

## Supporting Information

For

### STEREOSELECTIVE SYNTHESIS OF SPIROOXINDOLE DERIVATIVES USING ONE-POT MULTICOMPONENT CYCLOADDITION REACTION AND EVALUATION OF THEIR ANTIPROLIFERATIVE EFFICACY

**Rajat Ghosh,<sup>1</sup> Jorge B. Vitor,<sup>2</sup> Eduarda Mendes,<sup>2</sup> Alexandra Paulo,<sup>2</sup> Pratap Chandra Acharya<sup>1\*</sup>**

*<sup>1</sup>Department of Pharmacy, Tripura University, Suryamaninagar-799022, India.*

*<sup>2</sup>Faculty of Pharmacy, University of Lisbon, Av Prof Gama Pinto, Lisbon-1649003, Portugal.*

\*Corresponding author. Tel.: +91 381 237 9406; Fax: +91 381 237 4802.

E-mail: [pratapacharya@tripurauniv.in](mailto:pratapacharya@tripurauniv.in)

#### Table of Contents

1. <sup>1</sup> H and <sup>13</sup> C NMR spectra	S2
2. 2D-NMR spectra	S17
3. Mass Spectra	S19
4. HPLC Chromatograms	S24
5. 3D Structure	S35
6. SwissADME result	S36

# 1. <sup>1</sup>H and <sup>13</sup>C NMR spectra

Figure S1. <sup>1</sup>H NMR spectrum of 1,3-di(p-bromophenyl)prop-2-en-1-one (11a)

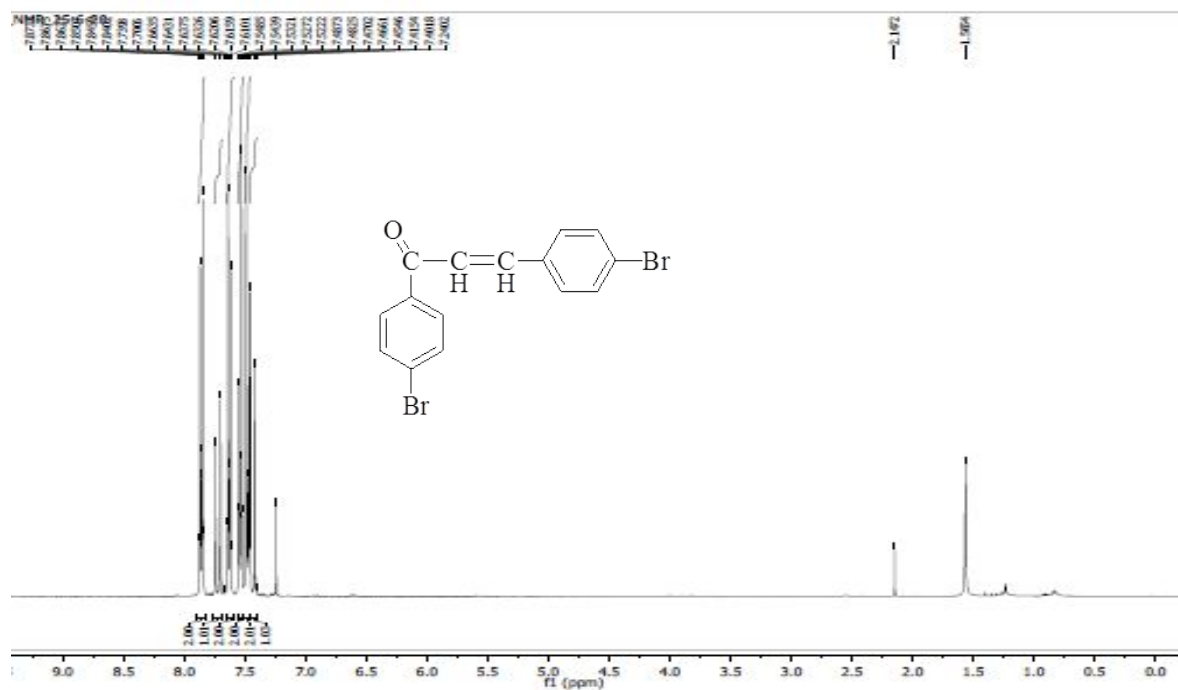
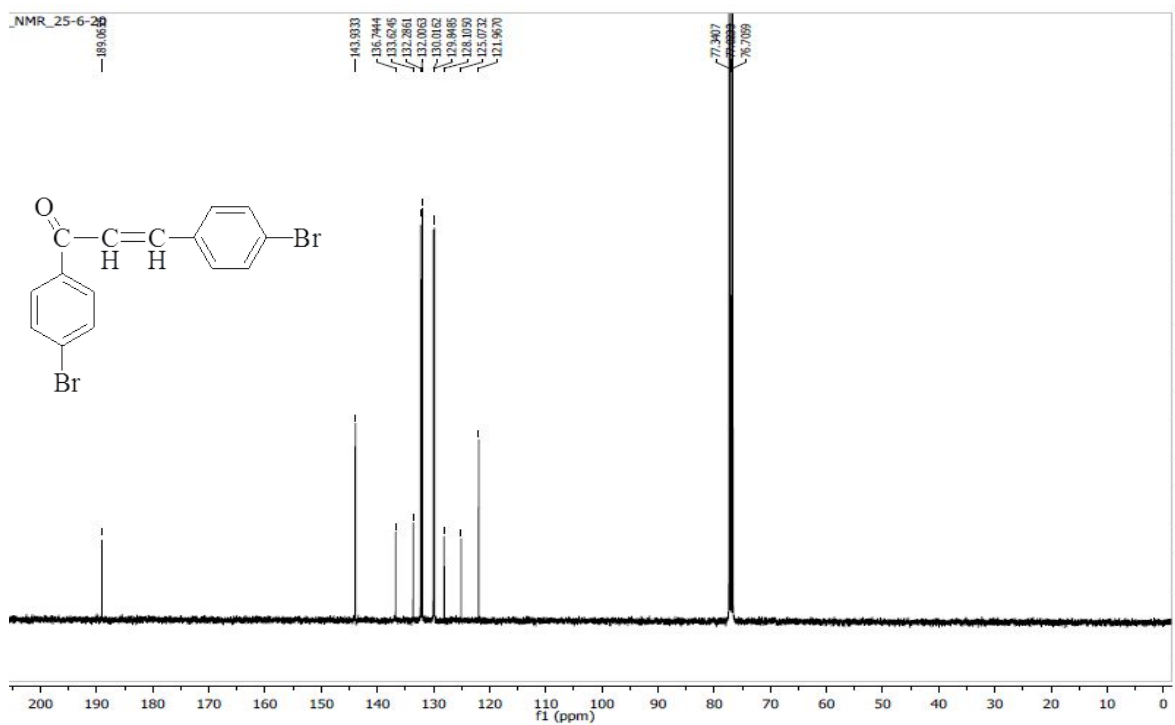
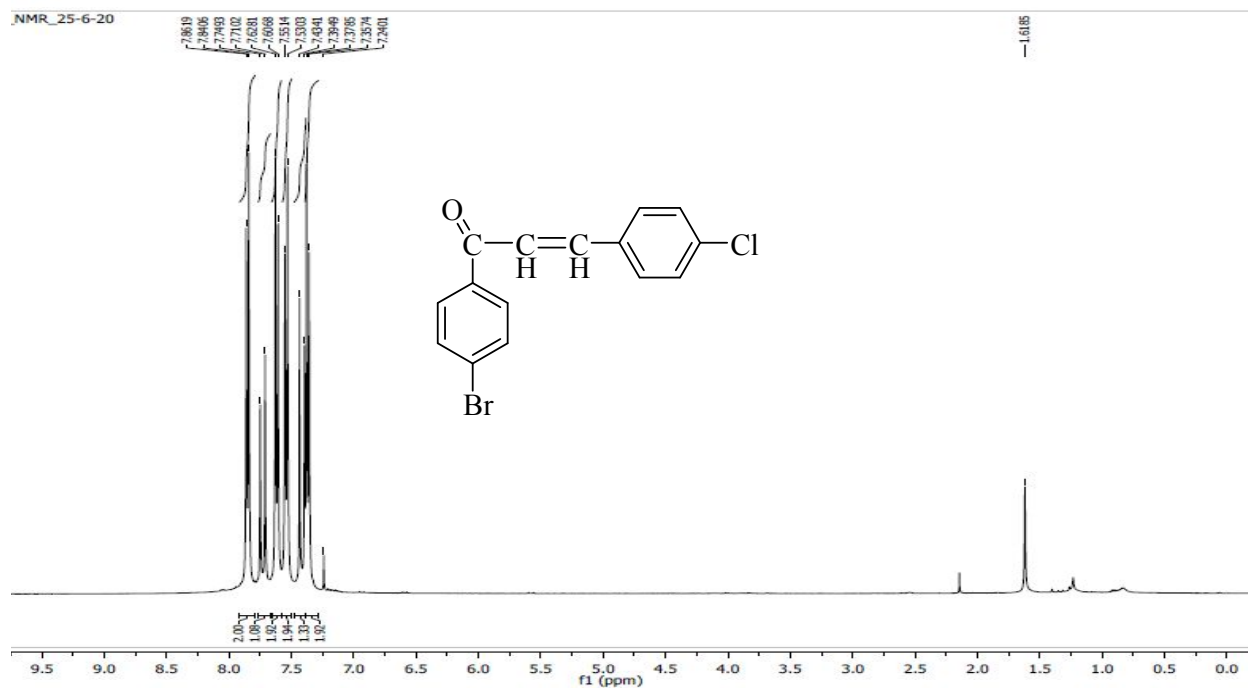


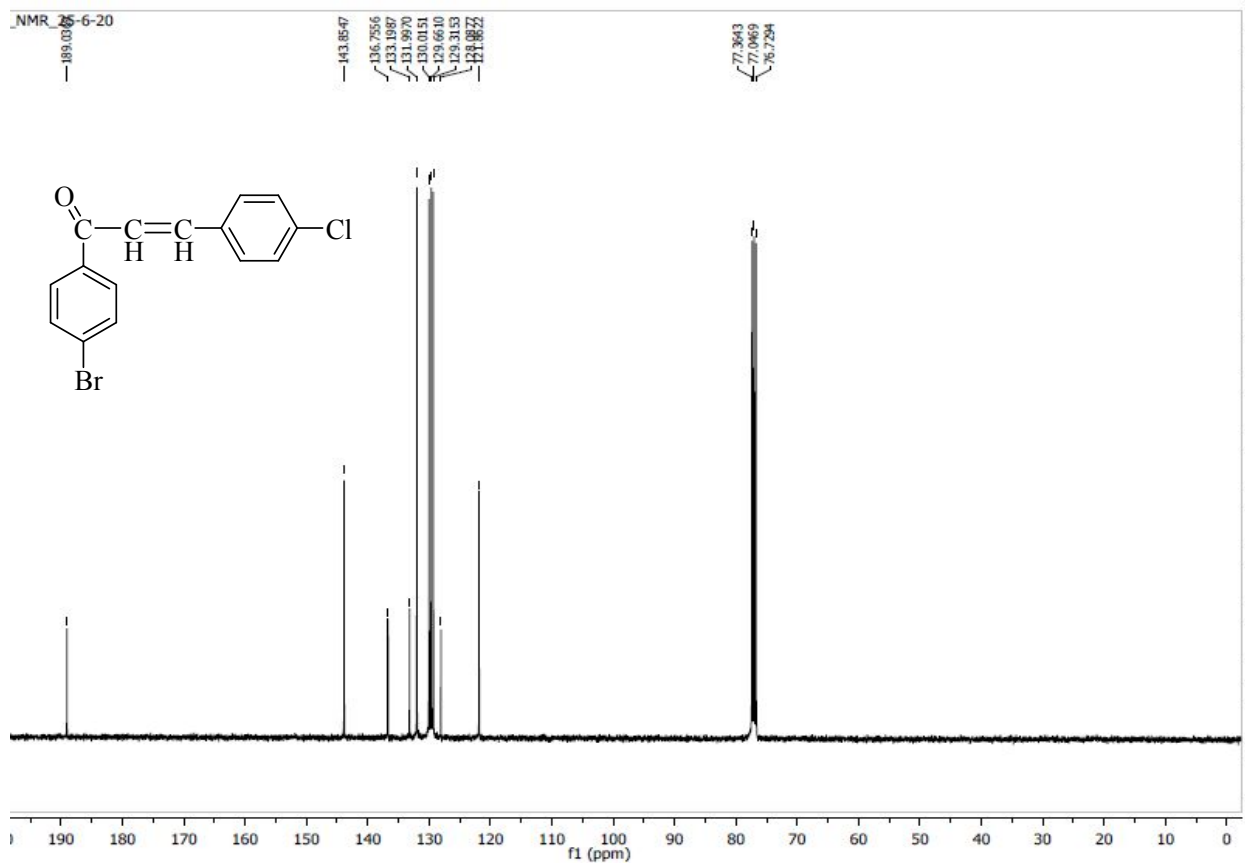
Figure S2. <sup>13</sup>C NMR spectrum of 1,3-di(p-bromophenyl)prop-2-en-1-one (11a)



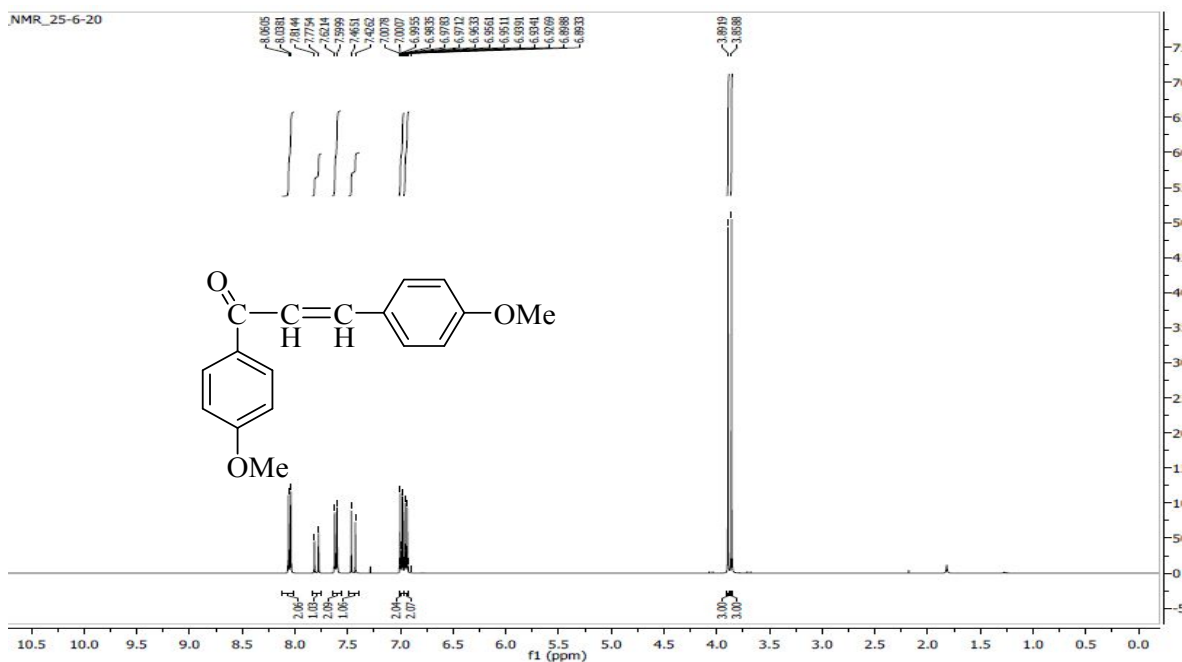
**Figure S3.**  $^1\text{H}$  NMR spectrum of 1-(p-bromophenyl)-3-(p-chlorophenyl)-prop-2-en-1-one (**11b**)



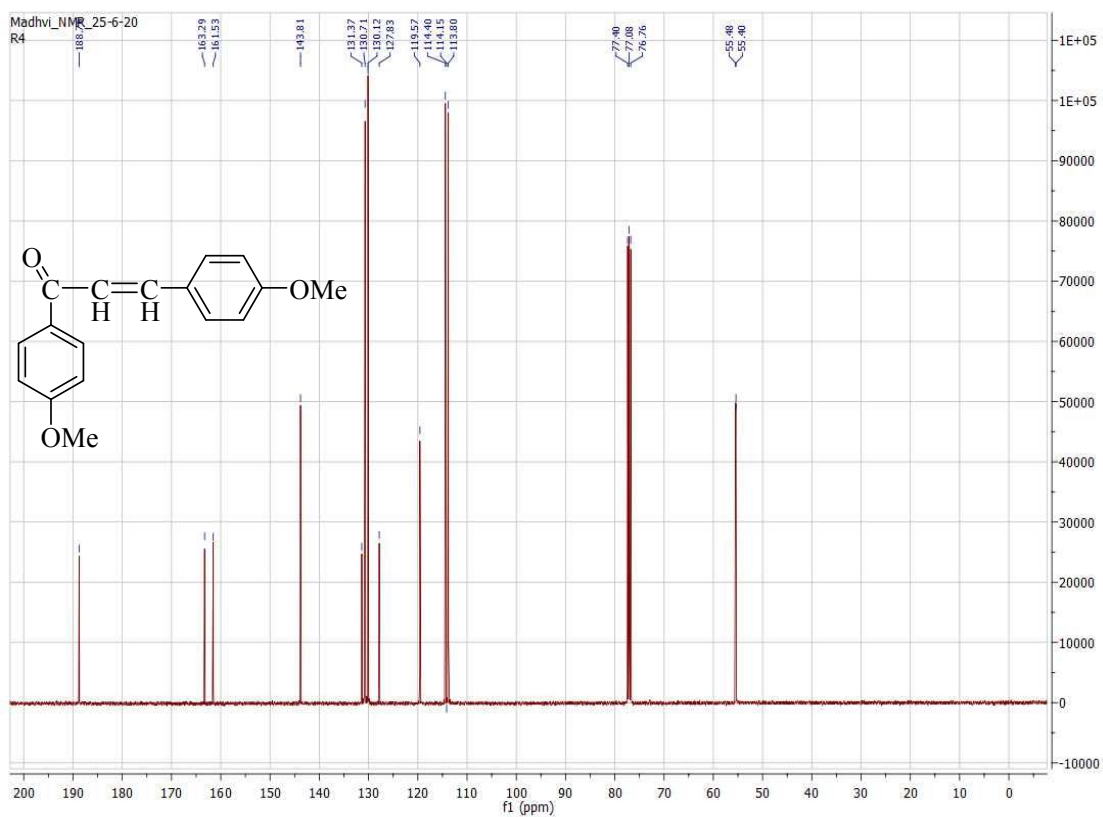
**Figure S4.**  $^{13}\text{C}$  NMR spectrum of 1-(p-bromophenyl)-3-(p-chlorophenyl)-prop-2-en-1-one (**11b**)



