RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 16101

Ring-opening cyclization of activated spiro-aziridine oxindoles with heteroarenes: a facile synthetic approach to spiro-oxindole-fused pyrroloindolines†

Sonal Bhandari, Sravani Sana, Vandana Lahoti, Ramya Tokala and Nagula Shankaraiah *

Received 22nd January 2020
Accepted 30th March 2020

DOI: 10.1039/d0ra00684j

rsc.li/rsc-advances

Herein, we report a facile tandem approach for the synthesis of both spiro-oxindole-fused pyrroloindolines and benzofurano-pyrrolidines *via* a Lewis acid-catalyzed domino ring-opening with concomitant ring annulation using activated spiro-aziridines and heteroarenes. This method offers a new class of novel spiro-fused polycyclic pyrrolidines in a one-pot and sustainable manner with good yields and high diastereoselectivity. In addition, the structure of **3d** was confirmed by single X-ray crystallography analysis.

Introduction

The use of natural products as drug leads has resulted in great demand for the synthetic community to develop effective strategies for the single-step synthesis of rare complicated heterocycles. Spiro-fused polycyclic pyrrolidine frameworks are the core skeletons of various architecturally complex molecules and natural product-like compounds as potential drug candidates.[1] Accordingly, direct access to spiro-fused polycyclic pyrrolidine derivatives in the minimum number of steps is an easily expanded approach for very quick optimization of their biological properties. Thus, versatile synthetic strategies have been developed, *e.g.*, [3 + 2] cycloaddition,[2] Pictet–Spengler,[3] Morita–Baylis–Hillman,[4] and Michael/Mannich [3 + 2] cycloaddition reactions.[5] The Lewis acid-catalyzed cascade annulation of heteroarenes has gained considerable attention for the development of fused pyrrolidines based on the tethered built-in nucleophilicity (ring-opening of aziridine) on the C-3 position and electrophilicity (intramolecular annulation) on the C-2 position of heteroarenes, thereby providing considerable synthetic benefits from the viewpoint of easy availability and accessibility to react with distinct reaction partners.[6]

Indole and benzofuran are the most important class of heteroarenes, exhibiting a broad spectrum of biological activities such as anti-tumor, analgesic, anti-microbial, anti-malarial, anti-diabetic, anti-tubercular, anti-HIV, and anti-oxidant activity, and thus are considered important templates for drug discovery.[7] Simultaneously, (hetero)arene-annulated tricyclic pyrrolidine frameworks are frequently encountered in numerous natural products and biologically significant molecules such as physostigmine and physovenine as acetyl cholinesterase inhibitors, and (−)-flustramine B as an anticancer agent (Fig. 1).[8] In addition, spiro-fused pyrrolidine functionalization at the C-3 position of oxindole has occupied a remarkable position in synthetic chemistry. A large group of diverse skeletons of spiro-fused pyrrolidines exists in natural products such as spirotryprostatine A and B, elacomine, and horsifiline, with various types of bioactivities as anti-tumor, anti-microbial and anti-malarial agents.[9]

Although the abovementioned reactions have made a significant contribution, the domino ring-opening and dearomative cyclization of activated aziridine with heteroarenes in the presence of a Lewis acid is fascinating. Owing to the rapid access to stereoselective heteroarene-annulated polycyclic derivatives and advances in the synthesis of natural products, this specific transformation has attracted attention from synthetic chemists.[10] In 2014, Wang and co-workers reported an asymmetric [3 + 2] cycloaddition for the construction of pyrroloindolines mediated by the *in situ* generation of a magnesium catalyst.[11] Subsequently, in 2015, Chai and co-workers established a copper-catalyzed [3 + 2] annulation of indoles with 2-arylaziridines, which could concisely furnish pyrroloindolines bearing multiple contiguous stereogenic centers with excellent regio-, diastereo- and enantioselectivity in one synthetic operation (Scheme 1a).[12] Recently, the catalyst-free "on-water" regio- and stereospecific ring-opening of spiro-aziridine oxindole was described by Hajra and co-workers to give enantiopure unsymmetrical 3,3′-bisindoles (Scheme 1b).[13]

Based on these established methods, in continuation of our research interest in the synthesis of spiro-oxindole derivatives,[14]

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad-500037, India. E-mail: shankar@niperhyd.ac.in

† Electronic supplementary information (ESI) available. CCDC 1970416. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra00684j

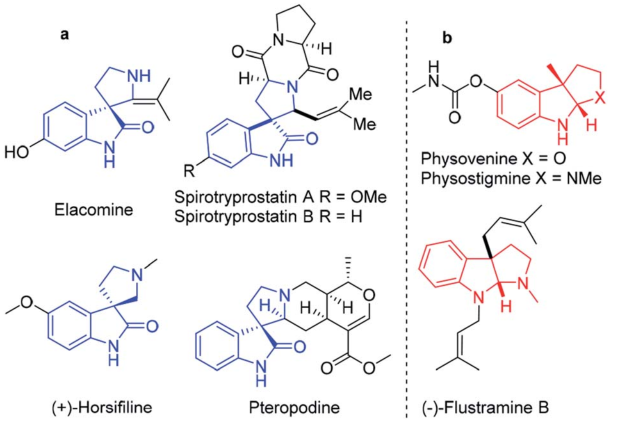
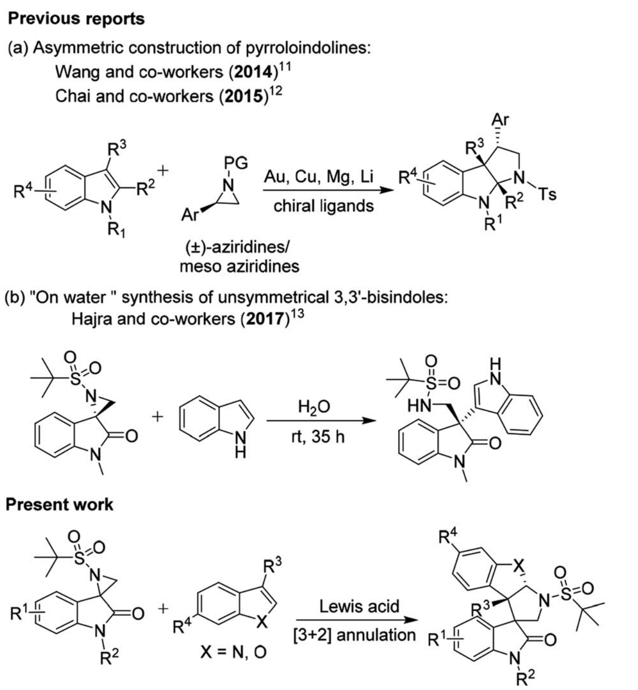


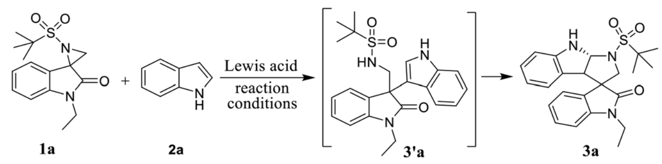
Fig. 1 (a) Spiro-oxindole-fused mono and tricyclic pyrrolidine alkaloid natural products and (b) heteroarene-fused tricyclic pyrrolidine natural products.



Scheme 1 Lewis acid-catalyzed ring-opening of spiro-oxindole aziridines with heteroarenes.

herein, we report the Lewis acid-catalyzed domino ring-opening (Friedel–Craft-type C–C bond formation) of activated spiro-aziridine oxindole with heteroarenes followed by intramolecular C-2 annulation. Although the ring-opening version of this reaction was promoted by copper and scandium triflates with moderate yields, C2 annulation was promoted using $BF_3\cdot OEt_2$ as a Lewis acid with good control of the diastereoselectivity. Irrespective of C3 substitution on heteroarenes, the reactions progressed smoothly with excellent regio- and diastereoselectivity.

