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Green Stereoselective Synthesis and *In Silico* Anticancer Evaluation of Tetrahydro-β-carboline-Derived Spiro Heterocycles

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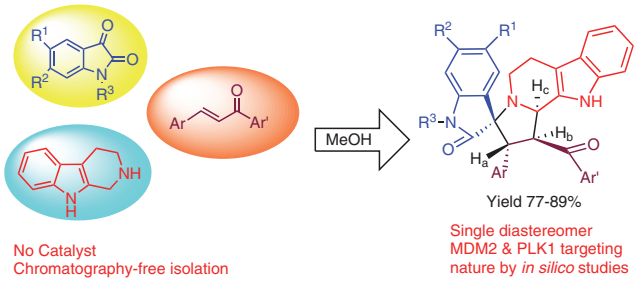

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Abstract A green stereoselective synthesis of spiroheterocycles incorporating a spirooxindole and a 1,2,3,4-tetrahydro-β-carboline (THβC) are demonstrated here by the one-pot, three-component reaction of THβC, isatins, and chalcones. Operational simplicity and chromatography-free isolation are the highlights of the reaction which resulted in densely substituted spiroheterocycles with four-contiguous stereocenters in excellent yields. The activity of the compounds as anticancer agents was studied *in silico* against MDM2 and PLK1 target proteins and they show excellent binding interactions compared to reference drugs.

Key words [3+2] cycloaddition, azomethine ylide, 1,2,3,4-tetrahydro-β-carboline, spiroheterocycles

The development of plant-based drug remedies for cancer is an urgent need in society and several efforts are in progress to address this matter.[1] In this context, among the natural alkaloids, β-carbolines and 1,2,3,4-tetrahydro-β-carbolines (THβCs) occupy a niche of their own. Being distributed widely in nature,[2] they are known to possess a wide range of biological activities[3] among which anticancer activity is substantial.[4] Figure 1 depicts the structures of commercially available β-carboline drugs and RSL3 (a ferroptosis activator),[5] all of which possess the THβC motif. On account of the latter being an important template for drug discovery and for combinatorial library synthesis, numerous methods have been devised for their synthesis by various research groups[6] and for their efficient transformation to β-carbolines by decarboxylative dearomatizations.[7] the molecular hybridization approach[8] has been widely used for the development of anticancer agents from β-carbo-

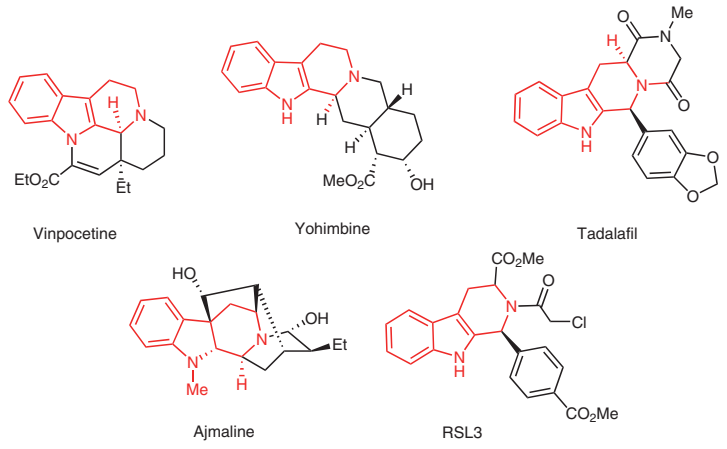

Figure 1 Structures of commercially available β-carboline drugs and RSL3

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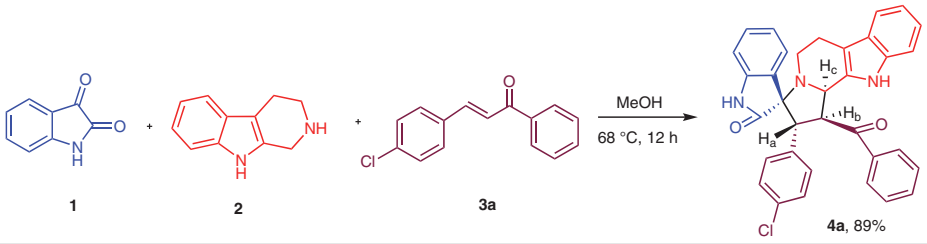


Scheme 1 1,3-Dipolar cycloaddition of 4-chlorochalcone with the azomethine ylide generated from isatin and THβC

lines.[9] Azomethine ylide (AY) based [3+2] cycloadditions is one of the promising strategies for the synthesis of molecular hybrids.[10] In this context, azomethine ylides generated from β-carbolines and 3,4-dihydro-β-carbolines were utilized as early as 1996 for the synthesis of pyrrolidine hybrid molecules, specifically indolizino[8,7-*b*]indole derivatives by 1,3-dipolar cycloaddition reactions.[11] However there has been only scant attempts to utilize THβC for azomethine ylide generation and for their subsequent cycloaddition.[12] Owing to our interest in the synthesis of bioactive spiroheterocycles, by AY generation from isatins and primary amines (*via* decarboxylative route)[13] and synthesis of pyrrolo[2,1-*a*]isoquinolines by reaction of AYs generated from cyclic secondary amines and isatins (*via* iminium route),[14] we decided to explore AY generation from THβC and its [3+2] cycloaddition to chalcones. The reaction culminated in the synthesis of densely functionalized THβC derivatives that were tested for anticancer activity by *in silico* docking studies.

As a pilot reaction, isatin **1**, THβC **2**, and 4-chlorochalcone (**3a**) (1:1:1 molar ratio) were refluxed in methanol for 12 h (Scheme 1). The reaction resulted in the precipitation of a compound that was isolated by careful filtration and was purified by washing with cold methanol. Detailed spectroscopic characterizations and CHN analysis of the compound confirmed its structure and elemental composition.

In the IR spectrum of compound **4a**, the benzoyl carbonyl and the amide carbonyl were observed at 1695 and 1620 cm^{-1} respectively. In the ^1H NMR spectrum, three protons H_a, H_b, and H_c were observed as a doublet at δ = 4.48 (J = 8.4 Hz), triplet at δ = 5.15 (J = 8.8 Hz), and doublet at δ = 5.86 (J = 9.2 Hz), respectively. The positive enhancement of H_c in the 1D NOE spectrum (when H_b was irradiated), confirmed the *cis* disposition of H_b with respect to H_c and *trans* disposition with H_a (Supporting Information, Figure S57). In the ^{13}C NMR spectrum, the spiro carbon was seen at δ = 75.8 while the carbons attached to H_a, H_b, and H_c were discernible at δ =57.3, 51.5, and 59.8, respectively. The negative signals at δ = 43.2 and 22.2 in DEPT-135 (Supporting Information, Figure S58) indicated the methylene carbons of the THβC moiety.

Figure 2 shows the major ^1H-^1H COSY and HMBC correlations for the compound **4a**. In the ^1H-^1H COSY spectrum (Supporting Information, Figure S59), H_a-H_b and H_b-H_c correlations confirmed the proposed structure and relative positions of H_a, H_b, and H_c. The strong single bond correlations of the stereocenter carbons with the hydrogens in the HSQC spectrum (Supporting Information, Figure S60) confirmed the position of attachment of H_a, H_b, and H_c. The regiochemistry of compound **4a** was established from the HMBC spectrum (Supporting Information, Figure S61) which showed three strong correlations of 1″ with the protons H_a, H_b, and H_c and a single correlation of 2′ with H_a. The spirocenter shows two strong correlations with the protons H_a and H_b while both the stereocenters 1 and 3″ exhibited two correlations with the protons at neighboring carbons. Carbon 2″ has two strong correlations with the protons H_a and H_c.

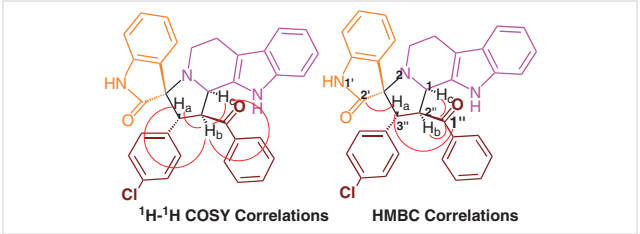


Figure 2 Selected COSY and HMBC correlations of compound **4a**

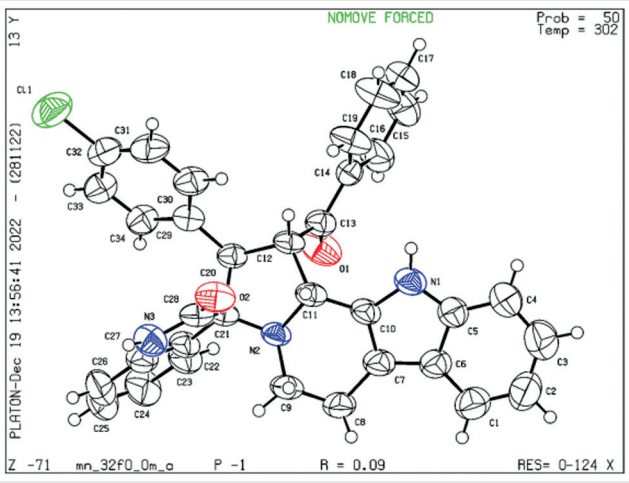


Figure 3 ORTEP diagram of **4a** (CCDC 2229729)

The structure was unambiguously confirmed by single-crystal X-ray analysis (Figure 3).