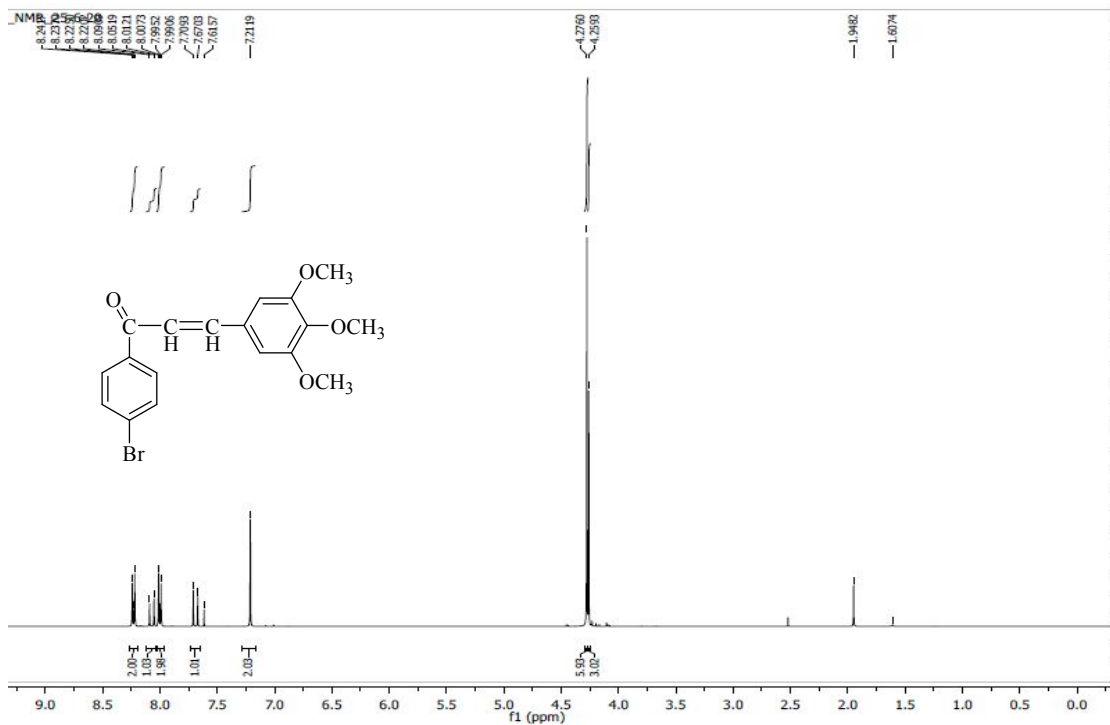
**Figure S5.**  $^1\text{H-NMR}$  spectrum of 1,3-di-(p-methoxyphenyl)-prop-2-en-1-one (**11c**)



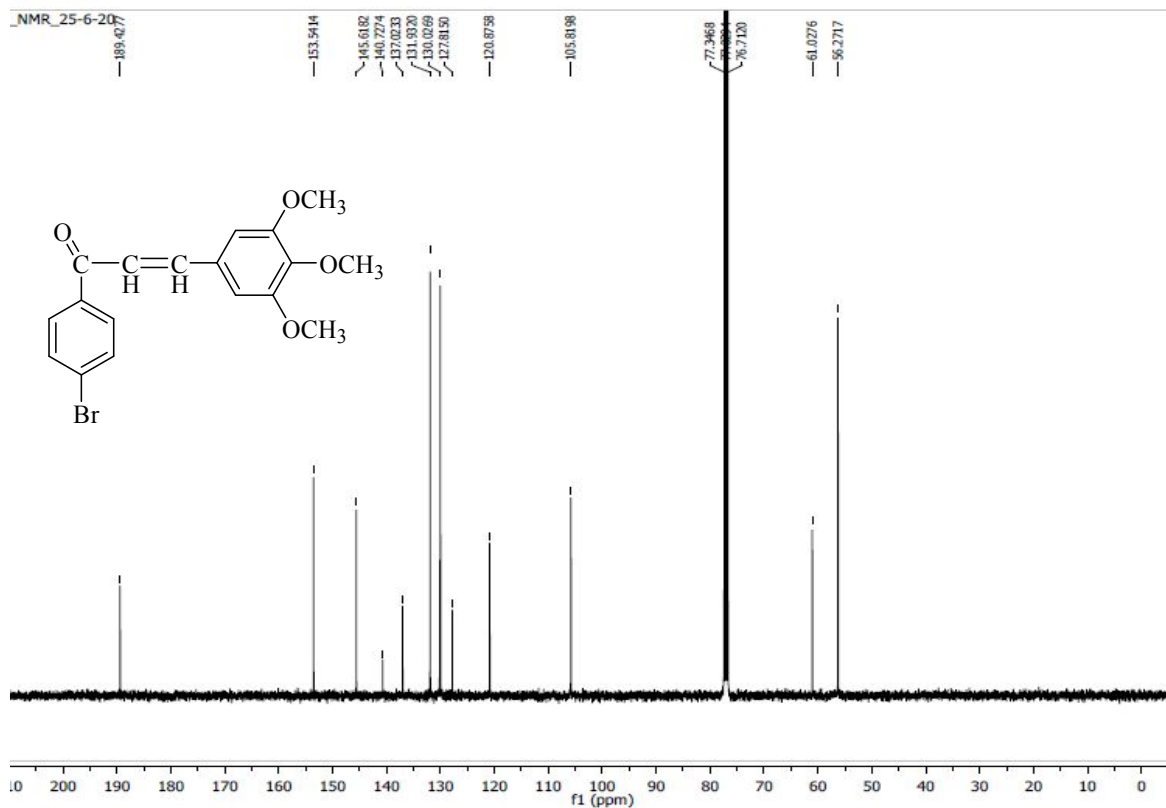
**Figure S6.**  $^{13}\text{C-NMR}$  spectrum of 1,3-di-(p-methoxyphenyl)-prop-2-en-1-one (**11c**)



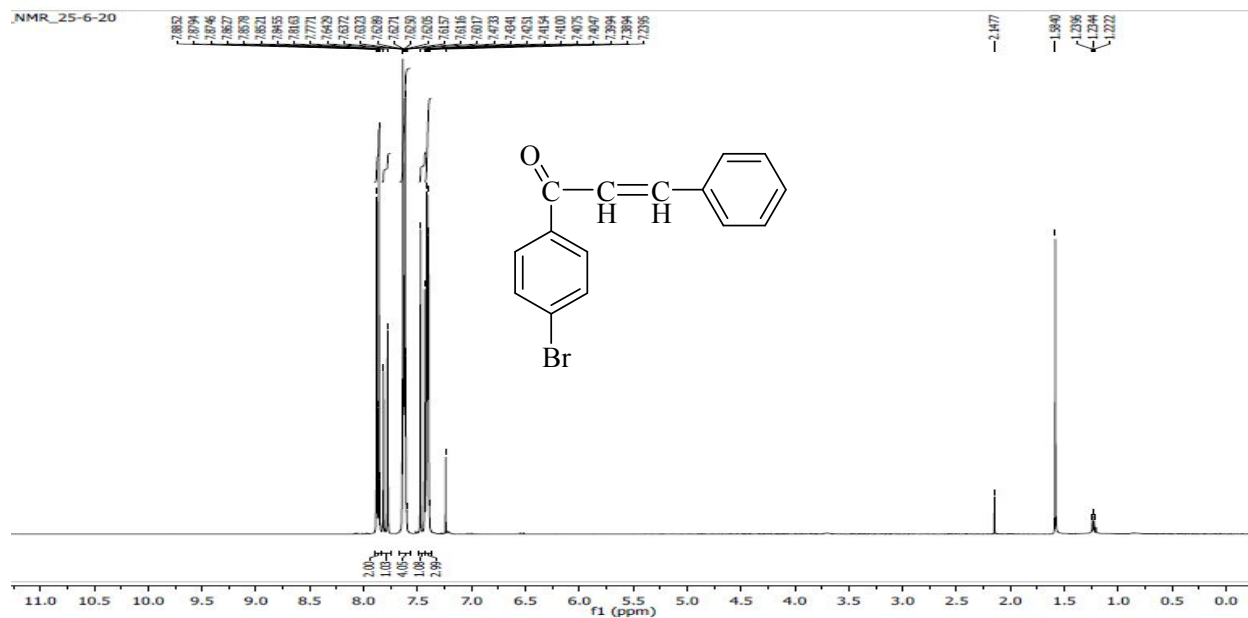
**Figure S7.**  $^1\text{H}$  NMR spectrum of 1-(p-bromophenyl)-3-(3,4,5-trimethoxy-phenyl)-prop-2-en-1-one (**11d**)



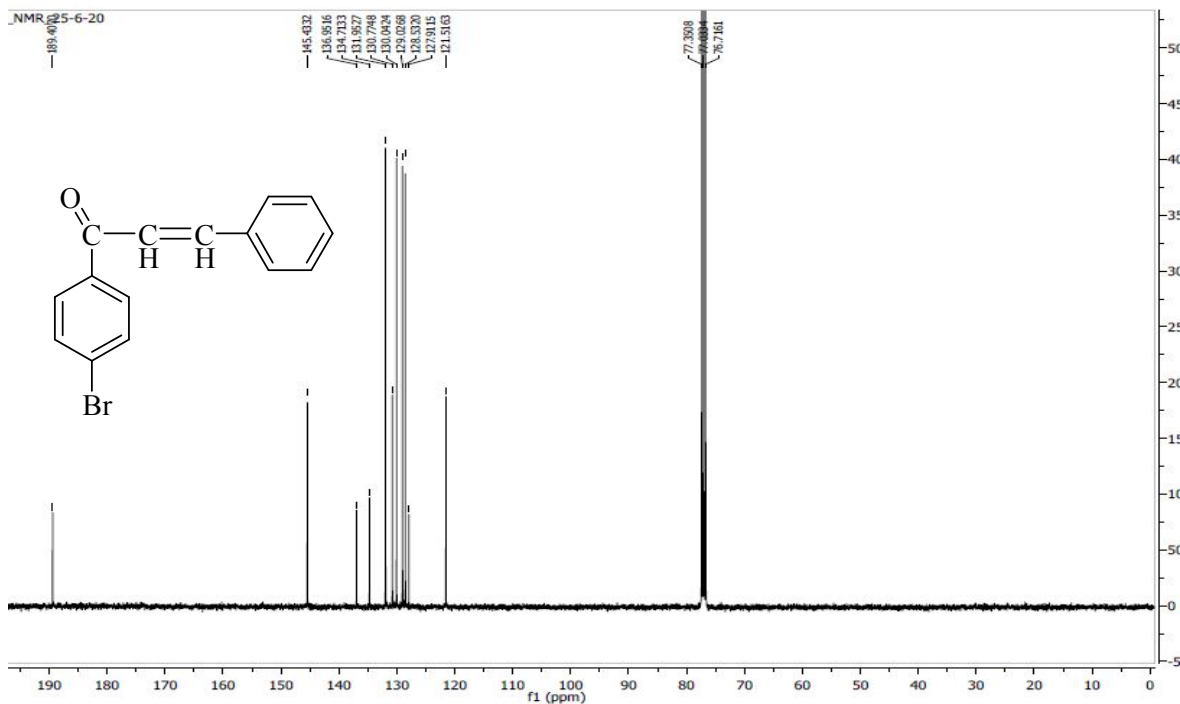
**Figure S8.**  $^{13}\text{C}$  NMR spectrum of 1-(p-bromophenyl)-3-(3,4,5-trimethoxy-phenyl)-prop-2-en-1-one (**11d**)



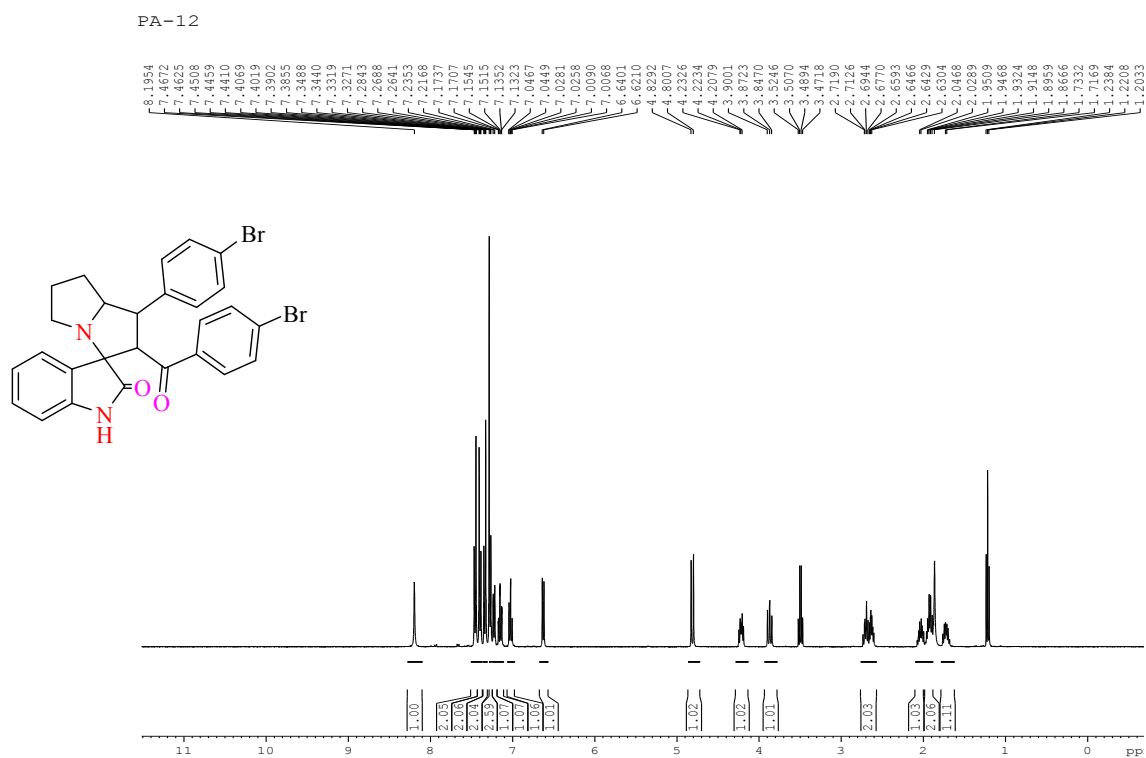
**Figure S9.**  $^1\text{H}$  NMR spectrum of 1-(p-bromophenyl)-3-phenyl-prop-2-en-1-one (**11e**)



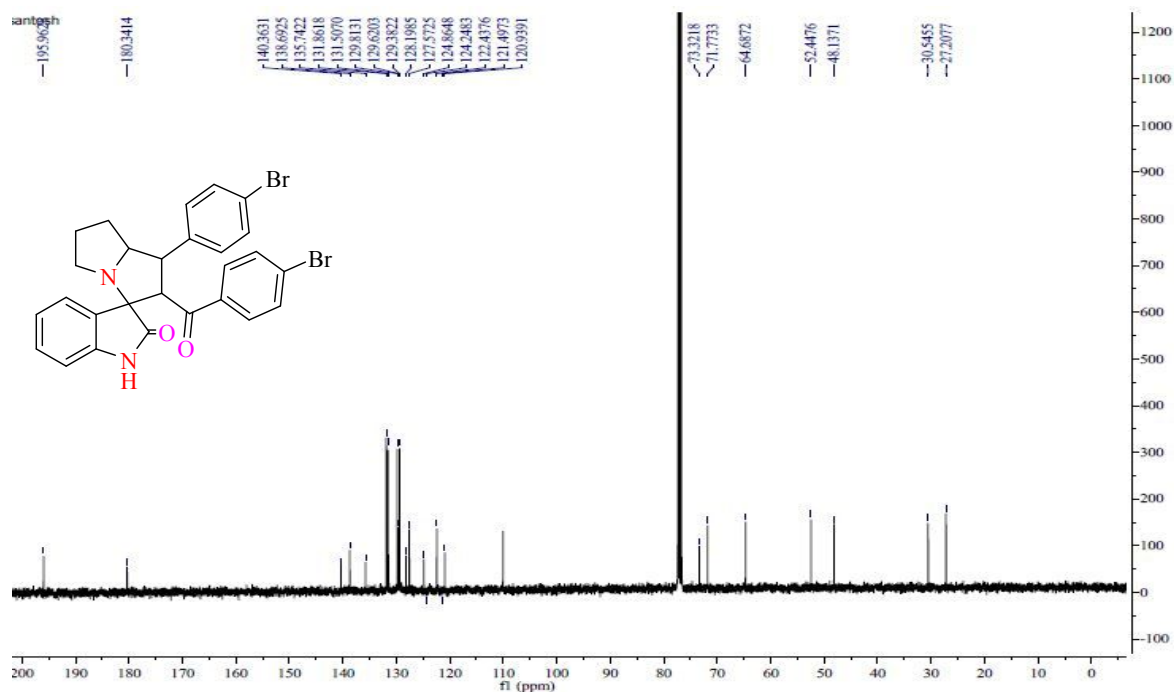
**Figure S10.**  $^{13}\text{C}$  NMR spectrum of 1-(p-bromophenyl)-3-phenyl-prop-2-en-1-one (**11e**)