Table 1 Optimization of the reaction conditions[a]



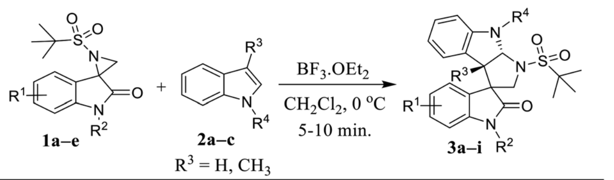
Entry	Catalyst (10 mol%)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%) 3′a	3a
1	$Sc(OTf)_3$	CH_3CN	25	4	46	0
2	$Bi(OTf)_3$	CH_3CN	25	12	25	0
3	$Yb(OTf)_3$	CH_3CN	25	10	Nr	Nr
4	$Cu(OTf)_2$	CH_3CN	25	6	35	0
5	$Sc(OTf)_3$	CH_2Cl_2	25	7	40	Trace
6	$Sc(OTf)_3$	CH_2Cl_2	0	30 min	0	0
7	$Sc(OTf)_3$	CH_3CN	80	30 min	20	0
8	$Sc(OTf)_3$	CH_3CN	80	4	0[d]	
9	$Sc(OTf)_3$	CH_2Cl_2	40	4	30	0
10	$BF_3\cdot OEt_2$	CH_3CN	25	3	0	35
11[e]	$BF_3\cdot OEt_2$	CH_3CN	80	3	0	Trace
12	$BF_3\cdot OEt_2$	CH_2Cl_2	25	30 min	0	45
13[c]	$BF_3\cdot OEt_2$	CH_2Cl_2	0	5 min	0	82
14[c]	$BF_3\cdot OEt_2$ (20)	CH_2Cl_2	0	5 min	0	80

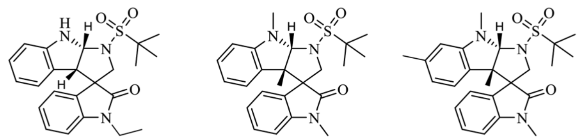
[a] All reactions were performed with 1.0 mmol of **1a** and 1.0 mmol of **2a** in (5 mL) of solvent in the presence of a Lewis acid catalyst (10 mol%) at room temperature. [b] Isolated yields. [c] The reaction was performed at 0 °C. [d] TLC was not clear. [e] The reaction was carried out at 80 °C. Nr: no reaction.

Results and discussion

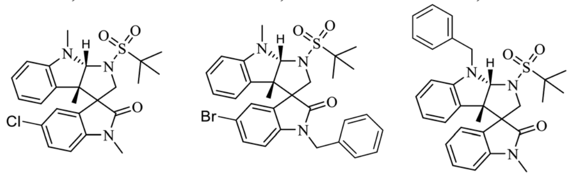
As illustrated in Table 1, the feasibility of the proposed domino reaction was first evaluated between activated spiro-aziridineoxindole **1a** and indole **2a** with $Sc(OTf)_3$ as a catalyst; however, the corresponding tetrahydropyrrolo[2,3-*b*]indole **3a** was not obtained, instead it gave 3,3′-bisindoles at room temperature (entries 1 and 5, Table 1). Lewis acids such as $Bi(OTf)_3$, $Yb(OTf)_3$ and the less acidic $Cu(OTf)_2$ also failed to afford the desired product **3a** (entries 2–4, Table 2). To check the impact of $Sc(OTf)_3$ on the intramolecular cyclization, the reaction was performed for different reaction times at varying temperature, but we were unsuccessful in obtaining the preferred product **3a** (entries 6–9, Table 2). We then investigated the reaction by employing $BF_3\cdot OEt_2$ as a Lewis acid for different reaction times at varying temperature (entries 10–14, Table 2). Next, by lowering the temperature to 0 °C, the reaction proceeded smoothly to afford the corresponding product **3a** with good yield (82%) and enhanced diastereoselectivity (dr: 9 : 1) (entry 9, Table 2). An increase in the catalyst loading up to 20 mol%, did not affect the reaction yield to a great extent. Thus, the use of 10 mol% of $BF_3\cdot OEt_2$ in CH_2Cl_2 at 0 °C (entry 9, Table 1) was found to be the optimum reaction conditions for this transformation. The strength of the Lewis acid critically influenced the formation of **3′a** and **3a**. Co-ordination of the Lewis acid on the nitrogen atom of the heteroarene was

Table 2 Lewis acid-catalyzed domino ring-opening and annulation reaction of spiro-oxindole aziridines with indoles[a]

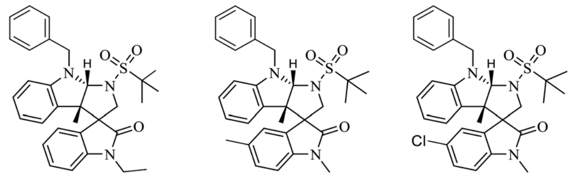




3a, 82% **3b**, 87% **3c**, 89%



3d, 65% **3e**, 62% **3f**, 79%



3g, 77% **3h**, 78% **3i**, 60%

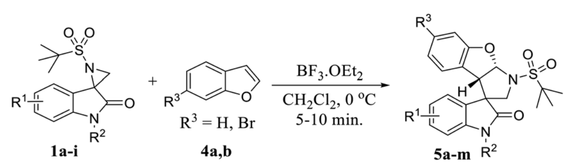
[a] Reactions were performed with 1.0 mmol of **1a** and 1.0 mmol of **2a** in CH_2Cl_2 (5 mL) in the presence of $BF_3 \cdot OEt_2$ (10 mol%) at 0 °C for 5–10 min.

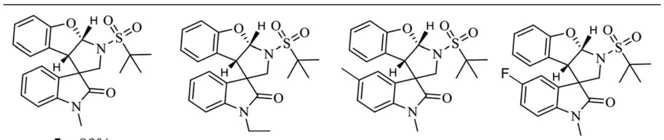
promoted by $BF_3 \cdot OEt_2$ because of its binding nature towards the weak bases.

With the optimized reaction conditions in hand, we next generalized the protocol with regard to different spiro-aziridine oxindole derivatives and 3-methyl indole, and the corresponding substituted tetrahydropyrrolo[2,3-*b*]indole products were obtained in moderate to good yields (Table 2). Spiro-aziridines **1a–e**, derived from substituted isatins, were prepared according to the previous literature methods.[15] The results showed that both the electron-donating and electron-withdrawing functional groups were well tolerated to give the desired products **3a–i**. For example, the electron-neutral and donating substituents (R^1, *e.g.* H and CH_3 in **3a–c** and **3f–h**, respectively) on the C5 position of oxindole reacted much faster with better yields (77–89%) than that with electron with-drawing groups (R^1, *e.g.* Cl and Br in **3d**, **3e** and **3i**) (60–65%). Subsequently, for the spiro-aziridines bearing different substituents on the N-atom of oxindole, that with benzyl groups were generally more sluggish (**3e**, 62% yield) in the reaction than that with ethyl and methyl groups, which is certainly due to bulky effect of benzyl group. Then, we explored the reaction scope with regard to different *N*-substituted indoles. Notably, the reaction of indole with a free N–H group was more time-consuming compared to that for the N-protected indole.

