E-Z Isomerization of 3-benzylidene-indolin-2-ones using a microfluidic photo-reactor

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1. General

1.1. Materials and methods

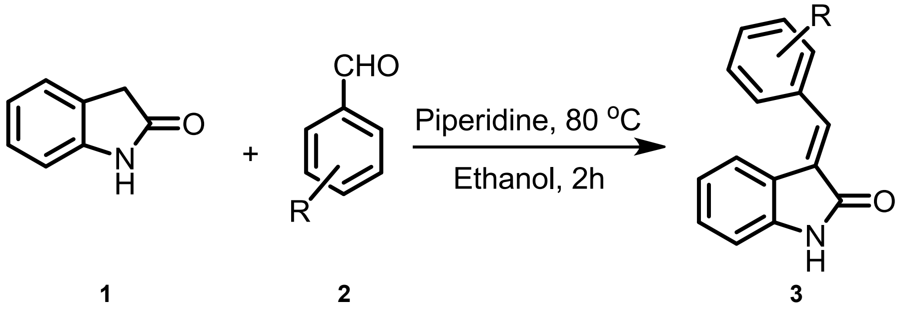
Most of the reagents and chemicals bought from sigma-aldrich as used as such without any further purification. Common organic chemicals and salts were purchased from Avra chemicals, India. Deionized water (18.2 mS conductivity) was used in all experiments. All work-up and purification procedures were carried out with reagent-grade solvents in air. Analytical thin-layer chromatography (TLC) was performed using analytical chromatography silica gel 60 F254 precoated plates (0.25 mm). The developed chromatogram was analysed by UV lamp (254 nm). PFA (id = 500 µm) tubing, T-junction, high-purity PTFE tubing was purchased from Upchurch IDEX HEALTH & SCIENCE. Asia syringe pump, heating system, back pressure controller (BPR), valve, catalytic reactor, Asia Manager PC software system bought from Syrris Asia System. Medium pressure lamp bought from lelesil Mumbai, India. Blue, red. Green LED and low pressure bulb bought from local market.

1.2. Analysis: High-resolution mass spectra (HRMS) were obtained from a JMS-T100TD instrument (DART) and Thermo Fisher Scientific Exactive (APCI). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 600, 500, 400 or 300 MHz in CDCl3 or DMSO-d6 solvent. Chemical shifts for 1H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quin = quintet, sext = sextet, m = multiplet), coupling constant (Hz), and integration. GC/MS analysis was conducted on an Simadzu technology GCMS-QP2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard) and inbuilt MS 5975C VL MSD system with triple axis detector. FTIR spectra were recorded on Alpha (Bruker) infrared Spectrophotometer.

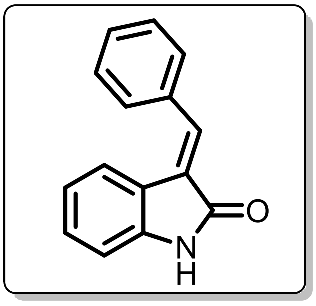
Abbreviations: Ethanol = EtOH, methanol = MeOH, dimethyl sulfoxide = DMSO, dichloromehane = $CHCl_2$, chloroform = $CHCl_3$, carbon tetrachloride = CCl_4, N, N-dimethylacetamide = DMA, acetonitrile = ACN, N, N-dimethyl formamide = DMF, tetrahydrofuran = THF, EtOAc = ethyl acetate.

2. General catalytic reaction procedure and characterization of products in details.

2.1. Preparation of starting materials 3a-3i:

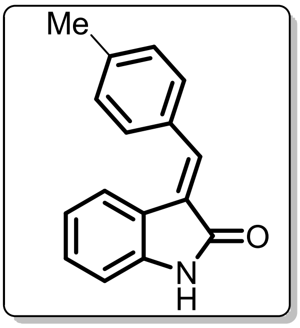


Previously reported method has been applied for the synthesis of starting materials.[1] To a stirred solution of oxindole (1) (1.0 eq) and appropriate aldehyde (**2a**-**2i**) (2.0 eq) in ethanol (5 mL) was treated with piperidine (0.1 eq), reflux for 2h. It was cooled evaporated the EtOH under reduced pressure to get crude, crude was washed with MeOH : Hexane (1:9) to give compound *E*-Isomer (**3a**-**3i**) and detail physical properties and spectra given below.

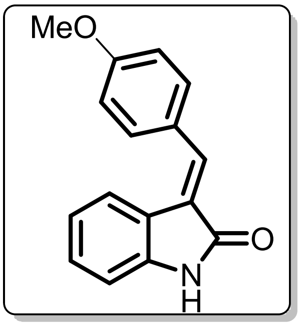


(*E*)-3-benzylideneindolin-2-one (3a): Starting material **3a** was prepared according to general procedure mentioned in section 2.1. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 90:10) to provide a yellow color solid 1.44 g (86% yield). The spectra data matched with values reported in the literature[2]. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.77 (s, 1H), 7.56-7.59 (m, 3H), 7.44-7.39 (m, 3H), 7.15 (td, *J* = 7.7, 1.1 Hz, 1H), 6.81-6.79 (m, 2H). **^{13}C NMR** (100 MHz, Acetone-d_6) δ 173.8, 148.2, 140.8, 140.3, 135.2, 134.7, 134.4, 133.9, 133.2, 127.9, 126.7, 126.3, 115.2. **IR** (**KBr**) ν_{max} = 739. 14, 1200.65, 1620.24, 1707.54, 3191.06 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{15}H_{12}NO$ $[M+H]^+$: 222.0919; found: 222.0910.

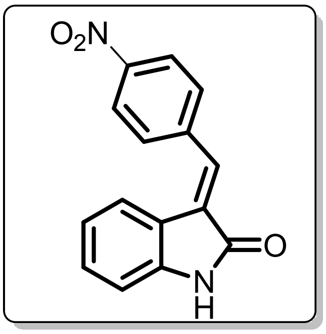
(*E*)-3-(4-methylbenzylidene)indolin-2-one (3b): Starting material **3b** was prepared according to general procedure mentioned in section 2.1. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 90:10) to provide a yellow color solid 790 mg (89% yield). The spectra data matched with values reported in the literature.[3] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 3.0 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.21 (td, *J* = 7.7, 0.9 Hz, 1H), 6.96-6.84 (m, 2H), 2.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.9, 141.7, 140.1, 137.8, 131.9, 129.7, 129.5, 129.4, 127.0, 122.9, 121.8, 121.7, 110.4, 21.6. **IR** (**KBr**) **ν_{max}** = 739.99, 1457.78, 1604.45, 1692.37, 3015.31 cm^{-1}. **HRMS (ESI) :** m/z calcd for $C_{16}H_{14}NO[M+H]^+$: 236.1075; found: 236.1053.



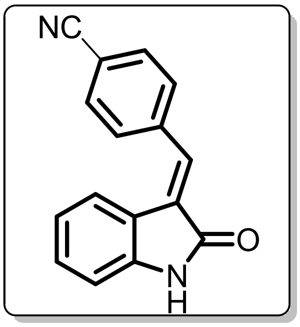
(***E*)-3-(4-methoxybenzylidene)indolin-2-one (3c)**: Starting material **3c** was prepared according to general procedure mentioned in section 2.1. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 90:10) to provide a deep yellow solid 780 mg (82% yield). The spectra data matched with values reported in the literature.[4] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.79 (s, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.90-6.88 (m, 2H), 3.89 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$+DMSO-d_6) δ 174.9, 165.5, 147.3, 141.1, 136.1, 134.2, 131.9, 131.0, 127.1, 126.5, 125., 118.8, 115.0, 60.1. **IR** (**KBr**) **ν_{max}** = 745.72, 1254.68, 1604.80, 1702.60, 3185.27 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{16}H_{14}NO_2$ $[M+H]^+$: 252.1025; found: 252.1015.



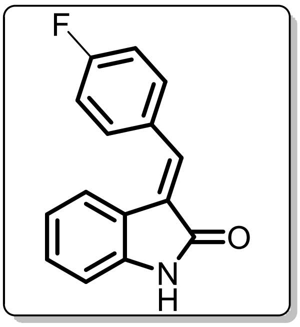
(*E*)-3-(4-nitrobenzylidene)indolin-2-one (3d): Starting material **3d** was prepared according to general procedure mentioned in section 2.1. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 90:10) to provide an orange color solid 800 mg (80% yield). The spectra data matched with values reported in the literature.[5] **^{1}H NMR** (300 MHz, $CDCl_3$+DMSO-d_6) δ 10.25 (s, 1H), 8.24 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.59 (s, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.73 (t, *J* = 7.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$+DMSO) δ 173.7, 152.5, 148.5, 146.7, 137.2, 135.7, 135.6, 134.9, 128.7, 127.8, 126.2, 125.4, 115.4. **IR** (**KBr**) ν_{max} = 770.19, 1345.90, 1712.69, 2947.06, 3173.90 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{15}H_{11}N_2O_3$ $[M+H]^+$: 267.0770; found: 267.0775.

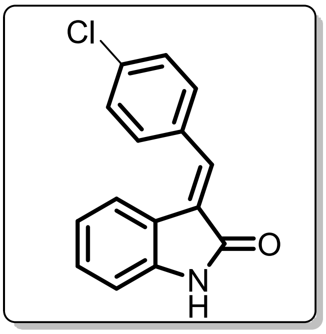


(*E*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile (3e): Starting material **3e** was prepared according to general procedure mentioned in section 2.1. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 90:10) to provide an orange solid 800 mg (86% yield). The spectra data matched with values reported in the literature.[6] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.81 – 7.72 (m, 5H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.31 – 7.22 (m, 1H), 6.89(m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$+DMSO-d_6) δ 169.0, 143.3,139.7,132.8, 132.2, 130.6, 130.3, 129.6, 122.7, 121.2, 120.5, 118.3, 112.2, 110.5. **IR** (**KBr**) ν_{max} = 627.94, 743.57, 1610.58, 1711.04, 2221.85, 2748.85, 3173.25 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{16}H_{11}N_2O[M+H]^+$: 247.0871; found : 247.0884.



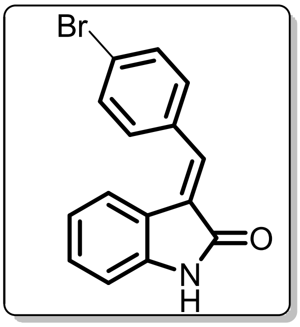
(*E*)-3-(4-fluorobenzylidene)indolin-2-one (3f): Starting material **3f** was prepared according to general procedure mentioned in section 2.1. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 90:10) to provide a light yellow solid 745 mg (82% yield). The spectra data matched with values reported in the literature.[6] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.78 (s, 1H), 7.69-7.64 (m, 2H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.25-7.15 (m, 3H), 6.91-6.87 (m,2H). **^{13}C NMR** (75 MHz, $CDCl_3$+DMSO-d_6) δ 174.5, 169.4, 166.1, 147.7, 139.6, 136.1, 136.0, 135.8, 135.8, 134.7, 132.9, 127.3, 126.0, 120.7, 120.4, 115.2. **IR (KBr)** ν_{max} = 782.56, 1605.52, 1709.78, 3025.70, 3144.68 cm^{-1}. **HRMS (ESI) :** m/z calcd for $C_{15}H_{11}NOF[M+H]^+$: 240.0825; found : 240.0820.



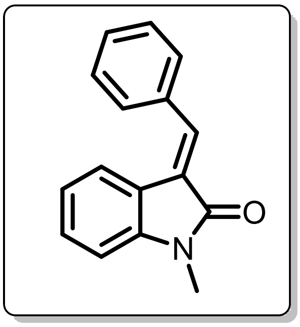


(*E*)-3-(4-chlorobenzylidene)indolin-2-one (3g): Starting material **3g** was prepared according to general procedure mentioned in section 2.1. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 90:10) to provide a light yellow solid 785 mg (82% yield). The spectra data matched with values reported in the literature.[6] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.75 (s, 1H), 7.59 -7.57 (m, 3H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 6.90-6.88 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$+DMSO-d_6) δ 169.6,142.7,135.0,134.6,133.4, 130.5, 130.0, 128.8, 128.6, 122.6, 121.2, 121.1, 110.4. **IR (KBr)** ν_{max} = 746.03, 1622.59, 1714.78, 3078.02, 3174.84 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{15}H_{11}NOCl[M+H]^+$: 256.0529; found: 256.0523.

(*E*)-3-(4-bromobenzylidene)indolin-2-one (3h): Starting material **3h** was prepared according to general procedure mentioned in section 2.1. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 90:10) to provide a light yellow solid 1.09 g (95% yield). mp: 193-195 °C. The spectra data matched with values reported in the literature.[1] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.72 (s, 1H), 7.63 – 7.51 (m, 5H), 7.25 – 7.21 (m, 1H), 6.91 – 6.86 (m, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 168.9, 143.6, 134.8, 134.2, 132.3, 131.8, 130.9, 128.6, 123.4, 123.0, 121.7, 121.1, 110.7. **IR** (**KBr**) **ν_{max}** = 744.99, 1468.79, 1621.59, 1713.85, 3078.37, 3174.68 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{15}H_{11}NOBr[M+H]^+$: 300.0024; found: 300.0020.



(*E*)-3-benzylidene-1-methylindolin-2-one (3i): Starting material **3i** was prepared according to general procedure mentioned in section 2.1. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 90:10) to provide a yellow solid 750 mg (73.52% yield). The spectra data matched with values reported in the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.66 – 7.61 (m, 3H), 7.49 – 7.40 (m, 3H), 7.29 – 7.25 (m, 1H), 6.88 (td, *J* = 7.6, 0.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 3.29 (s, 3H). **^{13}C NMR** (101MHz, $CDCl_3$): δ 168.5, 144.3, 137.2, 135.0, 129.8, 129.5, 129.3, 128.6, 127.2, 122.7, 121.8, 121.1, 108.2, 26.2. **IR** (**KBr**) **ν_{max}** = 749.73, 1606.28, 1703.78, 2927.62, 3021.68, 3056.48. **HRMS (ESI):** m/z calcd for $C_{16}H_{14}NO[M+H]^+$: 236.1075; found 236.1081.



2.2. Procedure for photo-flow under controlled condition for the synthesis of *Z*-isomer 4a-4i:

Homemade photo- batch reactor bought from lelesil Mumbai, India and slightly modified for the continuous flow reaction. The home-made photo-flow reactor detail design are available in our previous study.[7] A 0.25 M solution of E-oxindole was taken in bottle the reaction mixture was passed through perfluoroalkoxy (PFA) coil reactor [inner diameter (ID) 1.0 milimeter (mm)", length 9 meter, volume = 7.8 ml]. The tubing reactor was wrapped within the helical grooves around a cylindrical-shaped frame. The reactor was cooled by circulating chilled water. The cylindrical reactor was irradiated by medium pressure lamp beam of 250W Hg (Xe) arc lamp was placed in between the reactor (Figure S1). The product mixture from the end of capillary reactor as an outlet was collected into a flask.

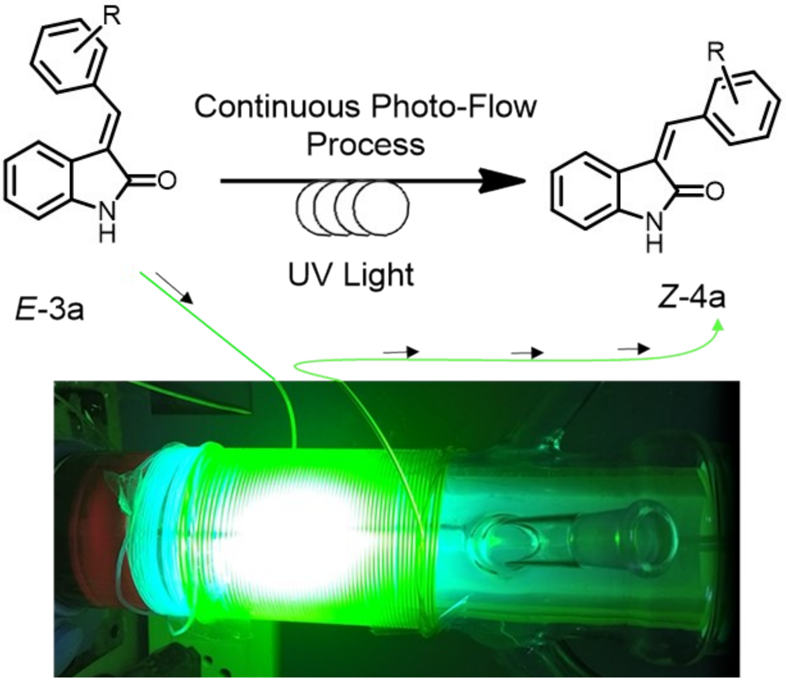


Figure S1. Flow-diagram of photo-flow isomerization reaction of 3-benzylidene-indolin-2-ones.

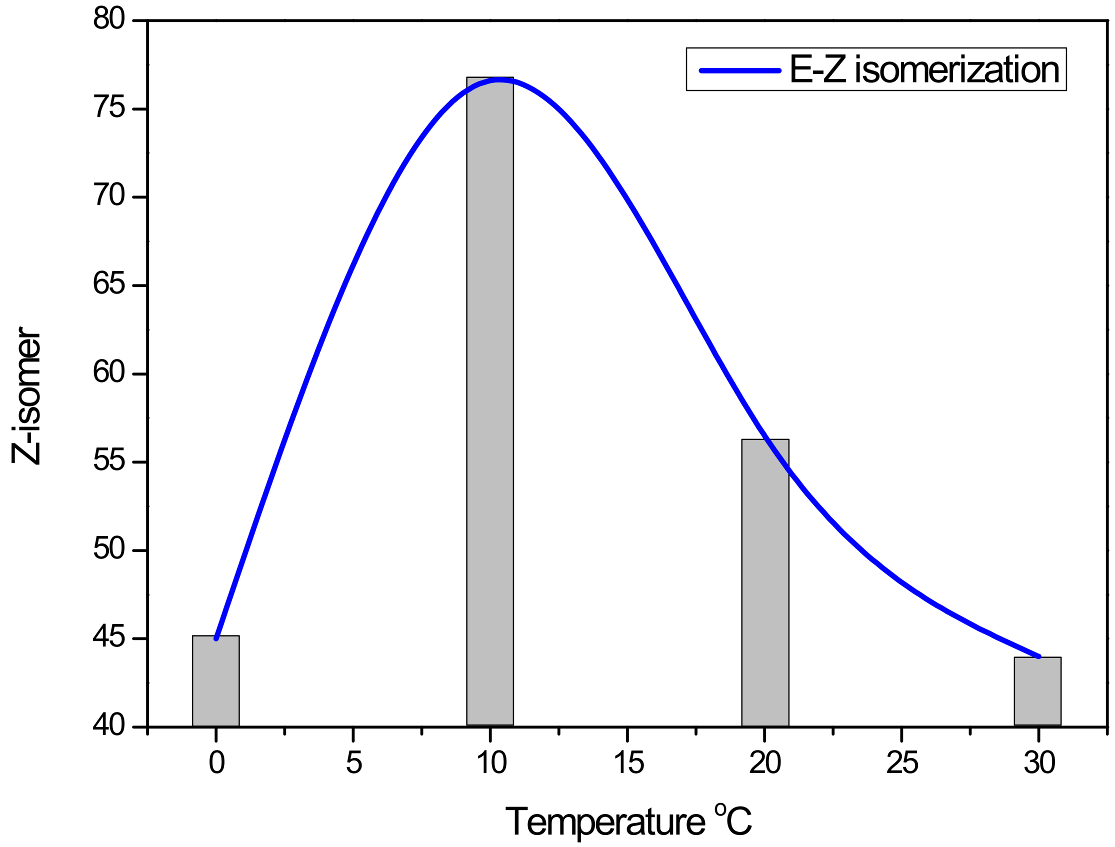
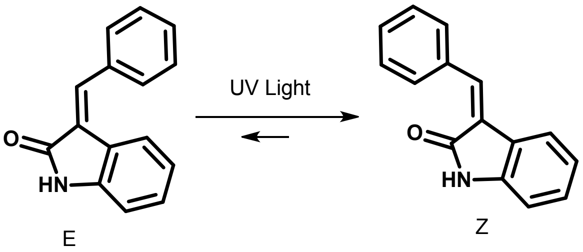


Figure S2. Temperature dependent study of model reaction **3a**.

Table S1. Solvent effect in photostationary state of model reaction **3a**.



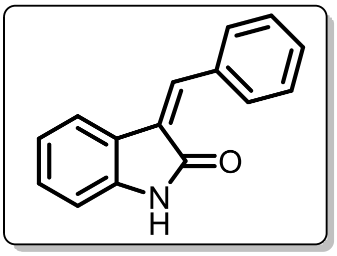
S.N.	**Solvent**	**Dipole moment**	**Relative dielectric constant**	**Light cut-off**	***E*-Isomer Yield (%)[a]**	***Z*-Isomer Yield (%)[a]**
1	Toluene	0.36	2.38	285	39	61
2	DMSO	3.96	46.45	277	43	57
3	CH_2Cl_2	1.6	8.93	230	61	39
4	$CHCl_3$	1.04	4.81	245	69	31
5	CCl_4	0	7.58	265	65	35
6	MeOH	1.7	32.66	205	36	64
7	Acetone	2.88	20.56	330	32	68
8	DMA	3.7	24.2	270	29	71
9	1,4-Dioxane	0.45	2.21	230	37	63
10	Pyridine	2.37	12.91	305	55	45
11	ACN	3.92	35.94	190	62	38
12	Chlorobenzene	1.54	31.2	-	44	56
13	DMF	3.86	19.9	268	34	76
14	Cyclohexanone	-	-	-	75	35

[a] Yields are based on the LC-MS.

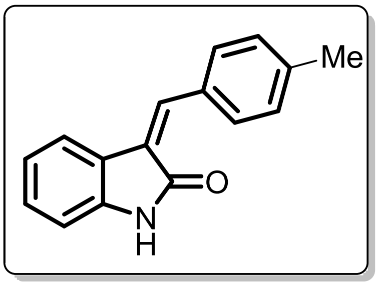
2.3. Procedure for integrated photo-flow condition for the synthesis of Z-isomer.

A 0.25 M solution of E-oxindole was taken in bottle the reaction mixture was passed through perfluoroalkoxy (PFA) coil reactor [inner diameter (ID) 1.0 milimeter (mm)", length 9 meter, volume = 7.8 ml]. The tubing reactor was wrapped within the helical grooves around a cylindrical-shaped frame. The reactor was cooled by circulating chilled water. The cylindrical reactor was irradiated by medium pressure lamp beam of 250W Hg (Xe) arc lamp was placed in between the reactor (Figure S1). The product mixture from the end of capillary reactor as an outlet was collected into a flask. The out-flowing product mixture was quenched with water and DCM solvent by introducing through an additional x-mixer to form organic-aqueous droplets. Complete extraction between the organic-aqueous segments was observed after 0.5 min retention time achieved by flowing through a PTFE capillary [(id= 1000 μm, length = 2.6 m, vol. = 2 mL]. Further, organic-aqueous segment was separated by passing through our designrd homemade micro separator and complete separation was achieved by regulating the back pressure and retention time (5.6 sec) along with the flow rate of DCM (1.25 mL/min) and water (1.25 mL/ min). The organic extract was concentrated and the resulting residue was purified by column chromatography (hexane/ethyl acetate) to give the product **4a-4h.**

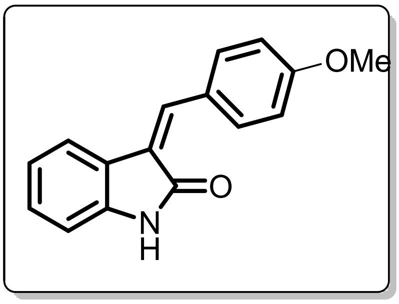
(*Z*)-3-benzylideneindolin-2-one (4a): 4a was prepared according to general procedure 2.



The crude material was purified by silica gel column chromatography (hexane/ethyl acetate; 70:30) to provide deep yellow solid (71% yield), EtOAc: Hexane (30:70); The spectral data matched with values reported in literature.[4] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 – 8.18 (m, 2H), 7.96 (s, 1H), 7.49 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.35 (m, 3H), 7.16 (td, *J* = 7.7, 1.1 Hz, 1H), 6.97 (td, *J* = 7.6, 0.9 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (125 MHz, Acetone-d_6) δ 167.1, 141.0, 136.5, 134.4, 132.1, 130.2, 128.9, 128.1, 126.9, 125.4, 121.2, 119.5, 109.3. **IR (KBr) ν_{max}** = 738.25, 1205.47, 1607.40, 1692.09, 2926.97, 3174.64, cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{15}H_{12}NO[M+H]^+$: 222.0919; found: 222.0911.

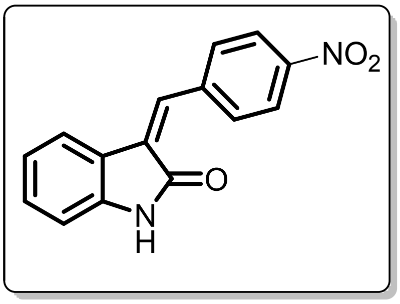


(*Z*)-3-(4-methylbenzylidene)indolin-2-one (4b): 4b was prepared according to general procedure 2. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate; 70:30) to provide yellow solid (58% yield), EtOAc : Hexane(30:70) ; The spectral data matched with values reported in literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.2 Hz, 2H), 7.78 (s, 1H), 7.54 – 7.50 (m, 2H), 7.27 (d, *J* = 6.9 Hz, 2H), 7.21 (dt, *J* = 7.7, 3.8 Hz, 1H), 7.04 (td, *J* = 7.6, 0.9 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 2.41 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$+DMSO-d_6) δ 167.8, 140.6, 140.5, 136.6, 131.9, 131.2, 128.8, 128.4, 126.0, 125.2, 121.0, 118.8, 109.5, 21.5. **IR (KBr) ν_{max}** = 736.04, 1202.63, 1605.85, 1689.22, 2926.16, 3028.13, 3172.19 cm^{-1}. **HRMS (ESI) :** m/z calcd for $C_{16}H_{14}NO[M+H]^+$: 236.1075; found:236.1067.



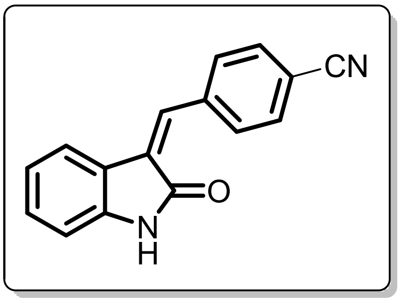
(*Z*)-3-(4-methoxybenzylidene)indolin-2-one (4c): 4c was prepared according to general procedure 2. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate; 70:30) to provide orange solid (59% yield), EtOAc : Hexane (30:70) ;The spectral data matched with values reported in literature.[4]

^{1}H NMR (300 MHz, CDCl$_3$) δ 8.37 (d, J = 8.8 Hz, 2H), 7.84 (s, 1H), 7.51 (t, J = 3.6 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.08 – 6.93 (m, 3H), 6.84 (d, J = 7.7 Hz, 1H), 3.88 (s, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$+DMSO-d$_6$) δ 172.8, 166.1, 145.2, 141.3, 139.1, 132.9, 131.9, 130.3, 129.4, 125.8, 123.5, 118.4, 114.3, 60.1. **IR** (**KBr**) ν_{max} = 775.30, 1215.61, 1601.54, 1690.61, 2930.18, 3014.35, 3169.98 cm^{-1}. **HRMS (ESI):** m/z calcd for C$_{16}$H$_{14}$NO$_2$[M+H]$^{+}$: 252.1025; found: 252.1016.

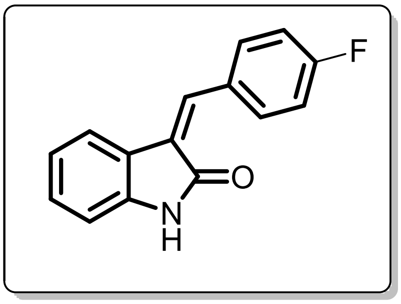


(*Z*)-3-(4-nitrobenzylidene)indolin-2-one (4d): 4d was prepared according to general procedure 2. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate; 70:30) to provide Red color solid 53 mg (53% yield), EtOAc : Hexane(30:70) ; The spectral data matched with values reported in literature.[5] **^{1}H NMR** (300 MHz, CDCl$_3$+DMSO-d$_6$) δ 10.13 (s, 1H), 8.40 (d, J = 8.8 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 5.1 Hz, 2H), 7.25 (t, J = 7.7 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$+DMSO) δ 166.7, 147.2, 141.5, 140.1, 132.9, 132.3, 130.3, 130.0, 129.8, 124.0, 123.6, 122.7, 121.1, 120.2, 109.5. **IR** (**KBr**) ν_{max} = 737.70, 782.41, 1151.20, 1329.75, 1580.17, 1683.10, 3144.60, cm^{-1}. **HRMS (ESI):** m/z calcd for C$_{15}$H$_{11}$N$_2$O$_3$[M+H]$^{+}$: 267.0770; found: 267.0763.

(*Z*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile (4e): **4e** was prepared according to general procedure 2. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate; 70:30) to provide Orange color solid 54 mg (54% yield), EtOAc : Hexane(30:70); mp: 203-205 °C; **^{1}H NMR** (500 MHz, CDCl$_3$) δ 8.29 (d, *J* = 8.4 Hz, 2H), 7.79 (s, 1H), 7.75 – 7.69 (m, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.49 (s, 1H), 7.29 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$+DMSO-d$_6$) δ 172.25, 146.35, 143.00, 138.06, 136.7, 136.4, 135.0, 134.7, 129.1, 126.3, 124.6, 123.5, 117.1, 114.8. **IR** (**KBr**) **ν_{max}** = 776.32, 1609.54, 1678.96, 2221.85, 3171.85, 3339.82 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{16}H_{11}N_2O[M+H]^+$: 247.0871; found: 247.0864.

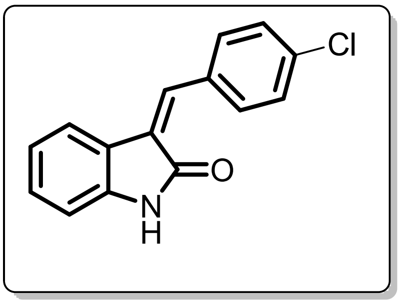


(*Z*)-3-(4-fluorobenzylidene)indolin-2-one (4f): **4f** was prepared according to general procedure 2. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate; 70:30) to provide dark yellow solid (66% Yield), EtOAc : Hexane (30:70) ; The spectral data matched with values reported in literature.[8]



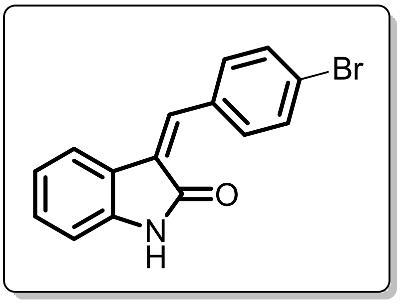
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.36 – 8.30 (m, 2H), 7.83 (s, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.21 (m, 1H), 7.13 (ddd, *J* = 9.8, 6.0, 2.6 Hz, 2H), 7.05 (td, *J* = 7.6, 0.9 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$+DMSO-d$_6$) δ 172.6, 169.9, 166.6, 145.6, 139.9, 139.1, 139.0, 135.2, 133.6, 131.5, 129.8, 126.0, 123.8, 120.0, 119.8, 114.5. **IR** (**KBr**) **ν_{max}** = 776.41, 1226.72, 1608.83, 1692.91, 2929.26, 3175.64 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{15}H_{11}NOF[M+H]^+$: 240.0825; found: 240.0815.

(*Z*)-3-(4-chlorobenzylidene)indolin-2-one (4g): **4g** was prepared according to general procedure 2. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate; 70:30) to provide light orange solid (68% yield), EtOAc : Hexane(30:70) ; The spectral data matched with values reported in literature.[8]

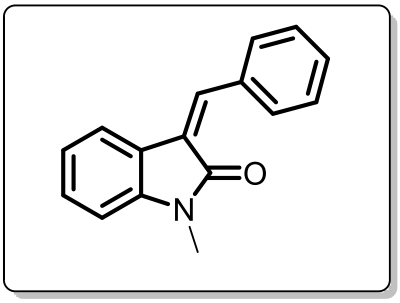


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.6 Hz, 2H), 7.67 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.48 (s, 1H), 7.43 – 7.40 (m, 2H), 7.23 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.05 (dt, *J* = 7.6, 3.8 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$+DMSO-d_6) δ 167.7, 140.8, 135.7, 134.8, 133.1, 132.4, 129.0, 128.2, 127.5, 124.8, 121.2, 119.1, 109.71. **IR** (**KBr**) **ν_{max}** = 735.52, 1472.27, 1600.97, 1681.75, 2922.76, 3166.68 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{15}H_{11}NOCl[M+H]^+$: 256.0529; found: 256.0521.

(*Z*)-3-(4-bromobenzylidene)indolin-2-one (4h): **4h** was prepared according to general procedure 2. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate; 70:30) to provide orange solid (64% yield), EtOAc : Hexane(30:70); mp: 223-225 °C. The spectral data matched with values reported in literature.[1] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 8.13 (m, 2H), 7.69 (s, 1H), 7.59 – 7.55 (m, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.45 (s, 1H), 7.25 – 7.22 (m, 1H), 7.05 (td, *J* = 7.6, 0.9 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$+DMSO-d_6) δ 167.3, 140.5, 134.3, 132.9, 132.4, 130.8, 128.6, 127.3, 124.3, 123.9, 120.8, 118.8, 109.3. **IR** (**KBr**) **ν_{max}** = 737.30, 1471.88, 1606.97, 1683.49, 2931.92, 3167.00 cm^{-1}. **HRMS (ESI):** m/z calcd for $C_{15}H_{11}NOBr[M+H]^+$: 300.0024; found: 300.0018.



(*Z*)-3-benzylideneindolin-2-one (4i): 4i was prepared according to general procedure 2. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate; 70:30) to provide deep yellow solid (70% yield), EtOAc : Hexane (30:70) ; The spectral data matched with values reported in literature.[4]



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dt, *J* = 4.2, 2.3 Hz, 2H), 7.57 – 7.51 (m, 2H), 7.48 – 7.40 (m, 3H), 7.29 (td, *J* = 2.9, 1.4 Hz, 1H), 7.07 (td, *J* = 7.6, 0.9 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.28 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1, 142.4, 137.0, 133.8 ,131.9, 130.5,128.9,128.3,126.1,124.4,121.8,118.9 ,107.9, 25.9. **IR (KBr) ν_{max}** = 751.30, 1479.79, 1615.43, 1697.90, 2928.57, 3059.88. **HRMS (ESI):** m/z calcd for $C_{16}H_{14}NO[M+H]^+$: 236.1075; found: 236.1081.

3. Procedure for photo-flow condition under the solar irradiation for the synthesis of Z-isomer 4a:

3.1 Fabrication of Solar panel for photo-flow reaction:

To fabricate the solar panel, reactor we have used foam sheet, Aluminum foil, PFA tubing, and cello-tape. Our polystyrene foam (length 50 cm X width 50 cm X height 6 cm) was covered by aluminum foil (0.016 mm) for reflecting of sun light. Manually, PFA tubing mounted over the aluminum covered surface (**Figure S3**). Finally, blue polyethylene film filter covered the solar panel reactor to make the equivalent to the blue LED light source.

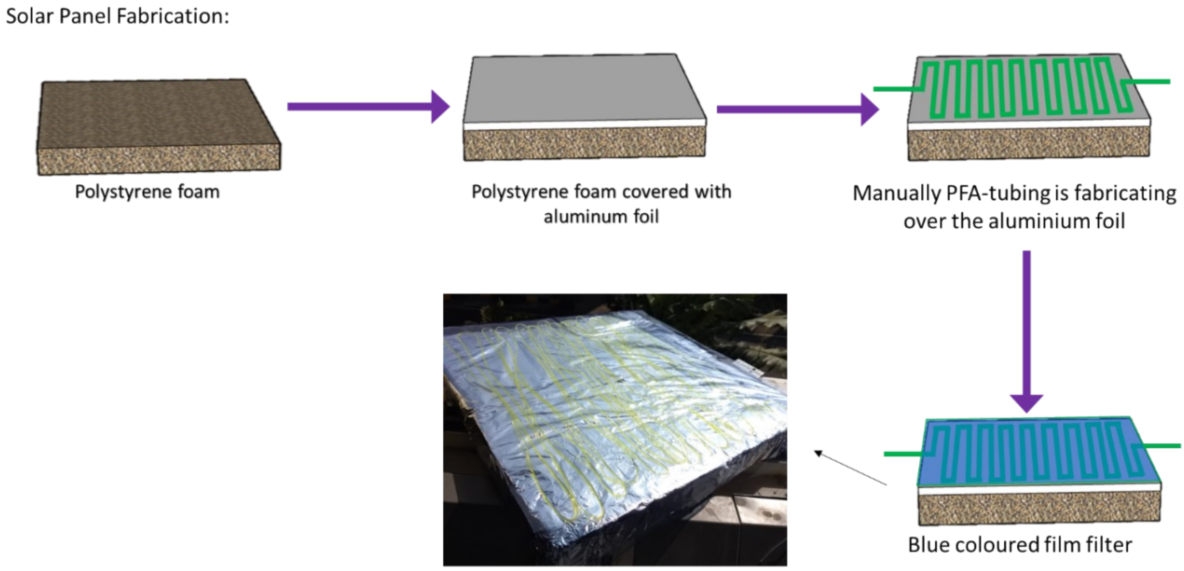


Figure S3. Fabrication of the solar panel reactor

3.2. Procedure for photo-flow condition under the solar irradiation for the synthesis of *Z*-isomer. A 0.25 M solution of *E*-3-benzylidene-indolin-2-ones in DMF was taken in bottle and was connected to pump, the mixture was introduced to a fabricated solar panel reactor that irradiated by sun light for day time from 10 am to 4 pm. According to the movement of sun light, the direction of solar panel reactor was manually adjusted to harvest the light best. The out-flowing product mixture was quenched with water and DCM solvent by introducing through an additional x-mixer to form organic-aqueous droplets. Complete extraction between the organic-aqueous segments was observed after 0.5 min retention time achieved by flowing through a PTFE capillary Further, organic-aqueous segment was separated by passing through our designed homemade micro separator and complete separation was achieved by regulating the back pressure and retention time (5.6 sec) along with the flow rate of DCM (1.25 mL/min) and water (1.25 mL/ min). The organic extract was concentrated and the resulting residue was purified by column chromatography (hexane/ethyl acetate) to give the product.

