Electronic Supplementary Material (ESI) for New Journal of Chemistry.

A strategic approach to the synthesis of functionalized spirooxindole pyrrolidine derivatives: *In vitro* antibacterial, antifungal, antimalarial and antitubercular studies

Saoussen Haddad,[a,c] Sarra Boudriga,[a] Tarunkumar Nanjibhai Akhaja,[b] Jignesh Priyakant Raval,[b] François Porzio,[c] Armand Soldera,[c] Moheddine Askri,[a,*] Michael Knorr,[d] Yoann Rousselin,[e] Marek M. Kubicki[e] and Dhanji Rajani[f]

[a]*Laboratory of Heterocyclic Chemistry Natural Products and Reactivity/CHPNR, Department of Chemistry, Faculty of Science of Monastir, 5000 Monastir, Tunisia.*E-mail: moheddine.askri@fsm.rnu.tn;*Tel*: +216 98676187
[b]*Department of Chemistry, UkaTarsadia University, Maliba Campus, Bardoli – Mahuva Road, Dist: Surat 394350, Gujarat, India*
[c]*Department of Chemistry, Quebec Center for Functional Materials, University of Sherbrooke, Sherbrooke, Québec, Canada, J1K 2R1*
[d]*Institute UTINAM - UMR CNRS 6213, University of Franche-Comté, 16 Route de Gray, F-25030 Besançon, France*
[e]*Institute of Molecular Chemistry - UMR CNRS 6302 , University of Bourgogne, 9 Avenue A. Savary, F-21078 Dijon, France*
[f]*Microcare Laboratories, Surat – 395001, Gujarat, India*

Supporting information

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1 DFT simulation

Table S1

Electronic energies of the *(E,E)*, *(Z,E)*, *(E,Z)* and *(Z,Z)* conformations of azomethine ylides **3a-b** calculated at the B3LYP/6-31G (d,p) level. For each molecule, the energy of the lowest conformation is set as the reference (0 kcal.mol^{-1}.).

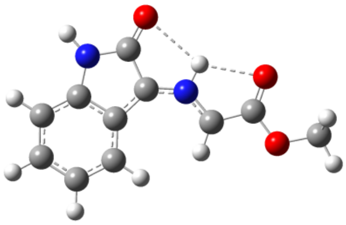
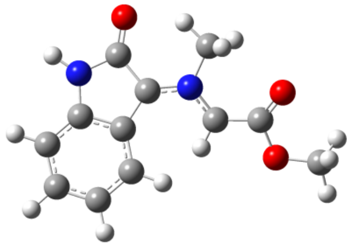
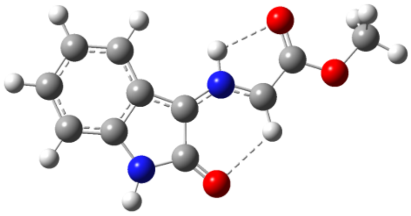
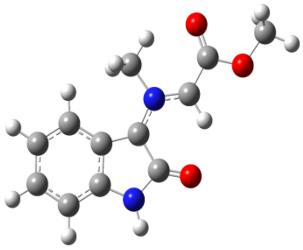
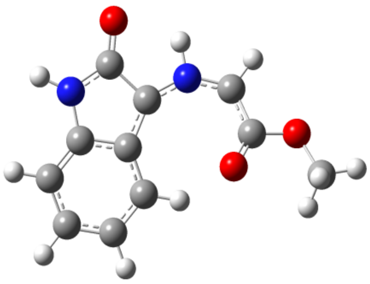
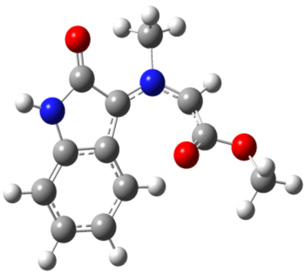
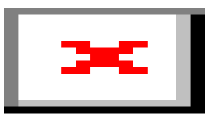
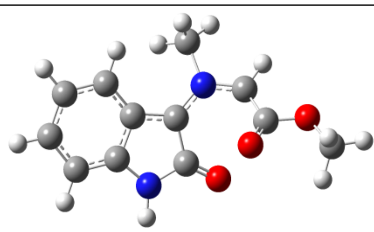
Conformations	***Isatin + Glycine methyl ester*** **3a**	***Isatin + Sarcosine methyl ester*** **3b**
E,E	 ***E*** = 0 kcal.mol^{-1}	 ***E*** = 0.6 kcal.mol^{-1}
Z,E	 ***E*** = 0.8 kcal.mol^{-1}	 ***E*** = 0 kcal.mol^{-1}
E,Z	 ***E*** = 8.0 kcal.mol^{-1}	 ***E*** = 5.1 kcal.mol^{-1}
Z,Z	 ***E*** = 16.0 kcal.mol^{-1}	 ***E*** = 7.6 kcal.mol^{-1}

Table S2
HOMO/LUMO energies, global electrophilicity, electronic chemical potential, chemical hardness of the species and index of reactants (in eV) calculated at the B3LYP/6-31G(d,p) level.

Structure	E_{HOMO} (eV)	E_{LUMO} (eV)	ω (eV)	μ (eV)	η (eV)
4a	-6.641	-2.045	2.051	-4.343	4.596
***Z,E*-3a**	-6.182	-2.333	2.354	-4.257	3.849
***E,E*-3a**	-6.292	-2.326	2.341	-4.309	3.966

Table S3
MO coefficients (in eV) and local electrophilicity indexes (according to the NBO scheme) for the reactive centers of the species involved in the 1,3-dipolar cycloaddition.

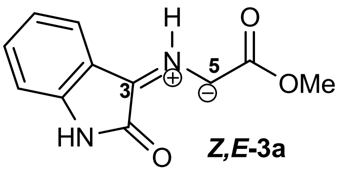
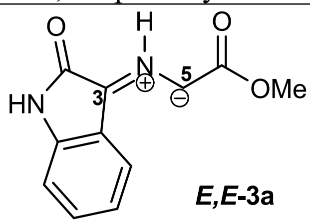
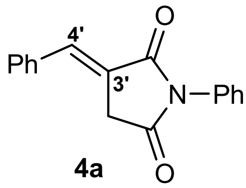
Structure	 ***Z,E*-3a**		 ***E,E*-3a**		 **4a**	
Site	**C-3**	**C-5**	**C-3**	**C-5**	**C-3'**	**C-4'**
f_k^+	0.076	0.095	0.076	0.095	0.087	0.0785
f_k^-	0.123	0.195	0.123	0.203	0.123	0.037

Table S4
Calculated activation energies (E_a, in kcal.mol^{-1}), variations in internal energy between reactants and products (ΔU, in kcal.mol^{-1}), reaction enthalpies (ΔH, in kcal.mol^{-1}), reaction entropies (ΔS, in cal.mol^{-1}.K^{-1}) and reaction Gibbs free energies at 298.15 K (ΔG, in kcal.mol^{-1}) calculated at the B3LYP/6-31G(d,p) level.

Structure	E_a	ΔU	ΔH	ΔS	ΔG
***endo*-5a**	31.9	-6.0	-3.7	-54.2	12.4
***exo*-5a**	28.9	-10.8	-8.4	-51.8	7.0
***endo*-5'a**	33.8	-2.8	-0.42	-54.7	15.91
***exo*-5'a**	41.8	-5.14	-2.69	-53.5	13.27

2 Biological evaluation

2.1 Antibacterial and antifungal activity

The MICs of the synthesized compounds were determined by the broth micro dilution method as described by Rattan [1].

All MTCC cultures were collected from the Institute of Microbial Technology, Chandigarh and tested against known drugs. Müller-Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 108

CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used as diluent to get the desired drug concentration to test upon standard bacterial strains.

2.2 Antimalarial activity

The synthesized compounds were also evaluated *in vitro* for antimalarial assay against *Plasmodium falciparum 3D7*-chloroquine-sensitive strain (Microcare laboratory and TRC, Surat, Gujarat, India) in 96-well microtitre plates, according to the microassay protocol of Rieckmann and co-workers with minor modifications [2]. The test concentration, which inhibited the complete maturation into schizonts, was recorded as the minimum inhibitory concentrations.

2.3 Antituberculosis activity

The preliminary screening of the title compounds for their *in vitro* antituberculosis activity of almost all newly synthesized compounds at (100 μg/mL concentration) against *Mycobacterium tuberculosis* $H_{37}Rv$ strain was determined by using a Löwenstein-Jensen medium (conventional method) as described by Rattan [1].

References

[1] A. Rattan, In *Antimicrobials in Laboratory Medicine*,ed.B. I. Churchill, Livingstone, New Delhi, 2000, pp. 85-108.

[2] (a) K. H. Rieckmann, G. H. Campbell, L. J. Sax, J. E. Mrema and M. Je, *Lancet*, 1978, **1**, 22; (b) Desjardins, R. E. In *Handbook of experimental pharmacology,*eds. W. Peters, W. H. G. Richards, , Springer, Berlin, 1984, pp. 179–200; (c) W.Trager and J. Jensen, *Science,*1976, 193, pp. 673-675; (d) C. Lambros and J. P. Vanderberg, *J. Parasitol*., 1979, **65**, 418.

3 Spectroscopic data of compounds 5

(2R, 3R*, 4R*, 5R*)-4-phenyl-spiro[2,3']-oxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5a**)*. White solid (41 mg, 87%); mp 184-185 °C; Found: C, 70.04; H, 4.78; N, 8.83. Anal Calcd for $C_{28}H_{23}N_3O_5$: C, 69.84; H, 4.81; N, 8.73 %. IR (ν_{max}, cm^{-1}): 1719 (C=O), 1775 (C=O), 3152 (N-H), 3297 (N-H); ^1H NMR: δ 2.56 (d,1H, C*H2*CONPh, *J* = 19.0 Hz), 2.78 (d, 1H, C*H2*CONPh, *J* = 19.0 Hz), 3.71 (s, 3H, OCH_3), 4.44 (d, 1H, H-4, *J* = 9.7 Hz), 5.24 (d, 1H, H-5, *J* = 9.7 Hz), 6.85-7.56 (m, 14H, Ar-H), 8.64 (bs, 1H, NH); ^{13}C NMR: δ36.1, 52.5, 57.3, 61.7, 64.7, 74.8, 110.7, 123.3, 124.5, 126.3, 126.5, 128.3, 128.8, 129.0, 129.3, 129.9, 130.8, 131.1, 136.0, 141.3, 171.5, 173.4, 177.6, 178.8.

(2R, 3R*, 4R*, 5R*)-4-(4-methylphenyl)-spiro[2,3']-oxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5b**)*. White solid (43 mg, 87%); mp 226-227 °C; Found: C, 70.34; H, 5.08; N, 8.58. Anal Calcd for $C_{29}H_{25}N_3O_5$: C, 70.29; H, 5.09; N, 8.48 %. IR (ν_{max}, cm^{-1}): 1719 (C=O), 1773 (C=O), 3152 (N-H), 3283 (N-H); ^1H NMR: δ 2.36 (s, 3H, CH_3), 2.55 (d, 1H, C*H2*CONPh, *J* = 18.9 Hz), 2.75 (d, 1H, C*H2*CONPh, *J* = 18.9 Hz), 3.69 (s, 3H, OCH_3), 4.34 (d, 1H, H-4, *J* = 9.6 Hz), 5.07 (d, 1H, H-5, *J* = 9.6 Hz), 6.78-7.46 (m, 13H, Ar-H), 7.82 (bs, 1H, NH); ^{13}C NMR: δ = 21.1, 36.2, 52.4, 57.4, 62.1, 65.0, 75.0, 110.2, 123.3, 125.4, 126.3, 126.5, 128.7, 129.0, 129.7, 129.9, 130.5, 131.22, 133.1, 137.9, 140.9, 172.1, 173.6, 177.9, 178.8.

(2R, 3R*, 4R*, 5R*)-4-(4-methoxyphenyl)-spiro[2,3']-oxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5c**)*. White solid (48 mg, 95%); mp 210-211 °C; Found: C, 68.21; H, 4.96; N, 7.98. Anal Calcd for $C_{29}H_{25}N_3O_6$: C, 68.09; H, 4.93; N, 8.21 %. IR (ν_{max}, cm^{-1}): 1717 (C=O), 1773 (C=O), 3156 (N-H), 3288 (N-H); ^1H NMR: δ 2.57 (d, 1H, C*H2*CONPh, *J* = 19.0 Hz), 2.76 (d, 1H, C*H2*CONPh, *J* = 19.0 Hz), 3.69 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.34 (d, 1H, H-4, *J* = 9.7 Hz), 5.05 (d, 1H, H-5, *J* = 9.7 Hz,), 6.79-7.44 (m, 13H, Ar-H), 8.45 (bs, 1H, NH); ^{13}C NMR: δ 36.2, 52.4, 55.2, 57.1, 62.1,65.2, 75.0, 110.4, 114.6, 123.2, 125.4, 126.2, 126.5, 128.2, 128.8, 129.0, 130.5, 131.0, 131.2, 141.1, 159.3, 172.1, 173.7, 178.3, 178.9.

(2R, 3R*, 4R*, 5R*)-4-(4-chlorophenyl)-spiro[2,3']-oxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5d**)*. White solid, (41 mg, 80%); mp 245-247°C; Found: C, 65.33; H, 4.25; N, 8.10. Anal Calcd for $C_{28}H_{22}ClN_3O_5$: C, 65.18; H, 4.30; N, 8.14 %. IR (ν_{max}, cm^{-1}): 1714 (C=O), 1772 (C=O), 3159 (N-H), 3296 (N-H); ^1H NMR:δ 2.50 (d, 1H, C*H2*CONPh, *J* = 18.9 Hz), 2.72 (d, 1H, C*H2*CONPh, *J* = 18.9 Hz), 3.70 (s, 3H, OCH_3), 4.32 (d, 1H, H-4, *J* = 9.4 Hz), 5.04 (d, 1H, H-5, *J* = 9.4 Hz), 6.78-7.49 (m, 14H, Ar-H and NH); ^{13}C NMR: δ 36.6, 52.5, 57.1, 62.0, 65.4, 74.5, 110.2, 115.7, 123.4, 126.4, 128.4, 128.7, 128.9, 129.0, 131.4, 130.9, 133.2, 133.8, 134.3, 140.8, 171.0, 172.6, 176.8, 178.1.

(2R, 3R*, 4R*, 5R*)-4-(4-bromophenyl)-spiro[2,3']-oxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5e**)*. White solid, (45 mg, 82%); mp 220-221°C; Found: C, 60.20; H, 3.93; N, 7.61. Anal Calcd for $C_{28}H_{22}BrN_3O_5$: C, 60.01; H, 3.96; N, 7.50 %. IR (ν_{max}, cm^{-1}): 1720 (C=O), 1774 (C=O), 3159 (N-H), 3289 (N-H); ^1H NMR: δ 2.49 (d, 1H, C*H2*CONPh ,*J*= 19.2 Hz), 2.70 (d, 1H, C*H2*CONPh, *J* = 19.2 Hz), 3.62 (s, 3H, OCH_3), 4.28 (d, 1H, H-4, *J* = 9.9 Hz), 5.03 (d, 1H, H-5, *J* = 9.9 Hz), 6.71-7.39 (m, 13H, Ar-H), 8.02 (bs, 1H, NH); ^{13}C NMR: δ 35.7, 51.9, 56.9, 61.6, 64.5, 74.5, 109.8, 122.8, 125.0,

125.8, 126.0, 128.2, 128.5, 129.2, 129.4, 130.0, 130.7, 132.7, 137.4, 140.5, 171.6, 173.1, 177.6, 178.3.

(2R, 3R*, 4R*, 5R*)-4-phenyl-spiro[2,3']-5'-bromooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5f**)*. White solid, (47 mg, 85%); mp 162-163°C; Found: C, 60.11; H, 3.98; N, 7.32. Anal Calcd for $C_{28}H_{22}BrN_3O_5$: C, 60.01; H, 3.96; N, 7.50 %. IR (ν_{max}, cm^{-1}): 1730 (C=O), 1778 (C=O), 3109 (N-H), 3304 (N-H); ^{1}H NMR: δ 2.58 (d, 1H, C*H2*CONPh, *J* = 19.0 Hz), 2.74 (d, 1H, C*H2*CONPh, *J*= 19.0 Hz), 3.73 (s, 3H, OCH_3), 4.39 (d, 1H, H-4, *J* = 9.6 Hz), 5.11 (d, 1H, H-5 *J* = 9.6 Hz), 6.72-7.26 (m, 13H, Ar-H), 8.33 (bs, 1H, NH); ^{13}C NMR: δ 35.6, 52.0, 56.7, 61.4, 64.4, 74.3, 111.3, 115.5, 125.8, 126.9, 127.8, 128.4, 128.7, 128.8, 129.01, 129.4, 130.5, 133.0, 135.6, 139.5, 171.3, 172.9, 177.0, 178.1.