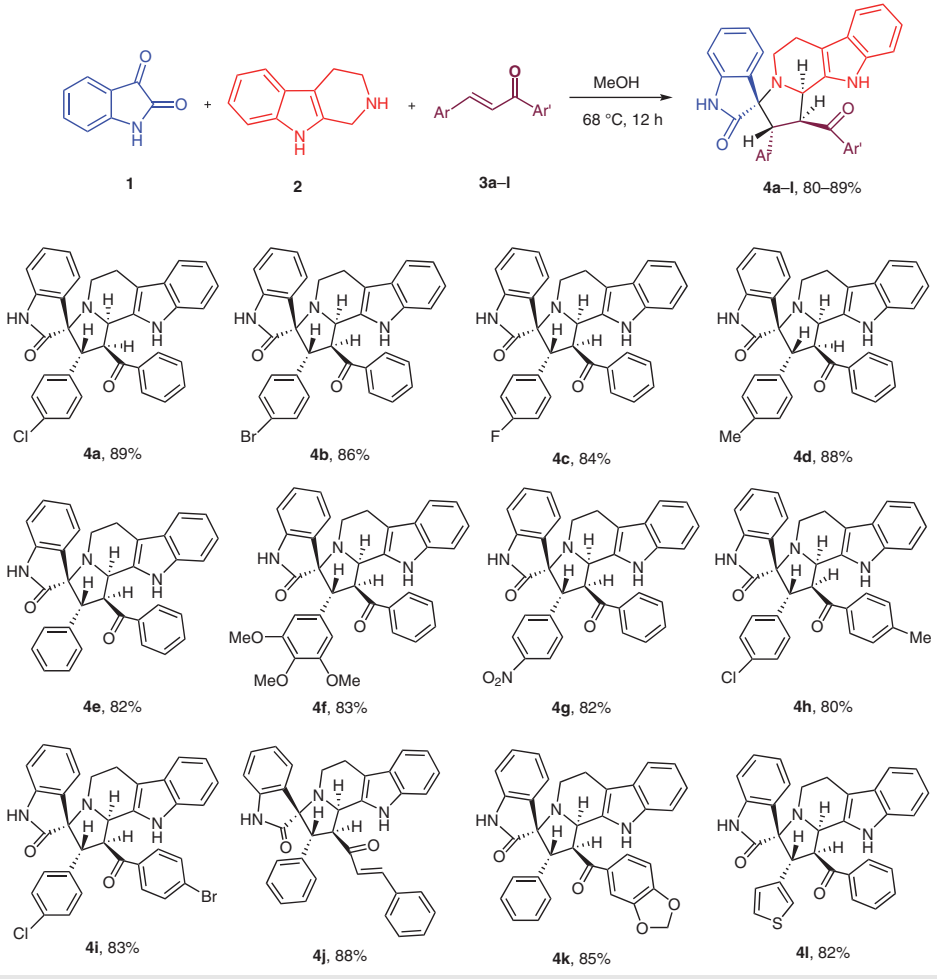
The generality of the reaction was proved by using various chalcone derivatives and substituted isatins (Scheme 2). Chalcones bearing both electron-withdrawing and -donating substituents reacted equally well with the AY generated from isatin and THβC and afforded the desired products **4a–i** with good yields of 80–89%. Products **4j–l** were obtained by reaction of divinyl chalcone, benzodioxolo-substituted chalcone, and heterocyclic chalcone, respectively, in good yields.

The effect of substitution in the isatin on the reaction was then explored by treatment of 4-chlorochalcone with the AY generated from substituted isatins and the results are depicted in Scheme 3. The *N*-alkyl isatins **1a–f**, 5-halo isatins **1g–m**, and 5-methoxy isatins **1n** and **1o** yielded the products **5a–f**, **5g–m**, and **5n**,**o** in comparable yields without much dependance on the substitution patterns. It was observed that no product was obtained using 4-bromo isatin while use of 6-chloro isatin **1p** yielded the product **5p** in good yield.

Table 1 Activation Parameters Obtained from Theoretical Calculations

$\Delta G^{\#}$ (kcal/mol)	$\Delta H^{\#}$ (kcal/mol)	$\Delta S^{\#}$ (cal/mol/K)
exo-TS	27.39	13.85
endo-TS	31.52	18.23

Mechanistically the reaction takes place through the generation of AY **II** via [1,5] H-shift of the Z-iminium ion **I** followed by deprotonation (Scheme 4).[14] Approach of the *exo-Re* face of **II** to the chalcone resulted in the formation of a single diastereomer which was confirmed by theoretical calculations. DFT calculations were performed at B3LYP/6-31G(d,p) level of theory.[15] The effect of methanol was investigated using a PCM approach.[16] Both the *endo* and *exo* approach of AY with the dipolarophile were computed and activation parameters obtained are given in the Table 1.

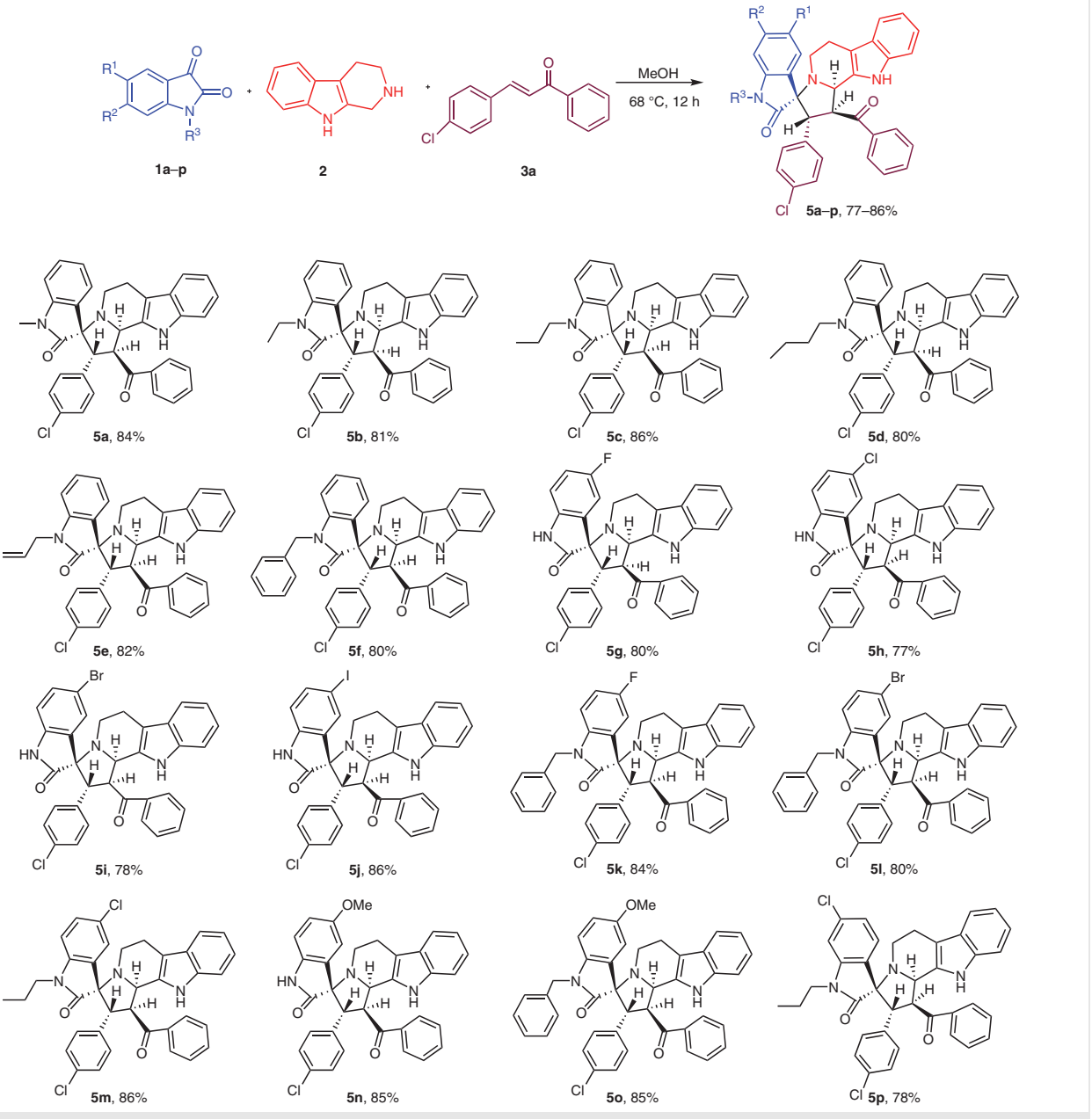


Scheme 2 1,3-Dipolar cycloaddition of chalcones with azomethine ylide generated from isatin and THβC