**Figure S11.**  $^1\text{H}$  NMR spectrum of p-bromo-phenyl-[1-(p-bromophenyl)-[3-spiro(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl]methanone (**14a**)

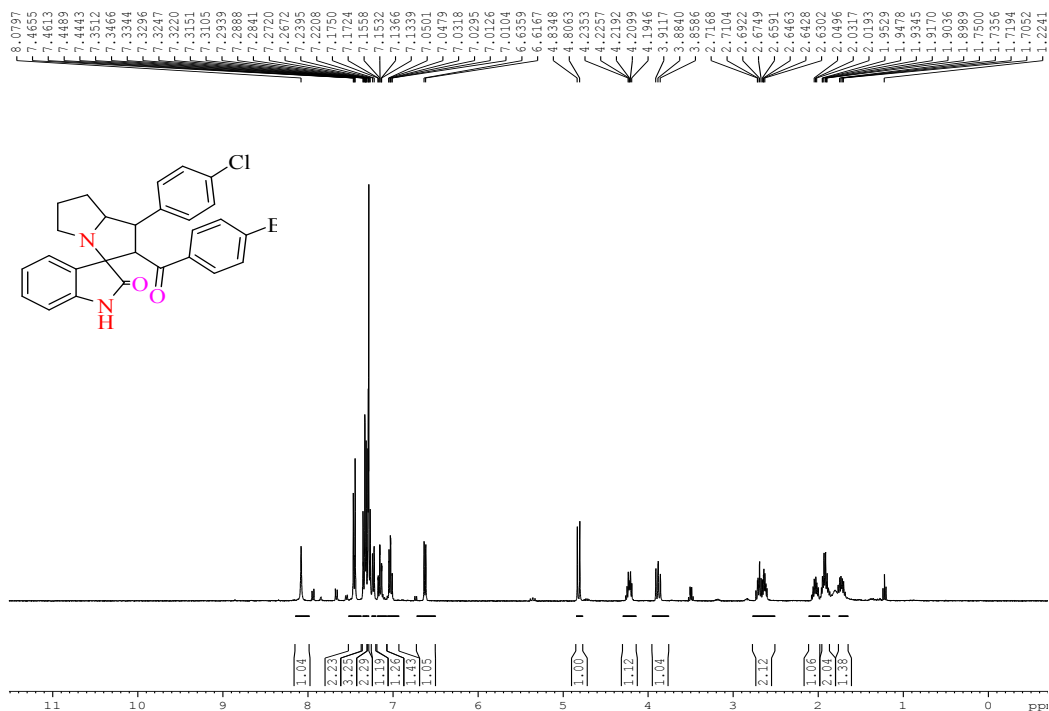


**Figure S12.**  $^{13}\text{C}$  NMR spectrum of p-bromo-phenyl-[1-(p-bromophenyl)-[3-spiro(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl]methanone (**14a**)

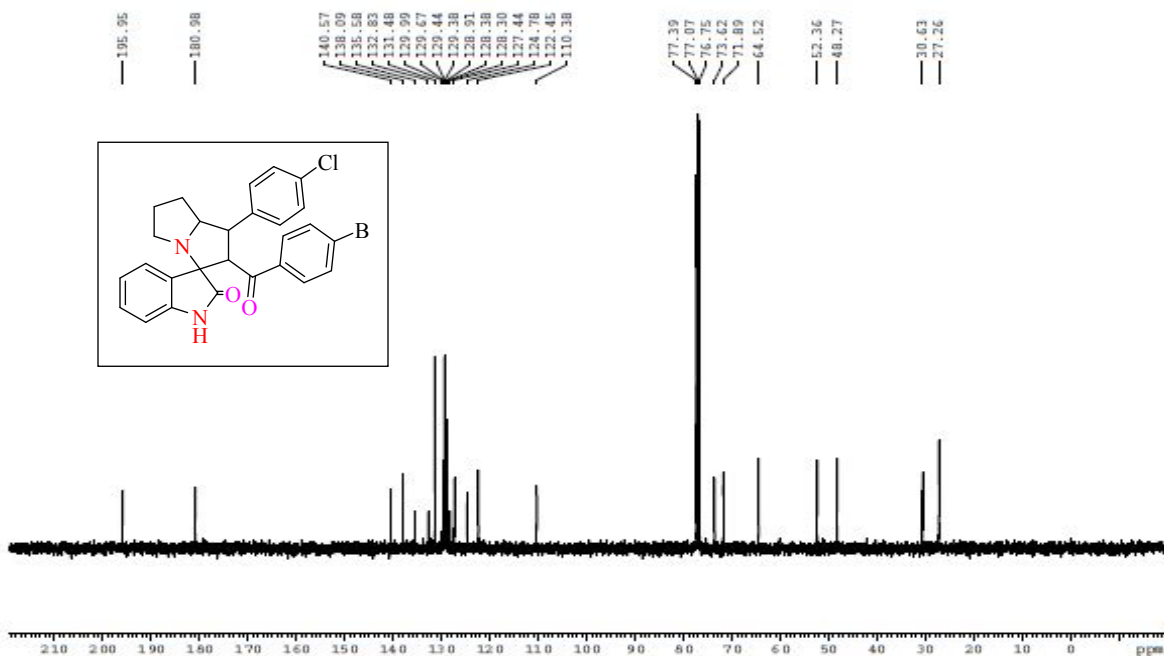


**Figure S13.**  $^1\text{H}$  NMR spectrum of p-bromo-phenyl-{1-(p-chlorophenyl)-[3-spiro-(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl} methanone (**14b**)

PA-13

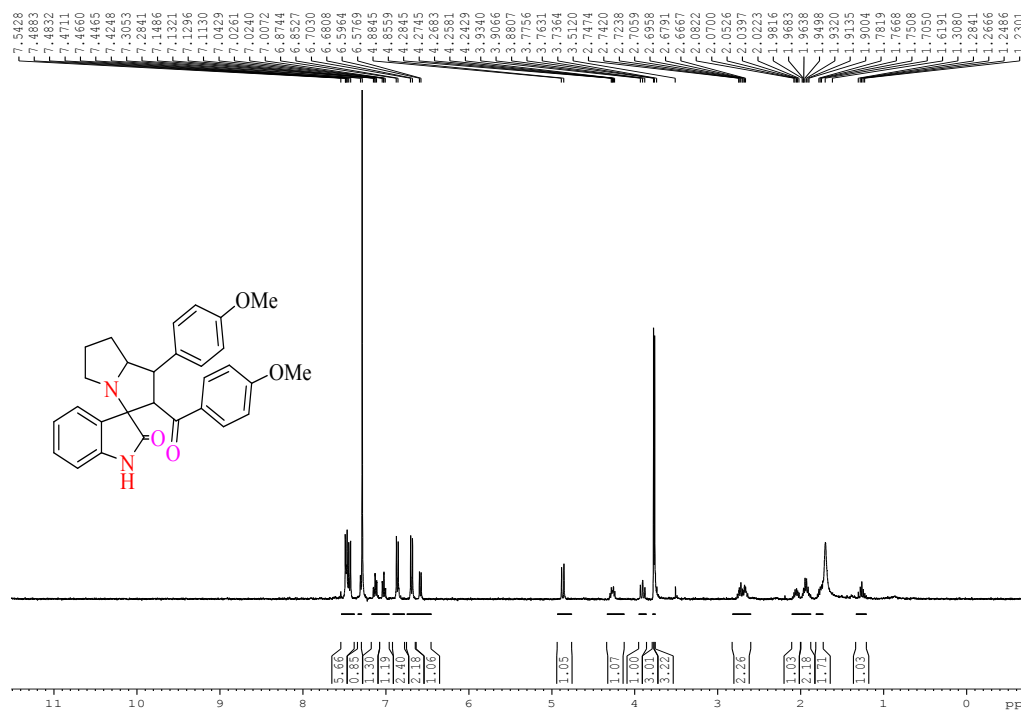


**Figure S14.**  $^{13}\text{C}$  NMR spectrum of p-bromo-phenyl-{1-(p-chlorophenyl)-[3-spiro-(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl} methanone (**14b**)

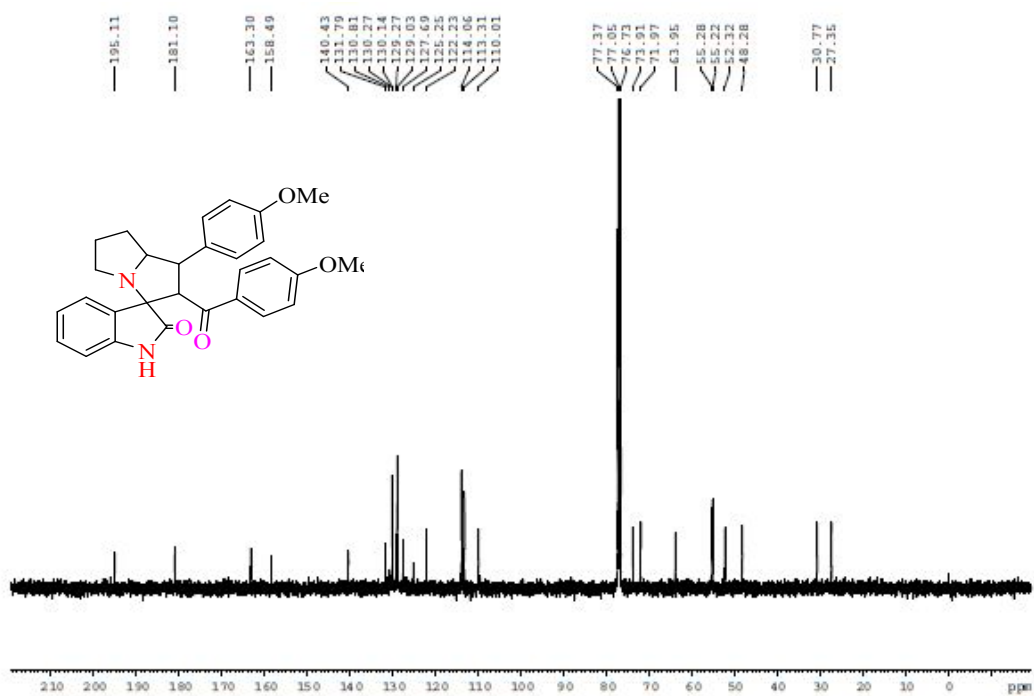




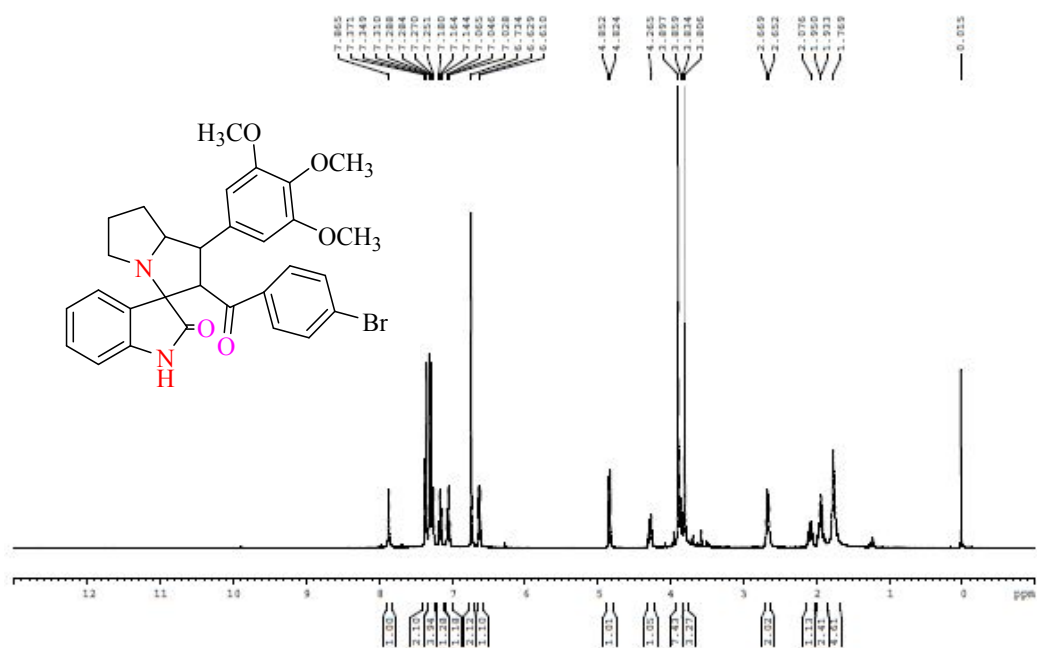
**Figure S15.**  $^1\text{H}$  NMR spectrum of p-methoxyphenyl-{1-(p-methoxyphenyl)-[3-spiro-(indolin-2-one-3-yl)] hexahydro-1H-pyrrolizin-2-yl} methanone (**14c**)



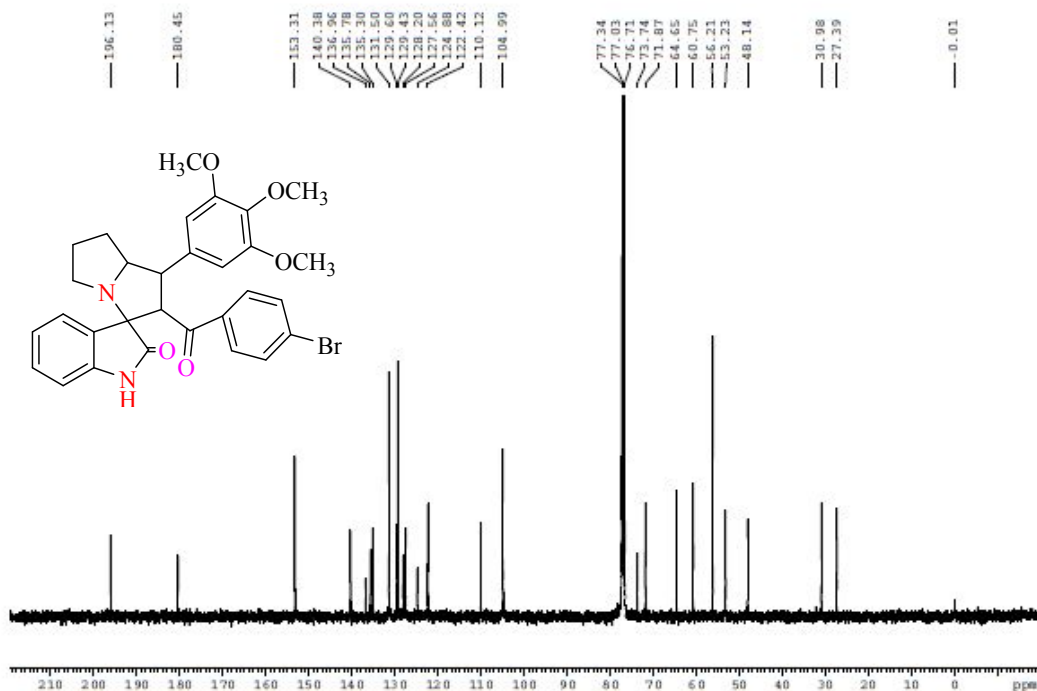
**Figure S16.**  $^{13}\text{C}$  NMR spectrum of 4 p-methoxyphenyl-{1-(p-methoxyphenyl)-[3-spiro-(indolin-2-one-3-yl)] hexahydro-1H-pyrrolizin-2-yl} methanone (**14c**)



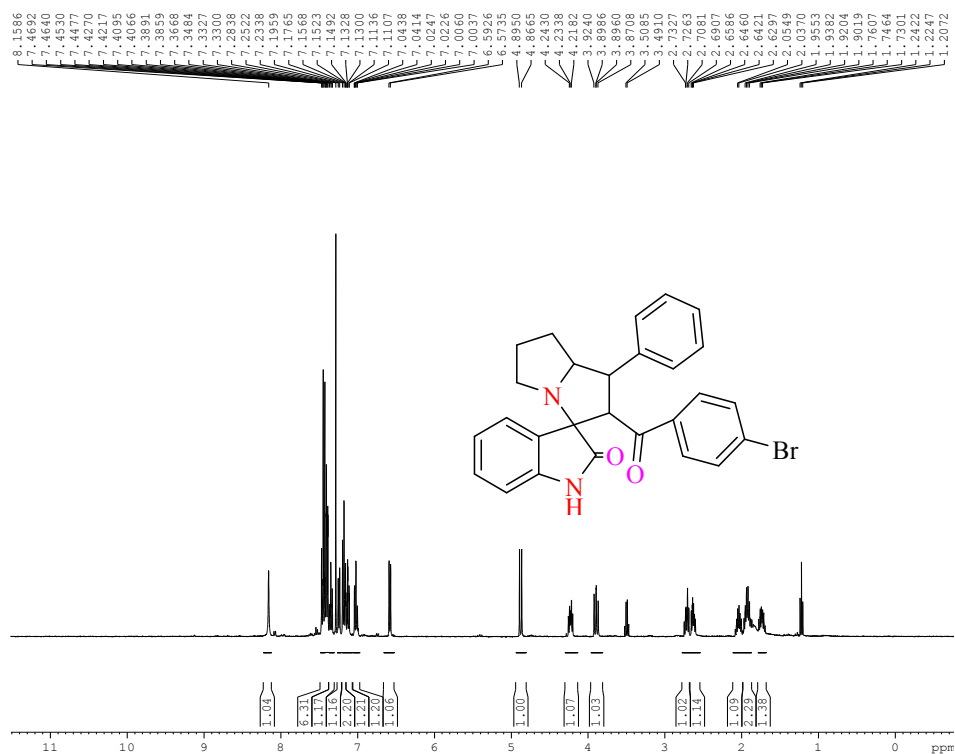
**Figure S17.**  $^1\text{H}$  NMR spectrum of p-bromophenyl-{1-(3,4,5-trimethoxy-phenyl)-[3-spiro-(indolin-2-one-3-yl)] hexahydro-1H-pyrrolizin-2-yl} methanone (**14d**)



