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Ultrasound-assigned synthesis of azlactone and its reactions with nucleophiles

Boris V. Paponov, Sergey V. Lvov, Ekaterina V. Ichetovkina, Ilya A. Panasenko and Stepan G. Stepanian

1. *Computational data for the isomers Z and E calculation at the B3LYP/6-31++G(d,p) level of theory.*

Computational procedure. The geometries and relative stability of the azlactone **1** isomers have been calculated at the DFT level of theory. The B3LYP functional [1-3] and the standard 6-31++G(d,p) (5d) basis set have been used in the calculations. Full geometry optimization was performed for two azlactone **1** isomers – Z and E without any symmetry constrains. Optimization converged to planar structures of the isomers and was followed by harmonic frequency calculations. No imaginary frequency was found in the calculations. It proves that the true minima were found. Harmonic frequencies were used to account for the ZPVE (zero-point vibrational energy) correction to the total energies of the azl isomers. All quantum-chemical calculations reported in this work have been performed using Gaussian 09 program package [4].

Results: The preferent formation of Z-isomer were explained due to the mutual repulsion of the carbonyl groups of oxindole and oxazolone moieties in E-isomer of azlactone **1** molecule. This hypothesis was confirmed by computational methods. Calculations performed at the B3LYP/6-31++G(d,p) level of theory with accounting for the ZPVE correction have predicted that the isomer Z is the most stable form of azlactone **1**. All quantum-chemical calculations reported in this work have been performed using Gaussian 09 program package.

Relative energy of the isomer E is 3.93 kJ/mol higher. To explain the stability order of the azlactone **1** isomers we analyzed atomic charges of the conformers and also calculated electrostatic potentials for both isomers which are presented in Figure 2. As it may be seen, both isomers have located near negatively charged atoms: two oxygens in the isomer E and oxygen and nitrogen in isomer Z but in the case of isomer E the repulsion between these atoms is stronger due to higher values of charges (in absolute values): -0.44e (O oxindole moiety), -0.40e (O phenyloxazolone moiety) in isomer E and -0.42e (O oxindole moiety), -0.18e (N phenyloxazolone moiety) in isomer Z. Thus, we can conclude that the main reason why the isomer E is less stable than isomer Z is the stronger Coulomb repulsion between two carboxyl oxygen atoms in isomer E.

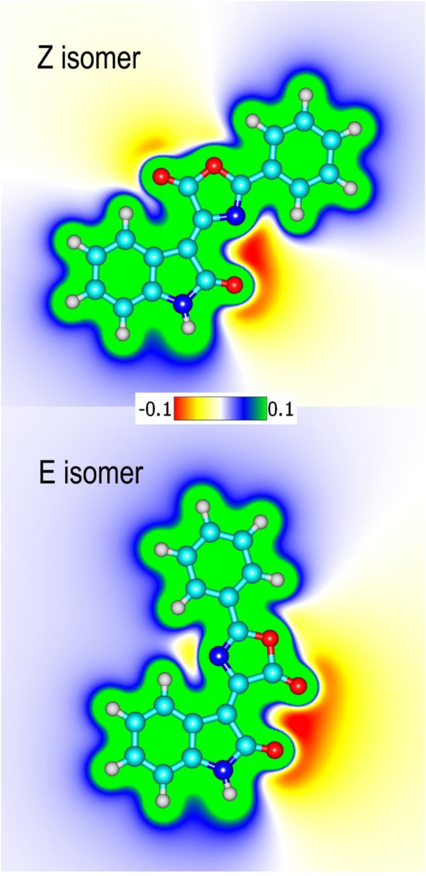

Figure 2.1. Electrostatic potential calculated for the isomers ***Z*** and ***E*** of molecule **1** at the B3LYP/6-31++G(d,p) level of theory.

References

1. A. D. Becke, *Phys. Rev. A,* 1988, **38,** 3098.
2. C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B,* 1988, **37**, 785.
3. S. H. Vosko, L. Wilk and M. Nusair, *Can. J. Phys.,* 1980, **58**, 1200.
4. *Gaussian 09*, *Revision A.02*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, Jr. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

Cartesian coordinates for molecule **1**:

Isomer Z . Total energy: -989.064887 a.u. (B3LYP/6-31++G(d,p) (5d)).

C	-0.952250	3.510909	0.000000
C	-1.676934	4.706593	0.000000
C	-3.077037	4.697527	0.000000
C	-3.792266	3.492362	0.000000
C	-1.643598	2.288446	0.000000
C	-3.065325	2.309207	0.000000
H	0.129019	3.521568	0.000000
H	-1.143969	5.652098	0.000000
H	-3.622273	5.637001	0.000000
H	-4.878030	3.485162	0.000000
C	-1.232257	0.890505	0.000000
C	-2.518814	0.068804	0.000000
N	-3.546288	1.003925	0.000000
O	-2.680756	-1.137169	0.000000
H	-4.516758	0.726889	0.000000
C	0.000000	0.287597	0.000000
C	1.341843	0.948313	0.000000
N	0.206325	-1.084130	0.000000
C	2.193439	-2.535800	0.000000
C	1.444234	-3.728390	0.000000
C	3.598929	-2.587231	0.000000
C	4.246048	-3.822436	0.000000
C	3.500607	-5.005930	0.000000
C	2.100475	-4.955726	0.000000
O	1.715523	2.094062	0.000000
H	4.170725	-1.665605	0.000000
H	5.331173	-3.861906	0.000000
H	4.008533	-5.966108	0.000000
H	1.523014	-5.875316	0.000000
O	2.250115	-0.111055	0.000000
C	1.489305	-1.263274	0.000000
H	0.360861	-3.667936	0.000000

Isomer E

C	2.264364	-1.458279	0.000000
C	3.468260	-2.169066	0.000000
C	3.470016	-3.570753	0.000000
C	2.273441	-4.300680	0.000000
C	1.055657	-2.167188	0.000000
C	1.081977	-3.585088	0.000000
H	2.250258	-0.375931	0.000000
H	4.410704	-1.630439	0.000000
H	4.415109	-4.106204	0.000000
H	2.280262	-5.386399	0.000000
C	-0.340324	-1.753773	0.000000
C	-1.161902	-3.030386	0.000000
N	-0.225332	-4.062061	0.000000
O	-2.367613	-3.192699	0.000000
H	-0.507670	-5.030973	0.000000
C	-0.825012	-0.472727	0.000000
C	-2.247573	-0.001428	0.000000
N	0.000000	0.645370	0.000000
C	-0.377928	3.083039	0.000000
C	0.991366	3.409197	0.000000
C	-1.341797	4.107433	0.000000
C	-0.936340	5.441616	0.000000
C	0.424893	5.762172	0.000000
C	1.386706	4.743653	0.000000
O	-3.325043	-0.518259	0.000000
H	-2.395561	3.851368	0.000000
H	-1.682043	6.230798	0.000000
H	0.737229	6.802483	0.000000
H	2.443460	4.993534	0.000000
O	-2.121172	1.414712	0.000000
C	-0.783808	1.683720	0.000000
H	1.724229	2.609803	0.000000

2. *Experimental data.*

Melting points were determined on a Kofler apparatus. The NMR spectra were recorded at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR spectra on a Bruker Avance DRX 400 spectrometer with TMS internal standard in DMSO-d_6. Mass spectra were taken on a Finnigan MAT 4651P instrument (EI, 70 eV). TLC was used to monitor the reactions and control the purity of products on plates Silufol UV-254; eluents of ethyl acetate/toluene (1:1) mixture, visualized under UV light or iodine fume. Ultrasound irradiation was carried out on Pro'sKit SS-808 Ultrasonic cleaner, 40W, 44 kHz.