(2R, 3R*, 4R*, 5R*)-4-(4-methylphenyl)-spiro[2,3']-5'-bromooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5g**)*. White solid, (47 mg, 83%); mp 216-217°C; Found: C, 60.42; H, 4.17; N, 7.43. Anal Calcd for $C_{29}H_{24}BrN_3O_5$: C, 60.64; H, 4.21; N, 7.32 %. IR (ν_{max}, cm^{-1}): 1734 (C=O), 1781 (C=O), 3208 (N-H), 3320 (N-H); ^{1}H NMR: δ 2.29 (s, 3H, CH_3), 2.49 (d, 1H, C*H2*CONPh, *J* = 18.9 Hz), 2.64 (d, 1H, C*H2*CONPh, *J* = 18.9 Hz), 3.63 (s, 3H, OCH_3), 4.26 (d, 1H, H-4, *J* = 9.6 Hz), 4.96 (d, 1H, H-5, *J* = 9.6 Hz), 6.63-7.88 (m, 12H, Ar-H), 8.02 (bs, 1H, NH);^{13}C NMR: δ 20.6, 35.5, 52.0, 56.5, 61.4, 64.3, 74.2, 111.2, 115.5, 125.8, 127.0, 128.3, 128.7, 129.0, 129.2, 129.5, 130.6, 132.4, 133.0, 137.5, 139.4, 171.3, 172.9, 176.9, 178.1.

(2R, 3R*, 4R*, 5R*)-4-(4-methoxyphenyl)-spiro[2,3']-5'-bromooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5h**)*. White solid, (51 mg, 87%); mp 252-253°C; Found: C, 59.12; H, 4.13; N, 7.01. Anal Calcd for $C_{29}H_{24}BrN_3O_6$: C, 58.99; H, 4.10; N, 7.12 %. IR (ν_{max}, cm^{-1}): 1715 (C=O), 1777 (C=O), 3280 (N-H), 3302 (N-H); ^{1}H NMR: δ 2.46 (d, 1H, C*H2*CONPh, *J* = 18.3 Hz), 2.83 (d, 1H, C*H2*CONPh, *J* = 18.3 Hz), 3.63 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.39 (d, 1H, H-4, *J* = 9.6 Hz), 4.89 (d, 1H, H-5, *J* = 9.6 Hz), 6.83-7.67 (m, 13H, Ar-H and NH); ^{13}C NMR: δ 35.4, 51.8, 53.4, 55.1, 61.1, 63.5, 73.7, 109.6, 114.3, 124.1, 124.5, 125.3, 125.5, 126.6, 128.2, 128.6, 129.7, 130.6, 142.6, 145.0, 159.3, 171.9, 172.6, 176.9, 178.0.

(2R, 3R*, 4R*, 5R*)-4-(4-chlorophenyl)-spiro[2,3']-5'-bromooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5i**)*. White solid, (54 mg, 85%); mp 250-251°C; Found: C, 56.36; H, 3.61; N, 6.88. Anal Calcd for $C_{28}H_{21}BrClN_3O_5$: C, 56.54; H, 3.56; N, 7.06 %. HRMS (ESI) calcd $[M + H]^+$ 594.0424 found 594.0425; IR (ν_{max}, cm^{-1}): 1715 (C=O), 1786 (C=O), 3166 (N-H), 3296 (N-H);^{1}H NMR: δ 2.44 (d, 1H, C*H2*CONPh, *J* = 18.9 Hz), 2.62 (d, 1H, C*H2*CONPh, *J* = 18.9 Hz), 3.63 (s, 3H, OCH_3), 4.25 (d, 1H, H-4, *J* = 9.6 Hz), 4.97 (d, 1H, H-5, *J* = 9.6 Hz,), 6.63-8.08 (m, 13H, Ar-H and NH); ^{13}C NMR: δ 35.7, 52.0, 56.0, 61.2, 64.7, 74.4, 111.4, 115.7, 125.7, 126.5, 128.4, 128.7, 128.9, 129.0, 130.4, 130.9, 133.2, 133.8, 134.3, 139.4, 171.0, 172.6, 176.8, 178.1.

(2R, 3R*, 4R*, 5R*)-4-(4-bromophenyl)-spiro[2,3']-5'-bromooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5j**)*. White solid, (56 mg, 89%); mp 190-191°C; Found: C, 52.32; H, 3.34; N, 6.43.Anal Calcd for $C_{28}H_{21}Br_2N_3O_5$: C, 52.61; H, 3.31; N, 6.57 %. IR (ν_{max}, cm^{-1}): 1718 (C=O), 1781 (C=O), 3193 (N-H), 3296 (N-H);^{1}H NMR:δ 2.53 (d, 1H, C*H2*CONPh, *J* = 19.0 Hz), 2.71 (d, 1H, C*H2*CONPh, *J* = 19.0 Hz), 3.73 (s, 3H, OCH_3), 4.25 (d, 1H, H-4, *J* = 9.7 Hz), 4.97 (d, 1H, H-5 *J* = 9.7 Hz), 6.71-7.59 (m, 12H, Ar-H), 8.15 (bs, 1H, NH); ^{13}C NMR: δ 35.7, 52.1, 56.1, 61.2, 64.7, 74.4, 111.4, 115.7, 122.0,

125.7, 126.4, 128.4, 128.7, 128.9, 130.4, 131.2, 132.0, 133.2, 134.8, 139.5, 171.0, 172.6, 176.8, 178.0.

(2R, 3R*, 4R*, 5R*)-4-phenyl-spiro[2,3']-5'-nitrooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5k**)*. White solid, (42 mg, 80%); mp 168-169°C; Found: C, 64.12; H, 4.25; N, 10.51. Anal Calcd for $C_{28}H_{22}N_4O_7$: C, 63.87; H, 4.21; N, 10.64 %. IR (ν_{max}, cm^{-1}): 1732 (C=O), 1780 (C=O), 3288 (N-H), 3309 (N-H);^{1}H NMR: δ 2.63 (d, 1H, C*H₂*CONPh*,* *J* = 18.9 Hz), 2.74 (d, 1H, C*H₂*CONPh, *J* = 18.9 Hz), 3.75 (s, 3H, OCH_3), 4.51 (d, 1H, H-4, *J* = 9.6 Hz), 5.07 (d, 1H, H-5, *J* = 9.6 Hz), 6.87-7.26 (m, 12H, Ar-H), 8.53 (bs, 1H, NH); ^{13}C NMR: δ 35.0, 52.8, 56,3, 61.4, 63.7, 73.5, 110.3, 115.5, 122.8, 125.7, 127.3, 128.6, 128.9, 129.1, 129.4, 129.6, 130.8, 134.8, 143.9, 146.2, 171.3, 172.9, 177.3, 178.1.

(2R, 3R*, 4R*, 5R*)-4-(4-methylphenyl)-spiro[2,3']-5'-nitrooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5l**)*. White solid, (47 mg, 88%); mp 233-234°C; Found: C, 70.01; H, 4.78; N, 8.56. Anal Calcd for $C_{29}H_{24}N_4O_7$: C, 69.84; H, 4.81; N, 8.73 %. IR (ν_{max}, cm^{-1}): 1733 (C=O), 1783 (C=O), 3200 (N-H), 3316 (N-H);^{1}H NMR: δ 2.38 (s, 3H, CH_3), 2.66 (d, 1H,C*H₂*CONPh, *J* = 18.9 Hz), 2.92 (d, 1H, C*H₂*CONPh, *J* = 18.9 Hz), 3.76 (s, 3H, OCH_3), 4.49 (d, 1H, H-4*,* *J* = 9.6 Hz), 5.08 (d, 1H, H-5, *J* = 9.6 Hz), 6.89-8.56 (m, 13H, Ar-H and NH); ^{13}C NMR: δ 21.1, 34.8, 52.9, 58,4, 61.4, 63.5, 73.5, 110.4, 115.5, 124.6, 125.8, 126.1, 127.1, 128.7, 129.0, 129.1, 130.1, 131.1, 138.8, 143.1, 145.4, 171.3, 172.8, 174.1, 177.7.

(2R, 3R*, 4R*, 5R*)-4-(4-methoxyphenyl)-spiro[2,3']-5'-nitrooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5m**)*. White solid, (47 mg, 85%); mp 240-241°C; Found: C, 62.75; H, 4.41; N, 9.77. Anal Calcd for $C_{29}H_{24}N_4O_8$: C, 62.59; H, 4.35; N, 10.07 %. IR (ν_{max}, cm^{-1}): 1748 (C=O), 1779 (C=O), 3214 (N-H), 3310 (N-H);^{1}H NMR: δ 2.66 (d, 1H, C*H₂*CONPh*,* *J* = 18.9 Hz), 2.90 (d, 1H, C*H₂*CONPh, *J* = 18.9 Hz), 3.76 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.47 (d, 1H, H-4, *J* = 10.0 Hz), 5.04 (d, 1H, H-5, *J* = 10.0 Hz), 6.90-8.55 (m, 13H, Ar-H and NH); ^{13}C NMR: δ 34.8, 51.8, 52.9, 55.2, 61.1, 63.5, 73.7, 109.6, 114.3,124.1, 124.5, 125.3, 125.5, 126.6, 128.2, 128.9, 129.1, 130.6, 142.6, 145.0, 159.3 171.9, 172.2, 176.9, 178.0.

(2R, 3R*, 4R*, 5R*)-4-(4-cholophenyl)-spiro[2,3']-5'-nitrooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5n**)*. White solid, (36 mg, 60%); mp 197-198°C; Found: C, 62.73; H, 4.29; N, 9.79. Anal Calcd for $C_{28}H_{21}ClN_4O_7$: C, 62.59; H, 4.35; N, 10.07%. IR (ν_{max}, cm^{-1}): 1727 (C=O), 1780 (C=O), 3255 (N-H), 3291 (N-H);^{1}H NMR: δ 2.59 (d, 1H, C*H₂*CONPh*,* *J* = 19.0 Hz), 2.83 (d, 1H, C*H₂*CONPh, *J* = 19.0 Hz), 3.47 (d, 1H, H-4, *J* = 9.4 Hz), 3.76 (s, 3H, OCH_3), 4.43 (d, 1H, H-5, *J* = 9.4 Hz), 6.89-8.48 (m, 13H, Ar-H and NH); ^{13}C NMR: δ 35.3, 52.8, 56.4, 61.6, 64.4, 74.1, 110.0, 116.4, 116.7, 125.7, 125.9, 127.2, 128.8, 129.1, 130.9, 131.0, 133.8, 134.6, 143.3, 145.3, 171.4, 172.6, 174.2, 177.3.

(2R, 3R*, 4R*, 5R*)-4-(4-bromophenyl)-spiro[2,3']-5'-nitrooxindole-spiro[3,3'']-5-carbomethoxypyrrolidine-3-N-phenylsuccinimide (**5o**)*. White solid, (49 mg, 82%); mp 235-236°C; Found: C, 55.73; H, 3.56; N, 9.35. Anal Calcd for $C_{28}H_{21}BrN_4O_7$: C, 55.55; H, 3.50; N, 9.25%. IR(ν_{max}, cm^{-1}): 1730 (C=O), 1784 (C=O), 3257 (N-H), 3284 (N-H); ^{1}H NMR: δ 2.58 (d, 1H, C*H₂*CONPh, *J* = 18.9 Hz), 2.84 (d, 1H, C*H₂*CONPh, *J* = 18.9 Hz), 3.76 (s, 3H, OCH_3), 4.43 (d, 1H, H-4, *J* = 9.6 Hz,), 5.03 (d, 1H, H-5, *J* = 9.6 Hz), 6.89-7.70 (m, 13H, Ar-H

and NH); ^{13}C NMR: δ = 35.3, 52.9, 56,4, 61.4, 64.2, 73.5, 110.5, 122.7, 125.6, 126.4, 129.0, 129.2, 130.7, 131.4, 131.5, 132.5, 132.6, 134.2, 143.9, 146.4, 171.2, 172.6, 177.5, 178.3.

(2R, 3R*, 4R*, 5R*)-4-phenyl-spiro[2,3']-oxindole-spiro[3,3'']-5-carbomethoxy-N-methylpyrrolidine-3-N-phenylsuccinimide (**5p**)*. White solid, (32 mg, 65%); mp 190-191°C; Found: C, 70.53; H, 4. 98; N, 8.32. Anal Calcd for $C_{29}H_{25}N_3O_5$: C, 70.29; H, 5.09; N, 8.48%. IR (ν_{max}, cm^{-1}): 1736 (C=O), 1782 (C=O), 3323 (N-H);^{1}H NMR: δ 2.20 (s, 3H, CH_3), 2.39 (d, 1H, C*H$_2$*CONPh, *J* = 18.9 Hz), 2.63 (d, 1H, C*H$_2$*CONPh*,* *J* = 18.9 Hz), 3.60 (s, 3H, OCH_3), 4.53 (d, 1H,H-4, *J* = 9.6 Hz,), 4.82 (d, 1H, H-5, *J* = 9.6 Hz), 6.69-7.43 (m, 14H, Ar-H), 7.79 (bs, 1H, NH); ^{13}C NMR: δ 34.2, 37.1, 52.2, 53.7, 59.9, 69.8, 79.0, 110.2, 123.6, 126.5, 128.0, 128.2, 128.6, 128.9, 129.0, 129.2, 130.1, 130.6, 131.3, 136.1, 141.3, 171.3, 173.3, 177.2, 177.4.

(2R, 3R*, 4R*, 5R*)-4-(4-methylphenyl)-spiro[2,3']-spiro[3,3'']-5-carbomethoxy-N-methylpyrrolidine-3-N-phenylsuccinimide (**5q**)*. White solid, (34 mg, 67%); mp 258-259 °C; Found: C, 70.98; H, 5.37; N, 8.19. Anal Calcd for $C_{30}H_{27}N_3O_5$: C, 70.71; H, 5.34; N, 8.25%. IR (ν_{max}, cm^{-1}): 1740 (C=O), 1780 (C=O), 3337 (N-H);^{1}H NMR: δ 2.22 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.43 (d, 1H, C*H$_2$*CONPh, *J* = 18.9 Hz), 2.63 (d, 1H, C*H$_2$*CONPh, *J* = 18.9 Hz), 3.62 (s, 3H, OCH_3), 4.51 (d, 1H, H-4, *J* = 9.7 Hz,), 4.82 (d, 1H, H-5, *J* = 9.7 Hz,), 6.71-7.46 (m, 13H, Ar-H), 7.98 (bs, 1H, NH); ^{13}C NMR: δ 33.7, 36.5, 51.7, 53.0, 59.3, 69.3, 78.4, 109.7, 123.0, 123.7, 126.0, 127.5, 128.1, 128.4, 129.4, 129.4, 130.1, 130.8, 132.3, 137.4, 140.9, 170.8, 172.9, 176.7, 177.0.

(2R, 3R*, 4R*, 5R*)-4-(4-chlorophenyl)-spiro[2,3']-spiro[3,3'']-5-carbomethoxy-N-methylpyrrolidine-3-N-phenylsuccinimide (**5r**)*. White solid, (33 mg, 63%); mp 247-248 °C; Found: C, 65.51; H, 4.62; N, 7.94. Anal Calcd for $C_{29}H_{24}ClN_3O_5$: C, 65.72; H, 4.56; N, 7.93%. IR (ν_{max}, cm^{-1}): 1733 (C=O), 1781 (C=O), 3337 (N-H);^{1}H NMR: δ 2.17 (s, 3H, CH_3), 2.35 (d, 1H, C*H$_2$*CONPh*,* *J* = 18.9 Hz), 2.63 (d, 1H, C*H$_2$*CONPh, *J* = 18.9 Hz), 3.61 (s, 3H, OCH_3), 4.47 (d, 1H, H-4, *J* = 9.4 Hz), 4.70 (d, 1H, H-5, *J* = 9.4 Hz,), 6.68-7.39 (m, 13H, Ar-H), 7.47 (bs, 1H, NH); ^{13}C NMR: δ 34.1, 37.0, 52.2, 53.1, 59.7, 70.1, 79.0, 110.1, 123.7, 123.7, 124.3, 126.4, 127.8, 128.6, 128.9, 129.4, 130.6, 131.2, 131.5, 134.2, 134.9, 141.2, 171.3, 173.0, 177.3, 177.3.