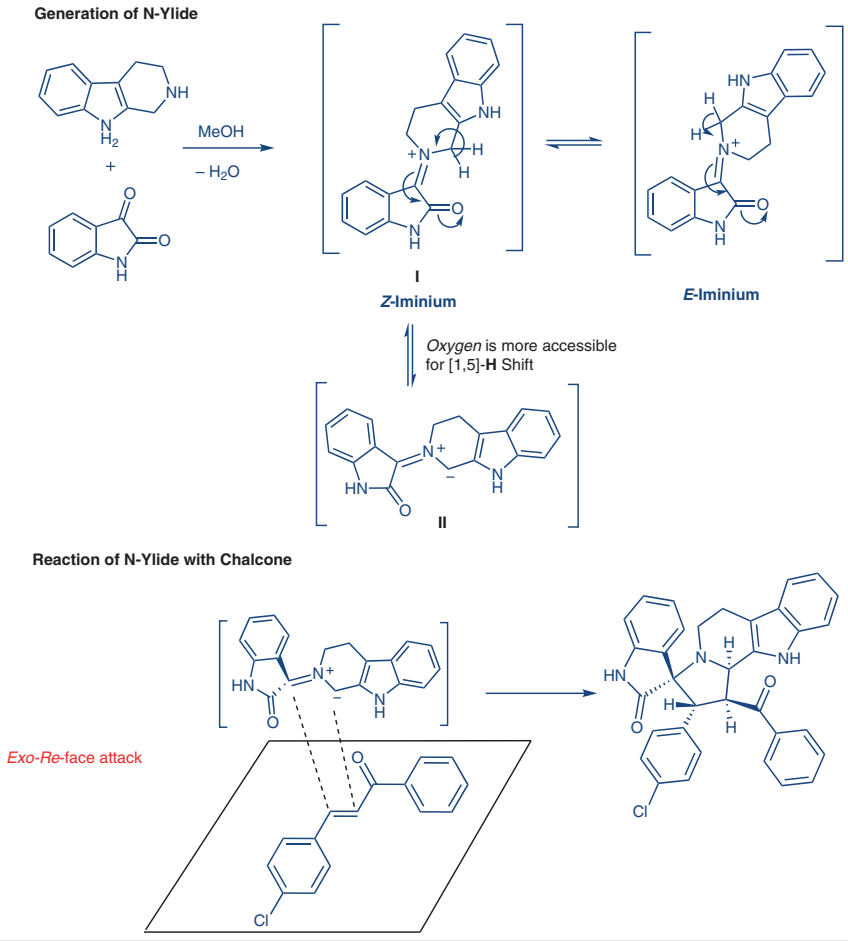
The energy of activation indicated that the reaction pathway is best proceeded through the *exo* TS (Figure 4). The theoretical calculations in the gas phase were also performed which suggest the transition structure that corresponds to the proposed addition is 6.06 kcal/mol more stable than the *endo* addition.

The calculated chemical potential of the ylide (–3.257 eV) was found to be higher than the dipolarophile (–4.396 eV) and the chemical hardness was found to be lower (2.463 eV) than the dipolarophile (4.043 eV). The electrophilicity index was also greater for the dipolarophile (2.390 eV) than the ylide (2.153 eV). All these data indicate the charge transfer from the ylide to the dipolarophile.

MDM2-p53 interaction proved to be an effective strategy in anticancer drug design and development. Similarly, drugs that can inhibit PLK1 protein overexpression have enhanced therapeutic effects for treating cancer and have been widely explored. Various natural as well as synthetic compounds have been reported to possess excellent anti-



Scheme 3 1,3-Dipolar cycloaddition of 4-chloro chalcone with azomethine ylide generated from isatins and THβC



Scheme 4 Mechanistic rationale

cancer potential due to their efficiency to inhibit MDM2 and PLK1 target proteins.[17] Based on this, ten selected derivatives incorporating oxindole and THβC moieties were subjected to molecular docking studies to evaluate their role as anticancer agents. For the study, MDM2 (PDB ID: 5LAW) and PLK1 (PDB ID: 3THB) were the selected protein targets and their structures were obtained from PDB. The binding interactions of the compound and the reference drugs[18] with the target proteins are summarized in Table 2.

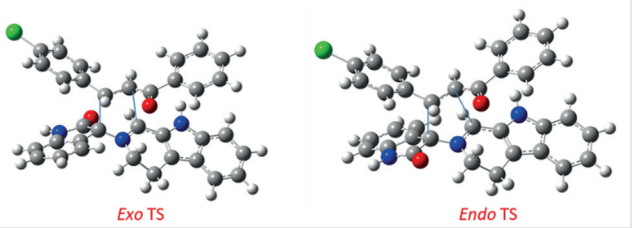
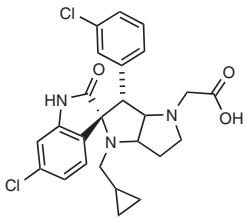
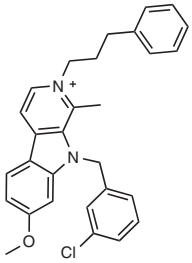


Figure 4 Optimized geometry of *exo* and *endo* TS at B3LYP/6-31G(d,p) level of theory

Results indicate that all compounds bind to the target proteins and among them **4c** showed the highest binding interaction with MDM2 with a binding energy –10.0 kcal/mol. It is seen from Figure 5A that the amino acid residues HIS 96, LEU 54, LEU 57, ILE 99, VAL 93, TYR 67, and ILE 19 of the MDM2 protein exhibit strong van der Waals and π interactions with the active sites of **4c**. It was also observed that among the different compounds, **4d** had highest binding interaction of –10.2 kcal/mol with PLK1 target protein and from Figure 5B it was seen that the amino acid residues GLU 140, LYS 61, CYS 67, ALA 80, LEU 59, and ARG 136 of the PLK1 shows strong H-bonds, van der Waals and π interactions with the active sites of **4d**. Further *in vitro* anticancer evaluation of compounds **4c** and **4d** is underway.

In conclusion, we have synthesized spirooxindole-tetrahydro-β-carboline molecular hybrid compounds via the 1,3-dipolar cycloaddition reaction of azomethine ylides generated from isatins and 1,2,3,4-tetrahydro-β-carboline with substituted chalcones. The products were obtained in excellent yields with high regio- and stereoselectivity. Selected compounds were subjected to *in silico* docking analy-

Table 2 Binding Energy of MDM2 (5LAW) and PLK1 (3THB) Proteins with the Synthesized Spiro Heterocycles

Entry	Compound	Molecular formula	Binding energy (kcal/mol)	
			MDM2	PLK1
1	**4a**	$C_{34}H_{26}ClN_3O_2$	–9.2	–8.3
2	**4b**	$C_{34}H_{26}BrN_3O_2$	–8.8	–8.3
3	**4c**	$C_{34}H_{26}FN_3O_2$	**–10.0**	–8.4
4	**4d**	$C_{35}H_{29}N_3O_2$	–9.2	**–10.2**
5	**4g**	$C_{37}H_{33}N_3O_5$	–7.6	–8.0
6	**5g**	$C_{34}H_{25}ClFN_3O_2$	–8.8	–10.0
7	**5h**	$C_{34}H_{25}Cl_2N_3O_2$	–8.8	–9.1
8	**5i**	$C_{34}H_{25}BrClN_3O_2$	–8.8	–8.6
9	**5j**	$C_{34}H_{25}ClIN_3O_2$	–8.9	–8.7
10	**5p**	$C_{37}H_{31}Cl_2N_3O_2$	–8.4	–9.6
11	reference compounds		 –7.9	 –9.4

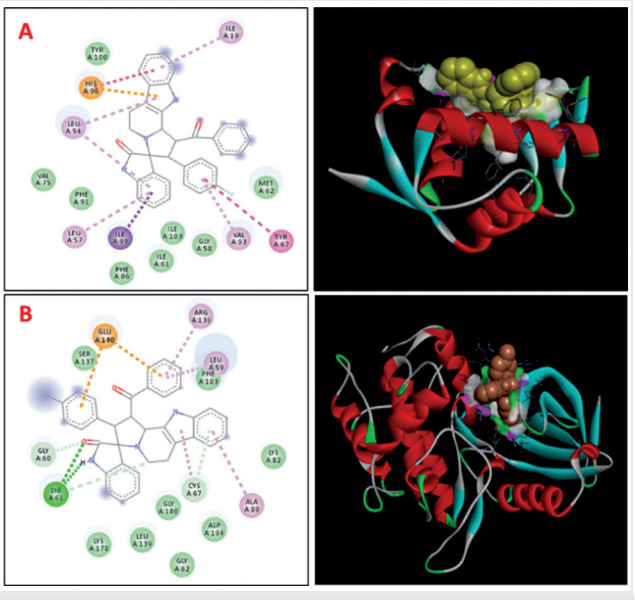


Figure 5 Molecular docking interactions (A) 2D and 3D pose of **4c** with MDM2 (5LAW); (B) 2D and 3D pose of **4d** with PLK1 (3THB)

sis against MDM2 and PLK1 target proteins and it was observed that compounds **4c** and **4d** showed maximum binding interactions with the target proteins.

For a procedure for the synthesis of chalcones see the Supporting Information. Tetrahydro betacarboline, isatin and haloisatins were purchased from Sigma-Aldrich.

Reaction of Azomethine Ylides Generated from Isatins and 1,2,3,4-Tetrahydro-β-carboline with Chalcones; General Procedure

Isatin, 1,2,3,4-tetrahydro-β-carboline, and chalcone (ratio 1:1:1, in their respective mmol) were added to a 50-mL round-bottom flask and then dissolved in MeOH (5 mL). The mixture was stirred and refluxed for 12 h (monitored by using TLC). When the reaction was complete, the precipitate formed was filtered, washed with cold MeOH, dried, and characterized.

1′-Benzoyl-2′-(4-chlorophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4a)

White powder; yield: 100 mg (89%); mp 202–204 °C.

IR: 3367, 3297, 2920, 2838, 1695, 1620, 1467 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.04 (m, 2 H), 7.67–7.64 (m, 2 H), 7.53 (uneven t, *J* = 9 Hz, 2 H), 7.41–7.38 (m, 1 H), 7.29–7.25 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.19–7.15 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.11–7.08 (m, 2 H), 7.05–7.00 (m, 5 H), 6.97 (s, 1 H), 6.94–6.91 (m, 1 H), 6.69 (d, *J* = 7.6 Hz, 1 H), 5.86 (d, *J* = 9.2 Hz, 1 H), 5.15 (t, *J* = 8.8 Hz, 1 H), 4.48 (d, *J* = 8.4 Hz, 1 H), 2.94–2.87 (m, 3 H), 2.66–2.58 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8, 177.8, 141.3, 138.0, 137.9, 135.7, 134.1, 133.7, 133.4, 131.7, 129.8, 129.6, 129.2, 128.4, 128.3, 128.0, 127.0, 125.2, 123.3, 121.5, 119.3, 118.1, 110.7, 110.5, 109.6, 75.8, 59.8, 57.3, 51.5, 43.2, 22.2.

