Organic & Biomolecular Chemistry

PAPER

Check for updates

Cite this: Org. Biomol. Chem., 2019, 17, 8832

Synthesis of new cyclazines and 4,5-diaryl-1*H*pyrrol-3(2*H*)-one units in discoipyrroles from indolizinone-DMAD cycloadducts[†]

Jais Kurian and Muraleedharan Kannoth M. 匝 *

The reaction of indolizinones with dimethyl acetylenedicarboxylate gave direct access to 3',8a-dihydrocyclopenta[*hi*]indolizin-8a-ol and 1*H*-pyrrol-3(2*H*)-one in good yields. The former skeleton is a precursor to cyclazines with nitrogen on the periphery, a hitherto un-accessed $10-\pi$ system. Their formation involves initial [4 + 2] or [8 + 2] modes of cycloadditions; the retro-Diels Alder reaction of the [4 + 2] cycloadduct leads to 1*H*-pyrrol-3(2*H*)-one, whereas [8 + 2] addition followed by π -reorganization leads to the azatricyle. Analysis of substituent effects on product distribution showed that electron donating groups on the C₃-aryl ring promote the formation of the azatricycle preponderantly. Treatment of one of these azatricycles (**3c**) with HBF₄ led to the formation of the 1*H*-pyrrol-3(2*H*)-one skeleton through the normal retro-Diels Alder pathway was employed in the total synthesis of Discoipyrrole C, which is a new lead against lung cancer.

Received 26th July 2019, Accepted 18th September 2019 DOI: 10.1039/c9ob01655d

rsc.li/obc

Introduction

In the realm of natural products, a large number of fused-ring organic scaffolds with heteroatoms at one of the peripheral positions, such as isodaphlongamine H and meloscine, are known (Fig. 1).¹ Their intriguing structures and distinct biological activities continue to attract the attention of synthetic and medicinal chemists.² Whilst most of these compounds possess a saturated carbon framework,3 there exists an analogous series, mostly of synthetic origin, which has continuous conjugation along the periphery.⁴ Most familiar examples are cyclazines, which have served as models to assess aromaticity and anti-aromaticity in extended π -systems with 4n/4n + 2 electrons.5 One of the simplest ways to access this skeleton is through addition of alkynes to indolizines in the presence of a noble metal catalyst.⁶ But its analog with nitrogen on the periphery, exemplified by X (Scheme 1), has remained elusive thus far. During our synthetic studies involving the indolizinone class of compounds, we have revealed a novel reaction pathway that gives access not only to the highly functionalized azatricycle VIII (Scheme 1), but also to the core structure in

discoipyrroles (IX) which themselves constitute an important group of bioactive alkaloids. Here, the azatricycle VIII could act as a direct precursor to X mentioned above.

Discoipyrroles A–D are produced by marine bacterium *Bacillus hunanensis* and are characterized by the presence of a 1*H*-pyrrol-3(2*H*)-one core. They have interesting biological activities, especially against the discoidin domain receptor-2 signaling pathway. These alkaloids are also known to exhibit selective cytotoxicity towards DDR2 mutant lung cancer cell lines with IC_{50} values in the nano-molar range.⁷

Our interest in the indolizinone class of compounds started after observing their structural resemblance to discoipyrroles. Initially, the indolizinone skeleton was accessed through the route reported by Kim et al.,8 but we soon realized that it is not chemically stable and could undergo peroxidation and the retro-Diels Alder reaction in the presence of oxygen and light. Analysis of the reaction mixture after exposure to UV light (352 nm) and oxygen using methanol as the solvent resulted in the isolation of 2a in 40% yield (Scheme 2) which was characterized by various spectro-analytical techniques (ESI⁺). We could secure crystals of 2a suitable for X-ray analysis from its MeOH: $CHCl_3$ (1:1) solution and the diffraction data unambiguously confirmed this structure (Fig. 2). Apart from its striking resemblance to Discoipyrrole C, isolation of 2a suggested involvement of 3-azacyclopentadienone as the intermediate and its interception by the nucleophilic solvent. The use of ethanol or isopropanol as the solvent led to the corresponding adducts in supportive of this mechanism (Scheme 2).



View Article Online

Department of Chemistry, Indian Institute of Technology Madras,

Chennai – 600 036, Tamil Nadu, India. E-mail: mkm@iitm.ac.in

[†]Electronic supplementary information (ESI) available: NMR spectra. X-ray data of compounds **2a**, **3a** and **17**. CCDC 1907329, 1908547 and 1908557. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/ c9ob01655d



Fig. 1 (a) Natural products with azatricyclic units (I–III); (b) discoipyrroles A, B and C (IV–VI).



Scheme 1 Different cycloaddition modes and products from the reaction of indolizinone with DMAD.



Scheme 2 Formation of 1*H*-pyrrol-3(2*H*)-one from indolizinone under photochemical conditions.



Literature analysis indicated that the indolizinone dienamine skeleton (**VII**, Scheme 1) has the propensity for [4 + 2] cycloaddition with dienophiles like maleic anhydride, methyl acrylate, *etc.* to give [2.2.2] azabicycles.⁹ Although these adducts are generally stable, the product from DMAD undergoes the retro-Diels Alder reaction leading to dimethyl phthalate as the major product. Though 3-azacyclopentadienone is the expected side product in this process, this was never isolated due to low stability. In another report, Hemming *et al.* have discussed the generation of this species *in situ* from azabicyclo [3.2.0] hept-2-en-4-ones and have used it for the synthesis of substituted pyridines.¹⁰ However, no other systematic study seems to have taken place to expand its application in chemical synthesis. Since our experiments showed the feasibility of trapping the 3-azacyclopentadienone intermediate using nucleophilic solvents (Scheme 2), additional efforts were put to expand its synthetic utility.

Results and discussion

Considering the poor solubility of indolizinone **1a** in methanol as well as its instability under UV light, the cycloaddition reaction was repeated with DMAD as the dienophile (1.5 equiv.) in a 1:1 benzene–methanol mixture at 80 °C (entry 2, Table 1).

Table 1 Reaction optimization



Entry	Variation from standard conditions ^{<i>a</i>}	Reaction time	Yield (%) 2 a ^b	Yield (%) 3a ^b
1	None	12 h	40	57
2	PhH : MeOH (1 : 1)	24 h	39	56
3	PhMe : MeOH (1 : 1)	24 h	38	57
4	PhMe	12 h	_	25
5	MeOH	48 h	10	30
6	PhMe : MeOH (5 : 1)	20 h	38	57
7	PhMe : MeOH (20 : 1)	12 h	20	50
8	100 °C	12 h	20	56
9	120 °C	12 h	10	55
10	70 °C	18 h	35	57
11	50 °C	48 h	5	56
12	PhMe: $H_2O(3:1)$	4 h	_	48

^{*a*} Reaction conditions: **1a** (0.3 mmol), DMAD (0.45 mmol), PhMe : MeOH (10 : 1; 3.3 mL), sealed tube, 80 °C, nitrogen atmosphere. ^{*b*} Isolated yield.

Organic & Biomolecular Chemistry

Interestingly, this condition also afforded the expected product 2a in 39% yield at the end of 24 h. Even more exciting was the isolation of another less polar product in 56% yield which showed a melting point of 150–152 °C ($R_f = 0.53$; 40% EtOAc/ hexane). HRMS analysis gave a peak at m/z = 442.1652, corresponding to the molecular formula $C_{27}H_{24}NO_5$ ([M + H]⁺). ¹H NMR signals corresponding to methyl esters at 3.93 and 3.42 ppm, an exchangeable proton at 4.28 ppm, and three olefinic protons at 5.92, 6.68 and 6.84 ppm indicated that the product likely arises through a different pathway. This was also evident from the ¹³C NMR spectrum which had no carbonyl carbon but instead had a new peak at 68.7 ppm corresponding to tertC-OH. These, along with COSY, HMBC and HSQC results, supported the presence of an azatricyclic structure 3a shown in Table 1. By systematic screening of a number of solvent systems, we succeeded in obtaining crystals suitable for X-ray analysis from MeOH-CH₂Cl₂ (1:1) and the diffraction data unambiguously confirmed the proposed structure for 3a (Fig. 2).

In the literature, there are many examples of transformations involving cycloaddition products, as in bicyclo[2.2.2] octenones,¹¹ 2-acylfuran-diethyl azodicarboxylate cycloadducts,¹² tetrahydropyranopyrrolone,¹³ 2-pyrone cycloadducts,¹⁴ and *3H*-indole styrylcyanines.¹⁵ Also, the Lewis acidcatalysed sequential tandem transformations of substituted [4 + 2] cycloadducts¹⁶ and functionalized diazanorbornenes provide easy access to diverse ring systems.¹⁷ In the present context, the reaction leads to a relatively strained tricyclic system with conjugation along the periphery with a central quaternary carbon which is remarkable.

Comparable yields of 2a and 3a were obtained on carrying out the reaction in the toluene–MeOH mixture (1:1, entry 3). The use of toluene alone (entry 4) resulted in only 3a in lower yield (25%) without any trace of 2a suggesting that the 3-azacyclopentadienone intermediate is intrinsically unstable. By varying the relative amounts of toluene and methanol (entries 1–7), a 10:1 proportion of these solvents turned out to be optimal that gave 2a and 3a in 40% and 57% respectively in 12 h (entry 1). An increase or decrease of reaction temperature in fact did not give any improvement in yields (entries 8–11). Nevertheless, the overall atom economy is high considering the total yields of both the products.

The substrate scope of this method was then investigated by varying the nature of C_2 and C_3 -aryl rings. As evident from Scheme 3, the presence of electron donating or withdrawing groups on the C_2 -aryl unit (**1a-c**: $R_1 = H$, *p*-OMe, *p*-NO₂; $R_2 =$ H) did not affect the relative yields of **2a-c** and **3a-c**. Although introduction of the -OMe group at the *meta* position of the aryl ring at C_3 carbon did not affect yield distribution (**2d-f** and **3d-f**), a prominent electronic effect was observed on keeping electron donating substituents at the *para* position (**2g-o** and **3g-o**). This resulted in higher yields of the tricyclic product 3 with a concomitant reduction in the yield of **2**. There was a clear unfavourable effect from the *ortho*-substituent in the C_2 -aryl ring irrespective of the electronic contribution from the C_3 unit in the formation of the azatricycle which is evident from entries **3p–s**. The outcome from **1u** also shows that the electron withdrawing substituent at the *para* position of the C_3 ring leads to a reduction in the yield of **3u** but favours the formation of **2u**.

Overall, the formation of products 2 and 3 seems to involve two modes of cycloadditions as shown in Scheme 4. The former product arises through the retro-Diels Alder reaction of the [4 + 2] cycloadduct, followed by trapping the 3-azacyclopentadienone intermediate with methanol (Path a, Scheme 4). At the same time, a [8 + 2] mode of cycloaddition between the dipolar species 1' and DMAD could lead to 1" that on π -reorganization and proton shift forms the azatricycle 3 (Path b). The *syn* orientation of methyl and hydroxyl groups in 3 suggests that cycloaddition occurs from the less hindered side as shown in Scheme 4. The fact that the electron donating effect from the C₃-aryl ring favours the formation of 3 tends to suggest better stabilization of the dipolar structure 1' and its reaction with DMAD.

Since π -reorganization and proton shift from C₈-H are essential for the formation of 3, we carried out an additional experiment with the C₈-methyl derivative 1v (Scheme 5). Interestingly, this resulted in the formation of only 2a in 51% yield without any trace of 3a.

Structurally, **3** can be considered as an immediate precursor for cyclazine analog **X** (Scheme 1) that was never synthesized before. As mentioned in the introduction, such systems are very important to understand the ring current effects in cyclic conjugated organic frameworks with $(4n + 2)\pi$ electrons. The ESI mass spectra of all tricyclic products (**3a–u**) prepared here had $[M + H - H_2O]^+$ as the base peak (ESI†). This indicated that the conjugated 10e species – cyclopenta [*hi*]indolizin-3-ium ion is formed under the condition of ionization. The ESI mass spectrum of azatricycle **3c** with the characteristic $[M + H - H_2O]^+$ peak is presented in Fig. 3 as a representative example.

In order to detect this 10e species, we performed a NMR experiment after treating a solution of 3c in CDCl₃ with HBF₄·Et₂O, at room temperature. Remarkably, the peak corresponding to the central CH₃ group underwent an upfield shift (from 0.81 ppm to -0.20 ppm) due to the shielding effect on these protons. Additionally, the olefinic ring protons, which were originally at 6.0, 6.72 and 6.78 ppm, moved downfield to 8.34, 8.60, and 9.46 ppm respectively as they are situated in the deshielding zone of the 10 π electron system. There was no significant change in these peak positions on lowering the temperature to -50 °C. Relevant regions from the ¹H NMR spectra of these compounds are presented in Fig. 4 (complete spectra are given in ESI-Fig. 154†).

An equally important outcome of the present work is the isolation of 1*H*-pyrrol-3(2*H*)-one derivatives (**2a–u**) which represent the core structural unit in discoipyrroles A–D. A literature search showed that Yan *et al.* in 2017 have reported the total synthesis of discoipyrrole C *via* the MoOPH-mediated oxidation of *N*-unsubstituted pyrroles with an overall yield of ~10% in 9 steps.¹⁸ Since we could readily access this skeleton through the retro-Diels Alder reaction of the indolizinone



Scheme 3 Substrate scope: product distribution as a function of substituents on 2- and 3-aryl units in indolizinones.



Scheme 4 Plausible mechanism.



Scheme 5 Reaction of 8-methyl substituted indolizinone with DMAD.



Fig. 3 ESI MS of azatricyclic product 3c.

cycloadduct, the methodology was extended for the synthesis of Discoipyrrole C (Scheme 6). The key intermediate 11 required for the synthesis of indolizinone precursor 14 was prepared in a straight-forward manner starting from isovaleric acid 6 through Weinreb amide formation (7), pyridine ortho acylation (9) and alkyne addition steps. The TBS group that was selected to survive the *n*-BuLi condition was then deprotected and then acetylated by treatment with AcCl in the presence of triethylamine, which afforded 12 in 95% yield (over 2 steps). Subjecting this product to tandem amino-palladation, reductive elimination and 1,2-alkyl shift gave the required indolizinone 14 in 80% yield.8 Treatment of 14 with DMAD in the toluene: methanol mixture (10:1) at 80 °C gave the tricyclic compound 15 along with the expected 1H-pyrrol-3(2H)one derivative 16 in 55% and 40% yield, respectively. This on deacetylation, followed by treatment with TFA in a 4:1 $CH_2Cl_2: H_2O$ mixture, gave the target Discoipyrrole C (17) in 88% yield. In comparison with the earlier synthesis,¹⁸ the overall yield of discoipyrrole C through this route is 13%. Its



Fig. 4 (a) Selected region from the ¹H NMR spectrum of the 10e aromatic species generated from 3c by treatment with HBF₄·Et₂O (solvent CDCl₃ at -50 °C). (b) Corresponding peaks from 3c.





Fig. 5 X-ray structure of discoipyrrole C (17).

structure was confirmed by various spectro analytical methods such as NMR, HRMS, *etc.* and matched well with the reported data (ESI[†]). Its crystals suitable for X-ray analysis were grown from the EtOAc: acetone (1:1) mixture and the diffraction data (Fig. 5) unambiguously confirmed the structure as the same as that reported for Discoipyrrole C (17).

Experimental section

General

Various starting materials used such as 2-acetyl pyridine, phenylacetylenes and iodobenzenes were accessed through Spectrochem or Sigma Aldrich, and were used as received unless otherwise indicated. The solvents benzene (PhH), tetrahydrofuran (THF) and toluene (PhMe) were dried over sodium/ benzophenone and distilled before use whereas dichloromethane (DCM) and acetonitrile (MeCN) were dried over CaH₂. Methanol was dried by refluxing over magnesium/ iodine. Column chromatography purification was carried out on 100–200 mesh silica gel using an EtOAc–hexane solvent system in a gradient mode. Thin layer chromatography was performed using 0.25 mm thick silica gel plates from Merck and the plates were analysed using either 254 nm UV light or ninhydrin staining.

¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer and the chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane, with *J* values in Hertz. The splitting patterns in ¹H NMR are reported as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, bs = broad singlet, appt = apparent triplet. ¹³C NMR data are reported with the solvent peak (CDCl₃ = 77.16, CD₃OD = 49.00) as the internal standard. High-resolution mass spectra (HRMS) were recorded on a Waters Q-TOF *micro*TM spectrometer with a lock spray source. Infrared spectra were recorded using a Nicolet 6700 FT-IR spectrometer.

General procedure for the synthesis of polysubstituted indolizinone (1a-d)

A solution containing a mixture of 4-aryl-2-(pyridin-2-yl)but-3yn-2-ols (0.6 mmol) and iodobenzene (0.9 mmol) in acetonitrile was admixed with Pd(PPh₃)₄ (5 mol%) and K₂CO₃ (1.5 mmol) under a nitrogen atmosphere. After heating this mixture for 13 h at 90 °C under stirring, it was concentrated under reduced pressure and the residue obtained was redissolved in ethyl acetate (50 mL) and washed with water (2 × 50 mL). The organic layer was separated and dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on a silica gel column using an ethyl acetate/hexane system.

8a-Methyl-2,3-diphenylindolizin-1(8aH)-one (1a). 91% yield (163 mg). Orange solid, m.p. 160–162 °C. $R_{\rm f}$ = 0.53 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.46–7.50 (m, 2H, ArH), 7.42–7.44 (m, 1H, ArH), 7.34–7.35 (m, 2H, ArH), 7.12–7.17 (m, 4H, ArH), 7.06–7.10 (m, 1H, ArH), 6.35 (d, J = 7.23 Hz, 1H, CH), 6.01 (d, J = 8.99 Hz, 1H, CH), 5.93–5.96 (m, 1H, CH), 5.32–5.35 (m, 1H, CH), 1.51 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 200.9, 167.8, 131.5, 130.5, 129.3, 129.2 (2C), 129.0 (2C), 128.8 (2C), 128.0 (2C), 126.0, 124.0, 123.2, 122.4, 110.1, 108.5, 67.6, 25.6. IR (KBr): 3051, 2958, 2922, 1673, 1607, 1542, 1414, 1372, 1322, 1169, 1076, 933, 752, 894, 518 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₁H₁₈NO 300.1388; found 300.1396.

2-(4-Methoxyphenyl)-8a-methyl-3-phenylindolizin-1(8*aH***)-one** (**1b**). 80% yield (158 mg). Red-coloured gum. $R_f = 0.40$ (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.27 (d, J =8.61 Hz, 2H, ArH), 7.13–7.19 (m, 4H, ArH), 7.07–7.10 (m, 1H, ArH), 6.94 (d, J = 8.52 Hz, 2H, ArH), 6.42 (d, J = 7.21 Hz, 1H, CH), 6.00 (d, J = 9.19 Hz, 1H, CH), 5.92–5.96 (m, 1H, CH), 5.32–5.35 (m, 1H, CH), 3.84 (s, 3H, OCH₃), 1.49 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 200.8, 167.9, 161.2, 131.4, 130.6 (2C), 129.0 (2C), 128.0 (2C), 125.9, 124.0, 123.4, 122.3, 121.1, 114.6 (2C), 108.4, 67.6, 55.5, 25.7 ppm. IR (KBr): 3055, 2927, 2839, 1669, 1545, 1422, 1369, 1324, 1287, 1248, 1246, 1174, 1033, 913, 830, 766, 705, 527, 451 cm⁻¹. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for C₂₂H₂₀NO₂ 330.1494; found 330.1490.

8a-Methyl-2-(4-nitrophenyl)-3-phenylindolizin-1(8*aH***)-one (1c).** 97% yield (200 mg). Orange solid, m.p. 54–56 °C. $R_{\rm f}$ = 0.36 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.98 (d, J = 8.81 Hz, 2H, ArH), 7.51–7.56 (m, 3H, ArH), 7.35 (bs, 2H, ArH), 7.30 (d, J = 8.73 Hz, 2H, ArH), 6.36 (d, J = 7.13 Hz, 1H, CH), 6.06 (d, J = 9.26 Hz, 1H, CH), 5.97–6.01 (m, 1H, CH), 5.43–5.46 (m, 1H, CH), 1.52 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.9, 169.2, 145.3, 139.1, 131.2, 129.8 (2C), 128.7, 128.6 (2C), 128.4 (2C), 124.6, 123.3 (2C), 122.6, 122.4, 110.3, 107.9, 68.3, 25.6 ppm. IR (KBr): 3061, 2923, 1675, 1591, 1513, 1426, 1331, 1177, 1109, 1071, 942, 851, 755, 697, 521 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₁H₁₇N₂O₃ 345.1239; found 345.1253.

3-(3-Methoxyphenyl)-8a-methyl-2-phenylindolizin-1(8aH)-one (**1d**). 90% yield (178 mg). Orange solid, m.p. 62–64 °C. $R_{\rm f}$ = 0.46 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.34–7.38 (m, 1H, ArH), 7.15–7.16 (m, 4H, ArH), 7.06–7.11 (m, 1H, ArH), 6.99 (d, *J* = 8.20 Hz, 1H, ArH), 6.92 (d, *J* = 7.38 Hz, 1H, ArH), 6.83 (s, 1H, ArH), 6.38 (d, *J* = 7.29 Hz, 1H, CH), 6.01 (d, *J* = 9.18 Hz, 1H, CH), 5.93–5.97 (m, 1H, CH), 5.32–5.35 (m, 1H, CH), 3.72 (s, 3H, OCH₃), 1.50 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 200.9, 167.6, 160.0, 131.0, 130.5, 130.4, 128.8 (2C), 128.0 (2C), 126.0, 123.9, 123.3, 122.4, 121.1, 116.2, 114.2, 110.0, 108.5, 67.6, 55.5, 25.6 ppm. IR (KBr): 3055, 2922, 2862, 1675, 1578, 1543, 1457, 1423, 1373, 1323, 1282, 1253, 1190, 1147, 1079, 1042, 851, 779, 696, 520 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₂H₂₀NO₂ 330.1494; found 330.1491.

3-(3-Methoxyphenyl)-2-(4-methoxyphenyl)-8a-methylindolizin-1(8aH)-one (1e). 84% yield (181 mg). Orange solid, m.p. 106–108 °C. $R_{\rm f}$ = 0.36 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.34–7.38 (m, 1H, ArH), 7.08 (d, J = 8.84 Hz, 2H, ArH), 6.99 (d, J = 7.45 Hz, 1H, ArH), 6.92 (d, J = 7.45 Hz, 1H, ArH), 6.83 (s, 1H, ArH), 6.71 (d, J = 8.38 Hz, 2H, ArH), 6.36 (d, J = 7.45 Hz, 1H, CH), 5.98 (d, J = 9.05 Hz, 1H, CH), 5.92–5.95 (m, 1H, CH), 5.30–5.33 (m, 1H, CH), 3.74 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 1.49 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 201.2, 166.8, 160.1, 158.0, 130.7, 130.4, 129.9 (2C), 123.7, 123.4, 123.3, 122.4, 121.2, 116.1, 114.3, 113.6 (2C), 109.8, 108.1, 67.5, 55.5, 55.3, 25.6 ppm. IR (KBr): 2926, 2863, 1670, 1544, 1459, 1371, 1322, 1285, 1248, 1175, 1038, 785, 524 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₃H₂₂NO₃ 360.1600; found 360.1599.

3-(3-Methoxyphenyl)-8a-methyl-2-(4-nitrophenyl)indolizin-1 (8a*H*)-one (1f). 92% yield (207 mg). Orange solid, m.p. 90–92 °C. $R_{\rm f}$ = 0.30 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.00 (d, J = 8.79 Hz, 2H, ArH), 7.41–7.45 (m, 1H, ArH), 7.34 (d, J = 9.14 Hz, 2H, ArH), 7.07 (dd, J = 2.05, 8.27 Hz, 1H, ArH), 6.92 (s, 1H, ArH), 6.83 (s, 1H, ArH), 6.39 (d, $J = 7.36 \text{ Hz}, 1\text{H}, C\text{H}, 6.06 \text{ (d}, J = 9.36 \text{ Hz}, 1\text{H}, C\text{H}), 5.97-6.01 \text{ (m, 1H, CH)}, 5.43-5.46 \text{ (m, 1H, CH)}, 3.78 \text{ (s, 3H, OCH}_3), 1.52 \text{ (s, 3H, CH}_3) \text{ ppm.}^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3): \delta 199.9, 169.1, 160.5, 145.2, 139.1, 131.1, 129.9, 128.3 (2C), 124.6, 123.3 (2C), 122.7, 122.4, 120.6, 116.5, 114.1, 110.3, 107.7, 68.3, 55.6, 25.7 \text{ ppm. IR (KBr): 3061, 2926, 2842, 1677, 1590, 1536, 1509, 1426, 1386, 1333, 1254, 1145, 1072, 1044, 984, 944, 903, 851, 782, 696, 523 \text{ cm}^{-1}$. HRMS (ESI) m/z: $[\text{M} + \text{H}]^+$ calcd for $C_{22}H_{19}N_2O_4$ 375.1345; found 375.1348.

3-(4-Methoxyphenyl)-8a-methyl-2-phenylindolizin-1(8*aH***)-one** (**1g**). 86% yield (170 mg). Orange solid, m.p. 128–130 °C. $R_{\rm f}$ = 0.40 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.27 (d, *J* = 8.61 Hz, 2H, ArH), 7.13–7.19 (m, 4H, ArH), 7.07–7.10 (m, 1H, ArH), 6.94 (d, *J* = 8.52 Hz, 2H, ArH), 6.42 (d, *J* = 7.21 Hz, 1H, CH), 6.00 (d, *J* = 9.19 Hz, 1H, CH), 5.95 (dd, *J* = 5.28, 9.19 Hz, 1H, CH), 5.32–5.35 (m, 1H, CH), 3.84 (s, 3H, OCH₃), 1.49 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 220.8, 167.9, 161.2, 131.4 (2C), 130.6 (2C), 129.0 (2C), 128.0, 125.9, 124.0, 123.4, 122.3, 121.1, 114.6 (2C), 108.4, 67.6, 55.5, 25.66 ppm. IR (KBr): 3052, 2923, 2850, 1669, 1607, 1545, 1509, 1487, 1416, 1374, 1324, 1300, 1255, 1179, 1076, 1029, 829, 739, 704, 594, 520 cm⁻¹. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for C₂₂H₂₀NO₂ 330.1494; found 330.1490.

2,3-Bis(4-methoxyphenyl)-8a-methylindolizin-1(8a*H***)-one (1h). 78% yield (168 mg). Orange solid, m.p. 62–64 °C. R_{\rm f} = 0.36 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): \delta 7.27 (d, J = 8.11 Hz, 2H, ArH), 7.07 (d, J = 8.48 Hz, 2H, ArH), 6.94 (d, J = 8.14 Hz, 2H, ArH), 6.73 (d, J = 8.14 Hz, 2H, ArH), 6.40 (d, J = 7.16 Hz, 1H, CH), 5.98 (d, J = 9.24 Hz, 1H, CH), 5.91–5.95 (m, 1H, CH), 5.29–5.33 (m, 1H, CH), 3.84 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 1.48 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): \delta 201.1, 167.1, 161.1, 157.9, 130.6 (2C), 130.1 (2C), 123.9, 123.5 (2C), 122.4, 121.3, 114.6 (2C), 113.6 (2C), 109.6, 108.0, 67.4, 55.5, 55.3, 25.6 ppm. IR (KBr): 2957, 2922, 2847, 1665, 1609, 1546, 1509, 1456, 1374, 1322, 1295, 1251, 1177, 1030, 827 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₃H₂₂NO₃ 360.1600; found 360.1597.**

3-(4-Methoxyphenyl)-8a-methyl-2-(4-nitrophenyl)indolizin-1(8aH)-one (1i). 93% yield (209 mg). Orange solid, m.p. 58–60 °C. $R_{\rm f}$ = 0.30 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.00 (d, *J* = 8.48 Hz, 2H, ArH), 7.33 (d, *J* = 8.52 Hz, 2H, ArH), 7.27 (d, *J* = 8.08 Hz, 2H, ArH), 7.01 (d, *J* = 8.52 Hz, 2H, ArH), 6.44 (d, *J* = 7.44 Hz, 1H, CH), 6.05 (d, *J* = 9.31 Hz, 1H, CH), 5.96–6.00 (m, 1H, CH), 5.43–5.46 (m, 1H, CH), 3.88 (s, 3H, OCH₃), 1.51 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.8, 169.4, 161.8, 145.2, 139.4, 130.3 (2C), 128.6 (2C), 124.7, 123.3, 122.9 (2C), 122.3, 120.3, 115.1 (2C), 110.2, 107.6, 68.3, 55.6, 25.7 ppm. IR (KBr): 2956, 2922, 1674, 1600, 1541, 1510, 1476, 1249, 1334, 1255, 1180, 1113, 1073, 1028, 824, 738, 701, 519 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₂H₁₉N₂O₄ 375.1345; found 375.1355.

8a-Methyl-3-(4-(methylthio)phenyl)-2-phenylindolizin-1(8aH)one (1j). 85% yield (176 mg). Orange solid, m.p. 108–110 °C. $R_{\rm f}$ = 0.43 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.23–7.28 (m, 4H, ArH), 7.14–7.19 (m, 3H, ArH), 7.08–7.12 (m, 2H, ArH), 6.39 (d, *J* = 7.19 Hz, 1H, CH), 6.00 (d, *J* = 9.21 Hz, 1H, CH), 5.92–5.97 (m, 1H, CH), 5.32–5.35 (m, 1H, CH), 2.50 (s, 3H, SCH₃), 1.49 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 200.8, 167.4, 142.3, 131.1, 129.4 (2C), 128.9 (2C), 128.1 (2C), 126.0 (3C), 125.1, 124.0, 123.3, 122.3, 110.0, 108.5, 67.7, 25.6, 15.0 ppm. IR (KBr): 3052, 2923, 1673, 1600, 1545, 1486, 1416, 1372, 1325, 1191, 1084, 947, 816, 741, 703, 584, 511, 479 cm⁻¹. HRMS (ESI) *m*/*z*: [M + H]⁺ calcd for C₂₂H₂₀NOS 346.1266; found 346.1271.

2-(4-Methoxyphenyl)-8a-methyl-3-(4-(methylthio)phenyl)indolizin-1(8aH)-one (1k). 79% yield (178 mg). Orange gum. $R_f = 0.33$ (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.26 (bs, 4H, ArH), 7.06 (d, J = 8.82 Hz, 2H, ArH), 6.73 (d, J = 8.82 Hz, 2H, ArH), 6.38 (d, J = 7.24 Hz, 1H, CH), 5.98 (d, J = 9.25 Hz, 1H, CH), 5.92–5.95 (m, 1H, CH), 5.30–5.33 (m, 1H, CH), 3.74 (s, 3H, OCH₃), 2.51 (s, 3H, SCH₃), 1.48 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 201.1, 166.6, 157.9, 142.1, 130.1 (2C), 129.4 (2C), 126.0 (2C), 125.3, 123.8, 123.33, 123.25, 122.4, 113.7 (2C), 109.8, 108.2, 67.5, 55.3, 25.6, 15.6 ppm. IR (KBr): 3049, 2924, 2844, 1670, 1601, 1545, 1425, 1370, 1323, 1293, 1246, 1177, 1084, 1031, 1031, 946, 812, 775, 716, 674, 529 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₃H₂₂NO₂S 376.1371; found 376.1379.