4 ^{1}H- and ^{13}C-NMR Spectra of compounds 5a-r (Fig. S1 to S36)

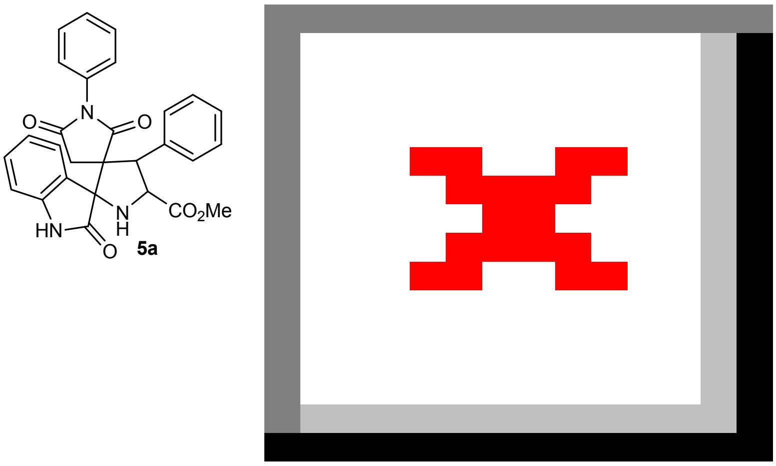


Fig. S1. ^{1}H NMR spectrum of **5a** in $CDCl_3$

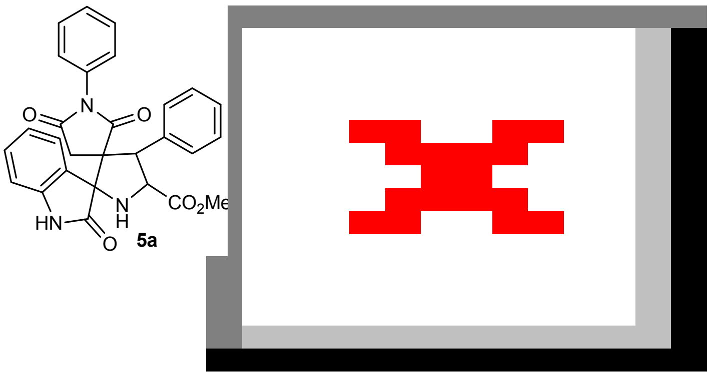


Fig. S2. ^{13}C NMR spectrum of **5a** in $CDCl_3$

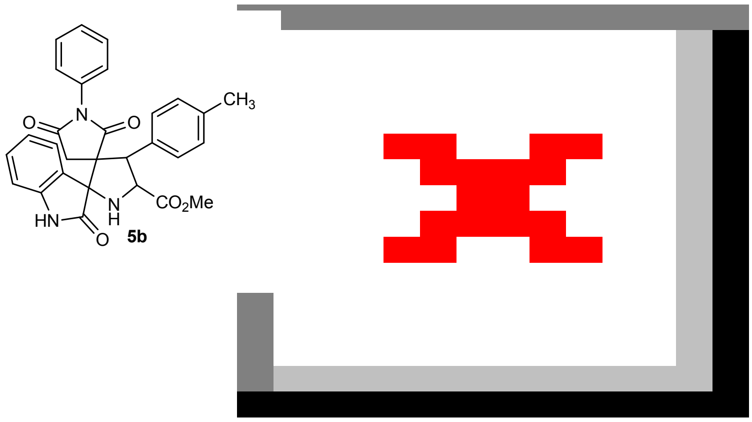


Fig. S3. ^{1}H NMR spectrum of **5b** in $CDCl_3$

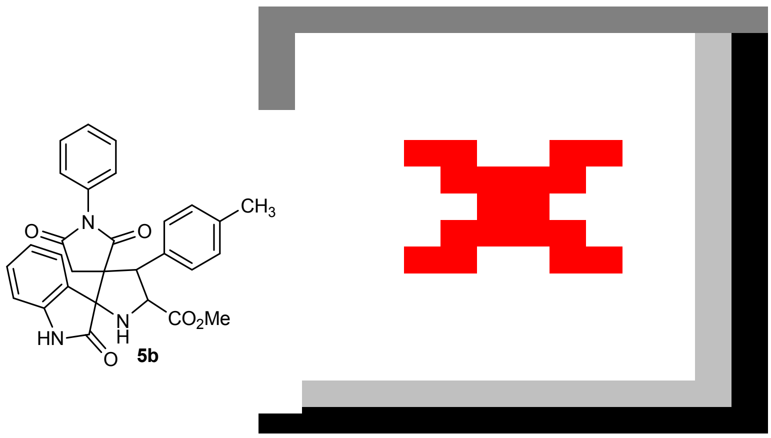


Fig. S4. ^{13}C NMR spectrum of **5b** in $CDCl_3$

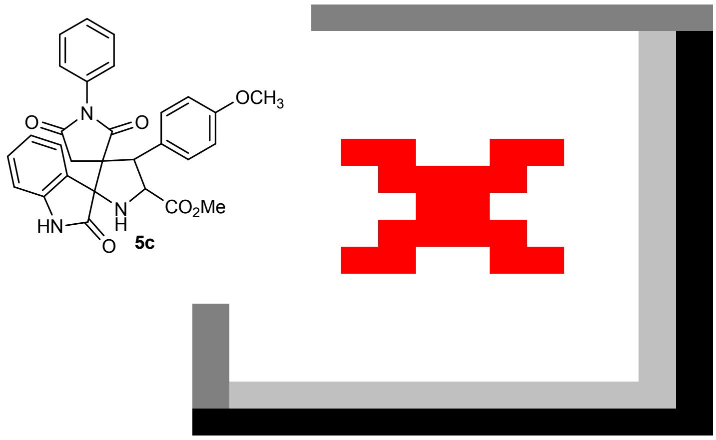


Fig. S5. ^{1}H NMR spectrum of **5c** in $CDCl_3$

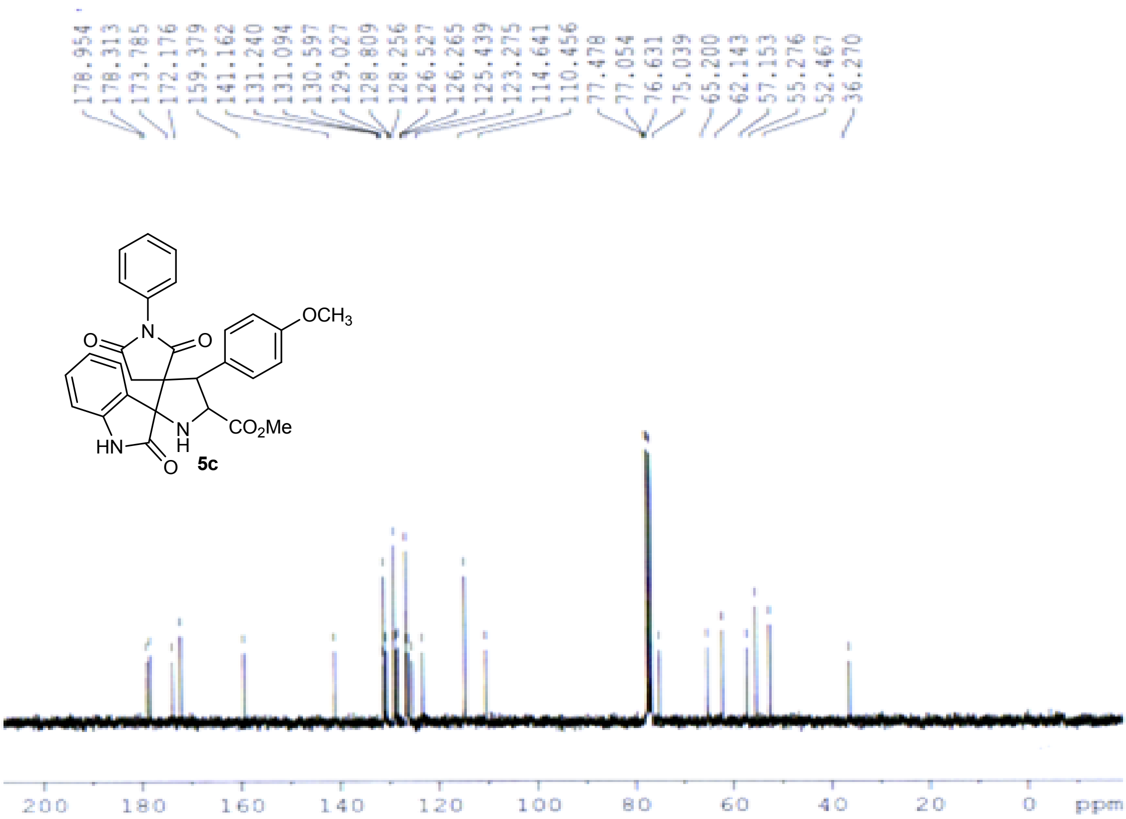