Anal. Calcd for $C_{34}H_{26}ClN_3O_2$: C, 75.06; H, 4.82; N, 7.72. Found: C, 75.08; H, 4.81; N, 7.73.

1′-Benzoyl-2′-(4-bromophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4b)

Yellow powder; yield: 86 mg (86%); mp 186–188 °C.

IR: 3334, 3055, 2917, 2850, 1680, 1602, 1464 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.2 Hz, 2 H), 7.66–7.59 (m, 3 H), 7.57–7.50 (m, 3 H), 7.41–7.38 (m, 2 H), 7.29–7.14 (m, 5 H), 6.97–6.92 (m, 3 H), 6.69 (d, *J* = 7.6 Hz, 1 H), 5.85 (d, *J* = 8.8 Hz, 1 H), 5.14 (t, *J* = 8.8 Hz, 1 H, CH), 4.45 (d, *J* = 8.4 Hz, 1 H), 2.94–2.85 (m, 3 H), 2.62–2.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 178.3, 141.3, 137.9, 135.7, 134.6, 133.7, 132.5, 131.7, 131.4, 130.5, 130.2, 129.7, 129.2, 128.4, 128.1, 127.9, 127.5, 127.0, 125.1, 123.3, 121.6, 121.5, 119.3, 118.1, 110.7, 110.5, 109.8, 75.9, 59.8, 57.3, 51.5, 43.2, 22.1.

Anal. Calcd for $C_{34}H_{26}BrN_3O_2$: C, 69.39; H, 4.45; N, 7.14. Found: C, 69.37; H, 4.44; N, 7.13.

1′-Benzoyl-2′-(4-fluorophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4c)

White powder; yield: 98 mg (84%); mp 232–234 °C.

IR: 3356, 3062, 2939, 2812, 1698, 1616, 1490 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.05 (m, 2 H), 7.67–7.63 (m, 2 H), 7.53 (t, *J* = 7.6 Hz, 2 H), 7.41–7.39 (m, 1 H), 7.28–7.24 (m, 1 H), 7.19–7.15 (m, 1 H), 7.10–6.99 (m, 6 H), 6.94–6.92 (m, 1 H), 6.80 (uneven t, *J* = 8.6 Hz, 2 H), 6.69 (d, *J* = 7.6 Hz, 1 H), 5.86 (d, *J* = 9.2 Hz, 1 H), 5.14 (t, *J* = 8.8 Hz, 1 H), 4.48 (d, *J* = 8.4 Hz, 1 H), 2.96–2.87 (m, 3 H), 2.63–2.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 177.9, 141.2, 138.0, 135.7, 133.7, 131.8, 130.1, 130.0, 129.6, 129.2, 128.3, 128.0, 127.0, 125.1, 123.2, 121.5, 119.3, 118.0, 115.2, 115.0, 110.7, 110.5, 109.5, 75.9, 59.8, 57.2, 51.7, 43.2, 22.2.

Anal. Calcd for $C_{34}H_{26}FN_3O_2$: C, 77.40; H, 4.97; N, 7.96. Found: C, 77.39; H, 4.96; N, 7.95.

1′-Benzoyl-2′-(*p*-tolyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4d)

Yellow powder; yield: 104 mg (88%); mp 220–222 °C.

IR: 3364, 3304, 2913, 2842, 1672, 1620, 1464 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05–8.03 (m, 2 H), 7.66–7.63 (m, 1 H), 7.61–7.59 (m, 1 H), 7.51–7.48 (m, 2 H), 7.40–7.38 (m, 1 H), 7.26–7.22 (m, 2 H), 7.18–7.14 (td, *J* = 7.6. 0.8 Hz, 1 H), 7.04–6.97 (m, 5 H), 6.95–6.89 (m, 3 H), 6.67 (d, *J* = 7.6 Hz, 1 H), 5.86 (d, *J* = 9.2 Hz, 1 H), 5.16 (uneven t, *J* =8.6 Hz, 1 H), 4.48 (d, *J* = 8 Hz, 1 H), 2.94–2.84 (m, 3 H), 2.63–2.59 (m, 1 H), 2.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4, 178.2, 141.4., 138.1, 137.0, 135.7, 132.5, 132.0, 129.4, 129.1, 129.2, 128.9, 128.47, 128.41, 128.3 127.1, 125.1, 123.1, 121.4, 119.2, 118.0, 110.6, 110.3, 109.5, 76.0, 59.8, 57.7, 51.7, 43.2, 22.2, 20.99.

Anal. Calcd for $C_{35}H_{29}N_3O_2$: C, 80.28; H, 5.58; N, 8.02. Found: C, 80.28; H, 5.57; N, 8.04.

1′-Benzoyl-2′-phenyl-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4e)

White powder; yield: 100 mg (82%); mp 241–243 °C.

IR: 3360, 3021, 2950, 2887, 1698, 1620, 1467 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.04 (m, 2 H), 7.68–7.61 (m, 2 H), 7.51 (uneven t, *J* = 7.6 Hz, 2 H), 7.41–7.38 (m, 1 H), 7.25–7.24 (m, 1 H), 7.19–7.17 (m, 1 H), 7.16–7.08 (m, 5 H), 7.05–6.91 (m, 5 H), 6.67 (d, *J* = 7.6 Hz, 1 H), 5.88 (d, *J* = 9.2 Hz, 1 H), 5.20 (t, *J* = 8.8 Hz, 1 H), 4.52 (d, *J* = 8.4 Hz, 1 H), 2.93–2.86 (m, 3 H), 2.65–2.62 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 177.9, 141.3, 138.1, 135.7, 135.6, 133.5, 132.0, 129.4, 129.1, 128.5, 128.3, 128.2, 127.4, 127.1, 125.2, 123.1, 121.4, 119.3, 118.0, 110.6, 110.4, 109.4, 75.9, 59.9, 58.0, 51.5, 43.2, 22.2.

Anal. Calcd for $C_{34}H_{27}N_3O_2$: C, 80.13; H, 5.34; N, 8.25. Found: C, 80.14; H, 5.35; N, 8.23.

1′-Benzoyl-2′-(4-nitrophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro-[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4f)

Yellow powder; yield: 98 mg (83%); mp 244–246 °C.

IR: 3367, 3058, 2932, 2805, 1695, 1616, 146 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.8 Hz, 2 H), 7.91 (d, *J* = 8.8 Hz, 2 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 7.31–7.29 (m, 4 H), 7.19 (d, *J* = 8 Hz, 2 H), 7.14–7.10 (m, 2 H), 7.09–7.03 (m, 4 H), 6.90 (t, *J* = 7.6 Hz, 1 H), 6.52 (d, *J* = 8.4 Hz, 1 H), 5.31 (d, *J* = 9.6 Hz, 1 H), 4.49–4.40 (m, 2 H), 2.99–2.92 (m, 1 H), 2.74–2.66 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.0, 179.5, 147.9, 147.5, 142.8, 136.7, 135.8, 133.8, 131.8, 130.4, 130.0, 129.6, 127.8, 126.7, 126.0, 124.9, 122.4, 121.3, 119.1, 118.0, 112.1, 109.9, 108.1, 70.8, 62.7, 61.3, 49.6, 42.4, 22.6.

Anal. Calcd for $C_{34}H_{26}N_4O_4$: C, 73.63; H, 4.73; N, 10.10. Found: C, 73.64; H, 4.75; N, 10.11.

1′-Benzoyl-2′-(3,4,5-trimethoxyphenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4g)

Yellow powder; yield: 76 mg (82%); mp 234–236 °C.

IR: 3345, 3055, 2913, 2835, 1669, 1620, 1467 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 2 H), 7.67–7.62 (m, 2 H), 7.54 (uneven t, *J* = 7.6 Hz, 2 H), 7.41–7.39 (m, 1 H), 7.27–7.23 (m, 1 H), 7.18–7.14 (m, 2 H), 7.05–7.00 (m, 3 H), 6.96–6.94 (m, 1 H), 6.69 (d, *J* = 7.6 Hz, 1 H), 6.25 (s, 2 H), 5.85 (d, *J* = 9.2 Hz, 1 H), 5.17 (t, *J* = 9 Hz, 1 H), 4.44 (d, *J* = 8.8 Hz, 1 H), 3.72 (s, 3 H), 3.59 (s, 6 H), 3.00–2.89 (m, 3 H), 2.64–2.61 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 177.9, 141.3, 152.6, 141.6, 138.0, 137.1, 135.7, 133.7, 132.0, 130.9, 129.4, 129.2, 128.4, 127.1, 125.1, 123.0, 121.5, 119.3, 118.0, 110.7, 110.5, 109.5, 105.2, 75.9, 60.7, 59.8, 58.4, 55.8, 51.3, 43.3, 22.2.

Anal. Calcd for $C_{37}H_{33}N_3O_5$: C, 74.11; H, 5.55; N, 7.01. Found: C, 74.10; H, 5.55; N, 7.03.

2′-(4-Chlorophenyl)-1′-(4-methylbenzoyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4h)

Light yellow powder; yield: 91 mg (80%); mp 236–238 °C.