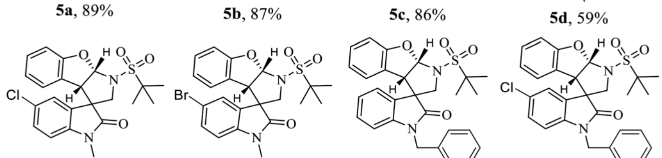
Then, the same set of reaction parameters were studied to extend the scope of various substituted spiro-aziridine oxindoles with benzofurans, and the results are compiled in Table 3. Under the optimized conditions, the transformation proceeded more smoothly using benzofurans than indole with respect to yield (**5a–m**, 55–89%) and diastereoselectivity. The reactions furnished the desired tetrahydropyrrolo[2,3-*b*]benzofurans in moderate to good yield and high diastereoselectivity with different substituents at the C5- and N1- positions of spiro-aziridine oxindoles **5a–i**. However, electron-donating substituents (**5c** and **5k**) at the C5-position of oxindole proved to be more efficient in this transformation, proceeding with higher yields (86% and 77%, respectively) than that with electron withdrawing groups (**5d–f**, **5h**, **5i** and **5m**, 79–55% yield). Particularly, spiro-aziridine bearing a fluoro substituent at the C5-position reacted very slowly, and even after a prolonged reaction time resulted in a low conversion (**5d**, 59% yield). Interestingly, the oxindole bearing an *N*-benzyl group was also tolerable in the reaction to afford the corresponding cyclized adducts in comparatively moderate yields (**5g–i** and **5l**, 79–68%) with different electronic nature at the C5-position of oxindole. Furthermore, C5-bromine-substituted benzofurans were tested, and the stereochemical integrity was uniformly maintained regardless of the substituent on the C5 and N1-positions of

Table 3 Lewis acid-catalyzed dearomative domino ring-opening and annulation of spiro-oxindole aziridine with benzofurans[a]

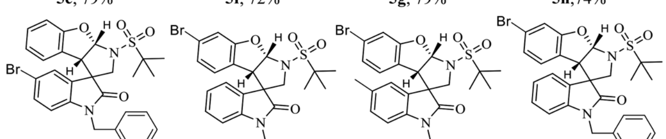




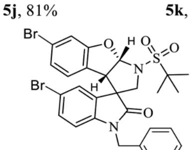
5a, 89% **5b**, 87% **5c**, 86% **5d**, 59%



5e, 79% **5f**, 72% **5g**, 79% **5h**,74%

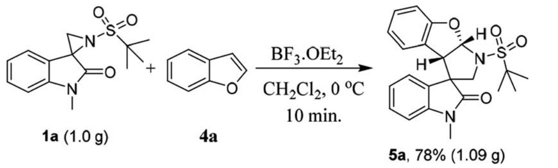


5i, 68% **5j**, 81% **5k**, 77% **5l**, 68%

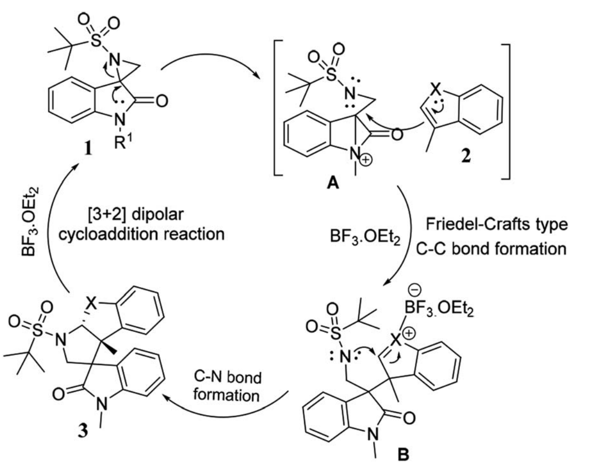


5m, 55%

[a] Reactions were performed with 1.0 mmol of **1a** and 1.0 mmol of **4a** in CH_2Cl_2 (5 mL) in the presence of $BF_3 \cdot OEt_2$ (10 mol%) at 0 °C for 5–10 min.



Scheme 2 Gram-scale reaction.



Scheme 3 Plausible reaction mechanism.

oxindole, but the yields were altered depending on their electronic nature (**5j–l**, 81–68%). Unfortunately, C5-brominated *N*-benzyl oxindole required a higher catalyst loading and longer reaction time to react with C6-bromo benzofuran, and the analogous cyclized product **5m** was obtained in poor yield (55%).

To determine the scalability of this method, a gram-scale reaction was performed under the optimized conditions. Satisfyingly, the reaction proceeded smoothly and afforded the desired product **5a** in 78% yield (Scheme 2).

The plausible mechanism for the synthesis of tetrahydropyrrolo [2,3-*b*] indoles **3a–i**, and tetrahydropyrrolo [2,3-*b*] benzofurans **5a–m** is depicted in Scheme 3. Specifically, highly reactive aziridine intermediate **A** is generated *via* the delocalization of a lone pair of electrons followed by the weakening of the C–N bond of the spiro-aziridine. In this process, the

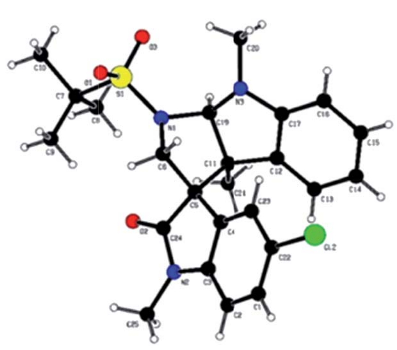


Fig. 2 Single X-ray crystal analysis of compound **3d**.

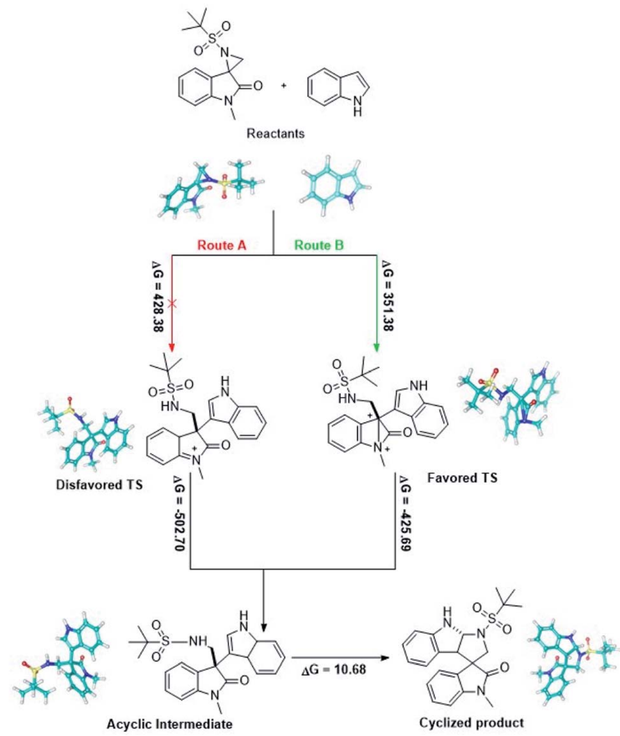


Fig. 3 Optimized B3LYP/6-31G** structures of the reaction; 3D structures represented in cyan color.

nucleophilic centre (C3) of the heteroarene attacks intermediate **A** *via* a Friedel–Crafts-type C–C bond formation, providing iminium/carbonium species **B**. The co-ordination of the Lewis acid on the heteroatom of the arene ring promotes the intramolecular nucleophilic attack of the nitrogen of the aziridine ring leading, to the formation of the corresponding dearomative cyclized spiro-fused tricyclic pyrrolidine **3** with the dissociation of $BF_3 \cdot OEt_2$. The stereochemical outcome of one of the cyclized compounds, **3d**, was confirmed by single X-ray diffraction analysis (Fig. 2).