Fig. S6. ^{13}C NMR spectrum of **5c** in $CDCl_3$

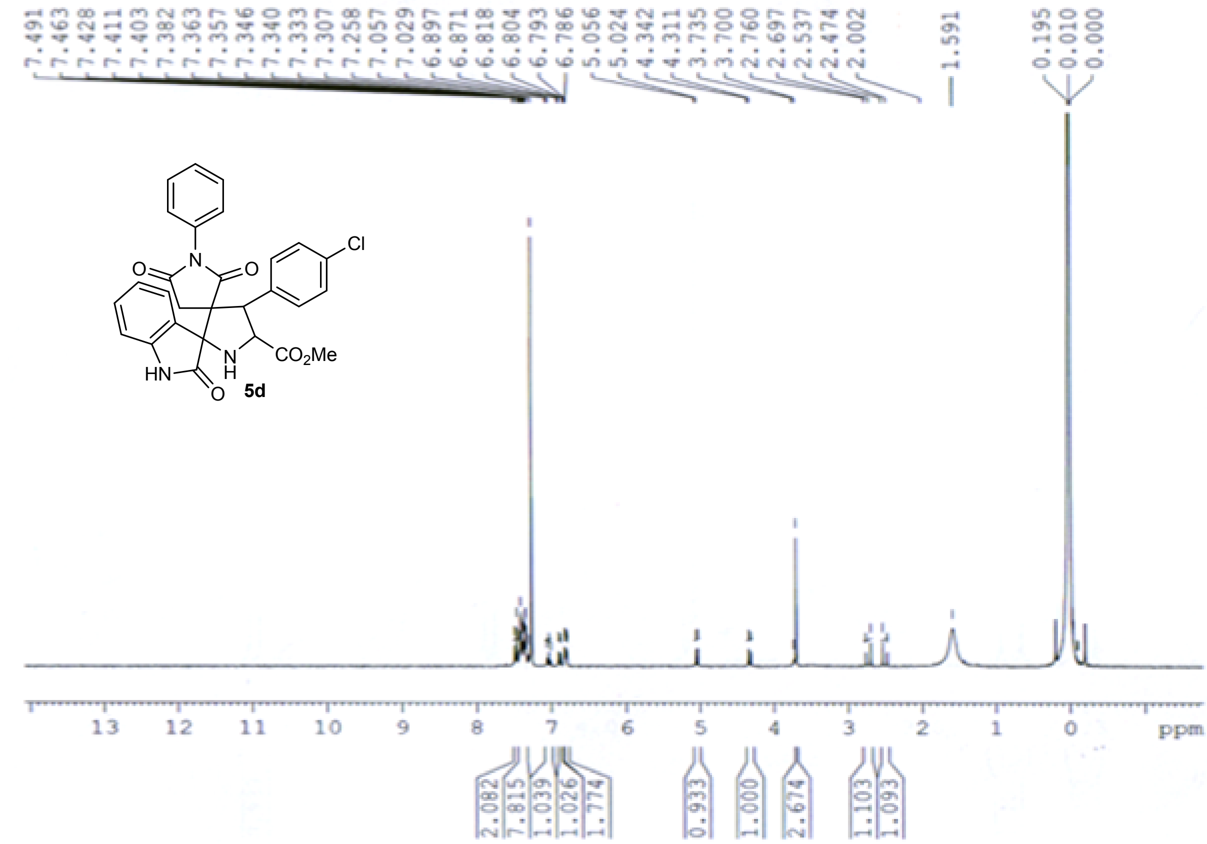


Fig. S7. ^{1}H NMR spectrum of **5d** in $CDCl_3$

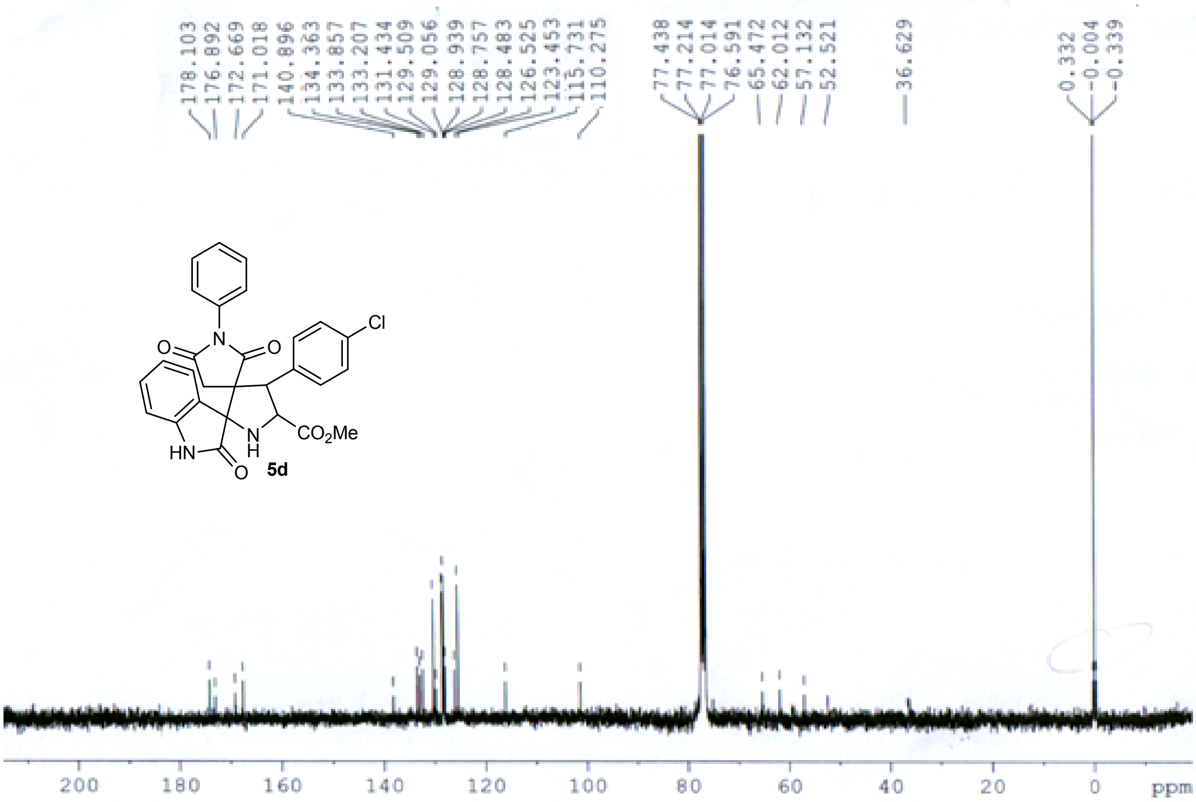


Fig. S8. ^{13}C NMR spectrum of **5d** in $CDCl_3$

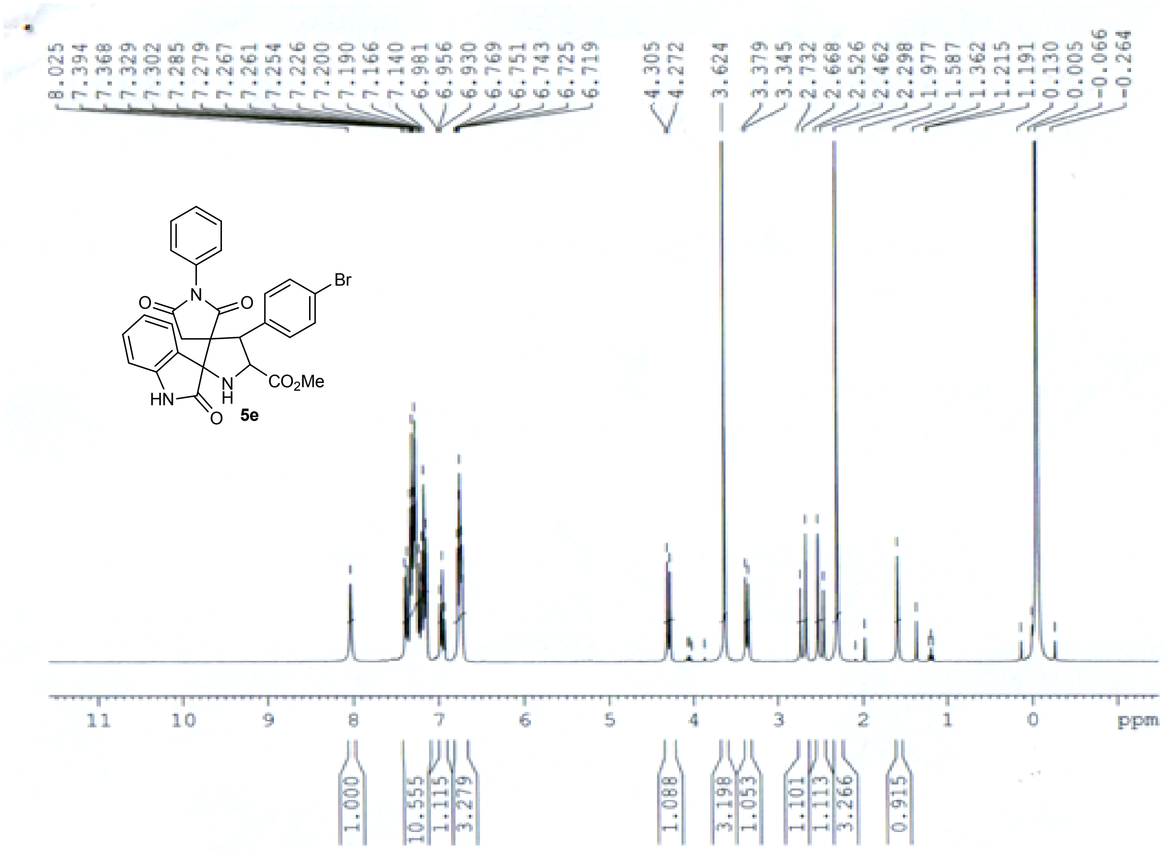


Fig. S9. ^{1}H NMR spectrum of **5e** in $CDCl_3$

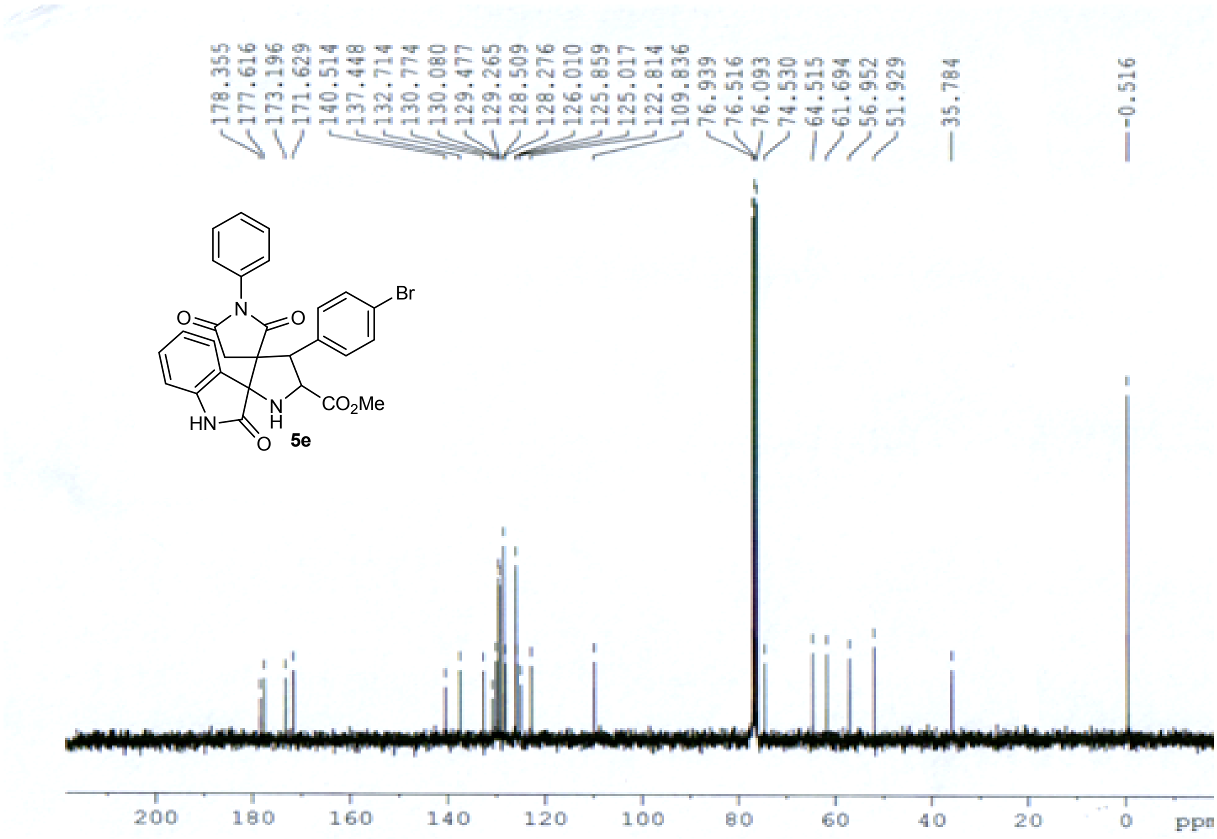


Fig. S10. ^{13}C NMR spectrum of **5e** in $CDCl_3$

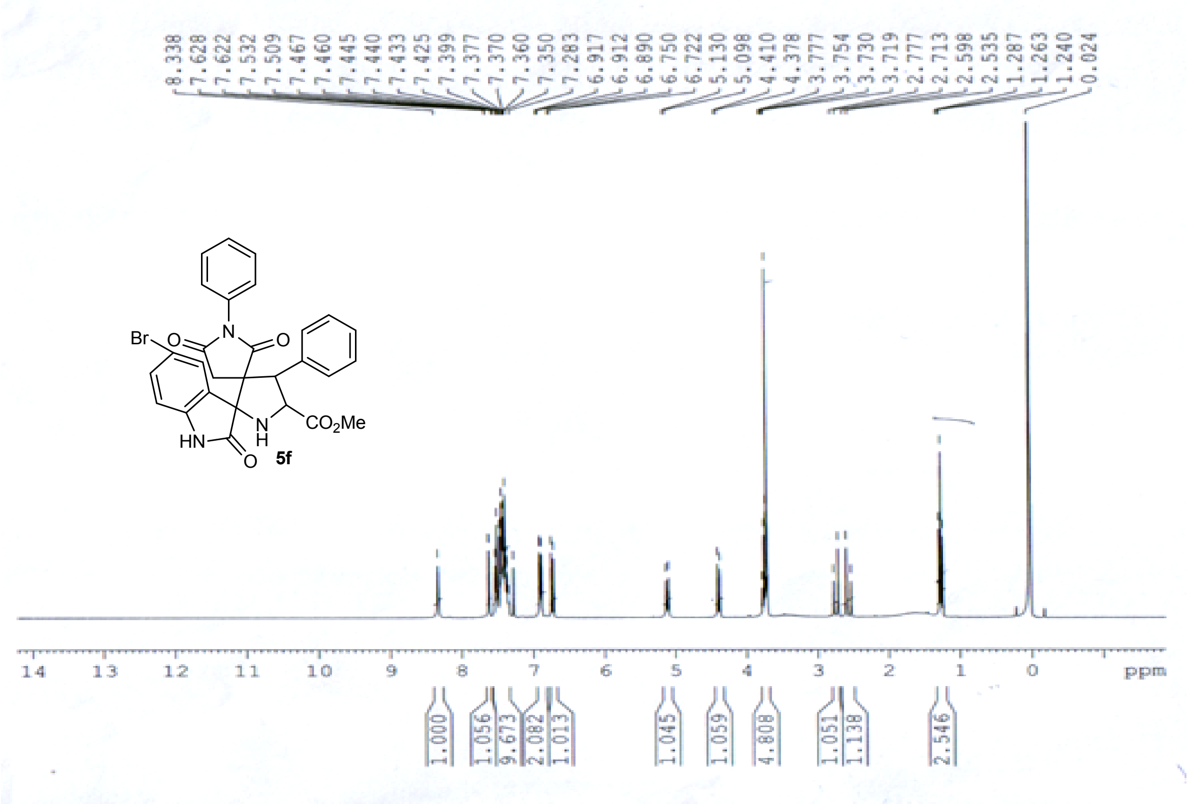


Fig. S11. ^{1}H NMR spectrum of **5f** in $CDCl_3$

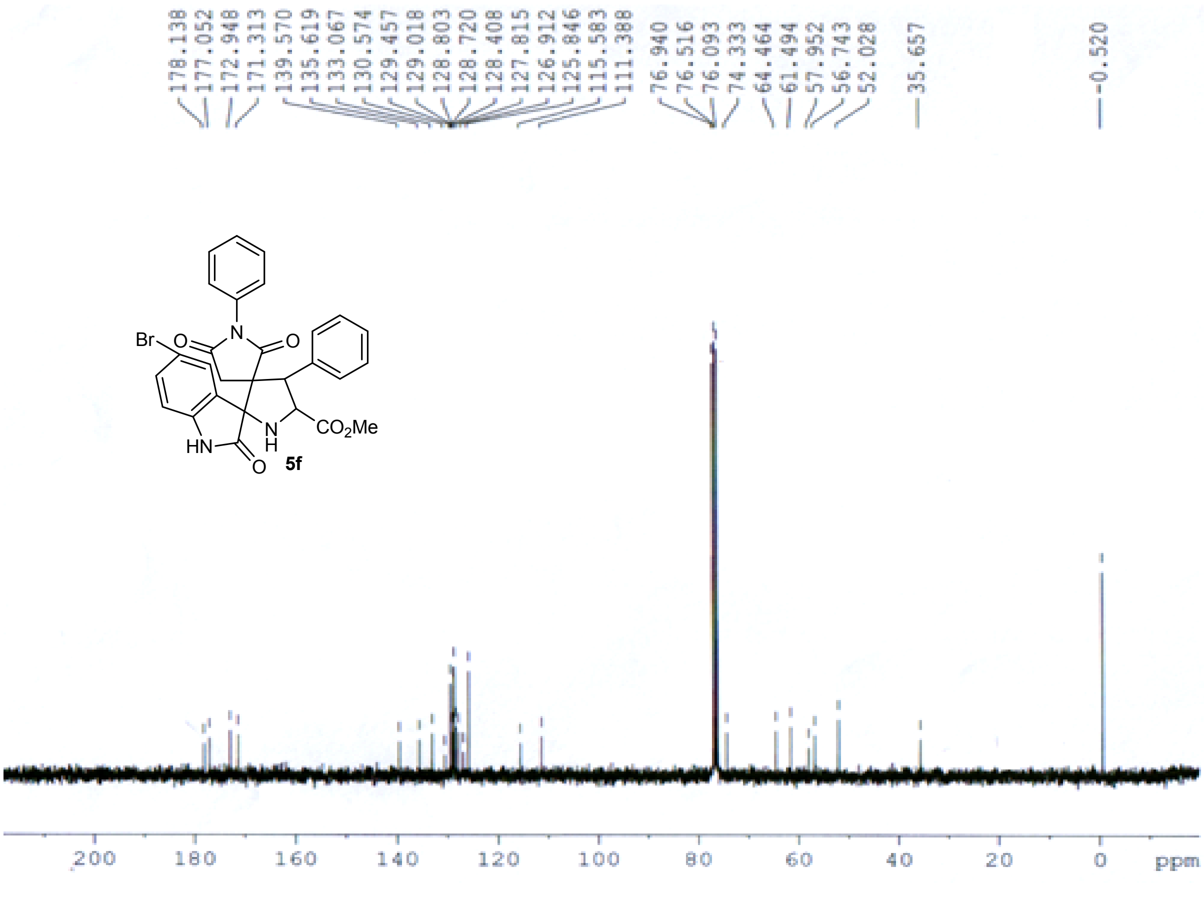