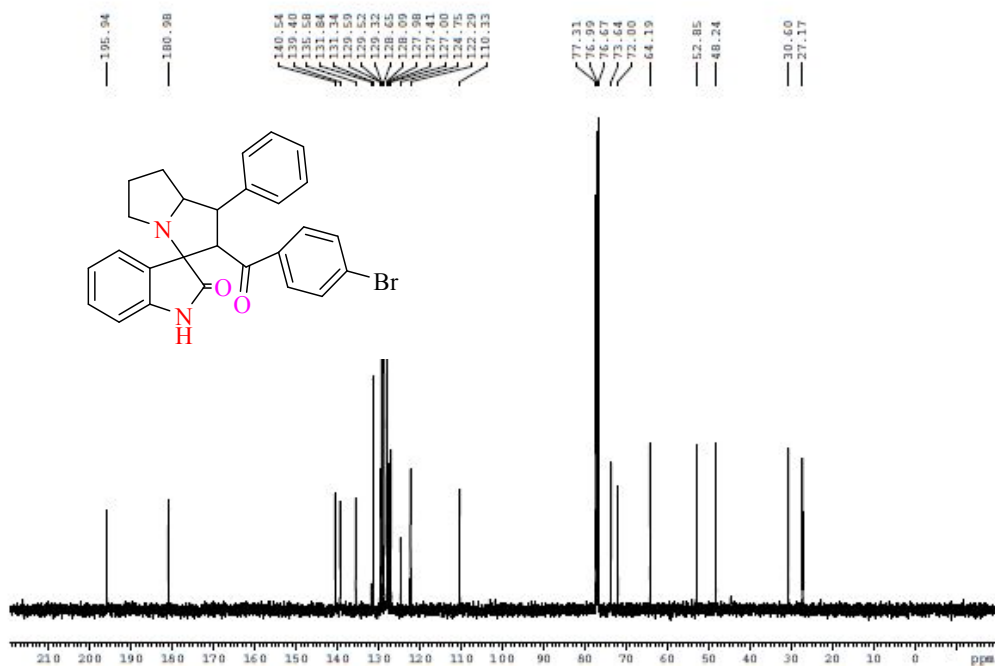
**Figure S-18.**  $^{13}\text{C}$  NMR spectrum of p-bromophenyl-{1-(3,4,5-trimethoxy-phenyl)-[3-spiro-(indolin-2-one-3-yl)] hexahydro-1H-pyrrolizin-2-yl} methanone (**14d**)



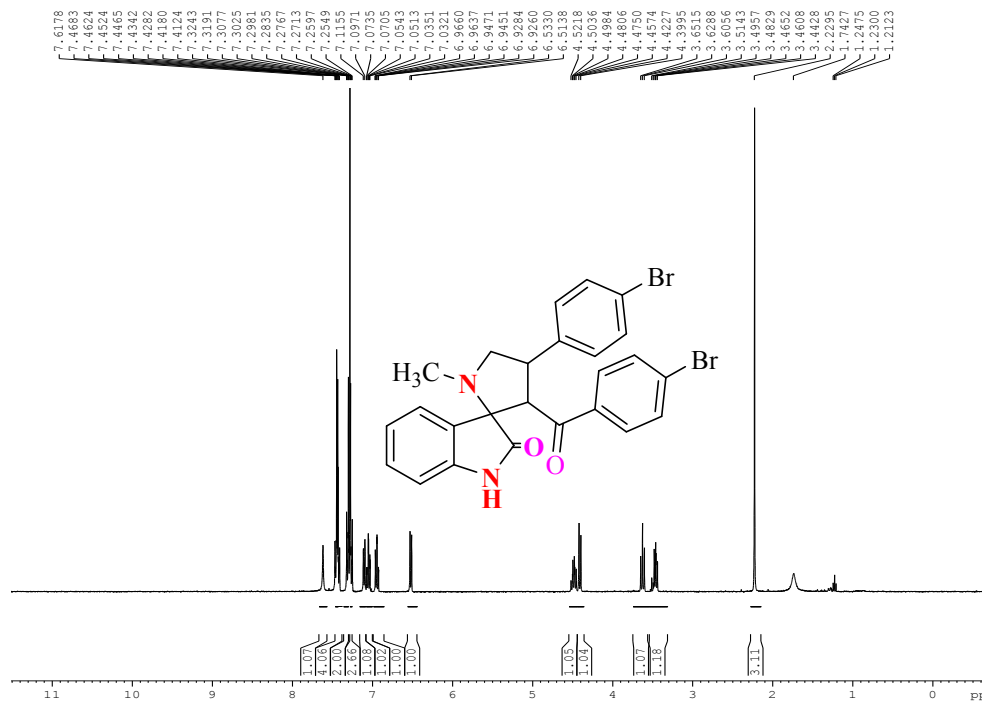
**Figure S19.**  $^1\text{H}$  NMR spectrum of p-bromo-phenyl-[1-(phenyl)-[3-spiro-(indolin-2-one-3-yl)]hexahydro-1H-pyrrolizin-2-yl] methanone (**14e**)



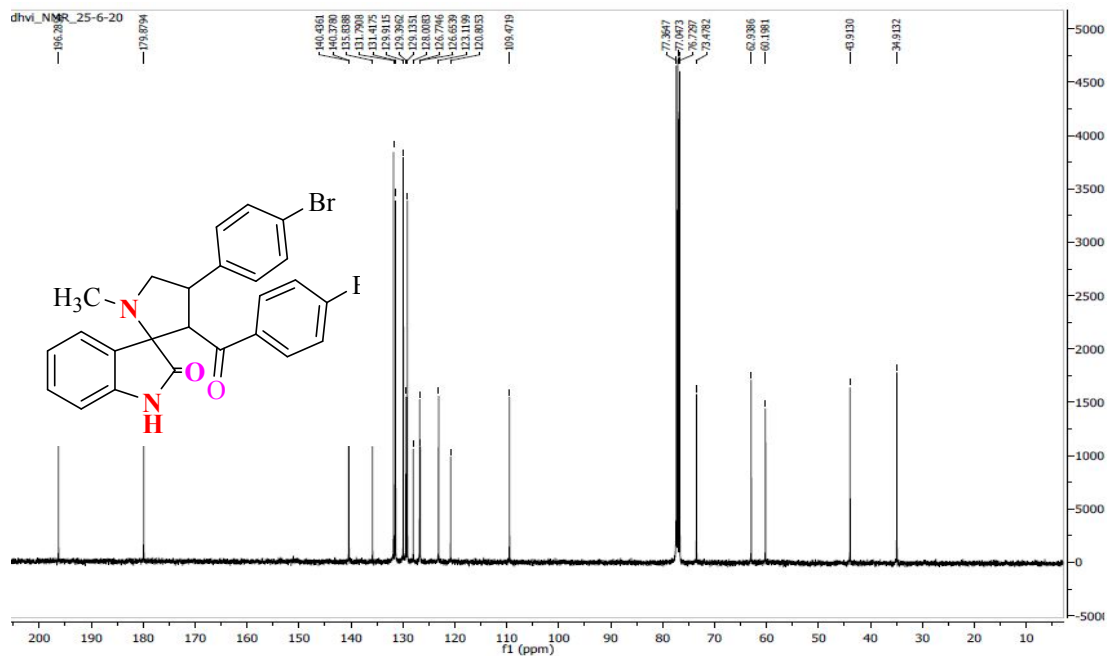
**Figure S20.**  $^{13}\text{C}$  NMR spectrum of p-bromo-phenyl-[1-(phenyl)-[3-spiro-(indolin-2-one-3-yl)]hexahydro-1H-pyrrolizin-2-yl] methanone (**14e**)



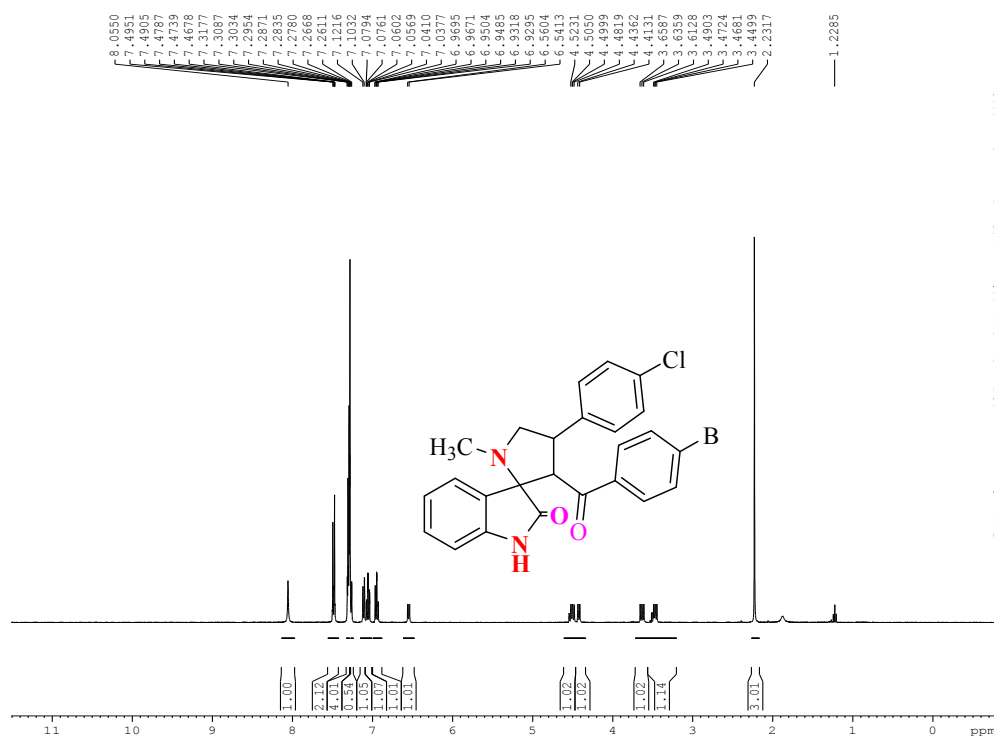
**Figure S21.**  $^1\text{H}$  NMR spectrum of p-bromophenyl-{4-(p-bromophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16a**)



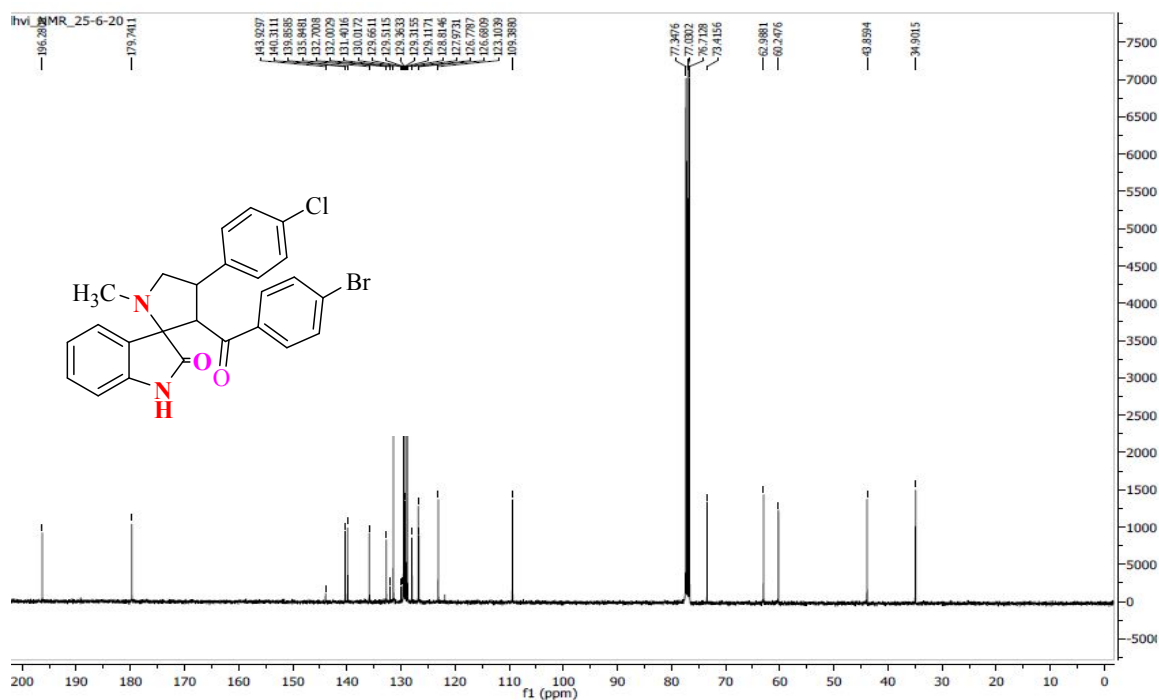
**Figure S22.**  $^{13}\text{C}$  NMR spectrum of p-bromophenyl-{4-(p-bromophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16a**)



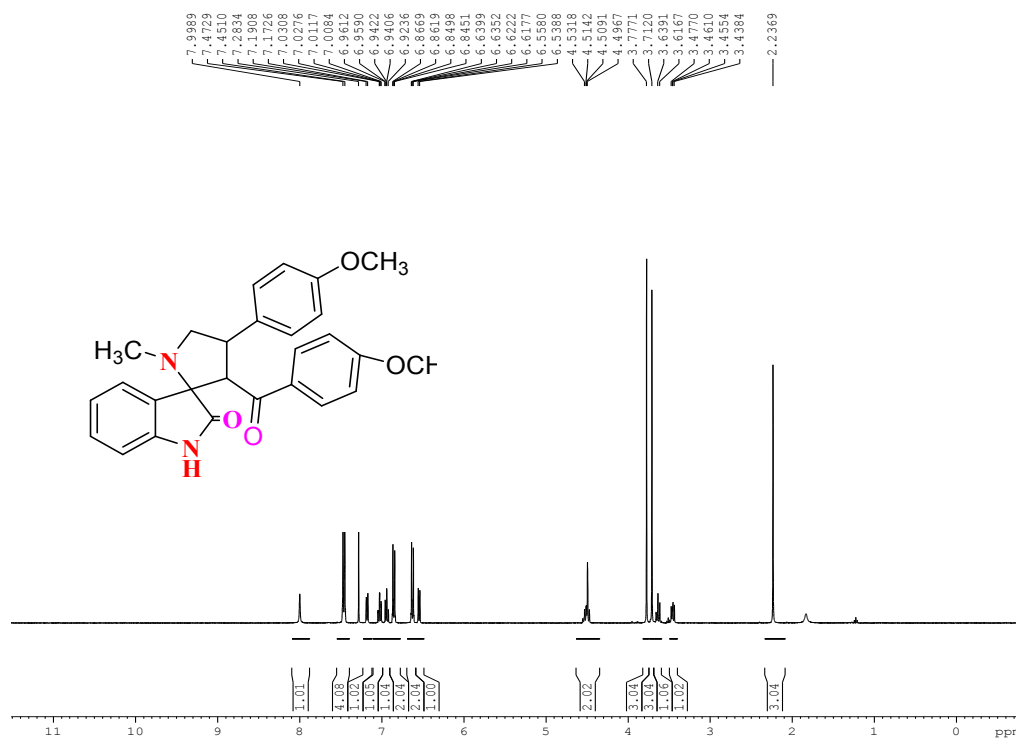
**Figure S23.**  $^1\text{H}$  NMR spectrum of p-bromophenyl-{4-(p-chlorophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16b**)



