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PAPER

Diastereoselective synthesis of spiro[cyclopropane-1,3'-indolin]-2'-ones through metal-free cyclopropanation using tosylhydrazone salts

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Transition metal-free diastereoselective cyclopropanation of 3-methyleneindolin-2-ones using tosylhydrazone salts as a safe alternative of diazo-compounds was achieved in high yields. All the synthesized compounds were evaluated for their biological activity against three different human cancer cell lines DU-145 (prostate cancer), Hela (cervical cancer) and A-549 (Lung cancer). Compound **3b** and **3i** exhibited promising anticancer activity (IC_{50} < 10 µM) against the studied cell lines.

Introduction

Indole is amongst the most prevalent scaffolds found in synthetic and natural products of biological and medicinal importance.[1] Therefore the development of efficient synthetic methods to prepare new types of indole molecules for screening in medicinal and pharmaceutical programmes is gaining enormous interest in both academia and industry. Among indole containing molecules, spiro-oxindoles have attracted much attention due to their interesting anticancer, antiviral, antimicrobial, anti-inflammatory and anti-HIV activities.[2] Spirotryptostatins **I**, Horsfiline **II**, Elacomine **III** and compounds of type **IV** have been recognised as potent anticancer agents (Figure 1).[3]

The cyclopropane unit is found as a part of the basic structural scaffold of many synthetic as well as natural products of biological interest.[4] Cyclopropane containing spiro-oxindoles **V** have been reported as potent HIV-1 non-nucleoside reverse transcriptase inhibitors whereas naturally occurring Hapalindolinone **VI** are reported as potent antagonists of vasopressin.[5] As a part of our ongoing interest towards stereoselective construction of new molecular libraries,[6] we were interested in synthesizing functionalised spiro[cyclopropane-1,3'-indolin]-2'-ones **VII**.

Due to their significant biological and pharmacological potential, numerous methods have been documented in the literature for the synthesis of spiro[cyclopropane-1,3'-indolin]-2'-ones. 3,3-*Di*-alkylation of 2-oxindoles with 1,2-dihalo alkanes is a popular strategy for the synthesis of spiroindolines, however it suffers inherently from the view-point of product diversity.[7] Corey-Chaykovsky cyclopropanation of 3-methyleneindolin-2-ones has been attempted by many researchers but it often suffers with the low yields of the products.[8] Recently, spiro[cyclopropane-1,3'-indolin]-2'-ones were synthesized by reacting pyridinium salts with 3-phenacylideneoxindoles under basic conditions.[9] Although this method provides highly diverse spirocyclic cyclopropanes, the competing formation of furan derivatives remains its major drawback.

Among the various methods of stereoselective cyclopropane construction, transition metal catalyzed cyclopropanation of alkenes using diazo-compounds is particularly important.[10] The reaction proceeds through a metal-carbene intermediate derived from catalytic decomposition of diazo-compounds and the selectivity depends largely on the catalyst used.[10-11] Additionally, these methods have the limitation of using explosive diazo compounds. Nevertheless, dirhodium tetraacetate catalyzed cyclopropanations using diazo-compounds have been attempted to synthesize spiro[cyclopropane-1,3'-indolin]-2'-ones by many researchers.[5b,12] However, these methods also suffer from the disadvantages of low yields, limited diversification points in the product and environmental concern.

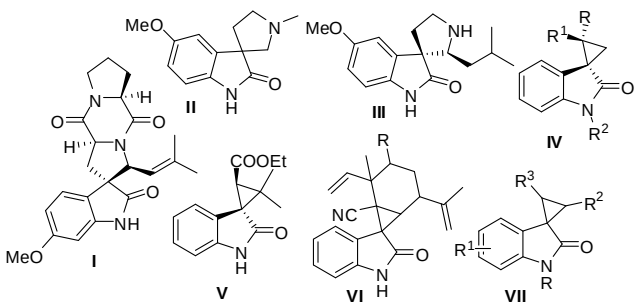


Figure 1. Chemical structures of some biologically important spiro-oxindole derivatives

To address the safety and instability concerns of the diazo-compounds, their in-situ generation and subsequent utilization have been preferred by many researchers.[13] Recently, a metal-free cyclopropanation of 3-methyleneindolin-2-ones via a [3+2] cycloaddition/ring contraction sequence using in situ generated 2,2,2-trifluorodiazoethane was reported.[14] Considering the merits and demerits of all these reports, it is obvious that the development of a promising strategy for the synthesis of diverse spiro[cyclopropane-1,3'-indolin]-2'-ones is needed. Presented in this letter are the results of in-situ generation of diazo-compounds from corresponding tosylhydrazone salts and their subsequent utilization for metal-free diastereoselective cyclopropanation of

3-methyleneindolin-2-ones (Figure 2).

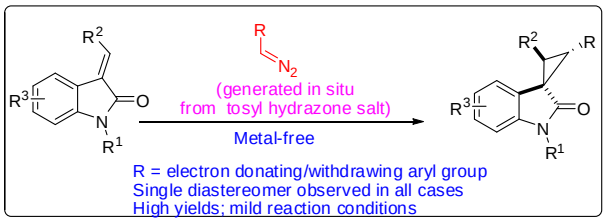
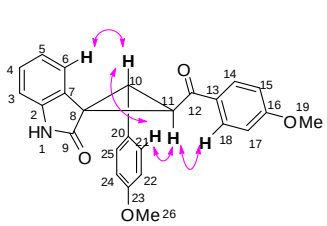


Figure 2. Synthesis of spiro[cyclopropane-1,3'-indolin]-2'-ones through diastereoselective cyclopropanation using in situ generated diazo-compounds

Results and discussion

At the onset we sought to identify a way to access the diazo compounds of interest from safer and relatively stable starting materials under mild conditions. Of the various available methods for their generation, we were particularly interested in the Bamford–Stevens reaction because of the ease of preparation of tosylhydrazone salt and generation of corresponding diazo-compound under mild conditions.[13c, 15] Thus, cyclopropanation of 3-methyleneindolin-2-one **1a** was attempted with tosylhydrazone salt **2a** under various conditions (Table 1). Among the several solvents attempted, a mixture of THF-acetonitrile (4:1, v/v) was found the best for the cyclopropanation of **1a** (Table 1, entry 5). However, a better yield of **3a** was realized using 10 mol% of benzyltriethylammonium chloride (BTEAC) as an additive to the reaction (Table 1, entry 6). BTEAC improves the reaction possibly by increasing the solubility of tosylhydrazone salt **2a** in the reaction medium. The yield of **3a** was further improved by taking tosylhydrazone salt in an excess amount (Table 1, entry 7 & 8). The reaction rate was accelerated at elevated temperature and 50 ^{0}C found the optimal temperature (Table 1, entry 9). However further increasing the reaction temperature led to a decreased yield of the product (Table 1, entry 10). It should be noted that under all these conditions, the reaction yielded a single diastereomeric product **3a** (determined by ^{1}H NMR spectra of the crude reaction product).