4. Spectra:

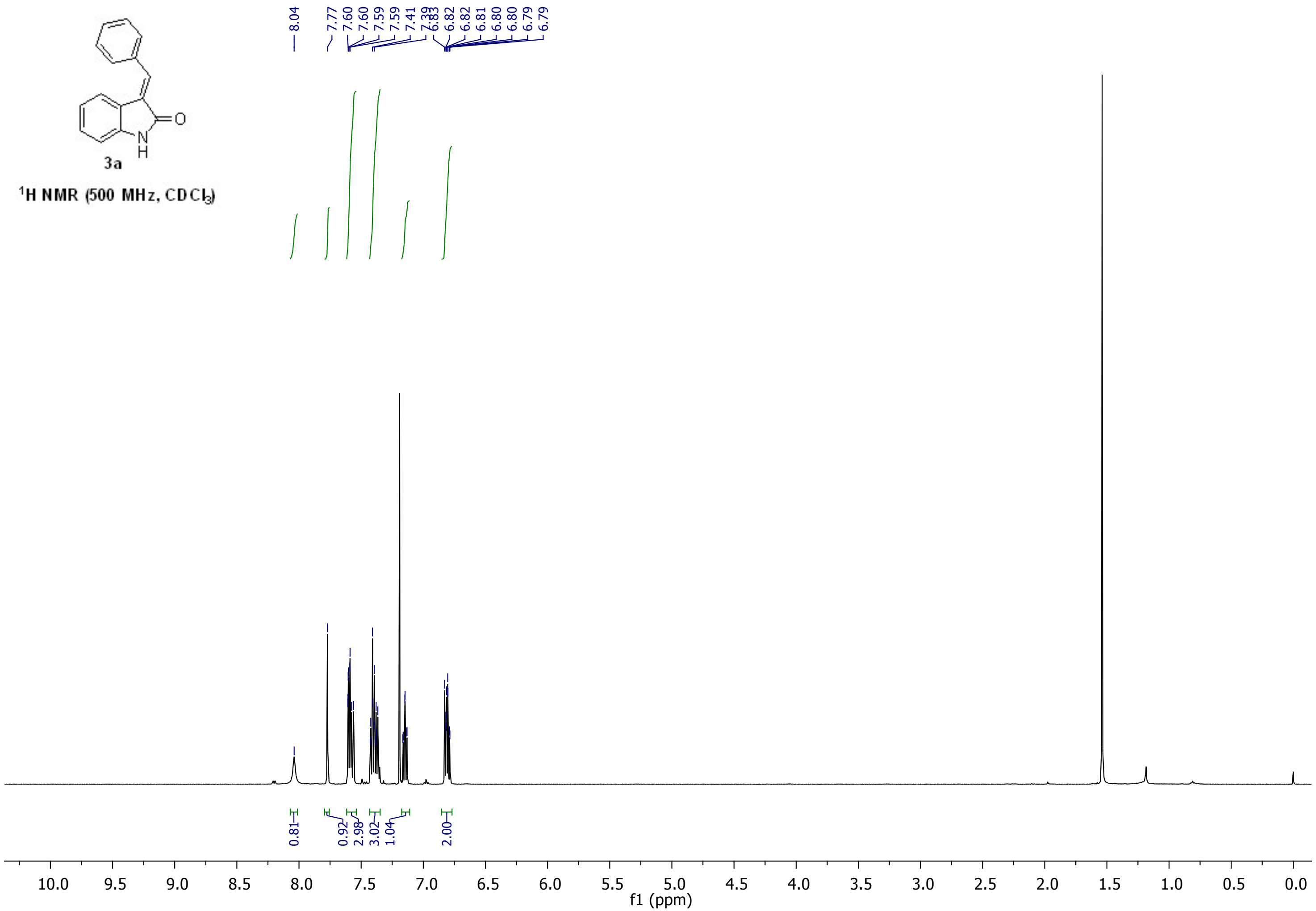


Figure S4: ^{1}H NMR Spectra of (*E*)-3-benzylideneindolin-2-one (**3a**)

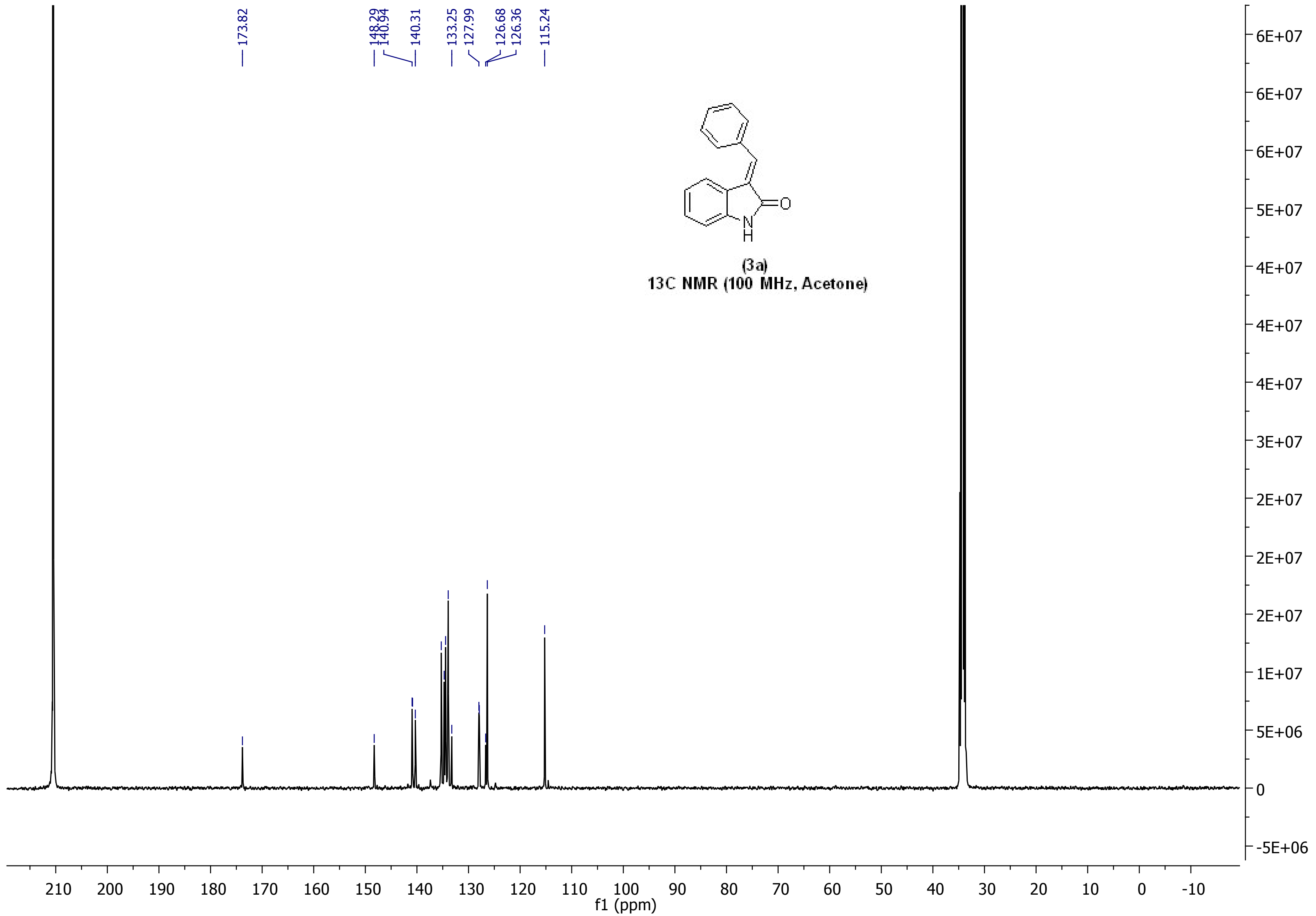


Figure S5: ^{13}C NMR Spectra of (*E*)-3-benzylideneindolin-2-one (**3a**)

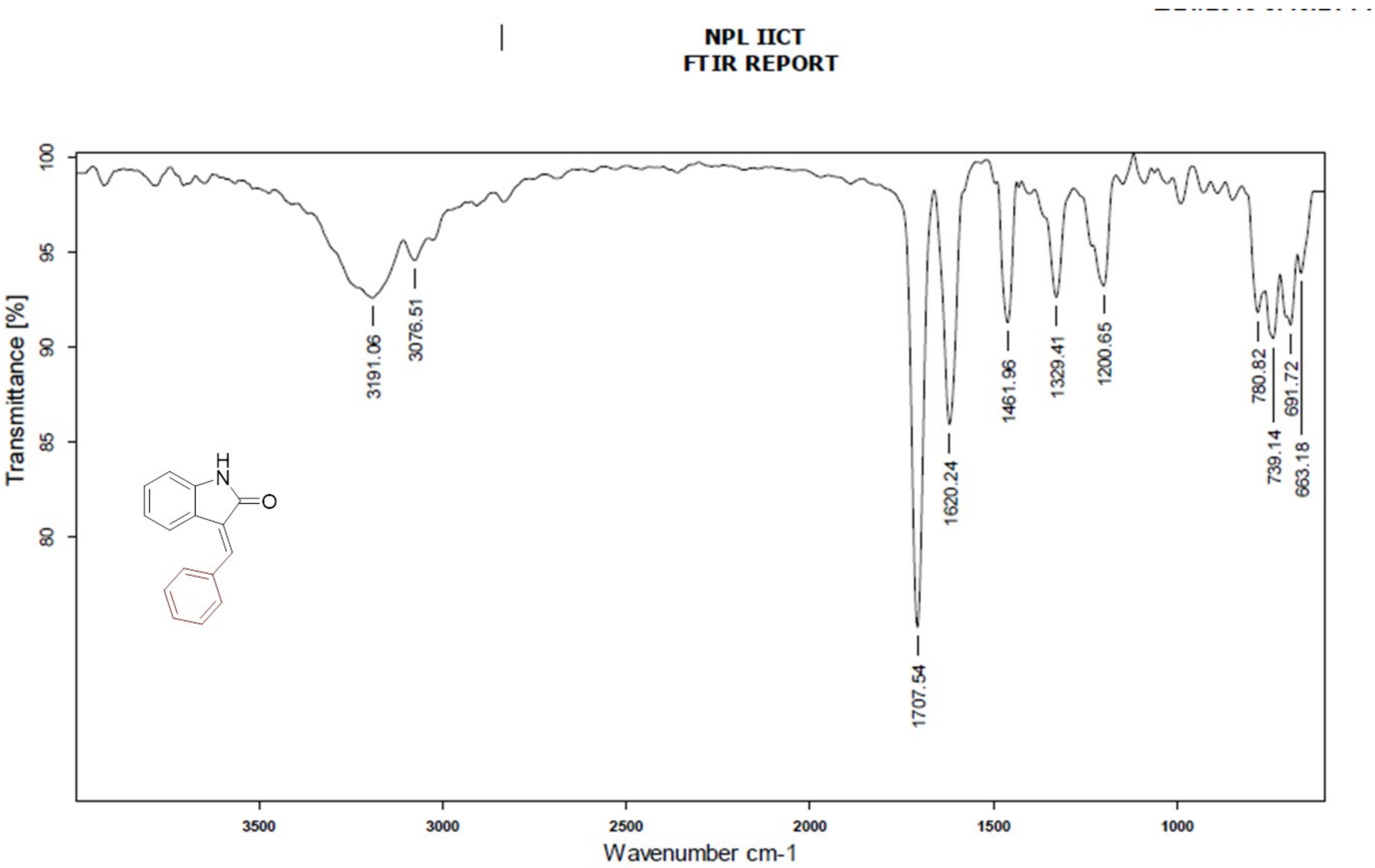


Figure S6: IR Specta of **(***E***)**-3-benzylideneindolin-2-one (**3a**)

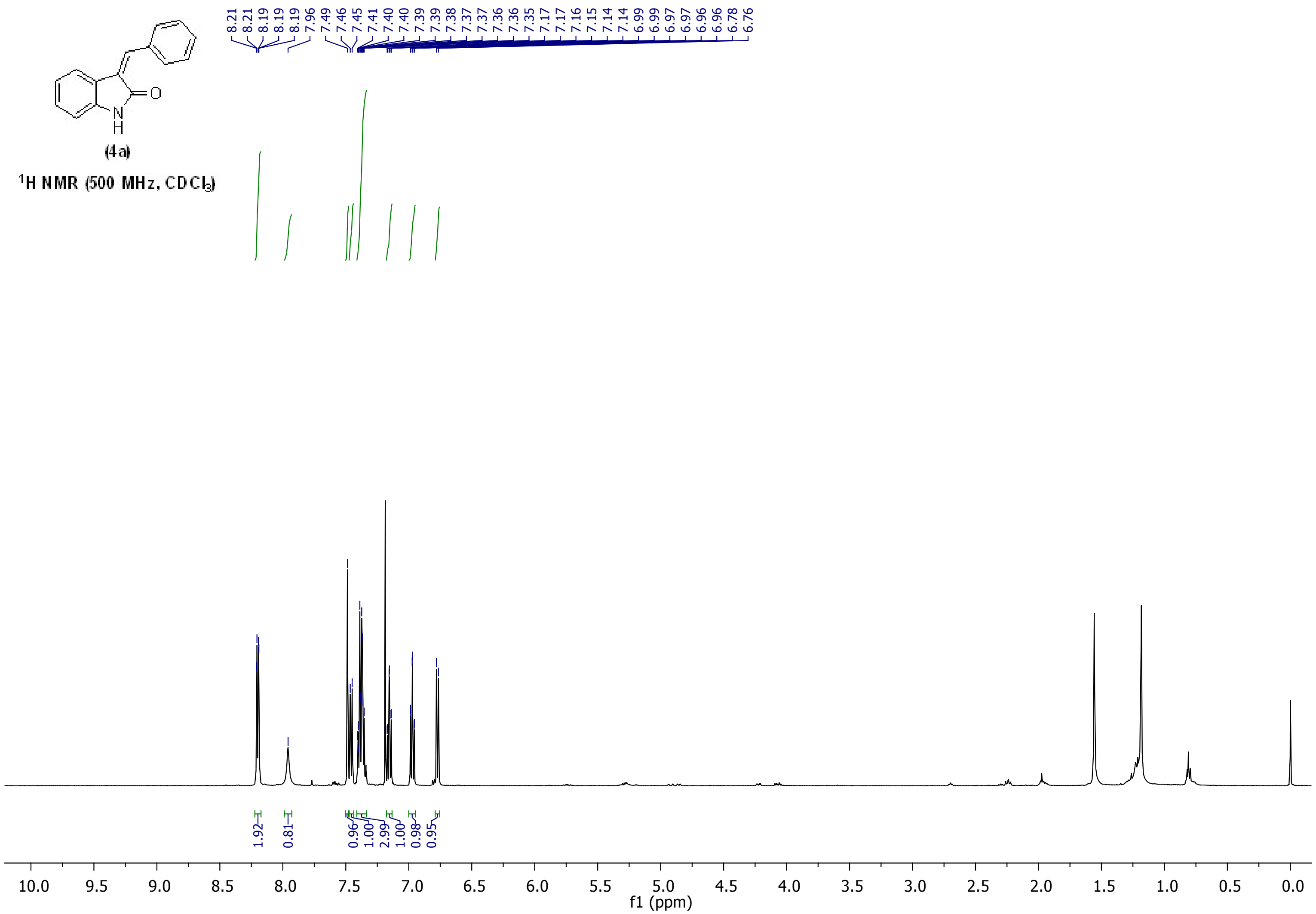


Figure S7: ^{1}H NMR of (*Z*)-3-benzylideneindolin-2-one (**4a**)

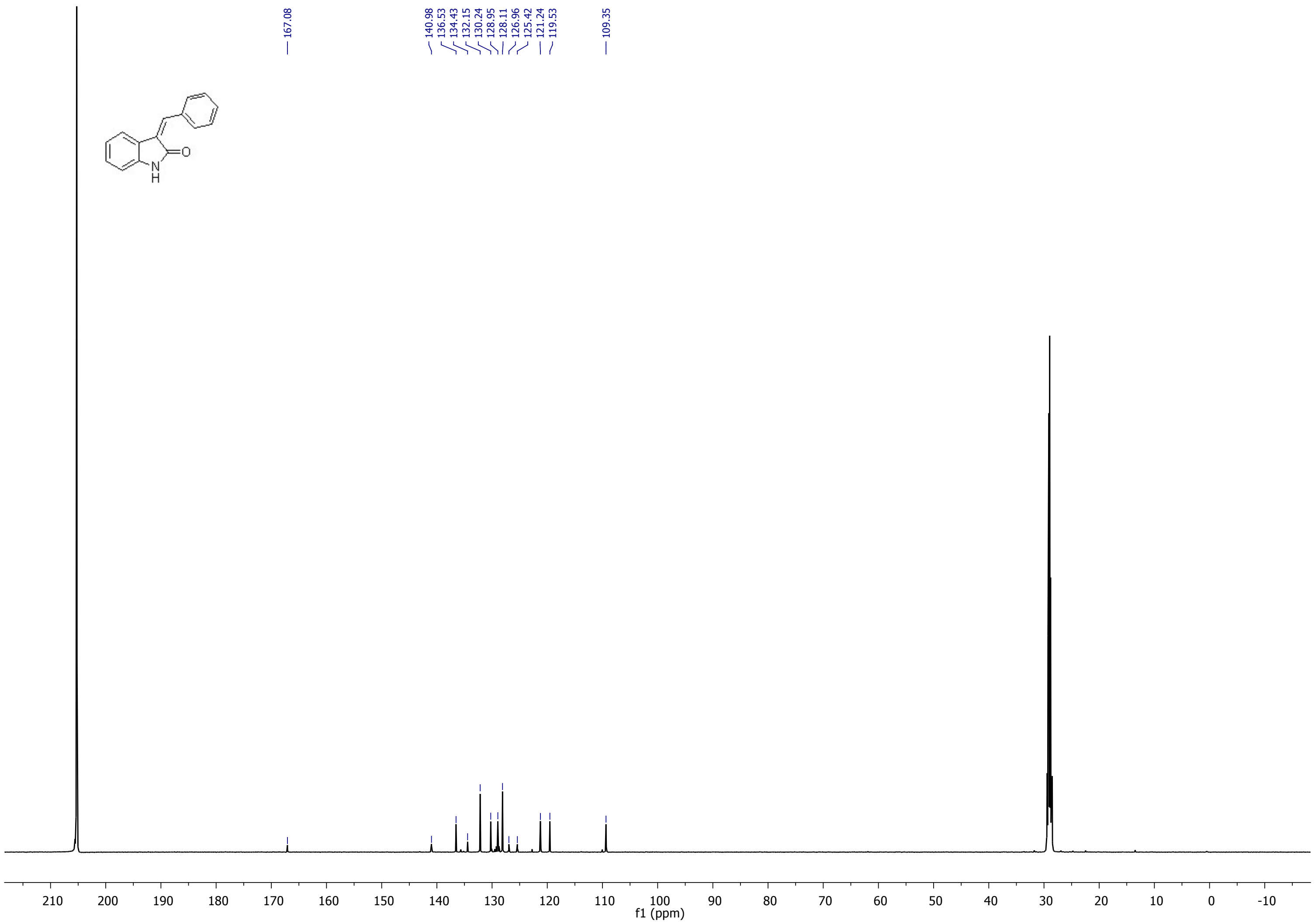


Figure S8: ^{13}C NMR Spectra of **(***Z***)**-3-benzylideneindolin-2-one (**4a**) .

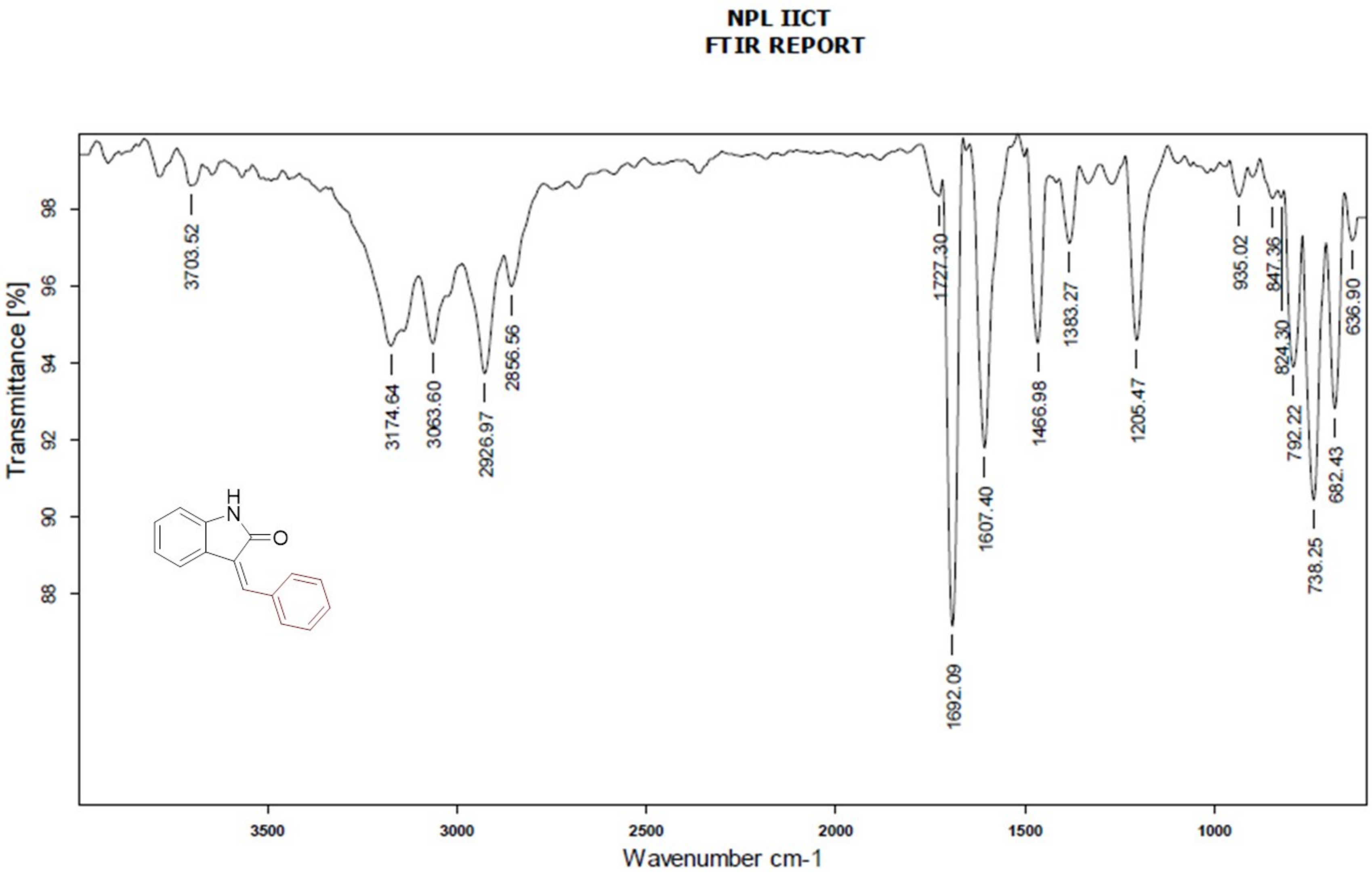


Figure S9: IR Spectra of **(***Z***)**-3-benzylideneindolin-2-one (**4a**)

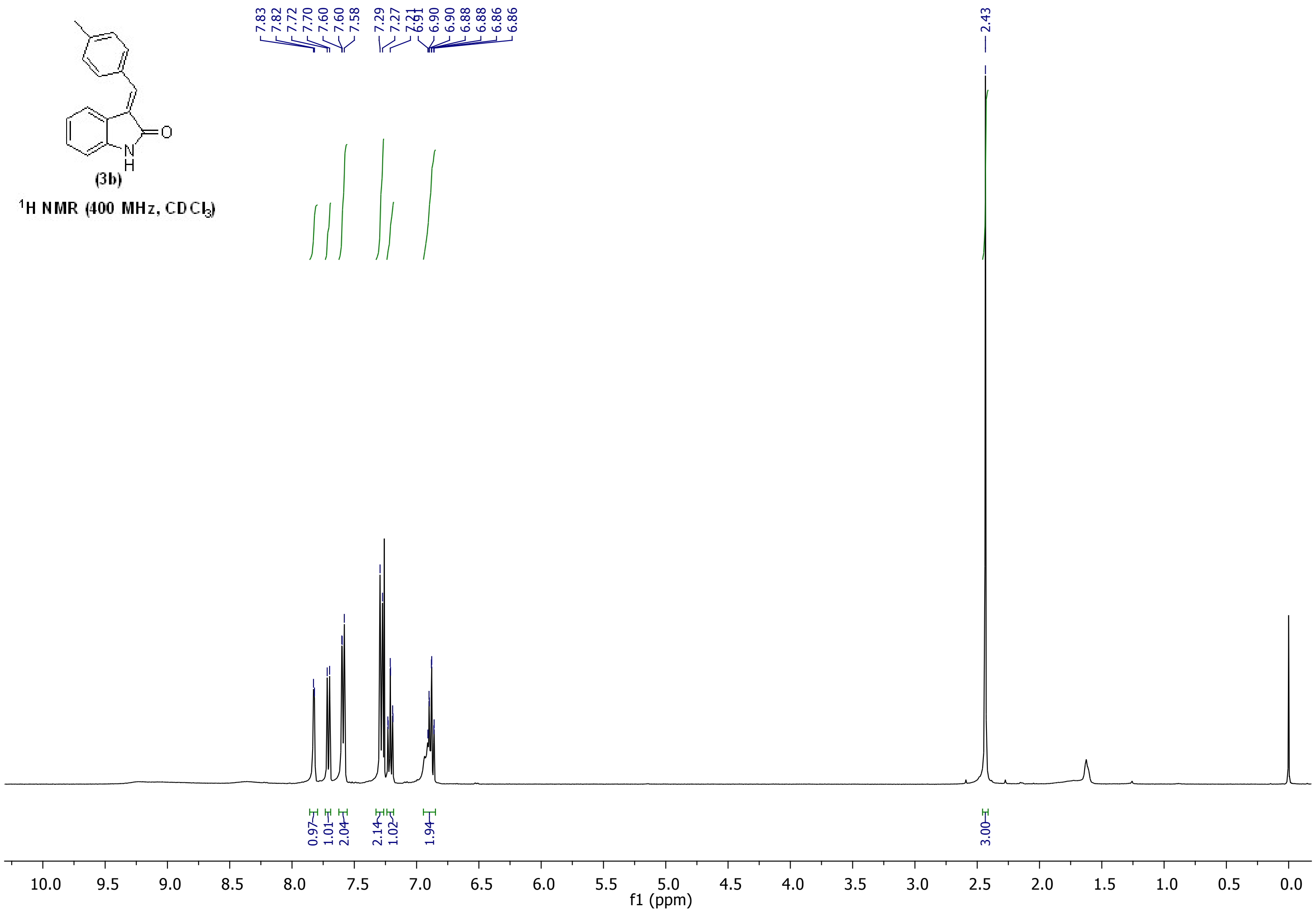


Figure S10: ^{1}H NMR Spectra of (*E*)-3-(4-methylbenzylidene)indolin-2-one (**3b**)

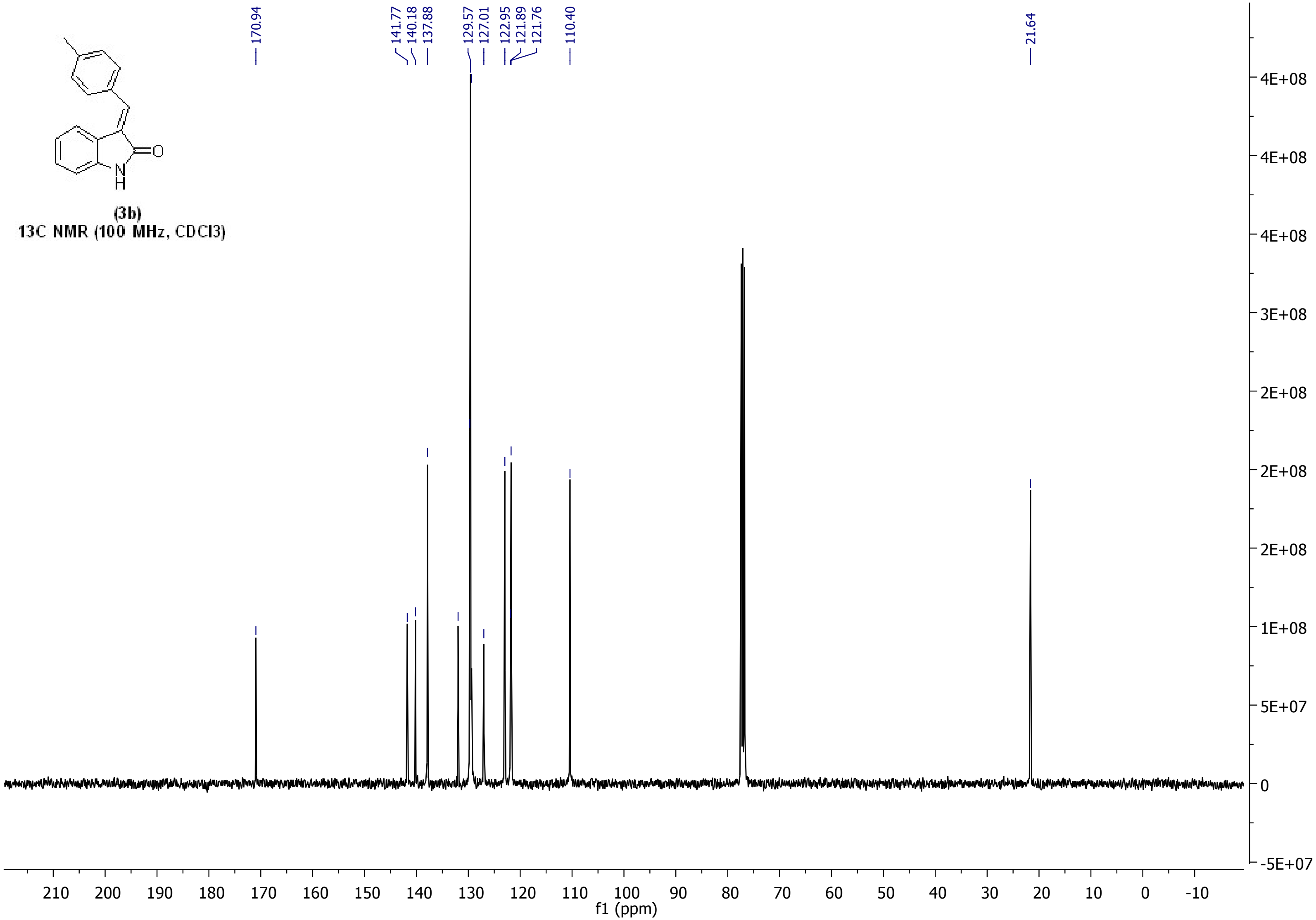


Figure S11: ^{13}C NMR Spectra of (*E*)-3-(4-methylbenzylidene)indolin-2-one (**3b**)

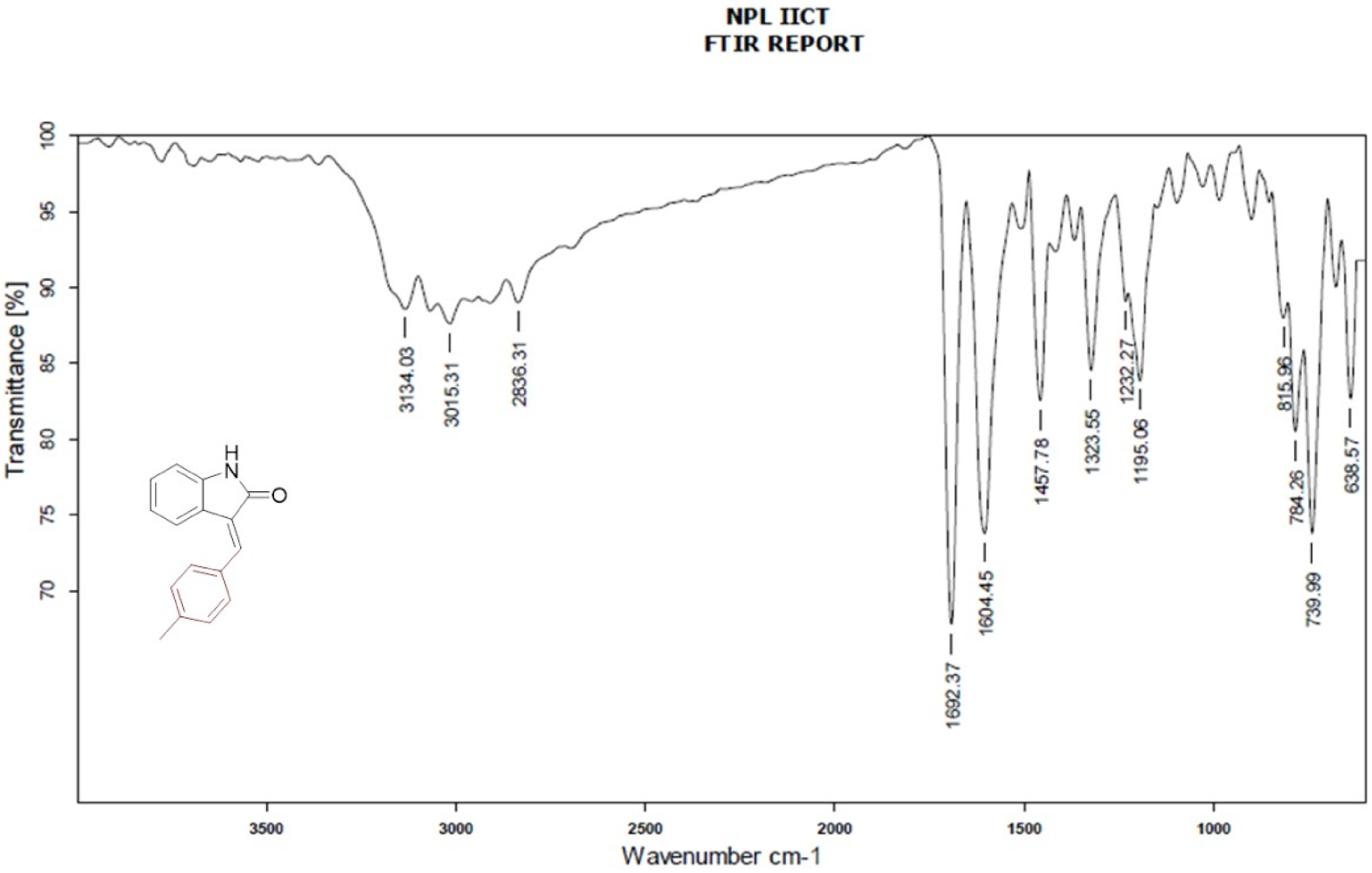


Figure S12: IR Spectra of (*E*)-3-(4-methylbenzylidene)indolin-2-one (**3b**)

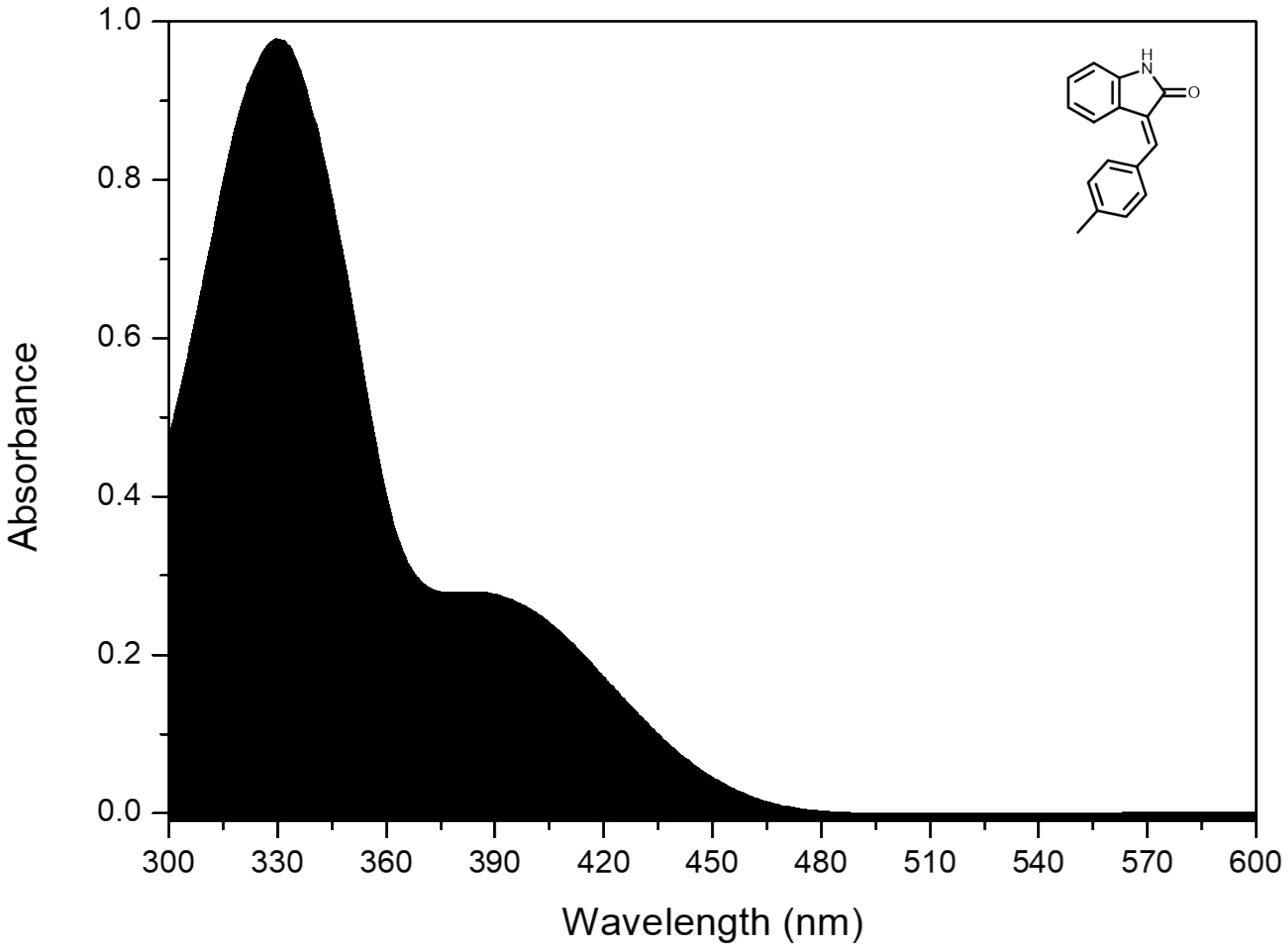


Figure S13: UV Spectra of (*E*)-3-(4-methylbenzylidene)indolin-2-one (**3b**)