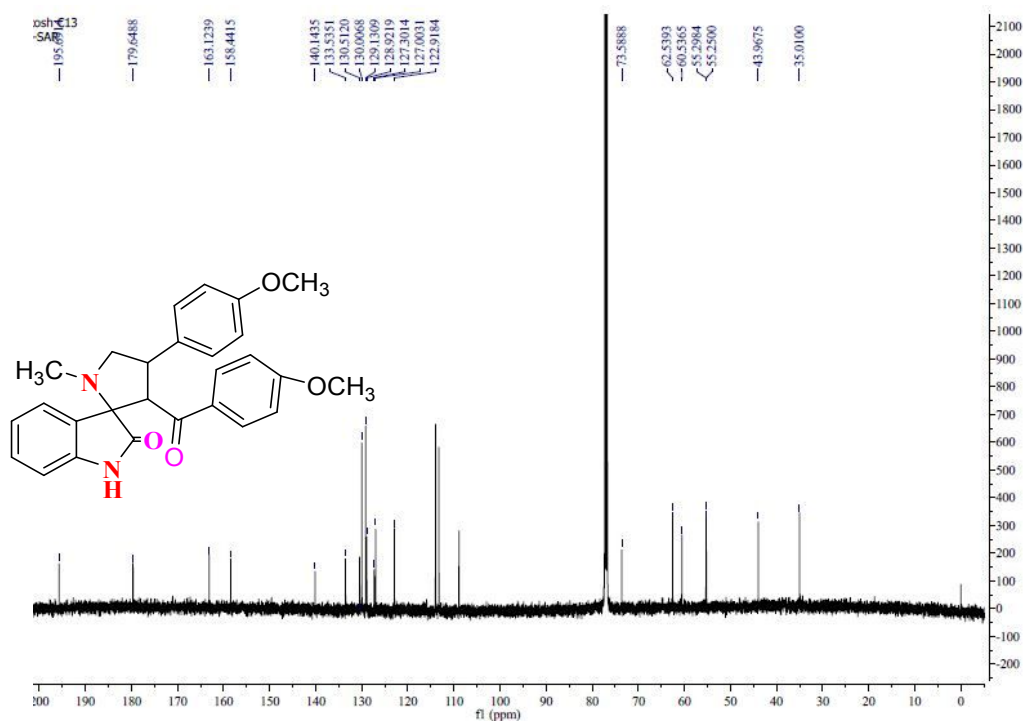
**Figure S24.**  $^{13}\text{C}$  NMR spectrum of p-bromophenyl-{4-(p-chlorophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16b**)



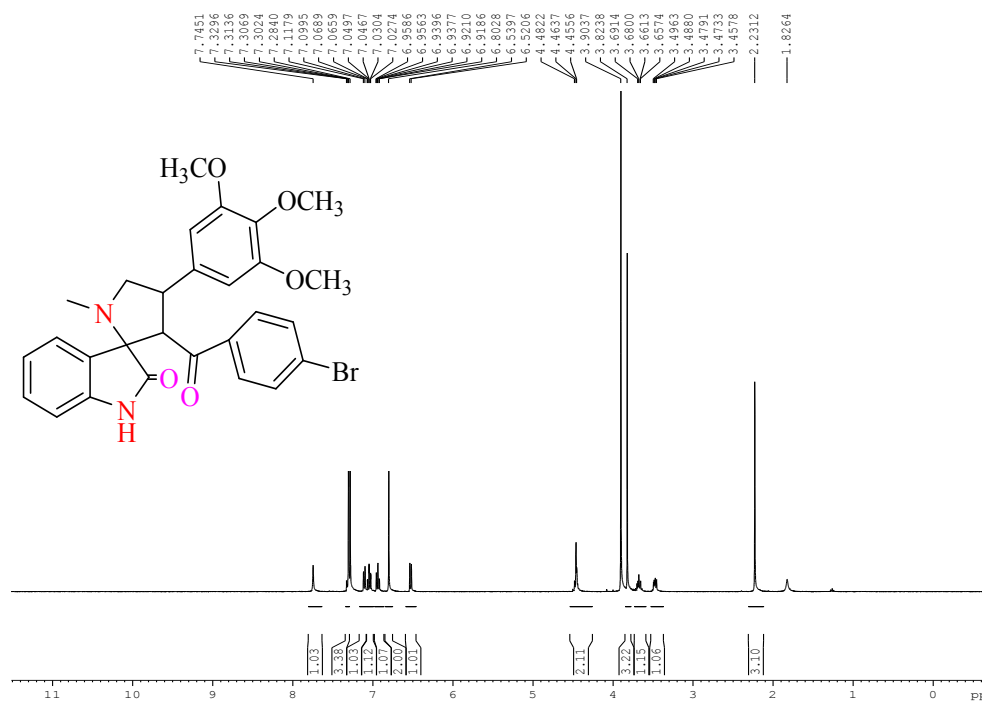
**Figure S25.**  $^1\text{H}$ NMR spectrum of p-methoxy-phenyl-{4-(p-methoxy-phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16c**)



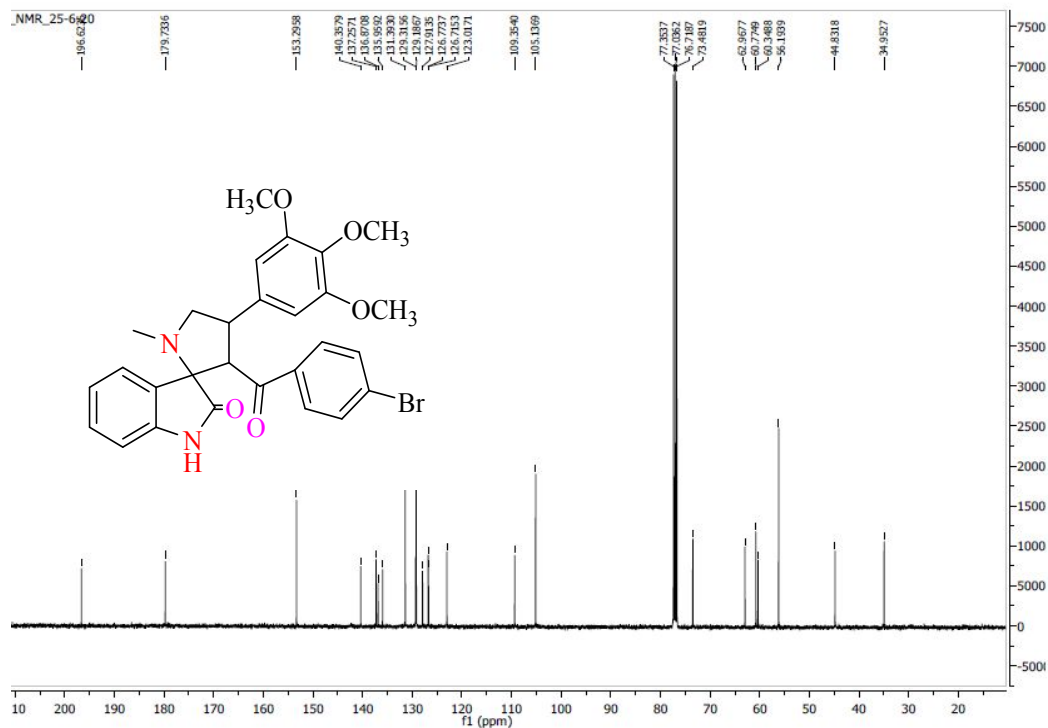
**Figure S26.**  $^{13}\text{C}$  NMR spectrum of p-methoxy-phenyl-{4-(p-methoxy-phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16c**)



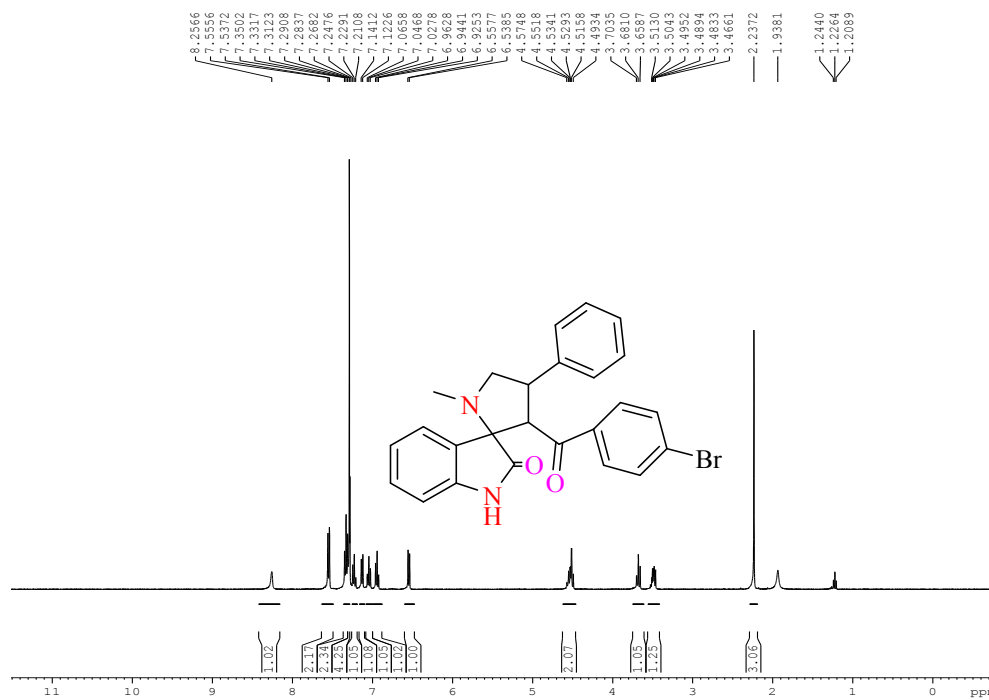
**Figure S27.**  $^1\text{H}$  NMR spectrum of p-bromophenyl-{4-(3,4,5-trimethoxy-phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16d**)



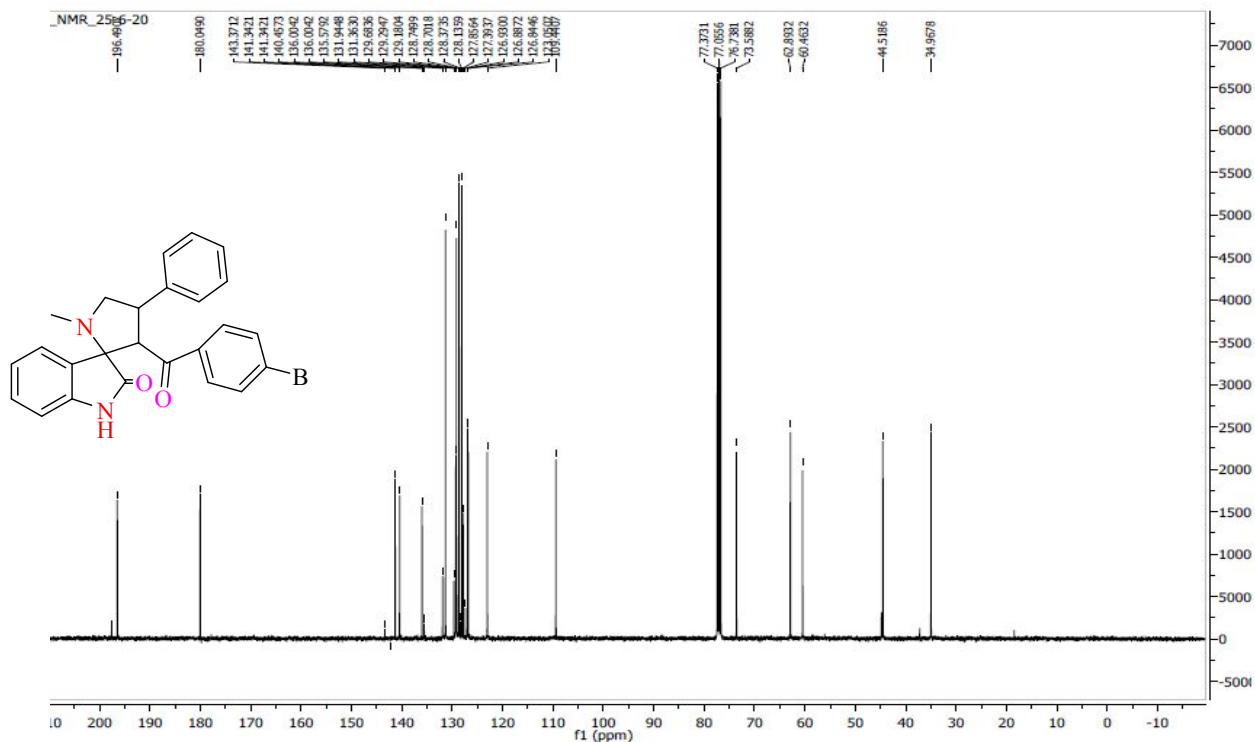
**Figure S28.**  $^{13}\text{C}$  NMR spectrum of p-bromophenyl-{4-(3,4,5-trimethoxy-phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16d**)



**Figure S29.**  $^1\text{H}$  NMR spectrum of p-bromo-phenyl-{4-(phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16e**)



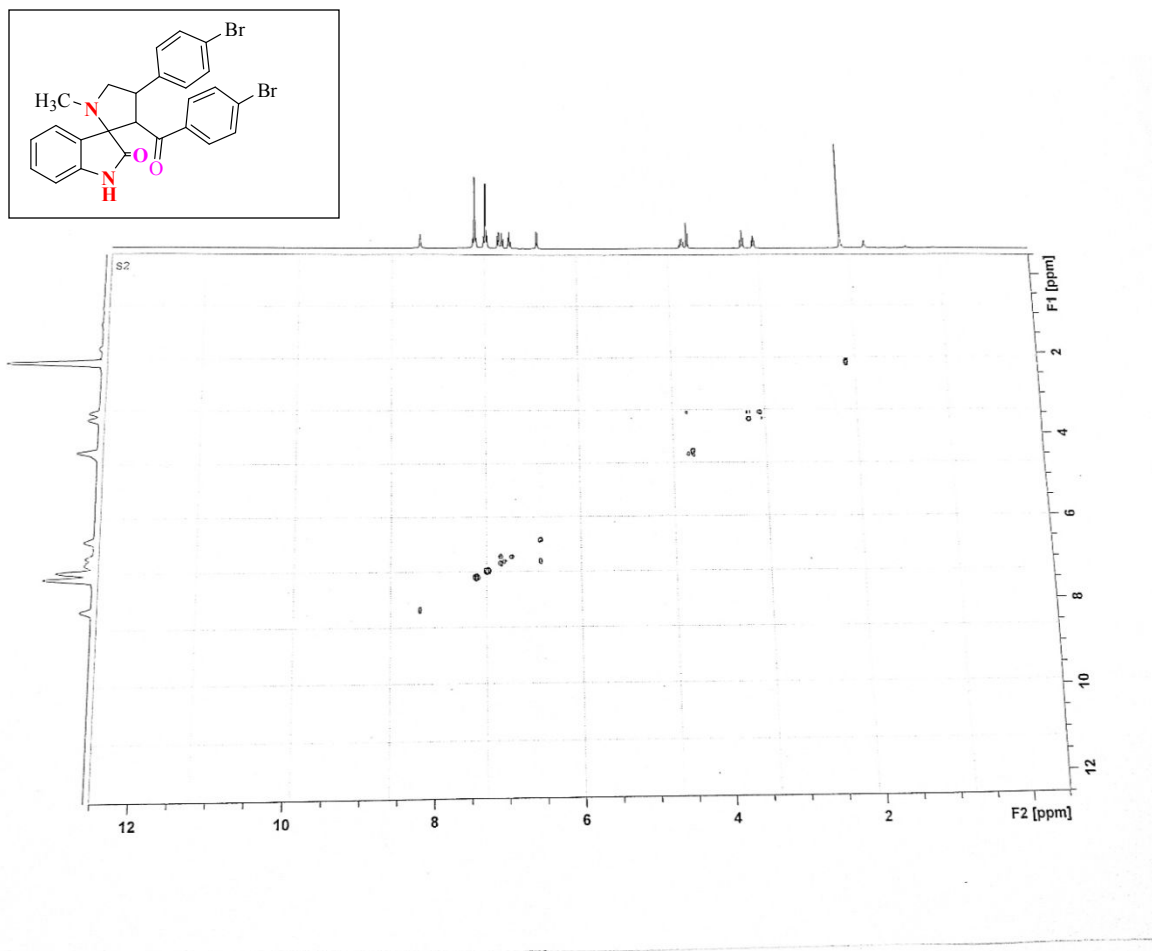
**Figure S30.**  $^{13}\text{C}$  NMR spectrum of p-bromo-phenyl-{4-(phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16e**)



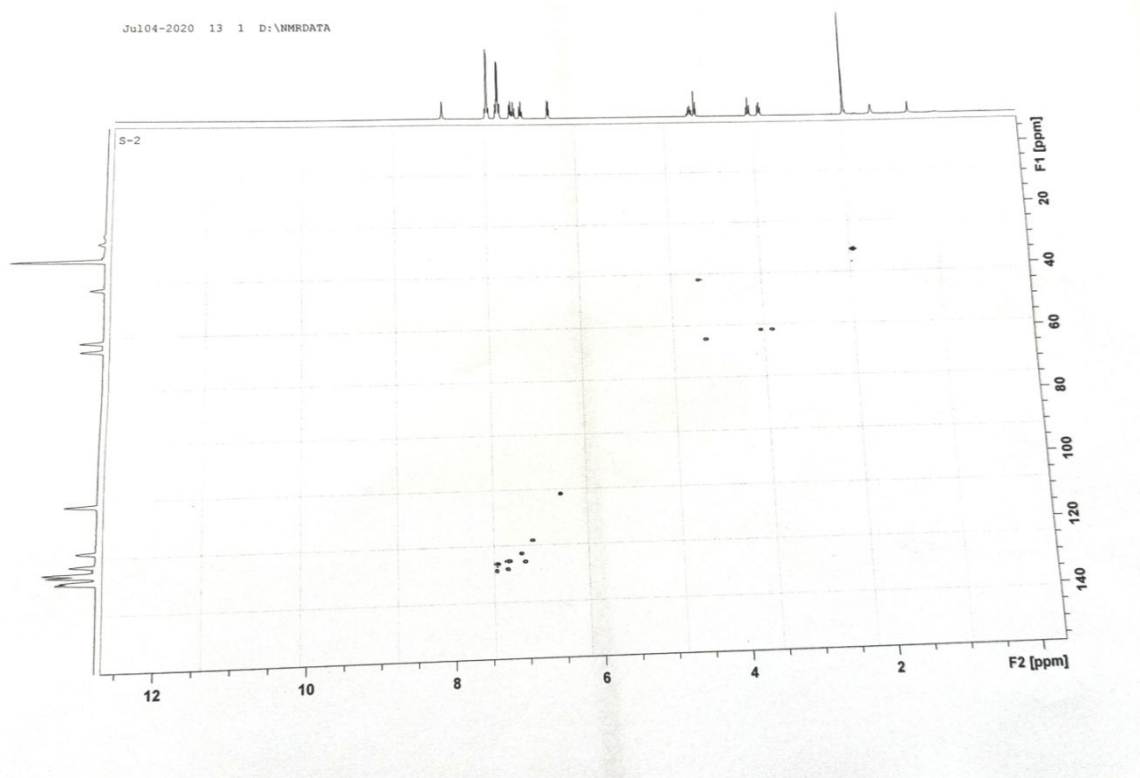
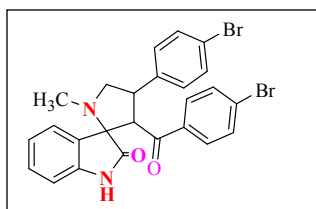