In silico DFT calculations

For further insight into mechanistic investigations and defining the different transition states, *in silico* density functional theory (DFT) calculations were performed using Schrödinger.[16] Full geometry optimizations were carried out using the B3LYP method and 6-31G** as the basis set. Single point energy for all the structures including reactants, probable transition states[13] (favored and disfavored), intermediates and products were calculated using Jaguar. According to the Δ*G* values, it was observed that the activation barrier for the formation of the favored and disfavored transition state is 351.38 and 428.38 kcal mol^{-1} respectively. Fig. 3 clearly presents the energy barrier for the formation of the acyclic intermediate and product *via* two transition states (TS). Moreover, the energy barrier through route **A** necessitates additional energy in comparison to route **B**, which supports the formation of a favourable TS in this reaction.

Conclusion

In summary, we developed a Lewis acid-mediated domino ring-opening with a concomitant annulation strategy for the synthesis of biologically significant spiro-fused tricyclic pyrrolidines. In particular, a variety of heterocyclic nucleophiles was investigated with different electronic nature on the aromatic ring of oxindole, which offered a one-step protocol for the synthesis spirocyclic scaffolds. The present protocol enables facile access to a variety of spiro-oxindole-fused pyrrolidines with distinct substitutions in a highly convergent and diastereoselective manner.

Experimental section

General information

All reagents and solvents were obtained from commercial suppliers and used without further purification. Analytical thin layer chromatography (TLC) was performed on MERCK precoated silica gel 60-F_{254} (0.5 mm) aluminum plates. Visualization of the spots on the TLC plates was achieved using UV light. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz spectrometer using tetramethylsilane (TMS) as the internal standard. Chemical shifts for ^{1}H and ^{13}C are reported in parts per million (ppm) downfield from tetramethylsilane. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), and m (multiplet). Coupling constant (*J*) values are reported in hertz (Hz). HRMS was performed using an Agilent QTOF 6540 series mass spectrometer. Wherever required, column chromatography was performed using silica gel (60–120 or 100–200) or neutral alumina.

General procedure for the synthesis of dihydrospiro[benzo [*e*] indole-1,3′-indolin]-2′-one (3a–i) and (5a–m)

A solution of indole (1.0 equiv.) and spiro-oxindole aziridine (1.0 equiv.) was added to 5 mL of dry DCM under an argon atmosphere at 0 °C. Then, a catalytic amount of $BF_3 \cdot OEt_2$ (10 mol%) was added and the progress of the reaction was monitored by TLC. After completion of the reaction, the suspension was extracted with ethyl acetate (3 × 5.0 mL), and washed with a 1 : 1 mixture of brine. The combined organic extracts were dried over anhydrous sodium sulphate. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel to afford the pure product.

1′-(*tert*-Butylsulfonyl)-1-ethyl-1′,3*a*′,8′,8*a*′-tetrahydro-2′*H*-spiro [indoline-3,3′-pyrrolo[2,3*b*]indol]-2-one (3a)

White solid; yield: 82%; mp: 204–207 °C; FT-IR (cm^{-1}): 3245, 2925, 1677, 1609, 1462, 1319, 740; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.09 (s, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.32 (dd, J = 7.7, 3.8 Hz, 1H), 7.19 (d, J = 7.3 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 6.63 (t, J = 6.3 Hz, 1H), 3.99 (d, J = 6.3 Hz, 2H), 3.80–3.77 (m, 2H), 2.89 (s, 1H), 2.73 (s, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.4, 143.6, 137.0, 131.1, 128.7, 125.8, 125.5, 124.1, 122.3, 121.5, 119.6, 119.0, 112.1, 108.7, 59.5, 53.3, 48.6, 34.8, 31.2, 24.5, 13.0; HRMS (ESI): *m*/*z* calc. for $C_{23}H_{27}N_3O_3S$ 426.1851, found 426.1861 [M + H]$^+$.

1′-(*tert*-Butylsulfonyl)-1,3*a*′,8′-trimethyl-1′,3*a*′,8′,8*a*′-tetrahydro-2′*H*-spiro[indoline-3,3′-pyrrolo[2,3*b*]indol]-2-one (3b)

Cream solid; yield: 87%; mp: 201–204 °C; FT-IR (cm^{-1}): 2922, 2852, 1709, 1610, 1308, 1122, 741; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.48 (d, J = 7.1 Hz, 1H), 7.38 (t, J = 8.3 Hz, 1H), 7.13–7.08 (m, 3H), 6.77 (d, J = 7.5 Hz, 1H), 6.62 (t, J = 7.0 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 5.45 (s, 1H), 3.76 (d, J = 10.4 Hz, 1H), 3.44 (d, J = 10.4 Hz, 1H), 3.10 (s, 3H), 3.03 (s, 3H), 1.34 (s, 9H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 174.0, 151.4, 144.0, 131.5, 129.2, 129.1, 128.9, 125.4, 125.2, 122.1, 118.0, 109.0, 108.2, 92.2, 61.1, 59.7, 58.7, 56.4, 36.7, 26.7, 24.8, 24.1; HRMS (ESI): *m*/*z* calc. for $C_{24}H_{29}N_3O_3S$ 440.2008, found 440.2000 [M + H]$^+$.

1′-(*tert*-Butylsulfonyl)-1,3*a*′,5,8′-tetramethyl-1′,3*a*′,8′,8*a*′-tetrahydro-2′*H*-spiro[indoline-3,3′-pyrrolo[2,3*b*]indol]-2-one (3c)

White solid; yield: 89%; mp: 205–208 °C; FT-IR (cm^{-1}): 2922, 1709, 1609, 1308, 742; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.05 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.60 (t, J = 12.1 Hz, 2H), 6.45 (t, J = 7.3 Hz, 1H), 6.39 (d, J = 7.1 Hz, 1H), 5.34 (s, 1H), 3.79 (d, J = 10.7 Hz, 1H), 3.46 (d, J = 10.7 Hz, 1H), 3.14 (s, 3H), 3.03 (s, 3H), 2.06 (s, 3H), 1.39 (s, 9H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.3, 151.5, 141.7, 131.7, 130.5, 129.1, 129.0, 127.4, 126.8, 124.4, 117.9, 108.2, 108.2, 93.3, 61.5, 59.0, 56.5, 35.9, 26.6, 24.3, 23.4, 21.0; HRMS (ESI): *m*/*z* calc. for $C_{25}H_{31}N_3O_3S$ 454.2164, found 454.2163 [M + H]$^+$.

1′-(*tert*-Butylsulfonyl)-5-chloro-1,3*a*′,8′-trimethyl-1′,3*a*′,8′,8*a*′-tetrahydro-2′*H*-spiro[indole ne-3,3′-pyrrolo[2,3*b*]indol]-2-one (3d)

White solid; yield: 65%; mp: 205–208 °C; FT-IR (cm^{-1}): 2922, 2852, 1709, 1610, 1308, 1122, 787, 741; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.22 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 9.8 Hz, 1H), 6.97 (d, J = 10.5 Hz, 1H), 6.88 (s, 1H), 6.63 (d, J = 9.2 Hz, 1H), 6.55–6.27 (m, 2H), 5.33 (s, 1H), 3.88 (d, J = 10.1 Hz, 1H), 3.53 (d, J = 8.1 Hz, 1H), 3.18 (s, 3H), 3.04 (s, 3H), 1.43 (s, 9H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 151.6, 142.7, 131.4, 130.5, 129.3, 128.4, 125.9, 125.5, 123.2, 118.4, 109.8, 108.6, 93.6, 61.5, 59.2, 58.9, 56.5, 36.1, 26.8, 24.3, 23.2; HRMS (ESI): *m*/*z* calc. for $C_{24}H_{28}ClN_3O_3S$ 474.1618, found 474.1616 [M + H]$^+$.