8a-Methyl-3-(4-(methylthio)phenyl)-2-(4-nitrophenyl)indolizin-1(8aH)-one (11). 87% yield (204 mg). Orange solid, m.p. 122–124 °C. $R_{\rm f}$ = 0.30 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.01 (d, J = 8.66 Hz, 2H, ArH), 7.31–7.34 (m, 4H, ArH), 7.24 (d, J = 7.80 Hz, 2H, ArH), 6.41 (d, J = 7.48 Hz, 1H, CH), 6.06 (d, J = 9.14 Hz, 1H, CH), 5.97–6.00 (m, 1H, CH), 5.43–5.46 (m, 1H, CH), 2.53 (s, 3H, SCH₃), 1.51 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.8, 168.9, 145.3, 143.6, 139.1, 129.0 (2C), 128.6 (2C), 126.3 (2C), 124.6, 124.3, 123.4 (2C), 122.7, 122.3, 110.3, 107.8, 68.3, 25.7, 15.0 ppm. IR (KBr): 2930, 2852, 1672, 1603, 1544, 1432, 1376, 1324, 1298, 1252, 1171, 1086, 1040, 1039, 814, 740, 588 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₂H₁₉N₂O₃S 391.1116; found 391.1109.

3-(3,4-Dimethoxyphenyl)-8a-methyl-2-phenylindolizin-1(8aH)one (1m). 83% yield (179 mg). Orange solid, m.p. 56–58 °C. $R_{\rm f} = 0.30$ (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.13–7.19 (m, 4H, ArH), 7.07–7.10 (m, 1H, ArH), 6.96 (d, J =8.57 Hz, 1H, ArH), 6.92 (d, J = 8.27 Hz, 1H, ArH), 6.73 (s, 1H, ArH), 6.47 (d, J = 7.12 Hz, 1H, CH), 6.00 (d, J = 9.23 Hz, 1H, CH), 5.93–5.96 (m, 1H, CH), 5.33–5.36 (m, 1H, CH), 3.92 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃), 1.50 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 200.8, 167.8, 150.7, 149.4, 131.3, 129.0 (2C), 128.0, (2C), 126.0, 124.0, 123.5, 122.3, 122.0, 121.3, 112.1, 111.4, 109.9, 108.4, 67.7, 56.0, 25.7 ppm. IR (KBr): 3056, 2930, 2839, 1669, 1602, 1543, 1512, 1489, 1421, 1384, 1322, 1256, 1188, 1143, 1076, 1026, 814, 737, 695, 616, 519 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₃H₂₂NO₃ 360.1600; found 360.1608.

3-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-8a-methylindolizin-1(8aH)-one (1n). 76% yield (178 mg). Orange solid, m.p. 52–54 °C. $R_{\rm f}$ = 0.16 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.07 (d, J = 7.85 Hz, 2H, ArH), 6.90–6.96 (m, 2H, ArH), 6.74 (d, J = 6.06 Hz, 2H, ArH), 6.71 (s, 1H, ArH), 6.44 (d, J = 7.13 Hz, 1H, CH), 5.98 (d, J = 9.12 Hz, 1H, CH), 5.91–5.95 (m, 1H, CH), 5.30–5.33 (m, 1H, CH), 3.92 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 1.49 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 201.1, 167.0, 157.9, 150.7, 149.4, 130.1 (2C), 123.9, 123.6 (2C), 122.4, 122.0, 121.5, 113.6 (2C), 112.1, 111.4, 109.6, 108.1, 67.5, 56.2, 56.1, 55.3, 25.6 ppm. IR (KBr): 3054, 2936, 2838, 1668, 1607, 1510, 1458, 1422, 1381, 1321, 1250, 1181, 1144, 1028, 936, 823, 725, 645, 527 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₄H₂₄NO₄ 390.1705; found 390.1710.

3-(3,4-Dimethoxyphenyl)-8a-methyl-2-(4-nitrophenyl)indolizin-1(8aH)-one (10). 90% yield (218 mg). Orange solid, m.p. 68–70 °C. $R_f = 0.13$ (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.01 (d, J = 8.63 Hz, 2H, ArH), 7.35 (d, J = 9.24 Hz, 2H, ArH), 6.92–6.98 (m, 2H, ArH), 6.76 (s, 1H, ArH), 6.47 (d, J = 7.39 Hz, 1H, CH), 6.06 (d, J = 9.24 Hz, 1H, CH), 5.97–6.00 (m, 1H, CH), 5.43–5.47 (m, 1H, CH), 3.95 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 1.52 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.8, 169.3, 151.3, 149.9, 145.1, 139.4, 128.5 (2C), 124.6, 123.3 (2C), 122.9, 122.3, 121.8, 120.5, 111.8, 111.2, 110.2, 107.5, 68.3, 56.3, 56.2, 25.7 ppm. IR (KBr): 3061, 2929, 2839, 1673, 1594, 1537, 1511, 1479, 1426, 1385, 1332, 1259, 1189, 1143, 1071, 1026, 853, 815, 696, 517 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₃H₂₁N₂O₅ 405.1450; found 405.1444.

(2,4-Dimethoxyphenyl)-8a-methyl-3-phenylindolizin-1(8a*H*)one (1p). 70% yield (150 mg). Orange gum. $R_f = 0.20$ (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.35 (d, J =4.88 Hz, 3H, ArH), 7.28–7.29 (m, 2H, ArH), 7.08 (d, J = 8.25 Hz, 1H, ArH), 6.47 (d, J = 7.57 Hz, 1H, ArH), 6.43 (dd, J = 1.97, 8.52 Hz, 1H, CH), 6.25 (s, 1H, ArH), 5.98 (d, J = 8.96 Hz, 1H, CH), 5.92–5.95 (m, 1H, CH), 5.29–5.32 (m, 1H, CH), 3.75 (s, 3H, OCH₃), 3.26 (s, 3H, OCH₃), 1.51 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 201.2, 168.2, 160.2, 158.0, 132.2, 130.9, 129.9, 129.4, 128.5, 128.3, 127.2, 123.7, 123.6, 122.3, 120.4, 112.5, 107.7, 104.4, 99.0, 67.4, 55.4, 54.8, 25.5 ppm. IR (KBr): 2929, 2838, 1672, 1618, 1550, 1489, 1458, 1423, 1384, 1316, 1260, 1202, 1154, 1038, 785, 706, 530 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₃H₂₂NO₃ 360.1600; found 360.1596.

2-(2,4-Dimethoxyphenyl)-3-(3-methoxyphenyl)-8a-methylindolizin-1(8aH)-one (1q). 77% yield (180 mg). Orange solid, m.p. 98–100 °C. R_f = 0.16 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.25–7.29 (m, 1H, ArH), 7.05 (d, *J* = 8.70 Hz, 1H, ArH), 6.88–6.91 (m, 2H, ArH), 6.78 (s, 1H, ArH), 6.50 (d, *J* = 7.07 Hz, 1H, ArH), 6.43 (dd, *J* = 8.38, 1.99 Hz, 1H, CH), 6.28 (bs, 1H, ArH), 5.98 (d, *J* = 9.16 Hz, 1H, CH), 5.91–5.95 (m, 1H, CH), 5.30–5.33 (m, 1H, CH), 3.75 (s, 3H, OCH₃), 3.67 (s, 3H, OCH₃), 3.33 (s, 3H, OCH₃), 1.51 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 201.3, 168.1, 160.2, 159.5, 158.2, 132.2, 131.5, 129.6, 123.7, 123.7, 122.3, 120.6, 115.9, 113.5, 112.6, 107.7, 104.5, 99.1, 67.4, 55.5, 55.4, 55.0, 25.5 ppm. IR (KBr): 2927, 2841, 1669, 1612, 1551, 1499, 1460, 1426, 1379, 1314, 1256, 1207, 1154, 1038, 779, 706, 521 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₄H₂₄NO₄ 390.1705; found 390.1701.

2-(2,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)-8a-methylindolizin-1(8a*H*)-one (1r). 67% yield (157 mg). Brown gum. $R_{\rm f} =$ 0.13 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.21 (d, *J* = 8.60 Hz, 2H, ArH), 7.04 (d, *J* = 8.34 Hz, 1H, ArH), 6.85 (d, *J* = 8.60 Hz, 2H, ArH), 6.50 (d, *J* = 7.21 Hz, 1H, ArH), 6.43 (dd, *J* = 8.44, 1.76 Hz, 1H, CH), 6.29 (bs, 1H, ArH), 5.97 (d, *J* = 9.22 Hz, 1H, CH), 5.91–5.94 (m, 1H, CH), 5.29–5.32 (m, 1H, CH), 3.79 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 3.34 (s, 3H, OCH₃), 1.49 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 201.1, 168.2, 160.8, 160.1, 158.2, 132.3, 130.5, 129.9 (2C), 123.79, 123.75, 122.2, 113.9 (2C), 112.8, 112.7, 107.6, 104.5, 99.1, 67.3, 55.4 (2C), 55.1, 25.5 ppm. IR (KBr): 2932, 2840, 1663, 1608, 1552, 1500, 1549, 1417, 1297, 1254, 1206, 1165, 1120, 1033, 937, 813, 729, 586, 524 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₄H₂₄NO₄ 390.1705; found 390.1697.

2-(2,4-Dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)-8a-methylindolizin-1(8aH)-one (1s). 60% yield (151 mg). Brown gum. $R_{\rm f} = 0.06$ (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.01 (d, J = 8.17 Hz, 1H, ArH), 6.92 (d, J = 8.17 Hz, 1H, ArH), 6.84 (d, J = 8.17 Hz, 1H, ArH), 6.73 (s, 1H, ArH), 6.57 (d, J = 6.91 Hz, 1H, ArH), 6.43 (dd, J = 1.89, 8.44 Hz, 1H, CH), 6.30 (bs, 1H, ArH), 5.98 (d, J = 9.28 Hz, 1H, CH), 5.91-5.95 (m, 1H, CH), 5.31-5.34 (m, 1H, CH), 3.88 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 3.66 (s, 3H, OCH₃), 3.38 (s, 3H, OCH₃), 1.51 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 201.1, 168.1, 160.3, 158.4, 150.3, 148.8, 132.4, 123.9, 123.8, 122.5, 122.2, 121.4, 113.0, 111.7, 110.8, 107.7, 107.6, 104.6, 99.1, 67.4, 56.0 (2C), 55.5, 55.2, 25.5 ppm. IR (KBr): 2931, 2838, 1655, 1605, 1605, 1548, 1520, 1464, 1304, 1262, 1240, 1208, 1141, 1025, 823, 764, 734, 698, 616, 525 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₅H₂₆NO₅ 420.1811; found 420.1818.

3-(4-Fluorophenyl)-8a-methyl-2-(4-nitrophenyl)indolizin-1(8aH)one (1t). 94% yield (204 mg). Orange solid, m.p. 90–92 °C. $R_f =$ 0.33 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.00 (d, J = 8.74 Hz, 2H, ArH), 7.34–7.37 (m, 2H, ArH), 7.29 (d, J =8.86 Hz, 2H, ArH), 7.20–7.24 (m, 2H, ArH), 6.35 (d, J = 7.29 Hz, 1H, CH), 6.06 (d, J = 9.32 Hz, 1H, CH), 5.97–6.01 (m, 1H, CH), 5.45–5.48 (m, 1H, CH), 1.51 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.8, 168.1, 165.4, 162.9, 145.4, 138.8, 131.0, 130.9, 128.6 (2C), 124.7, 123.4 (2C), 122.4 (2C), 117.3, 117.1, 110.6, 108.1, 68.4, 25.6 ppm. IR (KBr): 2922, 2922, 1674, 1599, 1509, 1430, 1332, 827, 702 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₁H₁₆FN₂O₃ 363.1145; found 363.1139.

8a-Methyl-2,3-bis(4-nitrophenyl)indolizin-1(8*aH*)-one (1u). 95% yield (222 mg). Red gum. $R_{\rm f}$ = 0.20 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.38 (d, J = 8.29 Hz, 2H, ArH), 8.01 (d, J = 8.88 Hz, 2H, ArH), 7.59 (d, J = 7.10 Hz, 2H, ArH), 7.25 (d, J = 8.29 Hz, 2H, ArH), 6.25 (d, J = 9.05 Hz, 1H, CH), 6.08 (d, J = 9.36 Hz, 1H, CH), 5.99–6.03 (m, 1H, CH), 5.48–5.51 (m, 1H, CH), 1.54 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.6, 166.1, 149.4, 145.8, 137.9, 135.1, 130.1 (2C), 128.7 (2C), 125.0 (2C), 124.7, 123.6 (2C), 122.4, 121.9, 111.2, 108.9, 68.6, 25.6 ppm. IR (KBr): 2924, 1673, 1605, 1507, 1459, 1366, 1286, 1239, 1190, 1030, 840, 737 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₁H₁₆N₃O₅ 390.1090; found 390.1088.

8,8a-Dimethyl-2,3-diphenylindolizin-1(8aH)-one (1v). 88% yield (165 mg). Orange solid, m.p. 134–136 °C. $R_{\rm f}$ = 0.63 (20% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.42–7.47 (m, 3H, ArH), 7.33–7.35 (m, 2H, ArH), 7.10–7.16 (m, 4H, ArH), 7.05–7.08 (m, 1H, ArH), 6.23 (d, *J* = 7.04 Hz, 1H, CH), 5.61 (d,

Organic & Biomolecular Chemistry

$$\begin{split} J &= 5.63 \text{ Hz}, 1\text{H}, \text{CH}), 5.27 - 5.30 \ (\text{m}, 1\text{H}, \text{CH}), 2.13 \ (\text{s}, 3\text{H}, \text{CH}_3), \\ 1.61 \ (\text{s}, 3\text{H}, \text{CH}_3) \text{ ppm}. \ ^{13}\text{C} \text{ NMR} \ (100 \text{ MHz}, \text{CDCl}_3): \delta \ 199.1, \\ 166.8, 135.2, 131.2, 130.3, 129.5, 129.1 \ (2\text{C}), 129.0 \ (2\text{C}), 128.9 \\ (2\text{C}), 128.0 \ (2\text{C}), 125.9, 120.8, 119.1, 110.5, 109.0, 69.5, 24.2, \\ 18.1 \text{ ppm}. \text{ IR} \ (\text{KBr}): 3057, 2972, 2922, 1668, 1603, 1551, 1416, \\ 1338, 1178, 1103, 1069, 1026, 939, 740, 694, 548 \ \text{cm}^{-1}. \text{ HRMS} \\ (\text{ESI}) \ m/z: \ [\text{M} \ + \ \text{H}]^+ \ \text{calcd} \ \text{for} \ \text{C}_{22}\text{H}_{20}\text{NO} \ 314.1545; \ \text{found} \\ 314.1539. \end{split}$$

General procedure for the synthesis of 2a-u and 3a-u

A solution containing a mixture of indolizinone 1 (0.3 mmol) and dimethyl acetylene dicarboxylate (0.45 mmol) in a toluene-methanol mixture (10:1; 3.0 mL:0.3 mL) was taken in a sealed tube under a nitrogen atmosphere and was heated at 80 °C for 12 h under stirring. After cooling to room temperature, the mixture was concentrated under reduced pressure and the crude residue was purified by silica gel chromatography using the EtOAc-hexane solvent system to obtain the products 2 and 3. The yields and spectral data of these compounds are presented below.

2-Methoxy-2-methyl-4,5-diphenyl-1*H***-pyrrol-3**(*2H*)**-one** (2a). 40% yield (34 mg). Yellow solid, m.p. 138–140 °C. $R_{\rm f}$ = 0.50 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.53 (d, *J* = 7.53 Hz, 2H, ArH), 7.48 (d, *J* = 6.93 Hz, 1H, ArH), 7.36–7.40 (m, 2H, ArH), 7.23–7.25 (m, 4H, ArH), 7.17–7.20 (m, 1H, ArH), 5.16 (s, 1H, NH), 3.26 (s, 3H, OCH₃), 1.60 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.1, 171.1, 131.9, 131.4, 131.0, 129.3 (2C), 129.0 (2C), 128.4 (2C), 128.3 (2C), 126.6, 112.3, 89.8, 51.7, 23.3 ppm. IR (KBr): 3255, 2926, 2850, 1778, 1658, 1598, 1546, 1449, 1147, 1054, 910, 697, 598 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₈H₁₈NO₂ 280.1338; found 280.1349.