## 2. 2D-NMR spectra

**Figure S31.** 2D NMR spectrum ( $^1\text{H}$ - $^1\text{H}$  COSY) of p-bromophenyl-{4-(p-bromophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16a**)

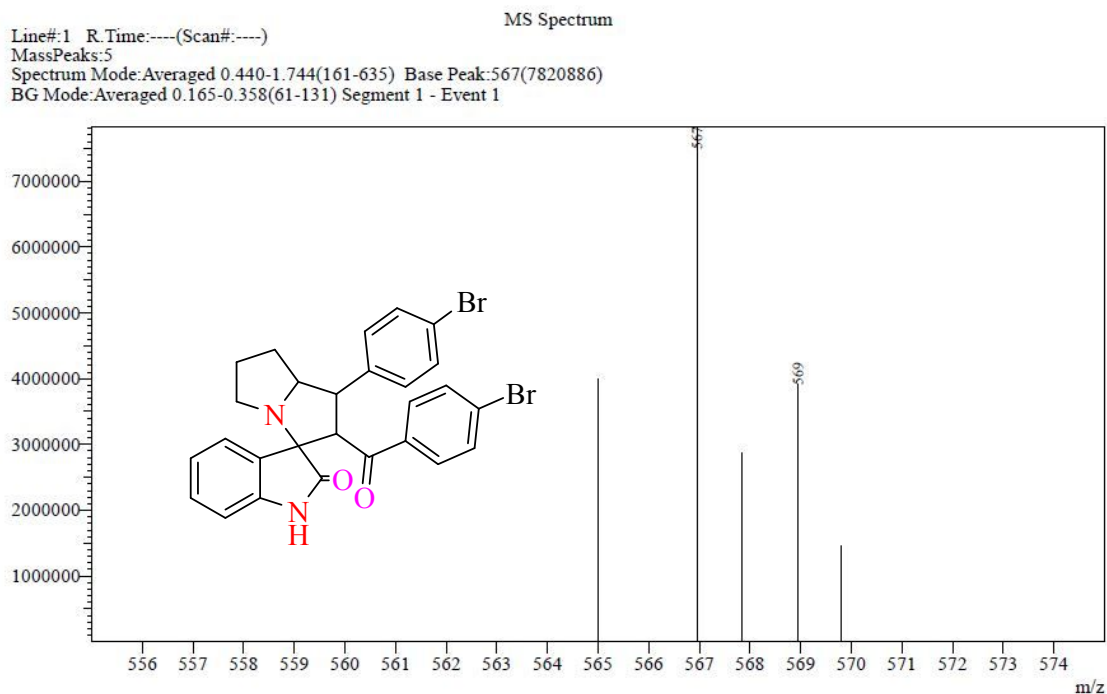


**Figure S32.** 2D NMR spectrum ( $^1\text{H}$ - $^{13}\text{C}$  COSY) of p-bromophenyl-{4-(p-bromophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16a**)

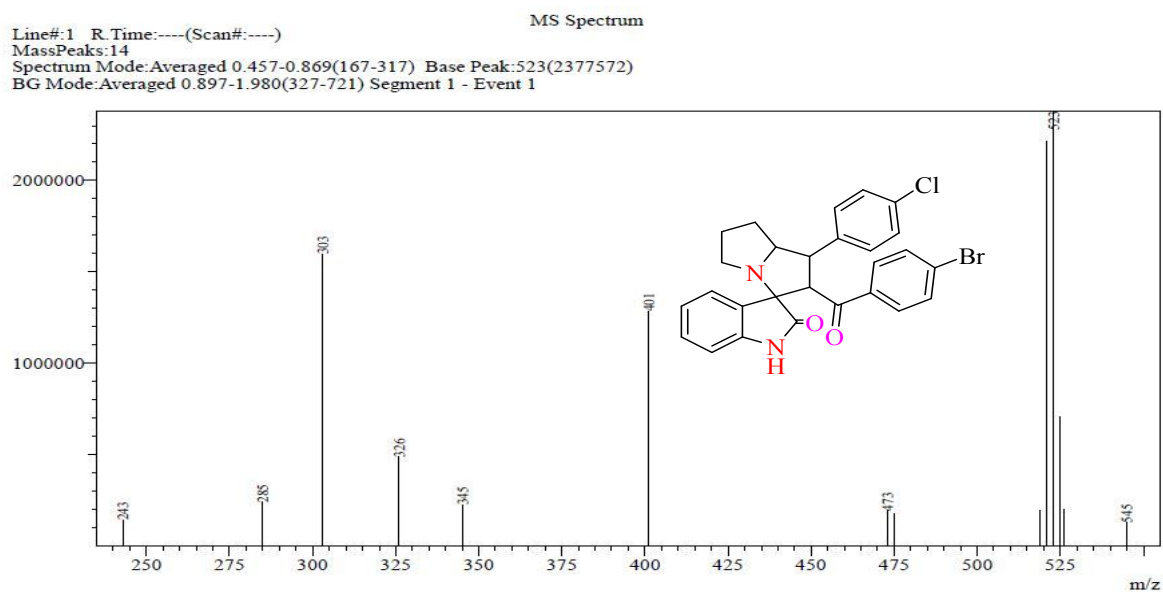


### 3. Mass spectra

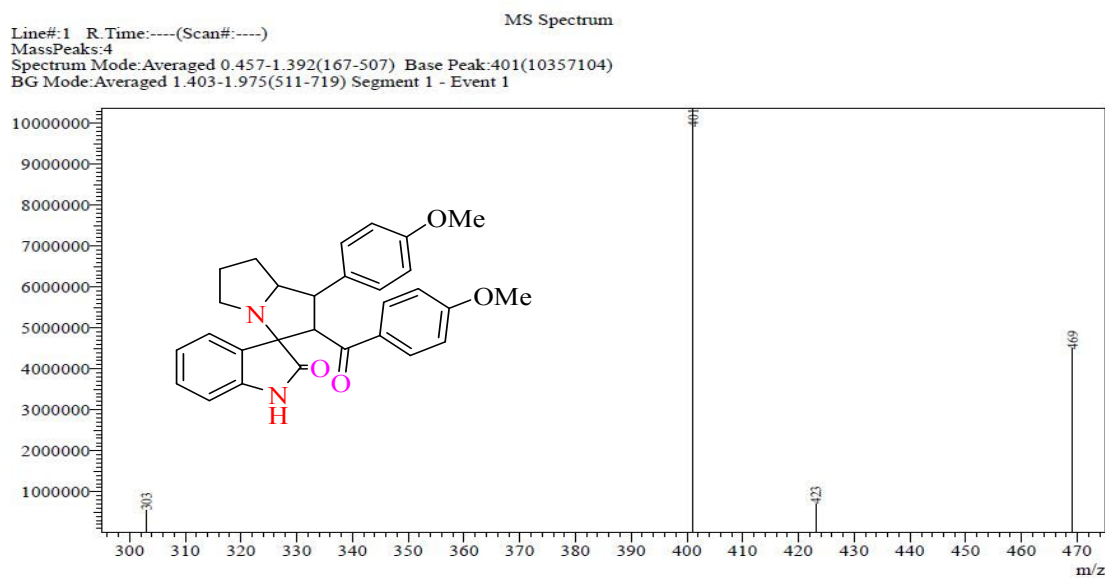
**Figure S-33.** Mass spectrum of p-bromophenyl-{1-(p-bromophenyl)-[3-spiro-(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl}methanone (**14a**)



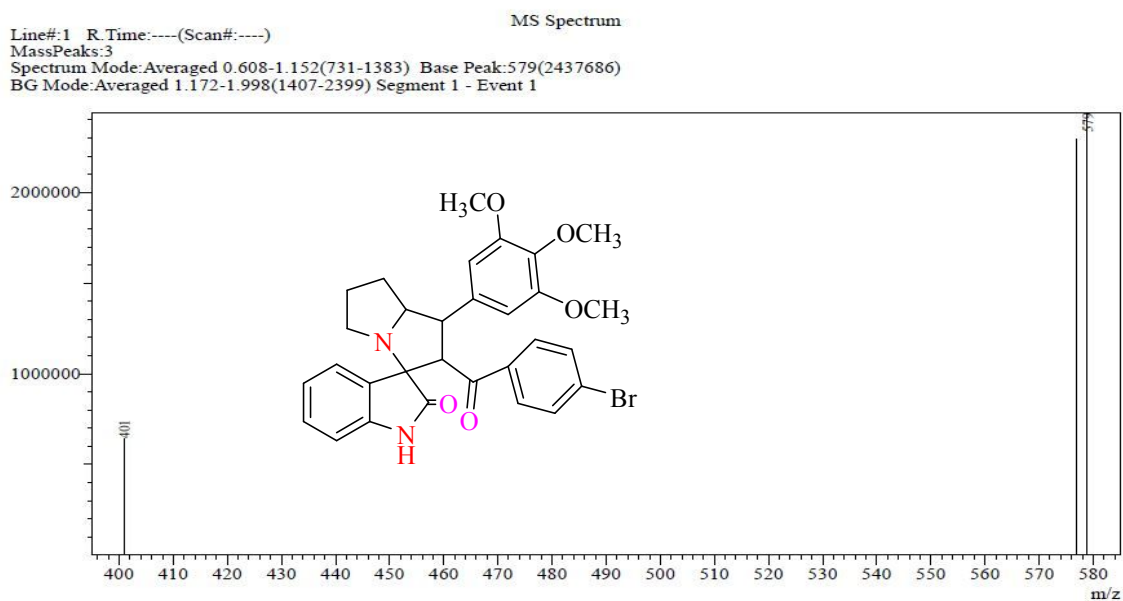
**Figure S34.** Mass spectrum of p-bromophenyl-{1-(p-chlorophenyl)-[3-spiro-(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl} methanone (**14b**)



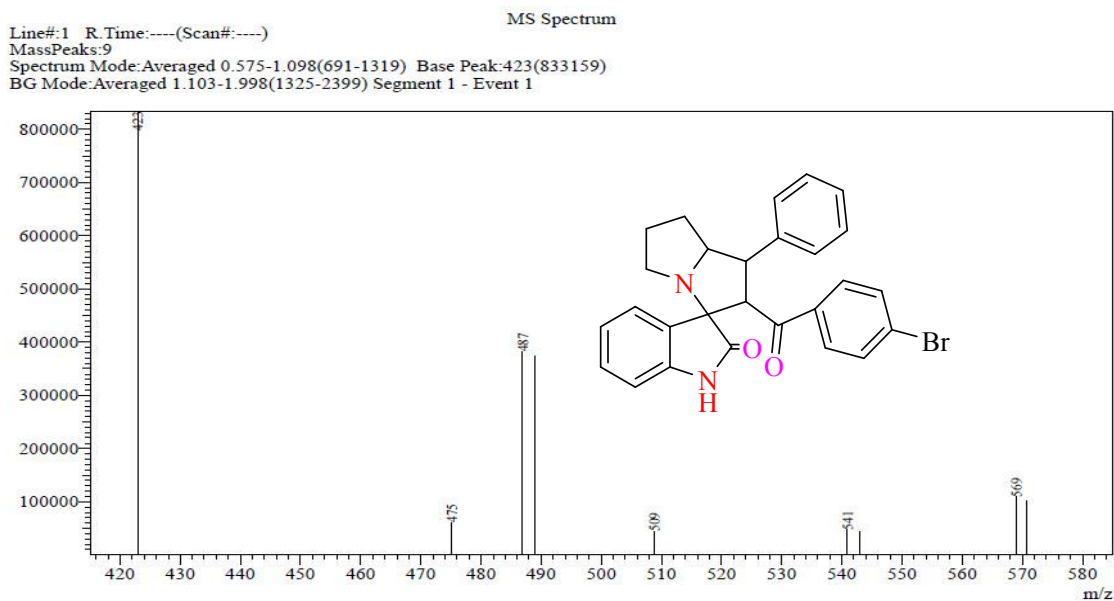
**Figure S35.** Mass spectrum of p-methoxyphenyl-{1-(p-methoxyphenyl)-[3-spiro-(indolin-2-one-3-yl)] hexahydro-1H-pyrrolizin-2-yl}methanone (**14c**)



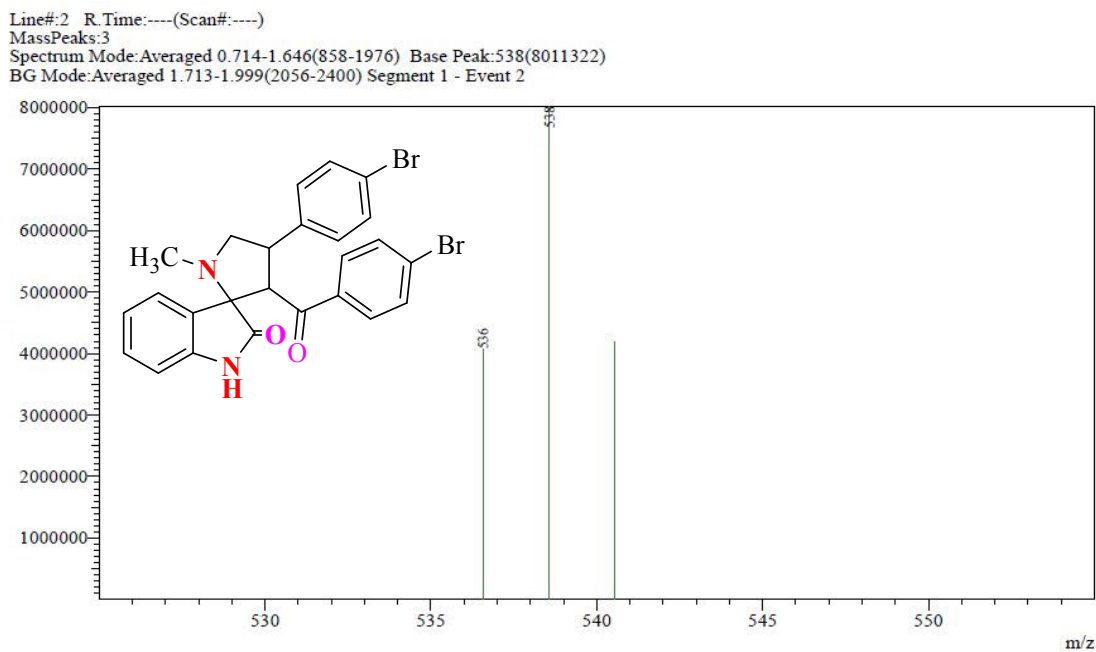
**Figure S36.** Mass spectrum of p-bromophenyl-{1-(3,4,5-trimethoxy-phenyl)-[3-spiro-(indolin-2-one-3-yl)] hexahydro-1H-pyrrolizin-2-yl} methanone (**14d**)



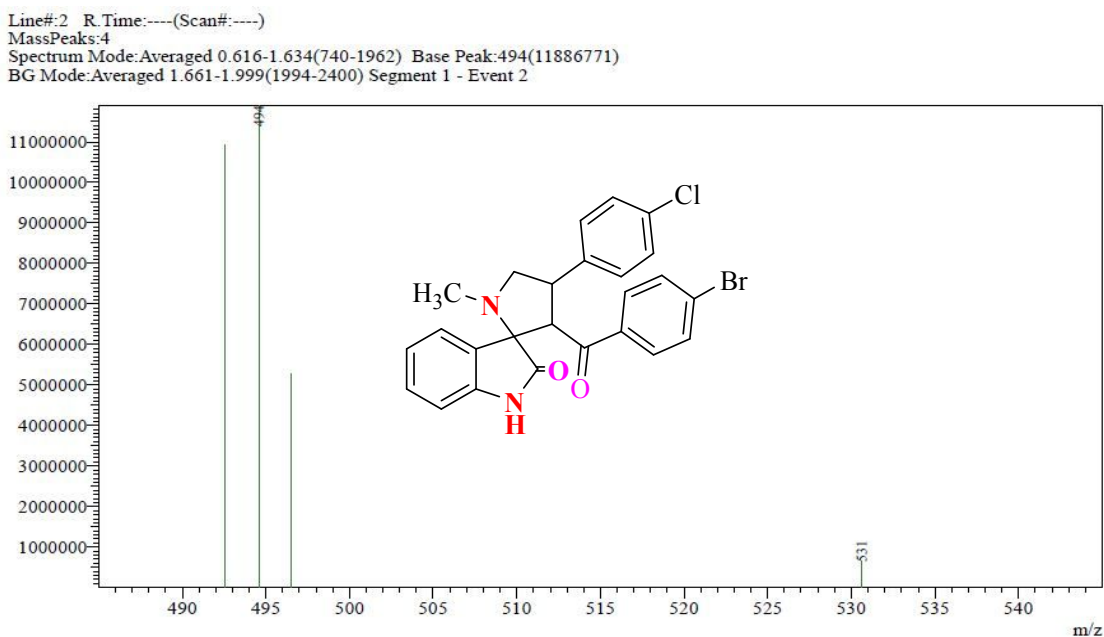
**Figure S37.** Mass spectrum of p-bromophenyl-{1-(phenyl)-[3-spiro-(indolin-2-one-3-yl)]hexahydro-1H-pyrrolizin-2-yl} methanone (**14e**)