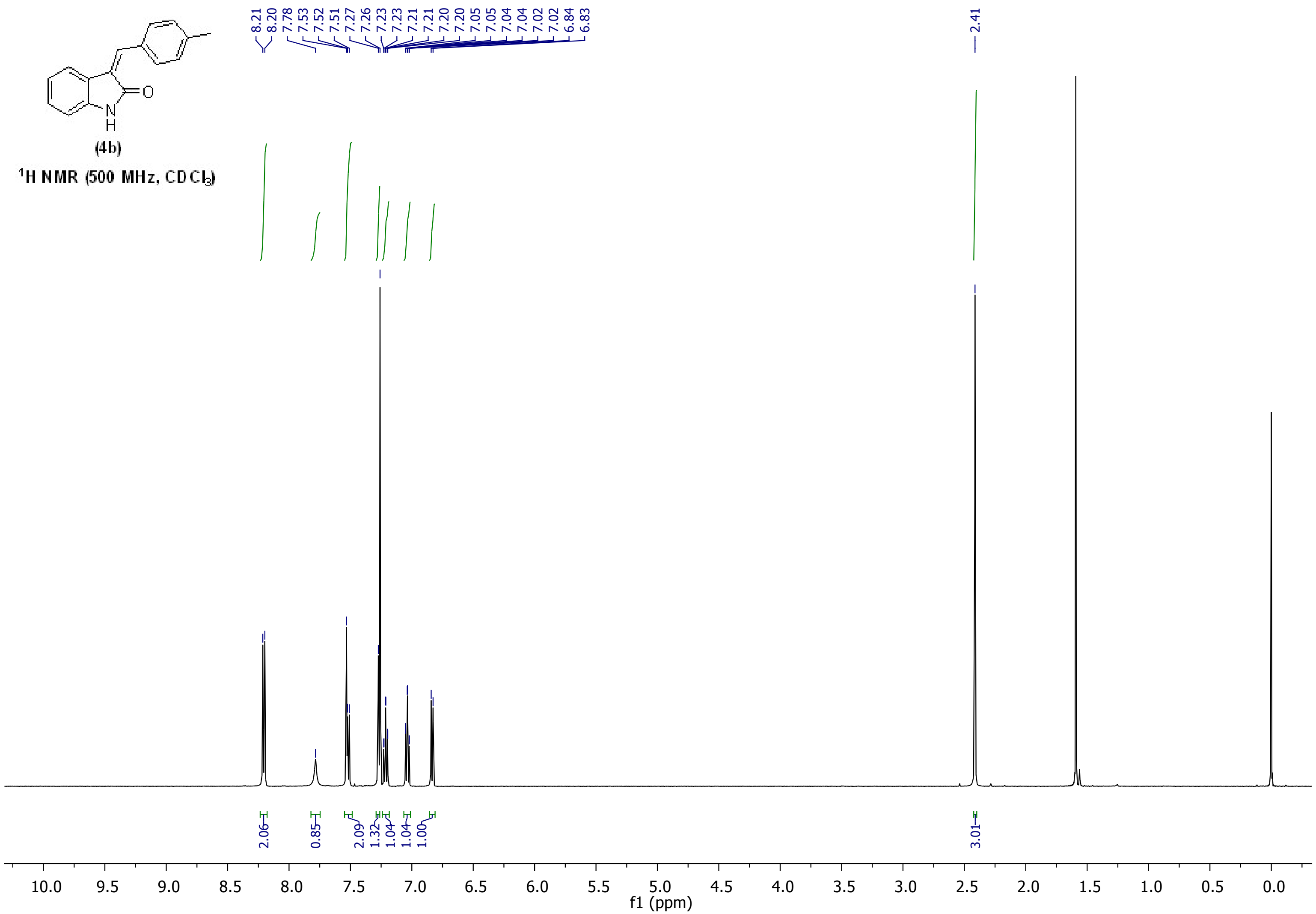


Figure S14: ^{1}H NMR Spectra of (*Z*)-3-(4-methylbenzylidene)indolin-2-one (**4b**)

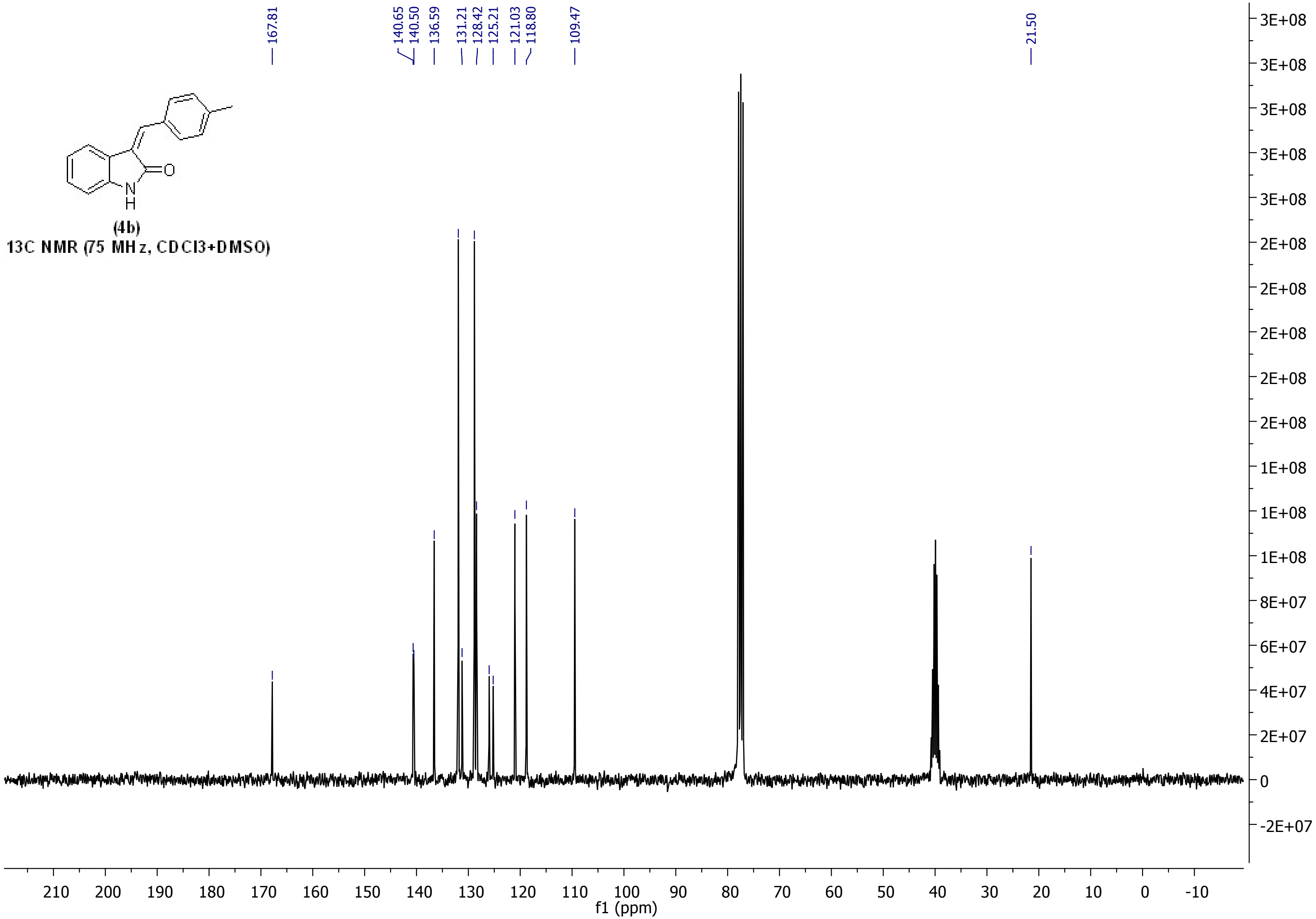


Figure S15: ^{13}C NMR Spectra of (*Z*)-3-(4-methylbenzylidene)indolin-2-one (**4b**)

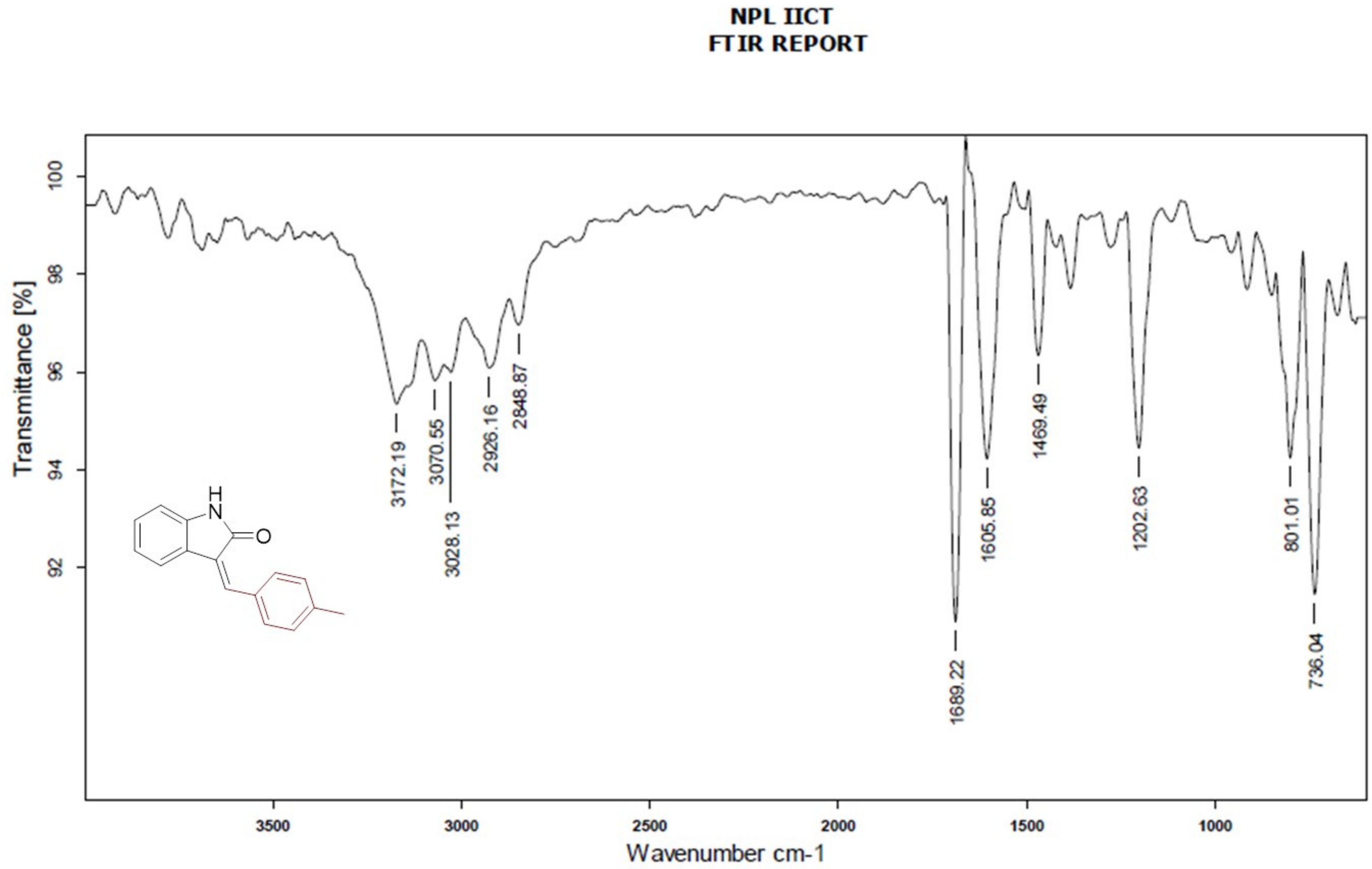


Figure S16: IR Spectra of (*Z*)-3-(4-methylbenzylidene)indolin-2-one (**4b**)

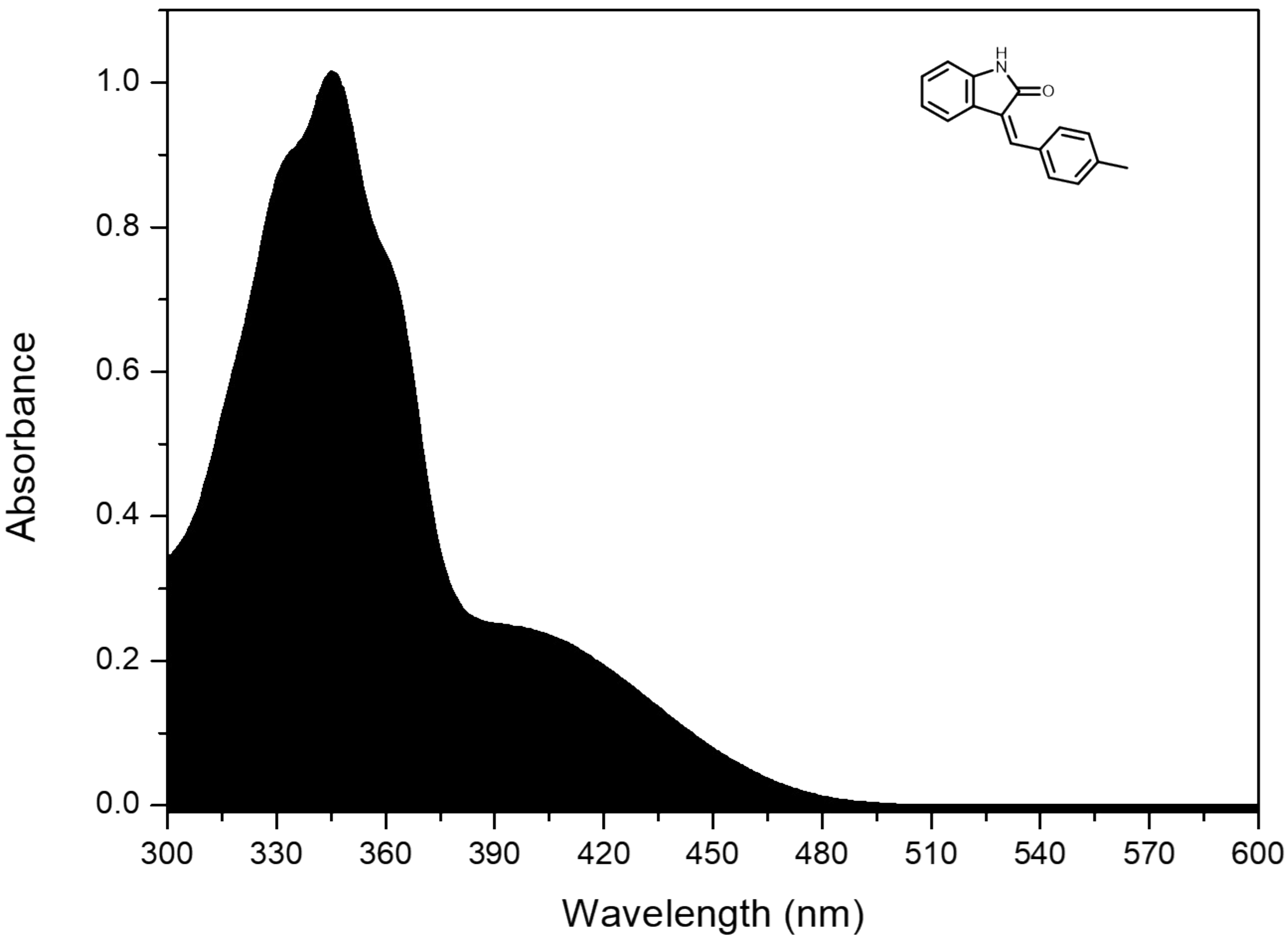


Figure S17: UV Spectra of (*Z*)-3-(4-methylbenzylidene)indolin-2-one (**4b**)

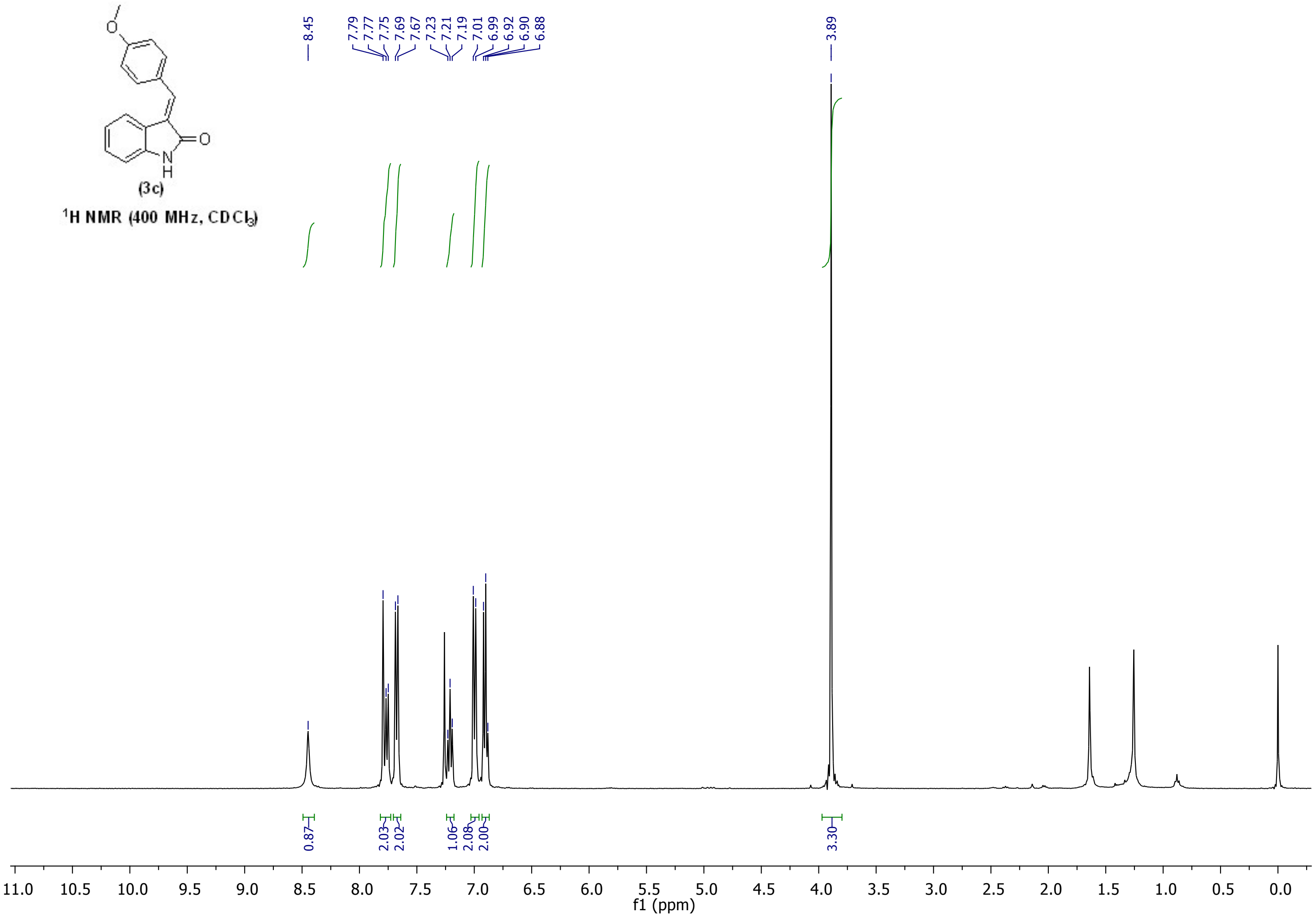


Figure S18: ^{1}H NMR Spectra of (*E*)-3-(4-methoxybenzylidene)indolin-2-one (**3c**)

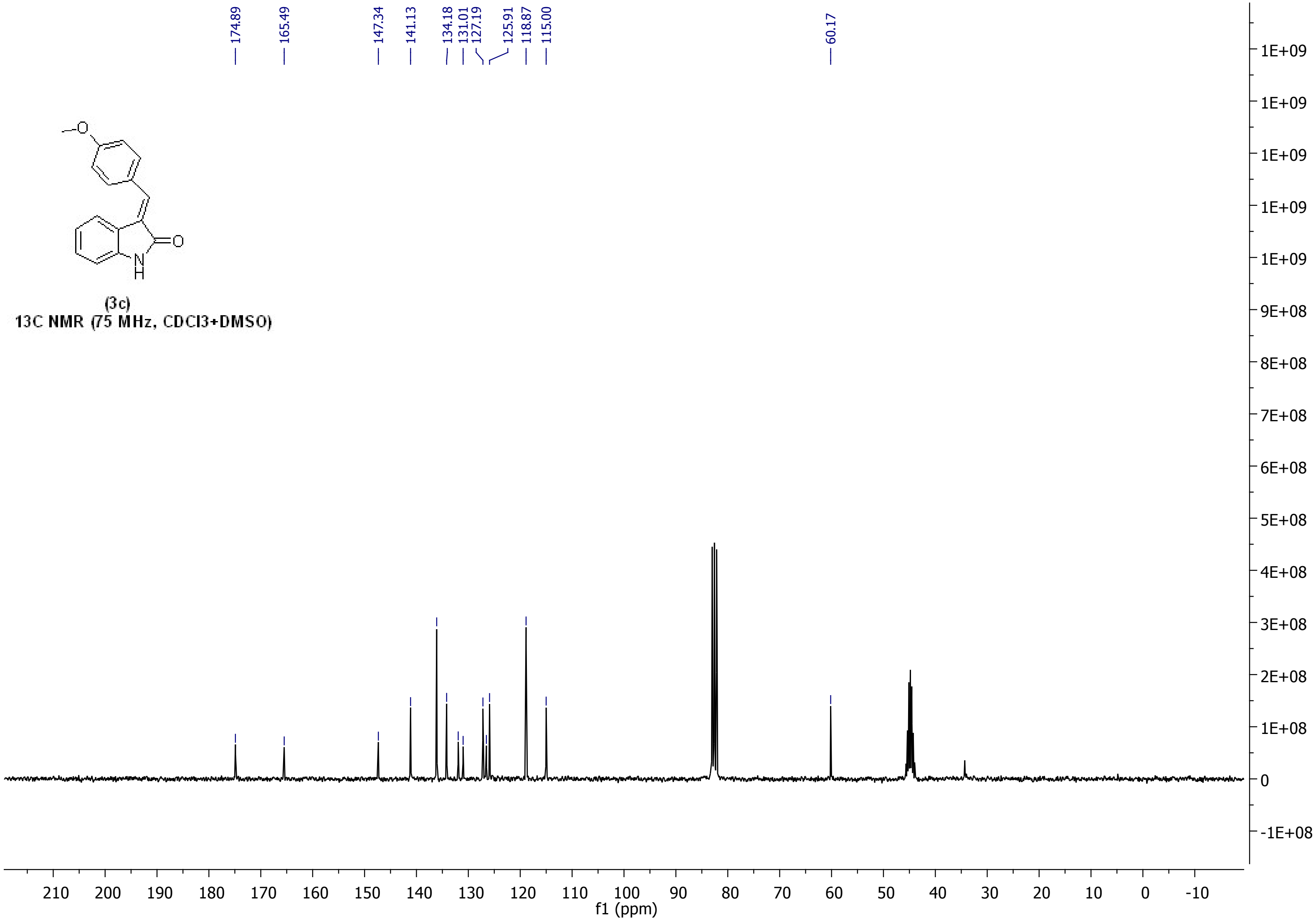


Figure S19: ^{13}C NMR Spectra of (*E*)-3-(4-methoxybenzylidene)indolin-2-one (**3c**)

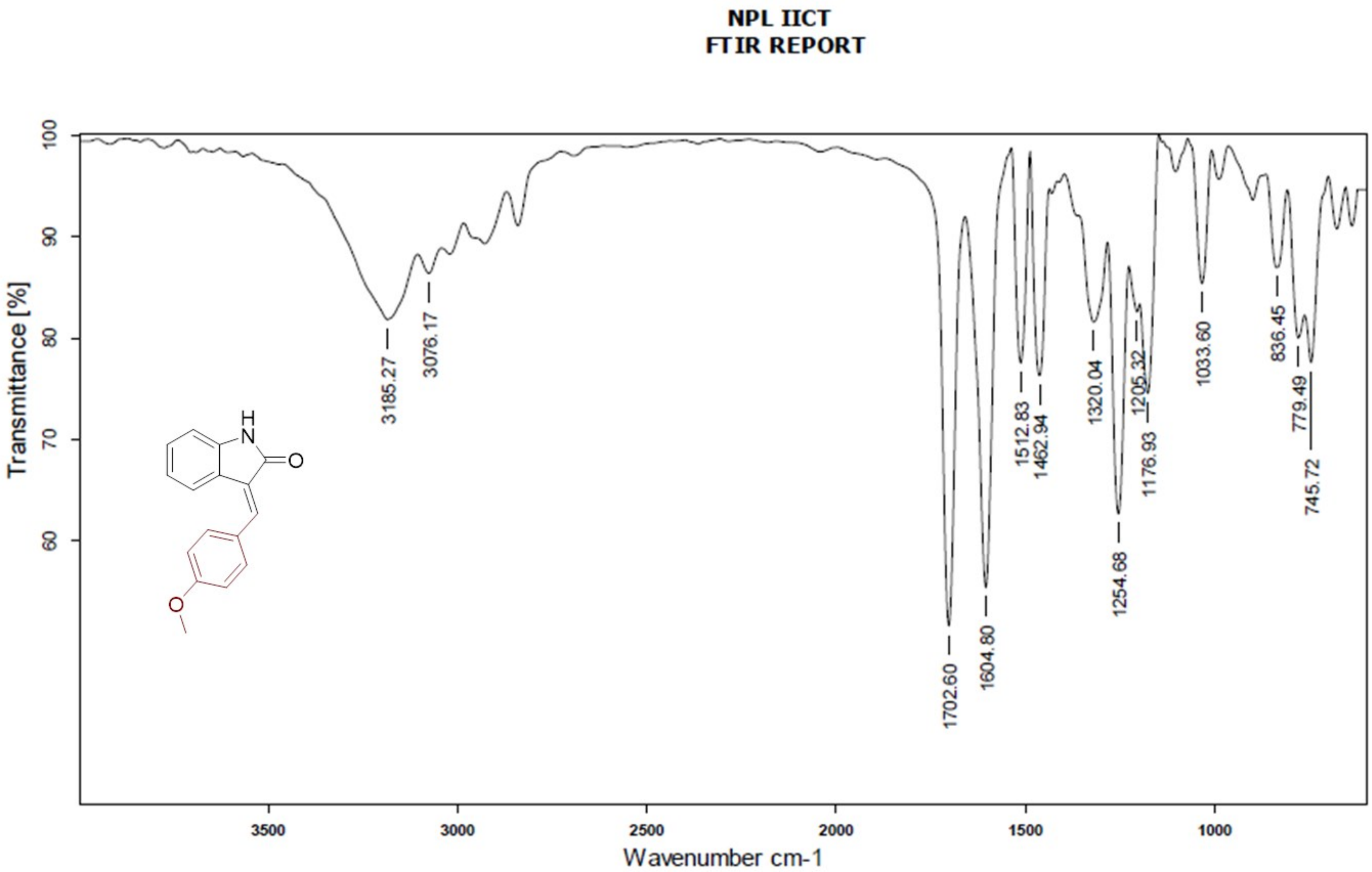


Figure S20: IR NMR Spectra of (*E*)-3-(4-methoxybenzylidene)indolin-2-one (**3c**)

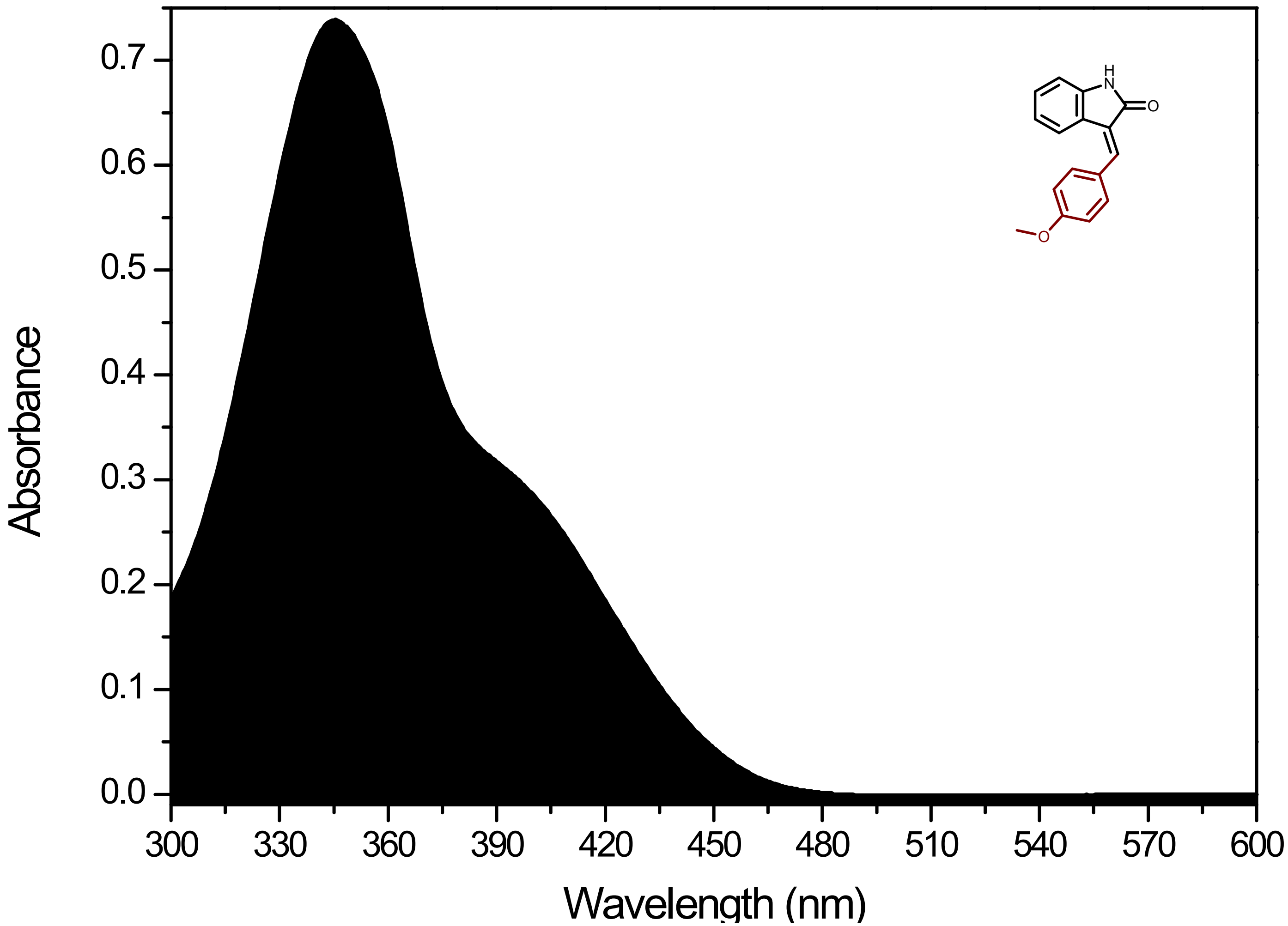


Figure S21: UV NMR Spectra of (*E*)-3-(4-methoxybenzylidene)indolin-2-one (**3c**)

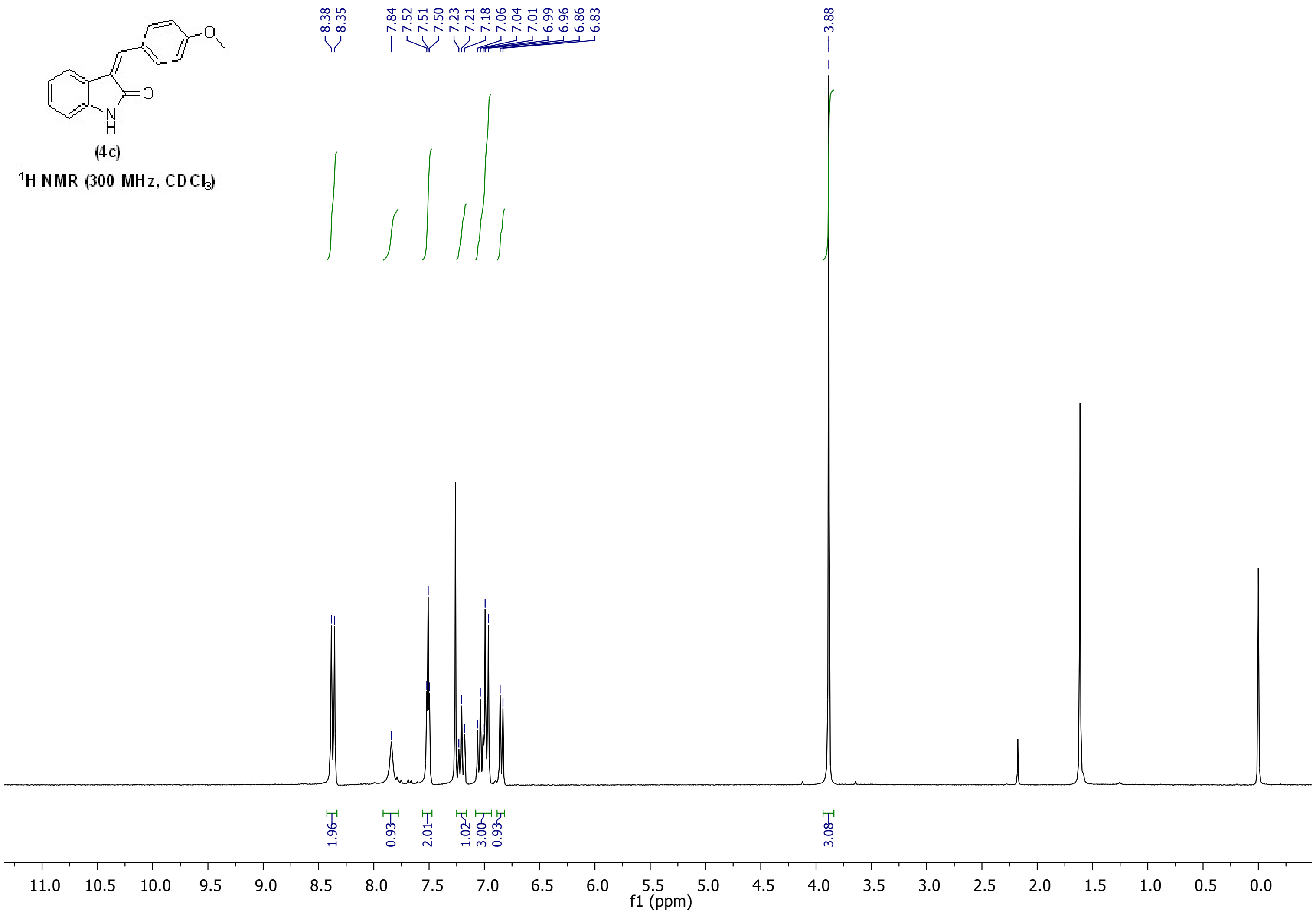


Figure S22: ^{1}H NMR Spectra of (*Z*)-3-(4-methoxybenzylidene)indolin-2-one (**4c**)

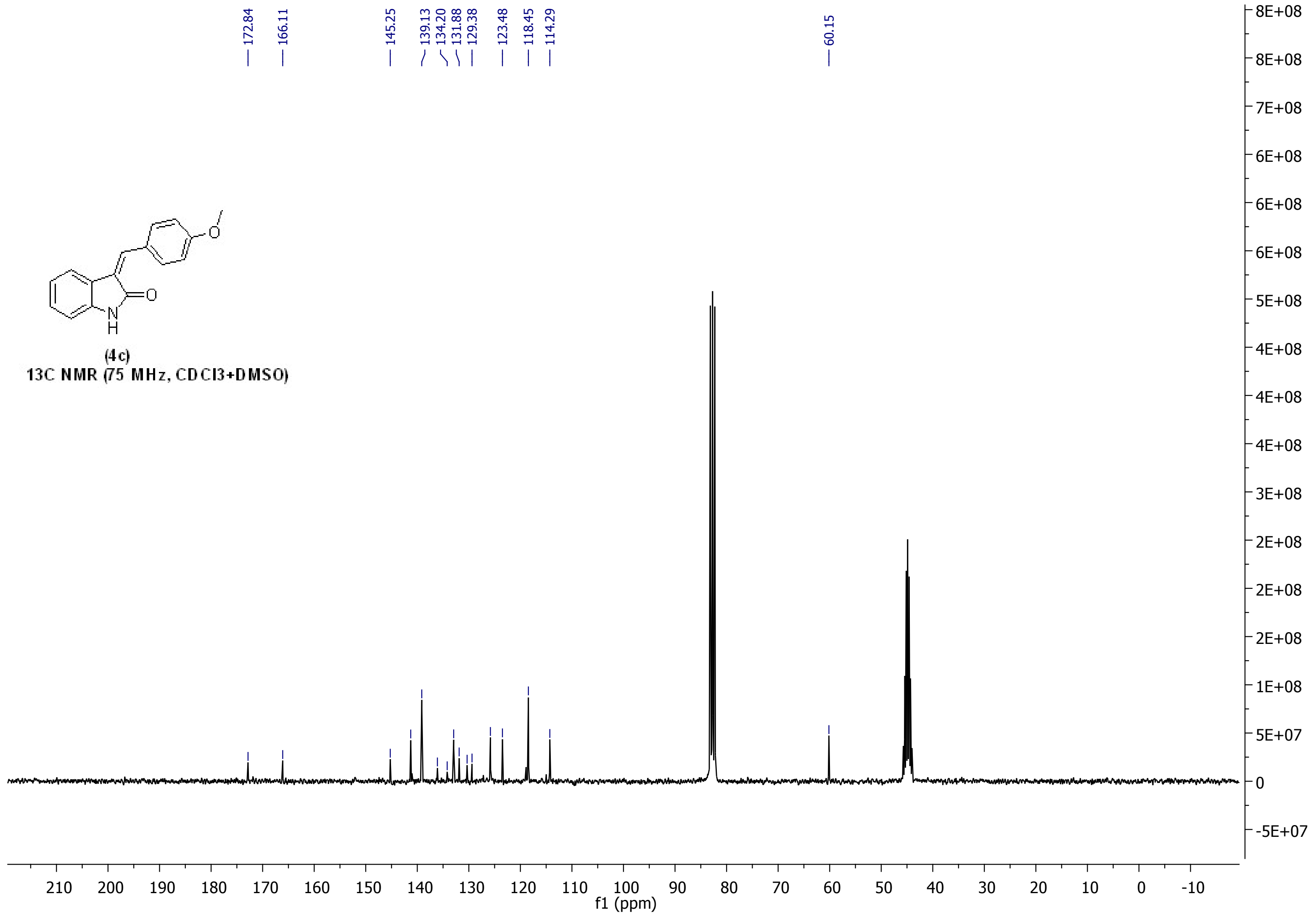


Figure S23: ^{13}C NMR Spectra of (*Z*)-3-(4-methoxybenzylidene)indolin-2-one (**4c**)

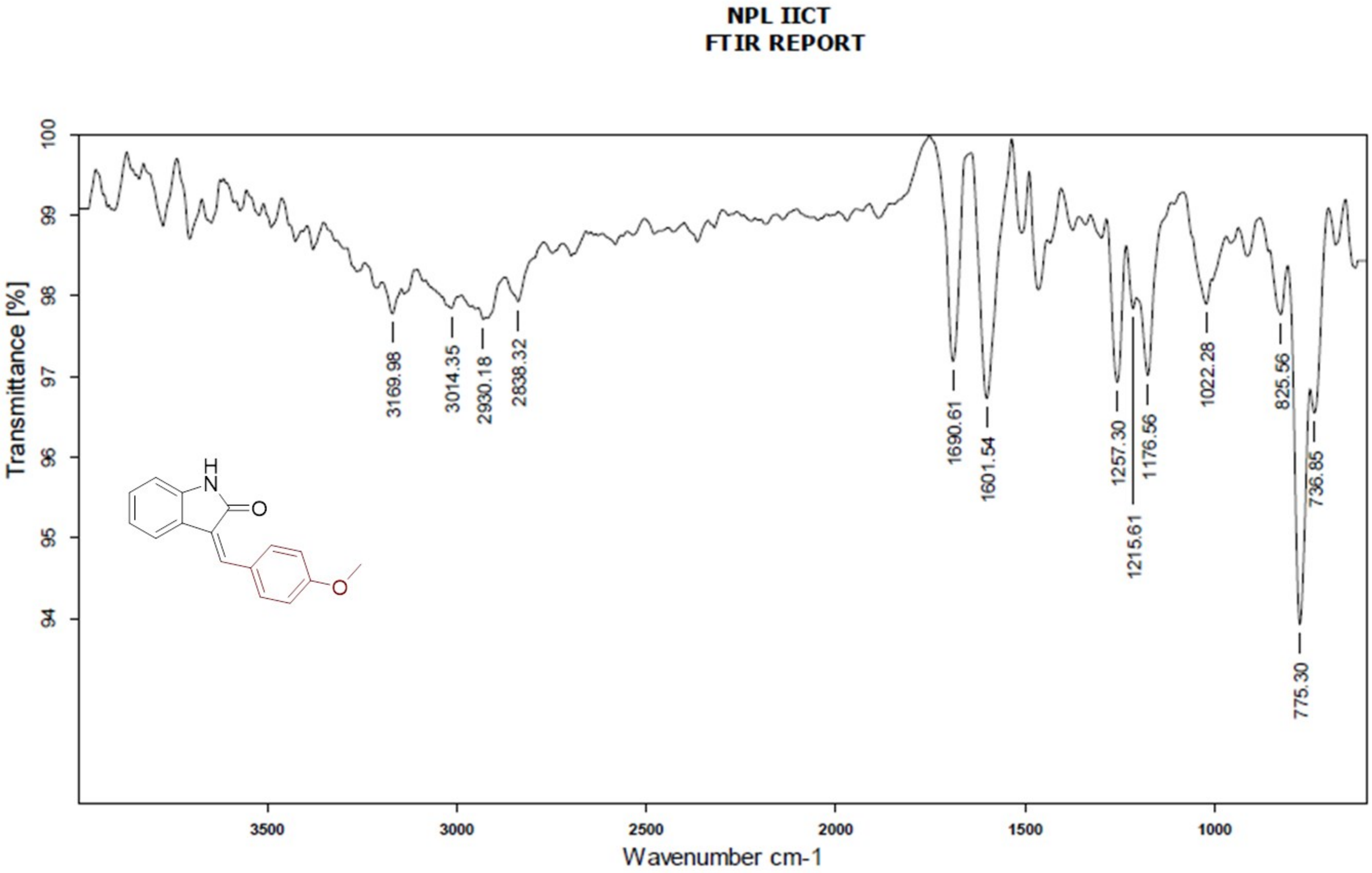


Figure S24: IR Spectra of (*Z*)-3-(4-methoxybenzylidene)indolin-2-one (**4c**)