1-Benzyl-5-bromo-1′-(*tert*-butylsulfonyl)-3*a*′,8′-dimethyl-1′,3*a*′,8′,8*a*′-tetrahydro-2′*H*-spiro[indoline-3,3′-pyrrolo[2,3*b*] indol]-2-one (3e)

White solid; yield: 62%; mp: 206–208 °C; FT-IR (cm^{-1}): 2977, 1713, 1609, 1487, 1308, 994, 752; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.35 (s, 1H), 7.34 (d, J = 9.6 Hz, 1H), 7.32–7.29 (m, 3H), 7.24 (t, J = 9.3 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 7.4 Hz, 1H), 6.59 (t, J = 8.7 Hz, 2H), 5.48 (s, 1H), 4.96 (d, J = 15.9 Hz, 1H), 4.75 (d, J = 16.0 Hz, 1H), 3.88 (d, J = 10.6 Hz, 1H), 3.50 (d, J = 4.6 Hz, 1H), 3.02 (s, 3H), 1.35 (s, 9H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.7, 151.5, 142.5, 136.4, 131.7, 131.0, 129.1, 128.6, 127.9, 127.6, 125.2, 118.2, 114.4, 111.5, 108.3, 92.2, 61.2, 60.0, 59.2, 56.5, 43.7, 36.8, 25.0, 24.2, 21.3, 14.5; HRMS (ESI): m/z calc. for $C_{30}H_{32}BrN_3O_3S$ 596.1406, found 596.1401 [M + 2H]$^+$.

8′-Benzyl-1′-(*tert*-butylsulfonyl)-1,3*a*′-dimethyl-1′,3*a*′,8′,8*a*′-tetrahydro-2′*H*-spiro[indoline-3,3′-pyrrolo[2,3*b*]indol]-2-one (3f)

Cream solid; yield: 79%; mp: 251–254 °C; FT-IR (cm^{-1}): 2983, 1711, 1611, 1306, 748; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.35 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 4.3, 4H), 7.11–7.09 (m, 1H), 7.08 (dd, J = 13.6, 7.8 Hz, 3H), 6.82 (d, J = 7.3 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.59 (t, J = 7.4 Hz, 1H), 5.67 (s, 1H), 4.78 (d, J = 15.7 Hz, 1H), 4.62 (d, J = 15.8 Hz, 1H), 3.72 (d, J = 10.4 Hz, 1H), 3.43 (d, J = 10.5 Hz, 1H), 3.12 (s, 3H), 1.35 (s, 9H), 0.58 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.7, 149.4, 143.8, 138.7, 131.4, 129.4, 129.0, 128.8, 128.3, 127.7, 126.0, 125.1, 122.3, 118.0, 109.1, 108.8, 89.0, 61.1, 59.8, 58.7, 56.7, 50.4, 26.8, 24.2, 23.3; HRMS (ESI): m/z calc. for $C_{30}H_{33}N_3O_3S$ 516.2321, found 516.2325 [M + H]$^+$.

8′-Benzyl-1′-(*tert*-butylsulfonyl)-1-ethyl-3*a*′-methyl-1′,3*a*′,8′,8*a*′-tetrahydro-2′*H*-spiro[indoline-3,3′-pyrrolo[2,3*b*]indol]-2-one (3g)

White solid; yield: 77%; mp: 185–188 °C; FT-IR (cm^{-1}): 2973, 1721, 1610, 1484, 1305, 731; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.44 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 3.7 Hz, 4H), 7.19 (s, 1H), 7.14–7.05 (m, 3H), 6.77 (d, J = 7.3 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.59 (t, J = 7.2 Hz, 1H), 5.67 (s, 1H), 4.77 (d, J = 15.8 Hz, 1H), 4.60 (d, J = 15.8 Hz, 1H), 3.75 (d, J = 10.0 Hz, 1H), 3.62–3.57 (m, 2H), 3.46 (d, J = 10.4 Hz, 1H), 1.36 (s, 9H), 1.12 (t, J = 6.8 Hz, 3H), 0.62 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.5, 149.5, 142.8, 138.7, 131.4, 129.4, 129.1, 128.8, 128.7, 128.2, 127.6, 125.7, 125.5, 122.1, 118.0, 109.1, 108.8, 89.2, 61.1, 59.6, 58.7, 56.6, 50.5, 34.7, 24.2, 23.3, 12.9; HRMS (ESI): m/z calc. for $C_{31}H_{35}N_3O_3S$ 530.2477, found 530.2492 [M + H]$^+$.

8′-Benzyl-1′-(*tert*-butylsulfonyl)-1,3*a*′,5-trimethyl-1′,3*a*′,8′,8*a*′-tetrahydro-2′*H*-spiro[indoline-3,3′-pyrrolo[2,3*b*]indol]-2-one (3h)

White solid; yield: 78%; mp: 195–198 °C; FT-IR (cm^{-1}): 2923, 2853, 1712, 1600, 1465, 1307, 1102, 709; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.25 (t, J = 4.1 Hz, 5H), 7.20–7.16 (m, 2H), 7.06 (t, J = 7.7 Hz 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.80 (d, J = 7.5 Hz 1H), 6.69 (d, J = 7.9 Hz, 1H), 6.58 (t, J = 7.8 Hz, 1H), 5.71 (s, 1H), 4.76 (d, J = 15.9 Hz, 1H), 4.64 (d, J = 15.9 Hz, 1H), 3.69 (d, J = 10.4 Hz, 1H), 3.44 (d, J = 10.4 Hz, 1H), 3.09 (s, 3H), 2.31 (s, 3H), 1.35 (s, 9H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.7, 149.2, 141.5, 138.7, 131.4, 131.1, 129.4, 129.1, 128.7, 128.7, 128.2, 127.6, 126.1, 125.9, 117.9, 108.7, 108.6, 89.2, 61.1, 59.6, 58.8, 56.7, 50.3, 26.8, 24.2, 23.5, 21.4; HRMS (ESI): m/z calc. for $C_{31}H_{35}N_3O_3S$ 530.2477, found 530.2472 [M + H]$^+$.

8′-Benzyl-1′-(*tert*-butylsulfonyl)-5-chloro-1,3*a*′-dimethyl-1′,3*a*′,8′,8*a*′-tetrahydro-2′*H*-spiro[indoline-3,3′-pyrrolo[2,3*b*]indol]-2-one (3i)

White solid; yield: 60%; mp: 184–187 °C; FT-IR (cm^{-1}): 2980, 2928, 1719, 1605, 1488, 1308, 748; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.31–7.26 (m, 5H), 7.24 (t, J = 6.7 Hz, 1H), 7.04 (t, J = 7.3 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.92 (s, 1H), 6.68 (d, J = 7.9 Hz, 1H), 6.49 (t, J = 7.3 Hz, 1H), 6.45 (d, J = 7.1 Hz, 1H), 5.60 (s, 1H), 4.90 (d, J = 15.8 Hz, 1H), 4.54 (d, J = 15.9 Hz, 1H), 3.83 (d, J = 10.9 Hz, 1H), 3.58 (d, J = 10.9 Hz, 1H), 3.16 (s, 3H), 1.40 (s, 9H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 175.8, 150.3, 143.1, 139.0, 131.4, 129.2, 128.8, 128.7, 128.0, 127.5, 126.1, 125.9, 124.5, 118.2, 110.0, 109.2, 90.4, 61.4, 59.1, 59.0, 56.1, 51.0, 26.7, 24.3, 22.6; HRMS (ESI): m/z calc. for $C_{30}H_{32}ClN_3O_3S$ 550.1931, found 550.1929 [M + H]$^+$.