IR: 3300, 3043, 2980, 2842, 1672, 1609, 1449 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.4 Hz, 2 H), 7.63 (d, *J* = 6.8 Hz, 1 H), 7.41–7.38 (m, 1 H), 7.33 (d, *J* = 8 Hz, 2 H), 7.28–7.24 (m, 1 H), 7.18–7.16 (m, 1 H), 7.15–7.13 (m, 1 H), 7.09–7.00 (m, 7 H), 6.95–6.93 (m, 1 H), 6.69 (d, *J* = 7.6 Hz, 1 H), 5.82 (d, *J* = 9.2 Hz, 1 H), 5.15 (t, *J* =9 Hz, 1 H), 4.46 (d, *J* = 8.4 Hz, 1 H), 2.94–2.89 (m, 3 H), 2.62–2.60 (m, 1 H), 2.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1, 178.0, 144.8, 141.3, 135.7, 135.3, 134.1, 133.3, 132.0, 130.0, 129.8, 129.6, 128.5, 128.4, 128.0, 127.1, 125.2, 123.2, 121.5, 119.3, 118.0, 110.7, 110.4, 109.6, 75.8, 59.8, 57.2, 51.3, 43.2, 22.1, 21.7.

Anal. Calcd for $C_{35}H_{28}ClN_3O_2$: C, 75.33; H, 5.06; N, 7.53. Found: C, 75.32; H, 5.07; N, 7.52.

1′-(4-Bromobenzoyl)-2′-(4-chlorophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4i)

White powder; yield: 80 mg (83%); mp 243–245 °C.

IR: 3215, 3051, 2917, 2846, 1702, 1679, 1464 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 2 Hz, 2 H), 7.63–7.58 (m, 2 H), 7.42–7.40 (m, 1 H), 7.29–7.27 (m, 1 H), 7.19–7.14 (m, 1 H), 7.10–6.98 (m, 10 H), 6.70 (d, *J* = 7.6 Hz, 1 H), 5.86 (d, *J* =9.2 Hz, 1 H), 4.99 (t, *J* = 8.8 Hz, 1 H), 4.38 (d, *J* = 8.4 Hz, 1 H), 2.95–2.88 (m, 3 H), 2.67–2.64 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7, 177.7, 141.3, 136.2, 135.8, 133.8, 133.6, 132.3, 131.6, 130.1, 129.8, 128.9, 128.5, 127.7, 127.0, 129.9, 123.3, 121.7, 119.5, 118.1, 110.8, 110.5, 109.8, 75.9, 59.6, 57.7, 52.7, 43.2, 22.2.

Anal. Calcd for $C_{34}H_{25}BrClN_3O_2$: C, 65.56; H, 4.05; N, 6.75. Found: C, 65.55; H, 4.80; N, 7.74.

1′-Cinnamoyl-2′-phenyl-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4j)

Yellow powder; yield: 101 mg (88%); mp 247–249 °C.

IR: 3286, 3081, 2954, 2820, 1702, 1657, 1587 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.56 (d, *J* = 16 Hz, 1 H), 7.50 (d, *J* = 7.2 Hz, 1 H), 7.43 (d *J* = 7.2 Hz, 1 H), 7.38–7.32 (m, 6 H), 7.29–7.27 (dd, *J* = 7.6, 1.0 Hz, 1 H), 7.23 (d, *J* = 7.2 Hz, 1 H), 7.17–7.12 (m, 4 H), 7.09–7.00 (m, 5 H), 6.69 (d *J* = 7.6 Hz, 1 H), 5.87 (d, *J* = 8.4 Hz, 1 H), 4.29–4.26 (m, 1 H), 4.16 (d, *J* = 6.8 Hz, 1 H), 3.02–2.89 (m, 3 H), 2.80–2.76 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 177.1, 143.4, 141.5, 136.2, 135.2, 134.7, 130.4, 128.9, 128.6, 128.2, 127.6, 127.1, 124.2, 123.8, 123.2, 121.4, 119.3, 117.9, 111.1, 109.68, 109.62, 76.0, 59.0, 58.8, 56.2, 43.2, 22.6.

Anal. Calcd for $C_{36}H_{29}N_3O_2$: C, 80.72; H, 5.46; N, 7.84. Found: C, 80.72; H, 5.47; N, 7.84.

1′-(Benzo[*d*][1,3]dioxole-5-carbonyl)-2′-phenyl-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4k)

White powder; yield: 93 mg (85%); mp 215–217 °C.

IR: 3341, 3047, 2883, 2831, 1706, 1616, 1484 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.81 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.63 (d, *J* = 7.2 Hz, 1 H), 7.58 (d, *J* = 1.6 Hz, 1 H), 7.42–7.40 (m, 1 H), 7.27–7.23 (m, 2 H), 7.18–7.01 (m, 10 H), 6.90 (d, *J* = 8 Hz, 1 H), 6.66 (d, *J* = 7.6 Hz, 1 H), 6.06 (s, 2 H), 5.82 (d, *J* = 9.2 Hz, 1 H), 5.11 (uneven t, *J* = 9 Hz, 1 H), 4.46 (d, *J* = 8.4 Hz, 1 H), 2.95–2.88 (m, 3 H), 2.65–2.61 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 178.0, 152.2, 148.6, 141.3, 135.7, 135.4, 132.5, 132.3, 129.5, 128.4, 128.2, 127.4, 127.2, 125.2, 124.8, 123.1, 121.4, 119.3, 118.1, 110.7, 110.3, 109.5, 108.4, 108.2, 102.1, 76.0, 59.7, 58.2, 51.5, 43.2, 22.1.

Anal. Calcd for $C_{35}H_{27}N_3O_4$: C, 75.93; H, 4.92; N, 7.59. Found: C, 75.94; H, 4.93; N, 7.59.

(1′*S*,2′*R*,3*S*,11b′*R*)-1′-Benzoyl-2′-(thiophen-3-yl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (4l)

White powder; yield: 98 mg (82%); mp 213–215 °C.

IR: 3312, 3051, 2913, 2831, 1695, 1650, 1464 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.09 (m, 2 H), 7.67–7.63 (m, 2 H), 7.53 (t, *J* = 7.8 Hz, 2 H), 7.40–7.38 (m, 1 H), 7.30–7.26 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.19–7.17 (m, 1 H), 7.17 (s, 1 H), 7.10–7.08 (m, 1 H), 7.05–6.99 (m, 3 H), 6.95–6.91 (m, 2 H), 6.75–6.73 (m, 2 H), 5.84 (d, *J* = 9.6 Hz, 1 H), 5.12 (uneven t, *J* = 8.8 Hz, 1 H), 4.61 (d, *J* = 8 Hz, 1 H), 2.95–2.85 (m, 3 H), 2.64–2.61 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.17, 178.0, 141.5, 137.9, 136.8, 135.6, 133.6, 131.9, 129.6, 129.2, 128.4, 128.2, 127.3, 127.0, 125.5, 125.0, 123.2, 122.5, 121.4, 119.3, 118.0, 110.3, 109.5, 75.2, 59.6, 53.3, 52.4, 43.2, 22.3.

Anal. Calcd for $C_{32}H_{25}N_3O_2S$: C, 74.54; H, 4.89; N, 8.15. Found: C, 74.55; H, 4.88; N, 8.17.

1′-Benzoyl-2′-(4-chlorophenyl)-1-methyl-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5a)

White powder; yield: 97 mg (84%); mp 240–242 °C.

IR: 3304, 3051, 2920, 2768, 1672, 1609, 1490 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.04 (m, 2 H), 7.67–7.63 (m, 2 H), 7.53 (t, *J* = 7.6 Hz, 2 H), 7.41–7.38 (m, 1 H), 7.35–7.31 (m, 1 H), 7.21–7.17 (m, 1 H), 7.07–6.98 (m, 7 H), 6.94–6.92 (m, 1 H), 6.68 (d, *J* = 8 Hz, 1 H), 5.91 (d, *J* = 9.2 Hz, 1 H), 5.16 (uneven t, *J* = 9 Hz, 1 H), 4.46 (d, *J* = 8.4 Hz, 1 H), 2.94–2.92 (m, 1 H), 2.89 (s, 3 H), 2.88–2.84 (m, 2 H), 2.63–2.59 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 176.4, 144.3, 137.9, 135.6, 134.1, 133.7, 133.3, 129.7, 129.6, 129.2, 128.3, 128.2, 127.3, 127.0, 124.6, 123.2, 121.4, 119.3, 118.0, 110.6, 110.4, 108.0, 75.9, 59.9, 57.4, 51.6, 43.2, 25.5, 22.2.

Anal. Calcd for $C_{35}H_{28}ClN_3O_2$: C, 75.33; H, 5.06; N, 7.53. Found: C, 75.35; H, 5.05; N, 7.52.

1′-Benzoyl-2′-(4-chlorophenyl)-1-ethyl-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5b)

White powder; yield: 95 mg (81%); mp 223–225 °C.

IR: 3669, 3297, 2920, 2783, 1672, 1605, 1486 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.05 (m, 2 H), 7.64 (t, *J* = 6.8 Hz, 2 H), 7.53 (t, *J* = 7.6 Hz, 2 H), 7.41–7.39 (m, 1 H), 7.34–7.30 (m, 1 H), 7.17 (uneven t, *J* = 7.4 Hz, 1 H), 7.07–6.92 (m, 8 H), 6.68 (d, *J* = 7.6 Hz, 1 H), 5.92 (d, *J* = 9.2 Hz, 1 H), 5.17 (t, *J* = 8.8 Hz, 1 H), 4.44 (d, *J* = 8.4 Hz, 1 H), 3.67–3.58 (m, 1 H), 3.33–3.24 (m, 1 H), 2.95–2.85 (m, 3 H), 2.63–2.59 (m, 1 H), 0.76 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.0, 176.0, 143.4, 137.9, 135.7, 134.0, 133.6, 133.3, 131.9, 129.6, 129.6, 128.3, 128.2, 127.6, 127.1, 124.8, 122.9, 121.4, 119.3, 118.0, 110.7, 110.5, 108.1, 75.7, 60.0, 57.5, 51.4, 43.2, 33.9, 22.1, 12.1.