5b: yellow needles, 168 mg (72%), mp 211−212 °C. MS (EI, 70 eV) *m*/*z* 336 (M^+); ^{1}H NMR (400 MHz, DMSO-D$_6$) δ ppm: 12.78 (s, 1H), 11.22 (s, 1H), 7.97 (d, *J* = 7. 2 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 2H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.4 Hz 1H), 7.07-6.93 (m, 2H), 4.50 (q, *J* = 13.8 Hz, 2H), 1.35 (t, *J* = 13.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-D$_6$) δ ppm 170.8, 164.0, 162.8, 140.2, 137.1, 133.8, 132.7, 129.7, 128.9, 128.0, 122.2, 120.8, 120.0, 110.9, 62.7, 14.0. Found (%): C, 67.87; H, 4.79; N, 8.31. Calc. for $C_{19}H_{16}N_2O_4$ (%): 67.85; H, 4.79; N, 8.33.

*(Z)-*N*-[2-(3-Methyl-1H-pyrazol-5-ylamino)-2-oxo-1-(2-oxoindolin-3-ylidene)ethyl]-benzamide* **6**. A solution of 200 mg (0.67 mmol) of **1** and 65 mg (0.67 mmol) of 3-methyl-5-amyno-1*H*-pyrazole in 5 ml ethanol was refluxed for 2 h, the product **6** was filtered off. Yellow powder, 170 mg (64%), mp 184−186 °C. MS (EI, 70 eV) *m*/*z* 387 (M^+); ^{1}H NMR (400 MHz, DMSO-D$_6$) δ ppm 12.92 (s, 1H), 12.21 (s, 1H), 11.27 (s, 1H), 11.16 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 2H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.7, 2H), 7.27-7.20 (m, 2H), 7.03-6.89 (m, 2H), 6.55 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-D$_6$) δ ppm 171.3, 163.3, 159.8, 155.9, 151.2, 139.6, 133.6, 132.5, 129.7, 128.0, 127.8, 122.0, 121.1, 121.0, 110.9, 110.3, 88.4, 14.3. Found (%): C, 65.06; H, 4.47; N, 18.03. Calc. for $C_{21}H_{17}N_5O_3$ (%): 65.11; H, 4.42; N, 18.08.

(Z)-3-(2-Oxoindolin-3-ylidene)-3,4-dihydroquinoxalin-2(1H)-one **7**. A solution of 200 mg (0.67 mmol) of **1** and 140 mg (1.30 mmol) of 1,2-diaminobenzene in 8 ml *n*-butanol was refluxed for 1 h, the product **7** was filtered off. Red powder, 170 mg (89%). All the physicochemical and spectral data for compound **7** correspond to those published in ref. 11 of the article.

*(Z)-1*H*-Indole-2,3-dione 3-hydrazone* **8**. A solution of 200 mg (0.67 mmol) of **1** and 0.1 ml of hydrazine-hydrate (98%) in 5 ml ethanol was refluxed for 1 h, the product **8** was filtered off. Yellow powder, 80 mg (74%). All the physicochemical and spectral data for compound **8** correspond to correspond to those published in refs. 1,2 of the article.

*(Z)-3-(4-Oxo-2-phenyl-1*H*-imidazol-5(4*H*)-ylidene)indolin-2-one* **9.** A solution of 600 mg (2.06 mmol) of **1** and 65 mg (2.17 mmol) of thiosemicarbazide in 5 ml DMF was refluxed for 4 h, the product **9** was filtered off. Orange powder, 355 mg (58%), mp 322−324 °C. MS (EI, 70 eV) *m*/*z* 289 (M^+); ^{1}H NMR (400 MHz, DMSO-D$_6$) δ ppm 13.28 (s, 1H), 12.24 (s, 1H), 9.32 (d, *J* = 8.2 Hz, 1H), 8.23 (d, *J* = 7.2 Hz, 2H), 7.56-7.49 (m, 4 H), 7.33 (t, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-D$_6$) δ ppm 170.9, 170.1,

158.1, 156.9, 141.1, 132.0, 130.1, 128.9, 128.1, 128.0, 123.3, 123.1, 122.9, 122.7, 110.5. Found (%): C, 78.56; H, 3.81; N, 14.53. Calc. for $C_{17}H_{11}N_3O_2$ (%):C, 78.58; H, 3.83; N, 14.53.

References

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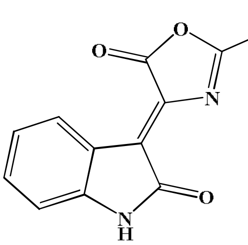
2 F. Knotz, *Sci. Pharm.,* 1970, **38**, 463.

3. NMR spectra of synthesized compounds.



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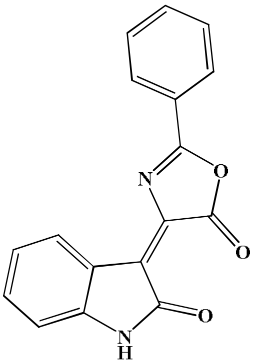

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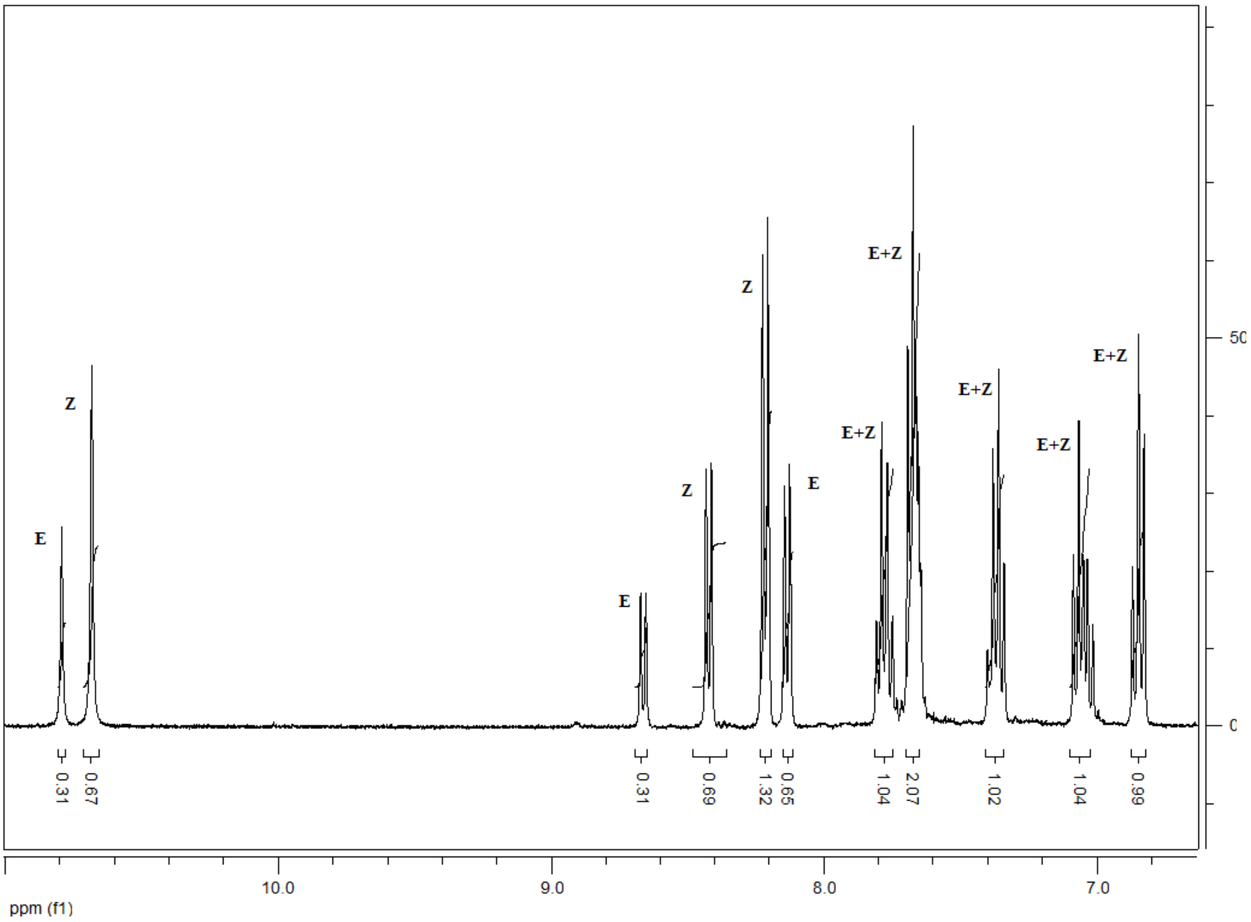
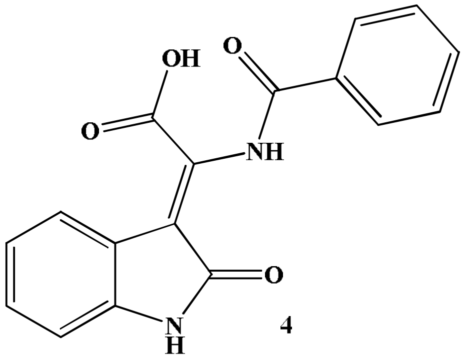