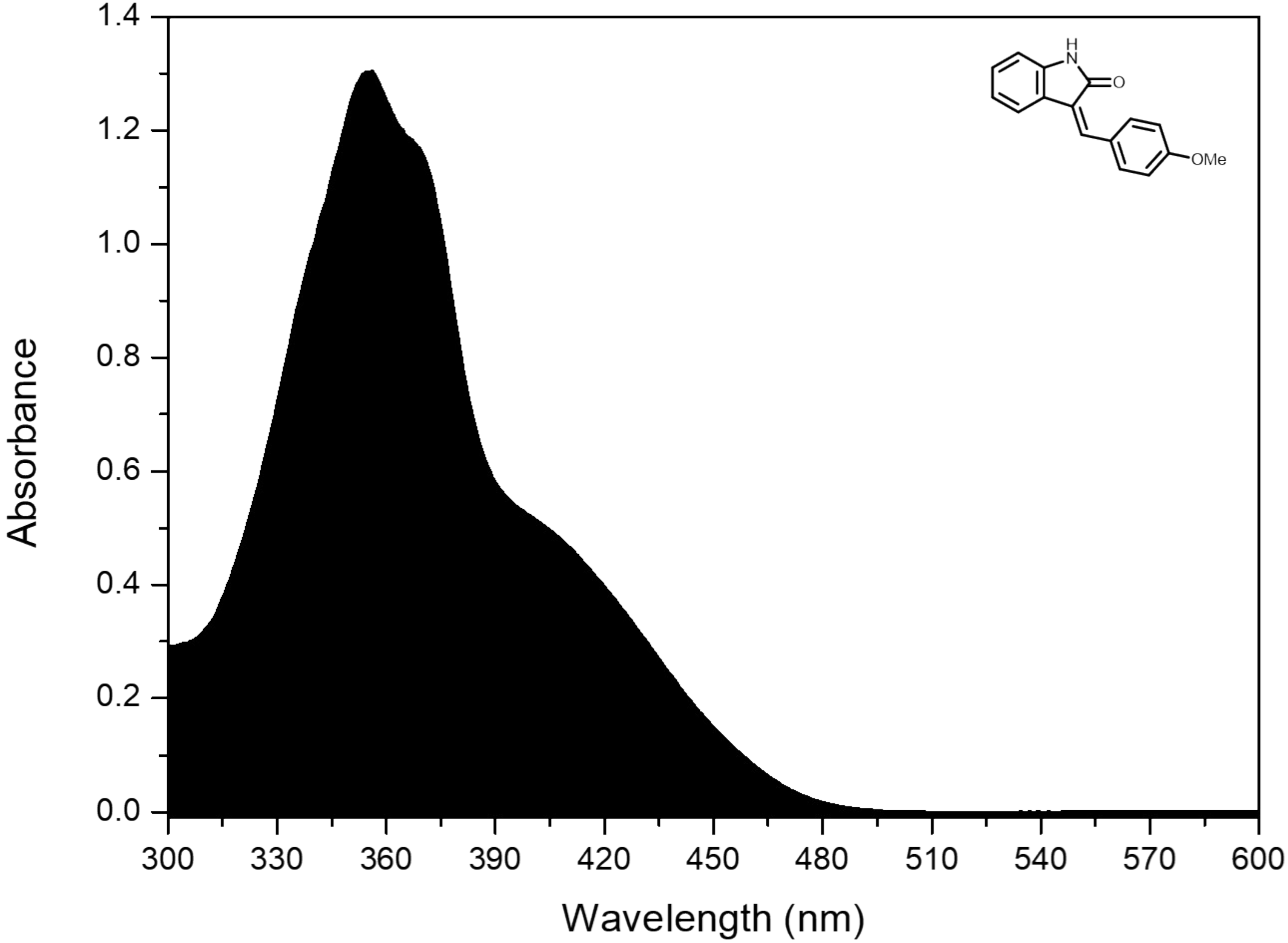


Figure S25: UV Spectra of (*Z*)-3-(4-methoxybenzylidene)indolin-2-one (**4c**)

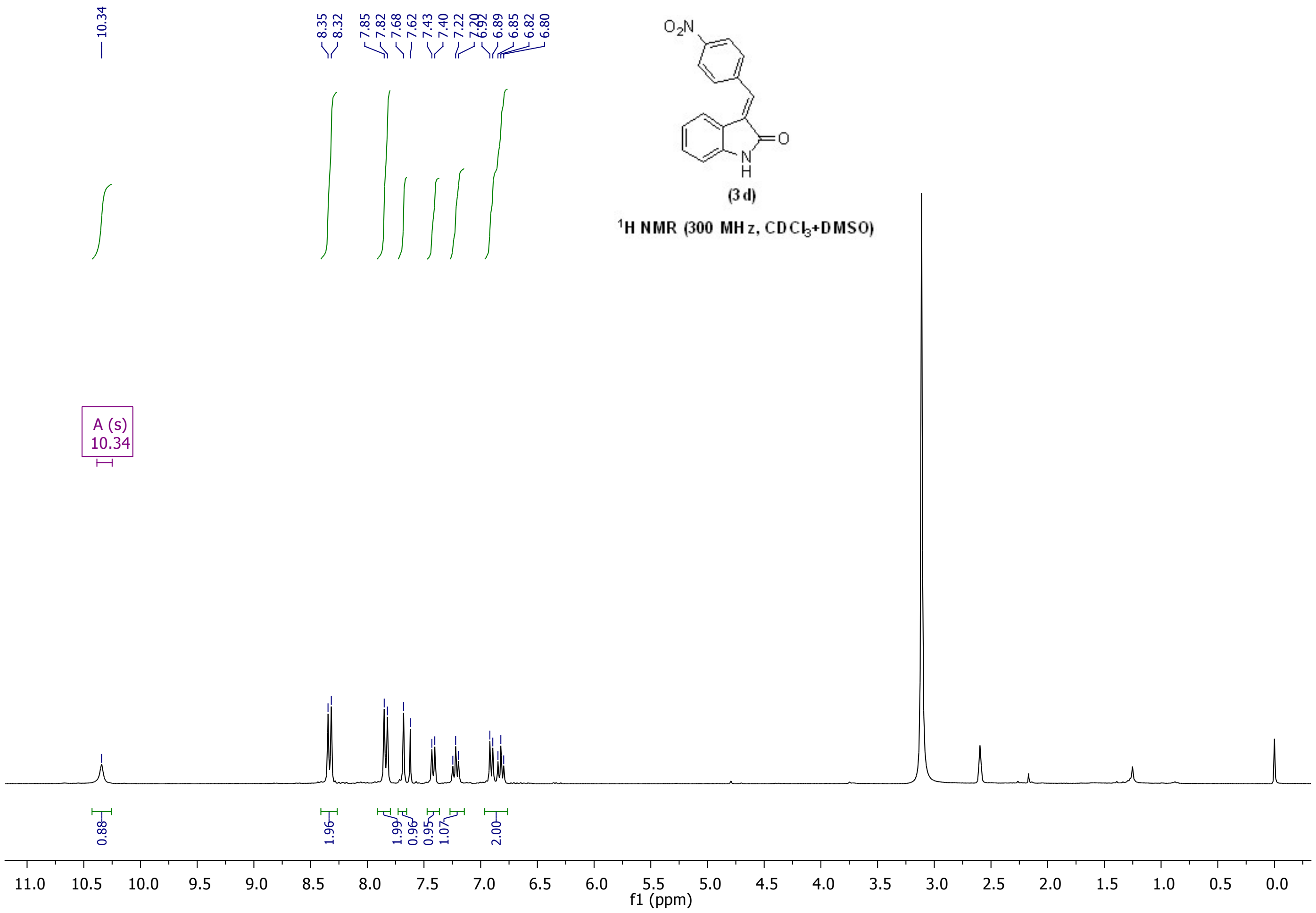


Figure S26: ^{1}H NMR Spectra of (*E*)-3-(4-nitrobenzylidene)indolin-2-one (**3d**)

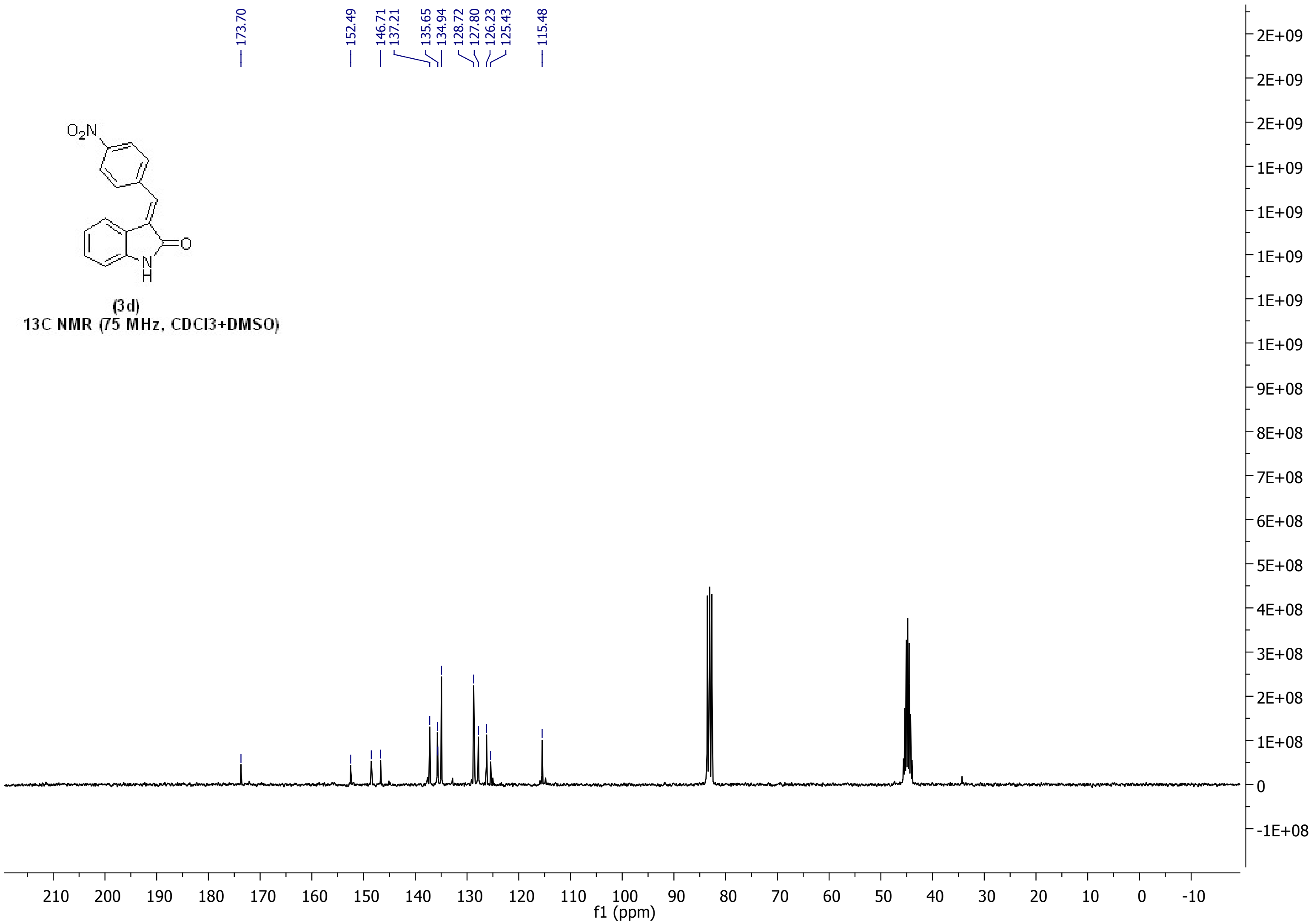


Figure S27: ^{13}C NMR Spectra of (*E*)-3-(4-nitrobenzylidene)indolin-2-one (**3d**)

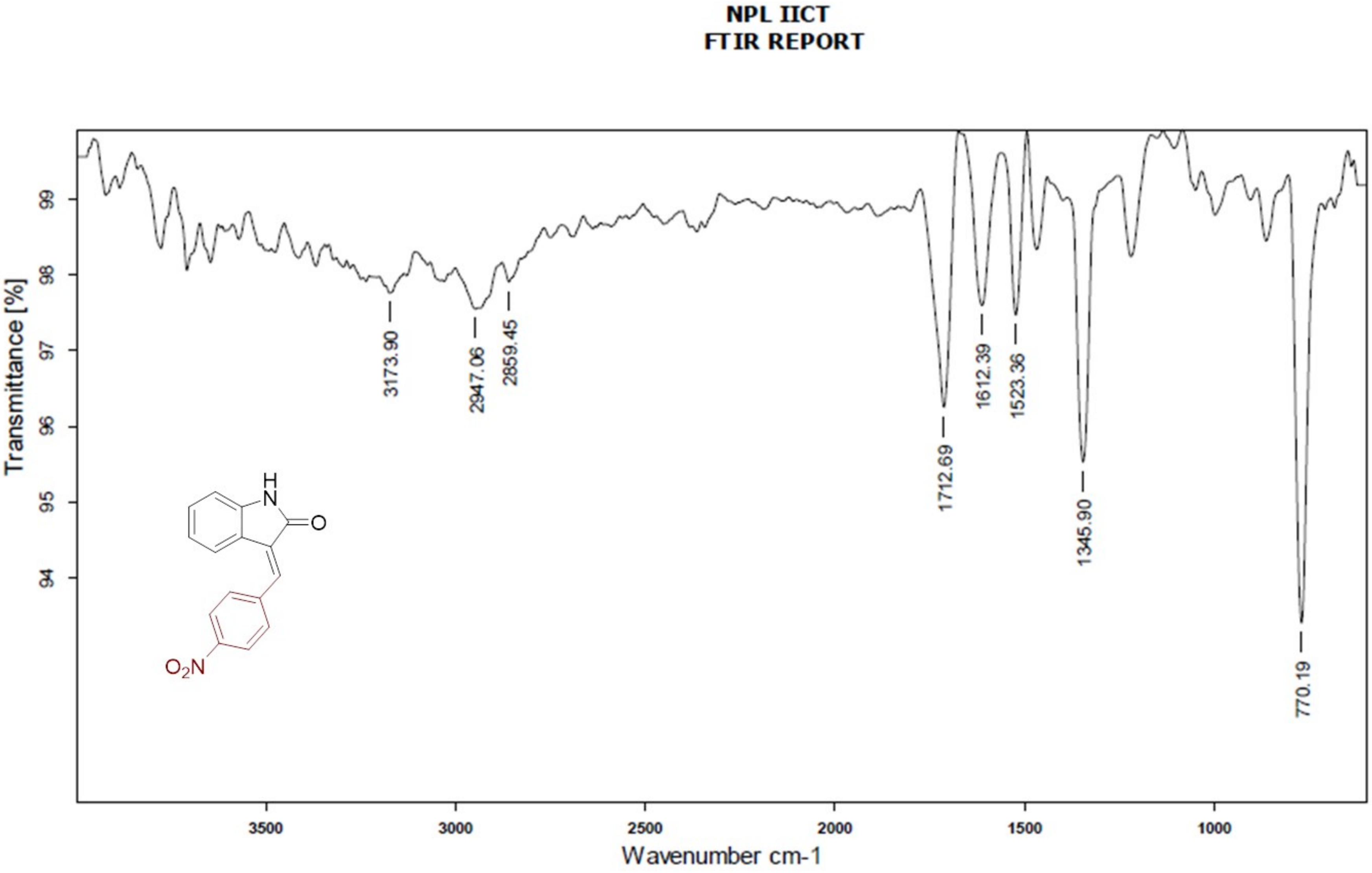


Figure S28: IR Spectra of (*E*)-3-(4-nitrobenzylidene)indolin-2-one (**3d**)

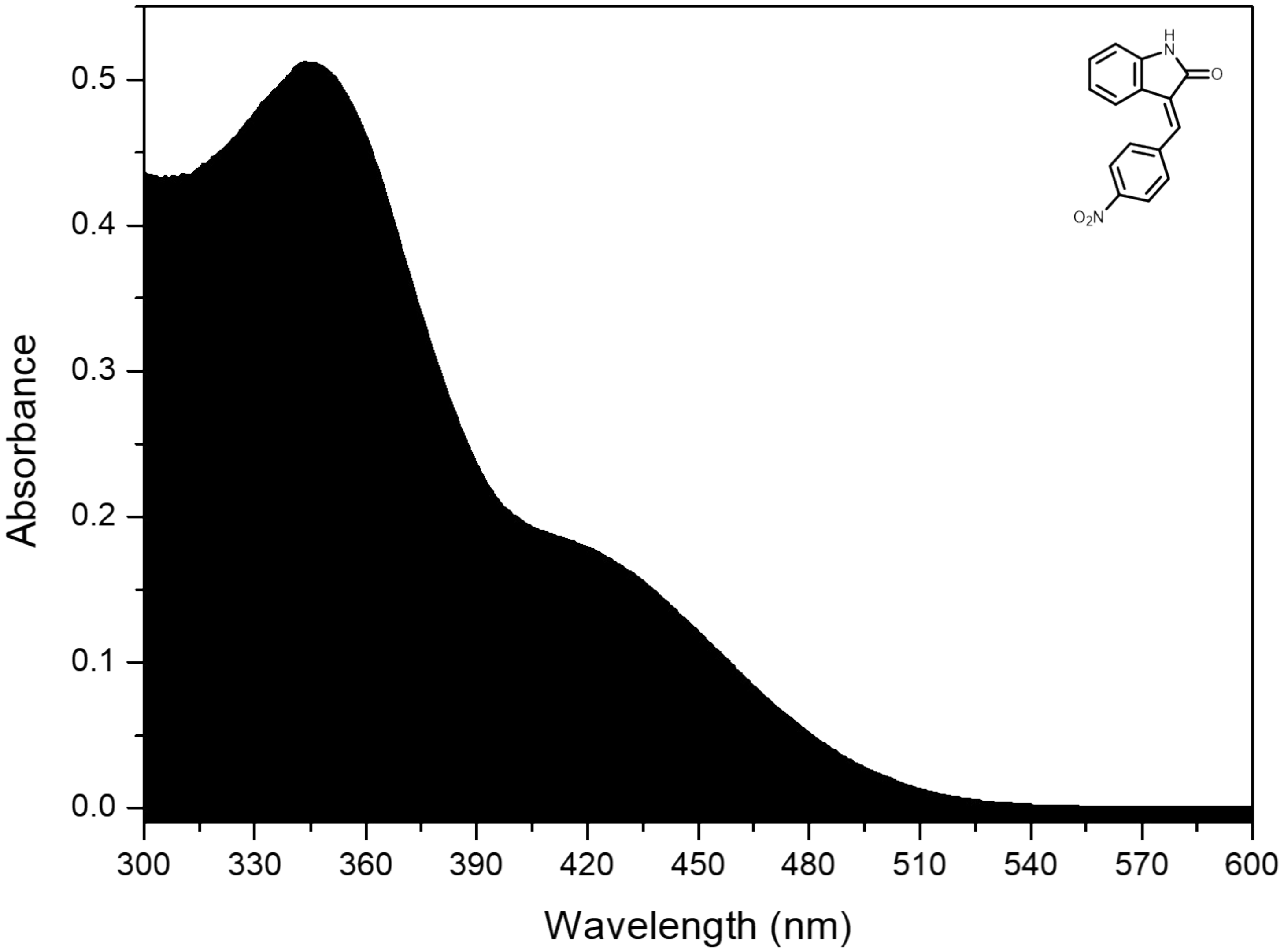


Figure S29: UV Spectra of (*E*)-3-(4-nitrobenzylidene)indolin-2-one (**3d**)

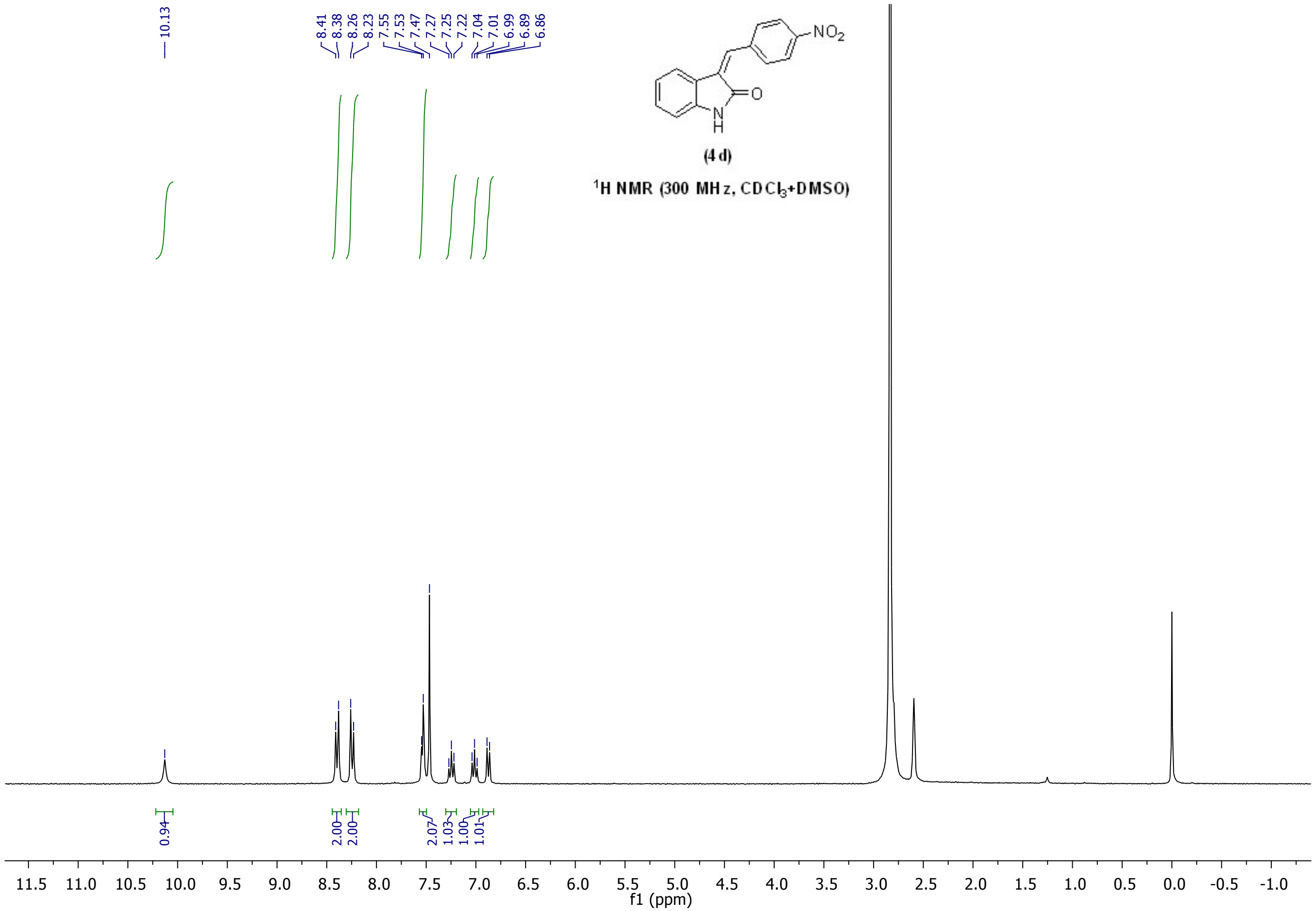


Figure S30: ^{1}H NMR Spectra of (*Z*)-3-(4-nitrobenzylidene)indolin-2-one (**4d**)

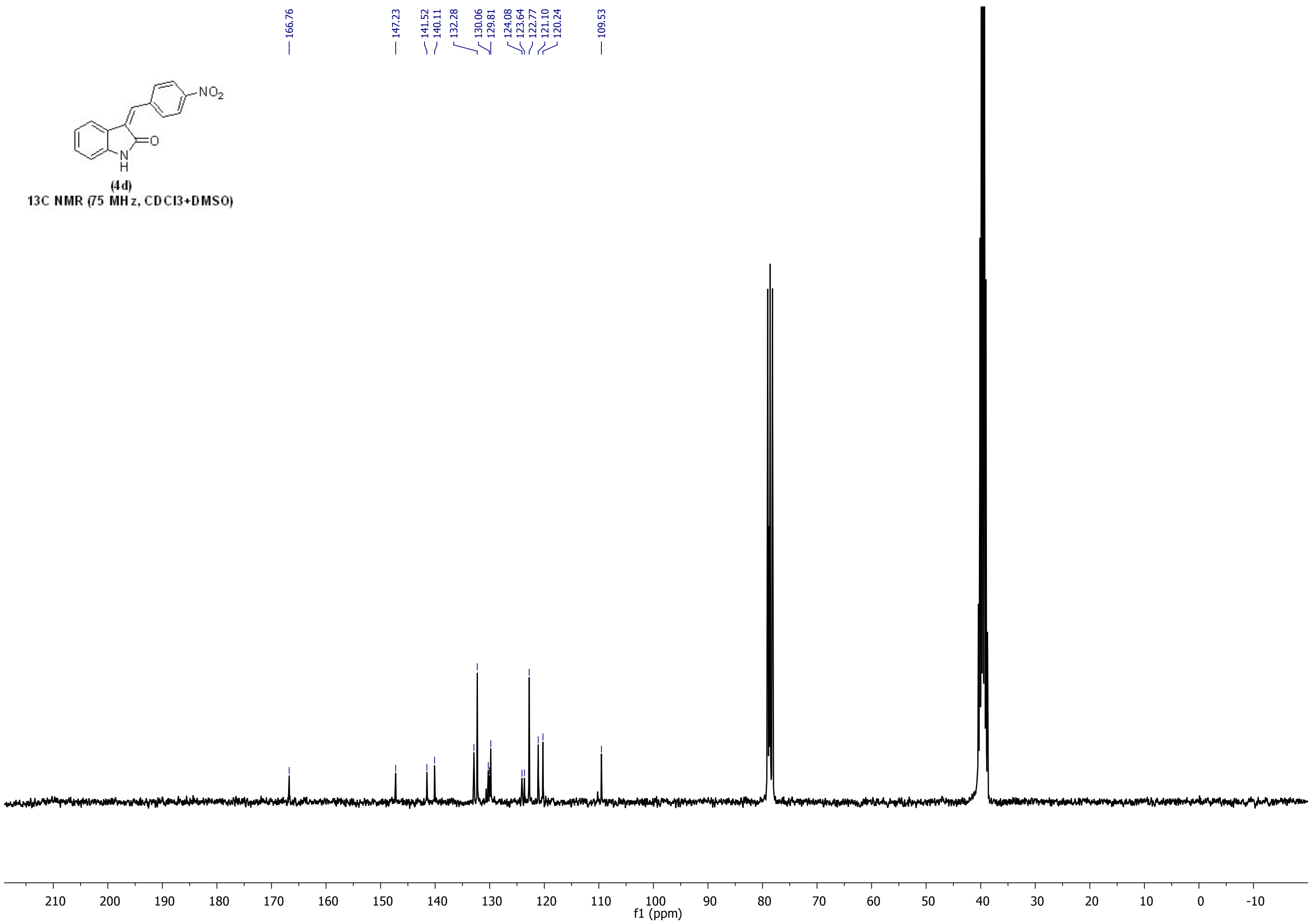


Figure S31: ^{13}C NMR Spectra of (*E*)-3-(4-nitrobenzylidene)indolin-2-one (**4d**)

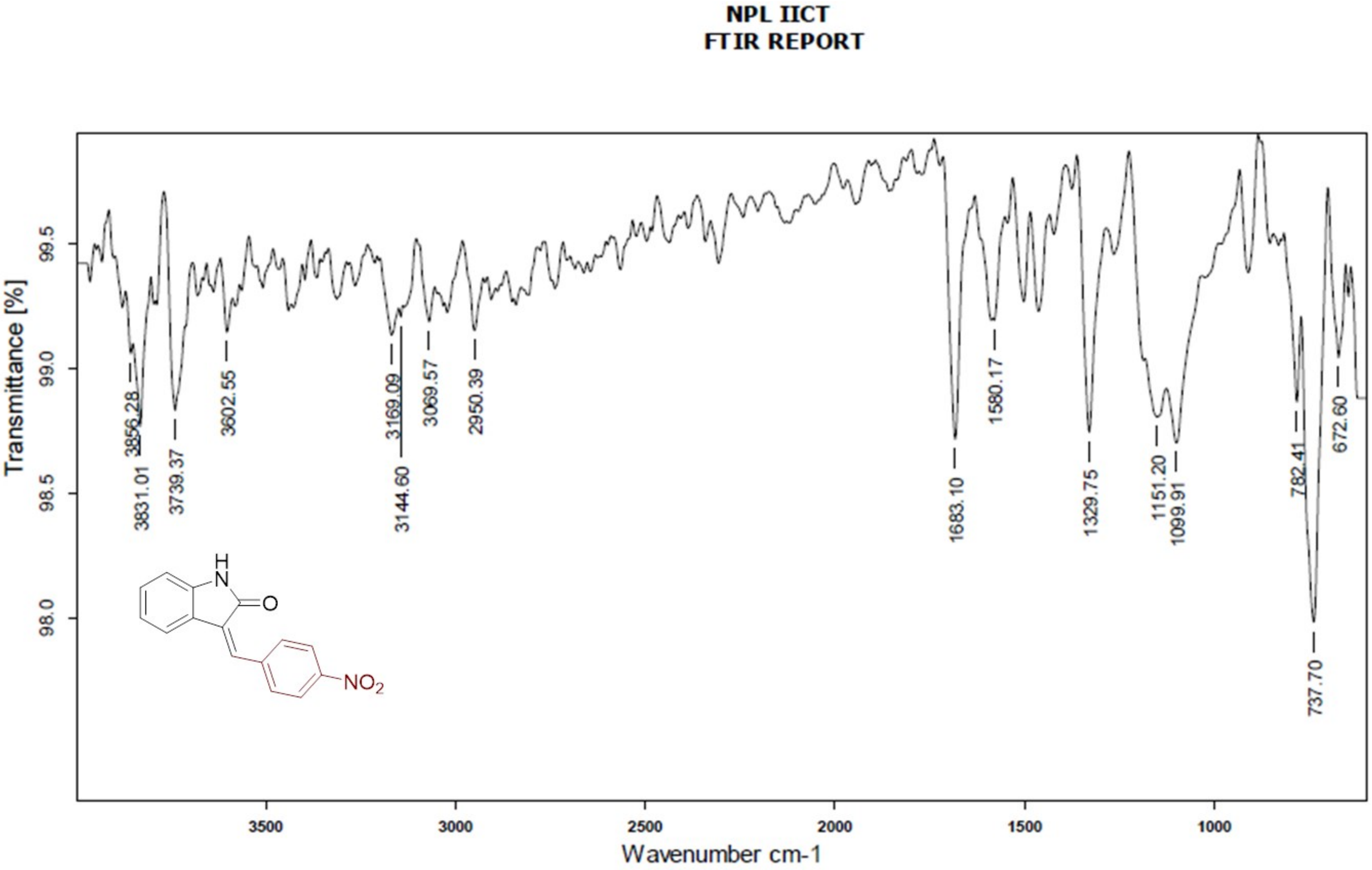


Figure S32: IR Spectra of (*Z*)-3-(4-nitrobenzylidene)indolin-2-one (**4d**)

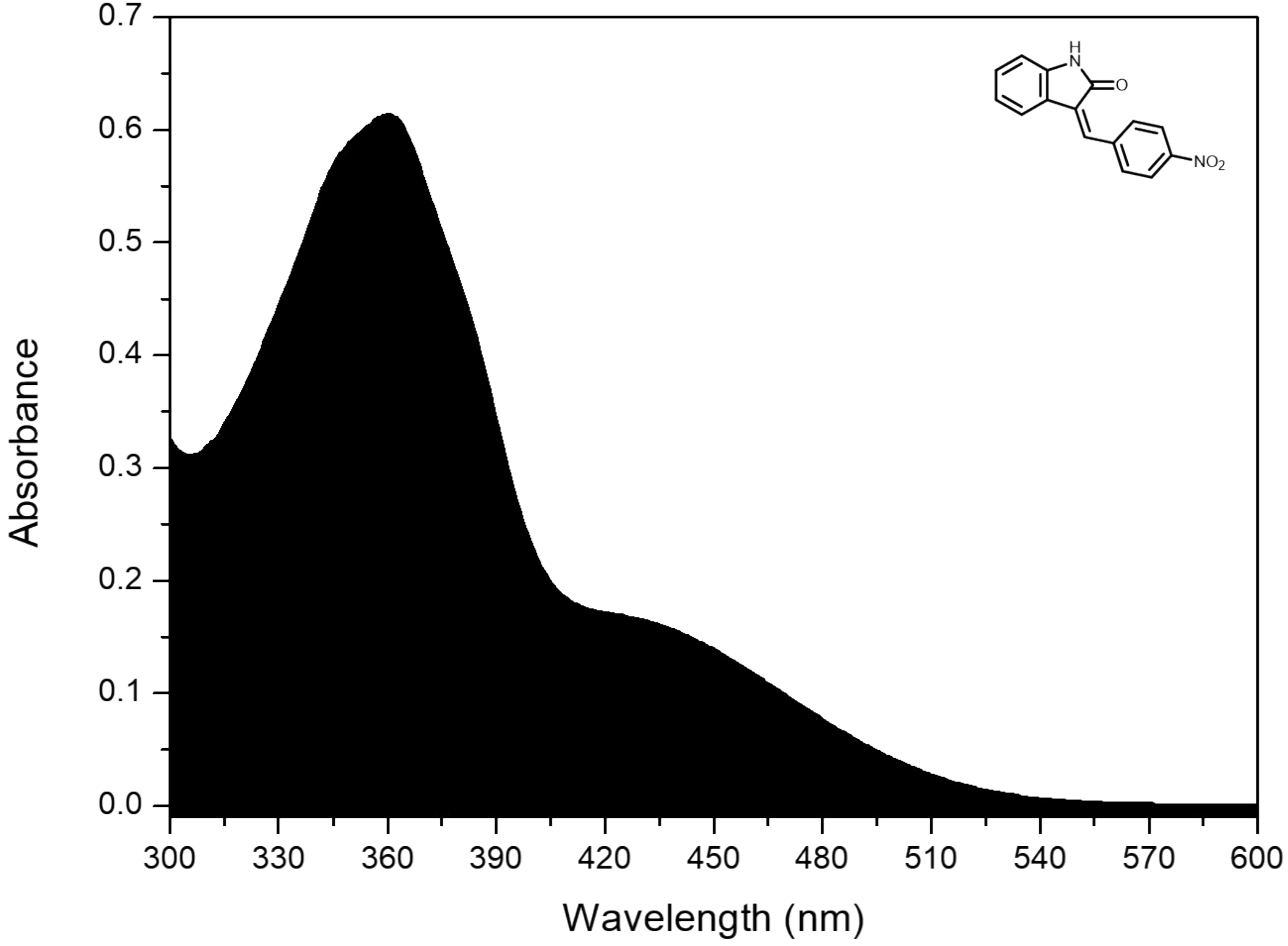


Figure S33: UV Spectra of (*Z*)-3-(4-nitrobenzylidene)indolin-2-one (**4d**)

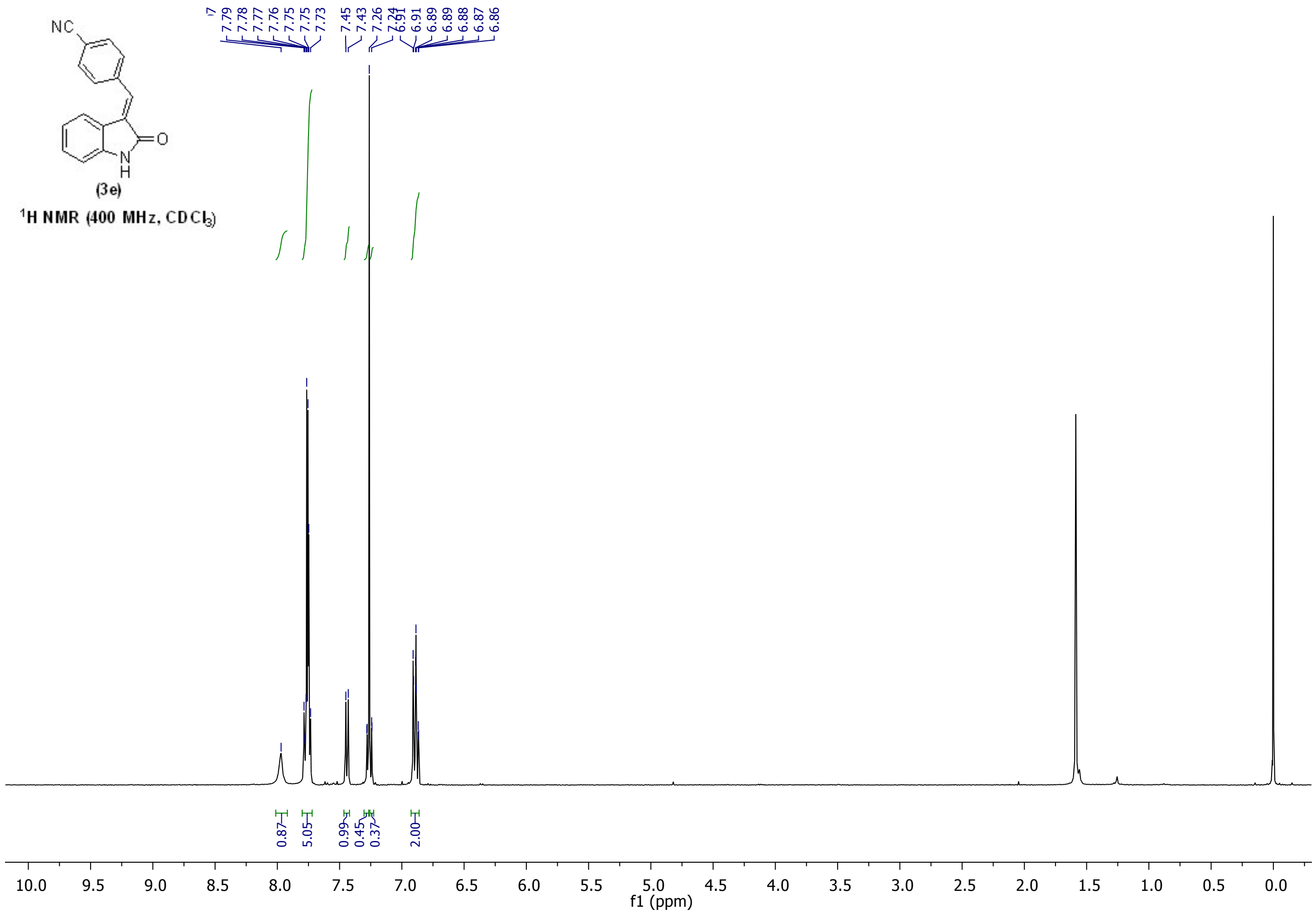


Figure S34: ^{1}H NMR Spectra of (*E*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile **(3e)**

