NJC

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *New J. Chem.*, 2021, 45, 2374

Received 4th December 2020,
Accepted 5th January 2021

DOI: 10.1039/d0nj05915c

rsc.li/njc

A three-component, general and practical route for diastereoselective synthesis of aza-spirocyclic pyrazolones *via* a decarboxylative annulation process†

Annapurna Awasthi,[ab] Pushpendra Yadav[ab] and Dharmendra Kumar Tiwari *[a]

An efficient, general, and practical route for highly diastereoselective synthesis of aza-spirocyclic pyrazolones from easily available α-amino acids, aldehydes, and alkylidene pyrazolones by means of a decarboxylative annulation process is reported. This high-yielding reaction proceeds through a [3+2]-cycloaddition reaction between alkylidene pyrazolones and a nonstabilized azomethine ylide generated *in situ*. This method provides easy and smooth access to a variety of highly functionalized aza-spirocyclic pyrazolones in excellent yields (up to 96%). The obtained spiro-pyrazolones comprise four contiguous stereogenic centers including a quaternary carbon center.

Pyrazolone and its derivatives are an important class of heterocycles present in various biologically important molecules and drugs present in the market (Fig. 1A–C). In addition, they are widely used in the fields of functional materials, coordination chemistry, dyes and pigments.[1–4] In the recent past, spirocyclic pyrazolones have received great attention from synthetic and medicinal chemists due to their frequent appearance in a large number of bioactive natural alkaloids and pharmaceutical agents (Fig. 1D–F), associated with numerous biological activities such as anti-bacterial, antidiabetic, analgesic, anti-inflammatory, PPAR α-antagonists, antiviral, anticancer, and type-4-phosphodiesterase inhibitor activities.[5,6]

Given the widespread use of spirocyclic pyrazolones in medicinally relevant compounds, much attention has been paid to the construction of these valuable scaffolds, and as a result, a large number of elegant methods have been developed in the recent past.[7–11] However, a careful literature survey reveals that only a few methods are reported for the synthesis of aza-spiropyrazolones, despite it being an important core structure of various biologically important molecules. In this regard, recently, we have demonstrated a highly diastereoselective synthesis of aza-spirocyclic pyrazolones from α-amino acids and alkylidene pyrazolones.[12] This reaction proceeds through an α-amino acid-mediated C–C double bond cleavage of unsaturated pyrazolones, which leads to *in situ* generation of azomethine ylides, which eventually undergo a [3+2]-cycloaddition reaction with another molecule of alkylidene pyrazolone to give the aza-spirocyclic pyrazolones (Scheme 1).

Although this methodology provides convenient access to aza-spirocyclic pyrazolones, the major drawbacks associated with this methodology are limited substrate scope, low yield, high reaction temperature (90 °C), prolonged reaction time (24 h), the formation of pyrazolone as a side product, and most importantly this reaction requires two equivalents of alkylidene pyrazolones. To overcome all of these shortcomings, the development of a mild, efficient and atom-economical methodology from readily available starting materials would be highly desirable. Our current research focuses on the development of new methods for the synthesis of biologically important heterocycles.[13] In view of the pharmaceutical importance of spirocyclic pyrazolones, we herein report a mild and efficient three-component approach for the synthesis of highly functionalized aza-spirocyclic pyrazolones from readily available starting materials. This one-pot tandem reaction proceeds through a [3+2]-cycloaddition reaction between

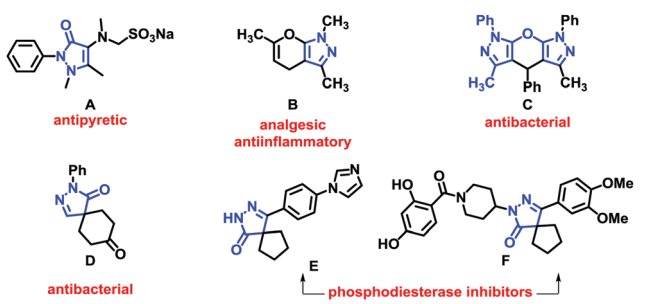
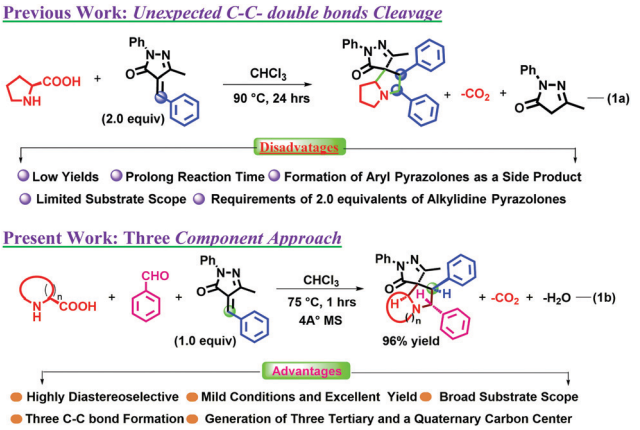