Dimethyl 8a-hydroxy-3'-methyl-1,2-diphenyl-3',8a-dihydrocyclopenta[*hi*]indolizine-7,8-dicarboxylate (3a). 57% yield (75 mg). Orange solid, m.p. 150–152 °C. $R_f = 0.53$ (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.23–7.24 (m, 3H, ArH), 7.17–7.18 (m, 5H, ArH), 7.08–7.09 (m, 2H, ArH), 6.84 (d, J = 6.55 Hz, 1H, CH), 6.68 (d, J = 5.76 Hz, 1H, CH), 5.91 (appt, J = 5.96 Hz, 1H, CH), 4.28 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.42 (s, 3H, OCH₃), 0.80 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.4, 165.3, 144.9, 143.8, 133.7, 132.1 (2C), 129.9, 129.4 (2C), 129.0, 128.9, 128.4 (3C), 127.6 (2C), 127.0, 126.3, 124.5, 119.8, 109.7, 91.9, 68.7, 52.7, 51.8, 13.3 ppm. IR (KBr): 3473, 2955, 2923, 1723, 1568, 1443, 1292, 1232, 737, 704 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₇H₂₄NO₅ 442.1654; found 442.1652.

2-Methoxy-4-(4-methoxyphenyl)-2-methyl-5-phenyl-1*H*-**pyrrol-3(2***H***)-one (2b). 37% yield (34 mg). Yellow solid, m.p. 150–152 °C. R_{\rm f} = 0.50 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): \delta 7.54 (d, J = 7.68 Hz, 2H, ArH), 7.46–7.50 (m, 1H, ArH), 7.37–7.40 (m, 2H, ArH), 7.17 (d, J = 8.41 Hz, 2H, ArH), 6.80 (d, J = 8.41 Hz, 2H, ArH), 4.96 (s, 1H, NH), 3.78 (s, 3H, OCH₃), 3.26 (s, 3H, OCH₃), 1.60 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): \delta 199.5, 170.3, 158.5, 131.8, 131.6, 130.5 (2C), 129.0 (2C), 128.4 (2C), 123.3, 114.0 (2C), 112.3, 89.6, 55.4, 51.7, 23.4 ppm. IR (KBr): 3441, 2954, 2922, 2860, 1776, 1649, 1514, 1459, 1372, 1298, 1251, 1154, 1035, 818, 695, 524 cm⁻¹.** HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}NO_3$ 310.1443; found 310.1450.

Dimethyl 8a-hydroxy-1-(4-methoxyphenyl)-3'-methyl-2-phenyl-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3b). 58% yield (82 mg). Yellow solid, m.p. 152–154 °C. $R_{\rm f}$ = 0.45 (40% EtOAc/hexane). ¹H NMR (400 MHz, $CDCl_3$): δ 7.24–7.26 (m, 3H, ArH), 7.16–7.18 (m, 2H, ArH), 6.99 (d, J = 8.63 Hz, 2H, ArH), 6.83 (d, J = 6.41 Hz, 1H, CH), 6.70 (d, J = 8.63 Hz, 2H, ArH), 6.67 (d, J = 5.77 Hz, 1H, CH), 5.90 (appt, J = 6.14 Hz, 1H, CH), 4.28 (s, 1H, OH), 3.92 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.47 (s, 3H, OCH₃), 0.79 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, $CDCl_3$): δ 165.43, 165.39, 158.7, 144.9, 143.6, 133.2 (2C), 130.0, 129.5 (2C), 129.0, 128.8, 128.4 (2C), 126.2, 125.6, 124.5, 119.8, 113.2 (2C), 109.6, 109.2, 91.9, 68.6, 55.2, 52.7, 51.9, 13.2 ppm. IR (KBr): 3482, 2924, 1729, 1605, 1507, 1567, 1459, 1366, 1286, 1239, 1190, 1030, 737 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₈H₂₆NO₆ 472.1760; found 472.1764.

2-Methoxy-2-methyl-4-(4-nitrophenyl)-5-phenyl-1*H*-pyrrol-3(2*H*)one (2c). 41% yield (40 mg). Orange solid, m.p. 132–134 °C. $R_f = 0.42$ (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, *J* = 8.68 Hz, 2H, ArH), 7.57–7.60 (m, 1H, ArH), 7.52 (d, *J* = 7.47 Hz, 2H, ArH), 7.48 (d, *J* = 7.32 Hz, 2H, ArH), 7.43 (d, *J* = 8.85 Hz, 2H, ArH), 5.42 (s, 1H, NH), 3.28 (s, 3H, OCH₃), 1.63 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ197.8, 172.7, 145.8, 138.4, 132.7, 130.7, 129.6 (2C), 129.0 (2C), 128.3 (2C), 123.6 (2C), 109.5, 90.4, 52.0, 23.2 ppm. IR (KBr): 3448, 2964, 2925, 2859, 1776, 1659, 1518, 1440, 1374, 1280, 1248, 1160, 1025, 816, 698, 540 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₈H₁₇N₂O₄ 325.1188; found 325.1171.

8a-hydroxy-3'-methyl-1-(4-nitrophenyl)-2-phenyl-Dimethyl 3',8a-dihydrocyclopenta[*hi*]indolizine-7,8-dicarboxylate (3c). 57% yield (83 mg). Orange solid, m.p. 124–126 °C. $R_{\rm f}$ = 0.43 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.99 (d, J = 8.59 Hz, 2H, ArH), 7.28-7.32 (m, 3H, ArH), 7.25-7.27 (m, 2H, ArH), 7.12 (d, J = 6.97 Hz, 2H, ArH), 6.78 (d, J = 6.50 Hz, 1H, CH), 6.72 (d, J = 5.75 Hz, 1H, CH), 5.99 (appt, J = 6.15 Hz, 1H, CH), 4.32 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 0.80 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.7, 164.9, 146.6, 143.2, 142.0, 132.5, (2C), 129.5, 129.4 (2C), 129.3, 128.9 (2C), 128.8, 127.3, 125.6, 123.7, 122.8 (2C), 120.0, 110.8, 107.3, 92.3, 69.0, 52.8, 52.2, 13.2 ppm. IR (KBr): 3468, 2940, 2851, 1725, 1591, 1511, 1439, 1341, 1236, 1107, 1060, 1004, 852, 702, 530 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₇H₂₃N₂O₇ 487.1505; found 487.1476.

2-Methoxy-5-(3-methoxyphenyl)-2-methyl-4-phenyl-1H-pyrrol-3(2H)-one (2d). 40% yield (37 mg). Yellow solid, m.p. 108–110 °C. $R_f = 0.50$ (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.29–7.33 (m, 1H, ArH), 7.26 (d, J = 4.58Hz, 4H, ArH), 7.17–7.21 (m, 1H, ArH), 7.13 (d, J = 7.41 Hz, 1H, ArH), 7.01–7.03 (m, 2H, ArH), 5.08 (s, 1H, NH), 3.66 (s, 3H, OCH₃), 3.28 (s, 3H, OCH₃), 1.61 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.1, 170.8, 159.8, 132.6, 131.0, 130.2, 129.4 (2C), 128.3 (2C), 126.7, 120.5, 118.0, 113.5, 112.6, 89.8, 55.4, 51.7, 23.4 ppm. IR (KBr): 3265, 2925, 1779, 1657, 1579, 1464, 1372, 1309, 1248, 1149, 1046, 985, 916, 866, 734, 608 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}NO_3$ 310.1443; found 310.1446.

Dimethyl-8a-hydroxy-2-(3-methoxyphenyl)-3'-methyl-1-phenyl-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3d). 56% yield (79 mg). Yellow solid, m.p. 134–136 °C. $R_{\rm f}$ = 0.45 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.14–7.17 (m, 4H, ArH), 7.09–7.10 (m, 2H, ArH), 6.89 (d, J = 6.14 Hz, 1H, ArH), 6.77-6.82 (m, 2H, ArH), 6.67 (d, J = 5.59 Hz, 1H, CH), 6.65 (s, 1H, CH), 5.92 (appt, J = 5.97 Hz, 1H, CH), 4.27 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.60 (s, 3H, OCH₃), 3.42 (s, 3H, OCH₃), 0.80 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.4, 165.3, 159.4, 144.8, 143.8, 133.8, 132.1 (2C), 131.1, 129.5, 129.1, 127.7 (2C), 127.0, 126.3, 124.4, 121.6, 119.8, 115.1, 114.6, 109.7 (2C), 91.9, 68.8, 55.3, 52.7, 51.8, 13.3 ppm. IR (KBr): 3486, 3050, 2995, 2948, 2843, 1726, 1577, 1478, 1437, 1356, 1290, 1235, 1051, 1002, 906, 851, 734, 454 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₈H₂₆NO₆ 472.1760; found 472.1764.

2-Methoxy-5-(3-methoxyphenyl)-4-(4-methoxyphenyl)-2-methyl-1H-pyrrol-3(2H)-one (2e). 35% yield (35 mg). Yellow solid, m.p. 94–96 °C. $R_{\rm f}$ = 0.50 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.28–7.32 (m, 1H, ArH), 7.18 (d, J = 8.56 Hz, 2H, ArH), 7.12 (d, J = 7.69 Hz, 1H, ArH), 7.00–7.03 (m, 2H, ArH), 6.81 (d, J = 8.78 Hz, 2H, ArH), 4.93 (s, 1H, NH), 3.78 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃), 3.26 (s, 3H, OCH₃), 1.60 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.5, 170.1, 159.8, 158.5, 132.8, 130.5 (2C), 130.2, 123.2, 120.6, 117.8, 113.9 (2C), 113.5, 112.5, 89.6, 55.4 (2C), 51.7, 23.5 ppm. IR (KBr): 3337, 2924, 2851, 1776, 1735, 1595, 1509, 1458, 1370, 1297, 1250, 1158, 1039, 918, 872, 787, 577, 527, 459 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₀H₂₂NO₄ 340.1549; found 340.1553.

Dimethyl,8a-hydroxy-2-(3-methoxyphenyl)-1-(4-methoxyphenyl)-3'-methyl-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3e). 59% yield (88 mg). Yellow solid, m.p. 102–104 °C. $R_{\rm f}$ = 0.42 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.16 (t, J = 7.87 Hz, 1H, ArH), 7.00 (d, J = 8.60 Hz, 2H, ArH), 6.87 (d, J = 6.39 Hz, 1H), 6.77-6.80 (m, 2H, ArH), 6.71 (d, J = 8.60 Hz, 2H, ArH), 6.66–6.68 (m, 2H, CH), 5.90 (appt, J = 6.13 Hz, 1H, CH), 4.27 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.63 (s, 3H, OCH₃), 3.47 (s, 3H, OCH₃), 0.79 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.4 (2C) 159.4, 158.7, 144.8, 143.7, 133.1 (2C), 131.2, 129.5, 129.1, 126.2, 125.6, 124.4, 121.7, 119.8, 115.0, 114.6, 113.2 (2C), 109.6, 109.2, 91.9, 68.7, 55.3, 55.2, 52.7, 51.9, 13.3 ppm. IR (KBr): 3483, 2945, 2841, 1727, 1579, 1469, 1437, 1286, 1239, 1184, 1104, 907, 836, 763, 724, 659, 620 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₉H₂₈NO₇ 502.1866; found 502.1871.

2-Methoxy-5-(3-methoxyphenyl)-2-methyl-4-(4-nitrophenyl) 1H-pyrrol-3(2H)-one (2f). 40% yield (43 mg). Yellow solid, m.p. 140–142 °C. $R_{\rm f}$ = 0.50 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.08 (d, J = 8.72 Hz, 2H, ArH), 7.45 (d, J = 8.71 Hz, 2H, ArH), 7.35–7.39 (m, 1H, ArH), 7.06–7.10 (m, 2H, ArH), 7.00 (s, 1H, ArH), 5.37 (s, 1H, NH), 3.75 (s, 3H, OCH₃), 3.28 (s, 3H, OCH₃), 1.62 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 197.8, 172.6, 160.2, 145.8, 138.4, 132.0, 130.8, 129.1 (2C), 123.6 (2C), 120.4, 118.1, 113.7, 109.6, 90.3, 55.6, 52.0, 23.2 ppm. IR (KBr): 3241, 2922, 1661, 1591, 1591, 1506, 1463, 1336, 1257, 1146, 1044, 849, 793 cm⁻¹. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for C₁₉H₁₉N₂O₅ 355.1294; found 355.1290.

Dimethyl 8a-hydroxy-2-(3-methoxyphenyl)-3'-methyl-1-(4nitrophenyl)-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3f). 54% yield (84 mg). Orange solid, m.p. 74–76 °C. $R_{\rm f}$ = 0.44 (40% EtOAc/hexane). ¹H NMR (400 MHz, $CDCl_3$): δ ¹H NMR (CDCl₃, 400 MHz): δ 8.00 (d, J = 8.31 Hz, 2H, ArH), 7.27 (d, J = 8.59 Hz, 2H, ArH), 7.20 (t, J = 7.87 Hz, 1H, ArH), 6.84 (m, 1H, ArH), 6.81 (d, J = 6.44 Hz, 1H, CH), 6.70-6.72 (m, 2H, ArH), 6.64 (s, 1H, CH), 6.00 (appt, J = 6.08 Hz, 1H, CH), 4.33 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.67 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 0.80 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.7, 164.9, 159.7, 146.6, 146.5, 143.2, 142.0, 132.5 (2C), 130.5, 130.0, 128.8, 127.3, 125.5, 122.7 (2C), 121.7, 120.0, 115.2, 114.8, 110.8, 107.2, 92.3, 69.0, 55.4, 52.8, 52.2, 13.2 ppm. IR (KBr): 3458, 2925, 1723, 1588, 1509, 1509, 1455, 1339, 1239, 1095, 847, 752 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₈H₂₅N₂O₈ 517.1611; found 517.1605.

2-Methoxy-5-(4-methoxyphenyl)-2-methyl-4-phenyl-1H-pyrrol-3(2H)-one (2g). 24% yield (22 mg). Yellow solid, m.p. 172–174 °C. $R_{\rm f}$ = 0.45 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.49 (d, J = 8.62 Hz, 2H, ArH), 7.27 (d, J = 4.08 Hz, 4H, ArH), 7.17–7.20 (m, 1H, ArH), 6.87 (d, J = 8.62 Hz, 2H, ArH), 5.00 (s, 1H, NH), 3.84 (s, 3H, OCH₃), 3.25 (s, 3H, OCH₃), 1.60 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 198.7, 170.6, 162.5, 131.3, 130.2 (2C), 129.4 (2C), 128.4 (2C), 126.5, 123.4, 114.4 (2C), 111.8, 89.8, 55.6, 51.7, 23.4 ppm. IR (KBr): 3256, 2953, 2925, 2846, 1658, 1604, 1488, 1375, 1312, 1174, 1128, 1028, 839, 705, 597 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₁₉H₂₀NO₃ 310.1443; found 310.1455.