Fig. S12. ^{13}C NMR spectrum of **5f** in $CDCl_3$

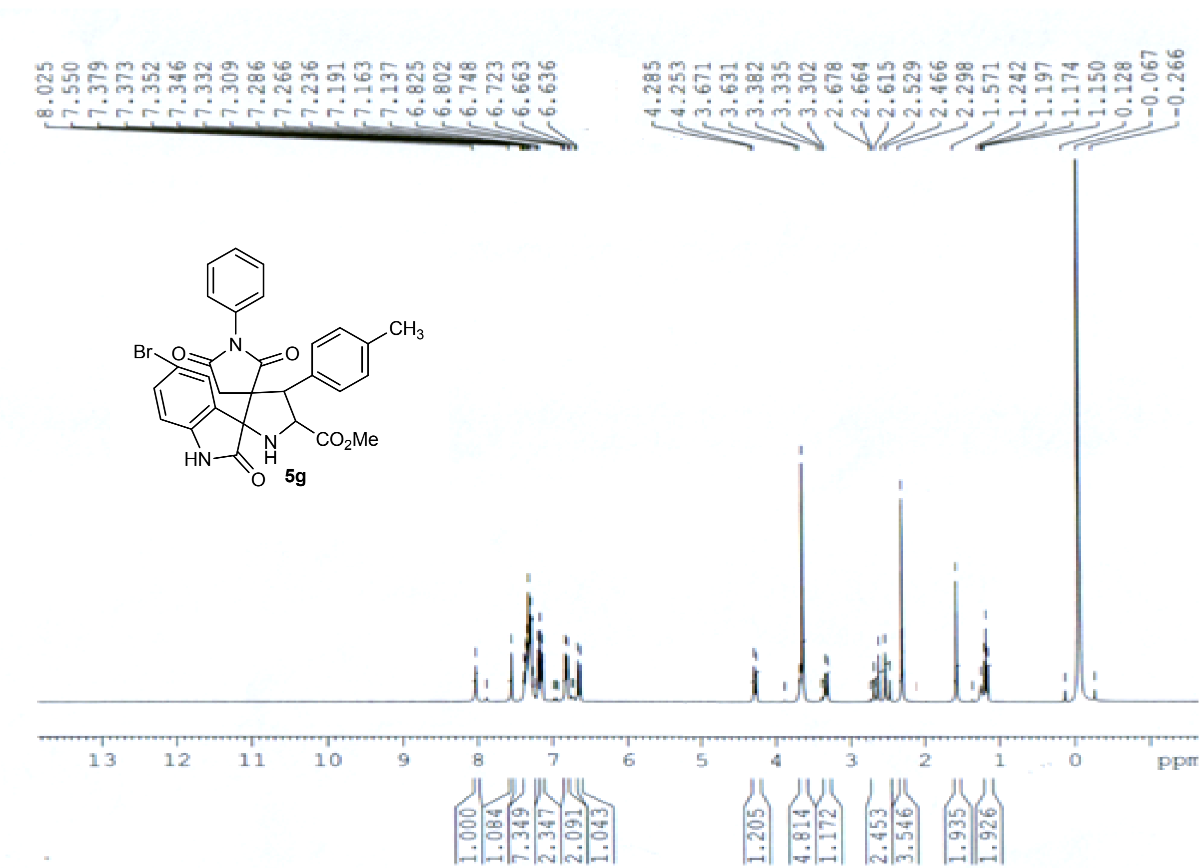


Fig. S13. ^{1}H NMR spectrum of **5g** in $CDCl_3$

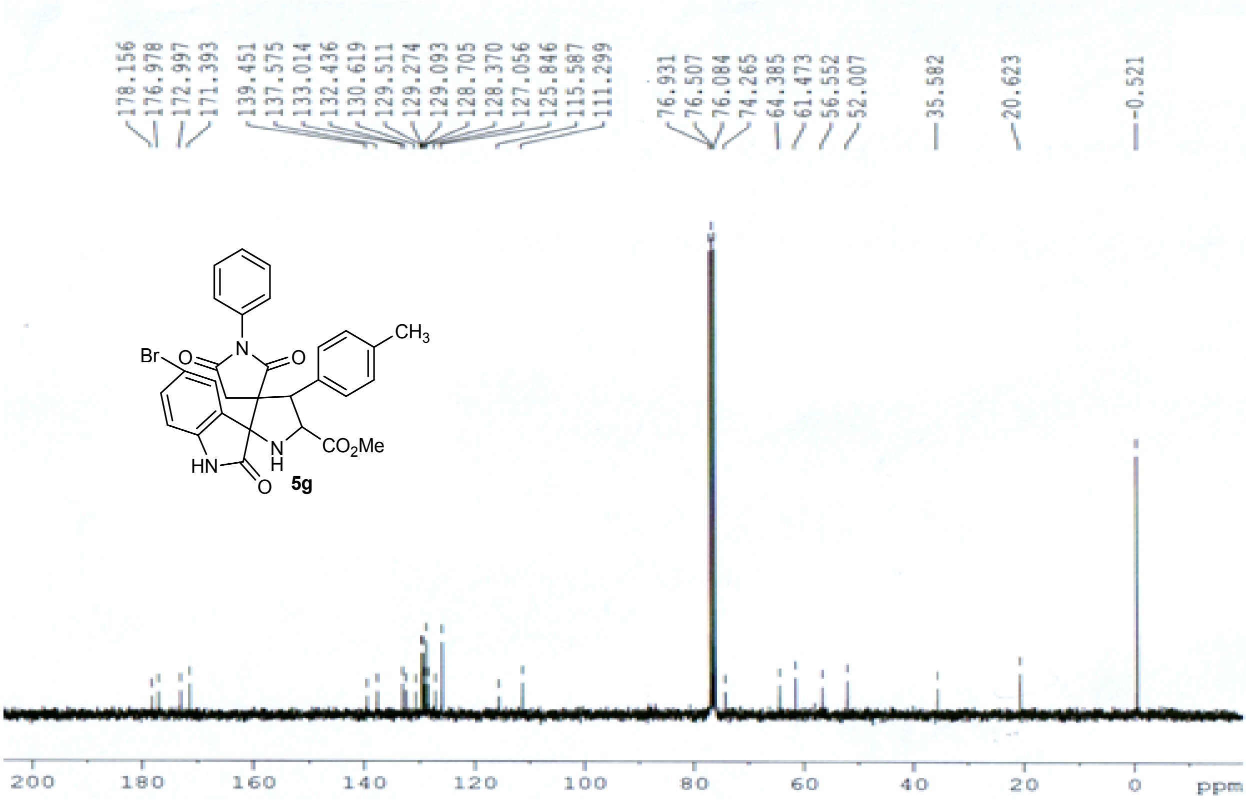


Fig. S14. ^{13}C NMR spectrum of **5g** in $CDCl_3$

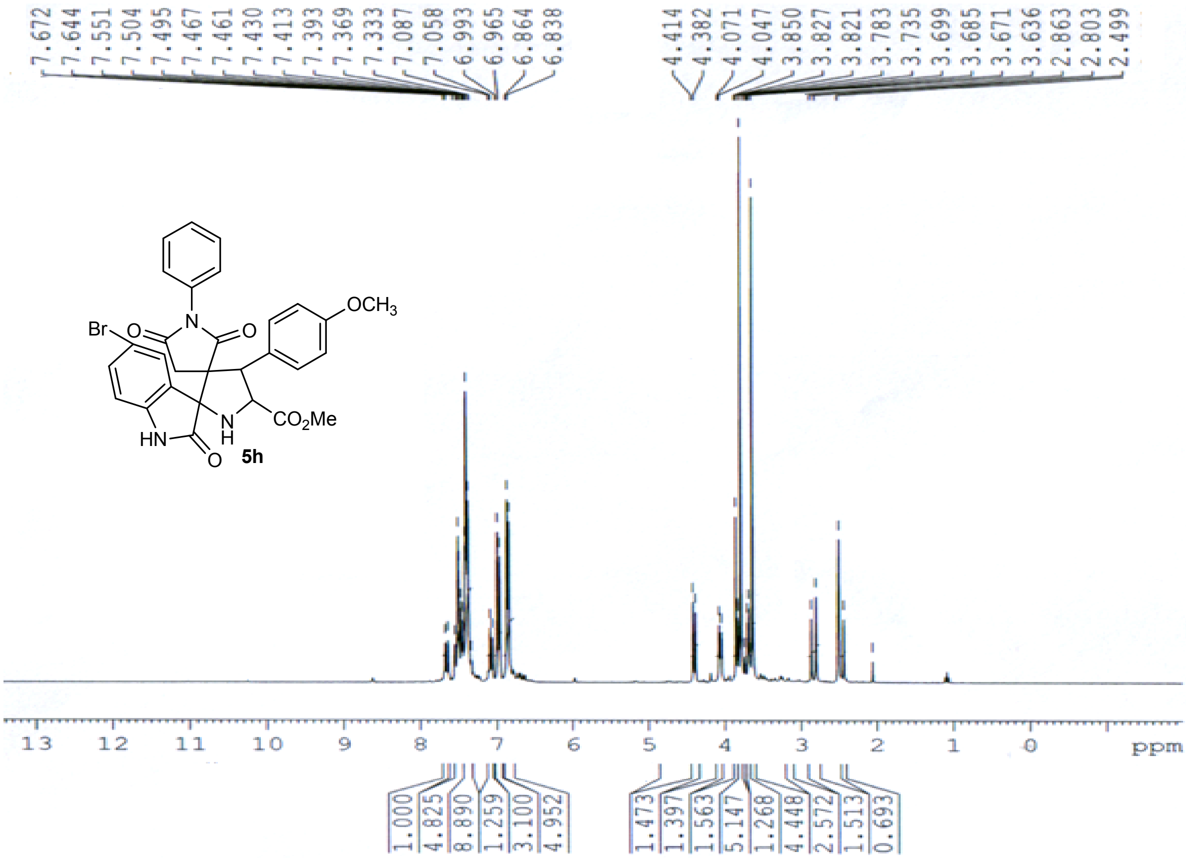


Fig. S15. ^{1}H NMR spectrum of **5h** in $CDCl_3$

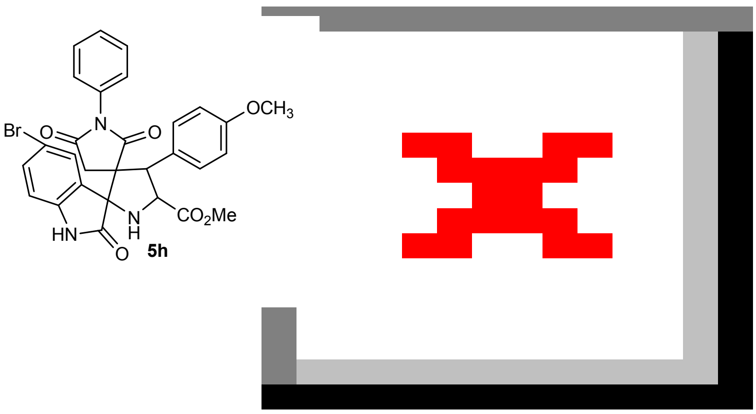


Fig. S16. ^{13}C NMR spectrum of **5h** in $CDCl_3$

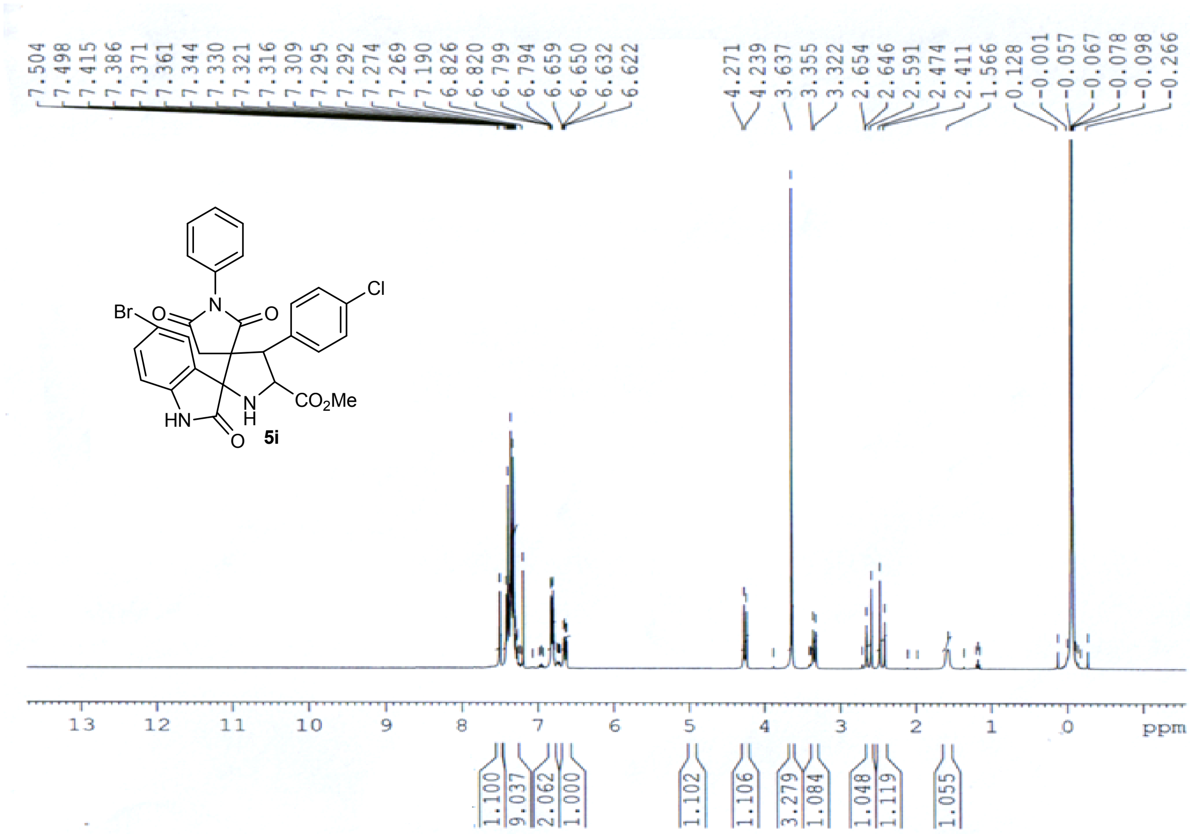


Fig. S17. ^{1}H NMR spectrum of **5i** in $CDCl_3$

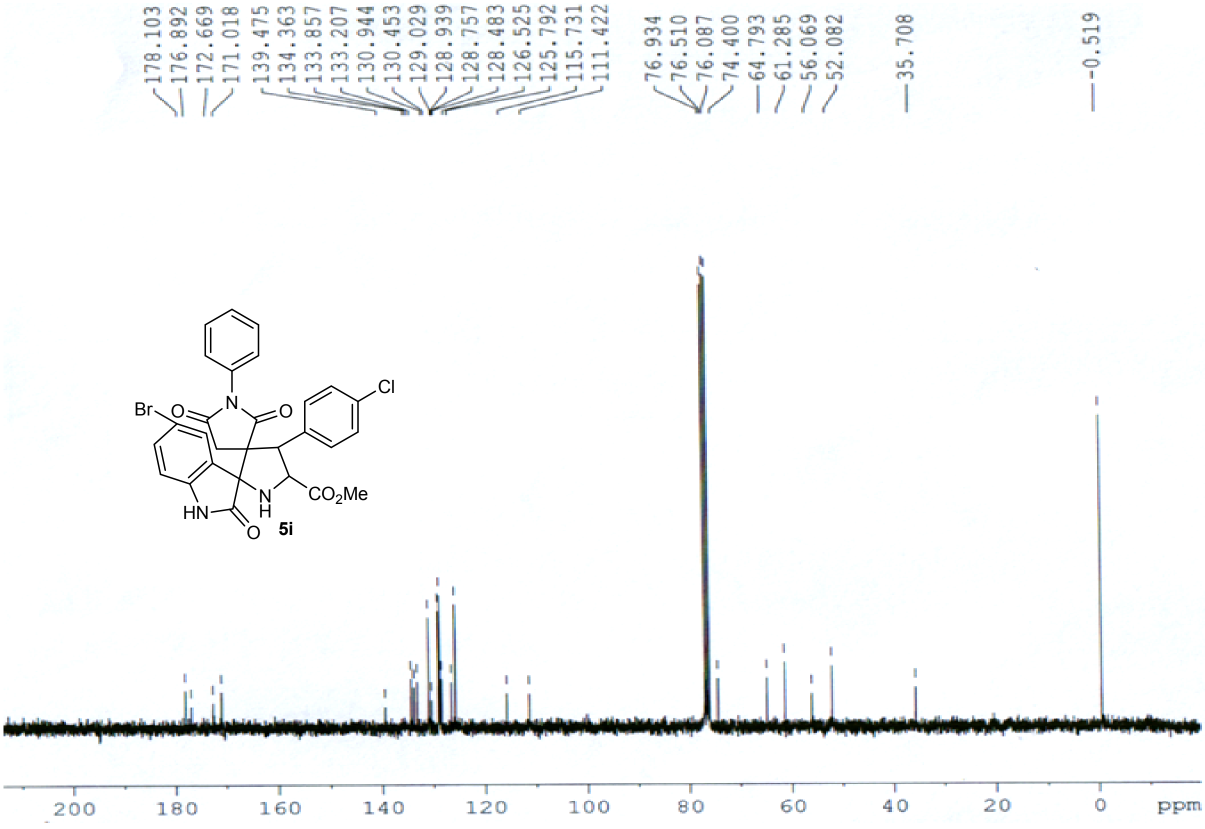


Fig. S18. ^{13}C NMR spectrum of **5i** in $CDCl_3$