Fig. 1 Biologically active molecules containing spiro-pyrazolone skeletons.

[a] *Molecular Synthesis and Drug Discovery Unit, Center of Biomedical Research (CBMR), SGPGIMS Campus, Raibareli Road, Lucknow, U.P. 226014, India. E-mail: dkt80.org@gmail.com, dktiwari@cbmr.res.in*

[b] *Department of Chemistry, Institute of Science, Banaras Hindu Universiy, 221005, U.P., India*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0nj05915c



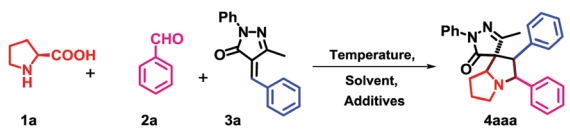
Scheme 1 Previous work on the synthesis of aza-spiropyrazolones (eqn (1a)) along with the present study (eqn (1b)).

alkylidene pyrazolones and azomethine ylides, generated *in situ* from cyclic α-amino acids and aldehydes.

Results and discussion

To investigate this one-pot tandem reaction, we selected L-proline (**1a**), benzaldehyde (**2a**), and alkylidene pyrazolone (**3a**) as model substrates for the optimization of the reaction conditions and the details are summarized in Table 1. Our first attempt by treating L-proline (**1a**, 1.0 mmol), benzaldehyde (**2a**, 1.0 mmol), and unsaturated pyrazolone (**2a**, 1.0 mmol) with anhydrous $CHCl_3$ (3.0 mL) at room temperature for 6 h was found to be unsuccessful and did not give any desired product (Table 1, entry 1). However, when the reaction mixture was heated at 60 °C for 6 hrs, the desired **4aaa** was obtained in 45% yield (entry 2). To our delight, the desired product **4aa** was obtained in 74% yield when the reaction temperature was increased to 75 °C (entry 3). At this stage, the product was well characterized by various spectroscopic techniques, including ^1H and ^{13}C NMR, and HRMS. The spectral data of **3aaa** were exactly matching with the previously reported compound.[12] It is also important to mention here that only one diastereomer was obtained in this one-pot tandem reaction.[14]

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a 4aaa

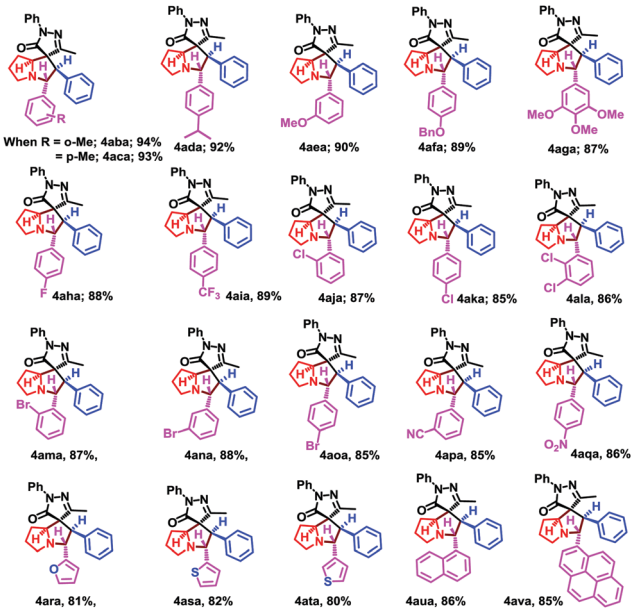
En	Solvent	Additive	Temp [°C]	Time [h]	Yields[b] (%)
1	$CHCl_3$	—	rt	6	n.o.[a]
2	$CHCl_3$	—	60	6	55[a]
3	$CHCl_3$	—	75	6	74[a]
4	$CHCl_3$	—	75	6	92[c]
5	$CHCl_3$	—	75	3	93[c]
6	$CHCl_3$	—	75	1	96[c]
7	$CHCl_3$	—	75	1/2	71[c]
8	$CHCl_3$	—	90C	1	95[c]
9	EDC	—	75	1	93[c]
10	CH_3CN	—	75	1	91[c]
11	THF	—	75	1	85[c]
12	Toluene	—	75	1	78[c]
14	Dioxane	—	75C	1	93[c]
15	DMSO	—	75	1	73[c]
16	DMF	—	75C	1	72[c]
17	EtOH	—	75	1	79[c]
18	MeOH	—	75	1	80[c]
19	$CHCl_3$	*p*-TSA	75	1	89[c]
20	$CHCl_3$	K_2CO_3	75	1	74[c]
21	$CHCl_3$	$Sc(OTf)_3$	75	1	85[d]
22	$CHCl_3$	$In(OTf)_3$	75	1	85[d]

