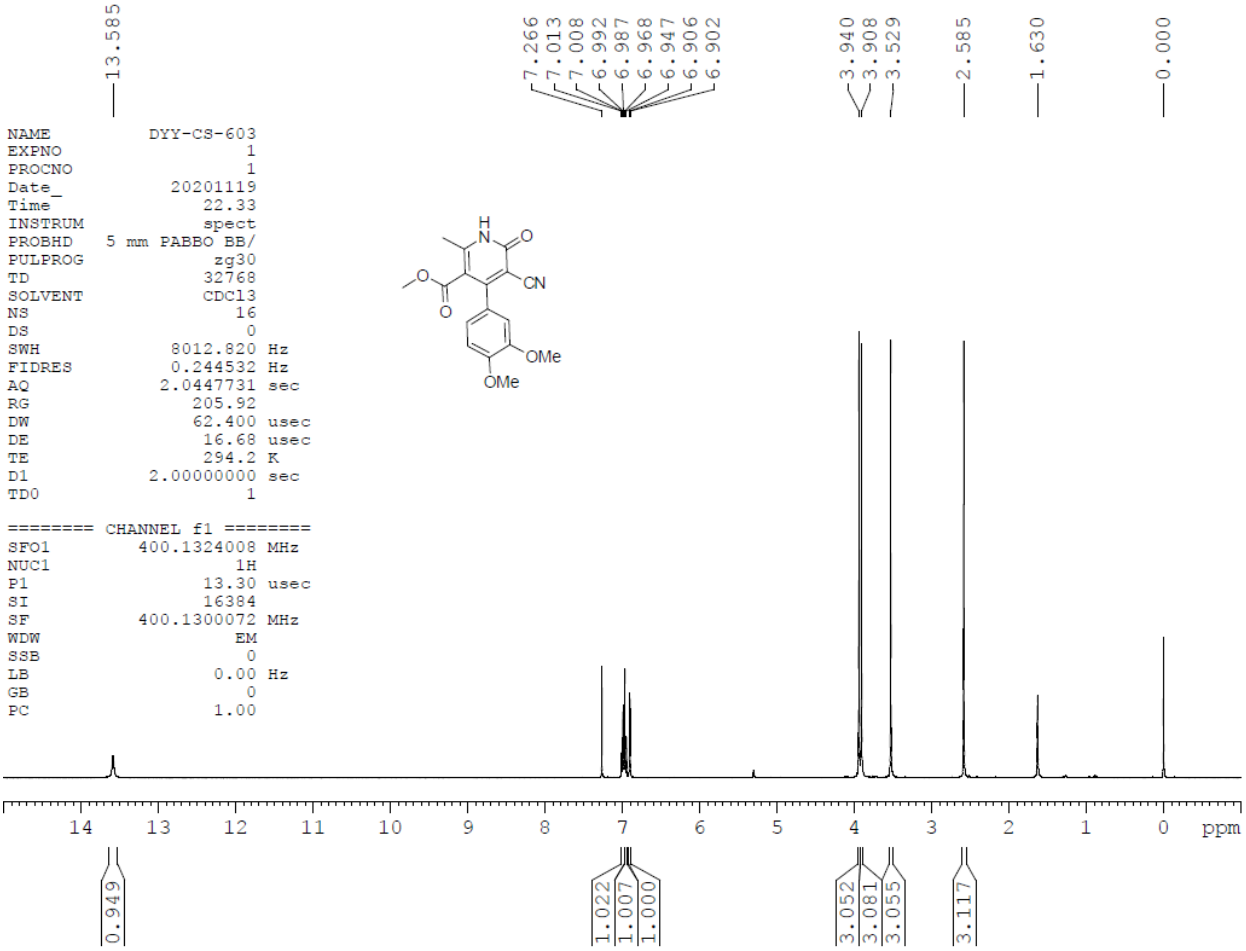
^{1}H NMR of compound **25** ($CDCl_3$)