Figure 1.1. ^{1}H NMR spectrum of azlactone **1** as mixture of *E*- and *Z*-isomers (1:2).



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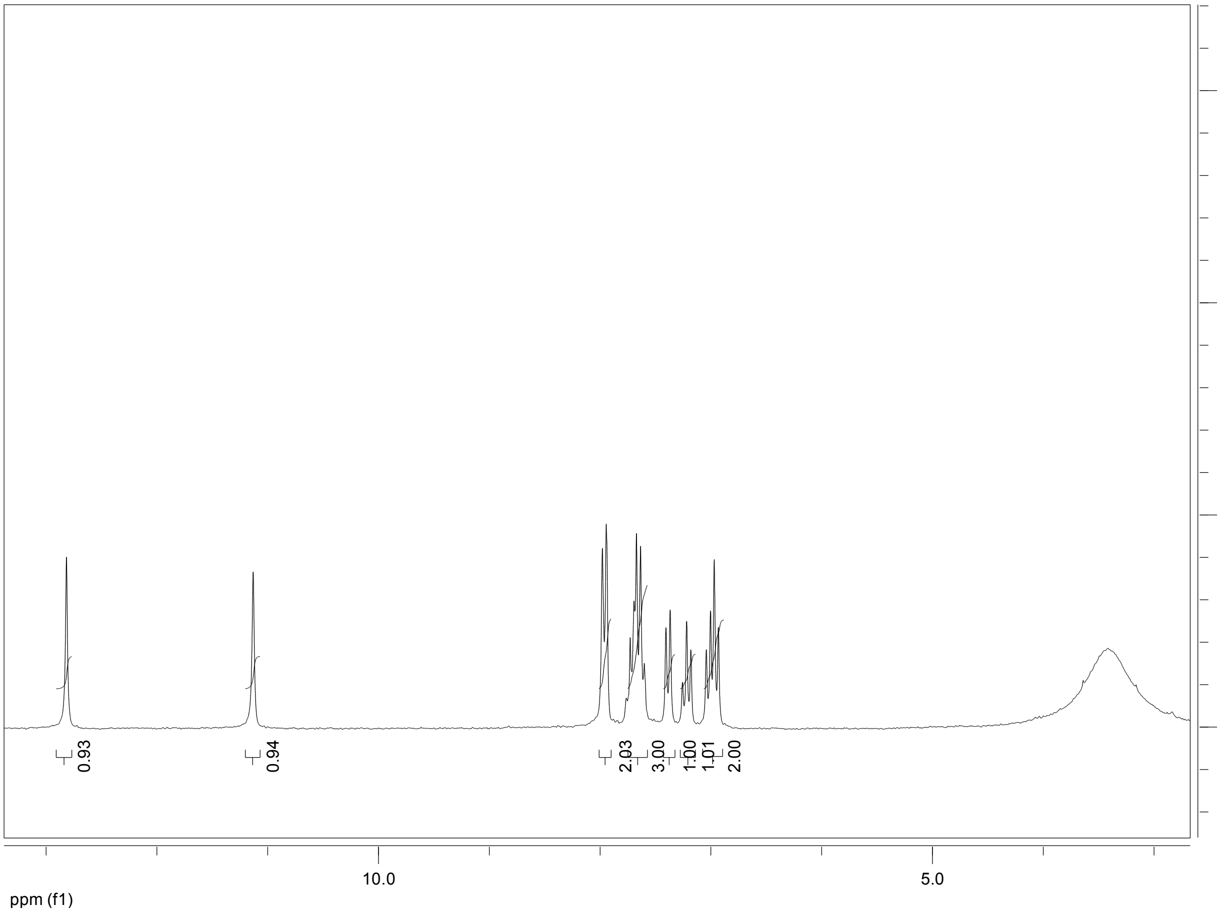
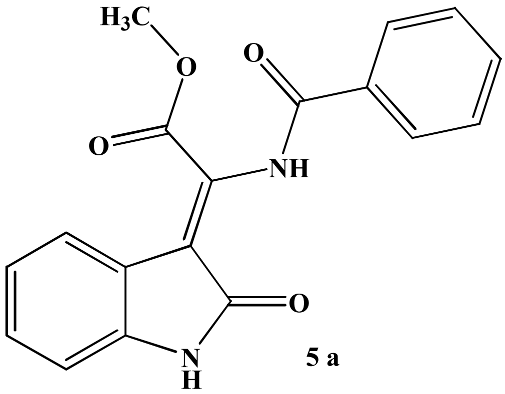


Figure 1.2. ^{1}H NMR spectrum of **4**.