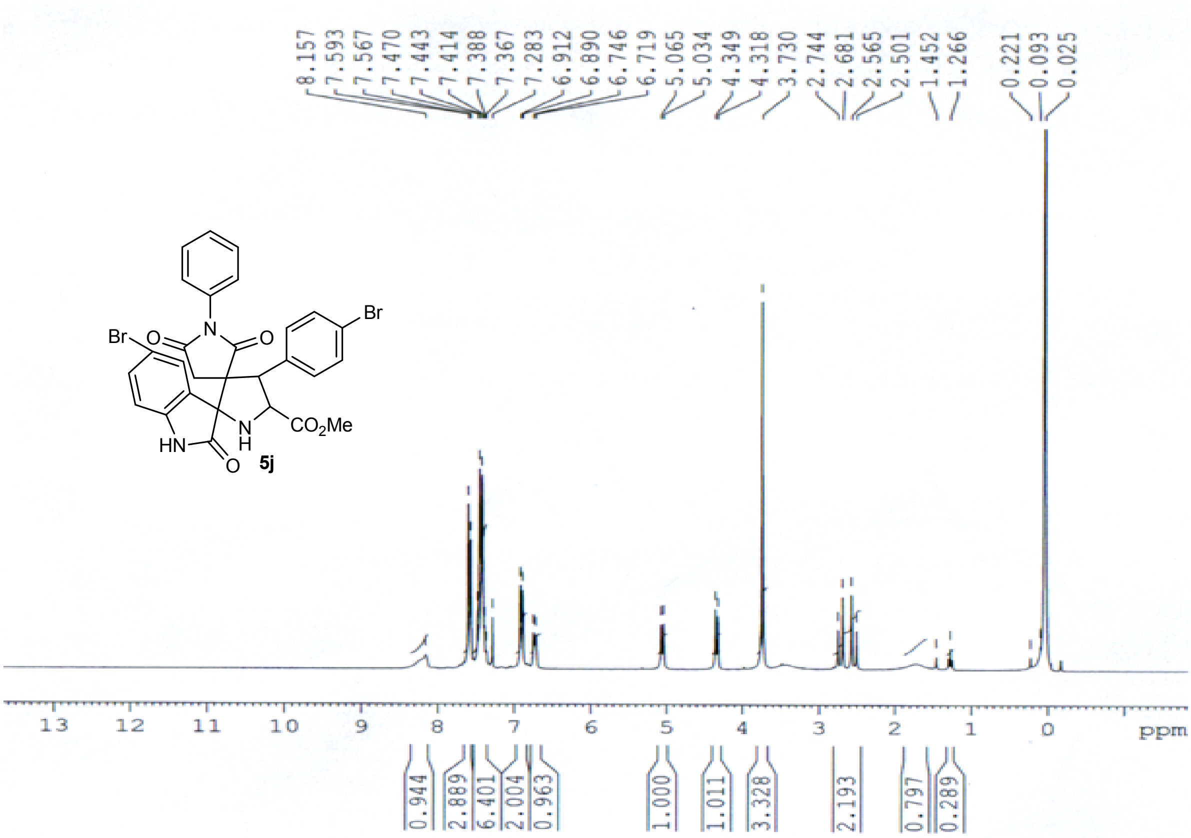


Fig. S19. ^{1}H NMR spectrum of **5j** in $CDCl_3$

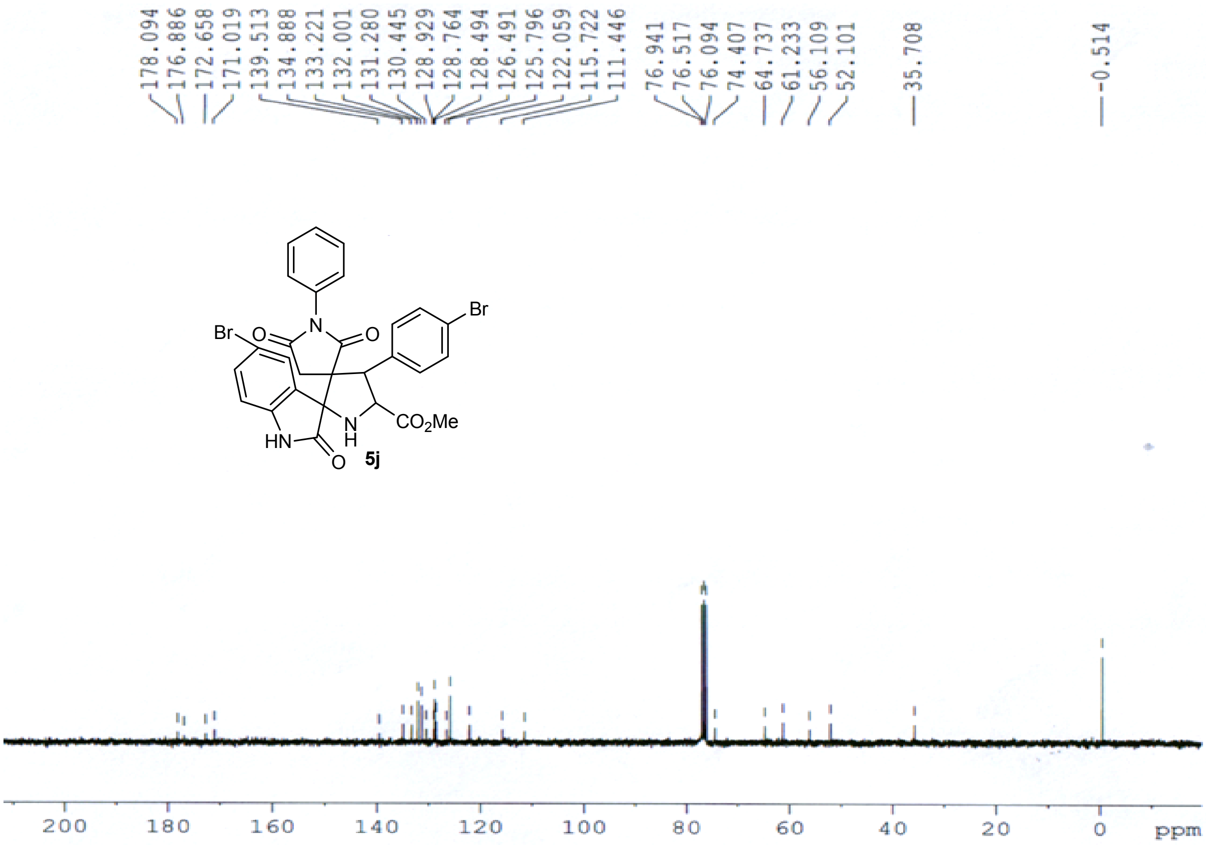


Fig. S20. ^{13}C NMR spectrum of **5j** in $CDCl_3$

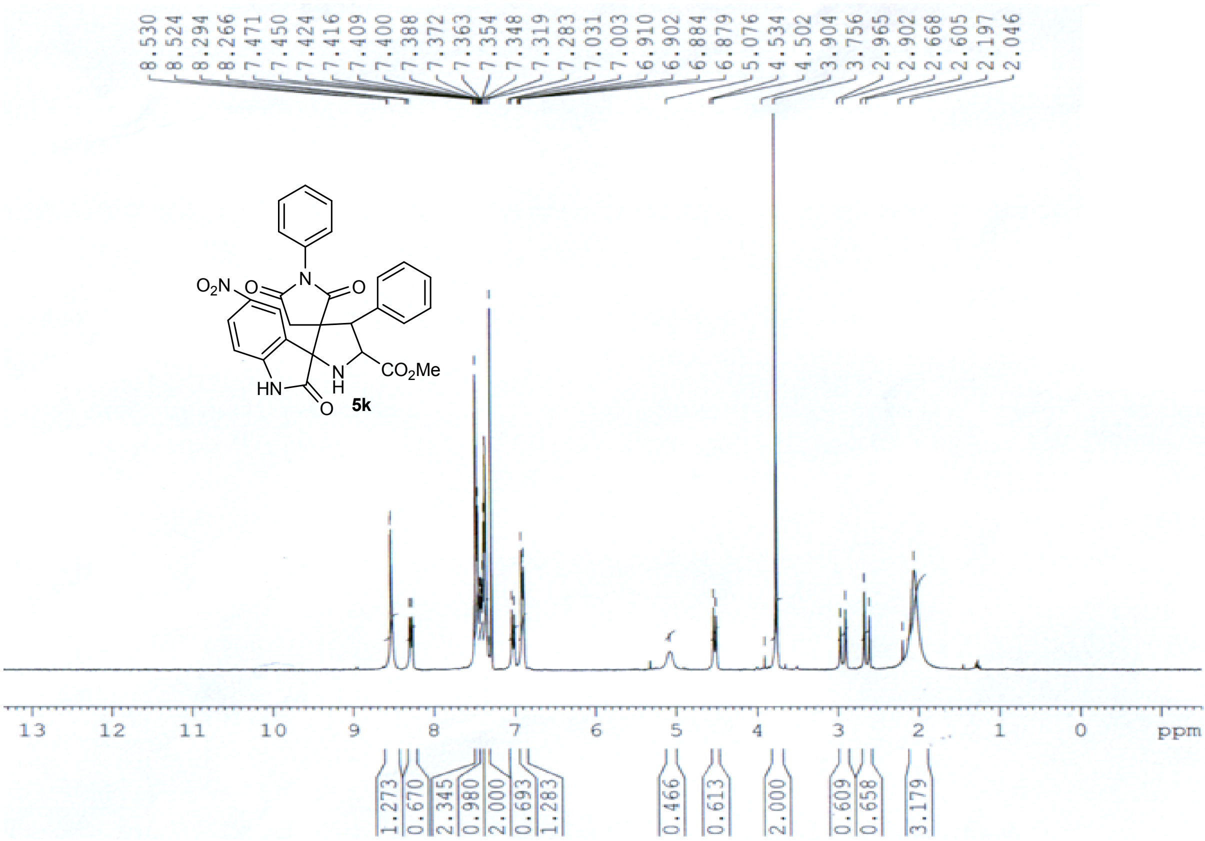


Fig. S21. ^{1}H NMR spectrum of **5k** in $CDCl_3$

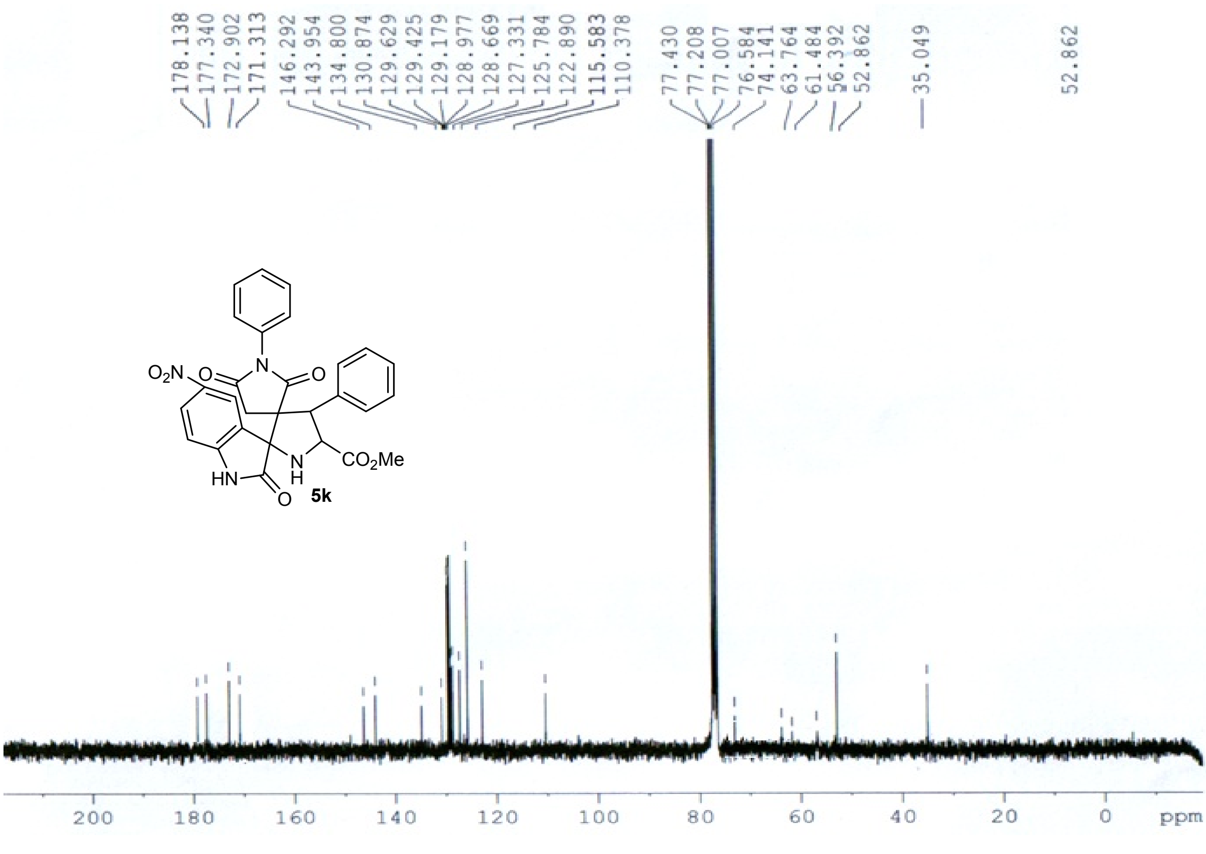


Fig. S22. ^{13}C NMR spectrum of **5k** in $CDCl_3$

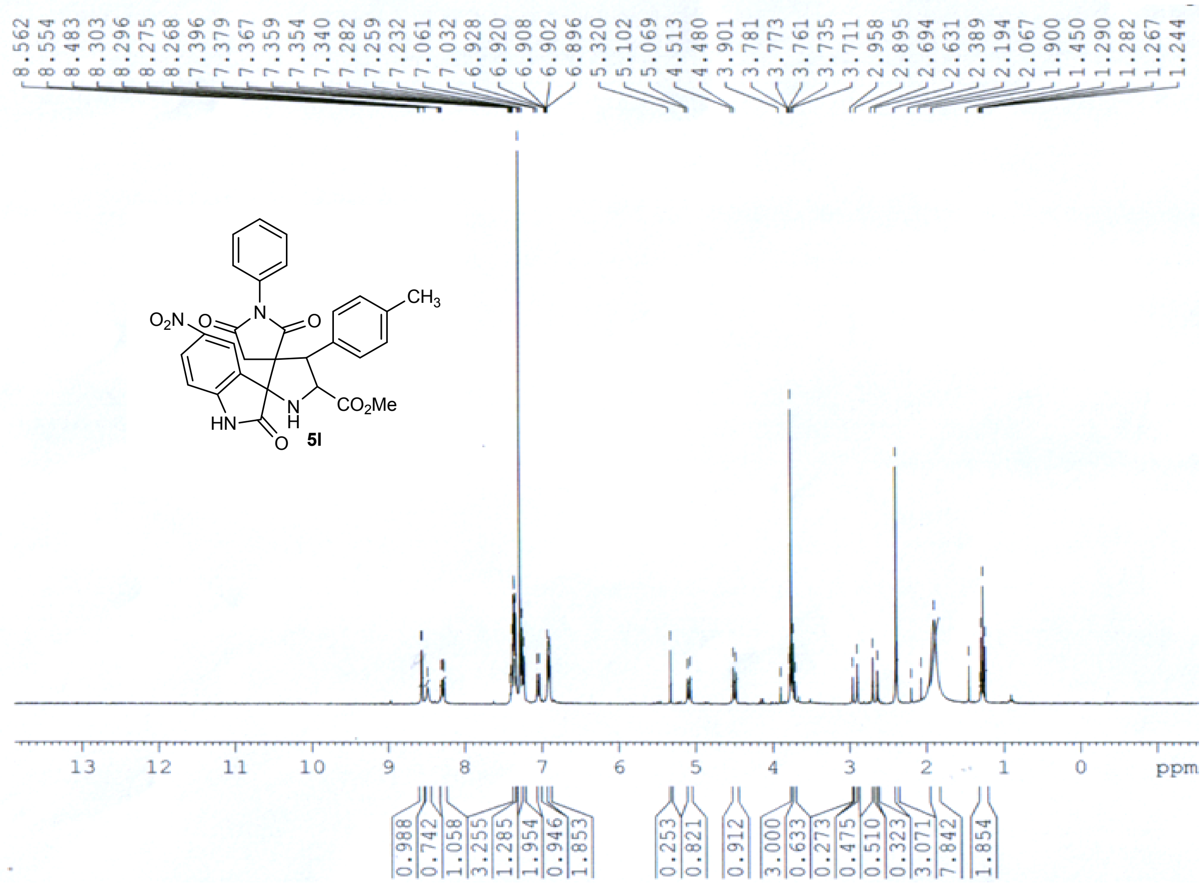


Fig. S23. ^{1}H NMR spectrum of **5l** in $CDCl_3$

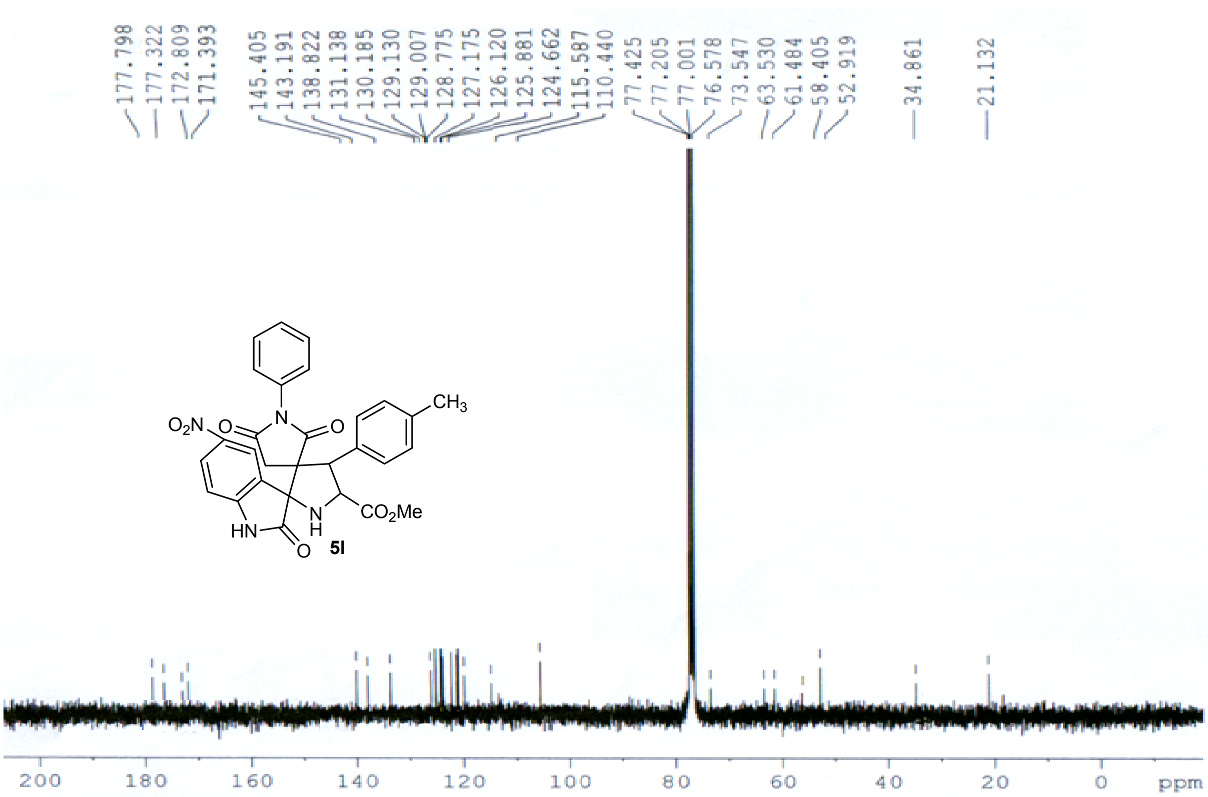


Fig. S24. ^{13}C NMR spectrum of **5l** in $CDCl_3$