1-(*tert*-Butylsulfonyl)-1′-methyl-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5a)

White solid; yield: 89%; mp: 233–236 °C; FT-IR (cm^{-1}): 2981, 2920, 1721, 1609, 1471, 1315, 753; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.52 (d, J = 7.1 Hz, 1H), 7.45–7.36 (m, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.16–7.06 (m, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 5.97 (d, J = 6.9 Hz, 1H), 5.21 (d, J = 6.9 Hz, 1H), 3.84 (d, J = 10.9 Hz, 1H), 3.60 (d, J = 10.9 Hz, 1H), 3.17 (s, 3H), 1.24 (d, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.2, 160.5, 143.6, 130.9, 129.4, 129.2, 127.6, 125.9, 123.8, 122.7, 121.0, 110.4, 109.1, 90.9, 66.5, 60.7, 56.7, 56.1, 26.8, 24.4; HRMS (ESI): m/z calc. for $C_{22}H_{24}N_3O_3S$ 413.1535, found 413.1533 [M + H]$^+$.

1-(*tert*-Butylsulfonyl)-1′-ethyl-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5b)

White solid; yield: 87%; mp: 185–188 °C; FT-IR (cm^{-1}): 3245, 2925, 1677, 1609, 1462, 1319, 1034, 740; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.53 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.13 (dd, J = 17.4, 7.7 Hz, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 5.97 (d, J = 6.9 Hz, 1H), 5.21 (d, J = 6.9 Hz, 1H), 3.84 (d, J = 10.0 Hz, 1H), 3.80–3.68 (m, 2H), 3.61 (d, J = 10.9 Hz, 1H), 1.24 (s, 9H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.8, 160.5, 142.5, 130.9, 129.4, 129.2, 127.6, 126.0, 124.0, 122.6, 121.0, 110.3, 109.1, 91.0, 66.3, 60.6, 56.6, 55.9, 34.8, 24.4, 12.9; HRMS (ESI): m/z calc. for $C_{23}H_{26}N_2O_4S$427.1692, found 427.1688 [M + H]$^+$.

1-(*tert*-Butylsulfonyl)-1′,5′-dimethyl-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5c)

Cream solid; yield: 86%; mp: 210–214 °C; FT-IR (cm^{-1}): 2923, 2858, 1704, 1620, 1499, 1308, 1129, 750; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.52 (d, J = 7.1 Hz, 1H), 7.33–7.22 (m, 2H), 7.19 (d, J = 8.5 Hz, 1H), 7.01–6.90 (m, 2H), 6.85 (t, J = 8.1 Hz, 1H), 5.96 (d, J = 6.9 Hz, 1H), 5.19 (d, J = 6.9 Hz, 1H), 3.80 (d, J = 10.8 Hz, 1H), 3.59 (d, J = 10.8 Hz, 1H), 3.14 (s, 3H), 2.31 (s, 3H), 1.23 (s, 9H);

^{13}CNMR (125 MHz, DMSO-d_6): δ 172.2, 160.5, 141.2, 131.7, 130.9, 129.4, 129.3, 127.6, 126.0, 124.6, 121.0, 110.3, 108.8, 90.9, 66.4, 60.7, 56.7, 56.0, 26.8, 24.4, 21.5; HRMS (ESI): *m*/*z* calc. for $C_{23}H_{26}N_2O_4S$ is 427.1692, found 427.1682 $[M + H]^+$.

1-(*tert*-Butylsulfonyl)-5′-fluoro-1′-methyl-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5d)

White solid; yield: 59%; mp: 234–236 °C; FT-IR (cm^{-1}): 2923, 2858, 1704, 1620, 1499, 1308, 1263, 750; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.52 (d, J = 7.3 Hz, 1H), 7.31–7.24 (m, 3H), 7.10–7.08 (m, 1H), 6.95 (t, J = 7.3 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.00 (d, J = 7.0 Hz, 1H), 5.25 (d, J = 7.0 Hz, 1H), 3.87 (d, J = 11.0 Hz, 1H), 3.60 (d, J = 11.0 Hz, 1H), 3.16 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.1, 160.5, 159.6, 157.7 (d, J_{C-F} = 237.2 Hz), 140.0, 131.0, 130.7 (d, J_{C-F} = 8.4 Hz), 127.6, 125.8, 121.2, 115.5 (d, J_{C-F} = 23.1 Hz), 112.2 (d, J_{C-F} = 25.8 Hz), 110.4, 109.9 (d, J_{C-F} = 8.0 Hz), 90.6, 66.3, 60.7, 57.1, 55.9, 27.0, 24.4; HRMS (ESI): *m*/*z* calc. for $C_{22}H_{23}FN_2O_4S$ 431.1441, found 431.1438 $[M + H]^+$.

1-(*tert*-Butylsulfonyl)-5′-chloro-1′-methyl-1,2-dihydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5e)

Off-white solid; yield: 79%; mp: 227–230 °C; FT-IR, (cm^{-1}): 3340, 2923, 1726, 1477, 1114, 763; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.52 (d, J = 7.3 Hz, 1H), 7.49 (d, J = 1.9 Hz, 1H), 7.47–7.45 (m, 1H), 7.28 (t, J = 8.2 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.96 (t, J = 7.3 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.00 (d, J = 7.0 Hz, 1H), 5.27 (d, J = 7.0 Hz, 1H), 3.88 (d, J = 11.0 Hz, 1H), 3.60 (d, J = 11.1 Hz, 1H), 3.16 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.9, 160.3, 142.7, 131.1, 130.9, 129.1, 127.6, 126.7, 125.7, 124.2, 121.2, 110.5, 110.4, 90.6, 66.3, 60.7, 56.9, 55.9, 27.0, 24.4; HRMS (ESI): *m*/*z* calc. for $C_{22}H_{23}ClN_2O_4S$ is 447.1145, found 447.1142 $[M + H]^+$.

5′-Bromo-1-(*tert*-butylsulfonyl)-1′-methyl-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5f)

White solid; yield: 72%; mp: 231–234 °C; FT-IR (cm^{-1}): 3340, 3245, 2923, 1726, 1477, 1300, 997, 662; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.60–7.57 (m, 2H), 7.52 (d, J = 6.9 Hz, 1H), 7.29 (t, J = 7.1 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.95 (t, J = 6.8 Hz, 1H), 6.86 (d, J = 7.7 Hz, 1H), 5.98 (d, J = 6.6 Hz,1H), 5.27 (d, J = 6.6 Hz, 1H), 3.88 (d, J = 11.0 Hz, 1H), 3.60 (d, J = 10.9 Hz, 1H), 3.15 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 171.8, 160.4, 143.1, 132.0, 131.5, 130.9, 127.6, 126.9, 125.7, 121.1, 114.4, 111.0, 110.3, 90.5, 66.4, 60.7, 56.9, 55.9, 26.9, 24.4; HRMS (ESI): *m*/*z* calc. for $C_{22}H_{23}BrN_2O_4S$ 493.0620, found 493.0618 $[M + 2H]^+$.