5 a

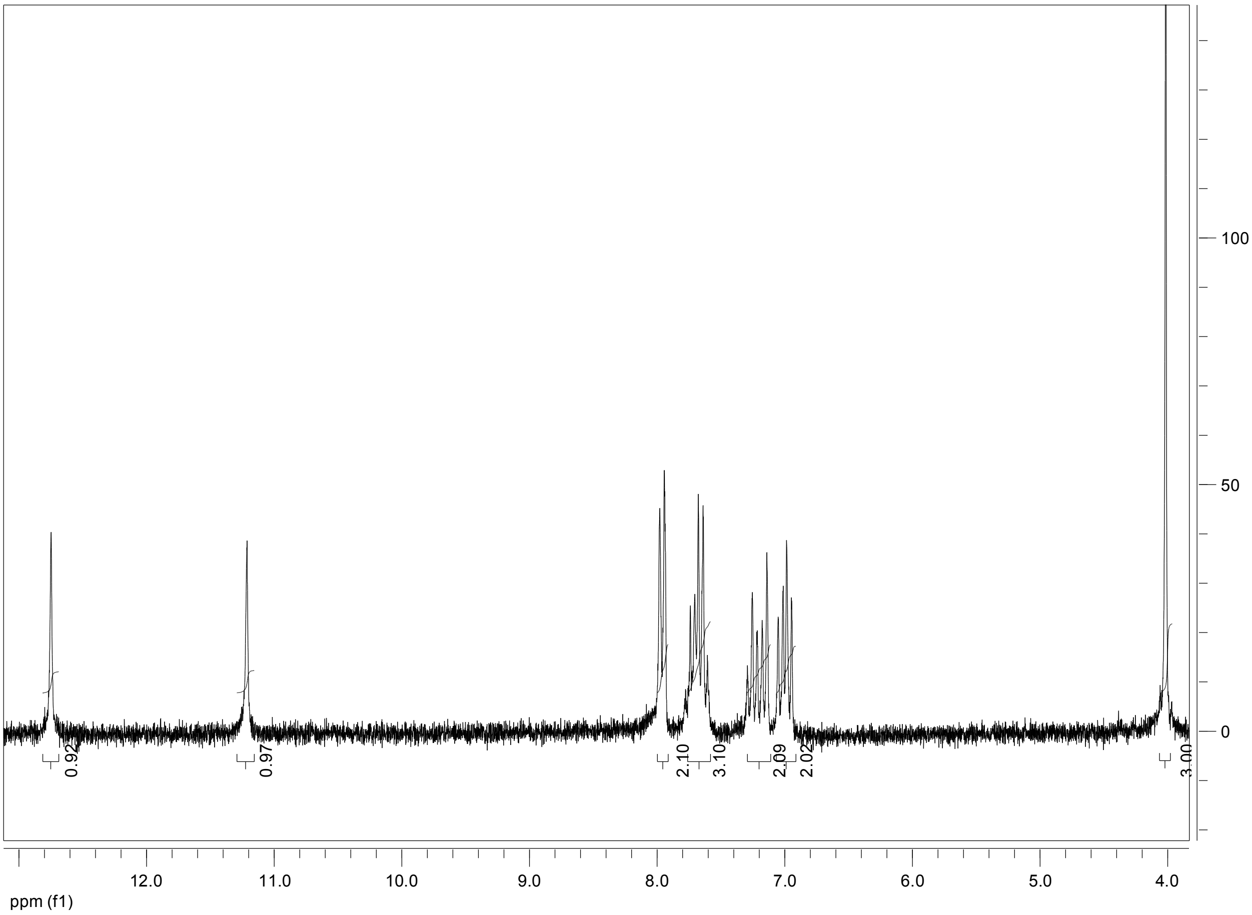


Figure 1.3. ^{1}H NMR spectrum of **5a**.

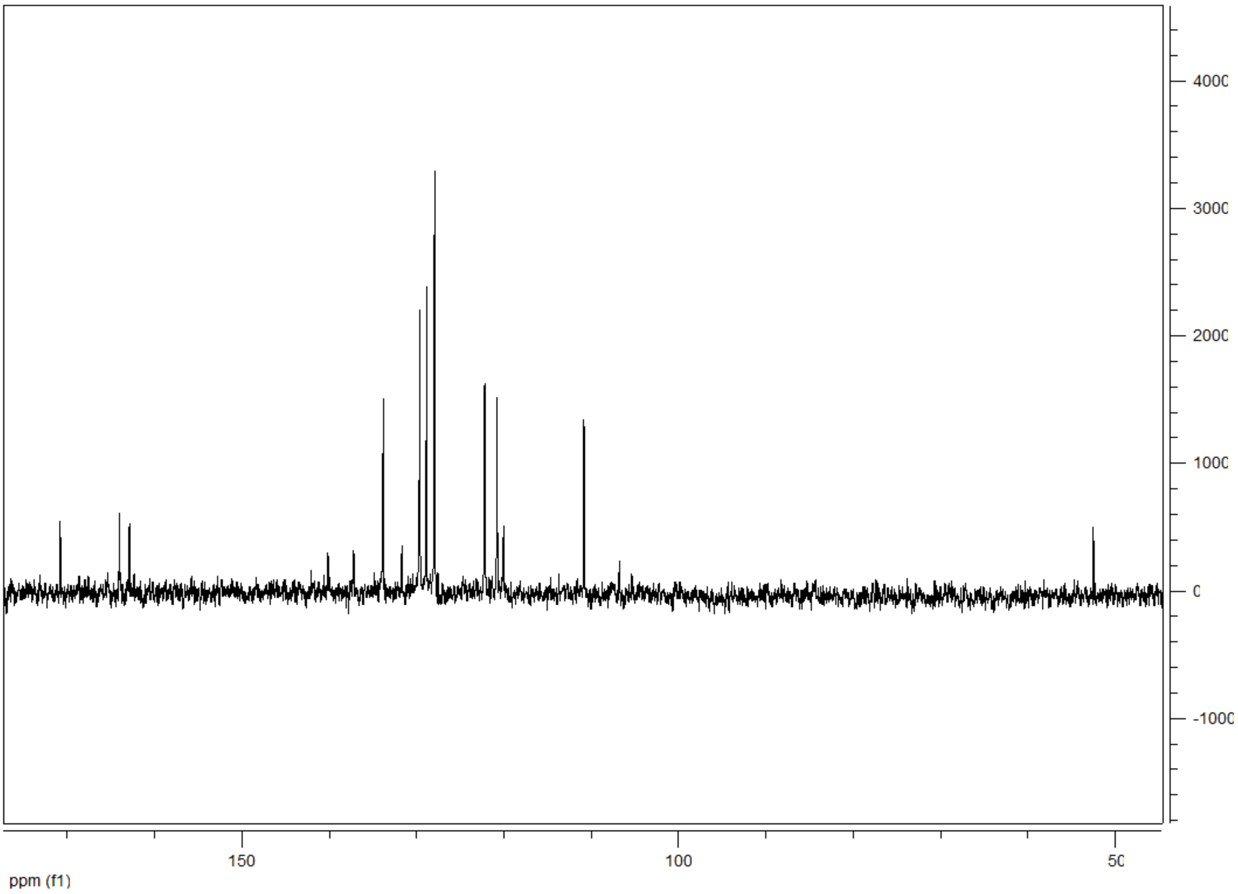
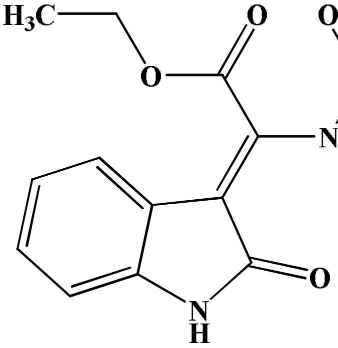


Figure 1.4. ^{13}C NMR spectrum of **5a**.