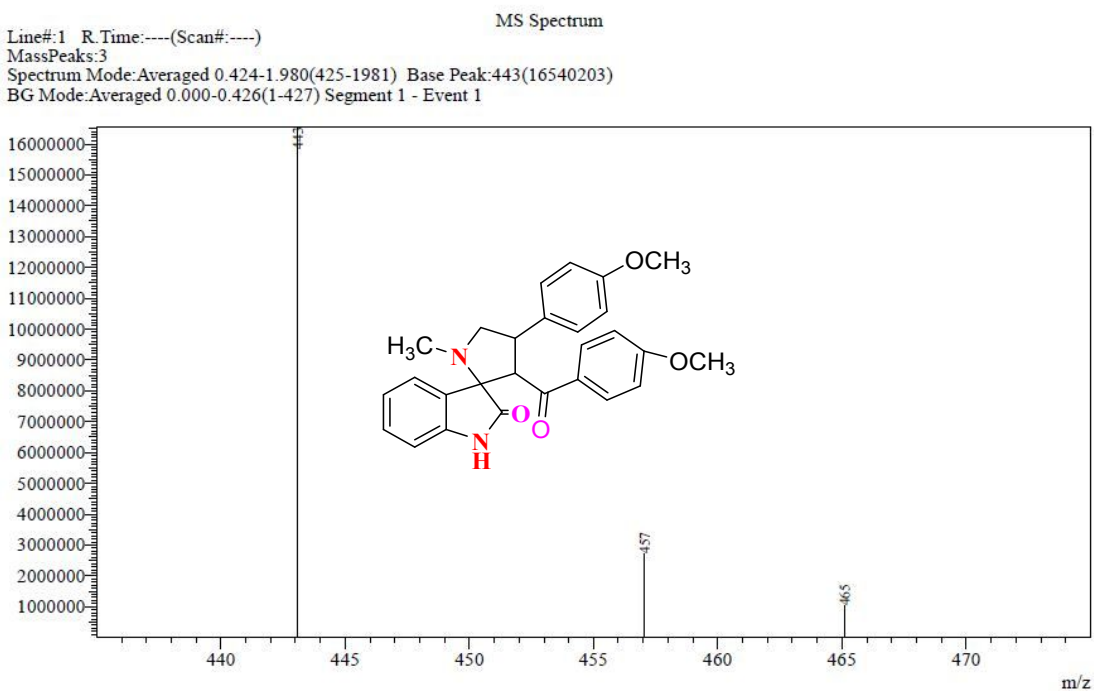
**Figure S38.** Mass spectrum of p-bromophenyl-{4-(p-bromophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16a**)



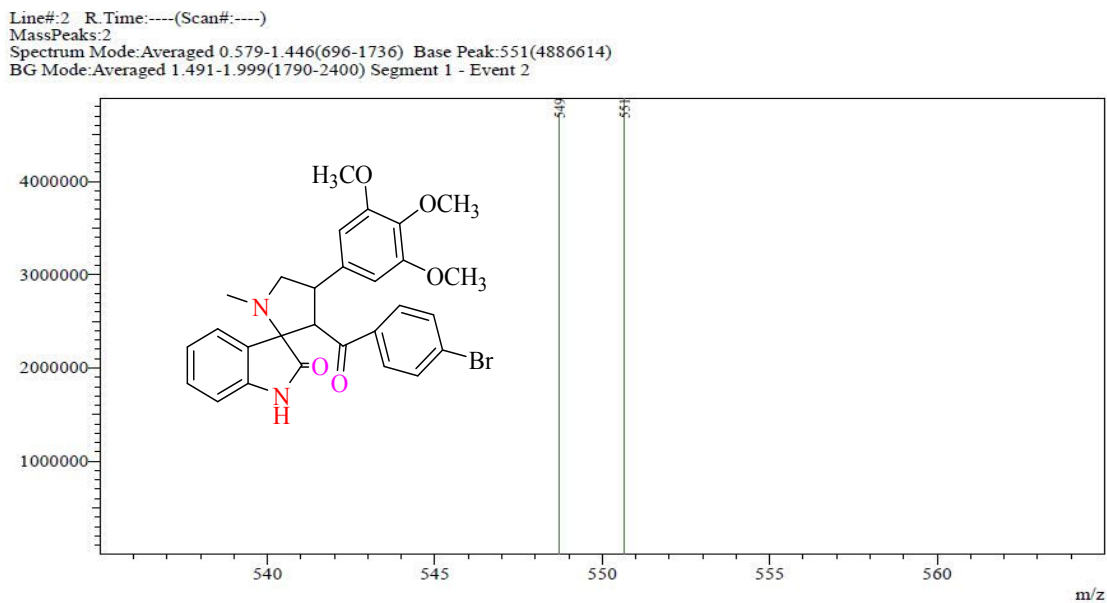
**Figure S39.** Mass spectrum of p-bromophenyl-{4-(p-chlorophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16b**)



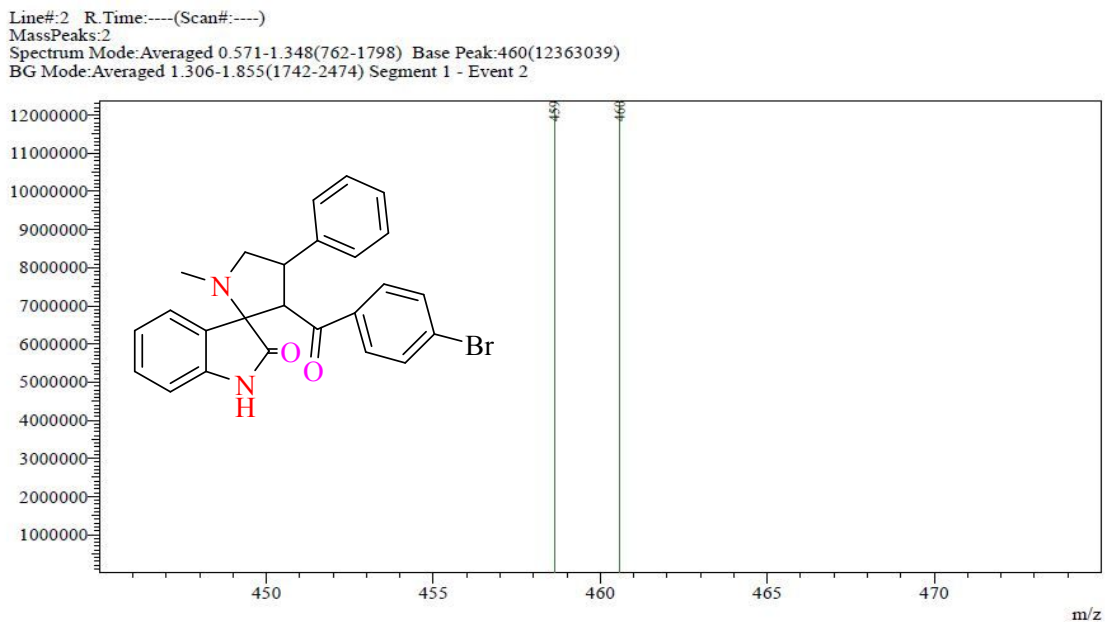
**Figure S40.** Mass spectrum of p-methoxyphenyl-{4-(p-methoxyphenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16c**)



**Figure S41.** Mass spectrum of p-bromo-phenyl-{4-(3,4,5-trimethoxyphenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16d**)



**Figure S42.** Mass spectrum of p-bromo-phenyl-{4-(phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16e**)

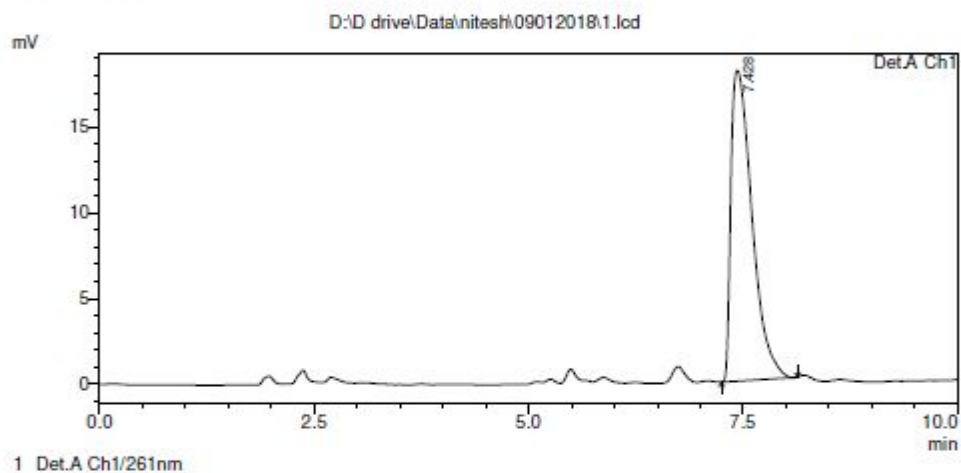


## 4. HPLC Chromatograms

**Figure S43.** Chromatogram of p-bromophenyl-{1-(p-bromophenyl)-[3-spiro-(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl} methanone (**14a**)

Acquired by : Admin  
Sample Name : 1  
Sample ID : 1  
Tray# : 2  
Vial # : 41  
Injection Volume : 10 uL  
Data File Name : 1.lcd  
Method File Name : 09112017\_ACN\_H2O\_70\_30\_UV.lcm  
Batch File Name : 09012018.lcb  
Report File Name : Default.lcr  
Data Acquired : 2/7/2018 8:49:44 PM  
Data Processed : 2/27/2018 11:16:35 AM

### <Chromatogram>



PeakTable

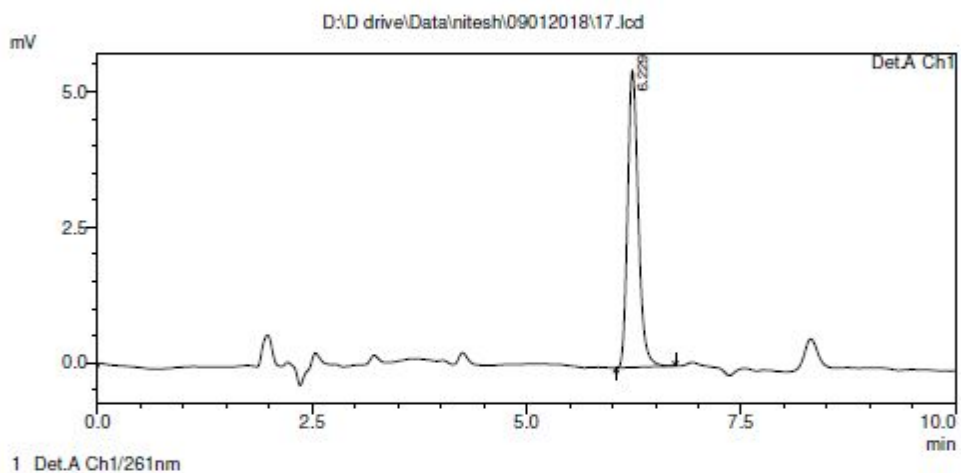
Peak#	Ret. Time	Area	Height	Area %	Height %
1	7.428	309820	18122	100.000	100.000
Total		309820	18122	100.000	100.000



**Figure S44.** Chromatogram of p-bromophenyl-{1-(p-chlorophenyl)-[3-spiro-(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl} methanone (**14b**)

Acquired by : Admin  
 Sample Name : 17  
 Sample ID : 17  
 Tray# : 2  
 Vial # : 57  
 Injection Volume : 10 uL  
 Data File Name : 17.lcd  
 Method File Name : 09112017\_ACN\_H2O\_70\_30\_UV.lcm  
 Batch File Name : 09012018.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 2/7/2018 11:40:52 PM  
 Data Processed : 2/7/2018 11:50:54 PM

<Chromatogram>



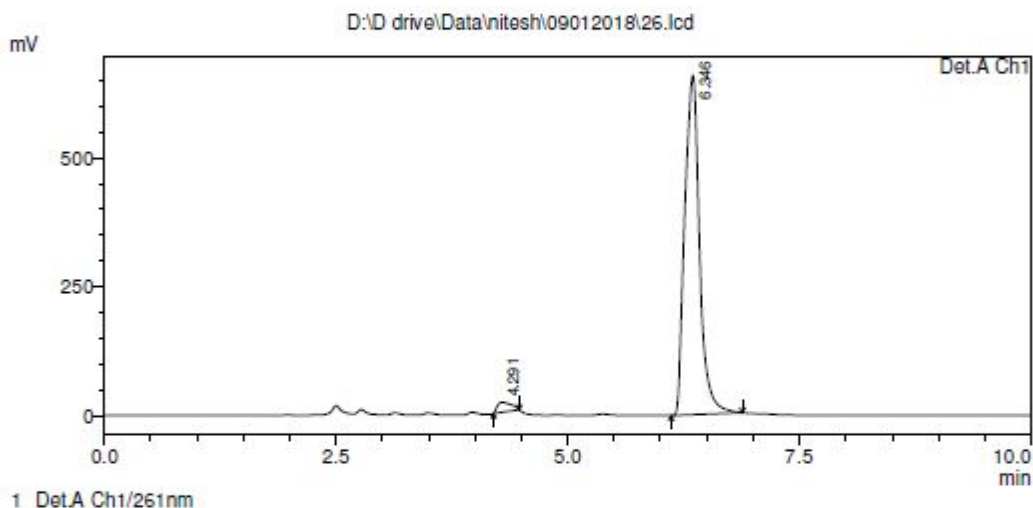
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.229	47681	5480	100.000	100.000
Total		47681	5480	100.000	100.000

**Figure S45.** Chromatogram of p-methoxy-phenyl-{1-(p-methoxyphenyl)-[3-spiro-(indolin-2-one-3-yl)] hexahydro-1H-pyrrolizin-2-yl} methanone (**14c**)

Acquired by : Admin  
 Sample Name : 25  
 Sample ID : 25  
 Tray# : 2  
 Vial # : 65  
 Injection Volume : 10 uL  
 Data File Name : 26.lcd  
 Method File Name : 09112017\_ACN\_H2O\_70\_30\_UV.lcm  
 Batch File Name : 09012018.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 2/8/2018 1:06:15 AM  
 Data Processed : 2/8/2018 1:16:17 AM

<Chromatogram>



Detector A Ch1 261nm

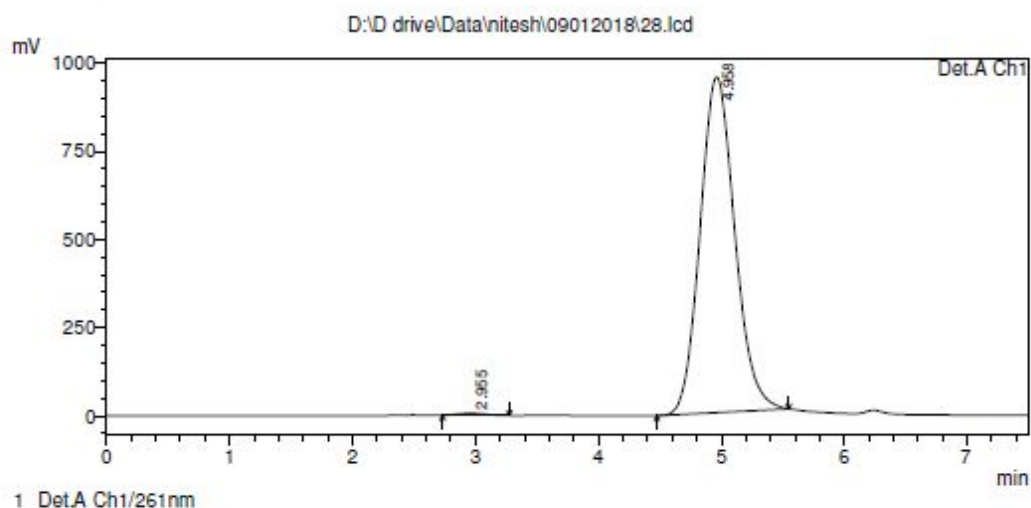
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.291	200171	19188	2.675	2.830
2	6.346	7282306	658838	97.325	97.170
Total		7482477	678026	100.000	100.000

**Figure S46.** Chromatogram of p-bromophenyl-{1-(3,4,5-trimethoxy-phenyl)-[3-spiro-(indolin-2-one-3-yl)] hexahydro-1H-pyrrolizin-2-yl} methanone (**14d**)

Acquired by : Admin  
 Sample Name : 27  
 Sample ID : 27  
 Tray# : 2  
 Vial # : 67  
 Injection Volume : 10 uL  
 Data File Name : 28.lcd  
 Method File Name : 09112017\_ACN\_H2O\_70\_30\_UV.lcm  
 Batch File Name : 09012018.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 2/8/2018 1:27:37 AM  
 Data Processed : 2/8/2018 1:37:40 AM