Anal. Calcd for $C_{36}H_{30}ClN_3O_2$: C, 75.58; H, 5.29; N, 7.34. Found: C, 75.57; H, 5.28; N, 7.33.

1′-Benzoyl-2′-(4-chlorophenyl)-1-propyl-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5c)

White powder; yield: 104 mg (86%); mp 205–207 °C.

IR: 3349, 3055, 2868, 2797, 1676, 1609, 1486 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.05 (m, 2 H), 7.66–7.63 (m, 2 H), 7.55–7.51 (m, 2 H), 7.40–7.38 (m, 1 H), 7.33–7.29 (m, 1 H), 7.19–7.15 (m, 1 H), 7.08–7.06 (m, 2 H), 7.04–6.98 (m, 5 H), 6.94–6.92 (m, 1 H), 6.68 (d, *J* = 7.6 Hz, 1 H), 5.91 (d, *J* = 9.2 Hz, 1 H), 5.17 (t, *J* = 8.8 Hz, 1 H), 4.46 (d, *J* = 8.4 Hz, 1 H), 3.57–3.50 (m, 1 H), 3.26–3.21 (m, 1 H), 2.92–2.83 (m, 3 H), 2.62–2.59 (m, 1 H), 1.30–1.21 (m, 2 H), 0.62 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.0, 176.2, 144.0, 137.9, 135.7, 134.1, 133.6, 133.4, 131.9, 129.9, 129.6, 129.2, 128.3, 128.2, 127.5, 127.1, 124.7, 122.9, 121.5, 119.3, 118.0, 110.7, 110.5, 108.3, 75.6, 59.9, 57.4, 51.5, 43.2, 41.0, 22.2, 20.5, 11.0.

Anal. Calcd for $C_{37}H_{32}ClN_3O_2$: C, 75.82; H, 5.50; N, 7.17. Found: C, 75.81; H, 5.51; N, 7.17.

1′-Benzoyl-1-butyl-2′-(4-chlorophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5d)

White powder; yield: 99 mg (80%); mp 210–212 °C.

IR: 3334, 3051, 2891, 2794, 1691, 1605, 1464 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8 Hz, 2 H), 7.65 (t, *J* = 7.6 Hz, 2 H), 7.53 (t, *J* = 7.6 Hz, 2 H), 7.40–7.38 (m, 1 H), 7.31 (tm, *J* = 7.6 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.08–6.96 (m, 7 H), 6.94–6.92 (m, 1 H), 6.68 (d, *J* = 8 Hz, 1 H), 5.90 (d, *J* = 9.2 Hz, 1 H), 5.17 (t, *J* = 8.8 Hz, 1 H), 4.46 (d, *J* = 8 Hz, 1 H), 3.61–3.56 (m, 1 H), 3.27–3.22 (m, 1 H), 2.94–2.82 (m, 3 H), 2.60 (d, *J* = 12.8 Hz, 1 H), 1.25–1.16 (m, 1 H), 1.13–1.06 (m, 1 H), 0.99–0.90 (m, 2 H); 0.80 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 176.1, 135.7, 134.1, 133.6, 133.4, 133.2, 131.9, 130.6, 130.1, 129.9, 129.6, 129.2, 128.3, 128.2, 127.7, 127.6, 127.1, 126.4, 125.3, 124.8, 123.1, 122.9, 121.5, 120.5, 119.3, 118.0, 110.7, 75.6, 59.9, 57.3, 51.5, 43.2, 39.2, 29.1, 22.1, 20.3, 13.7.

Anal. Calcd for $C_{38}H_{34}ClN_3O_2$: C, 76.05; H, 5.71; N, 7.00. Found: C, 76.06; H, 5.71; N, 7.01.

1-Allyl-1′-benzoyl-2′-(4-chlorophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5e)

Off white powder; yield: 98 mg (82%); mp 222–224 °C.

IR: 3334, 3051, 2846, 2786, 1672, 1605, 1460 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.6 Hz, 2 H), 7.67–7.63 (m, 2 H), 7.53 (uneven t, *J* = 7.6 Hz, 2 H), 7.49–7.31 (m, 1 H), 7.31–7.27 (m, 1 H), 7.18 (uneven t, *J* = 7.2 Hz, 1 H), 7.08–6.98 (m, 7 H), 6.94–6.92 (m, 1 H), 6.63 (d, *J* = 7.6 Hz, 1 H), 5.92 (d, *J* = 9.2 Hz, 1 H), 5.38–5.31 (m, 1 H) 5.18 (t, *J* = 8.8 Hz, 1 H), 4.91 (d, *J* = 10.4 Hz, 1 H), 4.49–4.42 (m, 2 H), 4.29–4.24 (m, 1 H), 3.87–3.81 (m, 1 H), 2.93–2.85 (m, 3 H), 2.64–2.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 176.0, 143.5, 137.9, 135.6, 134.0, 133.7, 133.4, 131.9, 130.5, 129.9, 129.6, 129.2, 128.3, 127.3, 127.1, 124.6, 123.1, 121.5, 119.3, 118.0, 116.6, 110.7, 110.5, 108.9, 75.9, 59.9, 57.5, 51.5, 43.2, 41.5, 22.2.

Anal. Calcd for $C_{37}H_{30}ClN_3O_2$: C, 76.08; H, 5.18; N, 7.19. Found: C, 76.06; H, 5.17; N, 7.17.

1′-Benzoyl-1-benzyl-2′-(4-chlorophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5f)

White powder; yield: 105 mg (80%); mp 246–248 °C.

IR: 3375, 3054, 2946, 2824, 1691, 1609, 1486 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.05 (m, 2 H), 7.69–7.64 (m, 2 H), 7.54 (uneven t, *J* = 7.8 Hz, 2 H), 7.41–7.39 (m, 1 H), 7.21–7.10 (m, 5 H), 7.07–7.00 (m, 7 H), 6.94–6.91 (m, 1 H), 6.54–6.52 (m, 2 H), 6.49–6.46 (m, 1 H), 5.95 (d, *J* = 9.2 Hz, 1 H), 5.23 (uneven t, *J* = 8.8 Hz, 1 H), 5.06 (d, *J* = 16 Hz, 1 H), 4.55 (d, *J* = 8.4 Hz, 1 H), 4.31 (d, *J* = 16 Hz, 1 H), 2.93–2.87 (m, 3 H), 2.64–2.61 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 176.7, 143.6, 138.0, 137.6, 134.9, 134.2, 133.7, 133.5, 131.8, 130.2, 129.6, 129.2, 128.6, 128.3, 127.3, 127.0, 126.4, 124.7, 123.2, 121.5, 119.3, 118.0, 110.7, 110.5, 109.2, 75.8, 59.9, 57.2, 51.6, 43.2, 22.2.

Anal. Calcd for $C_{41}H_{32}ClN_3O_2$: C, 77.65; H, 5.09; N, 6.63. Found: C, 77.64; H, 5.09; N, 6.64.

1′-Benzoyl-2′-(4-chlorophenyl)-5-fluoro-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5g)

Off white powder; yield: 93 mg (80%); mp 213–215 °C.

IR: 3431, 3300, 2909, 2820, 1713, 1676, 1482 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.02–8.00 (m, 2 H), 7.66 (uneven t, *J* = 7.4 Hz, 1 H), 7.53 (uneven t, *J* = 7.8 Hz, 2 H), 7.44–7.39 (m, 2 H), 7.14–6.89 (m, 10 H), 6.65–6.62 (m, 1 H), 5.85 (d, *J* = 9.2 Hz, 1 H), 5.11 (t, *J* = 8.6 Hz, 1 H), 4.44 (d, *J* = 8 Hz, 1 H), 2.93–2.86 (m, 3 H), 2.66–2.62 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 177.8, 138.0, 137.1, 135.6, 133.9, 133.7, 133.6, 131.5, 129.9, 129.3, 128.5, 128.2, 127.0, 121.6, 119.4, 118.1, 116.3, 116.1, 113.0, 112.0, 110.6, 110.4, 110.38, 110.30, 76.2, 60.0, 57.5, 51.4, 43.3, 22.2.

Anal. Calcd for $C_{34}H_{25}ClFN_3O_2$: C, 72.66; H, 4.48; N, 7.48. Found: C, 72.65; H, 4.49; N, 7.50.

1′-Benzoyl-5-chloro-2′-(4-chlorophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5h)

White powder; yield: 92 mg (77%); mp 214–216 °C.

IR: 3326, 2805, 1695, 1613, 1475 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.6 Hz, 2 H), 7.67–7.64 (m, 2 H), 7.54 (t, *J* = 7.6 Hz, 2 H), 7.41–7.39 (m, 1 H), 7.24 (d, *J* = 2 Hz, 1 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 7.04–7.02 (m, 2 H), 7.00 (s, 1 H), 6.91–6.89 (m, 2 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 5.85 (d, *J* = 9.6 Hz, 1 H), 5.10 (uneven t, *J* = 8.6 Hz, 1 H), 4.46 (d, *J* = 8 Hz, 1 H), 2.94–2.85 (m, 3 H), 2.67–2.63 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 175.1, 137.4, 135.8, 133.4, 131.6, 131.5, 131.4, 129.1, 127.7, 127.6, 127.0, 126.5, 126.3, 125.9, 124.7, 123.1, 122.9, 119.3, 117.1, 115.8, 108.4, 108.2, 73.7, 57.7, 55.3, 49.1, 41.0, 20.0.