5b

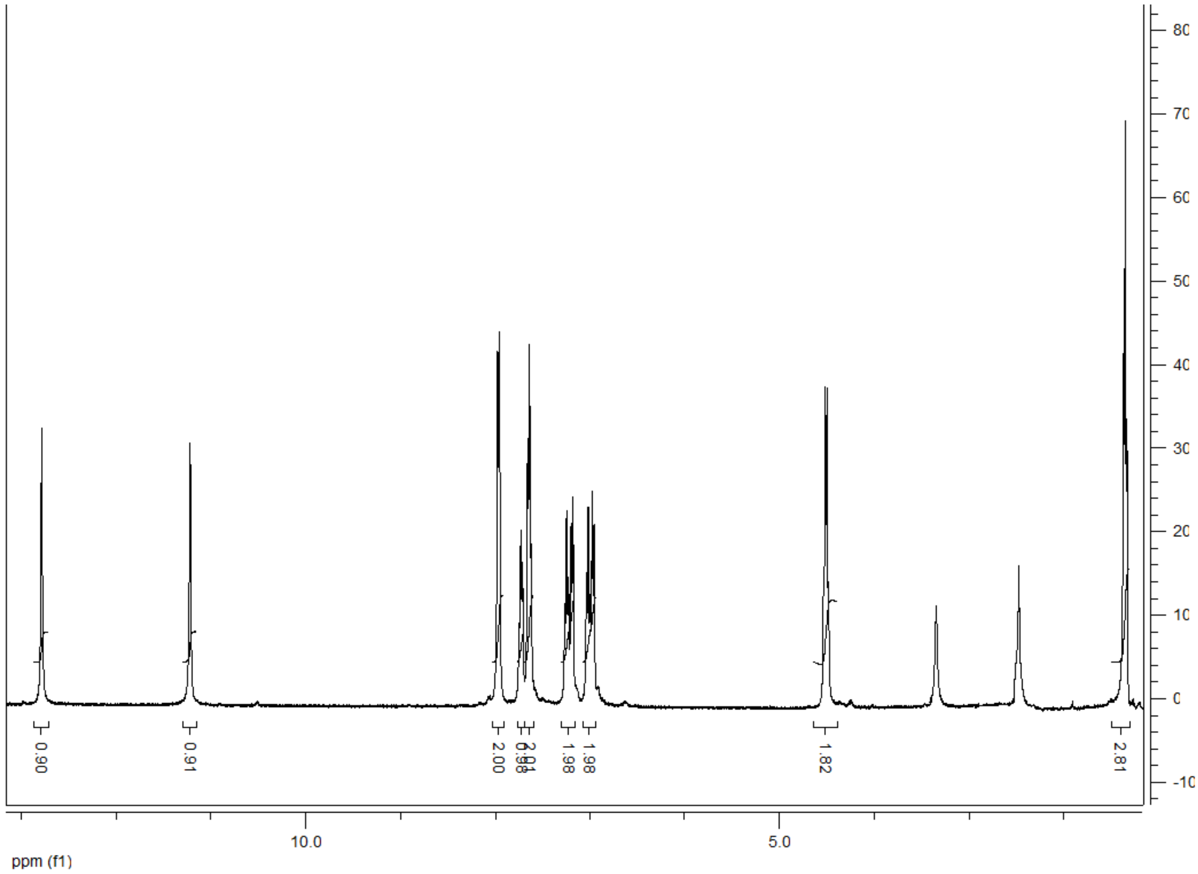


Figure 1.5. ^{1}H NMR spectrum of **5b**.

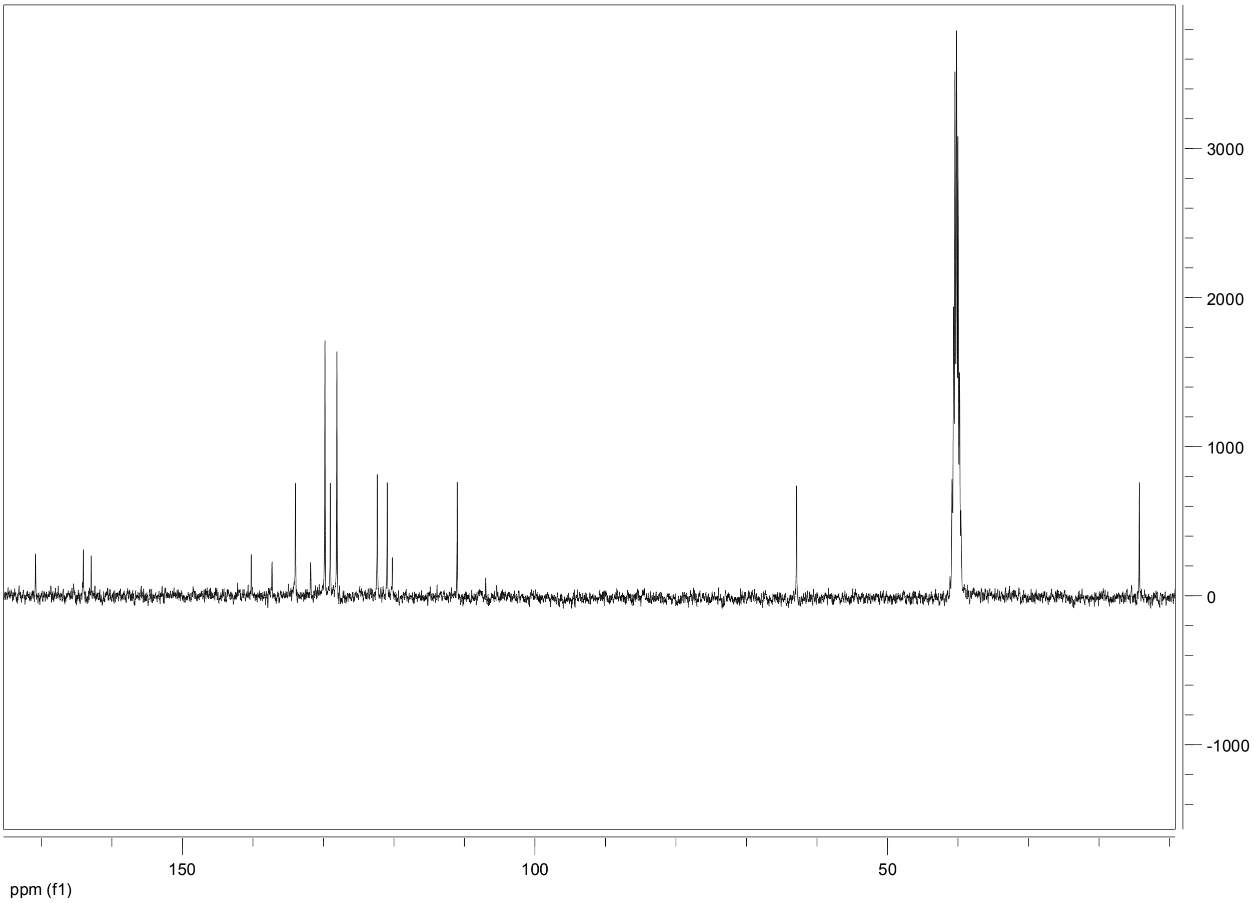
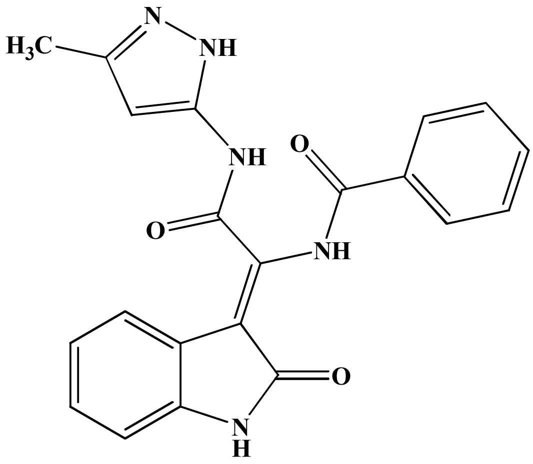


Figure 1.6. ^{13}C NMR spectrum of **5b**.