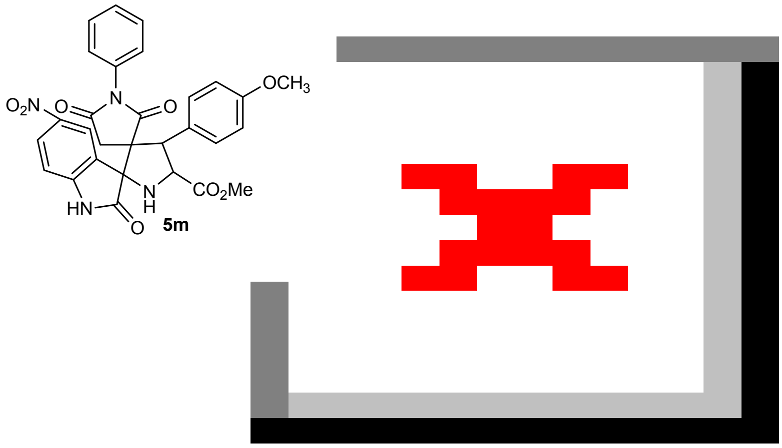


Fig. S25. ^{1}H NMR spectrum of **5m** in $CDCl_3$

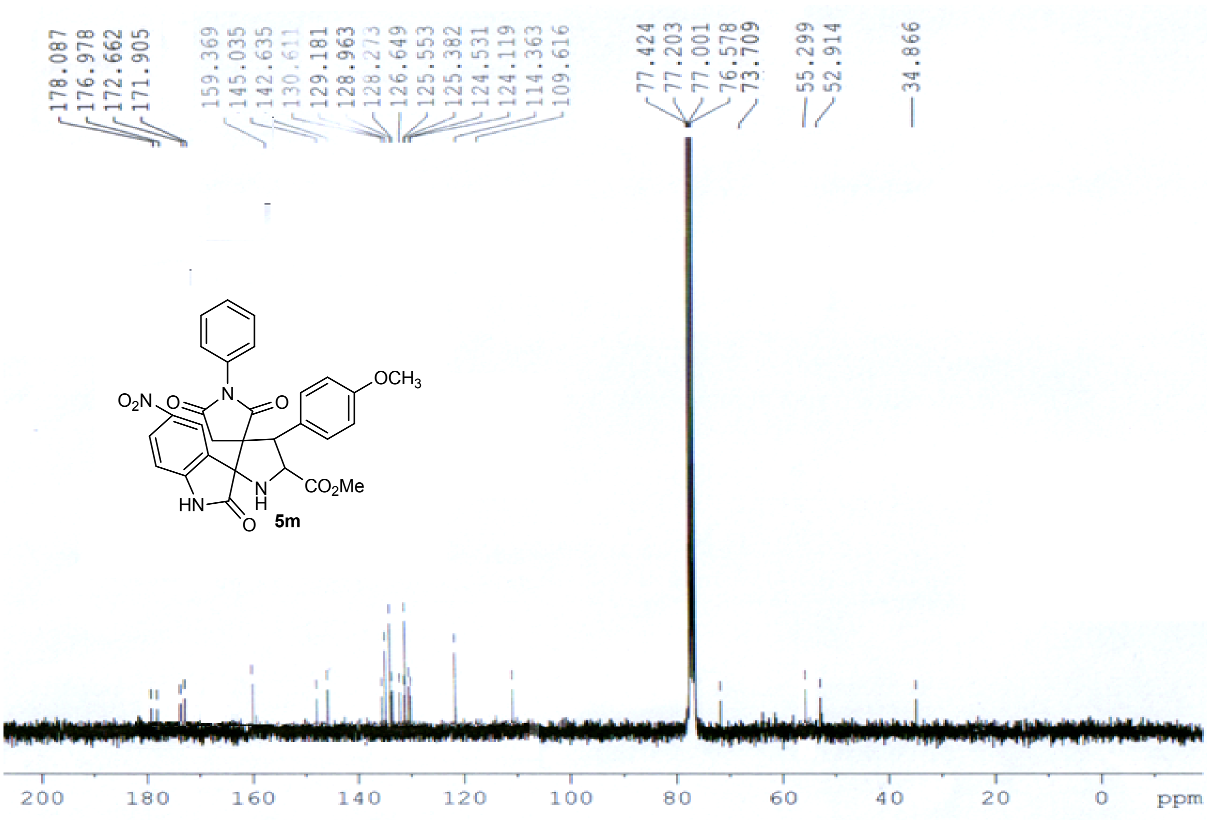


Fig. S26. ^{13}C NMR spectrum of **5m** in $CDCl_3$

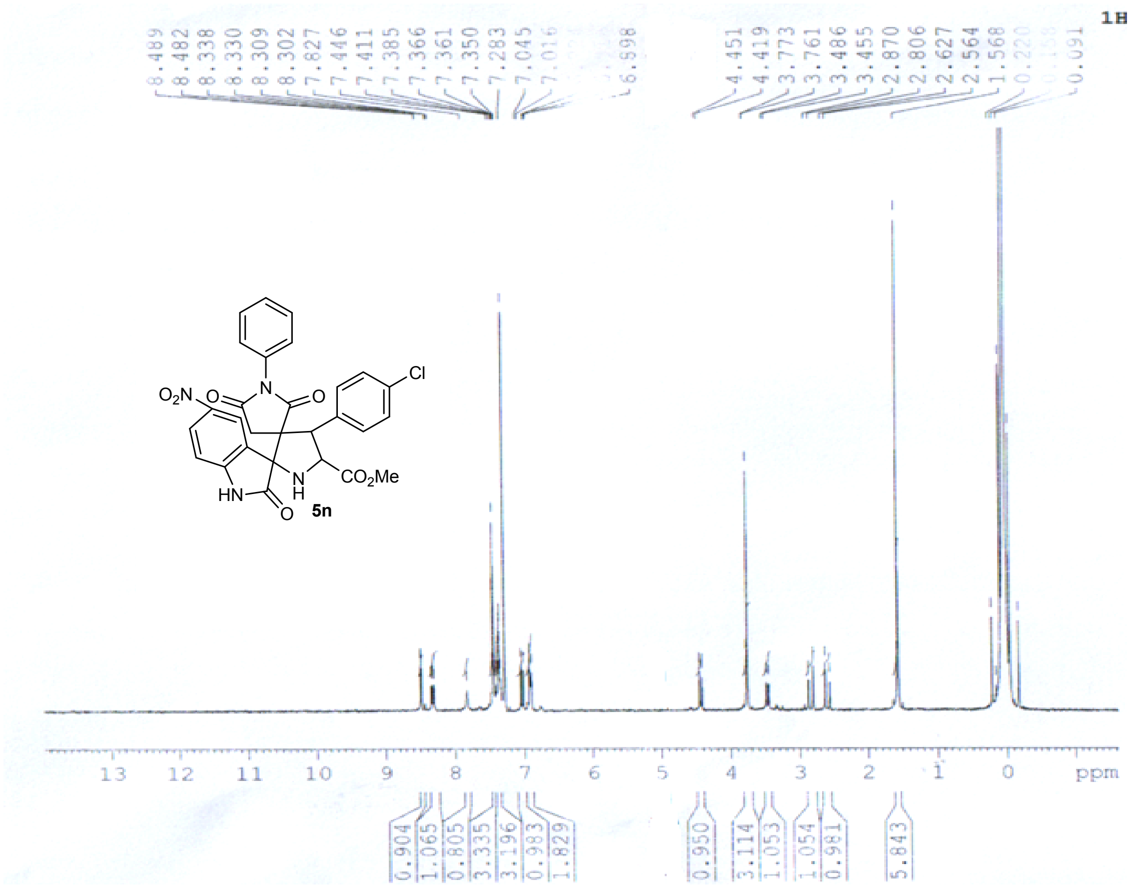


Fig. S27. ^{1}H NMR spectrum of **5n** in $CDCl_3$

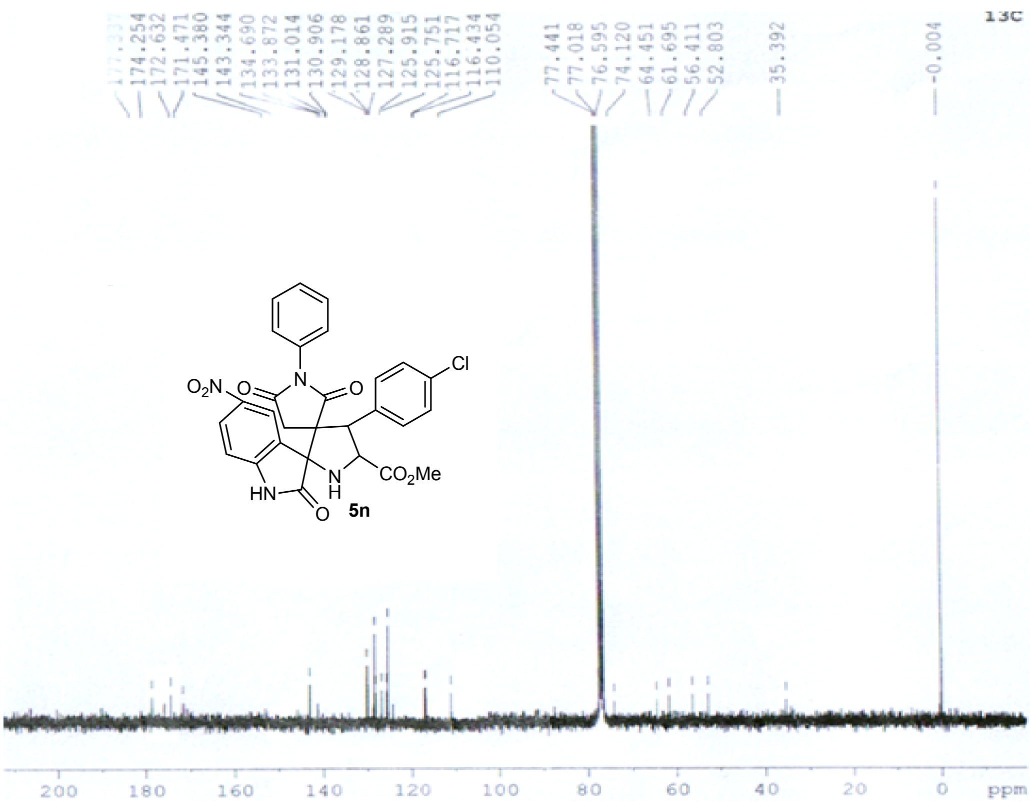


Fig. S28. ^{13}C NMR spectrum of **5n** in $CDCl_3$

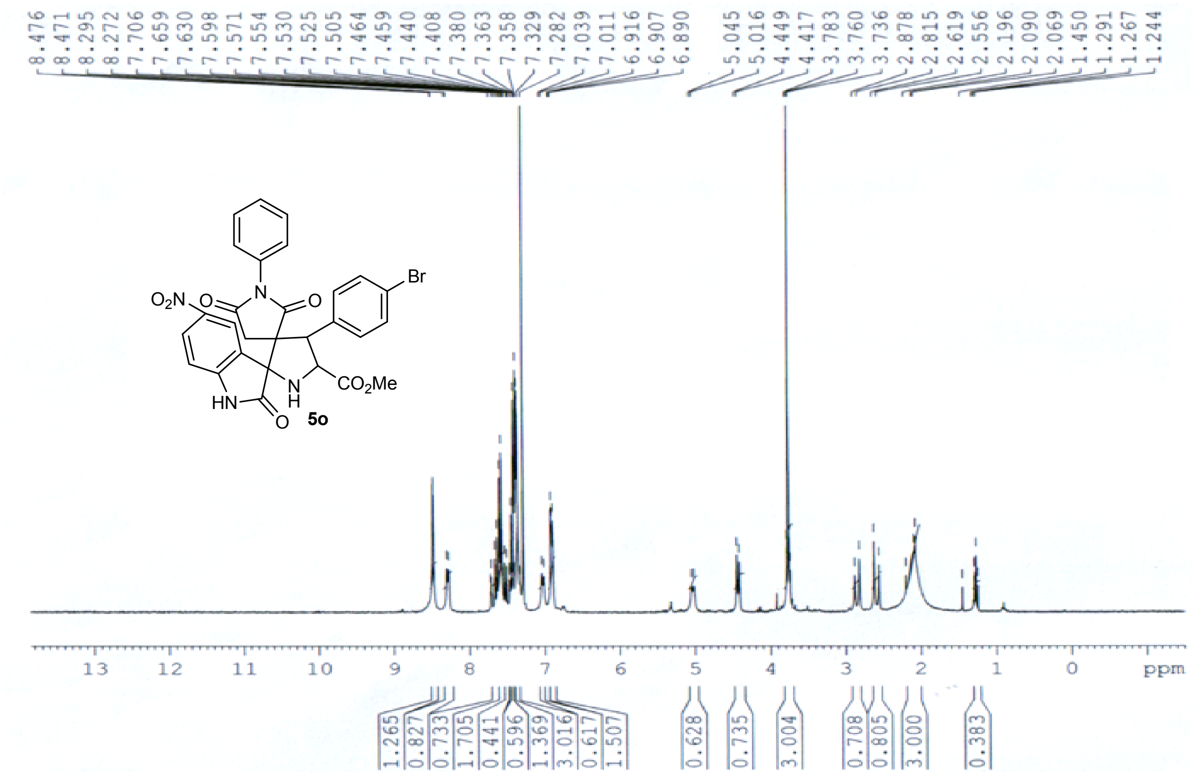


Fig. S29. ^{1}H NMR spectrum of **5o** in $CDCl_3$

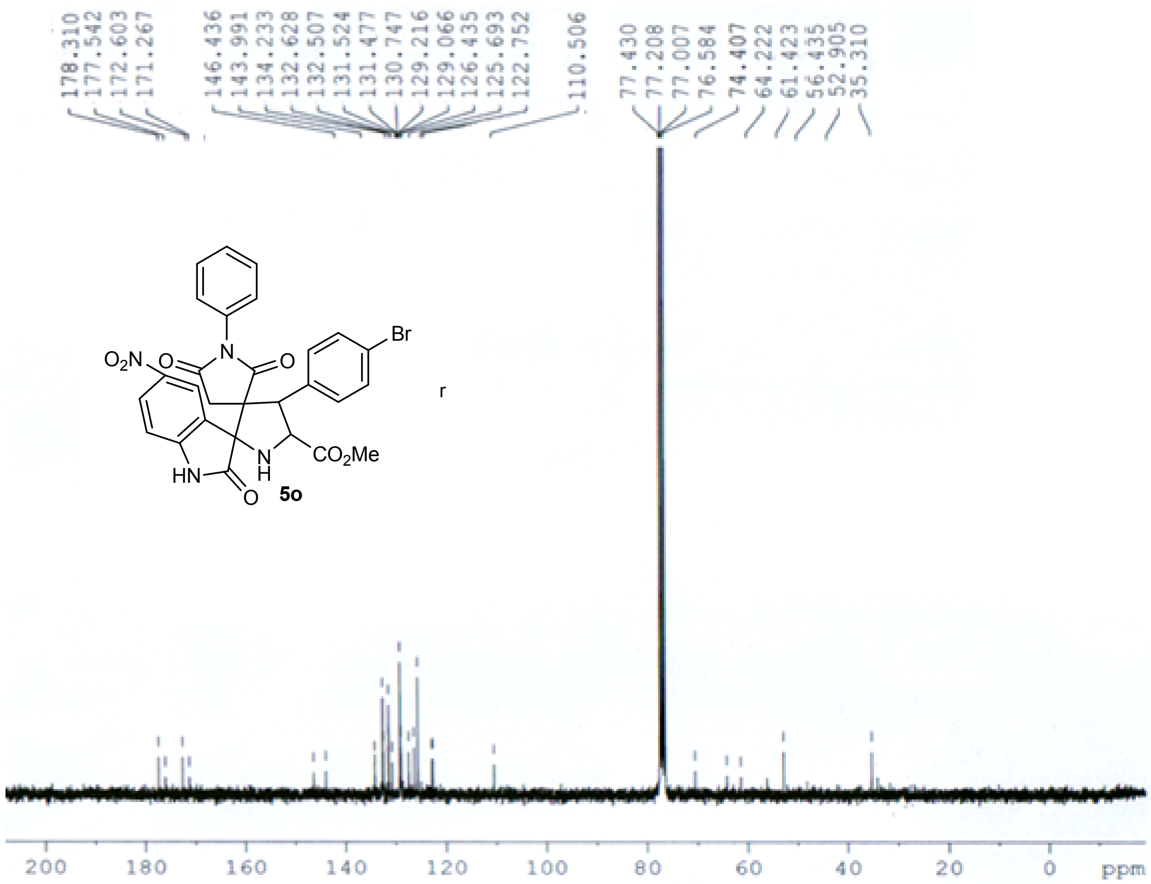


Fig. S30. ^{13}C NMR spectrum of **5o** in $CDCl_3$