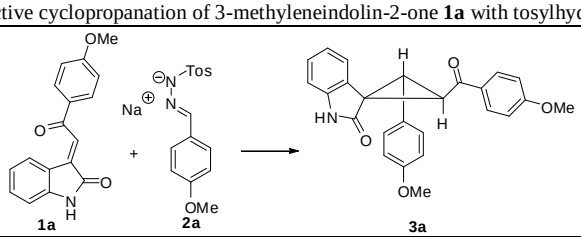


Chemical shift (ppm)
H1 = 8.15 (s)
H3 = 6.82 (d, *J* = 7.6 Hz)
H4 = 7.14 (dt, *J* = 1.0, 7.6 Hz)
H5 = 6.95 (dt , *J* = 0.9, 7.6 Hz)
H6 = 7.23 (d, *J* = 7.6 Hz)
H10 = 4.08 (d, *J* = 8.4 Hz)
H11 = 4.20 (d, *J* = 8.4 Hz)
H14, H18 = 7.90 (d, *J* = 8.9 Hz)
H15, H17 = 6.76 (d, *J* = 9.0 Hz)
H 19 = 3.74 (s)
H21, H25 = 7.26 (d, *J* = 7.8 Hz)
H22, H24 = 6.85 (d, *J* = 7.8 Hz)
H26 = 3.76 (s)

Figure 3. Characteristic NOE's of compound **3a** and chemical shifts of H atoms

The relative stereochemistry of the product **3a** was assigned based on NOESY correlations as pictorially represented in Figure 3. The NOE cross peak between one of the cyclopropyl H-atom at 4.20 ppm (H11) and *ortho*-H atoms of 4-methoxybenzoyl residue at 7.90 ppm (H14, H18) helped to identify the cyclopropyl ring H-atoms. The *ortho*-H atoms of 4-methoxyphenyl residue (H21, H25) at 7.26 ppm showed NOE cross peaks with the cyclopropyl ring H-atoms at 4.08 ppm (H10) and 4.20 ppm (H11). One of the aromatic-H atom from isatin residue (H6) at 7.23 ppm showed NOE cross peak with the cyclopropyl H10-atom at 4.08 ppm. It indicated that the orientation of the isatin aryl residue is *syn* to the cyclopropyl H-atom (H10) and *anti* to the 4-methoxyphenyl residue. The observation of NOE cross peaks H10/H6 and H21-/H11 along with $^3J_{H10-H11}$ = 8.4 Hz indicated *trans* orientation of H10 and H11. Thus, the structure of **3a** was deduced where the indoline carbonyl is pointing towards *p*-methoxyphenyl group attached on C10 and the phenyl residue of indoline is pointing towards *p*-methoxybenzoyl group on C11 as depicted in Figure 3.

Table 1. Optimization of the diastereoselective cyclopropanation of 3-methyleneindolin-2-one **1a** with tosylhydrazone salt **2a** [a]



Entry	Stoichiometry (**1a**:**2a**)	Solvent/additive	Temp. (^{0}C)	Time (h)	Yield (%)[b]
1	1:1	MeOH	30	24	25
2	1:1	CH_3CN	30	24	40
3	1:1	THF	30	24	30
4	1:1	DMF	30	24	19
5	1:1	THF-CH_3CN (4:1, v/v)	30	24	50
6	1:1	THF-CH_3CN (4:1, v/v) -BTEAC	30	24	70
7	1:1.2	THF-CH_3CN (4:1, v/v) -BTEAC	30	24	85
8	1:1.5	THF-CH_3CN (4:1, v/v) -BTEAC	30	24	86
9	1:1.2	THF-CH_3CN (4:1, v/v) -BTEAC	50	4	86
10	1:1.2	THF-CH_3CN (4:1, v/v) -BTEAC	70	4	75

[a] Reaction condition: **1a** (0.5 mmol), **2a** (stoichiometric or as mentioned above), solvent (2 ml), benzyltriethylammonium chloride (BTEAC) 10 mol%, stir. [b] Isolated yields which are not optimized.