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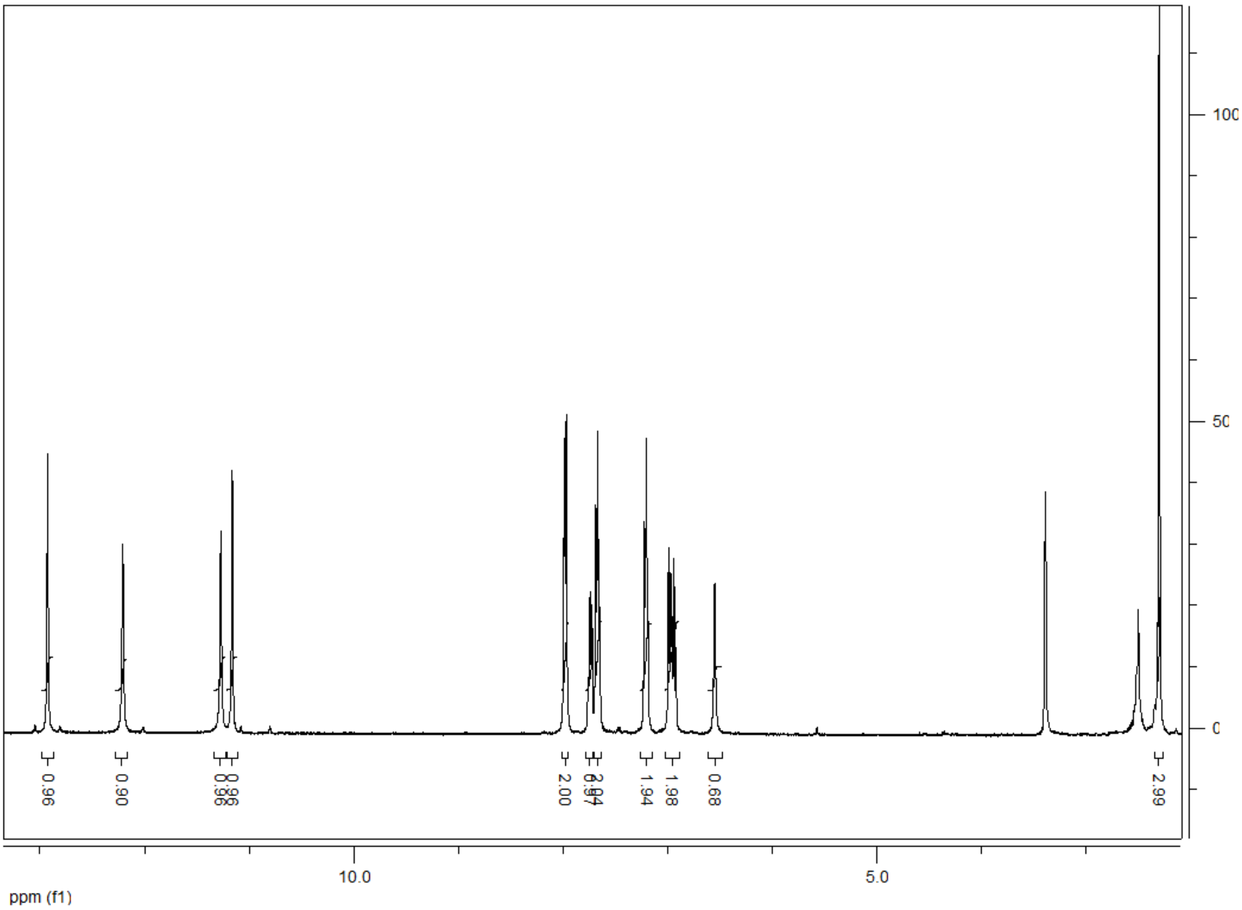


Figure 1.7. ^{1}H NMR spectrum of **6**.

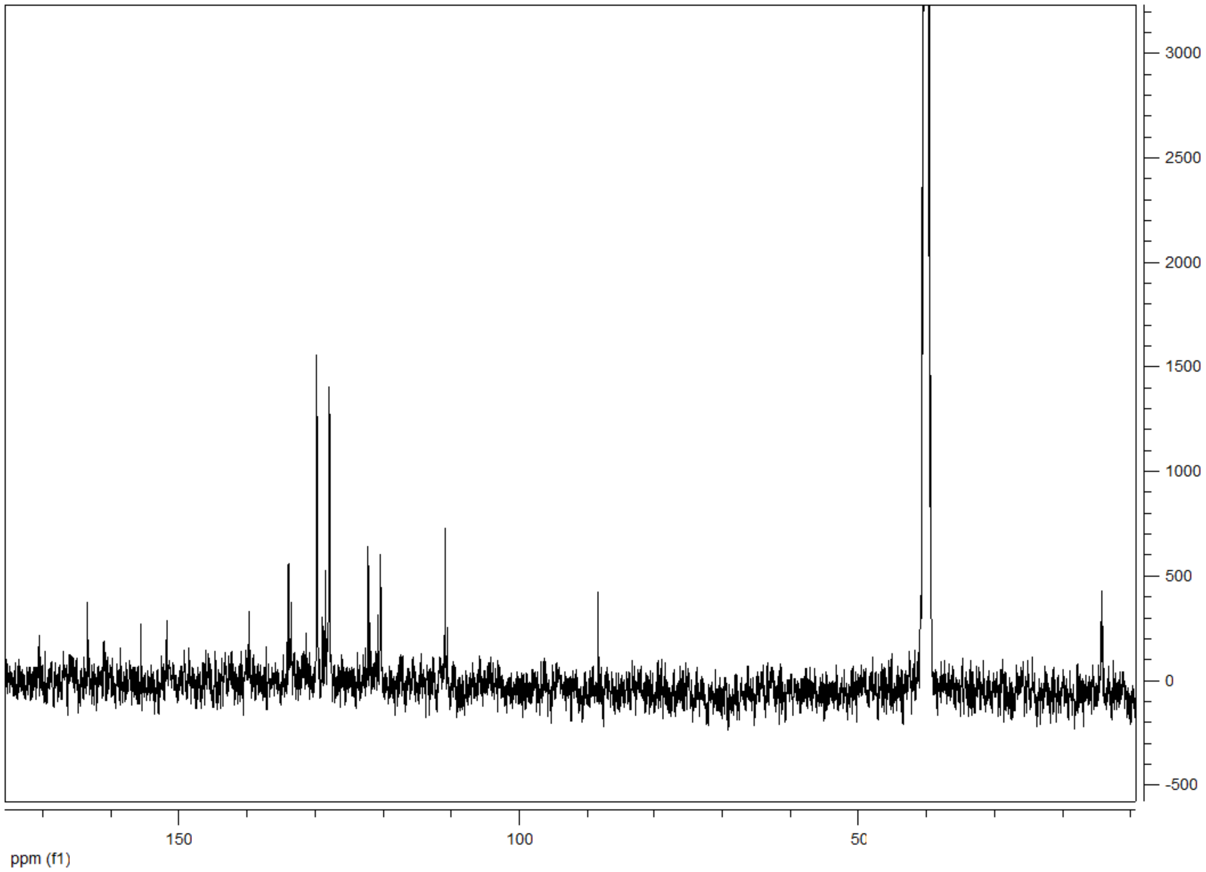
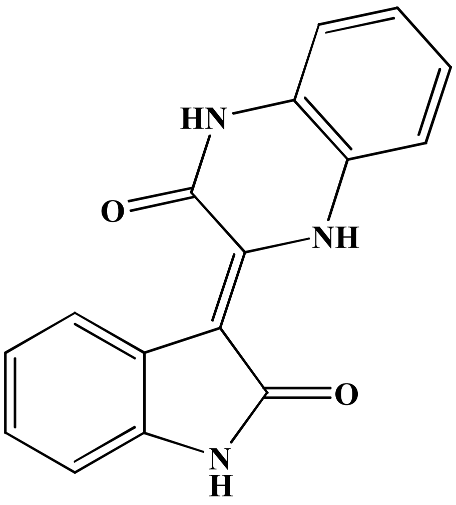


Figure 1.8. ^{13}C NMR spectrum of **6**.