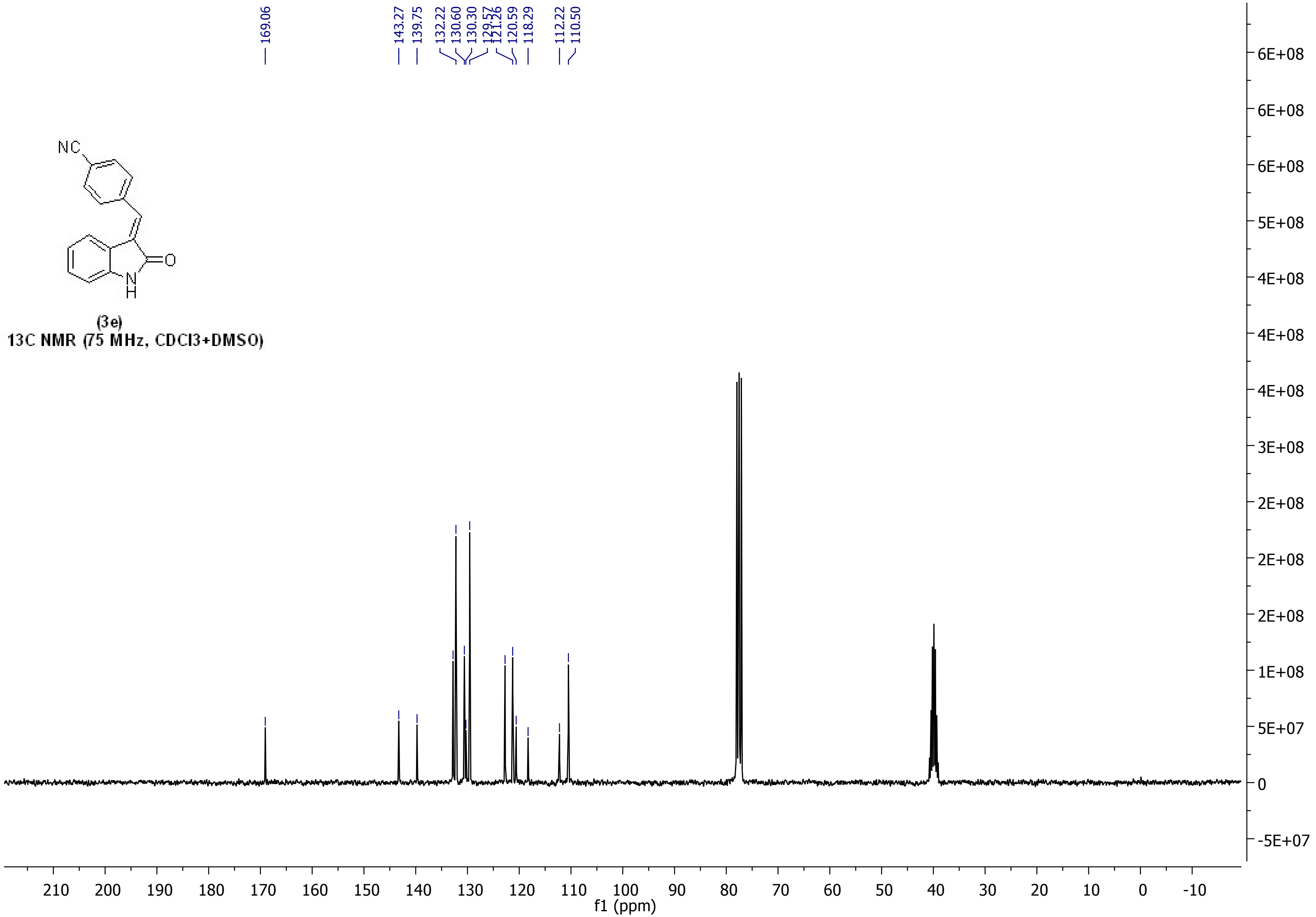


Figure S35: ^{13}C NMR Spectra of (*E*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile **(3e)**

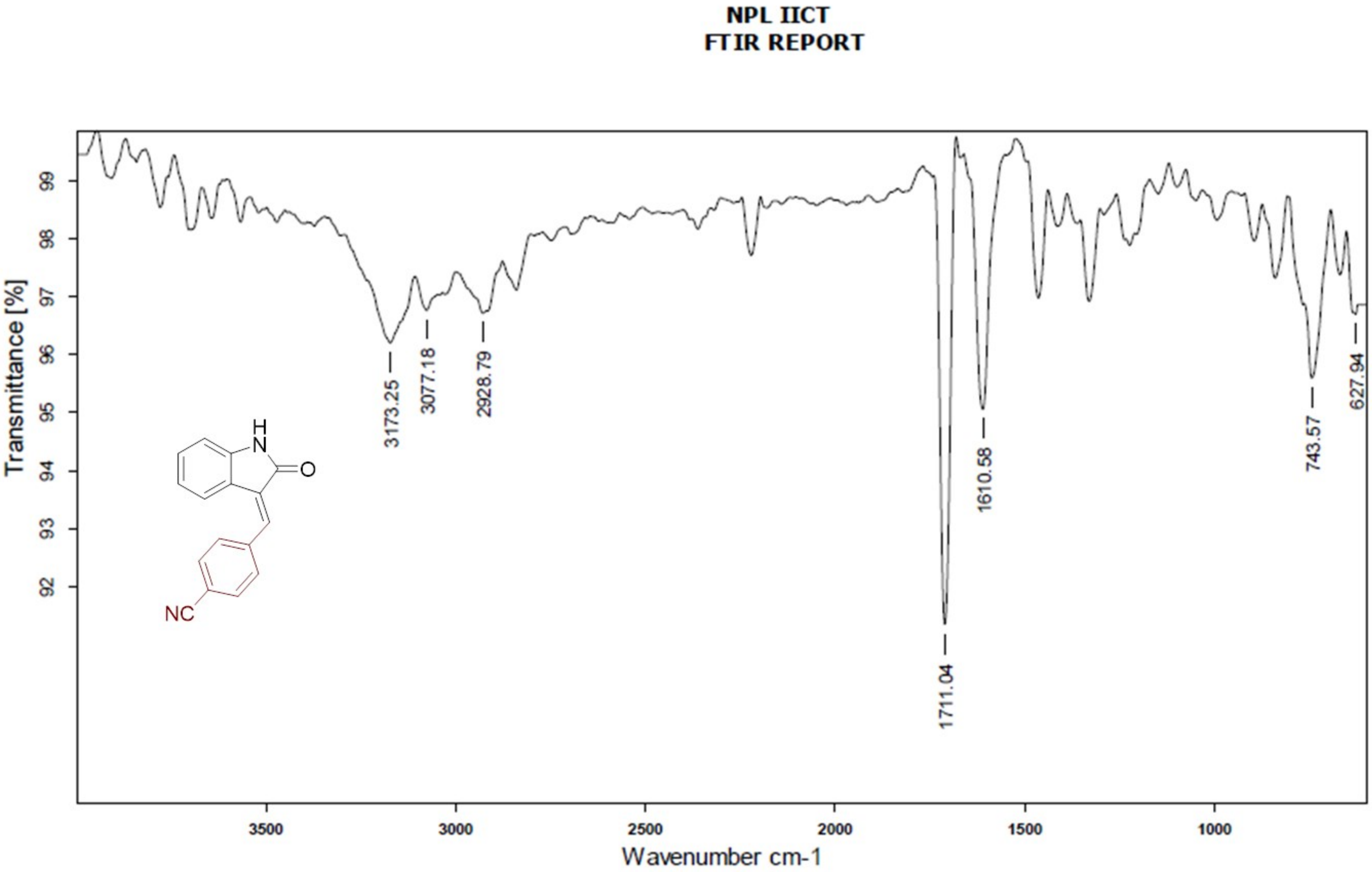


Figure S36: IR Spectra of (*E*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile **(3e)**

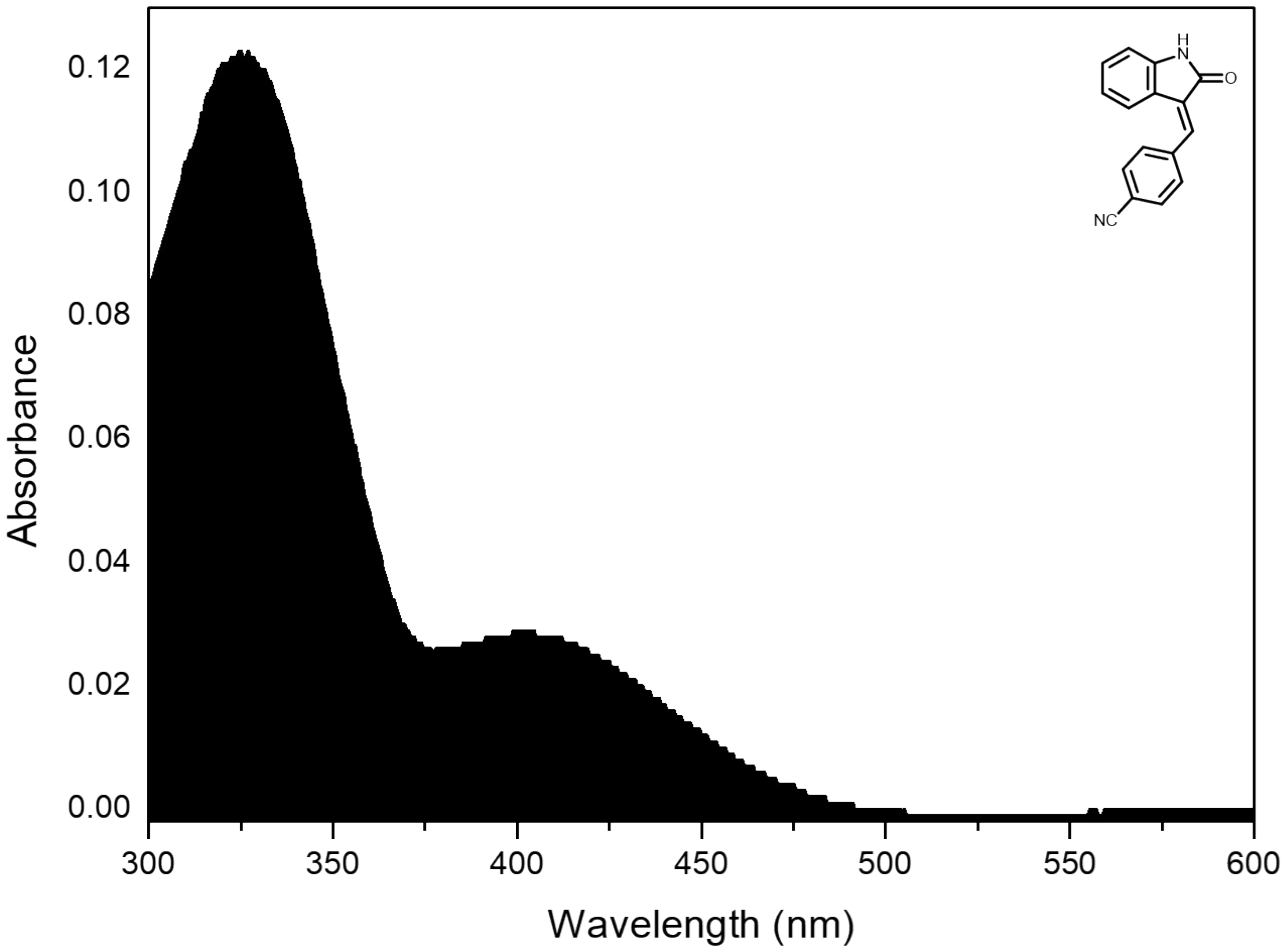


Figure S37: UV Spectra of (*E*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile **(3e)**

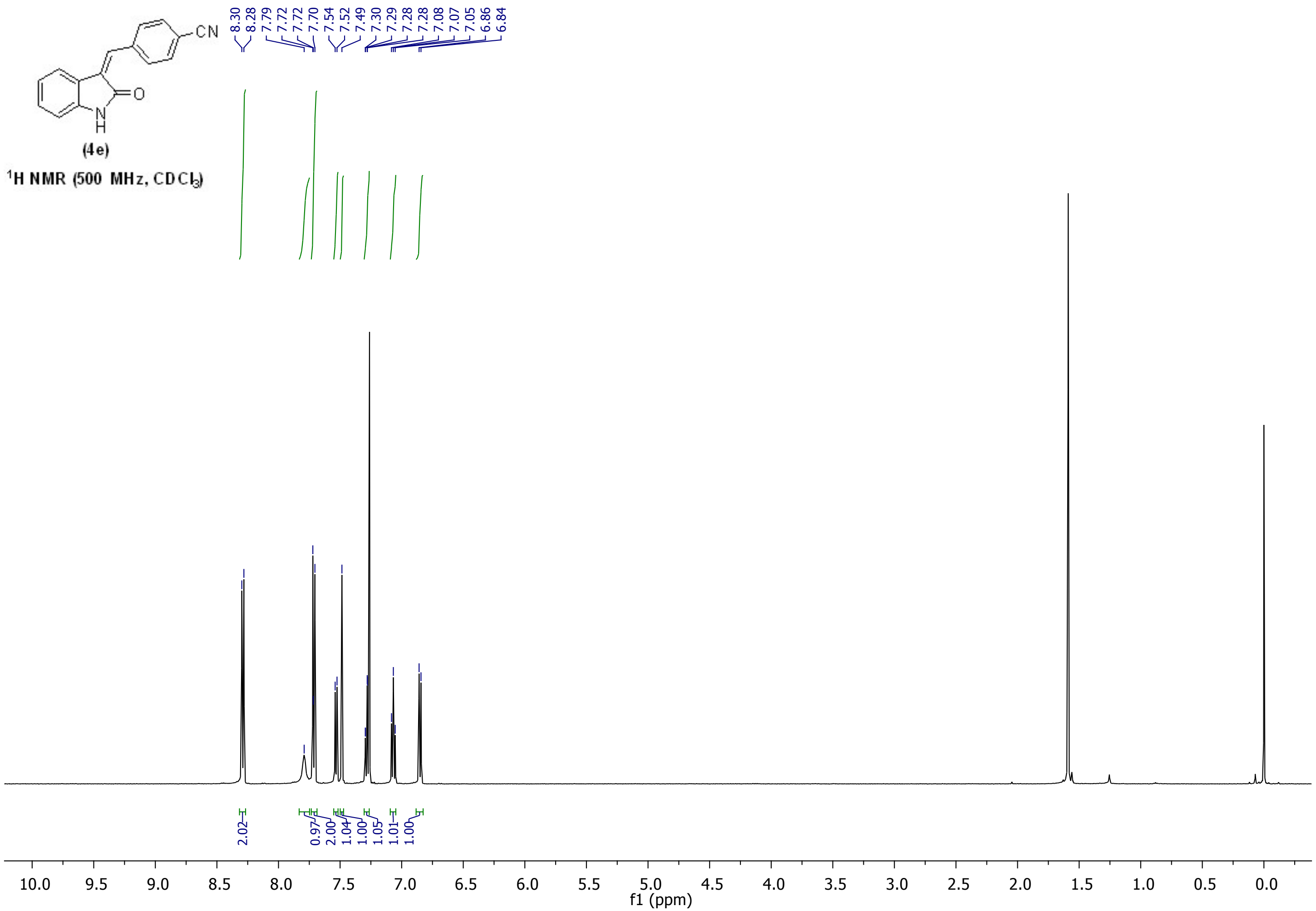


Figure S38: ^{1}H NMR Spectra of (*Z*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile **(3e)**

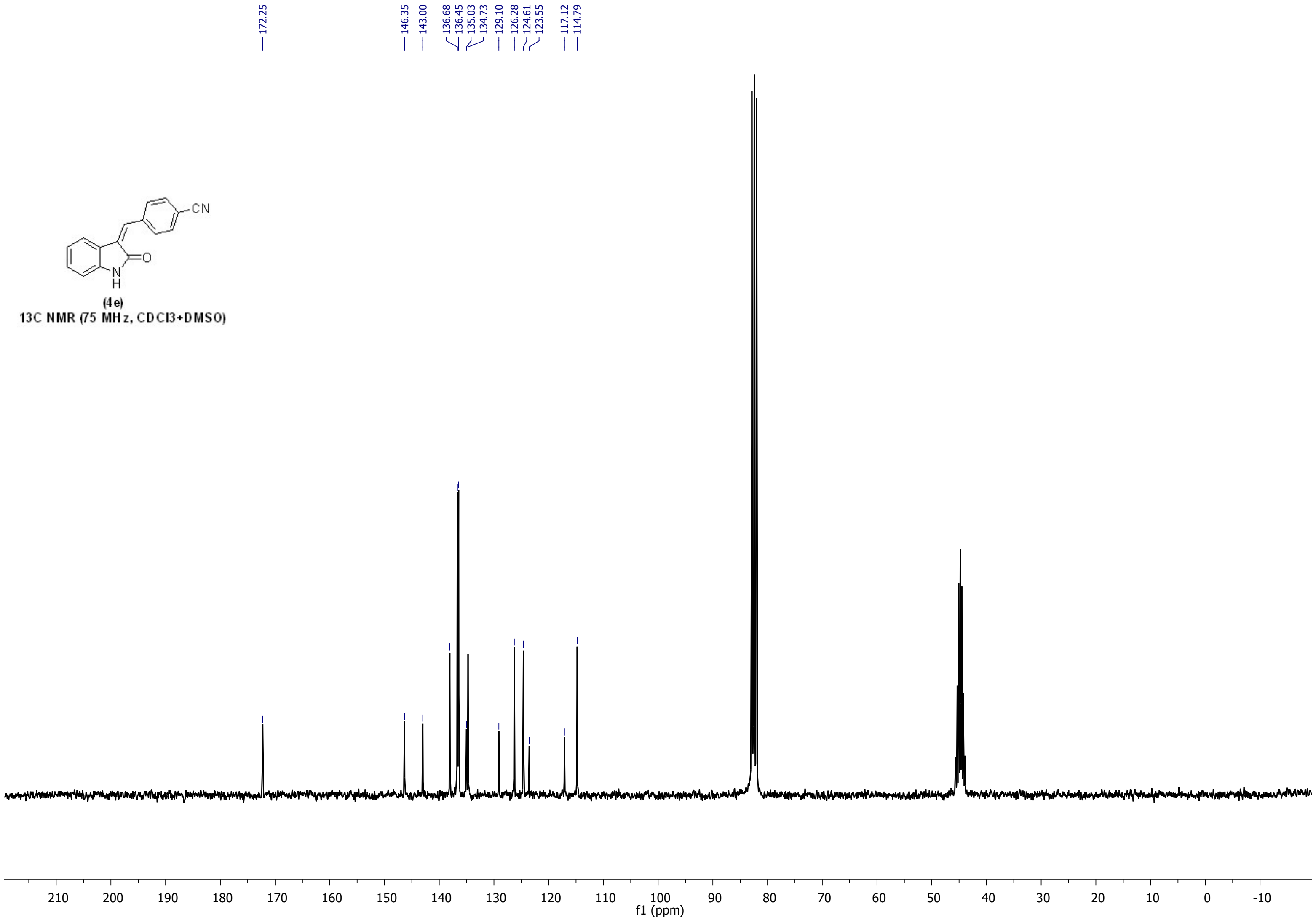


Figure S39: ^{13}CNMR Spectra of (*Z*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile **(4e)**

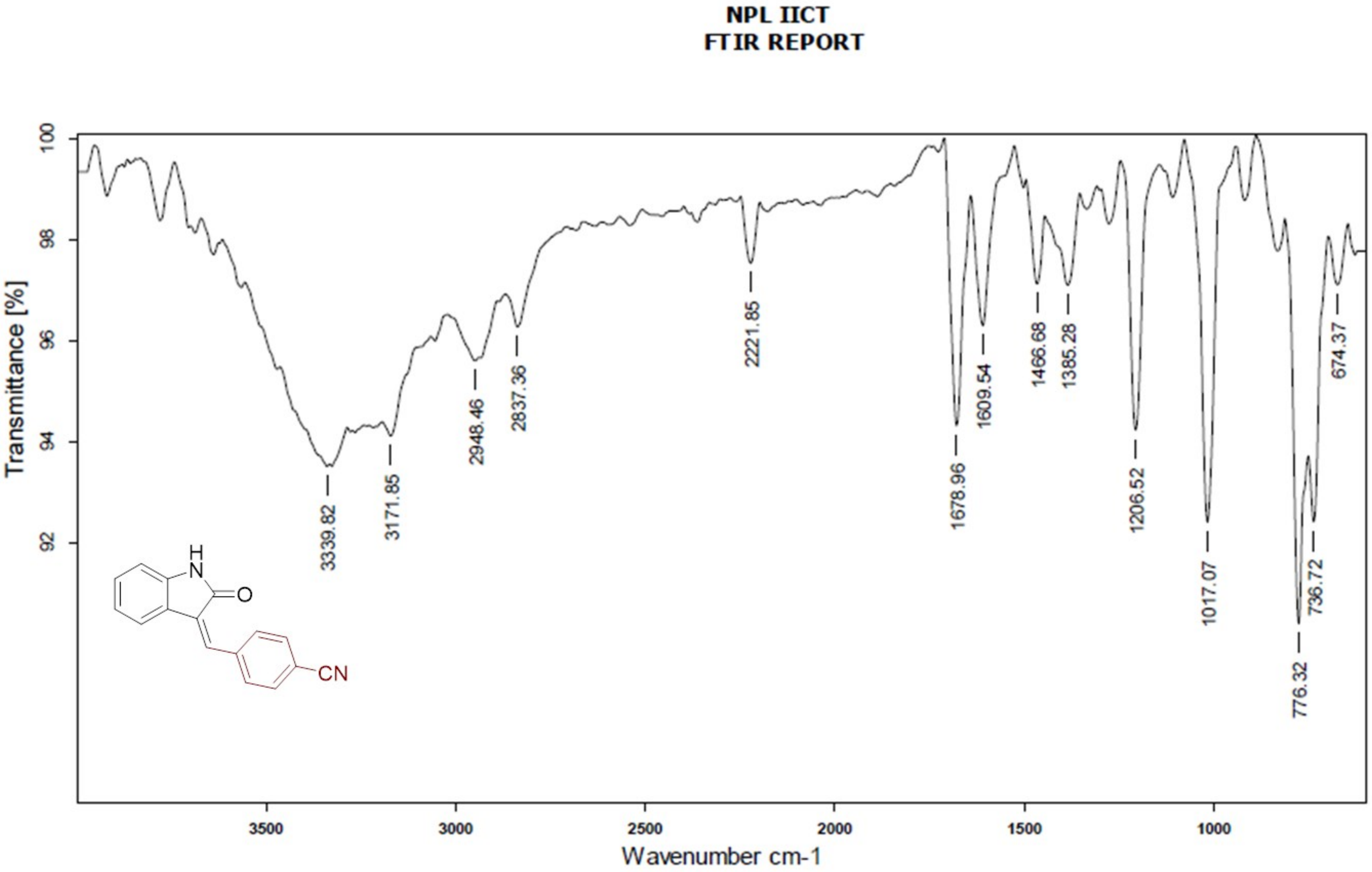


Figure S40: IR Spectra of (*Z*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile **(4e)**

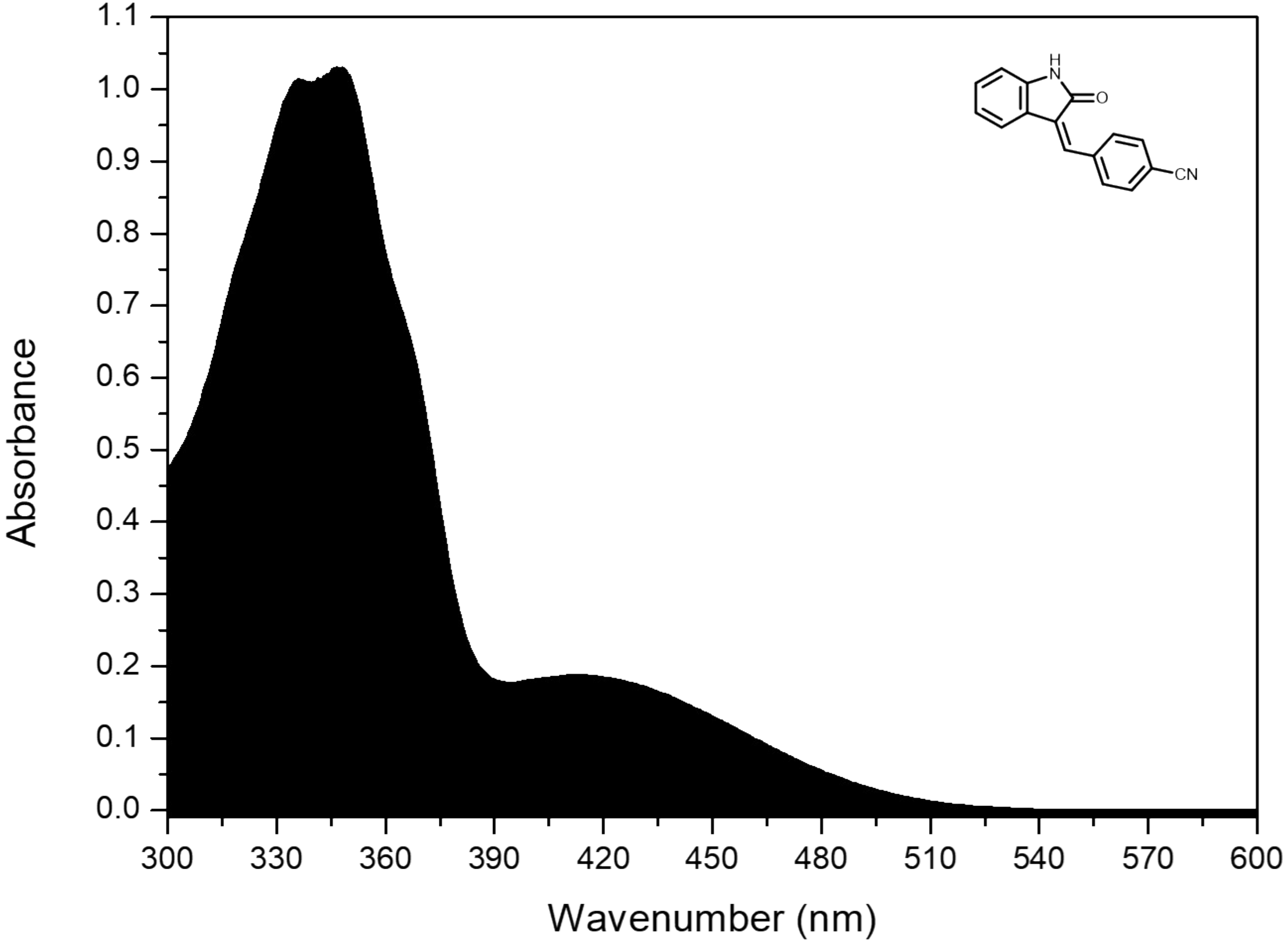


Figure S41: UV Spectra of (*Z*)-4-((2-oxoindolin-3-ylidene)methyl)benzonitrile **(4e)**

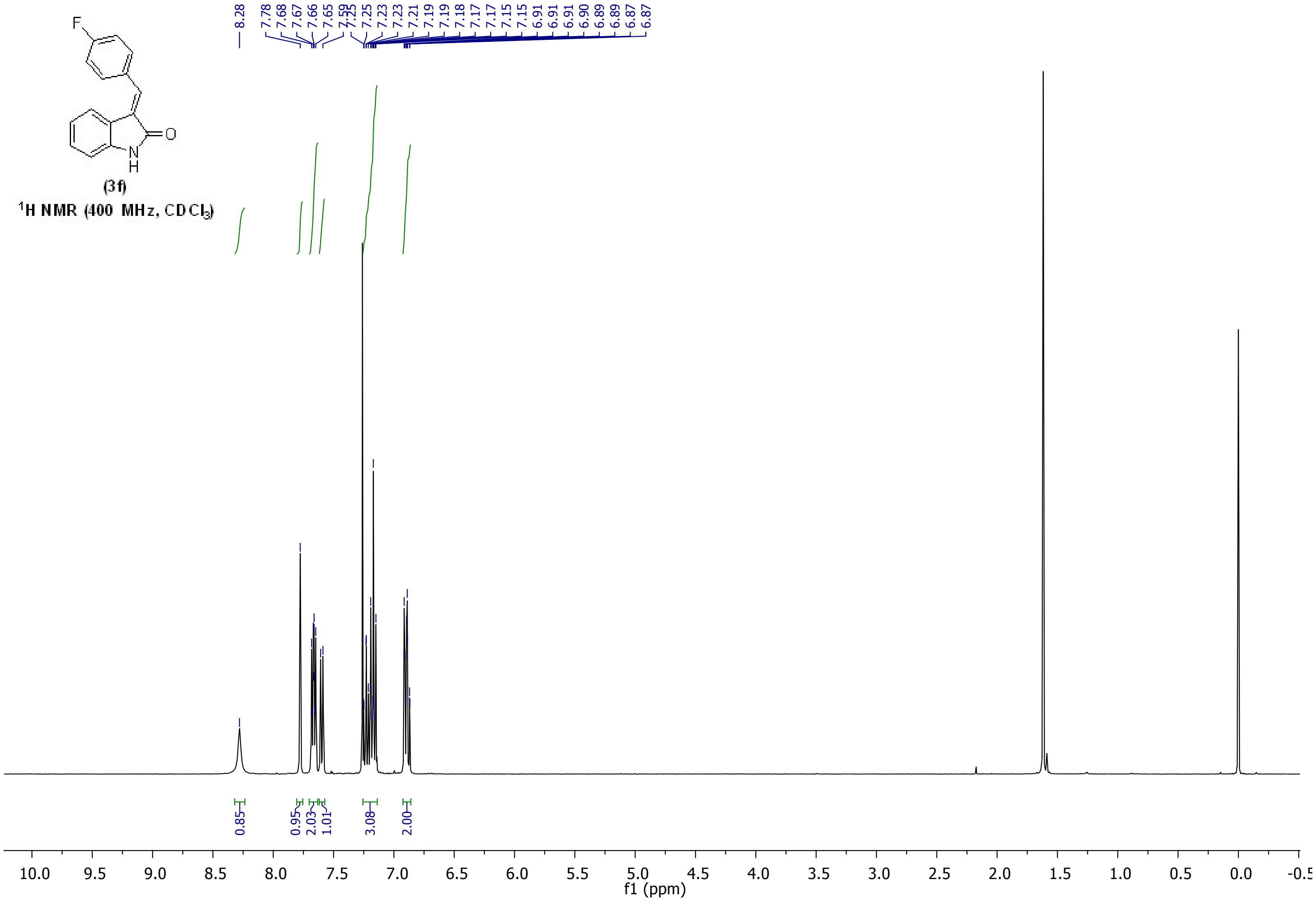


Figure S42: ^{1}H NMR Spectra of (*E*)-3-(4-fluorobenzylidene)indolin-2-one **(3f)**

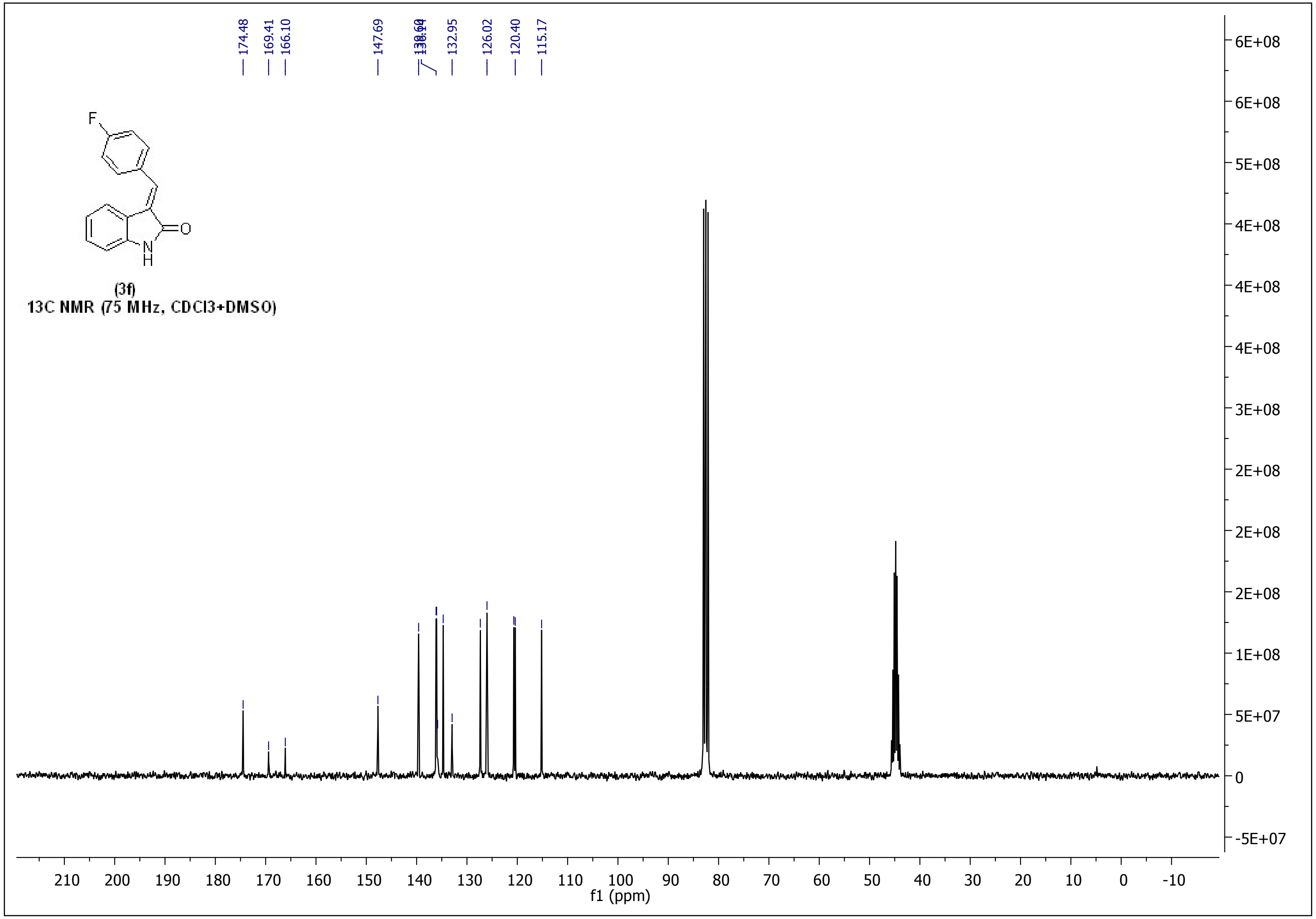


Figure S43: ^{13}CNMR Spectra of (*E*)-3-(4-fluorobenzylidene)indolin-2-one **(3f)**