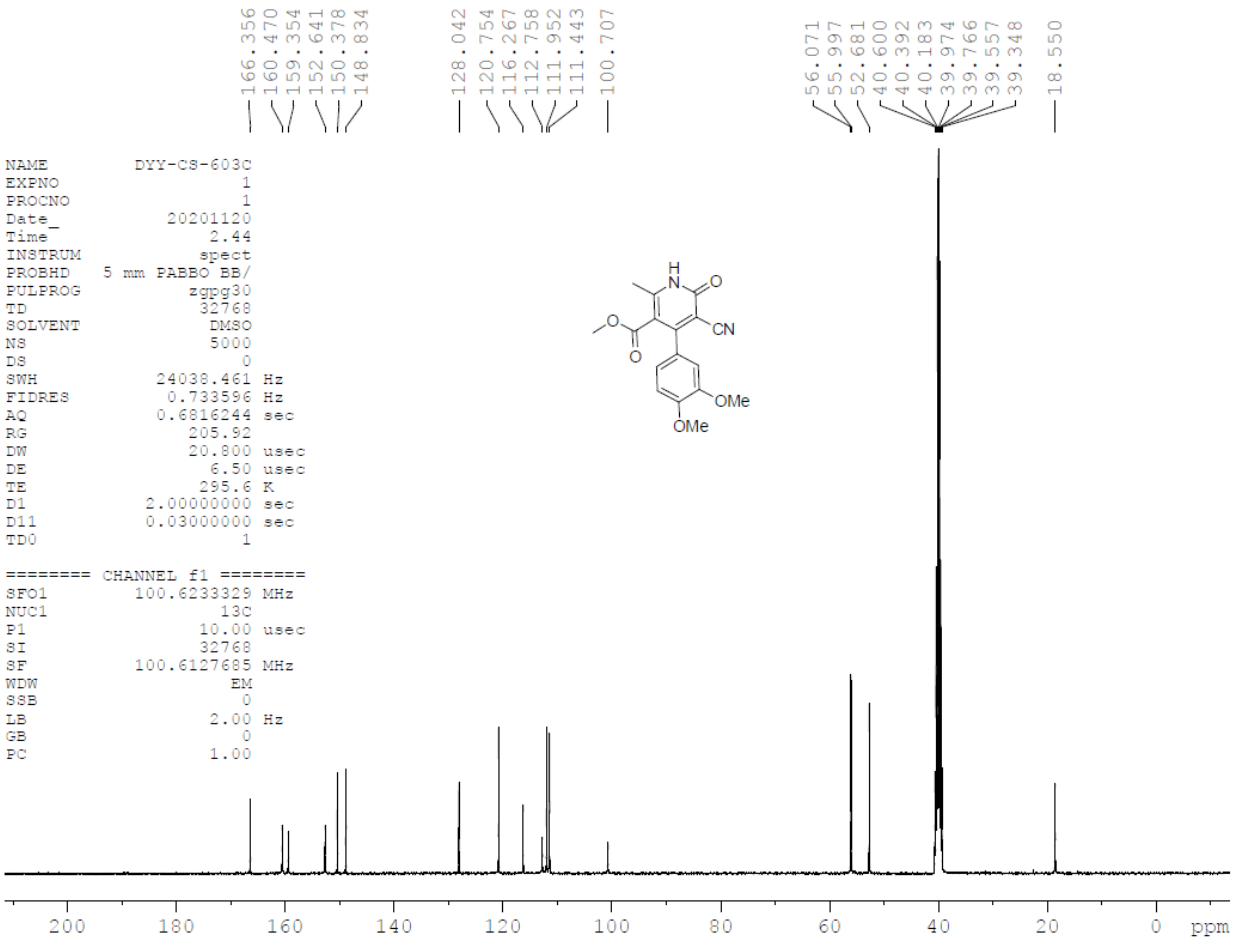
^{13}C NMR of compound **25** ($CDCl_3$)