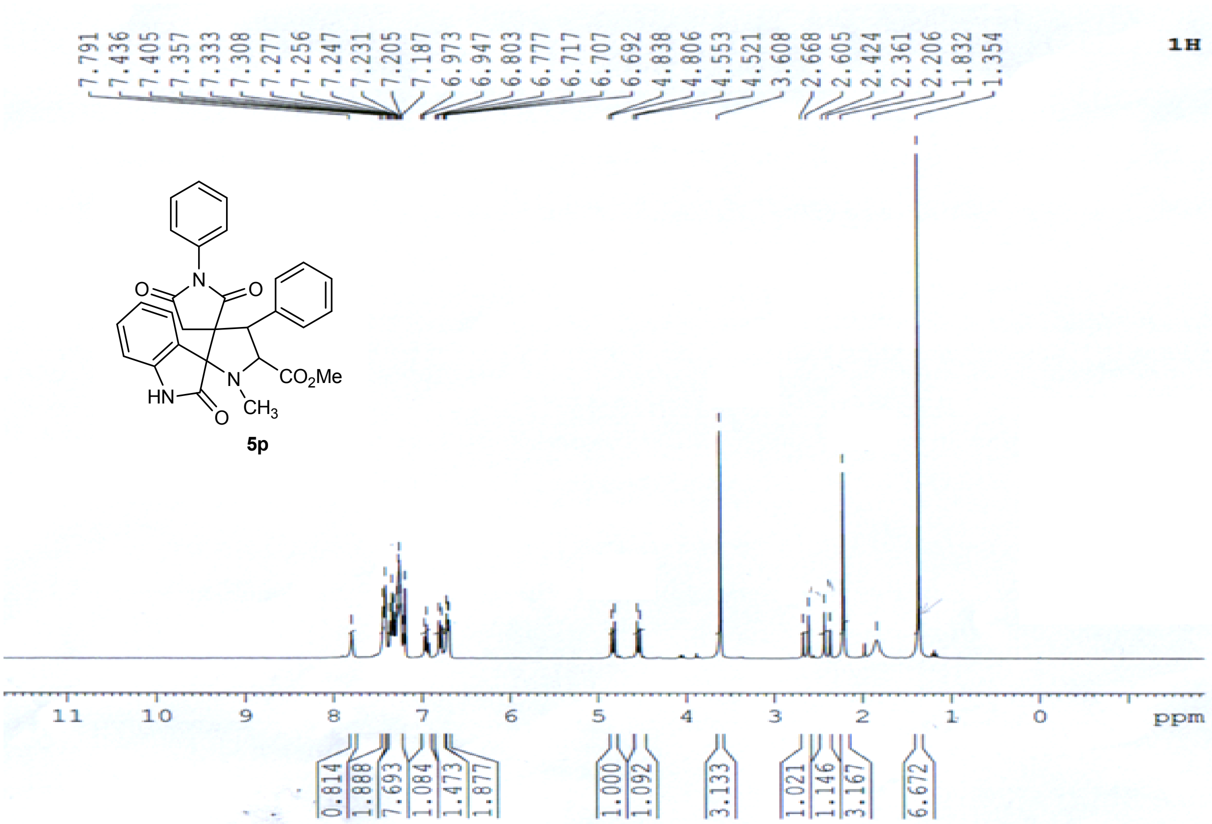


Fig. S31. ^{1}H NMR spectrum of **5p** in $CDCl_3$

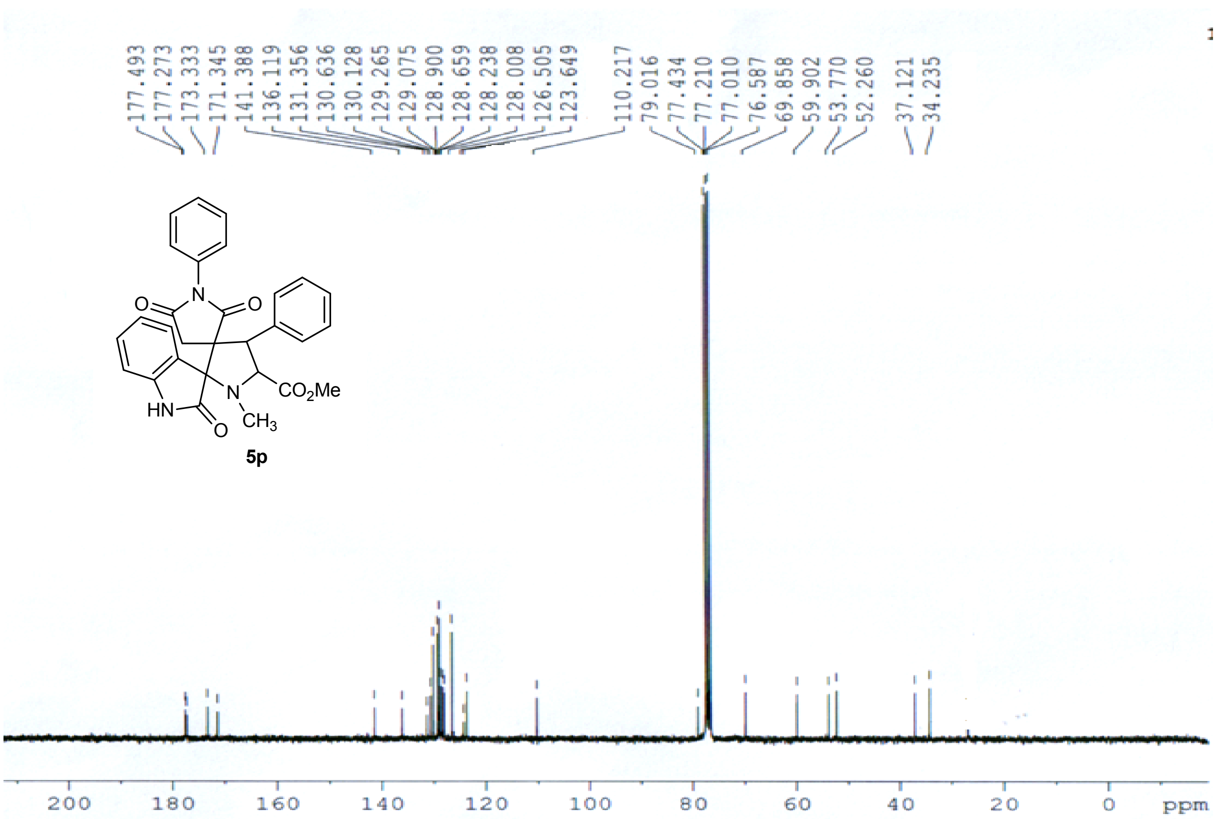


Fig. S32. ^{13}C NMR spectrum of **5p** in $CDCl_3$

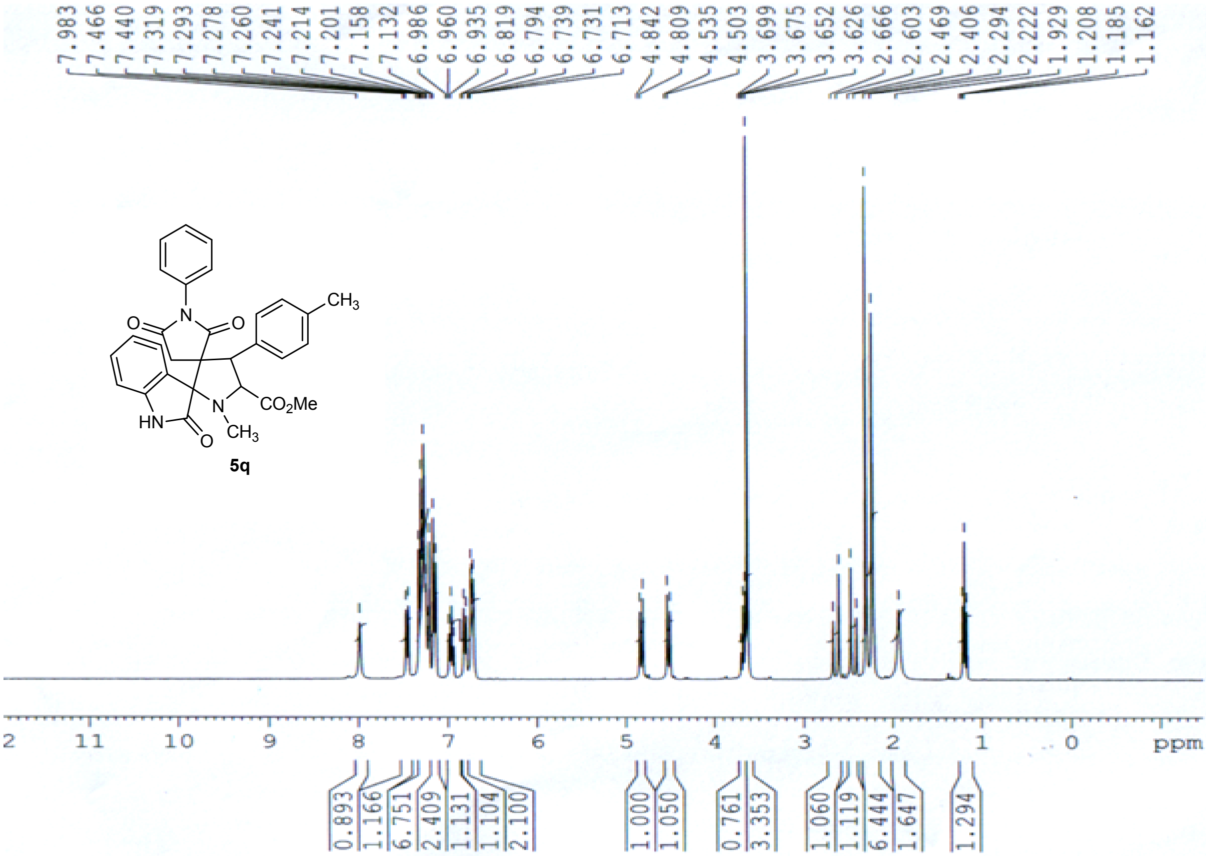


Fig. S33. ^{1}H NMR spectrum of **5q** in $CDCl_3$

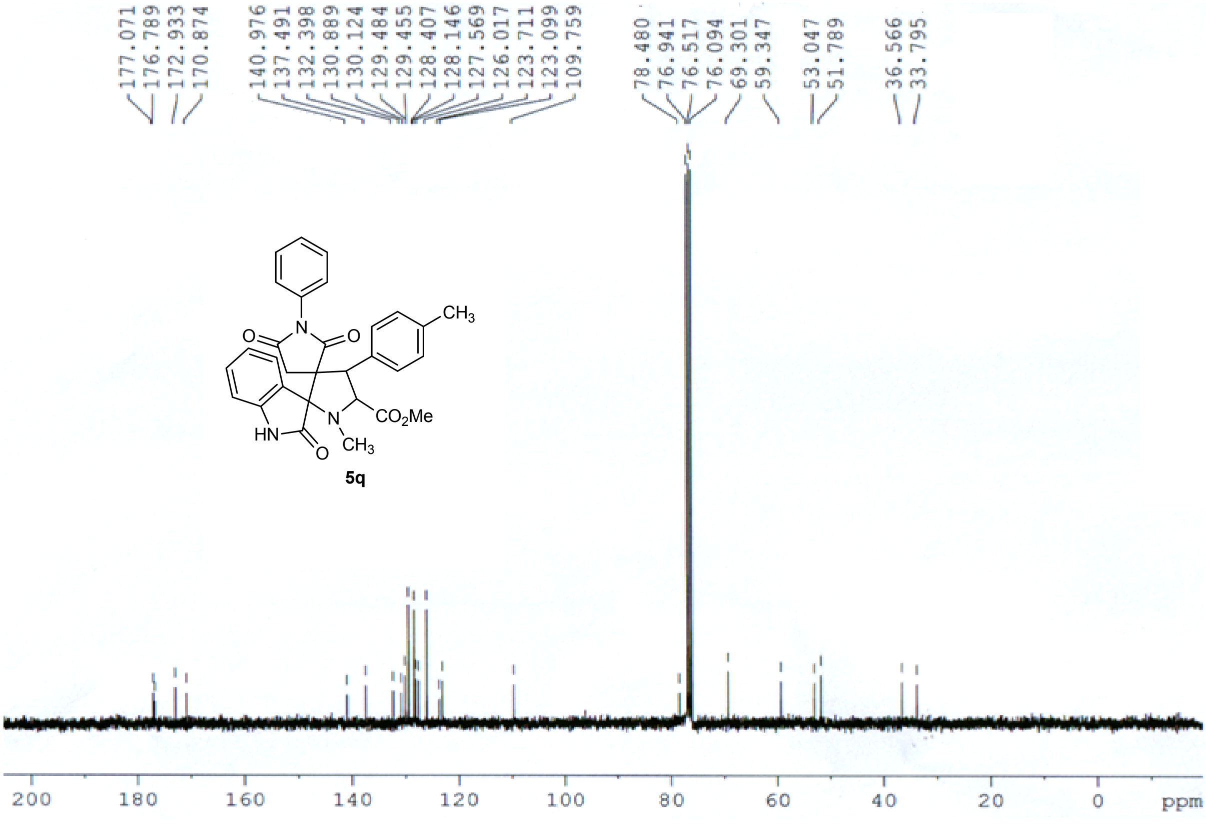


Fig. S34. ^{13}C NMR spectrum of **5q** in $CDCl_3$

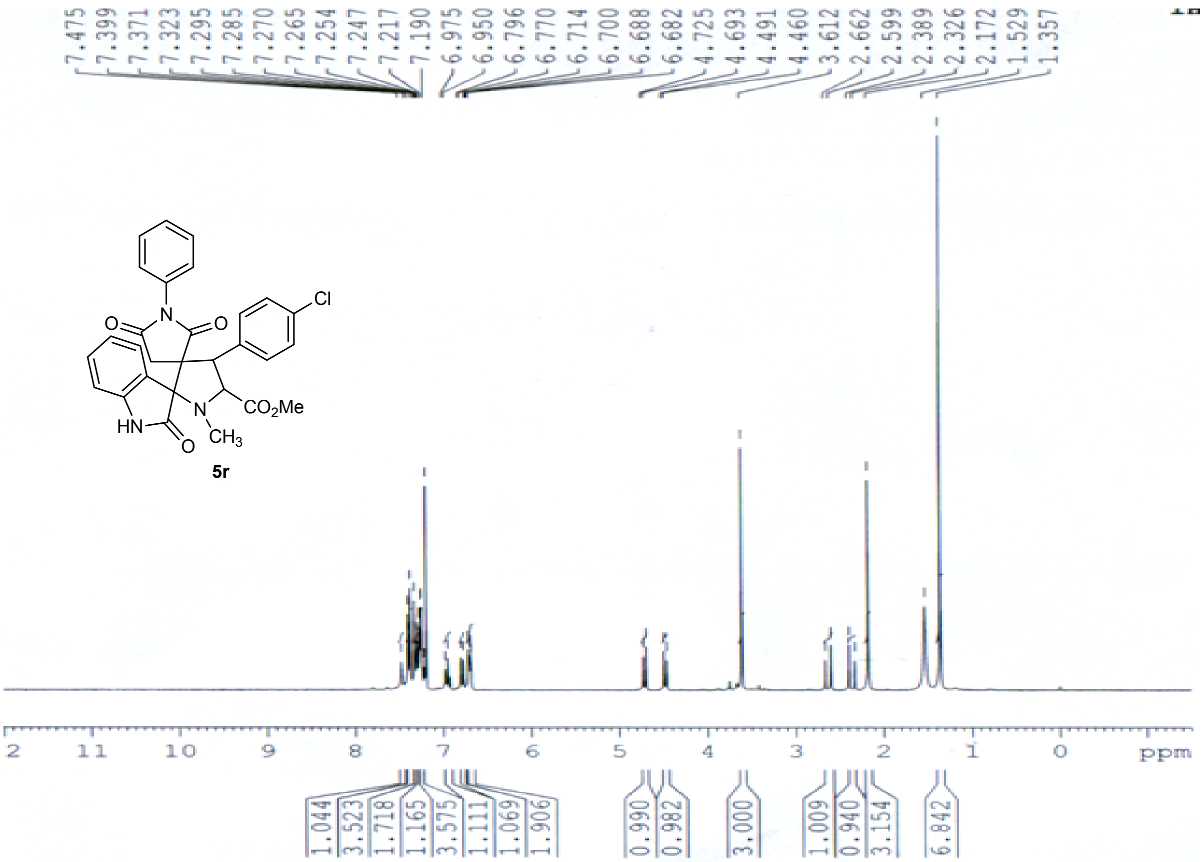


Fig. S35. ^{1}H NMR spectrum of **5r** in $CDCl_3$

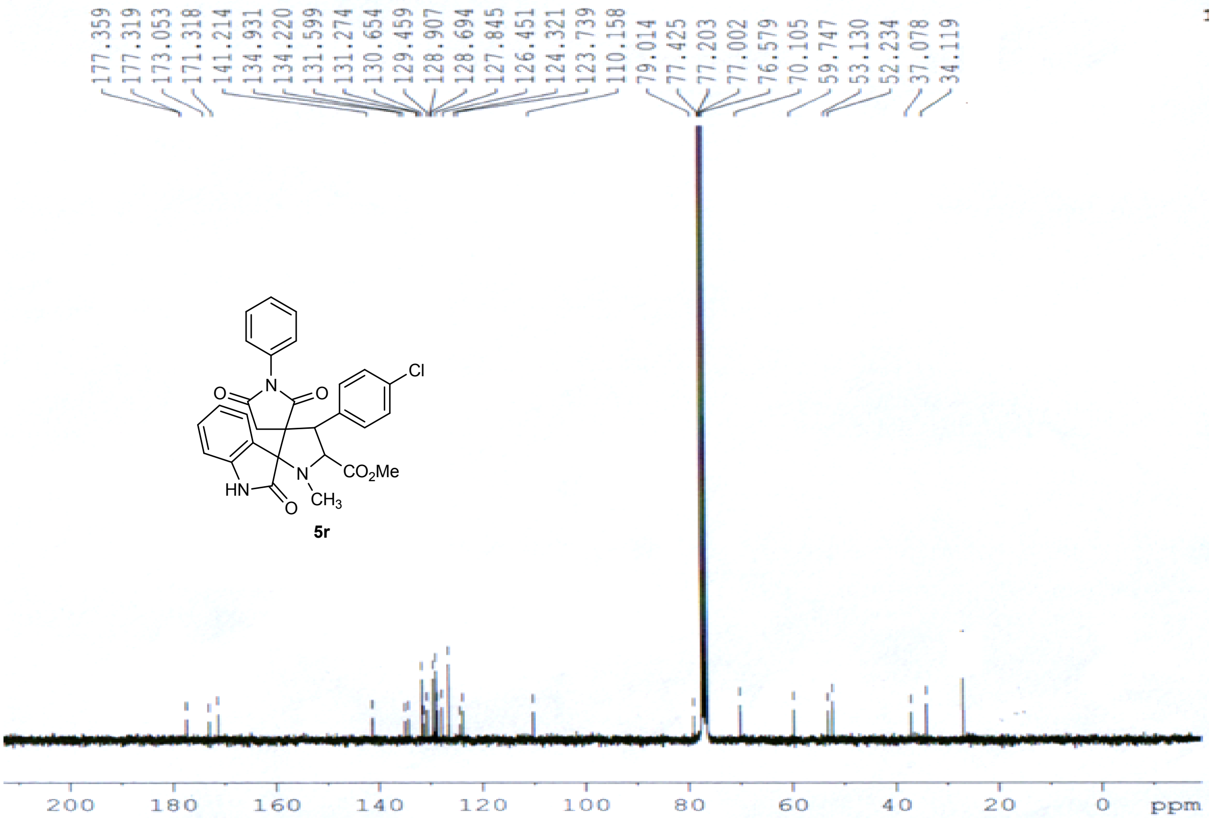


Fig. S36. ^{13}C NMR spectrum of **5r** in $CDCl_3$

5 HRMS Mass Spectrum of Compound 5i