1′-Benzyl-1-(*tert*-butylsulfonyl)-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5g)

White solid; yield: 79%; mp: 228–231 °C; FT-IR (cm^{-1}): 2965, 2935, 1713, 1729, 1466, 1307, 1128, 745; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.56 (d, J = 7.3 Hz, 1H), 7.49 (d, J = 7.4 Hz, 1H), 7.37–735 (m, 4H), 7.29 (t, J = 7.1 Hz, 3H), 7.11 (t, J = 7.5 Hz, 1H), 6.96 (t, J = 7.9 Hz, 2H), 6.86 (d, J = 8.1 Hz, 1H), 5.99 (d, J = 7.3 Hz, 1H), 5.34 (d, J = 7.3 Hz, 1H), 5.02 (d, J = 15.9 Hz, 1H), 4.85 (d, J = 15.9 Hz, 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.7, 160.5, 142.6, 136.6, 130.9, 129.4, 129.1, 128.9, 127.8, 127.8, 127.5, 125.9, 124.0, 122.9, 121.0, 110.2, 109.6, 90.8, 66.1, 60.7, 56.9, 55.8, 43.3, 24.4; HRMS (ESI): *m*/*z* calc. for $C_{28}H_{28}N_2O_4S$ 489.1848, found 489.1846 $[M + H]^+$.

1′-Benzyl-1-(*tert*-butylsulfonyl)-5′-chloro-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5h)

White solid; yield: 74%; mp: 231–234 °C; FT-IR (cm^{-1}): 3044, 2845, 1615, 1588, 1373, 1284, 834, 722, 585; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.58 (d, J = 6.3 Hz, 3H), 7.37 (m, 6H), 6.96 (d, J = 6.9 Hz, 2H), 6.86 (d, J = 7.0 Hz, 1H), 6.01 (d, J = 6.4 Hz, 1H), 5.39 (d, J = 6.0 Hz, 1H), 5.02 (d, J = 15.6 Hz, 1H), 4.84 (d, J = 16.5 Hz, 1H), 3.98 (d, J = 10.6 Hz, 1H), 3.67 (d, J = 11.2 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.4, 160.5, 141.6, 136.3, 130.9, 130.8, 129.1, 127.9, 127.7, 127.5, 127.0, 125.7, 124.5, 121.1, 111.0, 110.2, 90.4, 66.0, 60.8, 57.2, 55.6, 43.4, 24.4; HRMS (ESI): *m*/*z* calc. for $C_{28}H_{27}ClN_2O_4S$ 523.1458, found 525.1452 $[M + H]^+$.

1′-Benzyl-5′-bromo-1-(*tert*-butylsulfonyl)-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5i)

White solid; yield: 68%; mp: 224–227 °C; FT-IR, (cm^{-1}): 2970, 2113, 1737, 1709, 1305, 1119, 758; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.69 (d, J = 1.8 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.48 (dd, J = 8.3, 1.9 Hz, 1H), 7.34 (dd, J = 13.4, 6.9 Hz, 4H), 7.31–7.25 (m, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.98 (d, J = 7.4 Hz, 1H), 5.38 (d, J = 7.4 Hz, 1H), 5.00 (d, J = 16.0 Hz, 1H), 4.82 (d, J = 15.9 Hz, 1H), 3.97 (d, J = 10.9 Hz, 1H), 3.65 (d, J = 10.9 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.3, 160.5, 142.1, 136.3, 131.9, 131.2, 130.9, 129.1, 127.9, 127.7, 127.5, 127.2, 125.7, 121.1, 114.7, 111.5, 110.2, 90.5, 66.1, 60.86, 57.2, 55.9, 43.4, 24.4; HRMS (ESI): *m*/*z* calc. for $C_{28}H_{27}BrN_2O_4S$ 569.0933, found 569.0930 $[M + 2H]^+$.

6-Bromo-1-(*tert*-butylsulfonyl)-1′-methyl-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5j)

White solid; yield 81%; mp: 231–234 °C; FT-IR (cm^{-1}): 2972, 1713, 1613, 1466, 1315, 1282, 826, 746, 507; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.73 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.44–7.35 (m, 1H), 7.21 (d, J = 6.8 Hz, 1H), 7.15–7.06 (m, 2H), 6.91 (d, J = 8.2 Hz, 1H), 5.84 (d, J = 6.1 Hz, 1H), 5.35 (d, J = 6.1 Hz, 1H), 3.84 (d, J = 10.9 Hz, 1H), 3.60 (d, J = 10.8 Hz, 1H), 3.19 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 175.3, 159.4, 144.6, 133.6, 130.7, 129.6, 129.2, 126.2, 125.0, 122.6, 112.5, 112.4, 109.2, 89.1, 66.6, 61.6, 56.6, 55.6, 26.8, 24.3; HRMS (ESI): *m*/*z* calc. for $C_{22}H_{23}BrN_2O_4S$ 493.0620, found 493.0618 $[M + 2H]^+$.

6-Bromo-1-(*tert*-butylsulfonyl)-1′,5′-dimethyl-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*] pyrrole-3,3′-indolin]-2′-one (5k)

White solid; yield: 77%; mp: 228–231 °C; FT-IR (cm^{-1}): 3339, 2970, 2883, 1719, 1467, 1128, 950, 816, 595; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.63 (d, J = 2.0 Hz, 1H), 7.44 (dd, J = 8.6, 2.2 Hz, 1H), 7.29 (s, 1H), 7.20 (d, J = 7.8 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 5.94 (d, J = 7.3 Hz, 1H), 5.31 (d, J = 7.3 Hz, 1H), 3.79 (d, J = 10.7 Hz, 1H), 3.59 (d, J = 10.7 Hz, 1H), 3.12 (s, 3H), 2.32 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.3, 159.9, 141.3, 133.3, 131.8, 130.3, 129.6, 128.9, 128.5, 124.5, 112.4, 111.8, 108.8, 91.2, 65.7, 60.9, 56.7, 56.0, 26.8, 24.4, 21.2; HRMS (ESI): m/z calc. for $C_{23}H_{25}BrN_2O_4S$ 507.0776, found 507.0774 $[M + 2H]^+$.

1′-Benzyl-6-bromo-1-(*tert*-butylsulfonyl)-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5l)

White solid; yield: 68%; mp: 245–248 °C; FT-IR (cm^{-1}): 2970, 2113, 1737, 1709, 1305, 1119, 758; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.65 (s, 1H), 7.52 (d, J = 5.3 Hz, 1H), 7.43 (d, J = 6.5 Hz, 1H), 7.31 (m, 6H), 7.10 (s, 1H), 6.93 (d, J = 5.5 Hz, 1H), 6.81 (d, J = 5.9 Hz, 1H), 5.95 (d, J = 4.2 Hz, 1H), 5.44 (d, J = 4.7 Hz, 1H), 5.00 (d, J = 16.1 Hz, 1H), 4.78 (d, J = 14.7 Hz, 1H), 3.90 (d, J = 9.7 Hz, 1H), 3.65 (d, J = 9.4 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.9, 160.0, 142.8, 136.6, 133.3, 130.4, 129.5, 129.1, 128.7, 128.3, 127.8, 127.5, 124.0, 123.0, 112.3, 111.9, 109.6, 90.9, 65.3, 60.9, 57.0, 55.7, 43.2, 24.4; HRMS (ESI): m/z calc. for $C_{28}H_{27}BrN_2O_4S$ 569.0933, found 569.0928 $[M + 2H]^+$.

1′-Benzyl-5′,6-dibromo-1-(*tert*-butylsulfonyl)-1,2,3*a*,8*a*-tetrahydrospiro[benzofuro[2,3*b*]pyrrole-3,3′-indolin]-2′-one (5m)

White solid; yield: 55%; mp:242–245 °C; FT-IR (cm^{-1}): 3416, 2942, 2821, 2251, 1682, 1023, 758; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.78 (s, 1H), 7.67 (s, 1H), 7.50 (d, J = 7.0 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.35–7.29 (m, 5H), 6.92 (d, J = 7.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 5.95 (d, J = 7.5 Hz, 1H), 5.51 (d, J = 6.9 Hz, 1H), 5.02 (d, J = 15.6 Hz, 1H), 4.79 (d, J = 15.6 Hz, 1H), 3.96 (d, J = 10.2 Hz, 1H), 3.67 (d, J = 10.3 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.7, 160.6, 142.7, 136.7, 130.9, 129.4, 129.1, 128.9, 127.8, 127.8, 127.6, 125.9, 124.0, 122.9, 121.0, 110.2, 109.6, 90.8, 66.1, 60.8, 56.9, 55.8, 43.3, 24.4; HRMS (ESI): m/z calc. for $C_{28}H_{26}Br_2N_2O_4S$ 645.0058, found 645.0051 $[M + H]^+$.