Dimethyl 8a-hydroxy-2-(4-methoxyphenyl)-3'-methyl-1-phenyl-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3g). 66% yield (93 mg). Orange solid, m.p. 92–94 °C. R_f = 0.50 (40% EtOAc/hexane). ¹H NMR (400 MHz, $CDCl_3$): δ 7.17–7.18 (m, 3H, ArH), 7.07-7.12 (m, 4H, ArH), 6.88 (d, J = 6.57 Hz, 1H, CH), 6.76 (d, J = 8.59 Hz, 2H, ArH), 6.67 (d, J = 5.81 Hz, 1H, CH), 5.91 (appt, J = 6.21 Hz, 1H, CH), 4.25 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 3.42 (s, 3H, OCH₃), 0.79 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): 165.4, 165.3, 159.9, 144.7, 143.6, 133.9, 132.2 (2C), 130.7 (2C), 129.0, 127.6 (2C), 126.9, 126.2, 124.4, 122.0, 119.8, 113.9 (2C), 109.5, 109.0, 91.9, 68.6, 55.3, 52.7, 51.8, 13.2 ppm. IR (KBr): 3482, 2948, 2846, 1731, 1605, 1507, 1440, 1359, 1286, 1246, 1181, 1027, 840, 704, 643, 544, cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₈H₂₆NO₆ 472.1760; found 472.1755.

2-Methoxy-4,5-bis(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3(2*H*)one (2h). 22% yield (22 mg). Yellow solid, m.p. 140–142 °C. $R_f = 0.40$ (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.49 (d, J = 8.74 Hz, 2H, ArH), 7.17 (d, J = 8.74 Hz, 2H, ArH), 6.87 (d, J = 8.74 Hz, 2H, ArH), 6.81 (d, J = 8.40 Hz, 2H, ArH), 5.02 (s, 1H, NH), 3.83 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 3.23 (s, 3H, OCH₃), 1.58 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.1, 170.1, 162.4, 158.3, 130.5 (2C), 130.2 (2C), 123.7, 123.5, 114.3 (2C), 114.0 (2C), 111.5, 89.6, 55.6, 55.3, 51.6, 23.4 ppm. IR (KBr): 3354, 2940, 2838, 1775, 1718, 1658, View Article Online

1604, 1508, 1460, 1373, 1300, 1255, 1174, 1030, 910, 833, 733, 580, 523, cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}NO_4$ 340.1549; found 340.1555.

Dimethyl 8a-hydroxy-1,2-bis(4-methoxyphenyl)-3'-methyl-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3h). 69% yield (104 mg). Brown solid, m.p. 132-134 °C. R_f = 0.43 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.10 (d, J = 8.53 Hz, 2H, ArH), 6.99 (d, J = 8.53 Hz, 2H, ArH), 6.87 (d, J = 6.30 Hz, 1H, CH), 6.77 (d, J = 8.53 Hz, 2H, ArH), 6.71 (d, J = 8.90 Hz, 2H, ArH), 6.66 (d, J = 5.93 Hz, 1H, CH), 5.89 (appt, J = 6.31 Hz, 1H, CH), 4.26 (s, 1H, OH), 3.92 (s, 3H, OCH₃), 3.75 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 3.47 (s, 3H, OCH₃), 0.77 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.5, 165.4, 159.8, 158.7, 144.7, 143.5, 133.2 (2C), 130.8 (2C), 129.0, 126.1, 125.8, 124.4, 122.2, 119.8, 113.9 (2C), 113.2 (2C), 109.4, 108.5, 91.9, 68.6, 55.3, 55.2, 52.7, 51.9, 13.2 ppm. IR (KBr): 3473, 2947, 2845, 1731, 1605, 1568, 1510, 1442, 1359, 1285, 1245, 1177, 1103, 1062, 1030, 837, 732, 460 cm⁻¹. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for C₂₉H₂₈NO₇ 502.1866; found 502.1860.

2-Methoxy-5-(4-methoxyphenyl)-2-methyl-4-(4-nitrophenyl)-1*H*-pyrrol-3(2*H*)-one (2i). 32% yield (34 mg). Yellow solid, m.p. 130–132 °C. $R_{\rm f}$ = 0.43 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, J = 8.86 Hz, 2H, ArH), 7.47 (d, J = 5.31 Hz, 2H, ArH), 7.45 (d, J = 5.31 Hz, 2H, ArH), 6.94 (d, J = 8.75 Hz, 2H, ArH), 5.30 (s, 1H, NH), 3.87 (s, 3H, OCH₃), 3.26 (s, 3H, OCH₃), 1.61 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 197.5, 172.4, 163.2, 145.7, 139.0, 130.2 (2C), 129.2 (2C), 123.6 (2C), 122.5, 114.8 (2C), 108.8, 90.3, 55.7, 51.8, 23.2 ppm. IR (KBr): 3241, 2922, 2857, 2357, 1658, 1596, 1503, 1257, 1175, 1126, 1052, 1126, 1099, 838, 737, 689, 522 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₉H₁₉N₂O₅ 355.1294; found 355.1288.

Dimethyl 8a-hydroxy-2-(4-methoxyphenyl)-3'-methyl-1-(4nitrophenyl)-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3i). 55% yield (85 mg). Orange solid, m.p. 58-60 °C. R_f = 0.43 (40% EtOAc/hexane). ¹H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.88 Hz, 2H, ArH), 7.26 (d, J = 8.88 Hz, 2H, ArH), 7.04 (d, J = 8.88 Hz, 2H, ArH), 6.79–6.82 (m, 3H, ArH, CH), 6.71 (d, J = 5.46 Hz, 1H, CH), 5.89 (appt, J = 6.17 Hz, 1H, CH), 4.30 (s, 1H, OH), 3.92 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 3.53 (s, 3H, OCH₃), 0.78 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.7, 165.0, 160.4, 146.54, 146.48, 143.1, 142.3, 132.6 (2C), 130.8 (2C), 128.8, 127.2, 125.6, 122.7 (2C), 121.3, 120.0, 114.3 (2C), 110.7, 106.7, 92.2, 68.9, 55.4, 52.8, 52.2, 13.2 ppm. IR (KBr): 3456, 2926, 2849, 2361, 2333, 1727, 1599, 1511, 1440, 1342, 1243, 1024, 847, 703, 527 cm⁻¹. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for C₂₈H₂₅N₂O₈ 517.1611; found 517.1607.

2-Methoxy-2-methyl-5-(4-(methylthio)phenyl)-4-phenyl-1*H***pyrrol-3(2***H***)-one (2j). 26% yield (25 mg). Yellow solid, m.p. 150–152 °C. R_{\rm f} = 0.50 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.43–7.45 (m, 2H, ArH), 7.24–7.29 (m, 4H, ArH), 7.18–7.20 (m, 3H, ArH), 5.12 (s, 1H, NH), 3.26 (s, 3H, OCH₃), 2.50 (s, 3H, SCH₃), 1.60 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 198.9, 170.4, 144.4, 131.1, 129.3 (2C), 128.7 (2C), 128.4 (2C), 127.2, 126.7, 125.5 (2C), 112.1, 89.8, 51.7, 23.4, 14.9 ppm. IR (KBr): 3248, 2925, 2858, 1740, 1657, 1596, 1569,** 1472, 1374, 1303, 1142, 1066, 1024, 828, 742, 705, 596 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}NO_2S$ 326.1215; found 326.1221.

Dimethyl 8a-hydroxy-3'-methyl-2-(4-(methylthio)phenyl)-1phenyl-3',8a-dihydroxyclopenta[*hi*]indolizine-7,8-dicarboxylate (3j). 65% yield (95 mg). Orange solid, m.p. 48–50 °C. R_f = 0.53 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.17–7.19 (m, 3H, ArH), 7.06–7.09 (m, 6H, ArH), 6.85 (d, *J* = 6.45 Hz, 1H, CH), 6.67 (d, *J* = 5.73 Hz, 1H, CH), 5.91 (appt, *J* = 6.00 Hz, 1H, CH), 4.26 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.42 (s, 3H, OCH₃), 2.42 (s, 3H, SCH₃), 0.79 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.4, 165.3, 144.4, 143.8, 139.8, 133.7, 132.1 (2C), 129.7 (2C), 129.0, 127.7 (2C), 127.1, 126.3, 126.2, 125.7 (2C), 124.4, 119.8, 109.7, 109.5, 91.9, 68.7, 52.7, 51.8, 15.2, 13.29 ppm. IR (KBr): 3348, 2955, 2922, 2860, 1638, 1461, 1371, 1288, 1233, 1200, 707, 648, 564, 515 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd C₂₈H₂₆NO₅S 488.1532; found 488.1524.

2-Methoxy-4-(4-methoxyphenyl)-2-methyl-5-(4-(methylthio) phenyl)-1*H*-pyrrol-3(2*H*)-one (2k). 21% yield (22 mg). Yellow solid, m.p. 148–150 °C. R_f = 0.45 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.44 (d, *J* = 8.26 Hz, 2H, ArH), 7.17–7.20 (m, 4H, ArH), 6.82 (d, *J* = 8.90 Hz, 2H, ArH), 4.83 (s, 1H, NH), 3.79 (s, 3H, OCH₃), 3.25 (s, 3H, OCH₃), 2.50 (s, 3H, SCH₃), 1.59 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.3, 169.7, 158.5, 144.2, 130.5 (2C), 128.7 (2C), 127.4, 125.6 (2C), 123.4, 114.0 (2C), 112.2, 89.6, 55.4, 51.7, 23.5, 15.0 ppm. IR (KBr): 3257, 2924, 2844, 1768, 1659, 1591, 1516, 1454, 1371, 1295, 1249, 1169, 1029, 960, 824, 732, 580 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₀H₂₂NO₃S 356.1320; found 356.1327.

Dimethyl 8a-hydroxy-1-(4-methoxyphenyl)-3'-methyl-2-(4-(methylthio)phenyl)-3',8a-dihydro cyclopenta[hi]indolizine-7,8dicarboxylate (3k). 68% yield (106 mg). Yellow solid, m.p. 84–86 °C. $R_{\rm f} = 0.43$ (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.09 (s, 4H, ArH), 6.98 (d, J = 7.99 Hz, 2H, ArH), 6.84 (d, J = 6.22 Hz, 1H, CH), 6.71 (d, J = 7.99 Hz, 2H, ArH), 6.66 (d, J = 5.33 Hz, 1H, CH), 5.90 (appt, J = 5.77 Hz, 1H, CH), 4.27 (s, 1H, OH), 3.92 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 3.47 (s, 3H, OCH₃), 2.42 (s, 3H, SCH₃), 0.78 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.4 (2C), 158.7, 144.4, 143.6, 139.6, 133.2 (2C), 129.7 (2C), 129.0, 126.3, 126.2, 125.7 (2C), 125.5, 124.4, 119.8, 113.2 (2C), 109.6, 109.1, 91.8, 68.6, 55.2, 52.7, 51.9, 15.2, 13.3 ppm. IR (KBr): 3470, 2954, 2922, 2862, 1731, 1601, 1501, 1461, 1371, 1287, 1238, 1190, 1092, 968, 812, 775, 746, 702, 664, 590, 575, 544 cm⁻¹. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for C₂₉H₂₈NO₆S 518.1637; found 518.1626.

2-Methoxy-2-methyl-5-(4-(methylthio)phenyl)-4-(4-nitrophenyl)-1H-pyrrol-3(2H)-one (2l). 30% yield (33 mg). Yellow solid, m.p. 118–120 °C. $R_{\rm f}$ = 0.45 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.08 (d, J = 8.54 Hz, 2H, ArH), 7.40–7.45 (m, 4H, ArH), 7.24 (d, J = 8.15 Hz, 2H, ArH), 5.50 (s, 1H, NH), 3.25 (s, 3H, OCH₃), 2.51 (s, 3H, SCH₃), 1.60 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 197.6, 172.1, 145.8, 145.7, 138.7, 129.1 (2C), 128.6 (2C), 126.2, 125.8 (2C), 123.7 (2C), 109.2, 90.3, 51.9, 23.2, 14.9 ppm. IR (KBr): 3318, 2954, 2922, 2845, 1737, 1652, 1584, 1507, 1470, 1341, 1250, 1130, 1014, 840, 520 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_4S$ 371.1066; found 371.1078.

Dimethyl 8a-hydroxy-3'-methyl-2-(4-(methylthio)phenyl)-1-(4nitrophenyl)-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (31). 61% yield (98 mg). Orange solid, m.p. 74-76 °C. R_f = 0.44 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.00 (d, J = 8.84 Hz, 2H, ArH), 7.26 (d, J = 8.21 Hz, 2H, ArH), 7.12 (d, *J* = 8.21 Hz, 2H, ArH), 7.02 (d, *J* = 7.58 Hz, 2H, ArH), 6.80 (d, *J* = 6.94 Hz, 1H, CH), 6.71 (d, J = 5.68 Hz, 1H, CH), 5.99 (appt, J = 6.07 Hz, 1H, CH), 4.34 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 2.44 (s, 3H, SCH₃), 0.80 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.7, 165.0, 146.6, 146.2, 143.2, 142.0, 140.9, 132.6 (2C), 129.7 (2C), 128.7, 127.3, 125.9 (2C), 125.5, 125.4, 122.8 (2C), 120.0, 110.8, 107.2, 92.2, 67.0, 52.8, 52.2, 15.1, 13.2 ppm. IR (KBr): 3472, 2953, 2859, 1730, 1593, 1513, 1465, 1441, 1343, 1314, 1234, 1104, 1061, 1010, 854, 739, 705 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_7S$ 533.1382; found 533.1368.

5-(3,4-Dimethoxyphenyl)-2-methoxy-2-methyl-4-phenyl-1*H***-pyrrol-3(2***H***)-one (2m). 30% yield (31 mg). Yellow solid, m.p. 158–160 °C. R_f = 0.30 (60% EtOAc/hexane). 1¹H NMR (400 MHz, CDCl₃): δ 7.26–7.30 (m, 4H, ArH), 7.22–7.25 (m, 1H, ArH), 7.17–7.21 (m, 1H, ArH), 6.91 (s, 1H, ArH), 6.87 (d,** *J* **= 8.44 Hz, 1H, ArH), 4.97 (s, 1H, NH), 3.92 (s, 3H, OCH₃), 3.58 (s, 3H, OCH₃), 3.28 (s, 3H, OCH₃), 1.61 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 198.7, 170.5, 152.2, 148.9, 131.4, 129.7 (2C), 128.4 (2C), 126.7, 123.5, 121.3, 112.2, 111.8, 111.0, 89.8, 56.2, 55.8, 51.7, 23.5 ppm. IR (KBr): 3413, 2927, 2847, 1652, 1598, 1552, 1491, 1447, 1372, 1262, 1139, 1069, 1023, 865, 740, 704, 613, 584, 465 cm⁻¹. HRMS (ESI)** *m/z***: [M + H]⁺ calcd for C₂₀H₂₂NO₄ 340.1549; found 340.1556.**

Dimethyl-2-(3,4-dimethoxyphenyl)-8a-hydroxy-3'-methyl-1phenyl-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3m). 63% yield (96 mg). Brown solid, m.p. 58–60 °C. R_f = 0.40 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.17–7.18 (m, 3H, ArH), 7.09–7.10 (m, 2H, ArH), 6.95 (d, J = 6.53 Hz, 1H, ArH), 6.85 (d, J = 8.34 Hz, 1H, ArH), 6.75 (d, J = 8.34 Hz, 1H, CH), 6.67 (d, J = 5.80 Hz, 1H, CH), 6.56 (s, 1H, ArH), 5.92 (appt, J = 5.99 Hz, 1H, CH), 4.26 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.58 (s, 3H, OCH₃), 3.43 (s, 3H, OCH₃), 0.80 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.5, 165.3, 149.3, 148.6, 144.8, 143.8, 134.1, 132.2 (2C), 129.1, 127.7 (2C), 127.0, 126.3, 124.3, 122.1, 121.9, 119.9, 112.7, 110.8, 109.6, 109.0, 91.8, 68.8, 55.9, 55.8, 52.7, 51.8, 13.3 ppm. IR (KBr): 3493, 2945, 1730, 1605, 1570, 1512, 1442, 1232, 1140, 1062, 1024, 765, 737, 705 cm⁻¹. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for C₂₉H₂₈NO₇ 502.1866; found 502.1850.