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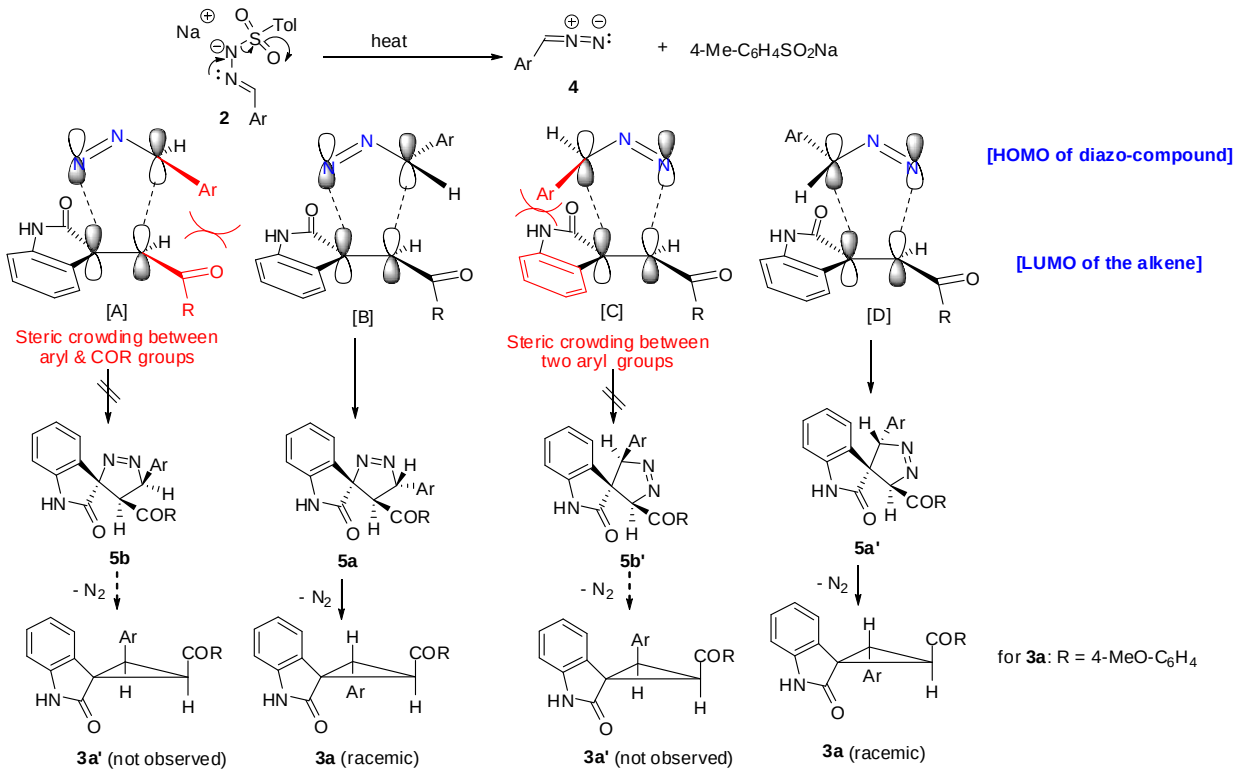
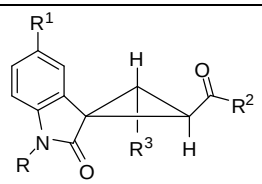


Figure 4. A plausible mechanism for diastereoselective formation of **3a** based on [3+2] dipolar cycloaddition reaction/ring contraction sequence

Table 2. Scope of the stereoselective cyclopropanation of 3-methyleneindolin-2-ones **1** with tosylhydrazone salt of benzaldehyde **2** [a]



3a-3p

Entry	R	R^1	R^2	R^3	Reaction time (h)	Product (Yield %)[b]
1	H	H	4-MeO-C_6H_4	4-MeO-C_6H_4	4	**3a** (86)
2	H	H	C_6H_5	4-MeO-C_6H_4	4	**3b** (87)
3	H	NO_2	OEt	4-MeO-C_6H_4	4	**3c** (75)
4	H	Br	4-Me-C_6H_4	C_6H_5	12	**3d** (85)
5	H	H	4-MeO-C_6H_4	C_6H_5	12	**3e** (85)
6	H	F	OEt	C_6H_5	12	**3f** (78)
7	H	H	4-MeO-C_6H_4	4-NO_2-C_6H_4	12	**3g** (81)
8	H	Cl	2-Naphthyl	4-NO_2-C_6H_4	12	**3h** (86)
9	H	Br	4-MeO-C_6H_4	4-$NO_2C_6H_4$	12	**3i** (88)
10	H	Br	4-Me-C_6H_4	4-$NO_2C_6H_4$	12	**3j** (81)
11	H	Br	4-Cl-C_6H_4	4-CN-C_6H_4	12	**3k** (81)
12	H	Br	4-MeO-C_6H_4	4-CN-C_6H_4	12	**3l** (84)
13	H	Br	4-Me-C_6H_4	4-CN-C_6H_4	12	**3m** (85)
14	H	H	4-MeO-C_6H_4	4-CN-C_6H_4	12	**3n** (80)
15	Me	H	4-Br-C_6H_4	4-MeO-C_6H_4	4	**3o** (82)
16	H	Cl	4-NO_2-C_6H_4	4-MeO-C_6H_4	4	**3p** (79)

[a] Reaction condition: **1** (0.5 mmol), **2** (0.6 mmol), THF-Acetonitrile (2 ml, 4:1, v/v), benzyltriethylammonium chloride (BTEAC) 10 mol%, 50 ^{0}C, stir.
[b] Isolated yields which are not optimized.

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Non-metal catalysed cyclopropanations of alkenes using diazo-compounds have been proposed to proceed through diastereoselective pyrazoline formation and subsequent loss of nitrogen with the retention of configuration.[13c,14,16] Therefore diastereoslective formation of **3a** can be explained by a plausible mechanism involving a HOMO (of aryl diazomethane)-LUMO (of alkene) controlled 1,3-dipolar cycloaddition reaction and subsequent nitrogen loss with the retention of configuration as depicted in Figure 4. The initial five-membered cycloadduct **5a** (or **5a'**) was never isolated in our experiments even when the reaction was performed at 30 ^{0}C. The alternative *cis*-diastereomer **3a'** was not observed plausibly due to steric crowding between aryl and aroyl groups (transition state A), and between two aromatic rings (transition state C) as depicted in Figure 4. Moreover, since the alkene **1a** can equally approach both faces of the aryl diazomethane **4**, the product **3a** must be a racemic mixture and indeed it was.

Having optimized reaction conditions for cyclopropanation at hand, a series of 3-methyleneindolin-2-ones were also subjected to cyclopropanation (Table 2). The reaction worked well with both electron donating and electron withdrawing aromatic aldehydes – tosylhydrazone salts leading to high yields of spiro[cyclopropane-1-3'-indolin]-2'-ones **3a-o** (75-88%). The cyclopropanation of 3-methyleneindolin-2-ones was faster with electron donating aromatic aldehyde-tosylhydrazone salts (Table 2; entry 1-3 & 15) compared to those with electron withdrawing aromatic aldehyde-tosylhydrazone salts. The yields were marginally affected by the substituent present in the oxindole or aryl part of alkene **1**. It is noteworthy that single diastereomeric products were obtained in all the reactions performed. The stereochemical assignment of the cyclopropane system was proved unambiguously by single crystal X-ray analysis of a typical compound **3g** (Figure 5).