In silico DFT calculations

All structures corresponding to the reactants, probable transition states and products were sketched using a 2D sketcher and prepared by Ligprep. Geometry optimization and single point energy calculation were performed, with DFT methods at the B3LYP level using the 6-311** basis set in Jaguar, Schrödinger. The optimized 3D pose of all the structures was imaged using Schrödinger.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Dr N. Shankaraiah and S. B. gratefully acknowledges to SERB, DST, Govt. of India for research grant (YSS-2015-001709) and provided fellowship. Authors are thankful to Dr Balasubramanyam Sridhar, for X-ray crystallography studies. NIPER Research Communication No. NIPER-H/2020/M002.

Notes and references

1 For Selected reviews, see (*a*) G. M. Cragg, D. J. Newman and K. M. Snader, *J. Nat. Prod.*, 1997, **60**, 52; (*b*) G. M. Rishton, *Am. J. Cardiol.*, 2008, **101**, 43; (*c*) A. L. Harvey, *Drug Discov. Today*, 2008, **13**, 894.

2 (*a*) R. Heesun, S. Jeongseob and M. K. Haye, *J. Org. Chem.*, 2018, **83**, 14102; (*b*) C. Gang, Y. Jing, G. Suo, H. Hongping, L. Shunlin, D. Yingtong, C. Ying, L. Yang and H. Xiaojiang, *Mol. Divers.*, 2012, **16**, 151.

3 (*a*) J. J. Badillo, A. Silva-García, B. H. Shupe, J. C. Fettinger and A. K. Franz, *Tetrahedron Lett.*, 2011, **52**, 5550; (*b*) V. A. Nancy, I. Alejandro, R. Angel, E. C. Luis, M. V. B. Unnamatla and G. Rocío, *New J. Chem.*, 2018, **42**, 1600.

4 (*a*) S. Ponnusamy, V. Baby and M. Suchithra, *Org. Lett.*, 2007, **9**, 4095; (*b*) S. Ponnusamy, V. Baby, S. Kodirajan and M. Suchitra, *Tetrahedron Lett.*, 2008, **49**, 2611; (*c*) L. Ye, S. Yong-Xing and D. Da-Ming, *Adv. Synth. Catal.*, 2018, **361**, 1064.

5 (*a*) T. Min-Chao, C. Xuan, L. Jun, H. Rong, T. Haiyan and W. Chun-Jiang, *Angew. Chem., Int. Ed.*, 2014, **5**, 4680; (*b*) R. Elisabetta, A. Giorgio, D. Monica, N. Marco, P. Andrea and P. Valentina, *Org. Biomol. Chem.*, 2016, **14**, 6095; (*c*) H. Wang and S. E. Reisman, *Angew. Chem., Int. Ed.*, 2014, **53**, 6206.

6 (*a*) Y. Dongxu, W. Linqing, H. Fengxia, L. Dan, Z. Depeng, C. Yiming, M. Yunxia, K. Weidong, S. Quantao and W. Rui, *Chem.–Eur. J.*, 2014, **20**, 1; (*b*) M. R. Settu, S. Ramakrishnan and K. M. Arasambattu, *Org. Lett.*, 2014, **16**, 2720.

7 For Selected reviews, see (*a*) T. P. Singh and O. M. Singh, *Mini Rev. Med. Chem.*, 2018, **18**, 9; (*b*) C. Navriti and S. Om, *Eur. J. Med. Chem.*, 2017, **134**, 159; (*c*) M. D. Kamal, *Expert Opin. Ther. Pat.*, 2013, **23**, 1133; (*d*) C. Karam, A. H. Rajeshwaria, S. Mahak, M. S. Amelia and S. K. Rangappa, *Pharmacol. Rep.*, 2017, **69**, 281.

8 (*a*) A. A. Andrey, V. V. Elena, S. V. Nataliya, G. M. Alexander, M. B. Ekaterina and Y. M. Mikhail, *J. Org. Chem.*, 2017, **82**, 5689; (*b*) C. Gang, Y. Jing, G. Suo, H. Hongping, L. Shunlin, D. Yingtong, C. Ying, L. Yang and H. Xiaojiang, *Mol. Divers.*, 2012, **16**, 151.

9 (*a*) P. R. Sebahar and R. M. Williams, *J. Am. Chem. Soc.*, 2000, **122**, 5666; (*ab*) B. A. Kumar, G. Gupta, S. Srivastava, A. K. Bishnoi, R. Saxena, R. Kant, R. S. Khanna, P. R. Maulik and A. Dwivedi, *RSC Adv.*, 2013, **3**, 4731.

10 (*a*) U. Loana, K. Philippe and M. Andre, *Angew. Chem., Int. Ed.*, 2000, **39**, 4615; (*b*) S. Yoshiaki, I. Shinya and N. Juzo, *Chem. Commun.*, 2002, **2**, 134; (*c*) S. Masthanvali, M. Abhijit, A. W. Imtiyaz and K. G. Manas, *J. Org. Chem.*, 2016, **81**, 6424.

11 W. Linqing, Y. Dongxu, H. Fengxia, L. Dan, Z. Depeng and W. Rui, *Org. Lett.*, 2015, **17**, 176.

12 C. Zhuo, Z. You-Min, Y. Pei-Jun, W. Shaoyin, W. Shaowu, L. Zhen and Y. Gaosheng, *J. Am. Chem. Soc.*, 2015, **137**, 10088.

13 H. Saumen, S. R. Somnath, S. A. Mohammad and D. Dhiraj, *Org. Lett.*, 2017, **19**, 4082.

14 (*a*) B. Sonal, S. Sravani, S. Balasubramanyam and N. Shankaraiah, *ChemistrySelect*, 2019, **4**, 1727; (*b*) B. Sonal, R. K. Amol, M. B. Deepti, S. Pankaj, T. Venu and N. Shankaraiah, *ChemistrySelect*, 2019, **3**, 6766; (*c*) P. Sharma, N. P. Kumar, N. H. Krishna, D. Prasanna and N. Shankaraiah, *Org. Chem. Front.*, 2016, **3**, 1503; (*d*) N. H. Krishna, A. P. Saraswati, M. Sathish, N. Shankaraiah and A. Kamal, *Chem. Commun.*, 2016, **52**, 4581; (*e*) K. R. Senwar, P. Sharma, S. Nekkanti, M. Sathish, A. Kamal, B. Sridhar and N. Shankaraiah, *New J. Chem.*, 2015, **39**, 3973.

15 (*a*) J. Li, T. Du, G. Zhang and Y. Peng, *Chem. Commun.*, 2013, **49**, 1330; (*b*) M. A. Marsini, J. T. Reeves, J. N. Desrosiers, M. A. Herbage, J. Savoie, Z. Li, K. R. Fandrick, C. A. Sader, B. McKibben and D. A. Gao, *Org. Lett.*, 2015, **17**, 5614; (*c*) S. Hajra, S. M. Aziz, B. Jana, P. Mahish and D. Das, *Org. Lett.*, 2016, **18**, 532.

16 *Schrödinger Release 2019-1, Jaguar (2019)*, Schrödinger, LLC, New York, NY, 2019.