Anal. Calcd for $C_{34}H_{25}Cl_2N_3O_2$: C, 70.59; H, 4.36; N, 7.26. Found: C, 70.58; H, 4.35; N, 7.25.

1′-Benzoyl-5-bromo-2′-(4-chlorophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5i)

Off white solid; yield: 100 mg (78%); mp 218–220 °C.

IR: 3435, 3196, 2943, 2801, 1695, 1613, 1464 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.2 Hz, 2 H), 7.81 (d, *J* = 1.6 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.54 (t, *J* = 7.8 Hz, 2 H), 7.41–7.39 (m, 2 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 7.04–7.01 (m, 2 H), 6.91–6.90 (m, 3 H), 6.59 (d, *J* = 8 Hz, 1 H), 5.85 (d, *J* = 8.8 Hz, 1 H), 5.10 (uneven t, *J* = 8.6 Hz, 1 H), 4.45 (d, *J* = 8 Hz, 1 H), 2.94–2.85 (m, 3 H), 2.67–2.63 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 177.3, 138.0, 135.7, 133.9, 133.7, 133.6, 132.6, 131.4, 130.3, 129.97, 129.90, 129.6, 129.3, 128.5, 128.4, 128.3, 128.2, 128.1, 127.0, 125.1, 121.6, 119.4, 118.1, 115.9, 111.2, 110.6, 110.4, 75.6, 59.8, 57.5, 51.5, 43.3, 22.2.

Anal. Calcd for $C_{34}H_{25}BrClN_3O_2$: C, 65.56; H, 4.05; N, 6.75. Found: C, 65.54; H, 4.04; N, 6.75.

1′-Benzoyl-2′-(4-chlorophenyl)-5-iodo-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5j)

White powder; yield: 119 mg (86%); mp 168–170 °C.

IR: 3353, 3192, 2939, 2797, 1695, 1605, 1464 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.99 (m, 2 H), 7.96 (d, 1.6 Hz, 1 H), 7.69–7.65 (m, 1 H), 7.61–7.58 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.54 (uneven t, *J* = 8.2 Hz, 2 H), 7.44–7.39 (m, 1 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 7.04–7.01 (m, 2 H), 6.96 (s, 1 H), 6.91–6.89 (m, 2 H), 6.49 (d, *J* = 8 Hz, 1 H), 5.84 (d, *J* = 9.2 Hz, 1 H), 5.10 (t, *J* = 8.4 Hz, 1 H), 4.44 (d, *J* = 8 Hz, 1 H), 2.94–2.84 (m, 3 H), 2.67–2.63 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 176.9, 140.9, 138.5, 135.6, 133.89, 133.82, 133.7, 131.4, 130.6, 129.9, 129.3, 128.6, 128.2, 127.0, 121.6, 119.4, 118.1, 111.6, 110.6, 75.8, 60.0, 57.5, 51.3, 43.3, 22.3.

Anal. Calcd for $C_{34}H_{25}ClIN_3O_2$: C, 60.96; H, 3.76; N, 6.27. Found: C, 60.95; H, 3.77; N, 6.29.

1′-Benzoyl-1-benzyl-2′-(4-chlorophenyl)-5-fluoro-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5k)

White powder; yield: 114 mg (84%); mp 234–236 °C.

IR: 3356, 3062, 2939, 2812, 1695, 1620, 1467 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.2 Hz, 2 H), 7.66 (uneven t, *J* = 7.4 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 2 H), 7.48–7.45 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.42–7.39 (m, 1 H), 7.19–7.09 (m, 7 H), 7.05–7.02 (m, 2 H), 6.97 (s, 1 H), 6.91–6.86 (m, 2 H), 6.51–6.49 (m, 2 H), 6.40–6.37 (m, 1 H), 5.95 (d, *J* = 8.8 Hz, 1 H), 5.19 (uneven t, *J* = 8.6 Hz, 1 H), 5.06 (d, *J* = 16 Hz, 1 H), 4.52 (d, *J* = 8 Hz, 1 H), 4.27 (d, *J* = 16 Hz, 1 H), 2.94–2.86 (m, 3 H), 2.67–2.63 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7, 176.0, 139.4, 138.1, 135.7, 134.6, 134.0, 133.77, 133.75, 131.5, 130.2, 129.49, 129.42, 129.3, 128.74, 128.71, 128.2, 127.5, 127.2, 126.4, 121.5, 119.4, 118.1, 116.2, 116.0, 112.7, 112.4, 110.7, 110.4, 110.0, 109.9, 76.0, 60.1, 57.5, 51.5, 43.3, 22.2.

Anal. Calcd for $C_{41}H_{31}ClFN_3O_2$: C, 75.51; H, 4.79; N, 6.44. Found: C, 75.50; H, 4.77; N, 6.45.

2′-Benzoyl-1-benzyl-5-bromo-1′-(4-chlorophenyl)-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5l)

White solid; yield: 118 mg (80%); mp 240–242 °C.

IR: 3390, 3047, 2902, 2797, 1695, 1605, 1467 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.01 (m, 2 H), 7.84 (d, *J* = 1.6 Hz, 1 H), 7.68–7.65 (m, 1 H), 7.54 (uneven t, *J* = 7.8 Hz, 2 H), 7.41–7.39 (m, 1 H), 7.32–7.29 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.19–7.07 (m, 7 H), 7.04–7.02 (m, 2 H), 6.95–6.91 (m, 1 H), 6.91–6.88 (m, 1 H), 6.53–6.48 (m, 2 H), 6.34 (d, *J* = 8.4 Hz, 1 H), 5.95 (d, *J* = 8.8 Hz, 1 H), 5.18 (t, *J* = 8.6 Hz, 1 H), 4.52 (d, *J* = 7.6 Hz, 1 H), 5.05 (d, *J* = 16 Hz, 1 H), 4.26 (d, *J* = 16.4 Hz, 1 H), 2.95–2.83 (m, 3 H), 2.67–2.63 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7, 175.6, 142.5, 138.1, 135.6, 134.4, 133.9, 133.8, 132.6, 131.4, 130.3, 130.2, 129.7, 129.3, 129.2, 128.78, 128.74, 128.6, 128.3, 128.2, 127.7, 127.5, 127.3, 127.0, 126.4, 126.3, 121.5, 119.4, 118.1, 116.1, 110.7, 110.6, 110.4, 75.8, 60.1, 57.5, 51.4, 43.3, 22.2.

Anal. Calcd for $C_{41}H_{31}BrClN_3O_2$: C, 69.06; H, 4.38; N, 5.89. Found: C, 69.07; H, 4.38; N, 5.90.

1′-Benzoyl-5-chloro-2′-(4-chlorophenyl)-1-propyl-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5m)

White powder; yield: 110 mg (86%); mp 227–229 °C.

IR: 3360, 3066, 2846, 2801, 1687, 1605, 1479 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8 Hz, 2 H), 7.65 (t, *J* = 7.2 Hz, 2 H), 7.53 (t, *J* = 7.2 Hz, 2 H), 7.41–7.39 (m, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 7.04–7.02 (m, 4 H), 6.94–6.90 (m, 2 H), 6.61 (d, *J* = 8.4 Hz, 1 H), 5.90 (d, *J* = 9.4 Hz, 1 H), 5.12 (uneven t, *J* = 8.4 Hz, 1 H), 4.44 (d, *J* = 8 Hz, 1 H), 3.54–3.48 (m, 1 H), 3.21–3.18 (m, 1 H), 2.93–2.80 (m, 3 H), 2.65–2.61 (m, 1 H), 1.27–1.20 (m, 2 H), 0.60 (uneven t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7, 175.8, 142.5, 138.1, 135.6, 133.9, 133.7, 133.6, 131.6, 129.9, 129.6, 129.5, 129.3, 128.49, 128.41, 128.2, 127.0, 125.0, 121.5, 119.4, 118.1, 110.6, 110.4, 109.2, 75.7, 60.1, 57.6, 51.4, 43.3, 41.1, 22.2, 20.4, 10.9.

Anal. Calcd for $C_{37}H_{31}Cl_2N_3O_2$: C, 71.61; H, 5.04; N, 6.77. Found: C, 71.63; H, 5.05; N, 6.77.

1′-Benzoyl-2′-(4-chlorophenyl)-5-methoxy-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5n)

Off white powder; yield: 101 mg (85%); mp 196–198 °C.

IR: 3345, 3170, 2932, 2805, 1687, 1609, 1486 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.04 (m, 2 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 7.8 Hz, 2 H), 7.40–7.38 (m, 1 H), 7.23 (d, *J* = 2.4 Hz, 1 H), 7.12–6.91 (m, 9 H), 6.82–6.79 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.61 (d, *J* = 8.4 Hz, 1 H), 5.85 (d, *J* = 9.2 Hz, 1 H), 5.14 (uneven t, *J* = 8.8 Hz, 1 H), 4.45 (d, *J* = 8.4 Hz, 1 H), 3.83 (s, 3 H), 2.95–2.87 (m, 3 H), 2.65–2.62 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 177.8, 156.4, 137.9, 135.6, 134.5, 134.1, 133.7, 133.4, 131.8, 129.9, 129.2, 128.4, 128.3, 127.0, 121.5, 119.3, 118.0, 115.0, 111.0, 110.7, 110.4, 110.2, 76.3, 59.9, 57.5, 55.9, 51.5, 43.2, 22.2.