All the synthesized compounds **(3a-o)** were evaluated for their anticancer activity against three different human cancer cell lines Hela (cervical cancer), A-549 (Lung cancer), DU-145 (prostate cancer). The MTT assay[17] was used in anticancer activity study and the values obtained were compared to the standard drug doxorubicin as shown in Table 3. Cells were grown in tissue culture flasks in DMEM or MEM supplemented with 10% fetal bovine serum with 1X stabilized antibiotic-antimycotic solution in a CO_2 incubator at 37 ^{0}C with 5% CO_2 and 90% relative humidity. The cells at sub confluent stage were harvested with 1X porcine pancreatic trypsin (Hi media) and seeded in required density in tissue culture plates for the assay. Cell viability was determined by MTT assay. The IC_{50} value of each compound was calculated by the excel curve software. Two compounds of the series (**3b** and **3i**) exhibited promising anticancer activity (IC_{50} < 10 μM).

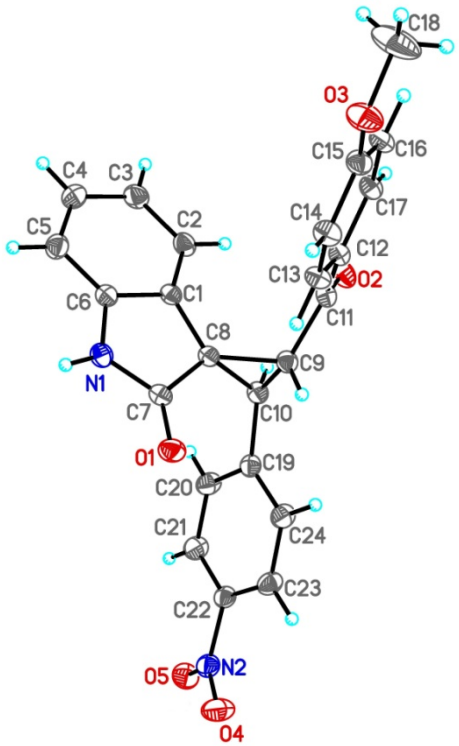

Figure 5. Stereochemical assignment of the compound **3g** by single crystal X-ray analysis (CCDC ref. no. 1016218)

Table 3. IC_{50} values[a] (in μM) for compounds **3a-o** in human cancer cell lines

Entry	Compounds	Hela[b]	A549[c]	DU-145[d]
1	**3a**	18.62	25.11	10.71
2	**3b**	**9.332**	20.12	**8.709**
3	**3c**	52.44	69.18	26.86
4	**3d**	12.58	30.67	15.84
5	**3e**	25.11	52.48	20.89
6	**3f**	20.50	16.48	14.79
7	**3g**	66.86	83.17	57.54
8	**3h**	19.65	29.31	17.78
9	**3i**	**9.54**	**9.332**	**4.897**
10	**3j**	16.59	19.26	14.79
11	**3k**	36.92	44.42	22.20
12	**3l**	69.29	87.09	63.77
13	**3m**	15.84	25.11	13.81
14	**3n**	19.95	25.86	16.36
15	**3o**	45.70	77.52	31.13
16	Doxorubicin	1.77	2.570	1.318

[a] 50% Inhibitory concentration and the values are average of three individual experiments after 48 h of drug treatment.
[b] Cervical cancer; [c] Lung cancer; [d] Prostate cancer.

Conclusions

In conclusion, we have developed a metal-free cyclopropanation of 3-methyleneindolin-2-ones using tosylhydrazone salts as a safe and stable precursor of diazo-compounds. The protocol provides an elegant way to access a series of diastereomerically pure spiro[cyclopropane-1,3'-indolin]-2'-ones. All the synthesized compounds were screened against three different human cancer cell lines and compound **3b** as well as **3i** showed promising anticancer activity.

Experimental

General information

All the reagents and chemicals were purchased from commercial sources and used without further any purification. Anhydrous solvents were purchased from Sigma-Aldrich Company and used without further any purification. Common laboratory solvents (LR grade) were purchased from domestic suppliers. Analytical thin layer chromatography was performed with E. Merck silica gel 60 F aluminium plates and visualized under UV 254 nm radiation. NMR spectra were measured with Brucker 300, 400, 500, and 600 MHz instruments. Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS. Coupling constants (*J*) are in hertz (Hz) and are unadjusted; therefore, due to limits in resolution, in some cases there are small differences (<1 Hz) in the measured *J* value of the same coupling constant determined from different signals. Splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; tt, triplet of triplets; m, multiplet; br, broad. IR spectra were recorded on a Perkin–Elmer FT-IR RXI spectrophotometer and values reported in cm^{-1}. ESI-MS spectra were obtained on a LCQ Advantage Ion trap mass spectrometer (Finnigan thermo fischer scientific) and High-resolution mass spectra (ESI-HRMS) were recorded on Agilent 6520 ESI-QTOP mass spectrometer. Melting points were determined on a Kofler block and are uncorrected. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and ESI-MS/HRMS analysis. The chromatographic solvents are mentioned as v/v ratios. Substituted 3-methyleneindolin-2-ones[18] and tosyl hydrazone sodium salts[19] were synthesized by literature procedures.

Typical experimental procedure of the catalyst-free cyclopropanation of substituted 3-methyleneindolin-2-ones with tosyl hydrazone salts

In a 25 ml round bottom flask, substituted 3-methyleneindolin-2-ones (0.5 mmol), tosyl hydrazone salt (0.6 mmol), 2 ml of THF-acetonitrile (4:1), and benzyltriethyl ammonium chloride (11.5 mg, 0.05 mmol) were taken and the reaction mixture was heated at 50 ^{0}C until complete consumption of the substrate. Next the reaction mixture was evaporated to yield a crude reaction product which was further purified by column chromatography.