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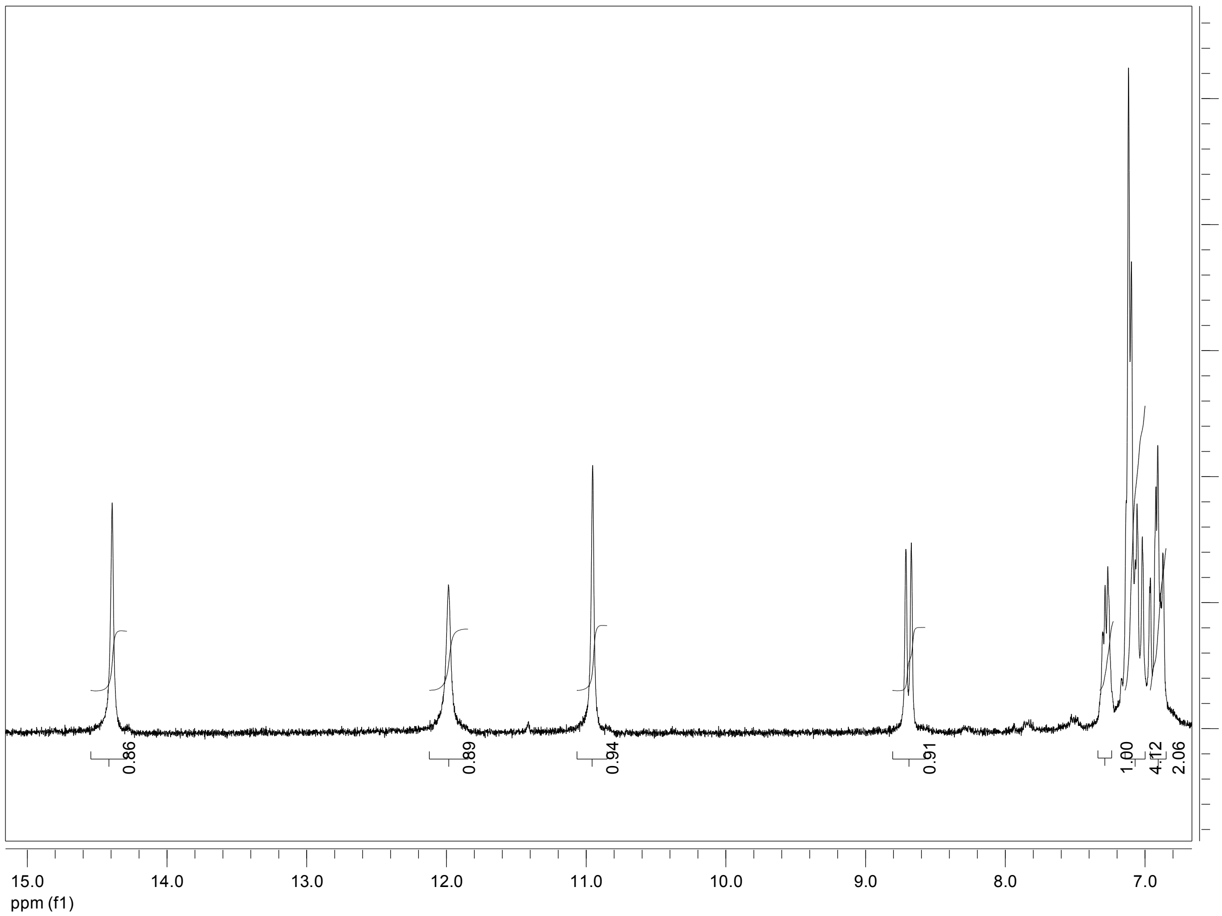


Figure 1.9. ^{1}H NMR spectrum of **7**.

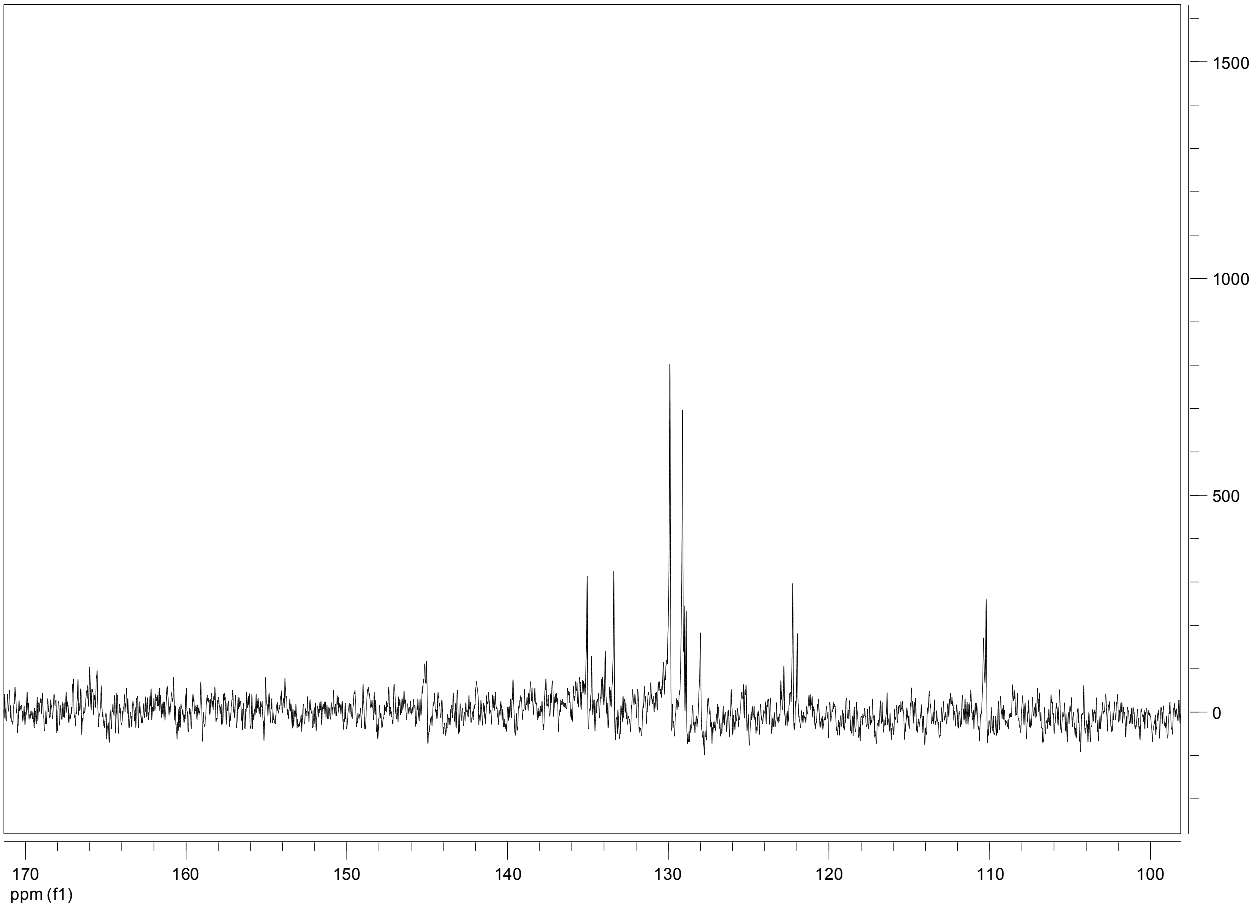
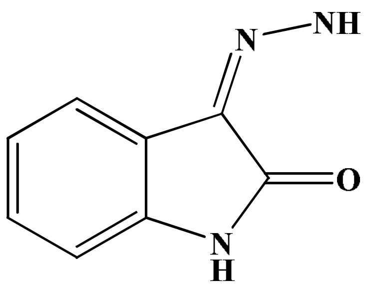


Figure 1.10. ^{13}C NMR spectrum of **7**.