<Chromatogram>



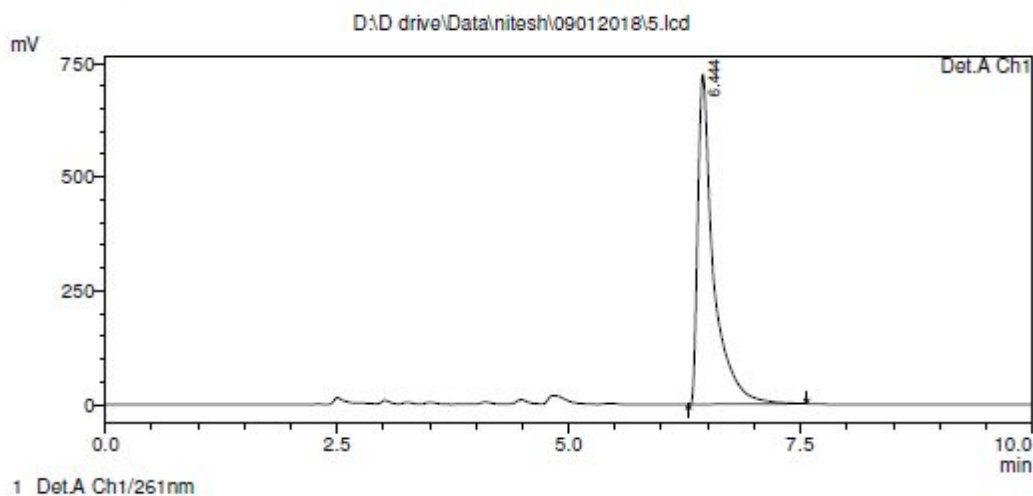
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.955	96068	6046	0.512	0.632
2	4.958	18653792	951266	99.488	99.368
Total		18749860	957312	100.000	100.000

**Figure S47.** Chromatogram of p-bromo-phenyl-{1-(phenyl)-[3-spiro-(indolin-2-one-3-yl)]hexahydro-1H-pyrrolizin-2-yl} methanone (**14e**)

Acquired by : Admin  
 Sample Name : 5  
 Sample ID : 5  
 Tray# : 2  
 Vial # : 45  
 Injection Volume : 10 uL  
 Data File Name : 5.lcd  
 Method File Name : 09112017\_ACN\_H2O\_70\_30\_UV.lcm  
 Batch File Name : 09012018.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 2/7/2018 9:32:30 PM  
 Data Processed : 2/7/2018 9:42:33 PM

<Chromatogram>



1 Det.A Ch1/261nm

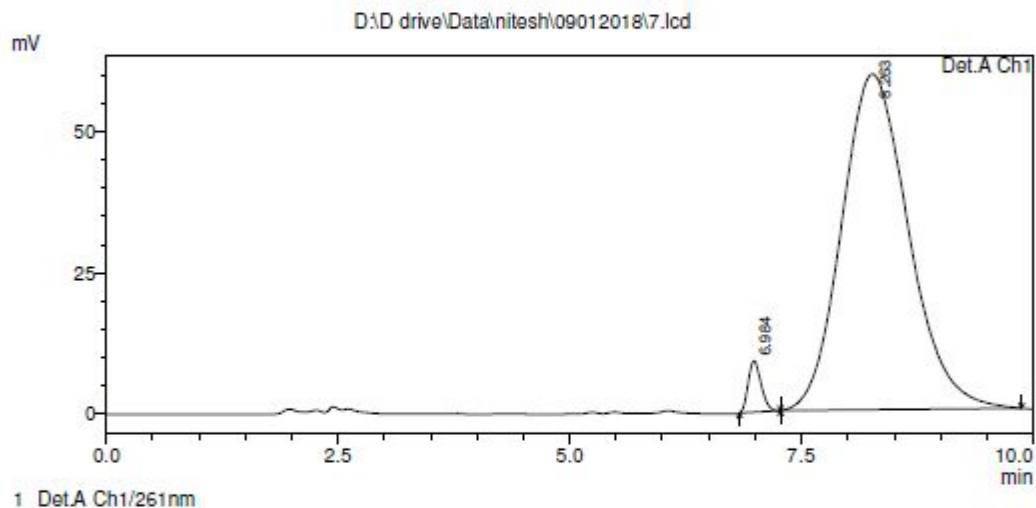
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.444	8547936	725848	100.000	100.000
Total		8547936	725848	100.000	100.000

**Figure S48.** Chromatogram of p-bromophenyl-{4-(p-bromophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16a**)

Acquired by : Admin  
 Sample Name : 7  
 Sample ID : 7  
 Tray# : 2  
 Vial # : 47  
 Injection Volume : 10 uL  
 Data File Name : 7.lcd  
 Method File Name : 09112017\_ACN\_H2O\_70\_30\_UV.lcm  
 Batch File Name : 09012018.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 2/7/2018 9:53:52 PM  
 Data Processed : 2/7/2018 10:03:55 PM

<Chromatogram>



Detector A Ch1 261nm

PeakTable

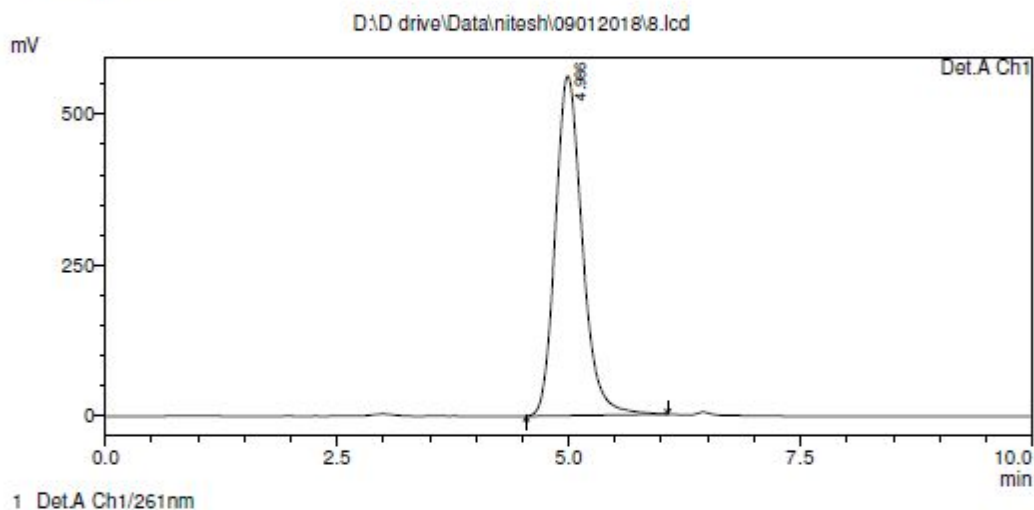
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.984	87976	9037	2.874	13.221
2	8.263	2973435	59318	97.126	86.779
Total		3061411	68355	100.000	100.000

**Figure S49.** Chromatogram of p-bromophenyl-{4-(p-chlorophenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16b**)

```

Acquired by      : Admin
Sample Name      : 8
Sample ID       : 8
Tray#          : 2
Vial #         : 48
Injection Volume : 10 uL
Data File Name  : 8.lcd
Method File Name : 09112017_ACN_H2O_70_30_UV.lcm
Batch File Name : 09012018.lcb
Report File Name : Default.lcr
Data Acquired   : 2/7/2018 10:04:34 PM
Data Processed  : 2/7/2018 10:14:37 PM
  
```

<Chromatogram>



PeakTable

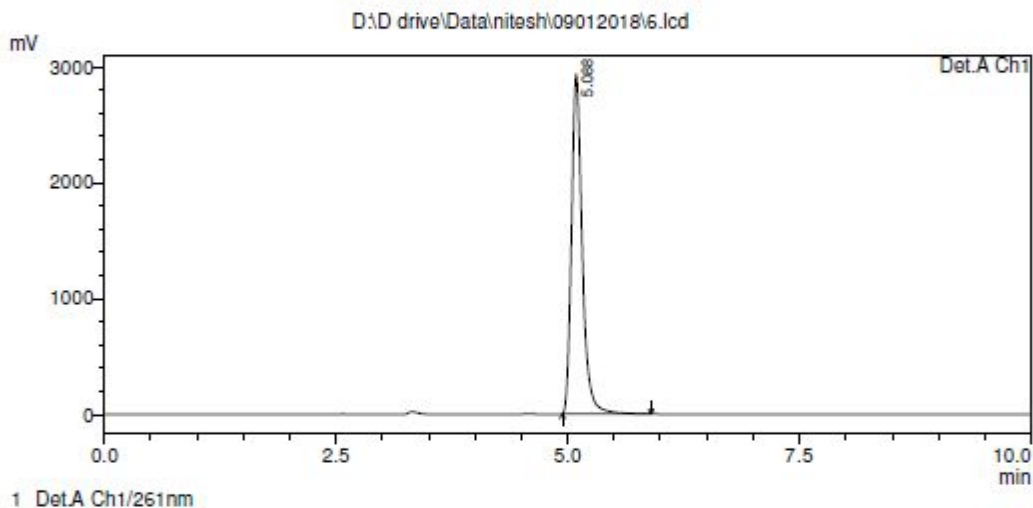
Detector A Ch1 261nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.986	11396633	562580	100.000	100.000
Total		11396633	562580	100.000	100.000

**Figure S50.** Chromatogram of p-methoxyphenyl-{4-(p-methoxy-phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16c**)

Acquired by : Admin  
 Sample Name : 6  
 Sample ID : 6  
 Tray# : 2  
 Vail # : 46  
 Injection Volume : 10 uL  
 Data File Name : 6.lcd  
 Method File Name : 09112017\_ACN\_H2O\_70\_30\_UV.lcm  
 Batch File Name : 09012018.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 2/7/2018 9:43:11 PM  
 Data Processed : 2/7/2018 9:53:14 PM

<Chromatogram>



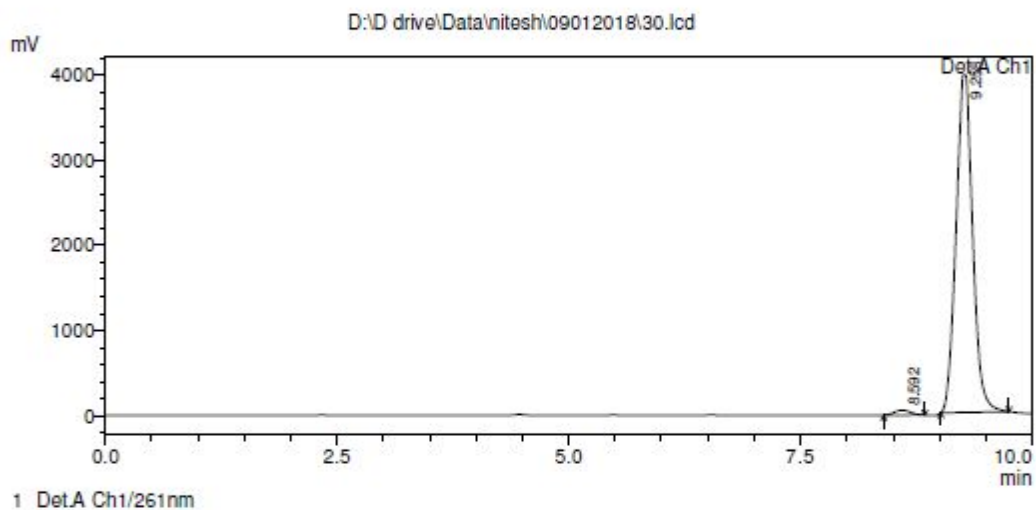
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.088	23598771	2932523	100.000	100.000
Total		23598771	2932523	100.000	100.000

**Figure S51.** Chromatogram of p-bromophenyl-{4-(3,4,5-trimethoxy-phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16d**)

Acquired by : Admin  
 Sample Name : 29  
 Sample ID : 29  
 Tray# : 2  
 Vial # : 69  
 Injection Volume : 10 uL  
 Data File Name : 30.lcd  
 Method File Name : 09112017\_ACN\_H2O\_70\_30\_UV.lcm  
 Batch File Name : 09012018.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 2/8/2018 1:49:02 AM  
 Data Processed : 2/8/2018 1:59:04 AM

<Chromatogram>



PeakTable

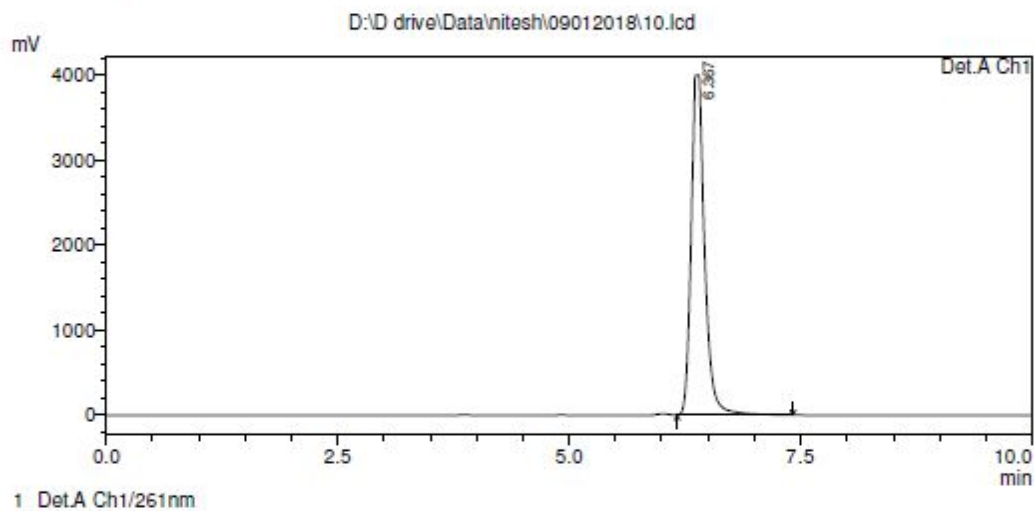
Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.592	710839	58650	1.414	1.458
2	9.258	49574317	3965219	98.586	98.542
Total		50285155	4023870	100.000	100.000



**Figure S52.** Chromatogram of p-bromophenyl-{4-(phenyl)-[2-spiro-(indolin-2-one-3-yl)]N-methyl-pyrrolidin-3-yl}-methanone (**16e**)

Acquired by : Admin  
 Sample Name : 10  
 Sample ID : 10  
 Tray# : 2  
 Vail # : 50  
 Injection Volume : 10 uL  
 Data File Name : 10.lcd  
 Method File Name : 09112017\_ACN\_H2O\_70\_30\_UV.lcm  
 Batch File Name : 09012018.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 2/7/2018 10:25:57 PM  
 Data Processed : 2/7/2018 10:35:59 PM

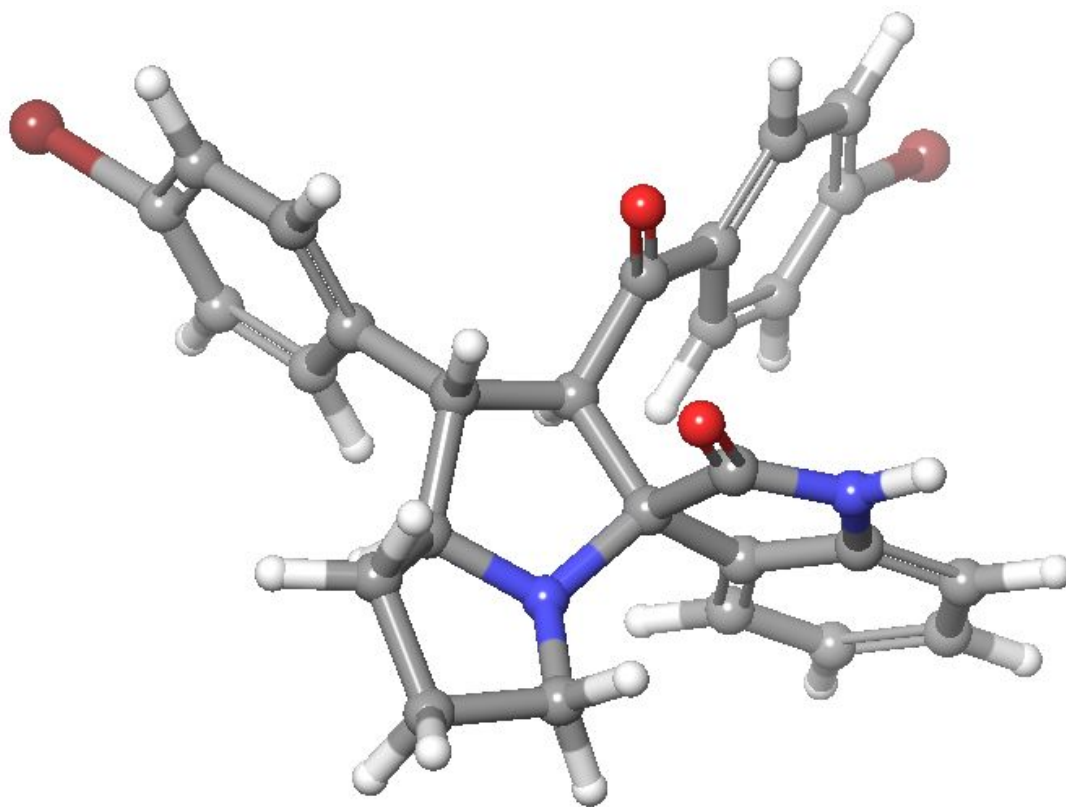
<Chromatogram>



PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.367	40497933	3997902	100.000	100.000
Total		40497933	3997902	100.000	100.000

**Figure S53.** 3D structure of p-bromo-phenyl-{1-(p-chlorophenyl)-[3-spiro-(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl} methanone (**14b**)



**Figure S54.** Swiss ADME prediction of p-bromo-phenyl-{1-(p-chlorophenyl)-[3-spiro-(indolin-2-one-3-yl)]-hexahydro-1H-pyrrolizin-2-yl} methanone (**14b**)