5-(3,4-Dimethoxyphenyl)-2-methoxy-4-(4-methoxyphenyl)-2methyl-1*H***-pyrrol-3(2***H***)-one (2n).** 26% yield (29 mg). Yellow solid, m.p. 142–144 °C. $R_{\rm f}$ = 0.23 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.19–7.24 (m, 3H, ArH), 6.97 (s, 1H, ArH), 6.87 (d, *J* = 8.49 Hz, 1H, ArH), 6.83 (d, *J* = 8.49 Hz, 2H, ArH), 4.94 (s, 1H, NH), 3.92 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.62 (s, 3H, OCH₃), 3.26 (s, 3H, OCH₃), 1.60 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.1, 170.0, 158.5, 152.1, 148.9, 130.8 (2C), 123.7 (2C), 121.4, 114.0 (2C), 111.9, 111.7, 111.0, 89.7, 56.1, 55.8, 55.4, 51.7, 23.5 ppm. IR (KBr): 3331, 2928, 2848, 1778, 1654, 1601, 1569, 1509, 1460, 1370, 1257, 1147, 1028, 915, 731 cm⁻¹. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}NO_5$ exact mass: 370.1654; found 370.1662.

Dimethyl 2-(3,4-dimethoxyphenyl)-8a-hydroxy-1-(4-methoxyphenyl)-3'-methyl-3',8a-dihydro cyclopenta[hi]indolizine-7,8dicarboxylate (3n). 65% yield (104 mg). Brown solid, m.p. 50–52 °C. $R_{\rm f}$ = 0.30 (40% EtOAc/hexane). ¹H NMR (400 MHz, $CDCl_3$): δ 7.00 (d, J = 8.51 Hz, 2H, ArH), 6.93 (d, J =6.44 Hz, 1H, ArH), 6.82 (d, J = 8.28 Hz, 1H, ArH), 6.75 (d, J = 8.28 Hz, 1H, CH), 6.71 (d, J = 8.51 Hz, 2H, ArH), 6.66 (d, J = 5.61 Hz, 1H, CH), 6.58 (s, 1H, ArH), 5.90 (appt, J = 6.16 Hz, 1H, CH), 4.27 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.62 (s, 3H, OCH₃), 3.48 (s, 3H, OCH₃), 0.79 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.5, 165.4, 158.7, 149.2, 148.6, 144.8, 143.6, 133.2 (2C), 129.1, 126.2, 125.9, 124.4, 122.3, 122.0, 119.8, 113.2 (2C), 112.7, 110.8, 109.5, 108.6, 91.8, 68.7, 55.9, 55.3, 52.7, 51.9, 13.3 ppm. IR (KBr): 3545, 2923, 2863, 1726, 1602, 1507, 1459, 1237, 1183, 1139, 1024, 728, 423 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₃₀H₃₀NO₈ 532.1971; found 532.1966.

5-(3,4-Dimethoxyphenyl)-2-methoxy-2-methyl-4-(4-nitrophenyl)-1H-pyrrol-3(2H)-one (20). 31% yield (36 mg). Yellow solid, m.p. 104–106 °C. R_f = 0.30 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.37 Hz, 2H, ArH), 7.48 (d, *J* = 8.37 Hz, 2H, ArH), 7.17 (d, *J* = 8.37 Hz, 1H, ArH), 6.93 (s, 1H, ArH), 6.90 (d, *J* = 8.35 Hz, 1H, ArH), 5.39 (s, 1H, NH), 3.94 (s, 3H, OCH₃), 3.70 (s, 3H, OCH₃), 3.26 (s, 3H, OCH₃), 1.62 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 197.5, 172.3, 152.9, 149.4, 145.7, 138.9, 129.3 (2C), 123.6 (2C), 122.6, 122.0, 111.4, 111.0, 109.0, 90.4, 56.3, 56.1, 51.9, 23.3 ppm. IR (KBr): 3310, 2953, 2920, 2858, 1733, 1659, 1592, 1500, 1461, 1334, 1262, 1138, 1019, 851, 582 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₀H₂₁N₂O₆ 385.1400; found 385.1405.

Dimethyl 2-(3,4-dimethoxyphenyl)-8a-hydroxy-3'-methyl-1-(4nitrophenyl)-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (30). 60% yield (98 mg). Orange solid, m.p. 90–92 °C. $R_{\rm f}$ = 0.33 (40% EtOAc/hexane). ¹H NMR (400 MHz, CD₃OD): δ 7.98 (d, J = 8.89 Hz, 2H, ArH), 7.43 (d, J = 8.89 Hz, 2H, ArH), 6.92 (d, J = 8.33 Hz, 1H, ArH), 6.80 (d, J = 6.66 Hz, 1H, CH), 6.75 (d, J = 8.30 Hz, 1H, CH), 6.67–6.69 (m, 2H, ArH), 6.08 (appt, J = 6.05 Hz, 1H, CH), 3.86 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.64 (s, 3H, OCH₃), 3.35 (s, 3H, OCH₃), 0.73 (s, 3H, CH₃) ppm; one exchangeable proton did not appear. 13C NMR (100 MHz, CD₃OD): δ 166.6, 166.5, 151.4, 150.6, 148.8, 147.4, 144.3, 143.1, 133.3 (2C), 131.2, 129.2, 129.0, 123.6, 123.4, 123.1 (2C), 119.3, 114.0, 112.8, 111.8, 106.7, 94.0, 69.8, 56.4, 56.3, 53.0, 51.9, 13.6 ppm. IR (KBr): 3392, 2930, 2840, 2364, 2342, 1724, 1589, 1510, 1459, 1342, 1213, 1027, 868, 713, 545 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₉H₂₇N₂O₉ 547.1717; found 547.1707.

4-(2,4-Dimethoxyphenyl)-2-methoxy-2-methyl-5-phenyl-1*H*pyrrol-3(2*H*)-one (2p). 38% yield (39 mg). Yellow solid, m.p. 62–64 °C. $R_{\rm f}$ = 0.33 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.48 (d, J = 7.85 Hz, 2H, ArH), 7.41–7.45 (m, 1H, ArH), 7.32–7.35 (m, 2H, ArH), 7.15 (d, J = 8.32 Hz, 1H, ArH), 6.50 (d, J = 8.30 Hz, 1H, ArH), 6.37 (s, 1H, ArH), 4.97 (s, 1H, NH), 3.80 (s, 3H, OCH₃), 3.36 (s, 3H, OCH₃), 3.28 (s, 3H, OCH₃), 1.60 (s, 3H, CH₃) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 199.7, 171.4, 160.5, 158.0, 132.7, 132.3, 131.4, 128.7 (2C), 127.2 (2C), 113.1, 109.2, 104.8, 99.4, 89.5, 55.5, 55.2, 51.7, 23.3 ppm. IR (KBr): 3252, 2926, 2857, 1659, 1600, 1553, 1576, 1461, 1375, 1299, 1208, 1152, 1039, 917, 830, 781, 731, 697, 573, 481 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₀H₂₂NO₄ 340.1549; found 340.1559.

Dimethyl 1-(2,4-dimethoxyphenyl)-8a-hydroxy-3'-methyl-2phenyl-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3p). 40% yield (60 mg). Orange solid, m.p. 54–56 °C. $R_f = 0.42$ (40% EtOAc/hexane). ¹H NMR (400 MHz, $CDCl_3$): δ 7.22 (bs, 3H, ArH), 7.17 (bs, 2H, ArH), 6.82 (d, J = 5.35 Hz, 2H, ArH), 6.55 (d, J = 5.74 Hz, 1H, CH), 6.33 (s, 1H, ArH), 6.27 (d, J = 8.03 Hz, 1H, CH), 5.84 (bs, 1H, CH), 3.92 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.61 (bs, 3H, OCH₃), 3.46 (s, 3H, OCH₃), 0.82 (s, 3H, CH_3) ppm; one exchangeable proton did not appear. ¹³C NMR (100 MHz, $CDCl_3$): δ 166.0, 164.8, 160.4, 159.7, 143.1, 134.8 (2C), 130.3, 129.1 (3C), 128.9, 128.67 (2C), 128.3 (4C), 126.6, 118.8, 109.9, 104.0, 98.1, 68.9, 55.3 (2C), 52.6, 51.5, 13.4 ppm. IR (KBr): 3461, 2923, 1730, 1607, 1459, 1371, 1294, 1210, 1371, 1294, 1210, 1160, 1105, 1035, 839, 736, 651 cm^{-1} . HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₉H₂₈NO₇ 502.1866; found 502.1894.

4-(2,4-Dimethoxyphenyl)-2-methoxy-5-(3-methoxyphenyl)-2methyl-1*H***-pyrrol-3(2***H***)-one (2q**). 39% yield (52 mg). Yellow solid, m.p. 110–112 °C. $R_f = 0.50$ (80% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.23 (d, J = 7.87 Hz, 1H, ArH), 7.12 (d, J =8.32 Hz, 1H, ArH), 7.08 (d, J = 7.65 Hz, 1H, ArH), 6.98 (s, 1H, ArH), 6.95 (d, J = 8.10 Hz, 1H, ArH), 6.48 (dd, J = 1.97, 8.33 Hz, 1H, ArH), 6.38 (d, J = 1.84 Hz, 1H, ArH), 5.05 (s, 1H, NH), 3.78 (s, 3H, OCH₃), 3.63 (s, 3H, OCH₃), 3.40 (s, 3H, OCH₃), 3.27 (s, 3H, OCH₃), 1.58 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.8, 171.1, 160.5, 159.6, 158.1, 133.7, 132.3, 129.8, 119.5, 117.6, 113.2, 112.3, 109.4, 104.8, 99.4, 89.5, 55.5, 55.3 (2C), 51.7, 23.3 ppm. IR (KBr): 3255, 2948, 2841, 1738, 1660, 1554, 1513, 1462, 1372, 1294, 1255, 1210, 1151, 1039, 937, 839, 785, 729, 572 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₁H₂₄NO₅ 370.1654; found 370.1661.

Dimethyl 1-(2,4-dimethoxyphenyl)-8a-hydroxy-2-(3-methoxyphenyl)-3'-methyl-3',8a-dihydro cyclopenta[hi]indolizine-7,8dicarboxylate (3q). 41% yield (65 mg). Orange solid, m.p. 74–76 °C. $R_{\rm f}$ = 0.30 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ ¹H NMR (CDCl₃, 400 MHz): δ 7.15 (t, J = 7.92 Hz, 1H, ArH), 6.87 (bs, 2H, ArH), 6.81 (d, J = 7.40 Hz, 1H, CH), 6.75-6.78 (m, 1H, ArH), 6.67 (s, 1H, ArH), 6.55 (d, J = 5.71 Hz, 1H, CH), 6.28-6.33 (m, 2H, ArH), 5.85 (bs, 1H, CH), 3.92 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.62 (bs, 3H, OCH₃), 3.45 (s, 3H, OCH₃), 0.82 (s, 3H, CH₃) ppm; one exchangeable proton did not appear. ¹³C NMR (100 MHz, $CDCl_3$): δ 166.0, 164.8, 160.5, 159.7, 159.3, 143.3, 134.7 (2C), 131.5, 129.3 (2C), 129.0, 126.5, 121.3 (2C), 118.9, 115.0 (2C), 114.1 (2C), 109.0, 104.0, 98.2, 68.9, 55.3 (2C), 55.2, 52.6, 51.5, 13.4 ppm. IR (KBr): 3485, 2953, 2922, 2861, 1735, 1705, 1602, 1460, 1368, 1294, 1232, 1162, 1036, 730, 620 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₃₀H₃₀NO₈ 532.1971; found 532.1975.

4-(2,4-Dimethoxyphenyl)-2-methoxy-5-(4-methoxyphenyl)-2methyl-1H-pyrrol-3(2H)-one (2r). 37% yield (41 mg). Yellow solid, m.p. 144–146 °C. $R_{\rm f}$ = 0.33 (60% EtOAc/hexane). ¹H NMR (400 MHz, CD₃OD): δ 7.47 (d, J = 8.75 Hz, 2H, ArH), 6.99 (d, J = 7.77 Hz, 1H, ArH), 6.98 (d, J = 8.75 Hz, 2H, ArH), 6.50–6.52 (m, 1H, ArH), 6.49 (s, 1H, ArH), 3.80 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.47 (s, 3H, OCH₃), 3.22 (s, 3H, OCH₃), 1.51 (s, 3H, CH₃) ppm; one exchangeable proton did not appear. ¹³C NMR (100 MHz, CD₃OD): δ 201.4, 175.6, 164.0, 162.0, 159.8, 133.6, 130.9 (2C), 125.0, 114.8 (3C), 107.4, 106.0, 99.9, 90.9, 55.9, 55.8, 55.7, 51.7, 22.8 ppm. IR (KBr): 3210, 2964, 2840, 1732, 1671, 1550, 1504, 1480, 1344, 1284, 1245, 1218, 1158, 1035, 845, 723, 568 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₁H₂₄NO₅ 370.1654; found 370.1666.

Dimethyl 1-(2,4-dimethoxyphenyl)-8a-hydroxy-2-(4-methoxyphenyl)-3'-methyl-3',8a-dihydro cyclopenta[hi]indolizines-7,8dicarboxylate (3r). 44% yield (70 mg). Brown solid, m.p. 64–66 °C. $R_{\rm f}$ = 0.30 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.08 (d, J = 8.71 Hz, 2H, ArH), 6.84 (bs, 2H, ArH), 6.74 (d, J = 8.51 Hz, 2H, ArH), 6.54 (d, J = 5.49 Hz, 1H, CH), 6.33 (s, 1H, ArH), 6.28 (d, J = 7.69 Hz, 1H, CH), 5.83 (bs, 1H, CH), 3.91 (s, 3H, OCH₃), 3.73 (s, 6H, OCH₃), 3.60 (bs, 3H, OCH₃), 3.45 (s, 3H, OCH₃), 0.80 (s, 3H, CH₃) ppm; one exchangeable proton did not appear. ¹³C NMR (100 MHz, CDCl₃): δ 166.0, 164.8, 160.4, 159.8, 159.7, 142.9, 134.8 (2C), 130.4 (3C), 129.0, 126.4, 122.4, 118.8, 113.7 (4C), 108.9, 103.9, 98.0, 92.0, 68.8, 55.3, 55.2, 52.5, 51.5, 13.4 ppm. IR (KBr): 3487, 2925, 2856, 1733, 1604, 1503, 1458, 1361, 1295, 1244, 1167, 1034, 838, 736 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₃₀H₃₀NO₈ 532.1971; found 532.1973.

4-(2,4-Dimethoxyphenyl)-5-(3,4-dimethoxyphenyl)-2-methoxy-2-methyl-1*H***-pyrrol-3(2***H***)-one (2s).** 34% yield (41 mg). Yellow solid, m.p. 136–138 °C. $R_{\rm f}$ = 0.45 (80% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.18 (d, *J* = 8.21 Hz, 1H, Ar**H**), 7.10 (d, *J* = 8.21 Hz, 1H, Ar**H**), 6.94 (s, 1H, Ar**H**), 6.82 (d, *J* = 8.57 Hz, 1H, Ar**H**), 6.49 (d, *J* = 8.57 Hz, 1H, Ar**H**), 6.41 (s, 1H, Ar**H**), 5.01 (s, 1H, NH), 3.88 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.58 (s, 3H, OCH₃), 3.47 (br, 3H, OCH₃), 3.27 (s, 3H, OCH₃), 1.59 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.4, 170.7, 160.6, 158.4, 151.8, 148.7, 132.5, 124.6, 120.4, 113.7, 110.8 (2C), 108.8, 104.9, 99.4, 89.5, 56.1, 55.7, 55.5, 51.6, 23.3 ppm. IR (KBr): 3257, 2933, 2841, 1728, 1658, 1604, 1523, 1463, 1374, 1293, 1212, 1149, 1030, 939, 824, 732, 571 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₂H₂₆NO₆ 400.1760; found 400.1764.