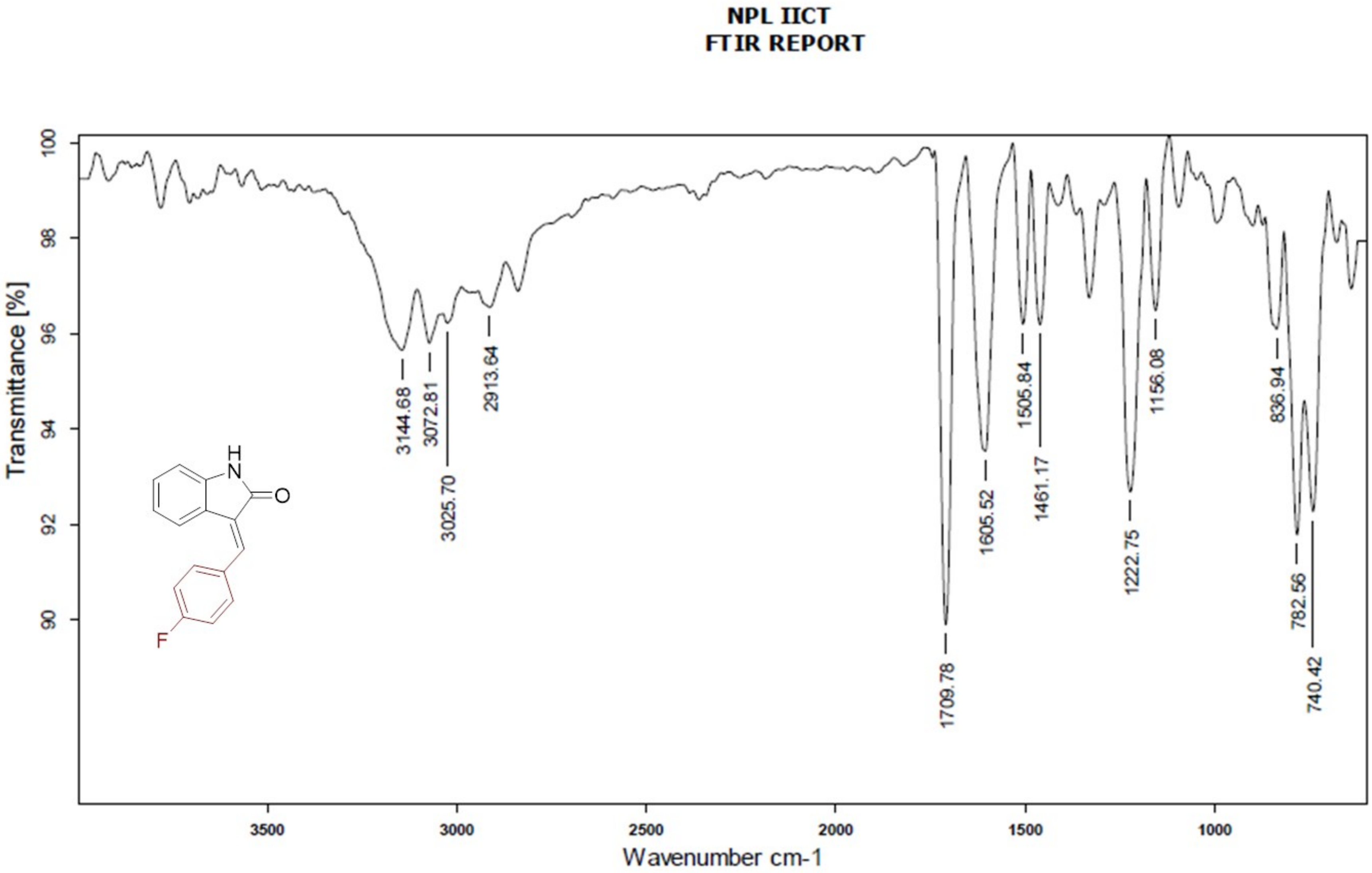


Figure S44: IR Spectra of (*E*)-3-(4-fluorobenzylidene)indolin-2-one **(3f)**

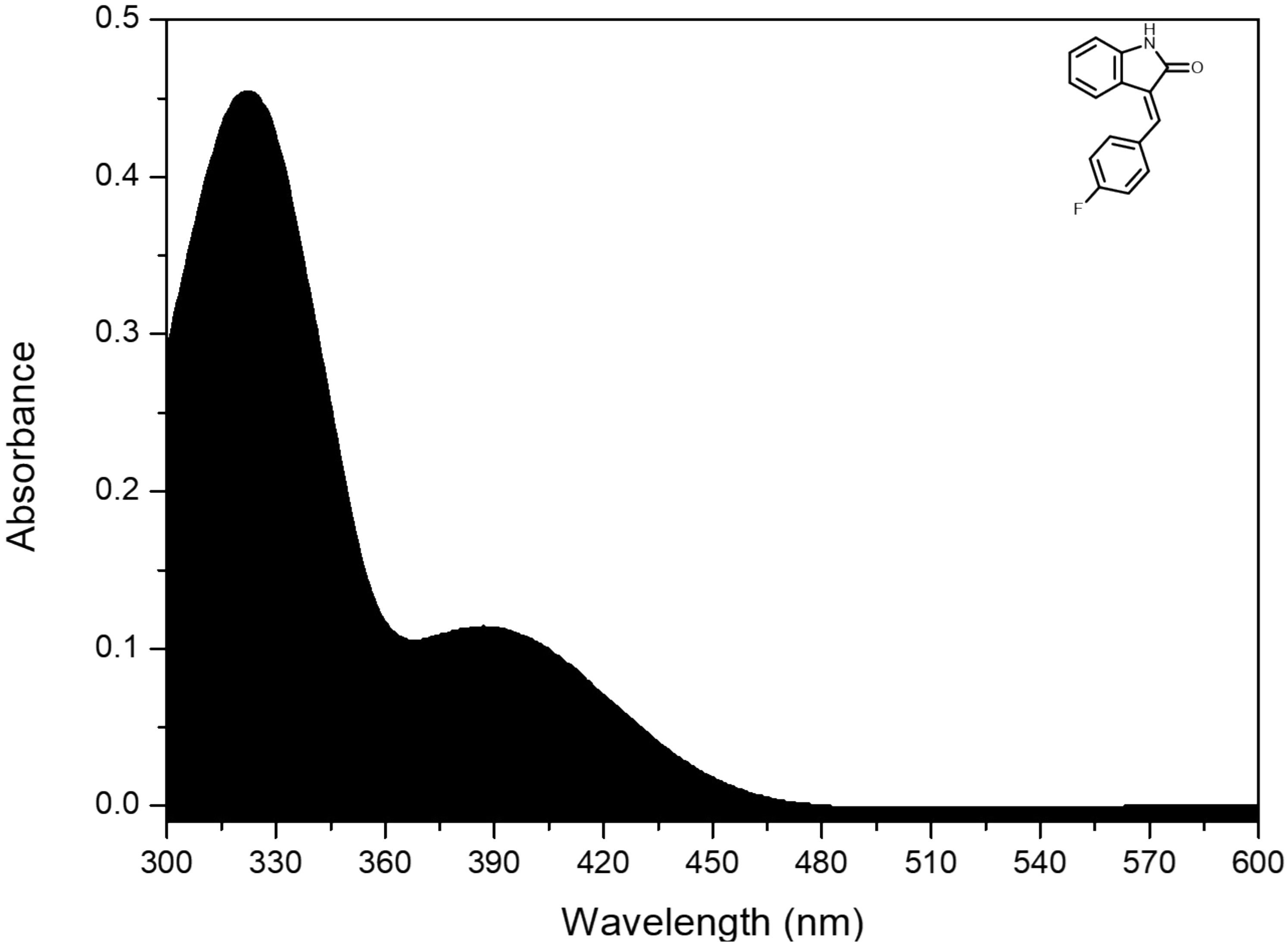


Figure S45: UV Spectra of (*E*)-3-(4-fluorobenzylidene)indolin-2-one **(3f)**

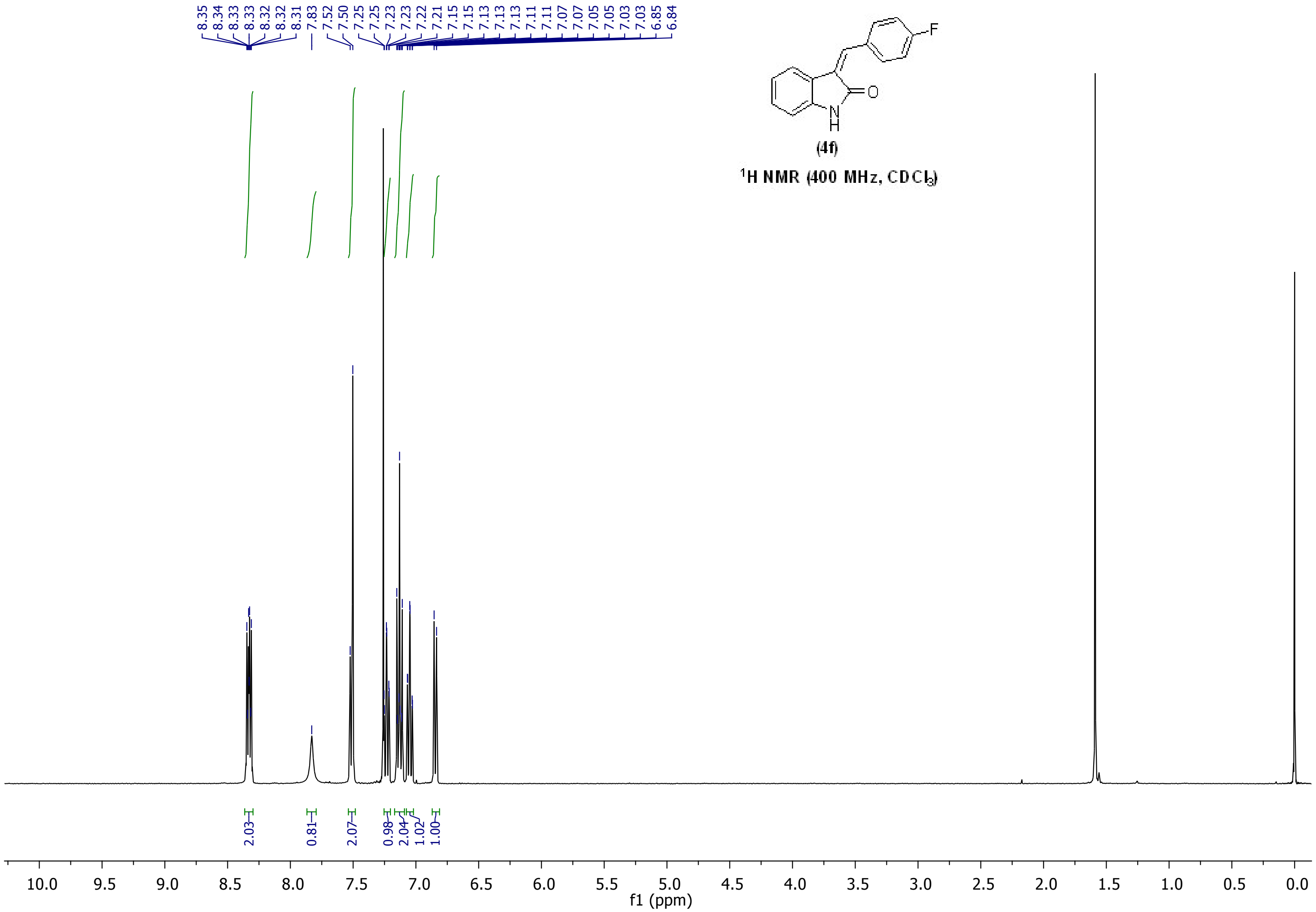


Figure S46: ^{1}H NMR spectra of (*Z*)-3-(4-fluorobenzylidene)indolin-2-one **(4f)**

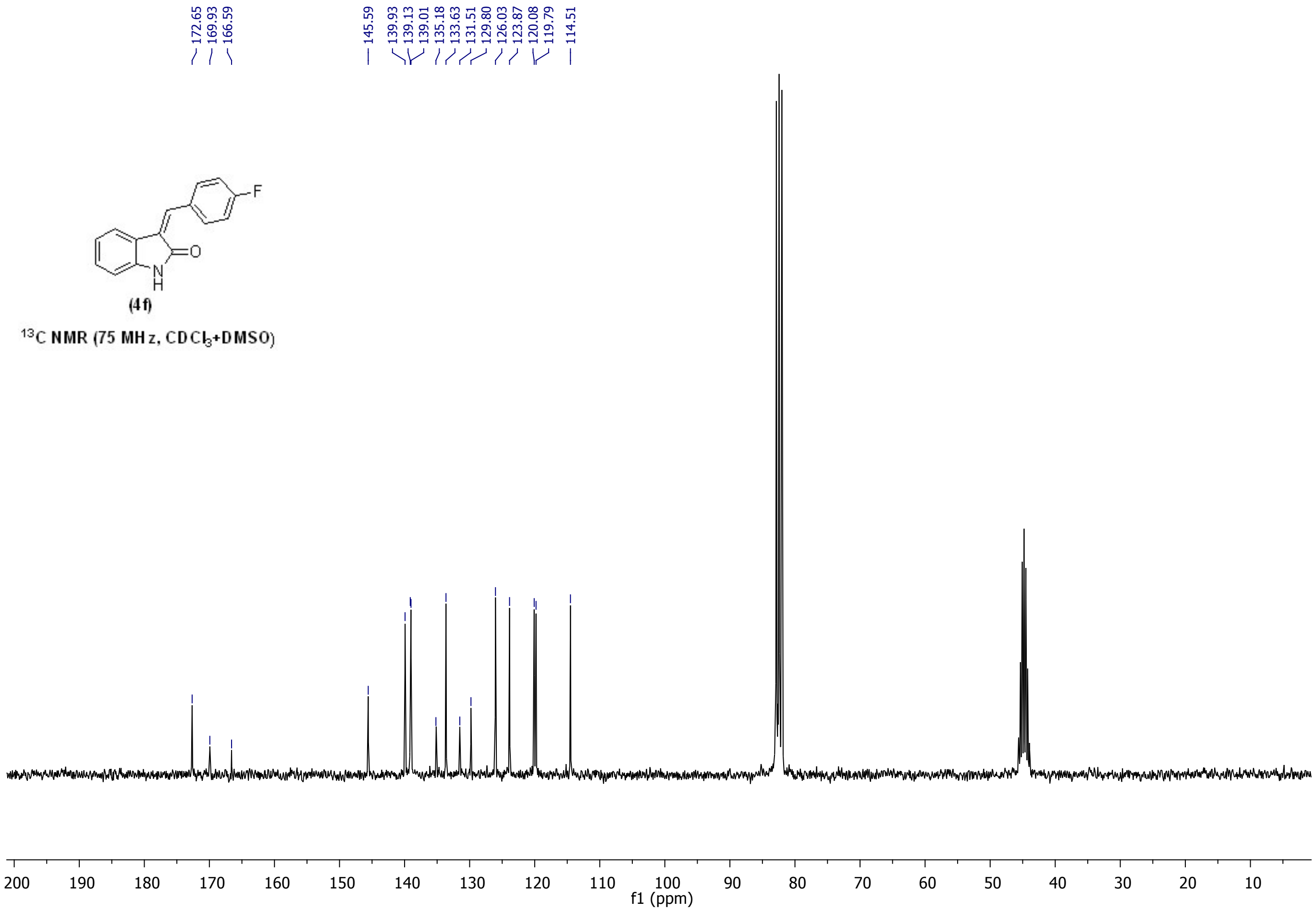


Figure S47: ^{13}C NMR spectra of (*Z*)-3-(4-fluorobenzylidene)indolin-2-one **(4f)**

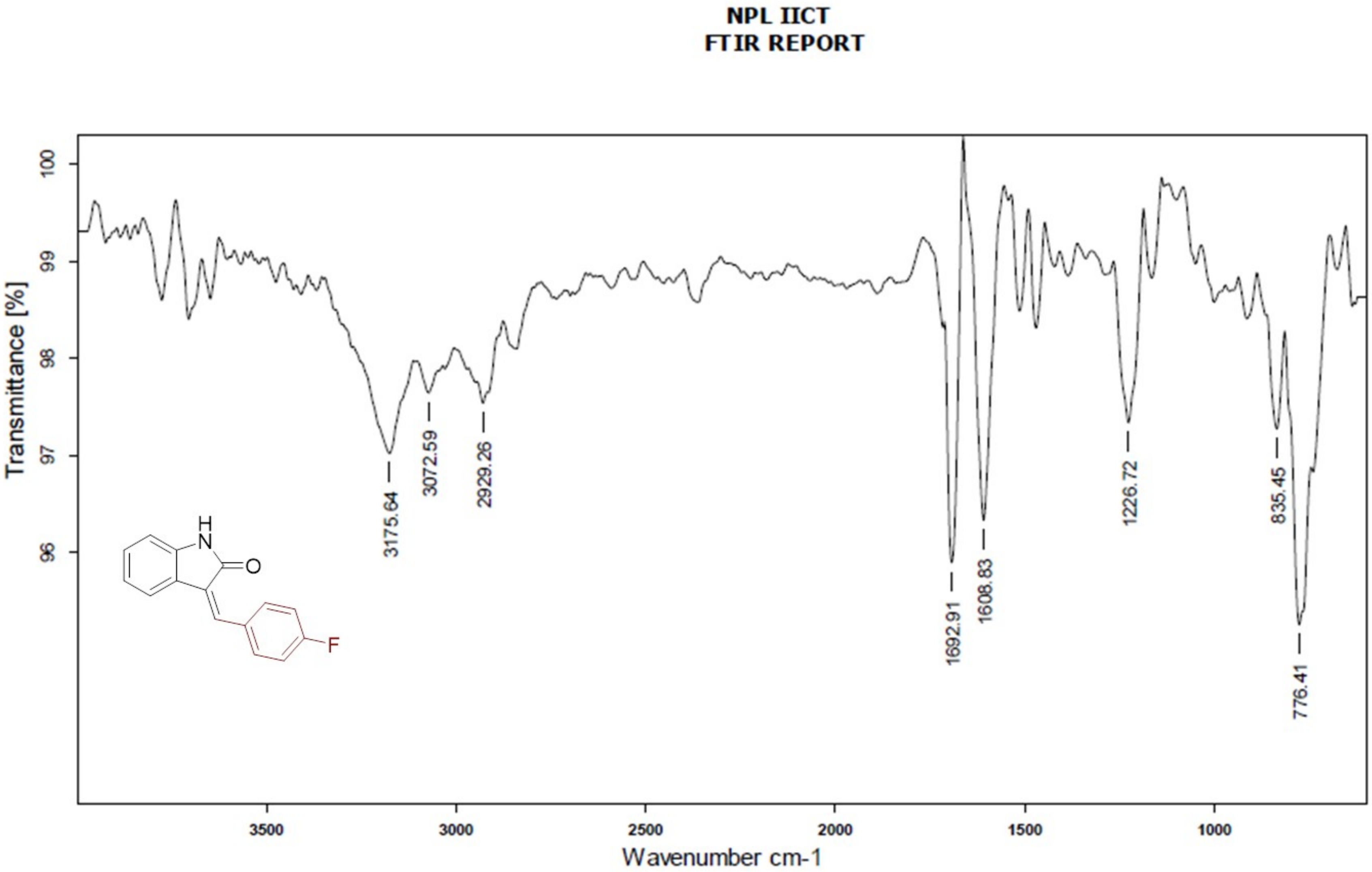


Figure S48: IR Spectra of (*Z*)-3-(4-fluorobenzylidene)indolin-2-one **(4f)**

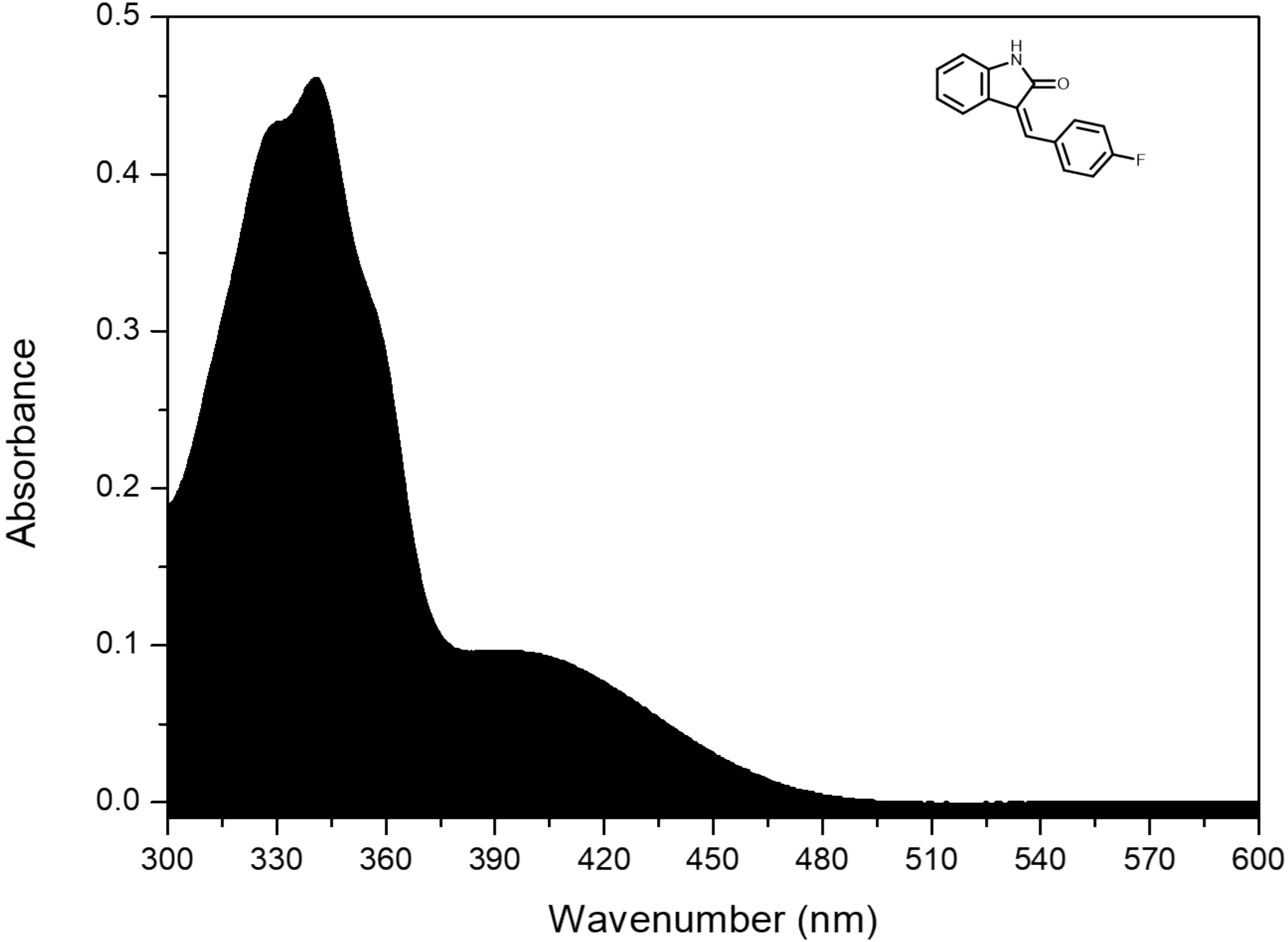


Figure S49: UV Spectra of (*Z*)-3-(4-fluorobenzylidene)indolin-2-one **(4f)**

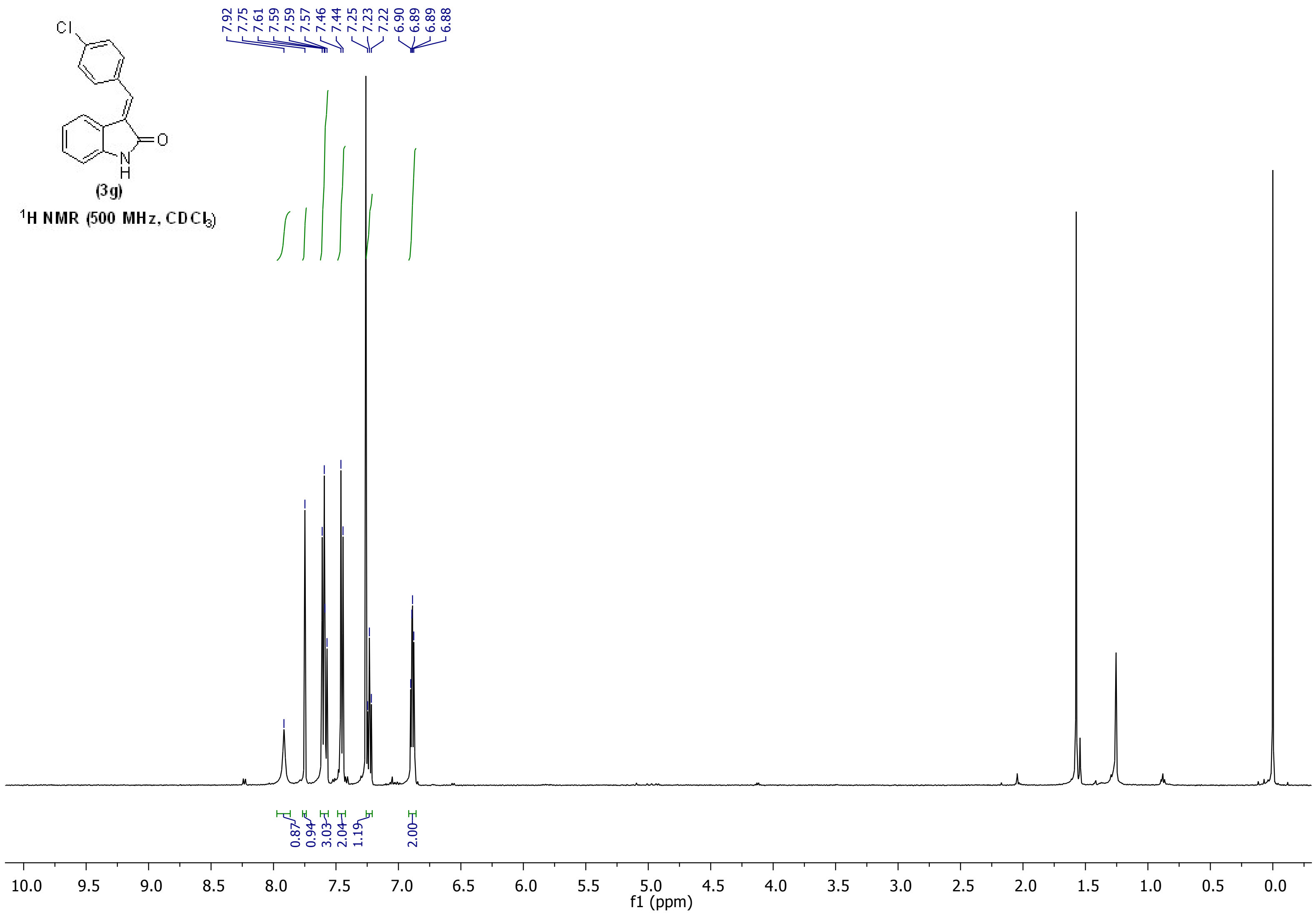


Figure S50: ^{1}H NMR Spectra of (*E*)-3-(4-chlorobenzylidene)indolin-2-one **(3g)**

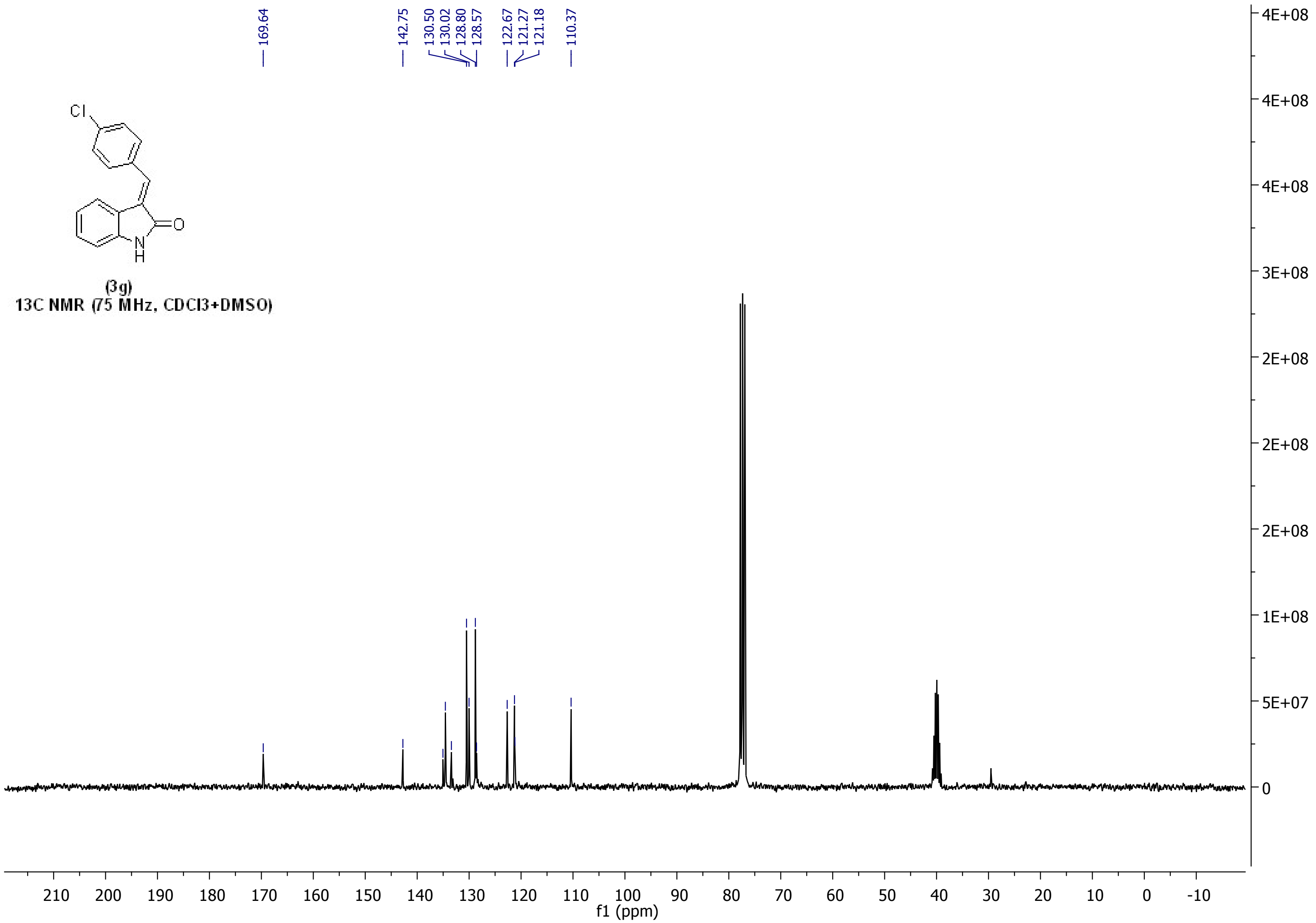


Figure S51: ^{13}CNMR Spectra of (*E*)-3-(4-chlorobenzylidene)indolin-2-one **(3g)**

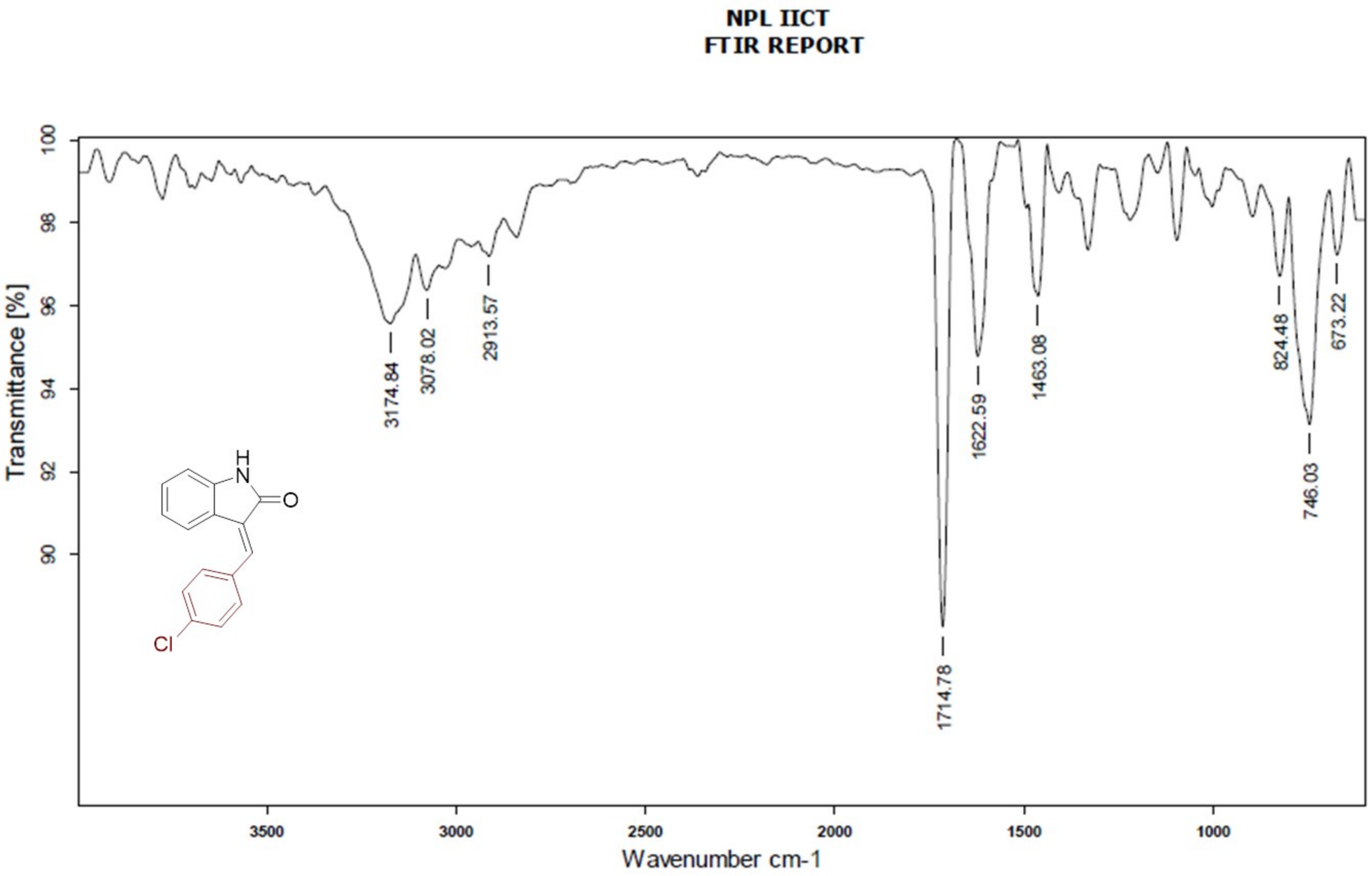


Figure S52: IR Spectra of (*E*)-3-(4-chlorobenzylidene)indolin-2-one **(3g)**

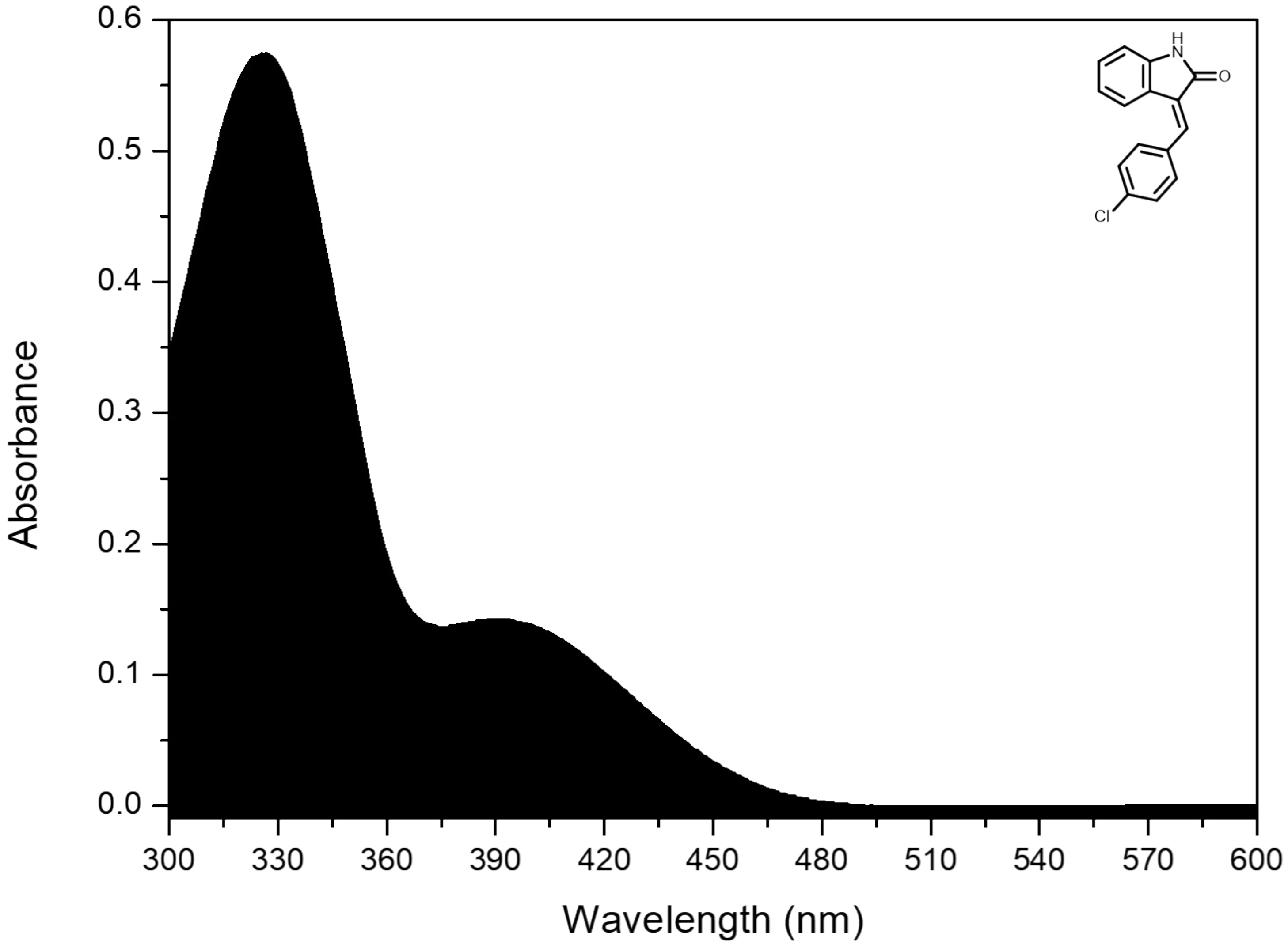


Figure S53: UV Spectra of (*E*)-3-(4-chlorobenzylidene)indolin-2-one **(3g)**

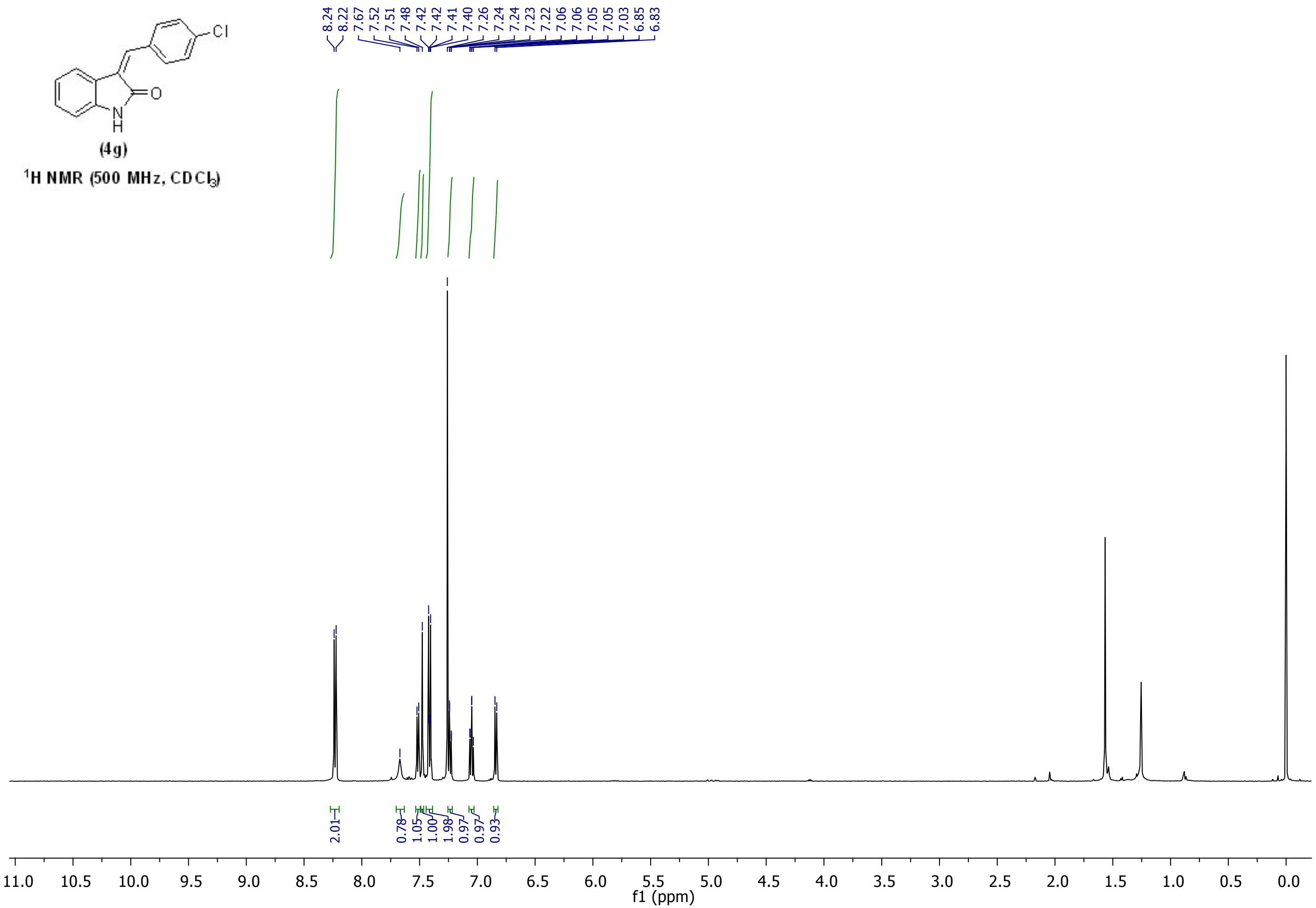


Figure S54: ^{1}H NMR Spectra of (*Z*)-3-(4-chlorobenzylidene)indolin-2-one **(4g)**