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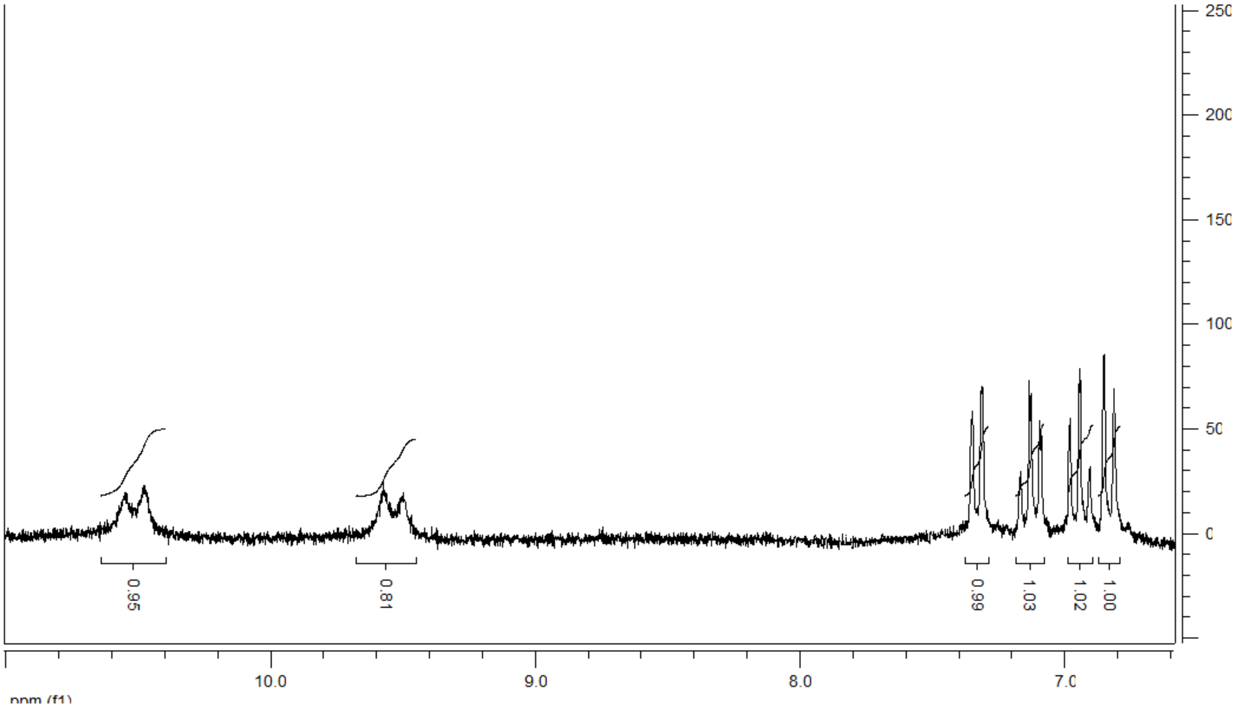
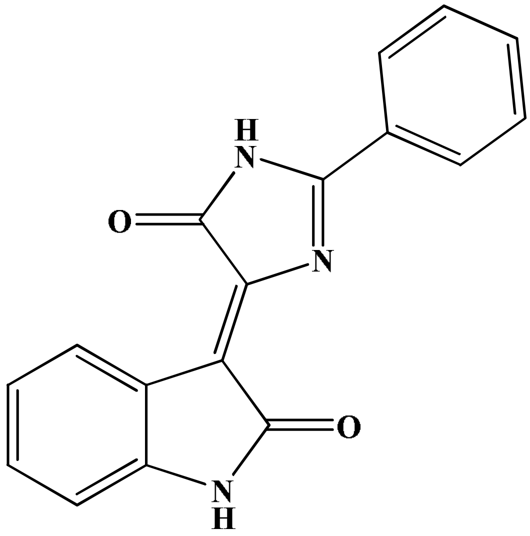


Figure 1.11. ^{1}H NMR spectrum of **8**.



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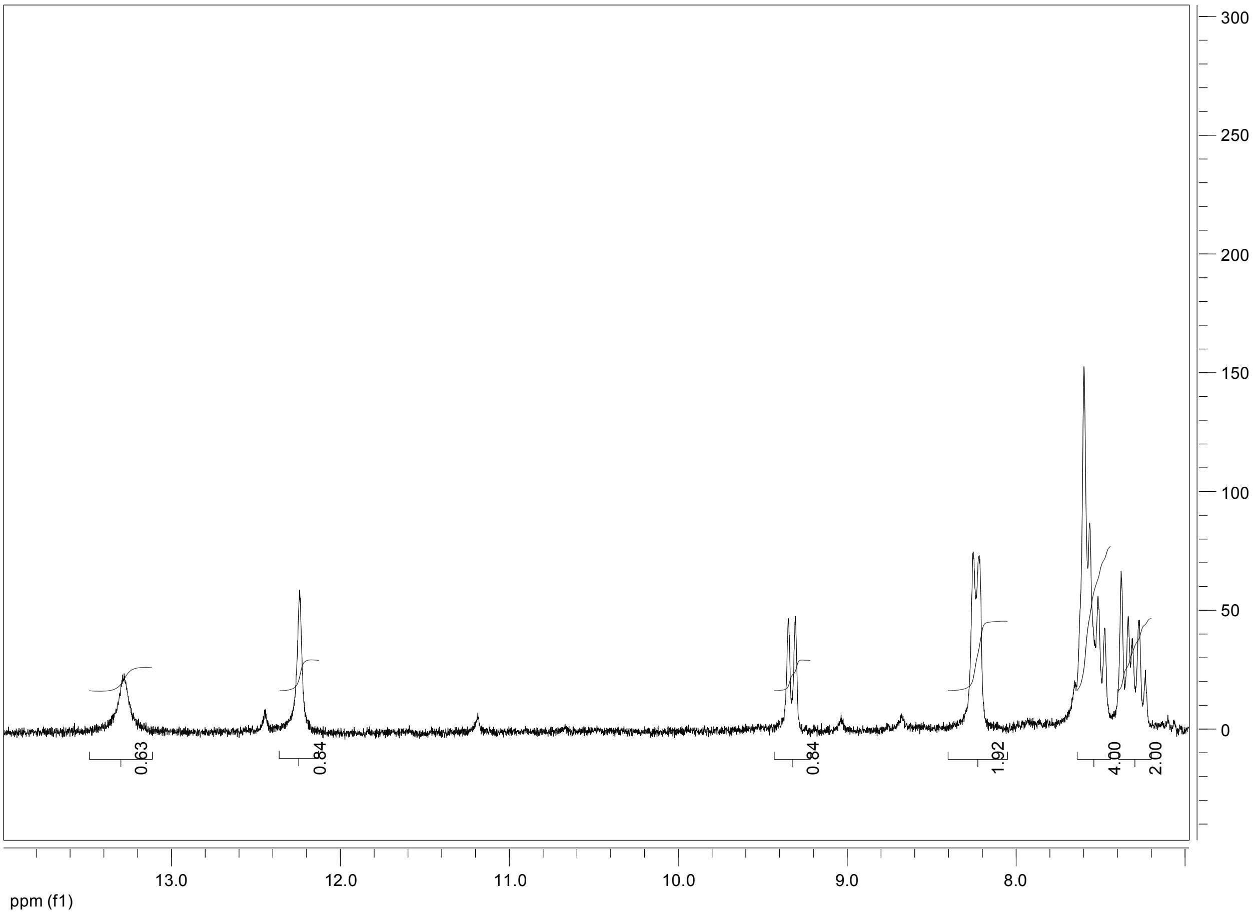

Figure 1.12. ^{1}H NMR spectrum of **9**.