2-(4-methoxybenzoyl)-3-(4-methoxyphenyl)spiro[cyclopropane-1,3'-indolin]-2'-one 3a

172 mg (86%) of **3a** was obtained as a pale yellow solid, R_f = 0.37 (ethyl acetate/*n*-hexane, 1:1), Mp. 216-217 ^{0}C; IR (KBr, cm^{-1}): 3229, 1709, 1676, 1659, 1598, 1572, 1517, 1471, 1259, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.08 (d, *J* = 8.4 Hz, 1H, CH), 4.20 (d, *J* = 8.4 Hz, 1H, CH), 6.76 (d, *J* = 9.0 Hz, 2H, ArH), 6.82 (d, *J* = 7.6 Hz, 1H, ArH), 6.85 (d, *J* = 7.8 Hz, 2H, ArH), 6.95 (dt, *J* = 0.9, 7.6 Hz, 1H, ArH), 7.14 (dt, *J* = 1.0, 7.6 Hz, 1H, ArH), 7.23 (d, 1H, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 2H, ArH), 7.90 (d, *J* = 8.9 Hz, 2H, ArH), 8.15 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 39.2, 41.5, 55.1, 55.4, 109.7, 113.5, 113.8, 122.1, 122.2, 125.3, 126.7, 127.3, 129.9, 130.3, 130.6, 140.8, 158.8, 163.8, 174.2, 191.1; HRMS (ESI, Orbitrap): calcd for $C_{24}H_{22}NO_4$ $[M+H]^+$ 400.15488; found 400.15392.

2-benzoyl-3-(4-methoxyphenyl)spiro[cyclopropane-1,3'-indolin]-2'-one 3b

161 mg (87%) of **3b** was obtained as a yellow solid, R_f = 0.50 (ethyl acetate/*n*-hexane, 1:1), Mp. 99-100 ^{0}C; IR (KBr, cm^{-1}): 3251, 1712, 1674, 1615, 1516, 1469, 1248, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.78 (s, 3H, OCH_3), 4.07 (d, *J* = 8.3 Hz, 1H, CH), 4.25 (d, *J* = 8.3 Hz, 1H, CH), 6.80-6.89 (m, 3H, ArH), 6.95 (t, *J* = 7.6 Hz, 1H, ArH), 7.13 (t, *J* = 7.6 Hz, 1H, ArH), 7.23-7.30 (m, 3H, ArH), 7.39 (t, *J* = 7.6 Hz, 2H, ArH), 7.52 (t, *J* = 7.3 Hz, 1H, ArH), 7.86 (bs, 1H, NH), 7.95 (d, J = 7.9 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 39.4, 41.4, 41.8, 55.1, 109.7, 113.5, 122.2, 122.2, 125.1, 126.5, 127.4, 128.4, 128.7, 130.2, 133.6, 136.9, 140.8, 158.8, 173.9, 192.9; HRMS (ESI, Orbitrap): calcd for $C_{24}H_{20}NO_3$ $[M+H]^+$ 370.14432; found 370.14588.

ethyl 3-(4-methoxyphenyl)-5'-nitro-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carboxylate 3c

143 mg (75%) of **3c** was obtained as a yellow solid, R_f = 0.45 (ethyl acetate/*n*-hexane, 1:1), Mp. 208-209 ^{0}C; IR (KBr, cm^{-1}): 3277, 1745, 1701, 1624, 1514, 1478, 1340, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (t, *J* = 7.2 Hz, 3H, CH_3), 3.35 (d, *J* = 8.3 Hz, 1H, CH), 3.74 (d, *J* = 8.3 Hz, 1H, CH), 4.17-4.30 (m, 2H, diastereotopic OCH_2), 6.70 (dd, *J* = 4.3 & 8.5 Hz, 1H, ArH), 6.92 (dt, *J* = 2.4 & 8.9 Hz, 1H, ArH), 7.19-7.36 (m, 5H, ArH), 8.50 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$ + $DMSOd_6$, 75 MHz) δ: 13.6, 37.2, 39.2, 40.1, 54. 7, 61.3, 109.0, 113.0, 118.0, 123.5, 123.9, 127.0, 129.7, 142.0, 148.0, 158.5, 167.6, 172.8; HRMS (ESI, Orbitrap): calcd for $C_{20}H_{19}N_2O_6$ $[M+H]^+$ 383.12431; found 383.12576.

5'-bromo-2-(4-methylbenzoyl)-3-phenylspiro[cyclopropane-1,3'-indolin]-2'-one 3d

184 mg (85%) of **3d** was obtained as a yellow solid, R_f = 0.50 (ethyl acetate/*n*-hexane, 1:1), Mp. 216-218 ^{0}C; IR (KBr, cm^{-1}): 3188, 3059, 2953, 1706, 1662, 1607, 1475, 1454, 1320, 1260, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.39 (s, 3H, CH_3), 4.10 (d, *J* = 8.4 Hz, 1H, CH), 4.28 (d, *J* = 8.4 Hz, 1H, CH), 6.70 (d, *J* = 8.2 Hz, 1H, ArH), 7.22 (d, *J* = 8.1 Hz, 2H, ArH), 7.27-7.35 (m, 6H, ArH), 7.44 (d, *J* = 1.5 Hz, 1H, ArH), 7.86 (bs, 1H, NH), 7.88 (d, *J* = 8.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 20.9, 39.2, 40.2, 40.9, 110.6, 113.2, 124.1, 126.6, 127.3, 127.7, 127.9, 128.4, 128.7, 129.4, 132.5, 133.7, 140.6, 144.0, 172.0, 191.6; HRMS (ESI, Orbitrap): calcd for $C_{24}H_{19}NO_2{}^{79}Br$ $[M+H]^+$ 432.05992; found 432.06163.

2-(4-methoxybenzoyl)-3-phenylspiro[cyclopropane-1,3'-indolin]-2'-one 3e

157 mg (85%) of **3e** was obtained as a pale yellow solid, R_f = 0.40 (ethyl acetate/*n*-hexane, 1:1), Mp. 203-204 ^{0}C; IR (KBr, cm^{-1}): 3145, 3038, 1706, 1662, 1620, 1599, 1582, 1471, 1316, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.75 (s, 3H, OCH_3), 4.12 (d, *J* = 8.3 Hz, 1H, CH), 4.21 (d, *J* = 8.3 Hz, 1H, CH), 6.70 (d, *J* = 8.9 Hz, 2H, ArH), 6.80 (d, *J* = 7.6 Hz, 1H, ArH), 6.93 (t, *J* = 8.3 Hz, 1H,