Dimethyl 1-(2,4-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)-8a-hydroxy-3'-methyl-3',8a-dihydro cyclopenta[*hi*]indolizine-7,8-dicarboxylate (3s). 43% yield (72 mg). Orange gum. R_f = 0.23 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 6.93 (bs, 2H, ArH), 6.84 (d, *J* = 7.84 Hz, 1H, ArH), 6.74 (d, *J* = 8.27 Hz, 1H, CH), 6.59 (s, 1H, ArH), 6.55 (d, *J* = 5.53 Hz, 1H, CH), 6.29–6.32 (m, 2H, ArH), 5.84 (bs, 1H, CH), 3.92 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.61 (bs, 6H, OCH₃), 3.45 (s, 3H, OCH₃), 0.82 (s, 3H, CH₃) ppm; one exchangeable proton did not appear. ¹³C NMR (100 MHz, CDCl₃): δ 166.0, 164.8, 160.5, 159.7, 149.1, 148.4, 143.0, 134.8 (3C), 129.0, 126.6, 122.6, 121.4, 119.0, 112.3 (2C), 110.7 (3C), 109.0, 104.0, 98.0, 68.8, 55.8 (2C), 55.7, 55.4, 52.6, 51.5, 13.4 ppm. IR (KBr): 3500, 2953, 2848, 1734, 1704, 1604, 1509, 1460, 1460, 1360, 1360, 1295, 1228, 1031, 915, 731, 639, 598 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₃₁H₃₂NO₉ 562.2077; found 562.2081.

5-(4-Fluorophenyl)-2-methoxy-2-methyl-4-(4-nitrophenyl)-1*H***-pyrrol-3(2***H***)-one (2t**). 30% yield (31 mg). Yellow solid, m.p. 174–176 °C. $R_{\rm f}$ = 0.50 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.88 Hz, 2H, ArH), 7.54 (dd, *J* = 7.24, 5.25 Hz, 2H, ArH), 7.41 (d, *J* = 8.74 Hz, 2H, ArH), 7.13–7.18 (m, 2H, ArH), 5.35 (s, 1H, NH), 3.28 (s, 3H, OCH₃), 1.63 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 197.7, 171.3, 146.0, 138.2, 130.7, 130.6, 129.2 (2C), 126.8, 123.7 (2C), 117.1, 116.9, 109.8, 90.4, 52.0, 23.2 ppm. IR (KBr): 3255, 2954, 2922, 2860, 1653, 1594, 1551, 1508, 1479, 1322, 1229, 1189, 1149, 1059, 970, 904, 835, 732, 581 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₈H₁₆FN₂O₄ 343.1094; found 343.1100.

Dimethyl 2-(4-fluorophenyl)-8a-hydroxy-3'-methyl-1-(4-nitrophenyl)-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (3t). 61% yield (92 mg). Orange solid, m.p. 140–142 °C. R_f = 0.45 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.00 (d, J = 8.40 Hz, 2H, ArH), 7.24 (d, J = 8.40 Hz, 2H, ArH), 7.10–7.13 (m, 2H, ArH), 6.96–7.00 (m, 2H, ArH), 6.73 (d, J = 6.40 Hz, 1H, CH), 6.71 (d, J = 5.60 Hz, 1H, CH), 6.01 (appt, J = 5.96 Hz, 1H, CH), 4.35 (s, 1H, OH), 3.93 (s, 3H, OCH₃), 3.53 (s, 3H, OCH₃), 0.80 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.6, 164.8, 146.7, 145.6, 143.3, 141.7, 132.5 (2C), 131.4, 131.3, 128.5, 127.5, 125.7, 125.3 (2C), 122.8 (2C), 120.0, 116.3, 116.0, 111.08, 107.5, 92.2, 69.0, 52.8, 52.2, 13.2 ppm. IR (KBr): 3471, 2955, 2923, 2862, 1728, 1596, 1512, 1462, 1345, 1314, 1232, 1201, 1163, 1102, 1061, 1008, 850, 737, 707 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₇H₂₂FN₂O₇ 505.1411; found 505.1407.

2-Methoxy-2-methyl-4,5-bis(4-nitrophenyl)-1H-pyrrol-3(2H)one (2u). 55% yield (61 mg). Orange solid, m.p. 136–138 °C. $R_f = 0.45$ (80% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃, CD₃OD): δ 8.25 (d, J = 8.29 Hz, 2H, ArH), 8.04 (d, J = 8.29 Hz, 2H, ArH), 7.69 (d, J = 8.29 Hz, 2H, ArH), 7.31 (d, J = 8.29 Hz, 2H, ArH), 3.24 (s, 3H, OCH₃), 1.56 (s, 3H, CH₃) ppm; one exchangeable proton did not appear. ¹³C NMR (100 MHz, CDCl₃, CD₃OD): δ 198.4, 170.5, 149.7, 145.9, 137.7, 136.7, 129.6 (2C), 129.0 (2C), 124.4 (2C), 123.8 (2C), 109.8, 90.4, 51.9, 22.6 ppm. IR (KBr): 3223, 2955, 2923, 2861, 2359, 2335, 1664, 1593, 1514, 1465, 1340, 1121, 1051, 968, 905, 855, 751, 606 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₈H₁₆N₃O₆ 370.1039; found 370.1035.

Dimethyl 8a-hydroxy-3'-methyl-1,2-bis(4-nitrophenyl)-3',8adihydrocyclopenta[*hi*]indolizine-7,8-dicarboxylate (3u). 40% yield (64 mg). Orange solid, m.p. 98–100 °C. R_f = 0.42 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.15 (d, *J* = 8.63 Hz, 2H, ArH), 8.03 (d, *J* = 8.63 Hz, 2H, ArH), 7.34 (d, *J* = 8.63 Hz, 2H, ArH), 7.24 (d, *J* = 8.63 Hz, 2H, ArH), 6.71 (d, *J* = 5.61 Hz, 1H, CH), 6.69 (d, *J* = 6.54 Hz, 1H, CH), 6.04 (appt, *J* = 6.29 Hz, 1H, CH), 4.46 (s, 1H, OH), 3.94 (s, 3H, OCH₃), 3.56 (s, 3H, OCH₃), 0.84 (s, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 165.5, 164.7, 148.3, 147.1, 144.2, 143.8, 140.8, 136.0, 132.5 (2C), 130.5 (2C), 128.3, 128.1, 125.8, 124.1 (2C), 123.0 (2C), 120.1, 111.9, 109.6, 92.3, 69.2, 52.9, 52.4, 13.4 ppm. IR (KBr): 3479, 2953, 2921, 2860, 1728, 1593, 1519, 1346, 1314, 1234, 1199, 1104, 1062, 1010, 855, 743, 514 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{22}N_3O_9$ 532.1356; found 532.1340.

Total synthesis of discoipyrrole C

Synthesis of N-methoxy-N,3-dimethylbutanamide (7). N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC·HCl) (4.5 g, 23.4 mmol) was added to a stirred solution containing a mixture of isovaleric acid 6 (2 g, 19.5 mmol), Et₃N (8.19 mL, 58.7 mmol) and N,O-dimethylhydroxylamine hydrochloride (2.47 g, 21.5 mmol) in dry CH₂Cl₂ (30 mL) under a nitrogen atmosphere. It was continued to stir at room temperature for 24 h and quenched with water. After separating the organic layer, the aqueous phase was extracted with EtOAc (3 \times 30 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (2 \times 50 mL) and dil. HCl (1 M, 2 \times 40 mL) followed by brine (20 mL). It was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel using the EtOAc-hexane solvent system to obtain the corresponding Weinreb amide 7. Yield 75% (2.13 g). Colourless liquid. $R_f = 0.43$ (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 3.60 (s, 3H, NCH₃), 3.10 (s, 3H, OCH₃), 2.23 (d, J = 7.0 Hz, 2H, CH₂), 2.04-2.14 (m, 1H, CH), 0.89 (d, J = 6.60 Hz, 6H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 174.1, 61.1, 40.6, 32.0, 25.1, 22.7 (2C) ppm. IR (KBr): 1640, 719, 707, 680, 396, 602, 487, 450 cm⁻¹. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for C₇H₁₆NO₂ 146.1181; found 146.1179.

Synthesis of 3-methyl-1-(pyridin-2-yl) butan-1-one (9). To a stirred solution of 2-bromopyridine 8 (1.16 mL, 12.3 mmol) in dry THF at -78 °C under a nitrogen atmosphere was added n-BuLi (7.75 mL, 12.3 mmol, 1.6 M solution in hexane). After 15 min, a solution of 7 (1.5 g, 10.3 mmol) in THF was added drop-wise to this mixture at -78 °C and the reaction was continued at the same temperature for 30 min and then at room temperature for 1 h. It was then quenched with saturated NH₄Cl at 0 °C and extracted with EtOAc (2 × 50 mL); the combined organic layers were dried over anhydrous Na2SO4 and concentrated under reduced pressure to obtain the crude residue. It was purified by column chromatography on silica gel using the EtOAc-hexane solvent system to obtain the pure product. Yield 80% (1.34 g). Colourless liquid. $R_{\rm f}$ = 0.60 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.66 (d, J = 4.60 Hz, 1H, ArH), 8.02 (d, J = 7.78 Hz, 1H, ArH), 7.79–7.83 (m, 1H, ArH), 7.42–7.45 (m, 1H, ArH), 3.09 (d, J = 6.71 Hz, 2H, CH₂), 2.25-2.35 (m, 1H, CH), 0.98 (d, J = 6.60 Hz, 6H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 201.9, 153.9, 149.0, 137.0, 127.1, 121.9, 46.5, 24.8, 22.8 (2C) ppm. IR (KBr): 3059, 2958, 2926, 2867, 1695, 1579, 1462, 1392, 1363, 1301, 1217, 1006, 913, 768, 735, 686, 592 cm⁻¹. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for C₁₀H₁₄NO 164.1075; found 164.1074.

Synthesis of 1-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-5methyl-3-(pyridin-2-yl)hex-1-yn-3-ol (11). A solution of *tert*butyl(4-ethynylphenoxy)dimethylsilane 10 (1.70 g, 7.35 mmol) in dry THF was taken in a 100 mL two neck round bottom flask, and cooled to -78 °C under a nitrogen atmosphere and

n-BuLi (6.79 mL, 7.35 mmol, 1.6 M solution in hexane) was added drop-wise under stirring. After 15 min, a solution of 3-methyl-1-(pyridin-2-yl) butan-1-one 9 (1 g, 6.12 mmol) in THF was added drop-wise to this mixture at the same temperature. The reaction was continued for 30 minutes, allowed to warm to room temperature and left stirring for an additional 1 h. It was then quenched with saturated NH₄Cl (100 ml) at 0 °C and extracted with EtOAc (3 \times 50 mL). The combined organic layers were dried over anhydrous Na2SO4 and concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel using the EtOAc-hexane solvent system to obtain the tertiary propargylic alcohol 11. Yield 82% (1.98 g); colourless liquid; $R_f = 0.66$ (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.52 (d, J = 4.67 Hz, 1H, ArH), 7.72-7.76 (m, 1H, ArH), 7.67-7.69 (m, 1H, ArH), δ 7.32 (d, J = 8.82 Hz, 2H, ArH), δ 7.23–7.24 (m, 1H, ArH), δ 6.75 (d, J = 8.82 Hz, 2H, ArH), 5.48 (s, 1H, OH), 2.00–2.07 (m, 2H, CH₂), 1.81-1.85 (m, 1H, CH), 1.01 (d, J = 6.37 Hz, 3H, CH_3 , 0.96 (s, 9H, CH_3), 0.89 (d, J = 6.42 Hz, 3H, $SiCH_3$), 0.18 (s, 6H, SiCH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 162.1, 156.1, 147.3, 137.3, 133.3 (2C), 122.8, 120.9, 120.2 (2C), 115.7, 90.8, 84.7, 72.2, 53.4, 25.8 (3C), 25.0, 24.4, 24.2, 18.3, -4.3 (2C) ppm. IR (KBr): 3368, 2952, 2864, 1597, 1506, 1468, 1394, 1263, 1158, 1033, 911, 840, 784, 680, 626 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₄H₃₄NO₂Si 396.2359; found 396.2361.

Synthesis of 4-(3-hydroxy-5-methyl-3-(pyridin-2-yl)hex-1-yn-1yl)phenyl acetate (12). DBU (0.60 ml, 4.04 mmol) was added to a stirred solution of 1-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-5methyl-3-(pyridin-2-yl)hex-1-yn-3-ol **11** (1.6 g, 4.04 mmol) in the CH₃CN : H₂O mixture (95 : 5) at room temperature. The reaction was continued for 15 min at the end of which TLC indicated complete consumption of the starting material. The reaction mixture was then quenched with sat. aq. NH₄Cl (50 mL), and extracted with CH₂Cl₂ (2 × 50 mL). The organic portion was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to obtain the crude de-silylated product. This was directly taken for acetylation without further purification as discussed below.

The de-silvlated product was dissolved in dry CH₂Cl₂ (15 mL), cooled to 0 °C and was admixed with Et₃N (0.85 mL, 6.06 mmol) and AcCl (0.721 mL, 10.1 mmol). After stirring at the same temperature for 0.5 h, the reaction mixture was quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel using the EtOAc-hexane solvent system. Yield 95% (1.30 g); colourless liquid; $R_f = 0.50$ (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 8.52 (d, J = 4.70 Hz, 1H, ArH), 7.73–7.77 (m, 1H, ArH), 7.66 (d, J = 7.56 Hz, 1H, ArH), 7.44 (d, J = 8.54 Hz, 2H, ArH), 7.24–7.27 (m, 1H, ArH), 7.03 (d, J = 8.54 Hz, 2H, ArH), 5.54 (s, 1H, OH), 2.28 (s, 3H, CH₃), 1.98-2.07 (m, 2H, CH₂), 1.80-1.86 (m, 1H, CH), 1.01 (d, *J* = 6.36 Hz, 3H, CH₃), 0.89 (d, *J* = 6.36 Hz, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 169.2, 161.7, 150.6, 147.4, 137.4, 133.0 (2C), 122.9, 121.7 (2C), 120.9, 120.6, 92.2, 83.8, 72.1, 53.3, 25.0, 24.3, 24.1, 21.2 ppm. IR (KBr): 3367, 2953, 2873, 1764, 1592, 1502, 1465, 1430, 1375, 1198, 1020, 911, 846, 784, 753, 627,

530 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₀H₂₂NO₃ 324.1600; found 324.1604.

Synthesis of (8a-isobutyl-1-oxo-1,8a-dihydroindolizine-2,3diyl)bis(4,1-phenylene) diacetate (14). A solution containing a mixture of 12 (1.2 g, 3.71 mmol) and aryl halide 13 (1.45 g, 5.56 mmol) in dry acetonitrile was admixed with $Pd(PPh_3)_4$ (214 mg, 5 mol%) and Et₃N (1.26 mL, 9.2 mmol) under a nitrogen atmosphere. After heating this mixture for 2 h at 90 °C under stirring, it was concentrated under reduced pressure and the residue obtained was re-dissolved in ethyl acetate (100 mL) and washed with water (2 \times 100 mL). The organic layer was separated and dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on a silica gel column using the ethyl acetate/hexane system. Yield 80% (1.35 g); orange solid; m.p. 152–154 °C. R_f = 0.46 (40% EtOAc/ hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.36 (d, J = 8.15 Hz, 2H, ArH), 7.21 (d, J = 8.47 Hz, 2H, ArH), 7.12 (d, J = 8.44 Hz, 2H, ArH), δ 6.89 (d, J = 8.80 Hz, 2H, ArH), 6.35 (d, J = 7.17 Hz, 1H, CH), 5.94 (d, J = 3.20 Hz, 2H, CH), 5.34–5.38 (m, 1H, CH), 2.32 (s, 3H, OCH₃), 2.24 (s, 3H, OCH₃), 1.84 (d, J = 4.99 Hz, 2H, CH₂), 1.74–1.80 (m, 1H, CH), 0.96 (d, J = 6.65 Hz, 3H, CH₃), 0.88 (d, J = 6.23 Hz, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 200.7, 169.5, 169.0, 168.3, 152.3, 148.9, 130.2 (2C), 129.7 (2C), 128.5, 126.6, 125.1, 123.8, 122.7 (2C), 122.3, 121.2 (2C), 111.3, 109.8, 70.9, 48.4, 24.8, 24.5, 23.5, 21.3 ppm. IR (KBr): 2956, 2873, 1762, 1674, 1611, 1547, 1503, 1425, 1371, 1324, 1200, 1054, 1011, 911, 841, 716, 668, 524 cm⁻¹. HRMS (ESI) m/z: $[M + H]^+$ calcd for C₂₈H₂₈NO₅ 458.1967; found 458.1965.