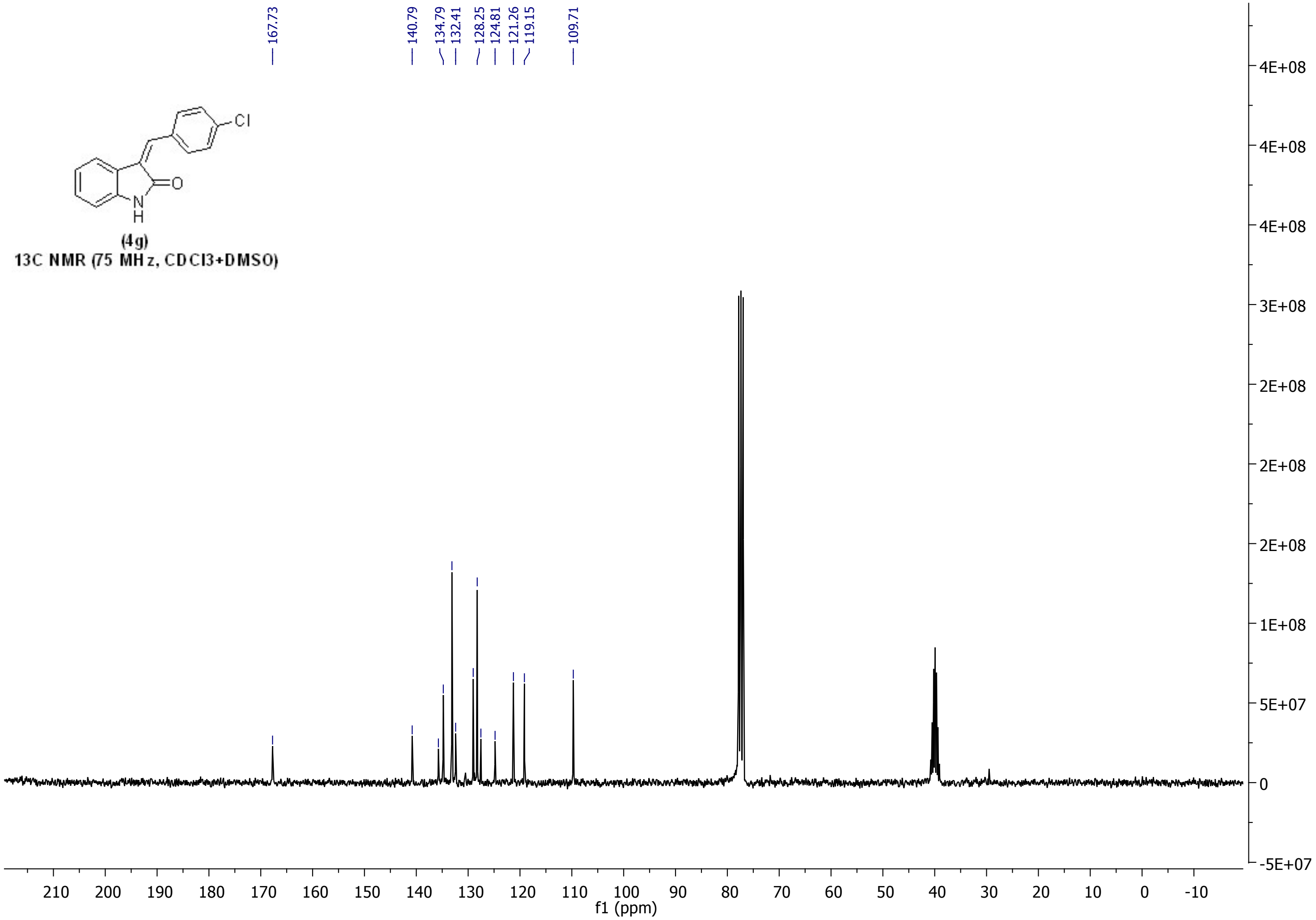


Figure S55: ^{13}C NMR Spectra of (*Z*)-3-(4-chlorobenzylidene)indolin-2-one **(4g)**

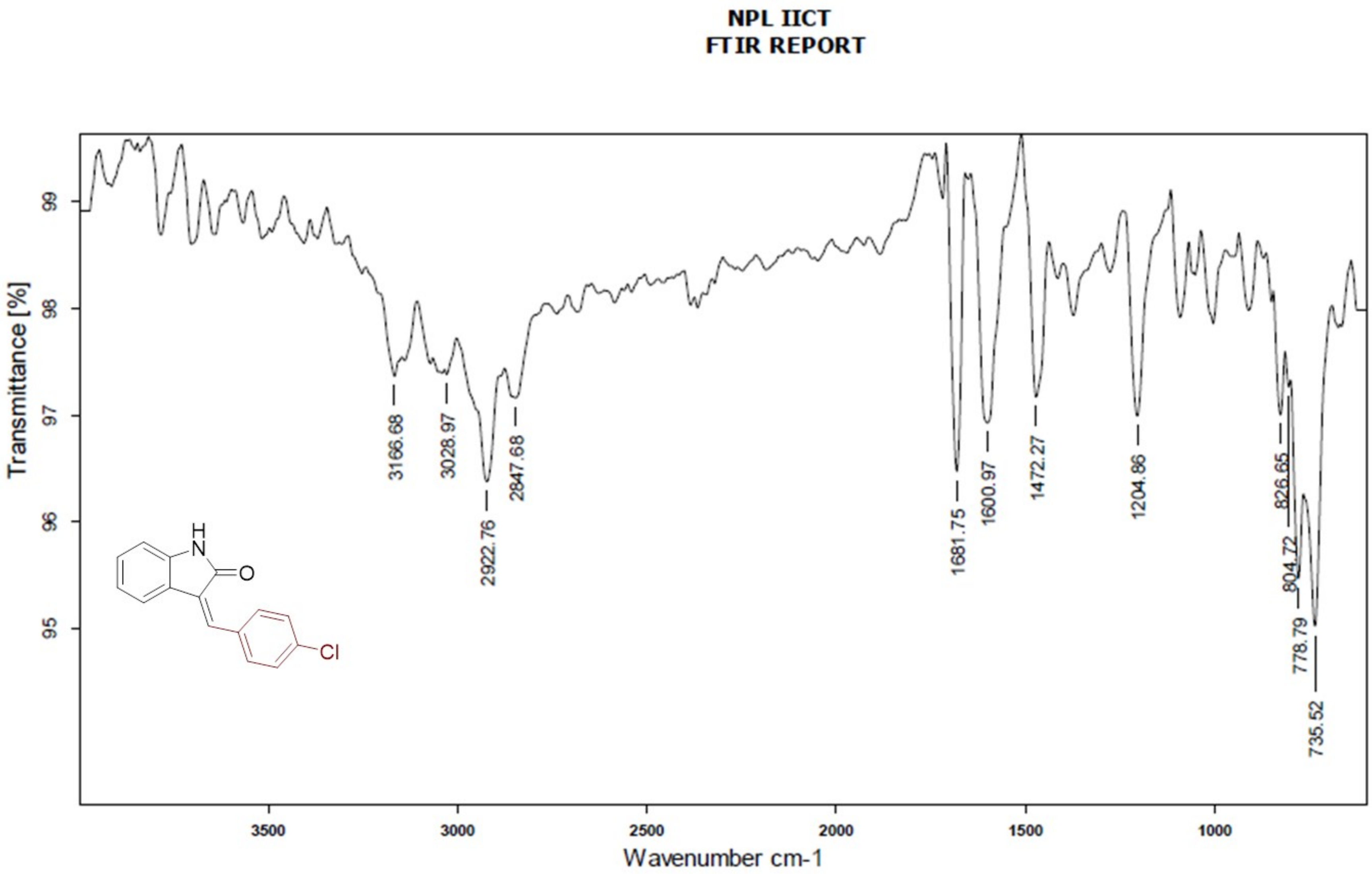


Figure S56: IR Spectra of (*Z*)-3-(4-chlorobenzylidene)indolin-2-one **(4g)**

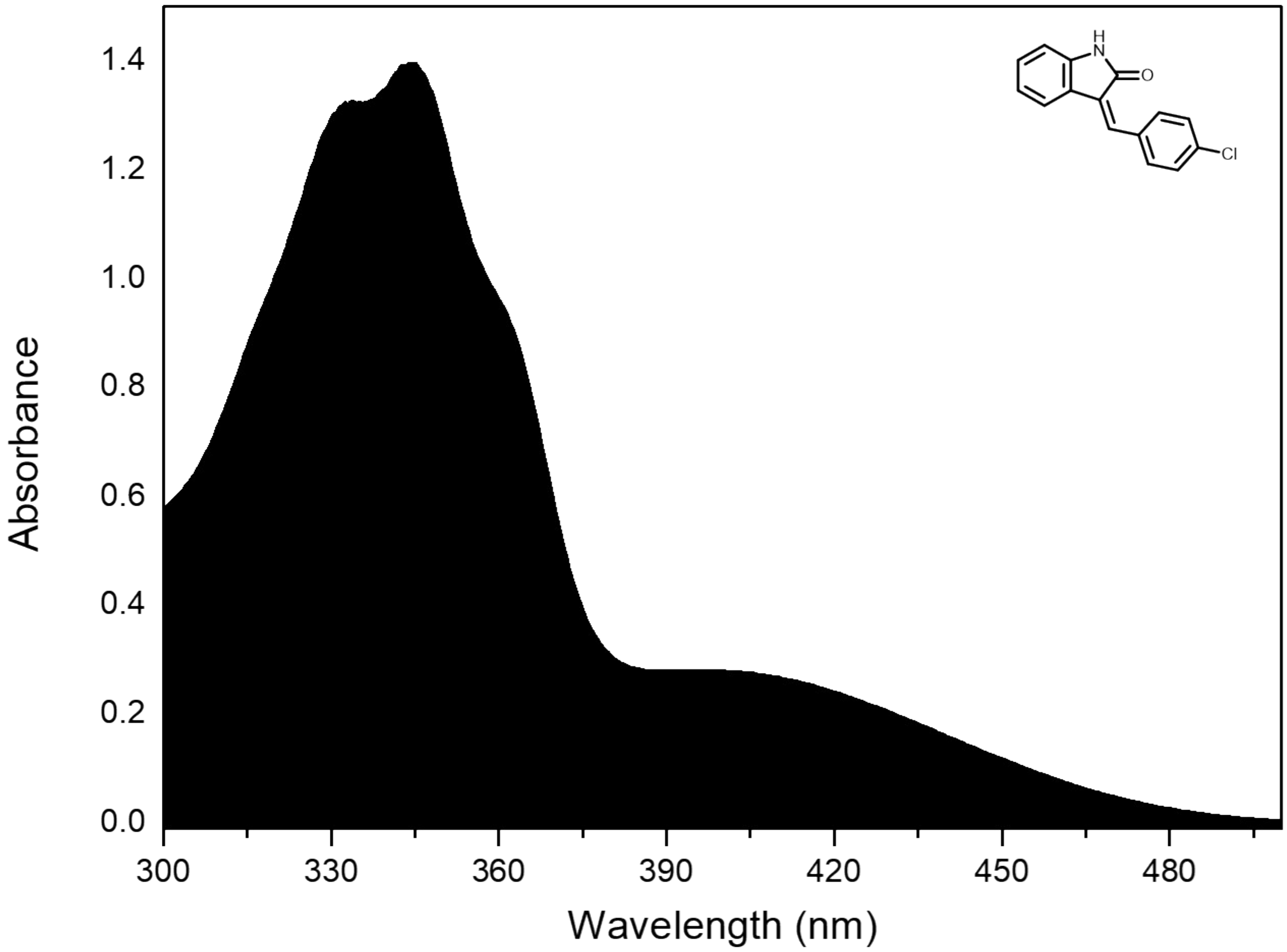


Figure S57: UV Spectra of (*Z*)-3-(4-chlorobenzylidene)indolin-2-one **(4g)**

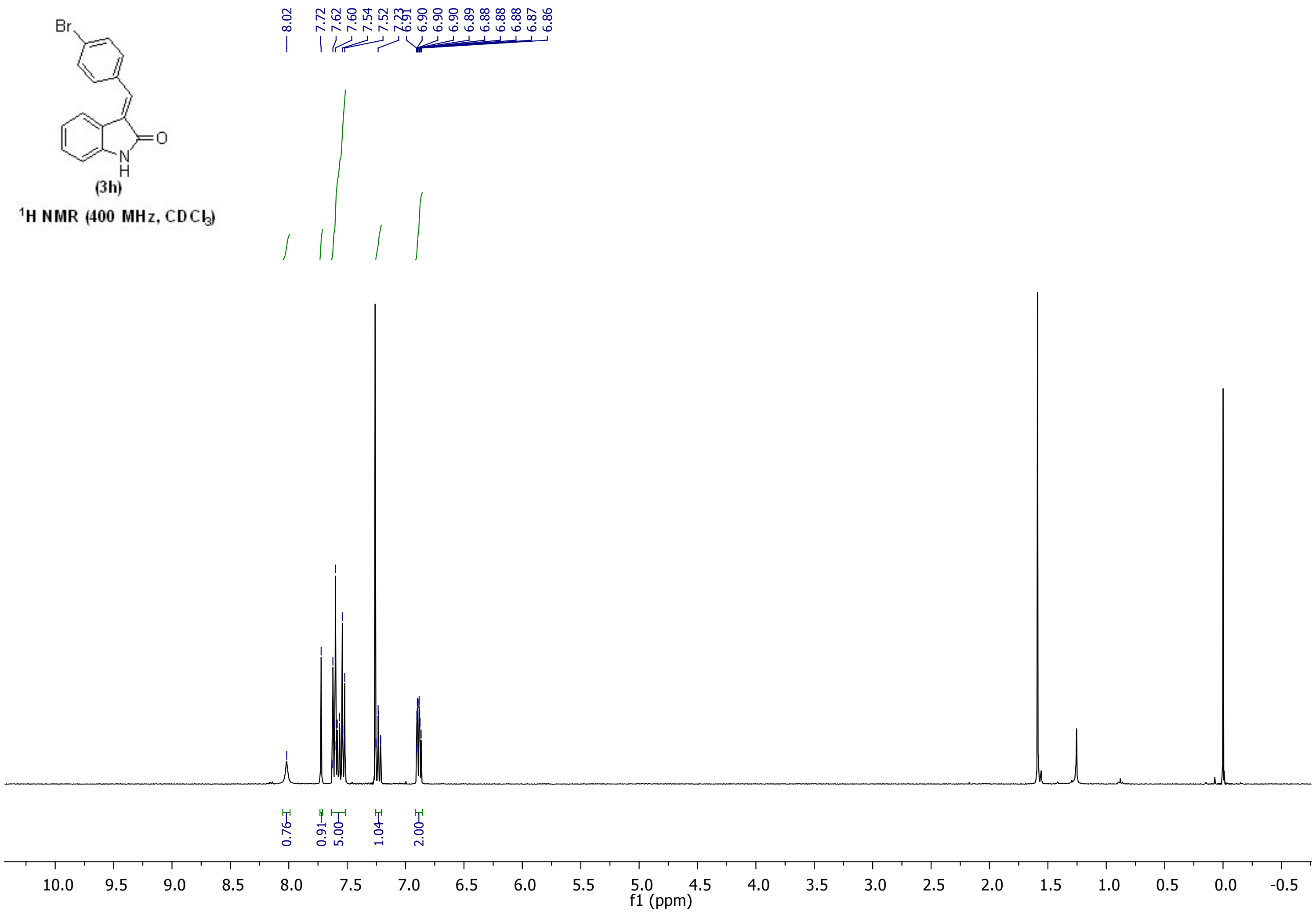


Figure S58: ^{1}H NMR Spectra of (*E*)-3-(4-bromobenzylidene)indolin-2-one **(3h)**

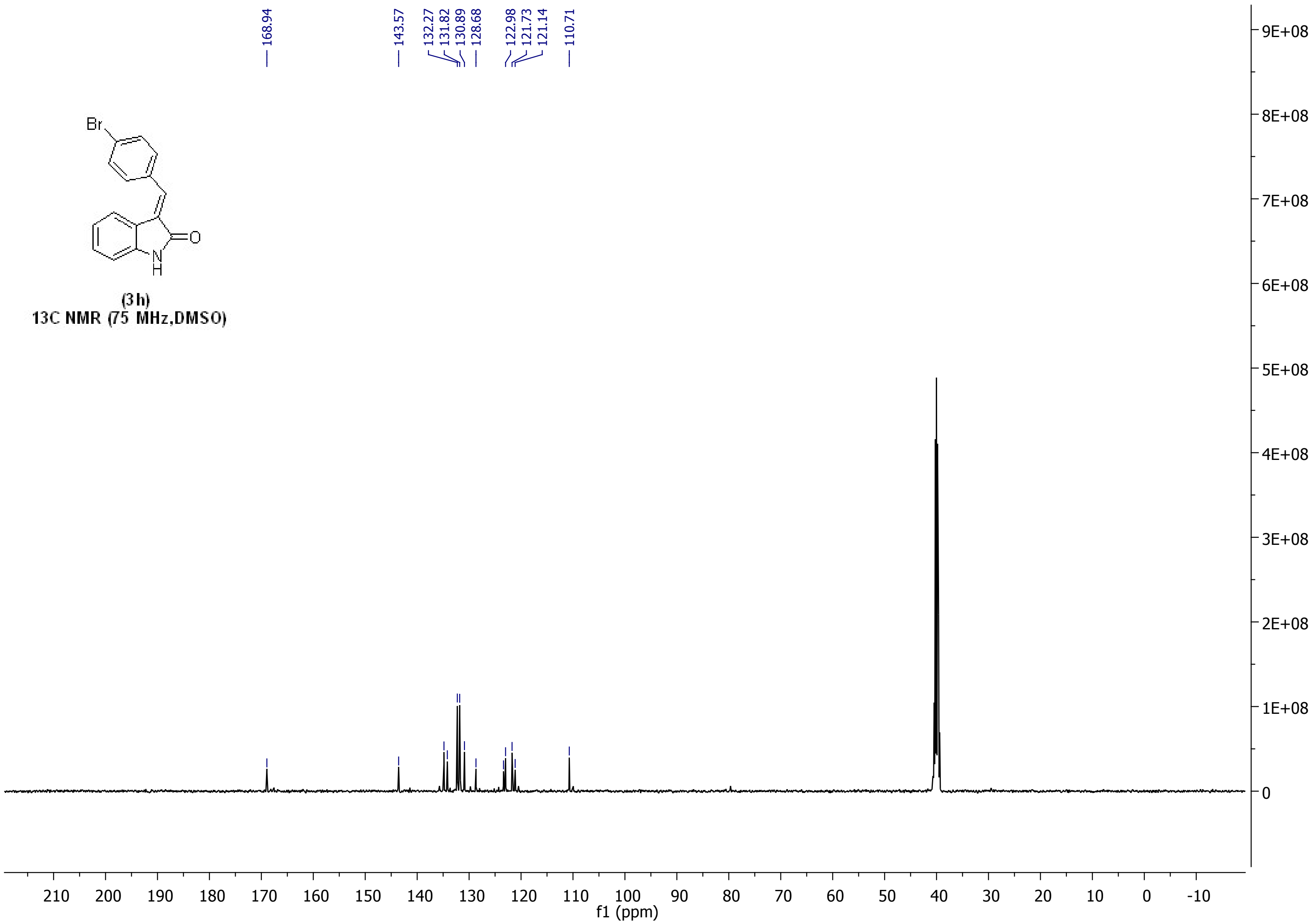


Figure S59: ^{13}CNMR Spectra of (*E*)-3-(4-bromobenzylidene)indolin-2-one **(3h)**

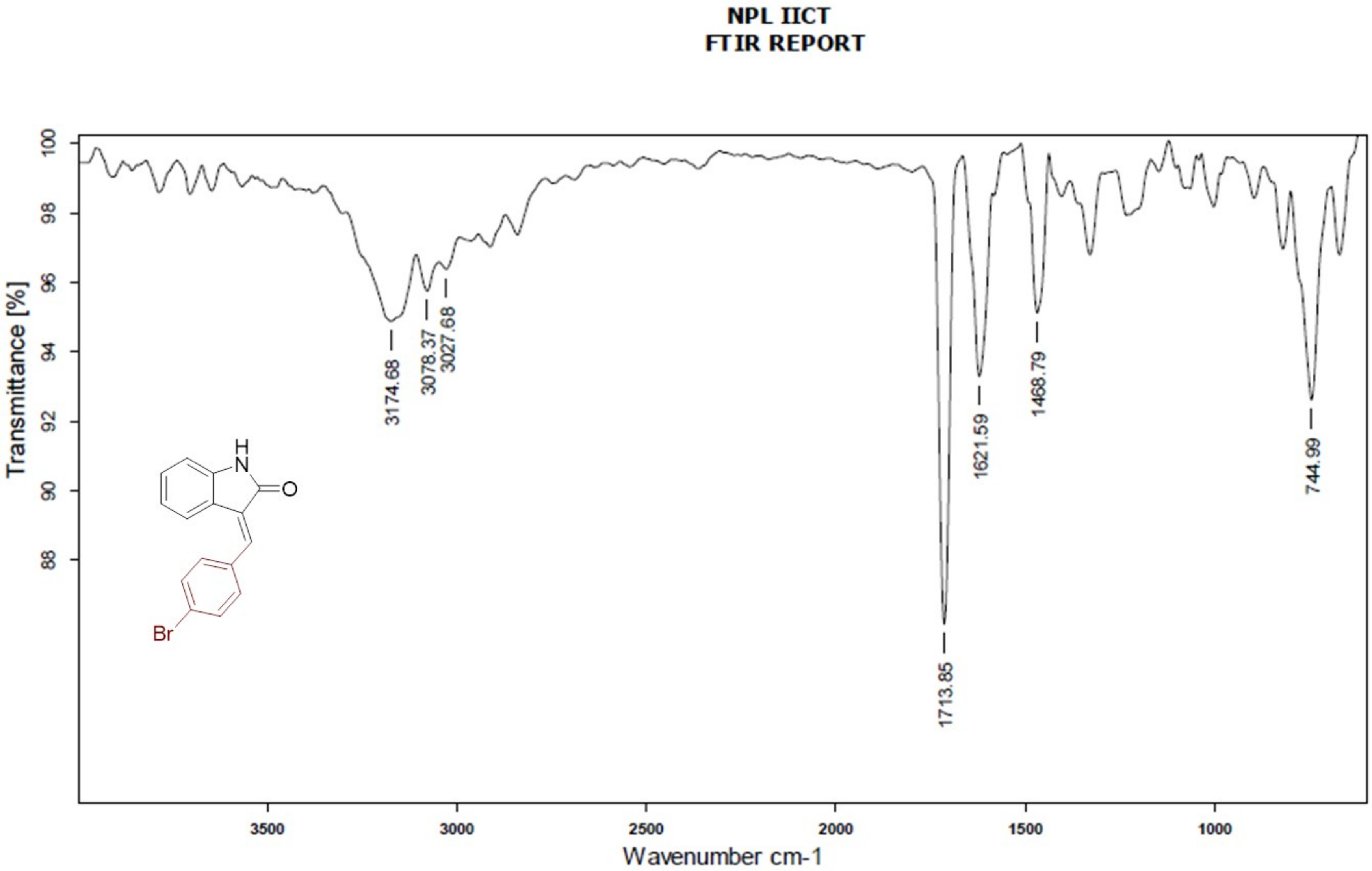


Figure S60: IR Spectra of (*E*)-3-(4-bromobenzylidene)indolin-2-one **(3h)**

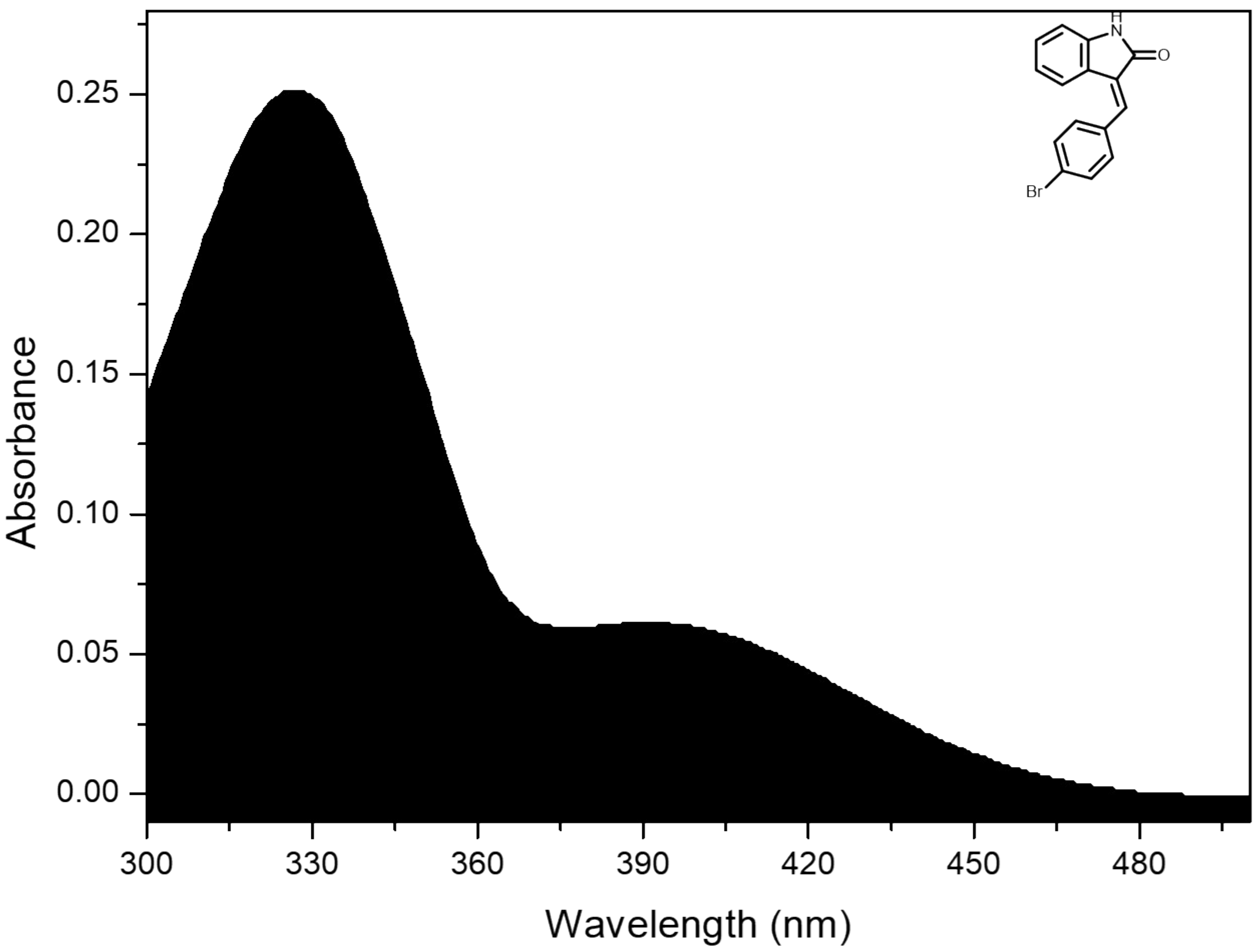


Figure S61: UV Spectra of (*E*)-3-(4-bromobenzylidene)indolin-2-one **(3h)**

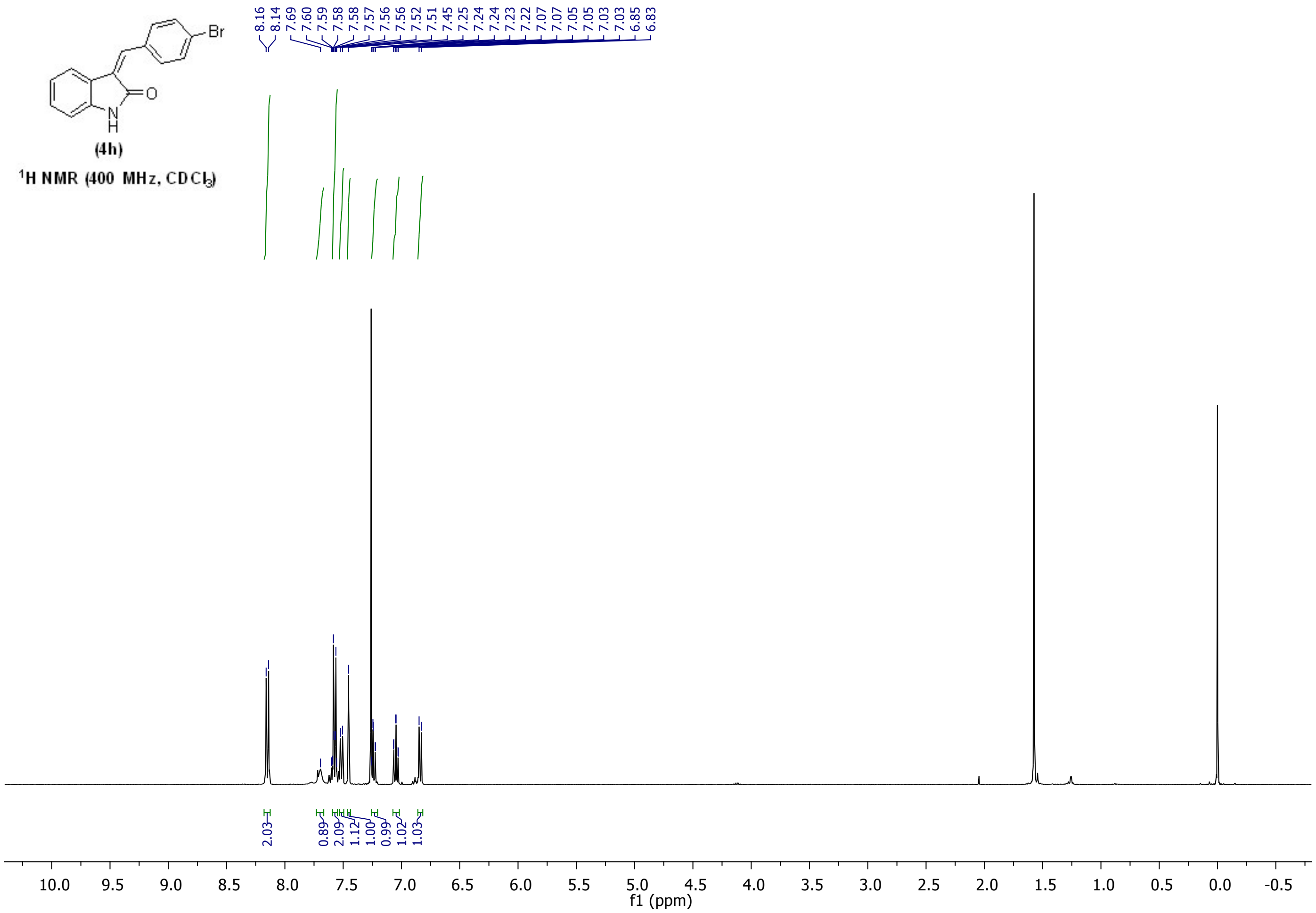


Figure S62: ^{1}H NMR Spectra of (*Z*)-3-(4-bromobenzylidene)indolin-2-one **(4h)**

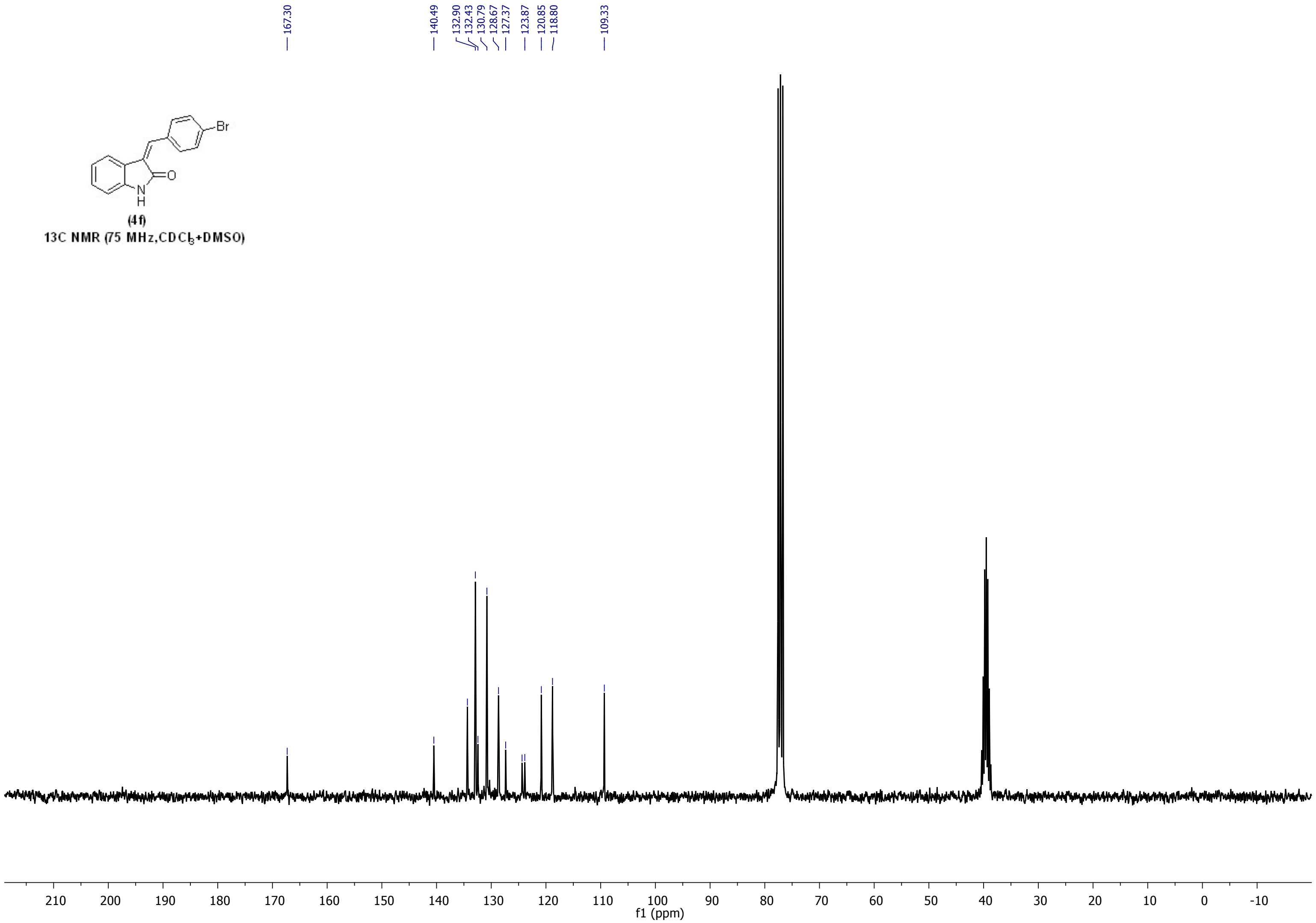


Figure S63: ^{13}C NMR Spectra of (*Z*)-3-(4-bromobenzylidene)indolin-2-one **(4h)**