ArH), 7.12 (dt, *J* = 0.9 & 7.7 Hz, 1H, ArH), 7.23-7.36 (m, 6H, ArH), 7.87 (d, *J* = 9.0 Hz, 2H, ArH), 8.63 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 38.7, 40.2, 40.9, 54.8, 109.2, 113.3, 120.9, 121.1, 125.9, 126.6, 126.7, 127.3, 128.6, 129.4, 130.0, 133.1, 141.4, 163.2, 172.8, 190.6; HRMS (ESI, Orbitrap): calcd for $C_{24}H_{20}NO_3$ $[M+H]^+$ 370.14432; found 370.14352.

ethyl 5'-fluoro-2'-oxo-3-phenylspiro[cyclopropane-1,3'-indoline]-2-carboxylate 3f

127 mg (78%) of **3f** was obtained as a white solid, R_f = 0.60 (ethyl acetate/*n*-hexane, 1:1), Mp. 163-164 ^{0}C; IR (KBr, cm^{-1}): 3203, 1725, 1702, 1481, 1469, 1307, 1219, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (t, *J* = 7.2 Hz, 3H, CH_3), 3.34 (d, *J* = 8.3 Hz, 1H, CH), 3.74 (d, *J* = 8.3 Hz, 1H, CH), 4.16-4.31 (m, 2H, diastereotopic OCH_2), 6.69 (dd, *J* = 4.3, 8.5 Hz, 1H, ArH), 6.89 (dt, *J* = 2.5, 8.7 Hz, 1H, ArH), 7.25-7.36 (m, 6H, ArH), 8.50 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.1, 37.3, 40.1, 40.7, 61.7, 110.3 (110.4 due to C-F coupling: d, J_{C-F} = 8.8 Hz), 110.6 (110.9 due to C-F coupling: d, J_{C-F} = 26.3 Hz), 113.8 (114.1 due to C-F coupling: d, J_{C-F} = 24.1 Hz), 127.6, 128.1, 128.5, 129.1, 132.5, 137.1, 147.5, 157.1 (160.3 due to C-F coupling d, J_{C-F} = 239.3 Hz), 168.2, 174.0; HRMS (ESI, Orbitrap): calcd for $C_{19}H_{17}NO_3F$ $[M+H]^+$ 326.11925; found 326.12038.

2-(4-methoxybenzoyl)-3-(4-nitrophenyl)spiro[cyclopropane-1,3'-indolin]-2'-one 3g

168 mg (81%) of **3g** was obtained as a pale yellow solid, R_f = 0.50 (ethyl acetate/*n*-hexane, 1:1), Mp. 200-201 ^{0}C; IR (KBr, cm^{-1}): 3383, 1713, 1699, 1667, 1595, 1515, 1350, 1324, 1310, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.83 (s, 3H, OCH_3), 4.14 (d, *J* = 8.3 Hz, 1H, CH), 4.23 (d, *J* = 8.3 Hz, 1H, CH), 6.82-6.90 (m, 3H, ArH), 6.97 (t, *J* = 7.6 Hz, 1H, ArH), 7.17 (dt, *J* = 0.9 & 7.7 Hz, 1H, ArH), 7.23 (d, *J* = 7.9 Hz, 1H, ArH), 7.51 (d, *J* = 8.7 Hz, 2H, ArH), 7.92 (d, *J* = 8.9 Hz, 3H, 2ArH + NH), 8.17 (d, *J* = 8.7 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 38.4, 40.9, 41.5, 55.5, 109.9, 114.0, 122.3, 122.6, 123.3, 125.7, 128.0, 129.6, 130.2, 130.8, 140.8, 141.2, 147.1, 164.2, 173.7, 190.1; HRMS (ESI, Orbitrap): calcd for $C_{24}H_{19}N_2O_5$ $[M+H]^+$ 415.12940; found 415.12821.

2-(2-naphthoyl)-5'-chloro-3-(4-nitrophenyl)spiro[cyclopropane-1,3'-indolin]-2'-one 3h

202 mg (86%) of **3h** was obtained as a pale yellow solid, R_f = 0.50 (ethyl acetate/*n*-hexane, 1:1), Mp. 268-270 ^{0}C; IR (KBr, cm^{-1}): 3264, 1713, 1665, 1621, 1516, 1343, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.20 (d, *J* = 8.2 Hz, 1H, CH), 4.47 (d, *J* = 8.2 Hz, 1H, CH), 6.81 (d, *J* = 8.4 Hz, 1H, ArH), 7.15 (dd, *J* = 2.1 & 8.4 Hz, 1H, ArH), 7.34 (d, *J* = 2.0 Hz, 1H, ArH), 7.55-7.58 (m, 3H, ArH), 7.61-7.64 (m, 1H, ArH), 7.86 (d, *J* = 8.2 Hz, 1H, ArH), 7.90 (d, *J* = 8.7 Hz, 1H, ArH), 7.96 (d, *J* = 8.1 Hz, 1H, ArH), 8.04 (dd, *J* = 1.7 & 8.5 Hz, 1H, ArH), 8.19 (d, *J* = 8.9 Hz, 2H, ArH), 8.40 (bs, 1H, NH), 8.51 (d, *J* = 1.2 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 125 MHz) δ: 37.2, 39.4, 40.5, 109.9, 120.9, 121.7, 122.2, 125.1, 125.9, 126.2, 126.4, 126.5, 127.5, 127.8, 128.4, 129.1, 129.2, 129.3, 130.9, 132.6, 134.4, 139.9, 145.6, 171.1, 190.6; HRMS (ESI, Orbitrap): calcd for $C_{27}H_{18}N_2O_4Cl$ $[M+H]^+$ 469.09551; found 469.09439.

5'-bromo-2-(4-methoxybenzoyl)-3-(4-nitrophenyl)spiro[cyclopropane-1,3'-indolin]-2'-one 3i

217 mg (88%) of **3i** was obtained as a orange solid, R_f = 0.38 (ethyl acetate/*n*-hexane, 1:1), Mp. 235-236 ^{0}C; IR (KBr, cm^{-1}): 3282, 2924, 1714, 1652, 1600, 1573, 1517, 1347, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.85 (s, 3H, OCH_3), 4.12 (d, *J* = 8.3 Hz, 1H, CH), 4.26 (d, *J* = 8.3 Hz, 1H, CH), 6.75 (d, *J* = 8.3 Hz, 1H, ArH), 6.91 (d, *J* = 9.0 Hz, 2H, ArH), 7.31 (dd, *J* = 1.9 & 8.1 Hz, 1H, ArH), 7.42 (d, *J* = 1.7 Hz, 1H, ArH), 7.50 (d, *J* = 8.5 Hz, 2H, ArH), 7.79 (bs, 1H, NH), 7.96 (d, *J* = 8.9 Hz, 2H, ArH), 8.17 (d, *J* = 8.7 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 37.31, 39.57, 40.33, 54.54, 110.52, 112.94, 113.10, 121.97, 123.88, 126.98, 128.59, 129.41, 129.70, 140.31, 145.95, 140.59, 163.15, 171.35, 189.15; HRMS (ESI, Orbitrap): calcd for $C_{24}H_{18}N_2O_5{}^{79}Br$ $[M+H]^+$ 493.03991; found 493.03919.