Anal. Calcd for $C_{35}H_{28}ClN_3O_3$: C, 73.23; H, 4.92; N, 7.32. Found: C, 73.23; H, 4.93; N, 7.33.

1′-Benzoyl-1-benzyl-2′-(4-chlorophenyl)-5-methoxy-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5o)

White powder; yield: 116 mg (85%); mp 248–250 °C.

IR: 3338, 3028, 2946, 2794, 1676, 1605, 1490 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.06 (m, 2 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.54 (uneven t, *J* = 7.8 Hz, 2 H), 7.41–7.39 (m, 1 H), 7.28 (d, *J* = 2.4 Hz, 1 H), 7.19–7.15 (m, 3 H), 7.13–7.07 (m, 4 H), 7.03–7.02 (m, 3 H), 6.93–6.91 (m, 1 H), 6.73–6.70 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.52–6.50 (m, 2 H), 6.37 (d, *J* = 8.8 Hz, 1 H), 5.95 (d, *J* = 9.2 Hz, 1 H), 5.22 (t, *J* = 8.8 Hz, 1 H), 5.04 (d, *J* = 16 Hz, 1 H), 4.52 (d, *J* = 8 Hz, 1 H), 4.27 (d, *J* = 16 Hz, 1 H), 3.81 (s, 3 H), 2.95–2.87 (m, 3 H), 2.66–2.62 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.0, 175.9, 156.5, 138.0, 136.9, 135.6, 135.0, 134.2, 133.7, 133.5, 131.9, 130.2, 129.2, 128.7, 128.63, 128.61, 128.3, 127.3, 127.0, 126.4, 121.5, 119.3, 118.0, 114.6, 111.0, 110.7, 110.4, 109.8, 76.1, 60.0, 57.4, 55.8, 51.5, 43.2, 22.2.

Anal. Calcd for $C_{42}H_{34}ClN_3O_3$: C, 75.95; H, 5.16; N, 6.33. Found: C, 75.94; H, 5.18; N, 6.36.

1′-Benzoyl-6-chloro-2′-(4-chlorophenyl)-1-propyl-1′,2′,5′,6′,11′,11b′-hexahydrospiro[indoline-3,3′-indolizino[8,7-*b*]indol]-2-one (5p)

Red powder; yield: 100 mg (78%); mp 241–243 °C.

IR: 3364, 3055, 2961, 2805, 1684, 1613, 1445 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.01 (m, 2 H), 7.66 (t, *J* = 7.2 Hz, 1 H), 7.59–7.51 (m, 3 H), 7.40–7.38 (m, 1 H), 7.11–7.07 (m, 4 H), 7.04–6.99 (m, 4 H), 6.95–6.91 (m, 1 H), 6.68 (d, *J* = 1.6 Hz, 1 H), 5.86 (d, *J* = 8.8 Hz, 1 H), 5.15 (uneven t, *J* = 8.6 Hz, 1 H), 4.43 (d, *J* = 8 Hz, 1 H), 3.55–3.48 (m, 1 H), 3.23–3.17 (m, 1 H), 2.89–2.81 (m, 3 H), 2.63–2.59 (m, 1 H), 1.29–1.22 (m, 2 H), 0.62 (uneven t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7, 176.2, 145.2, 138.0, 135.6, 135.4, 133.9, 133.7, 133.6, 131.7, 129.9, 129.3, 128.4, 128.2, 127.9, 127.3, 127.0, 126.1, 125.8, 122.9, 121.6, 119.4, 118.1, 110.7, 110.5, 108.9, 75.3, 59.9, 57.3, 51.3, 43.1, 41.1, 22.1, 20.4, 10.9.

Anal. Calcd for $C_{37}H_{31}Cl_2N_3O_2$: C, 71.61; H, 5.04; N, 6.77. Found: C, 71.62; H, 5.05; N, 6.78.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References

(1) Dehelean, C. A.; Marcovici, I.; Soica, C.; Mioc, M.; Coricovac, D.; Iurciuc, S.; Pinzaru, I. *Molecules* **2021**, *26*, 1109.
(2) (a) Wang, J.; Gong, F.; Liang, T.; Xie, Z.; Yang, Y.; Cao, C.; Chen, X. *Eur. J. Med. Chem.* **2021**, *225*, 113815. (b) Ahmad, I.; Fakhri, S.; Khan, H.; Jeandet, P.; Aschner, M.; Yu, Z. L. *Chem. Biol. Interact.* **2020**, *330*, 109229; and references cited therein.
(3) (a) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479. (b) Ashok, P.; Ganguly, S.; Murugesan, S. *Mini-Rev. Med. Chem.* **2013**, *13*, 1778. (c) Ashok, P.; Lathiya, H.; Murugesan, S. *Eur. J. Med. Chem.* **2015**, *97*, 928. (d) Dai, J.; Dan, W.; Schneider, U.; Wang, J. *Eur. J. Med. Chem.* **2018**, *157*, 622. (e) Ferraz, C. A. A.; de Oliveira Junior, R. G.; Picot, L.; da Silva Almeida, J. R. G.; Nunes, X. P. *Fitoterapia* **2019**, *137*, 104196. (f) Liu, W.; Liu, X.; Liu, W.; Gao, Y.; Wu, L.; Huang, Y.; Zhao, Q. *Eur. J. Med. Chem.* **2022**, *229*, 114095.
(4) (a) Zhang, M.; Sun, D. *Anti-Cancer Agents Med. Chem.* **2015**, *15*, 537. (b) Sahoo, C. R.; Paidesetty, S. K.; Padhy, R. N. *Eur. J. Med. Chem.* **2019**, *162*, 752. (c) Luo, B.; Song, X. *Eur. J. Med. Chem.* **2021**, *224*, 113688.
(5) Wang, L.; Chen, X.; Yan, C. *Genes Dis.* **2020**, *9*, 334.
(6) (a) Karpov, A. S.; Rominger, F.; Müller, T. J. *Org. Biomol. Chem.* **2005**, *3*, 4382. (b) Kulkarni, A.; Abid, M.; Toeroek, B.; Huang, X. *Tetrahedron Lett.* **2009**, *50*, 1791. (c) Maity, P.; Adhikari, D.; Jana, A. K. *Tetrahedron* **2019**, *75*, 965. (d) Avadhani, A.; Iniyavan, P.; Acharya, A.; Gautam, V.; Chakrabarti, S.; Ila, H. *ACS Omega* **2019**, *4*, 17910. (e) Yin, H.; Ma, Q.; Wang, Y.; Gu, X.; Feng, Z.; Wu, Y.; Wang, S. *RSC Adv.* **2021**, *11*, 19639. (f) Byeon, H. J.; Jung, K. H.; Moon, G. S.; Moon, S. K.; Lee, H. Y. *Sci. Rep.* **2020**, *10*, 1.
(7) (a) Meesala, R.; Mordi, M. N.; Mansor, S. M. *Synlett* **2014**, *25*, 120. (b) Kamal, A.; Sathish, M.; Prasanthi, A. V. G.; Chetna, J.; Tangella, Y.; Srinivasulu, V.; Alarifi, A. *RSC Adv.* **2015**, *5*, 90121.
(8) Ivasiv, V.; Albertini, C.; Gonçalves, A. E.; Rossi, M.; Bolognesi, M. L. *Curr. Top. Med. Chem.* **2019**, *19*, 1694.
(9) Soni, J. P.; Yeole, Y.; Shankaraiah, N. *RSC Med. Chem.* **2021**, *12*, 730.
(10) Singh, M.; Amrutha Krishnan, A. V.; Mandal, R.; Samanta, J.; Ravichandiran, V.; Natarajan, R.; Hazra, A. *Mol. Diversity* **2020**, *24*, 627.
(11) Poissonnet, G.; Théret-Bettiol, M. H.; Dodd, R. H. *J. Org. Chem.* **1996**, *61*, 2273.
(12) Zhang, X.; Liu, M.; Zhan, D.; Kaur, M.; Jasinski, J. P.; Zhang, W. *New J. Chem.* **2022**, *46*, 3866.
(13) (a) Vidya, S.; Priya, K.; Velayudhan Jayasree, D.; Deepthi, A.; Biju, P. G. *Synth. Commun.* **2019**, *49*, 1592. (b) Sathi, V.; Thomas, N. V.; Deepthi, A. *Org. Biomol. Chem.* **2020**, *18*, 7822. (c) Thomas, N. V.; Sathi, V.; Deepth, A. *J. Heterocycl. Chem.* **2022**, *59*, 1407.
(14) Thomas, N. V.; Meenakshy, C. B.; Leena, S. S.; Deepthi, A. *Synthesis* **2022**, *54*, 2885; and references cited therein.
(15) Caramori, G. F.; Galembeck, S. E.; Laali, K. K. *J. Org. Chem.* **2005**, *70*, 3242.
(16) Cammi, R.; Mennucci, B.; Tomasi, J. *J. Phys. Chem. A* **2000**, *104*, 5631.
(17) (a) Bhatia, R.; Kumar, B. *Eur. J. Med. Chem.* **2022**, *247*, 115020. (b) Tong, J. B.; Luo, D.; Bian, S.; Zhang, X. *J. Mol. Liq.* **2021**, *335*, 116235.
(18) (a) Gollner, A.; Rudolph, D.; Arnhof, H.; Bauer, M.; Blake, S. M.; Boehmelt, G.; McConnell, D. B. *J. Med. Chem.* **2016**, *59*, 10147. (b) Zhang, J.; Li, Y.; Guo, L.; Cao, R.; Zhao, P.; Jiang, W.; Si, S. *Cancer Biol. Ther.* **2009**, *8*, 2374.