Synthesis of (5-isobutyl-5-methoxy-4-oxo-4,5-dihydro-1*H*pyrrole-2,3-diyl)bis(4,1-phenylene) diacetate (16). A solution containing a mixture of (8a-isobutyl-1-oxo-1,8a-dihydroindolizine-2,3-diyl)bis(4,1-phenylene) diacetate 14 (1 g, 2.1 mmol) and dimethyl acetylene dicarboxylate (DMAD) (0.398 mL, 3.2 mmol) in a dry toluene–methanol mixture (10 mL : 1 mL) was taken in a sealed tube under a nitrogen atmosphere. The reaction mixture was heated at 80 °C for 12 h, cooled to room temperature and was concentrated under reduced pressure to obtain a crude residue. It was then purified by silica gel chromatography using the EtOAc–hexane solvent system to obtain products 15 and 16.

Dimethyl 1,2-bis(4-acetoxyphenyl)-8a-hydroxy-3'-isobutyl-3',8a-dihydrocyclopenta[hi]indolizine-7,8-dicarboxylate (15).55% yield (720 mg). Orange solid, m.p. 120–122 °C. R_f = 0.40 (40% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.18 (d, J = 8.31 Hz, 2H, ArH), 7.10 (d, J = 8.31 Hz, 2H, ArH), δ 7.01 (d, J = 8.49 Hz, 2H, ArH), 6.90 (d, J = 8.31 Hz, 2H, ArH), 6.83 (d, J = 6.50 Hz, 1H, CH), 6.68 (d, J = 5.89 Hz, 1H, CH), 5.91-5.94 (m, 1H, CH), 4.23 (s, 1H, OH), 3.92 (s, 3H, OCH₃), 3.41 (s, 3H, OCH₃), 2.26 (s, 3H, OCH₃), 2.24 (s, 3H, OCH₃), 1.65-1.74 (m, 1H, CH), 1.21 (dd, J = 13.86 Hz, 4.62 Hz, 1H, CH), 1.00 (dd, J = 13.86 Hz, 5.46 Hz, 1H, CH), 0.88 (d, J = 6.72 Hz, 6H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 169.4, 169.2, 165.4, 165.0, 151.0, 150.0, 144.6, 144.5, 133.0 (2C), 131.2, 130.5 (2C), 129.0, 127.3, 125.8, 124.1, 121.8 (2C), 120.8 (2C), 120.3, 109.9, 109.8, 92.6, 71.4, 52.7, 51.8, 35.8, 24.8, 24.3, 23.9, 21.5 (2C) ppm. IR

(KBr): 3484, 2954, 1745, 1710, 1639, 1570, 1502, 1436, 1366, 1288, 1199, 1199, 1018, 912, 734, 666 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₃₄H₃₄NO₉ 600.2234; found 600.2221.

(5-Isobutyl-5-methoxy-4-oxo-4,5-dihydro-1*H*-pyrrole-2,3-diyl) bis(4,1-phenylene) diacetate (16). 40% yield (382 mg). Yellow solid, m.p. 78–80 °C. R_f = 0.46 (60% EtOAc/hexane). ¹H NMR (400 MHz, CDCl₃): δ 7.57 (d, *J* = 8.32 Hz, 2H, ArH), 7.25 (d, *J* = 8.92 Hz, 2H, ArH), 7.15 (d, *J* = 8.62 Hz, 2H, ArH), 6.98 (d, *J* = 8.62 Hz, 2H, ArH), 5.13 (s, 1H, NH), 3.24 (s, 3H, OCH₃), 2.33 (s, 3H, OCH₃), 2.27 (s, 3H, OCH₃), 1.83–1.93 (m, 2H, CH₂), 1.76–1.79 (m, 1H, CH), 0.98 (d, *J* = 4.07 Hz, 3H, CH₃), 0.96 (d, *J* = 4.07 Hz, 3H, CH₃) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 199.2, 170.3, 169.6, 169.1, 153.3, 149.3, 130.0 (2C), 129.7 (2C), 128.8, 128.4, 122.6 (2C), 121.5 (2C), 112.2, 92.2, 53.6, 51.3, 45.4, 24.4, 24.2, 24.0, 21.30 ppm. IR (KBr): 3275, 2955, 2923, 2866, 1751, 1663, 1601, 1553, 1487, 1460, 1372, 1199, 1078, 1013, 912, 851, 735, 670, 521 cm⁻¹. HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₅H₂₈NO₆ 438.1917; found 438.1924.

Synthesis of 4,5-bis(4-hydroxyphenyl)-2-isobutyl-2-methoxy-1H-pyrrol-3(2H)-one (16a). Potassium carbonate (113 mg, 0.82 mmol) was added to a stirred solution of (5-isobutyl-5methoxy-4-oxo-4,5-dihydro-1H-pyrrole-2,3-diyl)bis(4,1-phenylene) diacetate 16 (300 mg, 0.68 mmol) in MeOH (20 mL) at 0 °C and the mixture was stirred at the same temperature for 1 h. After admixing with H₂O (30 mL), the mixture was concentrated under reduced pressure and the residue obtained was extracted with EtOAc (3×50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure and the yellow solid obtained was further purified by chromatography on silica gel using the EtOAc-hexane solvent system. Yield 96% (232 mg); yellow solid; m.p. 126–128 °C. R_f = 0.23 (60% EtOAc/hexane). ¹H NMR (400 MHz, CD₃OD,): δ 7.41 (d, J = 8.70 Hz, 2H, ArH), 6.95 (d, J = 8.52 Hz, 2H, ArH), 6.77 (d, J = 8.64 Hz, 2H, ArH), 6.71 (d, J = 8.50 Hz, 2H, ArH), 3.19 (s, 3H, OCH₃), 1.83-1.85 (m, 2H, CH₂), 1.67-1.74 (m, 1H, CH), 0.95 (d, J = 2.74 Hz, 3H, CH₃), 0.93 (d, J = 2.83 Hz, 3H, CH₃) ppm; three exchangeable protons did not appear. ¹³C NMR (100 MHz, CD₃OD): δ 200.7, 175.7, 162.5, 157.1, 131.9 (4C), 124.4, 122.6, 116.4 (2C), 116.2 (2C), 111.6, 93.6, 51.0, 46.3, 24.8, 24.7 (2C) ppm. IR (KBr): 3290, 2926, 1643, 1600, 1537, 1455, 1368, 1239, 1176, 1176, 1070, 831, 569, 518 cm⁻¹. HRMS (ESI) *m/z*: [M + H^{+}_{1} calcd for $C_{21}H_{24}NO_{4}$ 354.1705; found 354.1709.

Synthesis of 2-hydroxy-4,5-bis(4-hydroxyphenyl)-2-isobutyl-1*H*-pyrrol-3(2*H*)-one (17). To a stirred suspension of 4,5-bis(4hydroxyphenyl)-2-isobutyl-2-methoxy-1*H*-pyrrol-3(2*H*)-one **16a** (200 mg, 0.56 mmol) in a mixture of CH_2Cl_2 (20 mL) and H_2O (5 mL) at 0 °C under a nitrogen atmosphere was added trifluoroacetic acid (2.04 mL, 29.0 mmol) drop-wise, over a period of 5 min. After stirring for 25 min, this mixture was admixed with H_2O (50 mL) followed by EtOAc (50 mL) at the same temperature. The organic phase was separated and washed with H_2O (1 × 50 mL), followed by a saturated aqueous solution of NaHCO₃ (2 × 50 mL) at 0 °C until the pH of the aqueous washings was between 5 and 7. The organic layer was then separated, dried (Na₂SO₄), and concentrated under reduced pressure, and the resulting residue was purified by column chromatography using the EtOAc–hexane solvent system. Yield 88% (173 mg); yellow solid; m.p. (decomposed above 140 °C). $R_{\rm f} = 0.20$ (60% EtOAc/hexane). ¹H NMR (400 MHz, CD₃OD): δ 7.38 (d, J = 8.73 Hz, 2H, ArH), 6.96 (d, J = 8.69 Hz, 2H, ArH), 6.75 (d, J = 8.86 Hz, 2H, ArH), 6.70 (d, J = 8.69 Hz, 2H, ArH), 1.87 (d, J = 6.07 Hz, 2H, CH₂), 1.63–1.75 (m, 1H, CH), 0.95 (d, J = 2.74 Hz, 3H, CH₃), 0.93 (d, J = 2.83 Hz, 3H, CH₃) ppm; four exchangeable protons did not appear. ¹³C NMR (100 MHz, CD₃OD): δ 202.1, 174.4, 162.1, 156.9, 131.9 (2C), 131.8 (2C), 124.9, 123.0, 116.3 (2C), 116.0 (2C), 108.9, 88.8, 46.7, 25.1, 24.7, 24.6 ppm. IR (KBr): 3278, 2926, 1596, 1533, 1440, 1361, 1235, 1173, 1102, 831, 569 cm⁻¹. HRMS (ESI) m/z: [M + H]⁺ calcd for C₂₀H₂₂NO₄ 340.1549; found 340.1552.

Conclusions

Published on 18 September 2019. Downloaded by Northwestern University on 1/2/2020 7:11:08 PM.

In summary, indolizinones and DMAD exhibited two different cycloaddition modes and subsequent bond reorganization possibilities, leading to 1H-pyrrol-3(2H)-one (2) and 3',8a-dihydrocyclopenta[hi]indolizin-8a-ol (3) in a combined yield of 77-98%. The former group of compounds (2) arises through the retro-Diels Alder reaction of [4 + 2] cycloadducts whereas the latter (3) requires [8 + 2] cycloaddition followed by π -reorganization. Electron donating substituents on the C₃-aryl ring were found to promote the formation of an azatricycle, which indicates better stabilization and reactivity of the 8π cycloaddition partner involved in the reaction. Formation of 10e aromatic species from this azatricycle was demonstrated through an NMR experiment by treating 3c with HBF₄·Et₂O, which resulted in characteristic shifts of CH₃ and olefinic proton signals. The retro-Diels Alder product 3-azacyclopentadienone is intrinsically unstable but can be trapped using a nucleophilic solvent like methanol. Remarkably, the resulting methanol adducts represent the core of discoipyrroles, which are promising leads against cancer. This was advantageously used for the total synthesis of discoipyrrole C.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

Financial support to this work by SERB, DST (EMR/2016/003973) is gratefully acknowledged. We thank the Dept. of Chemistry, IIT Madras and DST-FIST facility for instrumentation support. We also thank Mr V. Ramkumar, IITM for X-ray analysis. JK thanks IIT Madras for his research fellowship.

References

1 (a) M. J. Mphahlele, T. A. Khoza and P. Mabeta, *Molecules*, 2016, **22**, 55; (b) S. Kotha and R. Gunta, *J. Org. Chem.*, 2017,

82, 8527–8535; (*c*) R. S. Ali and H. A. Saad, *Molecules*, 2018, **23**, 693.

- 2 (a) A. K. Chattopadhyay, V. L. Ly, S. Jakkepally, G. Berger and S. Hanessian, Angew. Chem., Int. Ed., 2016, 55, 2577–2581;
 (b) S. A. Snyder, Chimia, 2017, 71, 802–809; (c) L.-W. Guo and Y.-L. Zhou, Phytochemistry, 1993, 34, 563–566.
- 3 (a) Z.-J. Zhan, C.-R. Zhang and J.-M. Yue, *Tetrahedron*, 2005,
 61, 11038–11045; (b) S.-P. Yang, H. Zhang, C.-R. Zhang,
 H.-D. Cheng and J.-M. Yue, *J. Nat. Prod.*, 2006, 69, 79–82;
 (c) H. Zhang and D. P. Curran, *J. Am. Chem. Soc.*, 2011, 133, 10376–10378.
- 4 (a) T. L. Gilchrist, C. W. Rees, D. Tuddenham and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1980, 691– 692; (b) T. L. Gilchrist, D. Tuddenham, R. McCague, C. J. Moody and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 1981, 657–658.
- 5 (a) R. J. Windgassen Jr., W. H. Saunders Jr. and V. Boekelheide, J. Am. Chem. Soc., 1959, 81, 1459–1465;
 (b) R. M. Acheson and D. A. Robinson, Chem. Commun., 1967, 175–176; (c) A. I. Gerasyuto and R. P. Hsung, J. Org. Chem., 2007, 72, 2476–2484.
- 6 (a) A. Galbraith, T. Small, R. A. Barnes and V. Boekelheide, J. Am. Chem. Soc., 1961, 83, 453–458; (b) Y. Tominaga,
 Y. Shiroshita, T. Kurokawa, H. Gotou, Y. Matsuda and A. Hosomi, J. Heterocycl. Chem., 1989, 26, 477–487.
- 7 Y. Hu, M. B. Potts, D. Colosimo, M. L. Herrera-Herrera,
 A. G. Legako, M. Yousufuddin, M. A. White and
 J. B. MacMillan, *J. Am. Chem. Soc.*, 2013, 135, 13387–13392.
- 8 H. Cho and I. Kim, *Tetrahedron*, 2012, **68**, 5464–5480.
- 9 A. R. Hardin Narayan and R. Sarpong, *Org. Biomol. Chem.*, 2012, **10**, 70–78.
- 10 K. Hemming, M. N. Khan, V. V. R. Kondakal, A. Pitard, M. I. Qamar and C. R. Rice, *Org. Lett.*, 2012, 14, 126–129.
- 11 C.-P. Chang, C.-H. Chen, G. J. Chuang and C.-C. Liao, *Tetrahedron Lett.*, 2009, **50**, 3414–3417.
- M. E. Gonzalez-Rosende, J. Sepulveda-Arques, E. Zaballos-Garcia, L. R. Domingo, R. J. Zaragoza, W. B. Jennings, S. E. Lawrence and D. O'Leary, *J. Chem. Soc., Perkin Trans.* 2, 1999, 73–80.
- 13 D. Kalaitzakis, M. Triantafyllakis, G. I. Ioannou and G. Vassilikogiannakis, Angew. Chem., Int. Ed., 2017, 56, 4020–4023.
- 14 K. Afarinkia, V. Vinader, T. D. Nelson and G. H. Posner, *Tetrahedron*, 1992, **48**, 9111–9171.
- A. Thottiparambil, I. Purushothaman, S. De, P. Parameswaran, P. S. Beegum, P. K. Sudhadevi Antharjanam and L. Chakkumkumarath, *Tetrahedron*, 2018, 74, 2999–3006.
- 16 D. Liang, Y. Zou, Q. Wang and A. Goeke, *J. Org. Chem.*, 2014, **79**, 6726–6731.
- 17 (a) A. P. Luna, M. Cesario, M. Bonin and L. Micouin, Org. Lett., 2003, 5, 4771–4774; (b) A. Vijayan, T. V. Baiju,
 S. Varughese and K. V. Radhakrishnan, Tetrahedron Lett., 2016, 57, 2965–2968; (c) P. Preethanuj, V. Jijitha, A. Vijayan,
 J. John and K. V. Radhakrishnan, Synthesis, 2017, 1816–1833.
- 18 Q. Yan, X. Ma, M. G. Banwell and J. S. Ward, *J. Nat. Prod.*, 2017, **80**, 3305–3313.