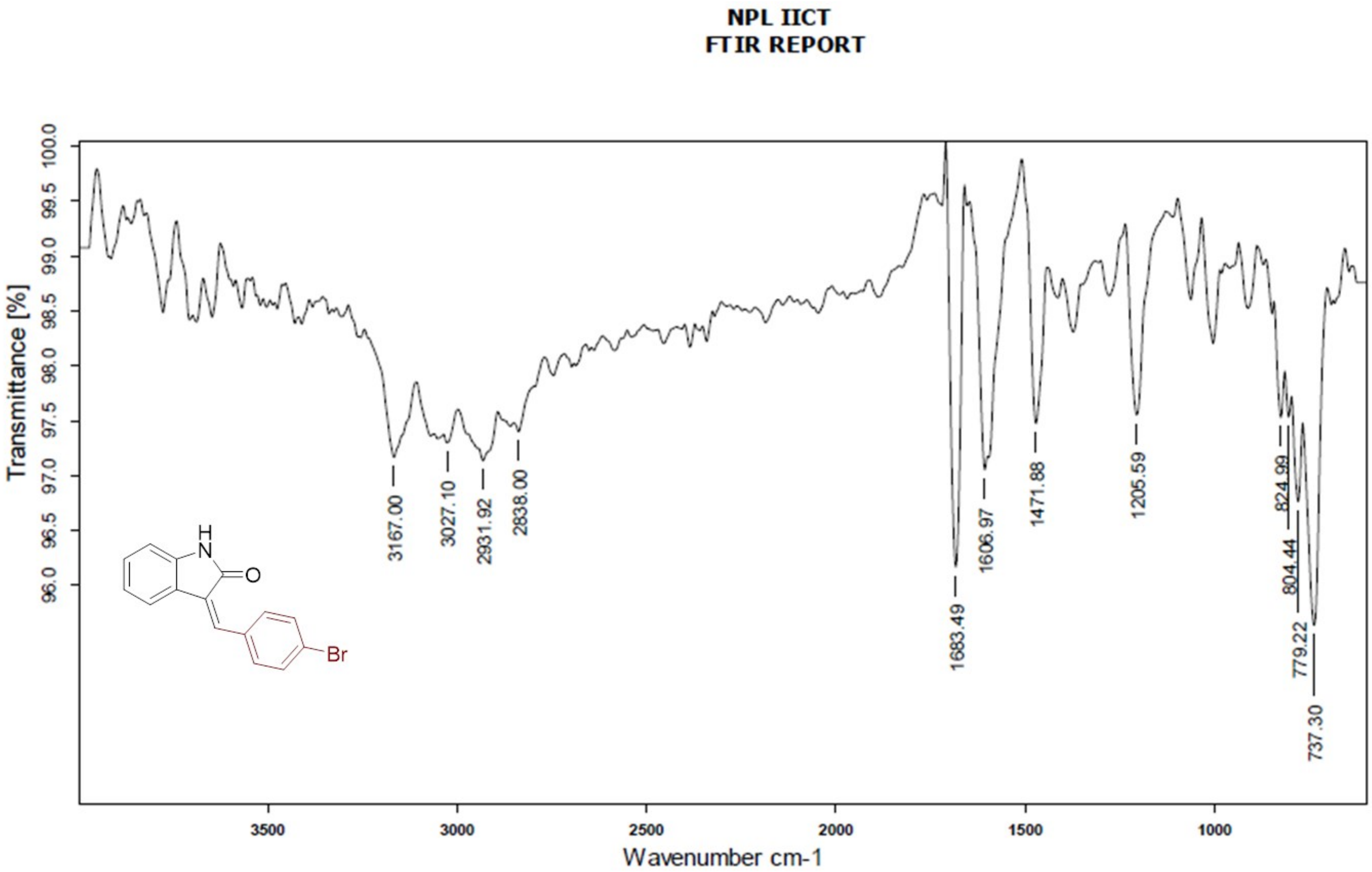


Figure S64: IR Spectra of (*Z*)-3-(4-bromobenzylidene)indolin-2-one **(4h)**

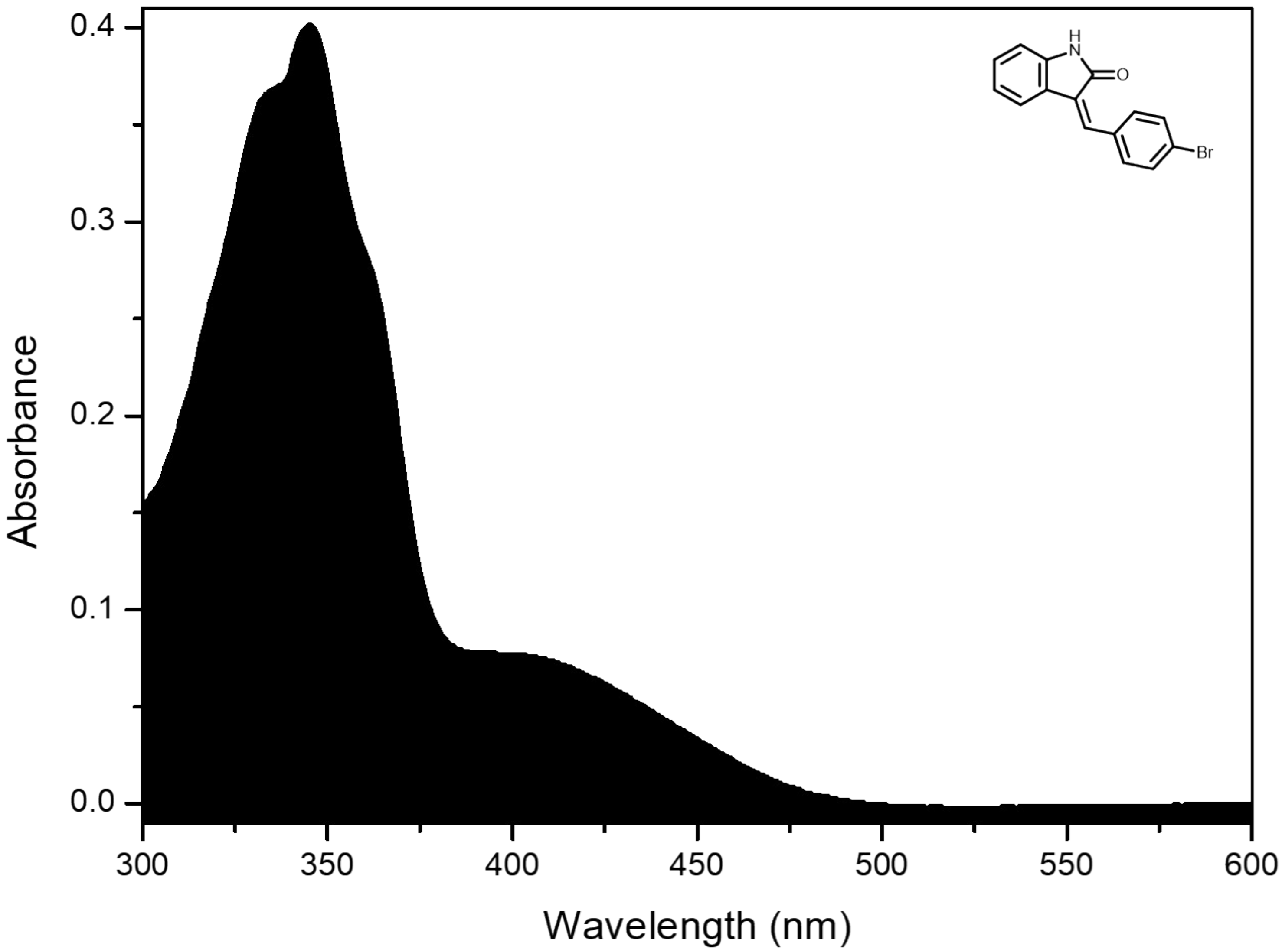


Figure S65: UV Spectra of (*Z*)-3-(4-bromobenzylidene)indolin-2-one **(4h)**

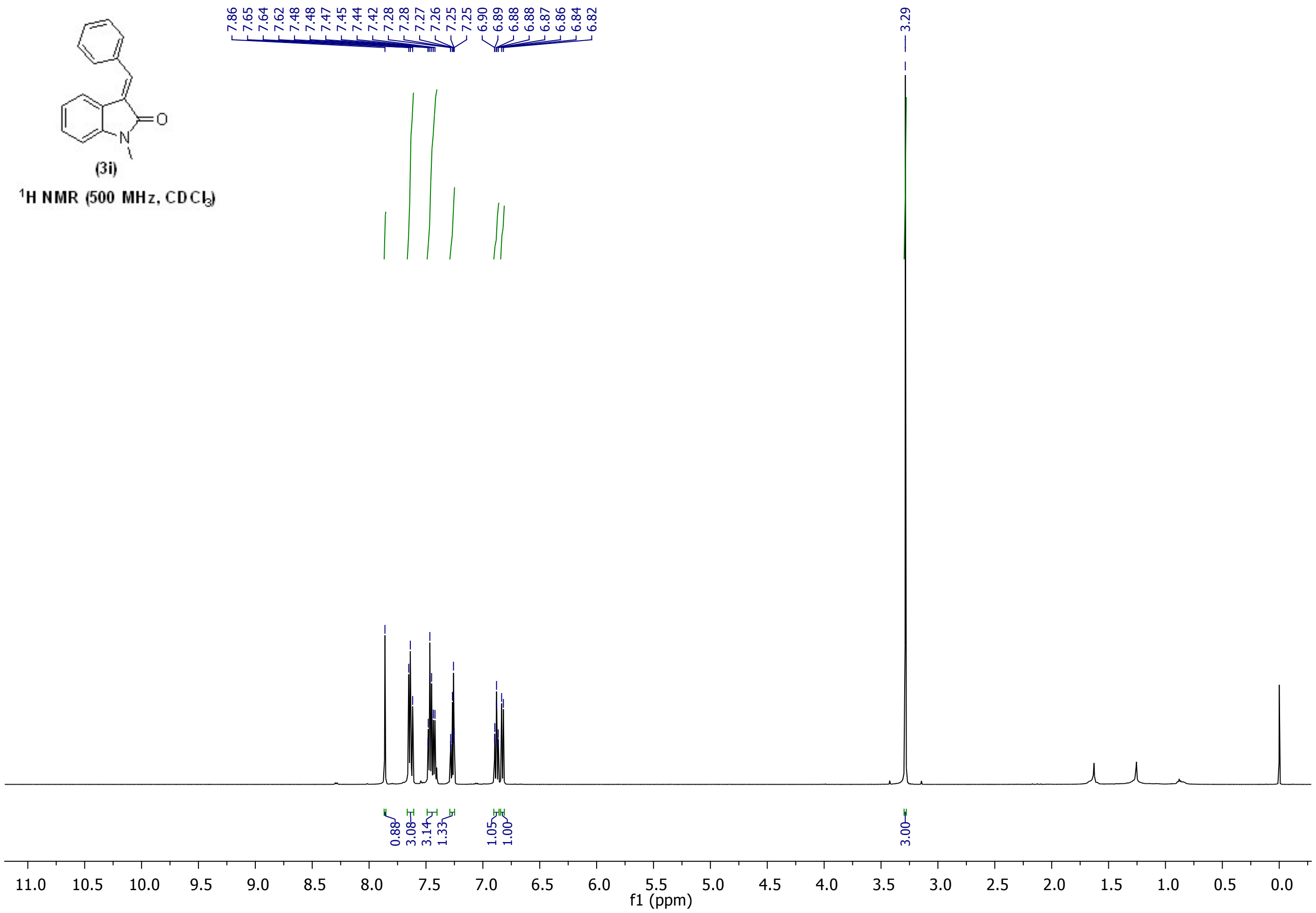


Figure S66: ^{1}HNMR Spectra of (*E*)-3-benzylidene-1-methylindolin-2-one **(3i)**

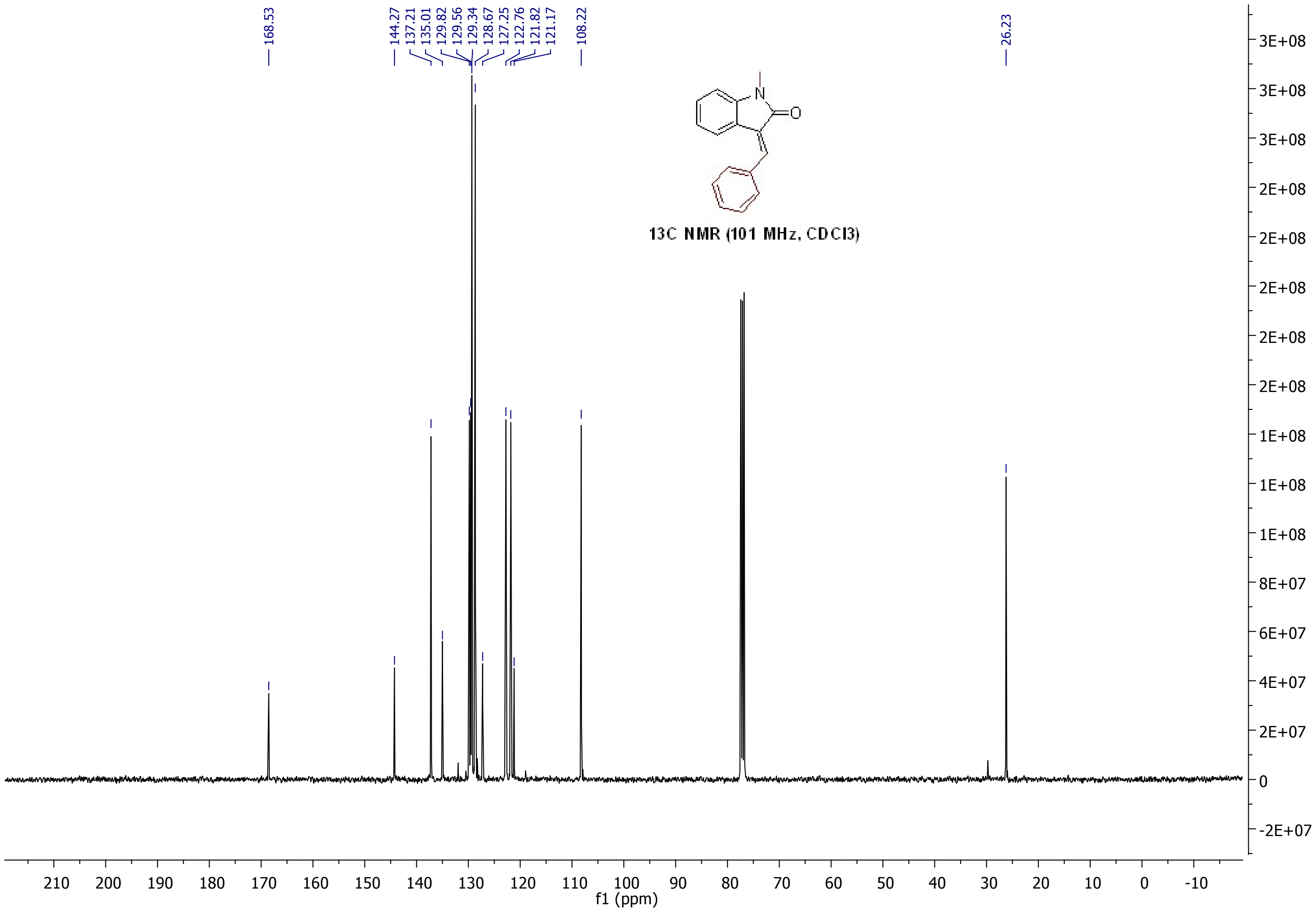


Figure S67: ^{13}C NMR Spectra of (*E*)-3-benzylidene-1-methylindolin-2-one **(3i)**

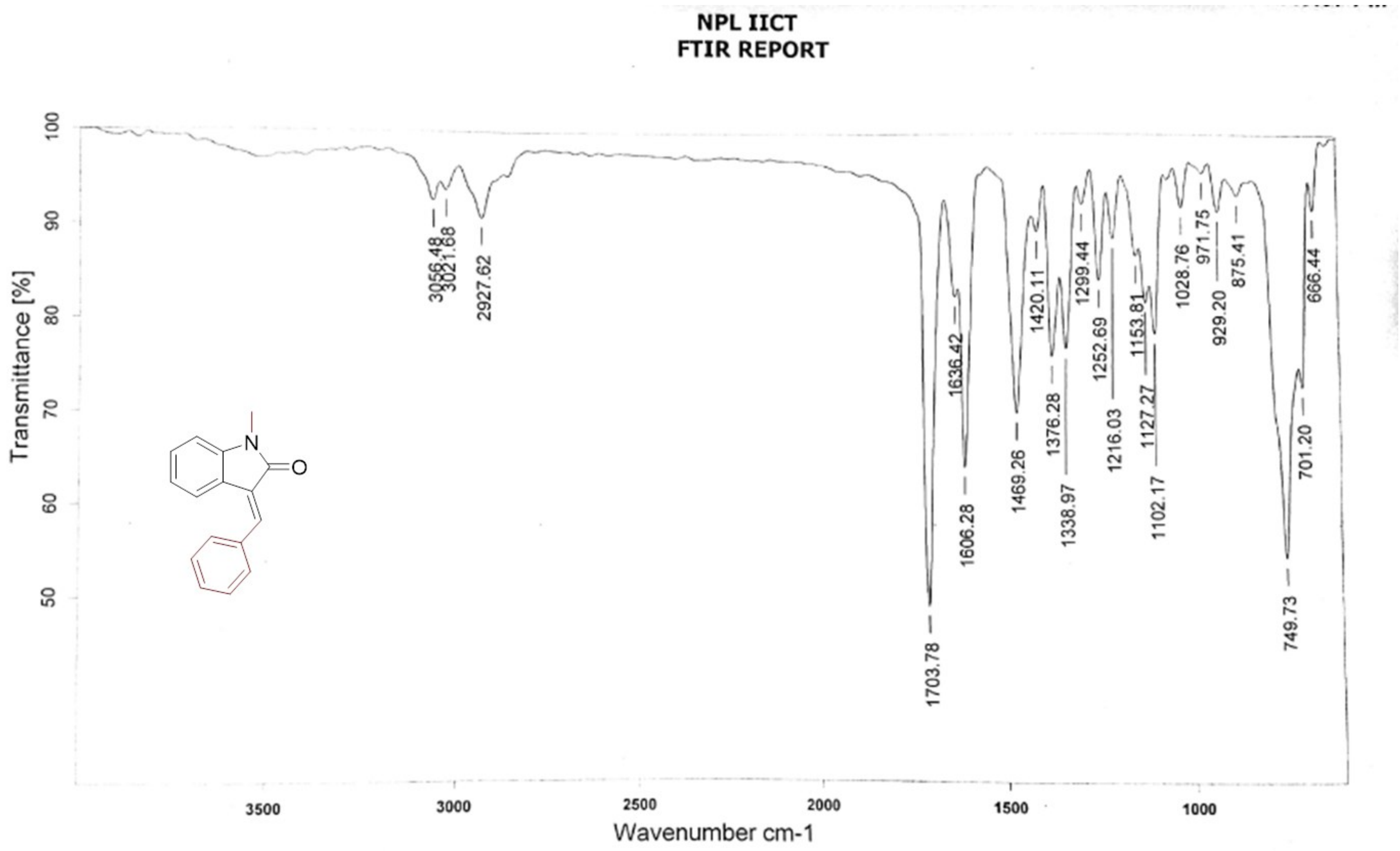


Figure S68: IR Spectra of (*E*)-3-benzylidene-1-methylindolin-2-one **(3i)**

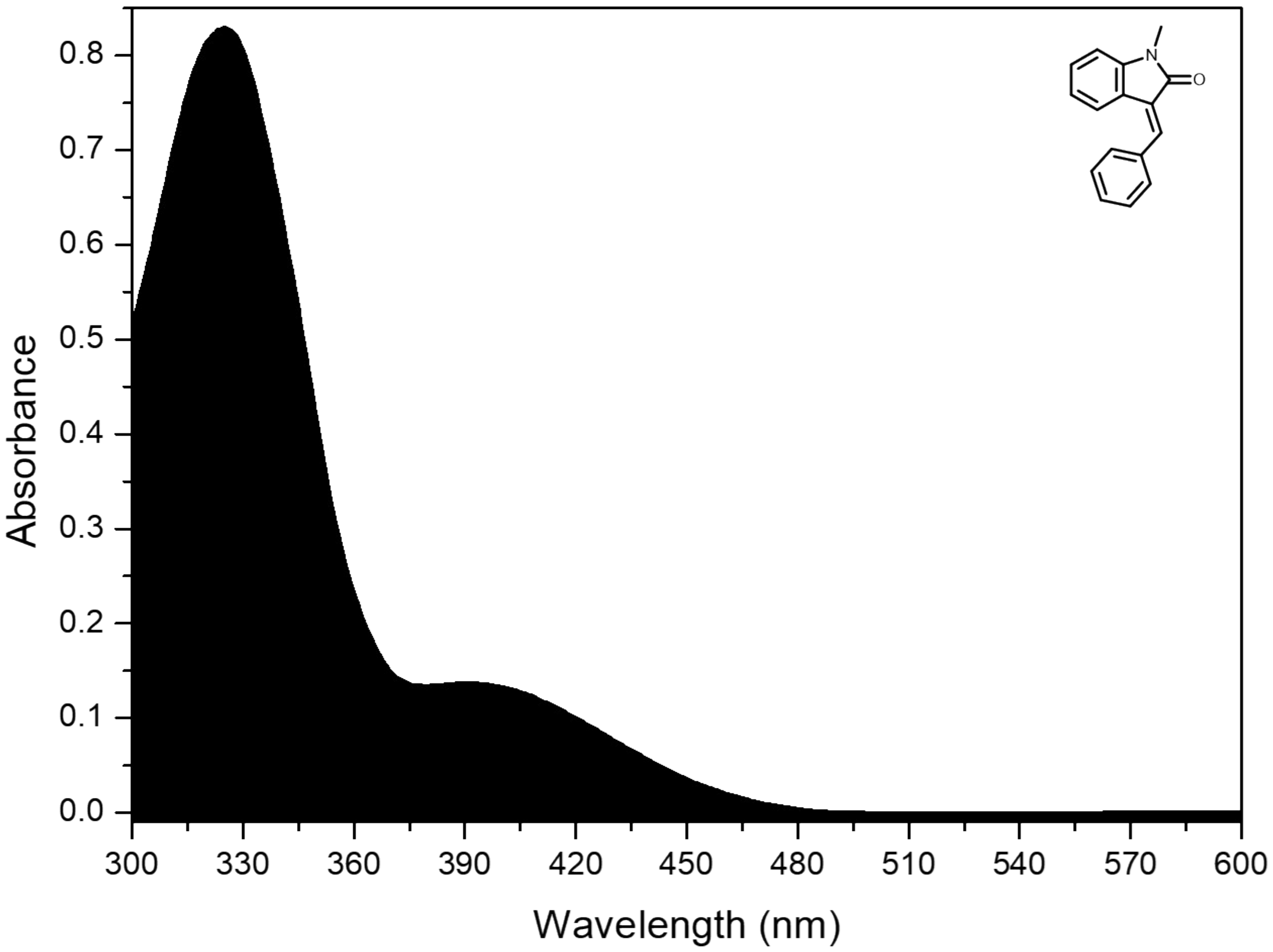


Figure S69: UV Spectra of (*E*)-3-benzylidene-1-methylindolin-2-one **(3i)**

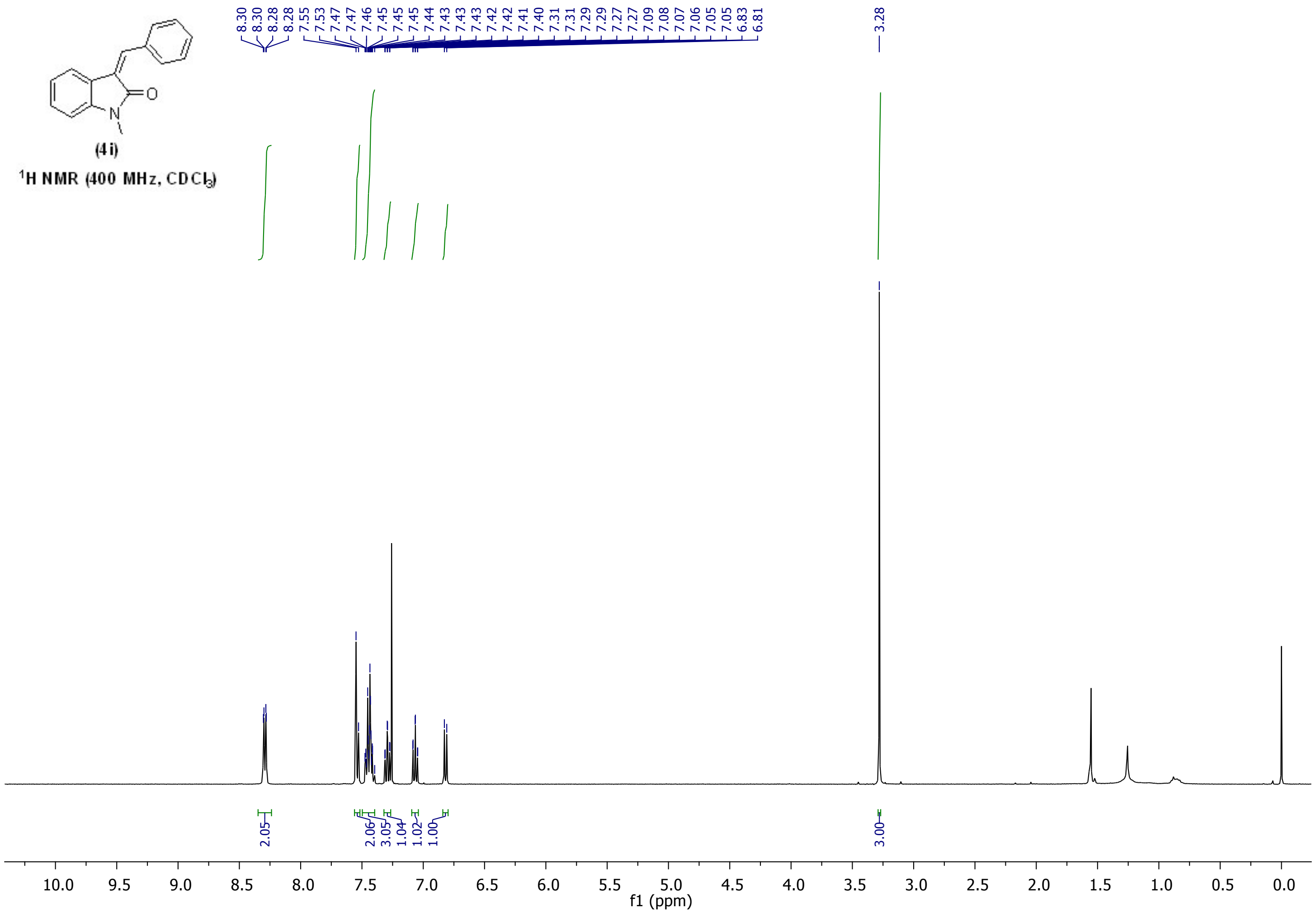


Figure S70: ^{1}HNMR Spectra of (*Z*)-3-benzylidene-1-methylindolin-2-one **(4i)**

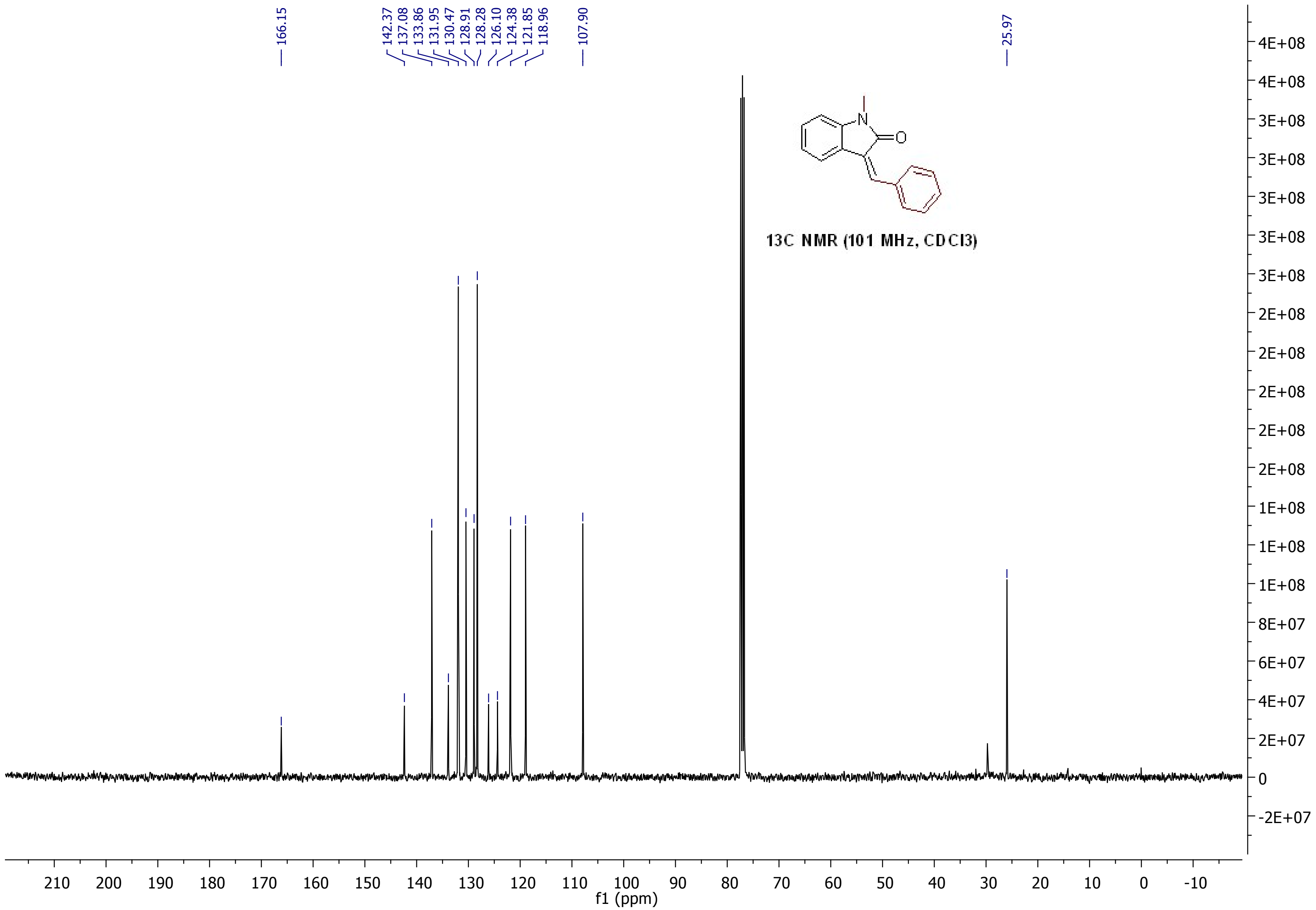


Figure S71: ^{13}CNMR Spectra of (*Z*)-3-benzylidene-1-methylindolin-2-one **(4i)**

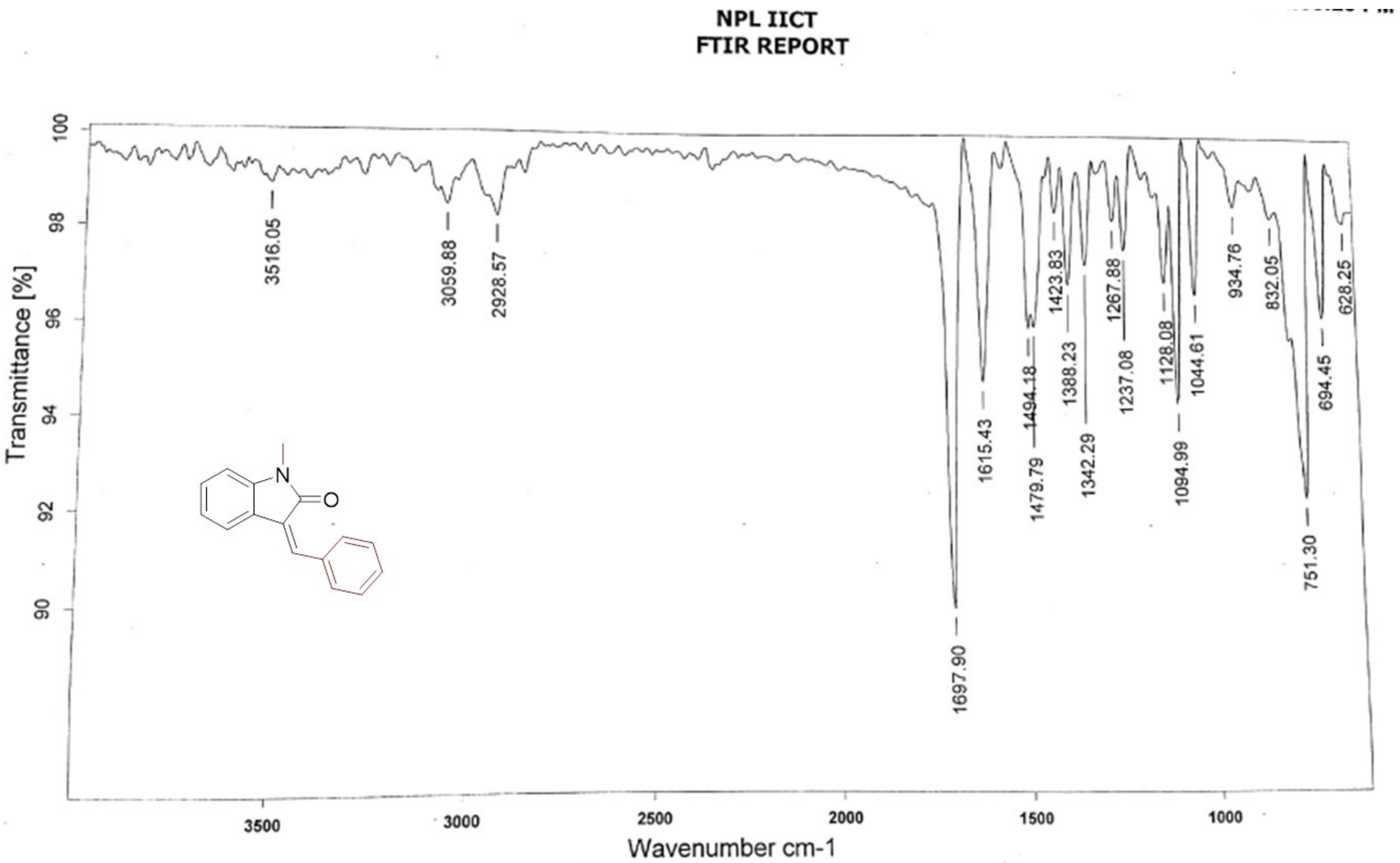


Figure S72: IR Spectra of (*Z*)-3-benzylidene-1-methylindolin-2-one **(4i)**

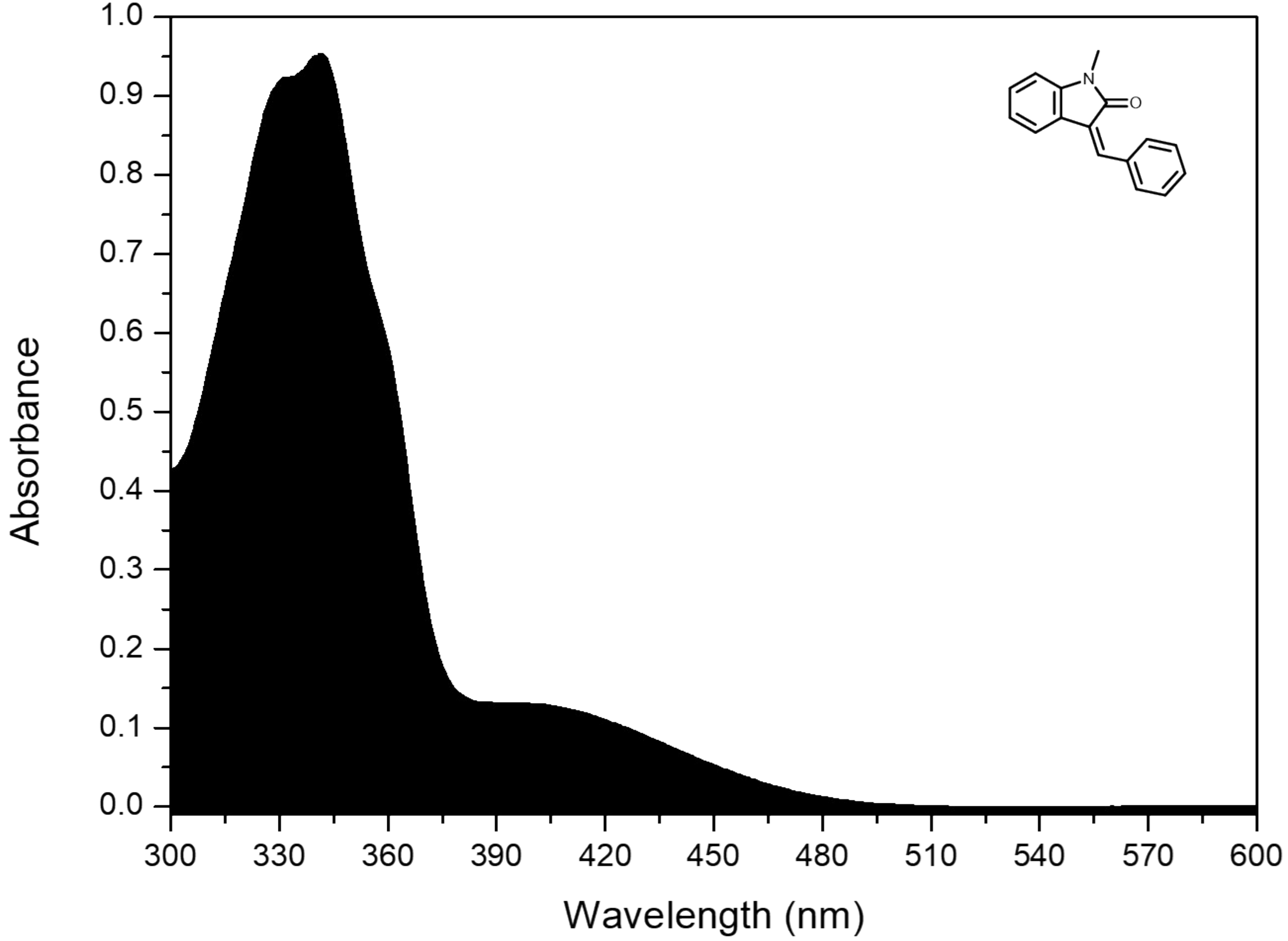
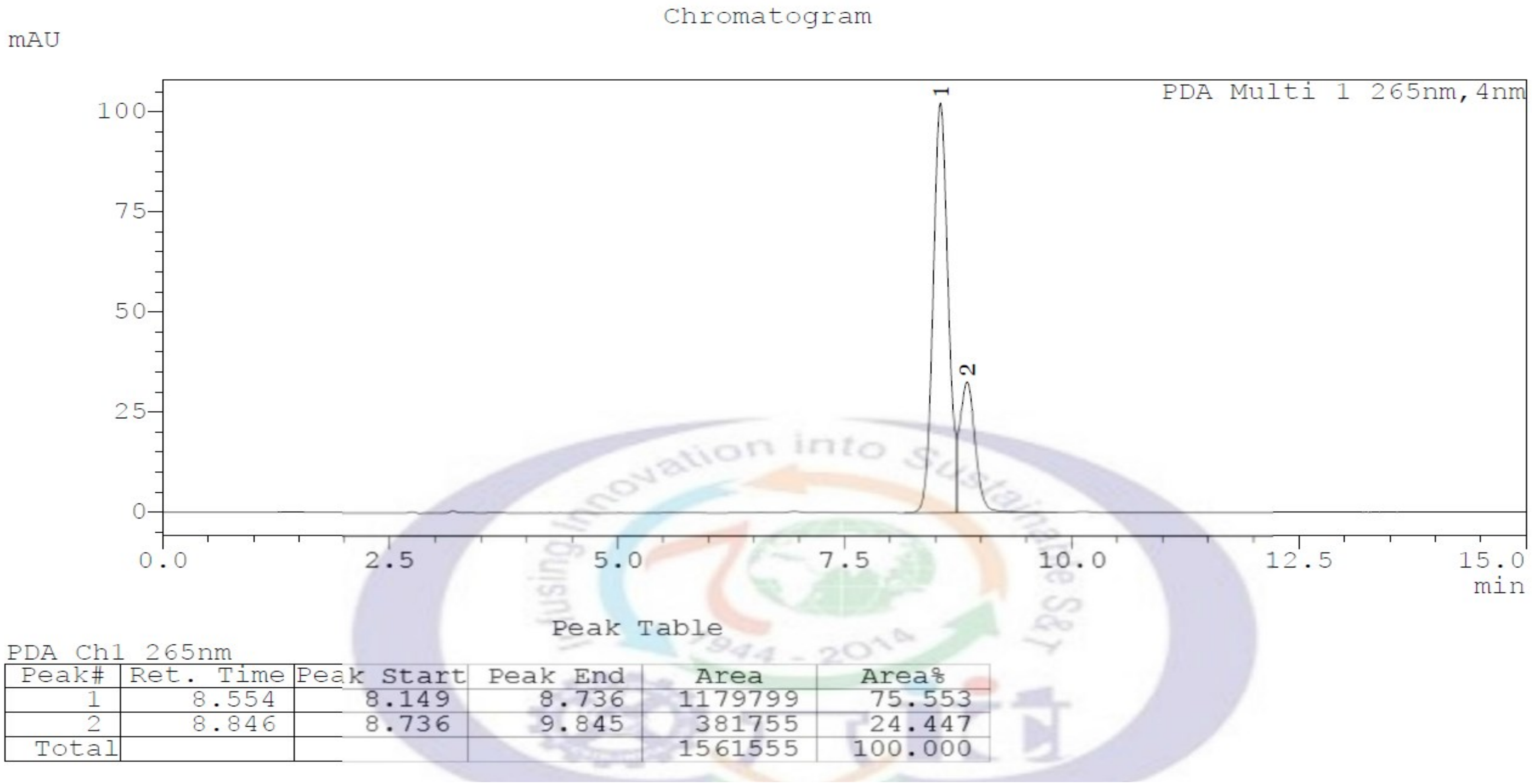


Figure S73: UV Spectra of (*Z*)-3-benzylidene-1-methylindolin-2-one **(4i).**



Peak Table

PDA Ch1 265nm

Peak#	Ret. Time	Peak Start	Peak End	Area	Area%
1	8.554	8.149	8.736	1179799	75.553
2	8.846	8.736	9.845	381755	24.447
Total				1561555	100.000

Figure S74: LC-MS spectra of *E*-*Z* crude mixture **(4a:3a).**

5. Troubleshooting.

Question: Where to buy the PFA tubing?

Answer: Our PFA tubing was purchased from chromatopack, Hyderabad.

Question: Aside from the PFA tubing described, can we use different tubing?

Answer: Yes. Any transparent, solvent, and pressure resistance tubing material can be used to flow the solution for photo-flow reaction.

Question: Does other tube id work?

Answer. Other higher tube id (e.g., 2-5 mm) also work, but they tend to give lower yields.

Question: Does UV index and light intensity affect the reaction?

Answer: Yes, Hyderabad average UV index is around 8-10 and average light intensity 5.13 KWh/m^2. We have conducted the experiment only when light intensity is more than 20000 lux. Experiment running time 10 am – 4 pm and yield are based on average of three experiments.

Question: Where to buy the micro-separator?

Answer: We have transferred micro-separator technology to Amar Equipment, Mumbai (https://www.amarequip.com/metal-micromixer/continuous-flow-reactors) and anyone can purchase and used as such.

Question: Does rainy or cloudy day experiment affect the reaction?

Answer: Yes, we have manually controlled the experiment (10 am - 4 pm, light intensity >20000 lux) and avoided to do the experiment on the cloudy or rainy days. Real-time reaction control for direct isomerization of oxindole under fluctuating irradiance (cloudy or rainy days) work is under progress in our lab.

Movie S1: Photo-flow protocols for controlled isomerization reaction.

Movie S2: Micro-separation experiment has been performed similar to our standard procedure. The separation of the aq. and organic phase has been observed in the form of color difference during as shown in the supporting video.

6. References

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