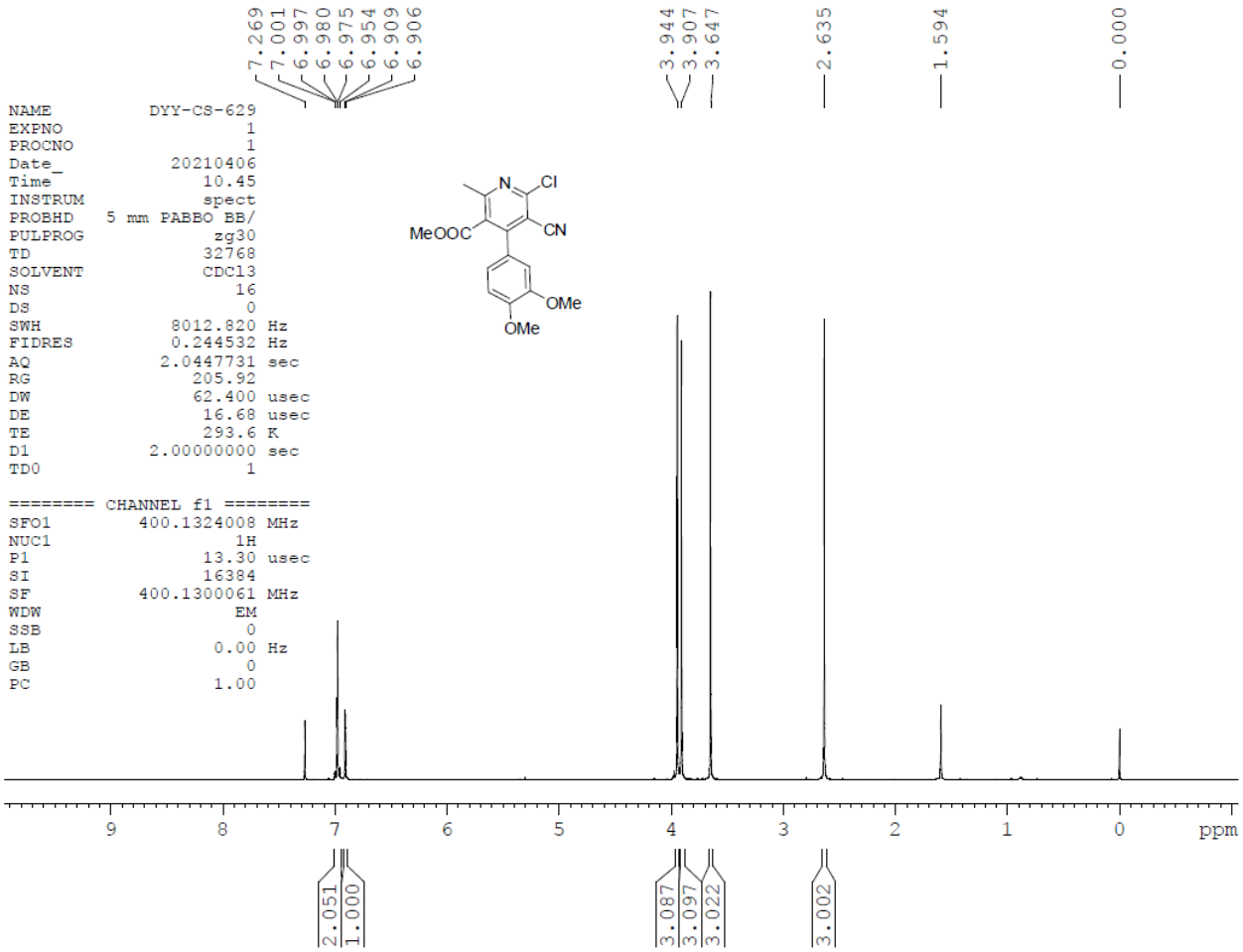
^{1}H NMR of compound **26** ($CDCl_3$)



^{13}C NMR of compound **26** (DMSO-d_6)



^{1}H NMR of compound **27** ($CDCl_3$)



^{13}C NMR of compound **27** ($CDCl_3$)