5'-bromo-2-(4-methylbenzoyl)-3-(4-nitrophenyl)spiro[cyclopropane-1,3'-indolin]-2'-one 3j

193 mg (81%) of **3j** was obtained as a yellow solid, R_f = 0.58 (ethyl acetate/*n*-hexane, 1:1), Mp. 271-272 ^{0}C; IR (KBr, cm^{-1}): 3345, 1712, 1670, 1601, 1512, 1476, 1443, 1347, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.40 (s, 3H, CH_3), 4.12 (d, *J* = 8.5 Hz, 1H, CH), 4.28 (d, *J* = 8.5 Hz, 1H, CH), 6.74 (d, *J* = 8.3 Hz, 1H, ArH), 7.24-7.27 (m, 2H, ArH), 7.31 (dd, *J* = 1.9 & 8.3 Hz, 1H, ArH), 7.42 (d, *J* = 1.9 Hz, 1H, ArH), 7.50 (d, *J* = 8.5 Hz, 2H, ArH), 7.87 (d, *J* = 8.1 Hz, 2H, ArH), 7.99 (bs, 1H, NH), 8.17 (d, *J* = 8.7 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 21.1, 37.9, 38.3, 41.0, 111.1, 122.6, 124.5, 127.3, 128.0, 129.0, 129.7, 129.8, 130.1, 131.2, 133.6, 140.6, 140.9, 144.5, 172.0, 191.1; HRMS (ESI, Orbitrap): calcd for $C_{24}H_{18}N_2O_4{}^{79}Br$ $[M+H]^+$ 477.04499; found 477.04380.

4-(5'-bromo-2-(4-chlorobenzoyl)-2'-oxospiro[cyclopropane-1,3'-indoline]-3-yl)benzonitrile 3k

194 mg (81%) of **3k** was obtained as a pale yellow solid, R_f = 0.61 (ethyl acetate/*n*-hexane, 1:1), Mp. 277-278 ^{0}C; IR (KBr, cm^{-1}): 3251, 2242, 1712, 1676, 1608, 1588, 1477, 1443, 1212, ^{1}H NMR ($CDCl_3$ +DMSO-d_6, 300 MHz) δ: 4.03 (d, *J* = 8.1 Hz, 1H, CH), 4.18 (d, *J* = 8.1 Hz, 1H, CH), 6.80 (d, *J* = 8.1 Hz, 1H, ArH), 7.25-7.29 (m, 2H, ArH), 7.43-7.49 (m, 4H, ArH), 7.60 (d, *J* = 8.3 Hz, 2H, ArH), 7.90 (d, *J* = 8.5 Hz, 2H, ArH), 10.40 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ: 37.5, 39.4, 40.4, 109.7, 110.5, 112.8, 117.5, 123.7, 126.5, 128.0, 128.7, 129.1, 129.4, 130.5, 133.8, 137.6, 138.9, 140.5, 171.0, 189.9; HRMS (ESI, Orbitrap): calcd for $C_{24}H_{15}N_2O_2{}^{79}BrCl$ $[M+H]^+$ 477.00054; found 476.99872.

4-(5'-bromo-2-(4-methoxybenzoyl)-2'-oxospiro[cyclopropane-1,3'-indoline]-3-yl)benzonitrile 3l

199 mg (84%) of **3l** was obtained as a orange solid, R_f =0.66 (ethyl acetate/*n*-hexane, 1:1), Mp. 220-221 ^{0}C; IR (KBr, cm^{-1}): 3281, 2228, 1715, 1667, 1599, 1574, 1476, 1323, 1263, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.85 (s, 3H, OCH_3), 4.09 (d, *J* = 8.2 Hz, 1H, CH), 4.23 (d, *J* = 8.2 Hz, 1H, CH), 6.76 (d, *J* = 8.2 Hz, 1H, ArH), 6.89 (d, *J* = 8.7 Hz, 2H, ArH), 7.31 (d, *J* = 8.2 Hz, 1H, ArH), 7.41 (s, 1H, ArH), 7.45 (d, *J* = 8.1 Hz, 2H, ArH), 7.60 (d, *J* = 8.1 Hz, 2H, ArH), 7.95 (d, *J* = 8.7 Hz, 2H, ArH), 8.26 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 39.1, 40.7, 41.2, 55.5, 111.3, 114.0, 115.3, 118.6, 125.5, 127.9, 129.4, 129.8, 130.0, 130.8, 131.8, 134.0, 138.5, 139.9, 164.3, 173.3, 189.8; HRMS (ESI, Orbitrap): calcd for $C_{25}H_{18}N_2O_3{}^{79}Br$ $[M+H]^+$ 473.05008; found 473.04895.

4-(5'-bromo-2-(4-methylbenzoyl)-2'-oxospiro[cyclopropane-1,3'-indoline]-3-yl)benzonitrile 3m

194 mg (85%) of **3m** was obtained as a pale yellow solid, R_f = 0.51 (ethyl acetate/*n*-hexane, 1:1), Mp. 254-256 ^{0}C; IR (KBr, cm^{-1}): 3266, 2243, 1713, 1670, 1607, 1477, 1444, 1209, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.40 (s, 3H, CH_3), 4.09 (d, *J* = 8.2 Hz, 1H, CH), 4.26 (d, *J* = 8.2 Hz, 1H, CH), 6.72 (d, *J* = 8.2 Hz, 1H, ArH), 7.23 (d, *J* = 8.1 Hz, 2H, ArH), 7.31 (dd, *J* = 2.0 & 8.4 Hz, 1H, ArH), 7.41 (d, *J* = 1.8 Hz, 1H, ArH), 7.45 (d, *J* = 8.1 Hz, 2H, ArH), 7.60 (d, *J* = 8.2 Hz, 2H, ArH), 7.86 (d, *J* = 8.2 Hz, 2H, ArH), 8.17 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$ + $DMSOd_6$, 75 MHz) δ: 21.1, 38.2, 40.0, 41.0, 110.4, 111.0, 113.6, 118.1, 124.4, 127.4, 127.9, 128.9, 129.6, 129.9, 131.2, 133.5, 138.4, 140.8, 144.5, 171.9, 191.1; HRMS (ESI, Orbitrap): calcd for $C_{25}H_{18}N_2O_2{}^{79}Br$ $[M+H]^+$ 457.05517; found 457.05736.

4-(2-(4-methoxybenzoyl)-2'-oxospiro[cyclopropane-1,3'-indoline]-3-yl)benzonitrile 3n

158 mg (80%) of **3n** was obtained as a pale yellow solid, R_f = 0.37 (ethyl acetate/*n*-hexane, 1:1), Mp. 140-141 ^{0}C; IR (KBr, cm^{-1}): 3284, 2228, 1714, 1667, 1599, 1574, 1511, 1470, 1348, 1264, ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.82 (s, 3H, OCH_3), 4.11 (d, *J* = 8.1 Hz, 1H, CH), 4.21 (d, *J* = 8.1 Hz, 1H, CH), 6.81-6.86 (m, 3H, ArH), 6.97 (dt, *J* = 0.9 & 7.6 Hz, 1H, ArH), 7.18 (dt, *J* = 1.1 & 7.7 Hz, 1H, ArH), 7.23 (d, *J* = 7.7 Hz, 1H, ArH), 7.46 (d, *J* = 8.1 Hz, 2H, ArH), 7.60 (d, *J* = 8.4 Hz, 2H, ArH), 7.91 (d, *J* = 9.0 Hz, 2H, ArH), 8.05 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 38.6, 40.8, 41.4, 55.5, 109.9, 111.2, 114.0, 118.7, 122.3, 122.6, 125.8, 127.9, 129.6, 130.1, 130.8, 131.8, 139.1, 140.8, 164.1, 173.7, 190.2; HRMS (ESI, Orbitrap): calcd for $C_{25}H_{19}N_2O_3$ $[M+H]^+$ 395.13957; found 395.13852.

2-(4-bromobenzoyl)-3-(4-methoxyphenyl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one 3o

189 mg (82%) of **3o** was obtained as a pale yellow solid, R_f = 0.60 (ethyl acetate/*n*-hexane, 2:3), Mp. 206-207 ^{0}C; IR (KBr, cm^{-1}): 3054, 2930, 1705, 1673, 1613, 1584, 1492, 1469, 1347, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.24 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 4.06 (d, *J* = 8.3 Hz, 1H, CH), 4.21 (d, *J* = 8.3 Hz, 1H, CH), 6.80-6.90 (m, 3H, ArH), 6.98 (t, *J* = 7.6 Hz, 1H, ArH), 7.22-7.30 (m, 4H, ArH), 7.55 (d, *J* = 8.3 Hz, 2H, ArH), 7.81 (d, *J* = 8.3 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 26.7, 39.3, 41.0, 41.8, 55.1, 108.0, 113.5, 121.8, 122.4, 124.8, 125.8, 127.5, 128.9, 129.9, 130.2, 132.0, 135.7, 143.7, 158.9, 171.8, 192.1; HRMS (ESI, Orbitrap): calcd for $C_{25}H_{21}NO_3{}^{79}Br$ $[M+H]^+$ 462.07048; found 462.07266.

5'-chloro-2-(4-methoxyphenyl)-3-(4-nitrobenzoyl)spiro[cyclopropane-1,3'-indolin]-2'-one 3p

177 mg (79%) of **3p** was obtained as a pale yellow solid, R_f = 0.45 (ethyl acetate/*n*-hexane, 1:2), Mp. 116-117 ^{0}C; IR (KBr, cm^{-1}): 3253, 2924, 2852, 1715, 1638, 1526, 1469, 1318, 1250, ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.74 (s, 3H, OCH_3), 4.00 (d, *J* = 8.3 Hz, 1H, CH), 4.40 (d, *J* = 8.3 Hz, 1H, CH), 6.83-6.89 (m, 3H, ArH), 7.01 (d, *J* = 1.9 Hz, 1H, ArH), 7.18 (dd, *J* = 2.0, 8.3 Hz, 1H, ArH), 7.33 (d, *J* = 8.5 Hz, 2H, ArH), 8.10 (d, *J* = 8.9 Hz, 2H, ArH), 8.33 (d, *J* = 8.7 Hz, 2H, ArH), 10.80 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 39.7 & 40.2 (buried in DMSO-d_6), 41.2, 55.9, 110.8, 113.1, 113.8, 121.2, 124.1, 124.6, 125.1, 127.2, 127.9, 129.4, 130.5, 141.0, 150.1, 158.4, 171.8, 192.2; HRMS (ESI, Orbitrap): calcd for $C_{24}H_{18}N_2O_5Cl$ $[M+H]^+$ 449.09042; found 449.09062.

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Diastereoselective synthesis of spiro[cyclopropane-1,3'-indolin]-2'-ones through metal-free cyclopropanation using tosylhydrazone salts

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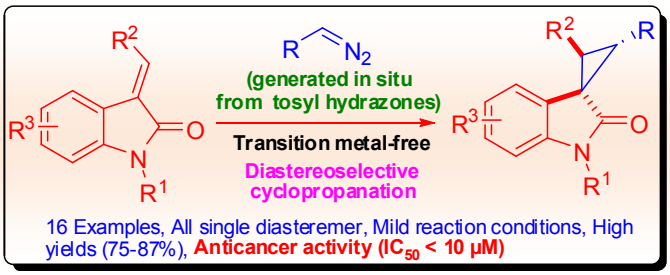

Anticancer spiro[cyclopropane-1,3'-indolin]-2'-ones are accessible through a transition metal-free diastereoselective cyclopropanation using in-situ generated diazo-compounds.