[a] Reaction was performed using **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol) solvent (3.0 mL), under N_2 atmosphere. [b] Isolated yields. [c] When 4 Å MS was used. [d] When 10 mole% of catalyst was used.

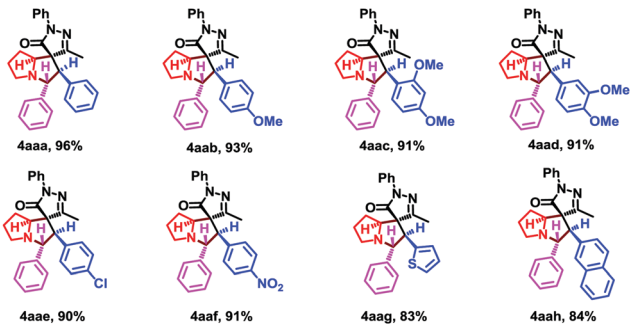
As water is expected as the by-product, the use of 4 Å molecular sieves improved the yield to a greater extent (92%) (entry 4). Furthermore, almost a similar yield of the desired **4aaa** was obtained when the reaction time was reduced to 3 h from 6 h (entry 5). To our delight, a slight increase in the yield (96%) of the desired **4aaa** was noticed when the reaction time was reduced to an hour (entry 6). Further decreasing the reaction time to 30 mins provided an inferior yield (71%) of the required product **4aaa** (entry 7). No improvement in the reaction yield was noticed by increasing the reaction temperature to 90 °C from 75 °C (entry 8). Afterwards, to improve the reaction yield, a range of non-polar and polar solvents, including ethylene dichloride (EDC), acetonitrile (CH_3CN), tetrahydrofuran (THF), toluene, dioxane, DMSO, DMF, EtOH and MeOH, were screened; however, all of them provided the corresponding desired product (**4aaa**) in diminished yields (entries 9–18). In order to further improve the yield, the reaction was performed in the presence of stoichiometric amounts of acid (*p*-TSA) and base (K_2CO_3); however, in both cases, the desired product **4aaa** was obtained in low yields (entries 19 and 20). Furthermore, employing a catalytic amount of Lewis acids such as $Sc(OTf)_3$ and $In(OTf)_3$ was also found to be unsuccessful to increase the yield of the desired product (entries 21 and 22).

After having the optimized reaction conditions in hand, the substrate scope of this three-component tandem reaction was evaluated with respect to various α-amino acids (**1a–1f**), aldehydes (**2a–2v**), and alkylidene pyrazolones (**3a–3i**) (Schemes 2–4). Initially, various aldehydes (**2a–2o**) having both electron-donating (**2b–2g**) and electron-withdrawing groups (**2h–2q**) on the aromatic rings readily participated in this one-pot tandem reaction to furnish a wide range of aza-spirocyclic pyrazolones (**4aba–4aqa**) in excellent yields. Various functional groups, such as methoxy (**2e**), benzyloxy (**2f**), trimethoxy (**2g**), fluoro (**2h**), trifluoromethyl (CF_3, **2i**), chloro (**2j–2l**), bromo (**2m–2o**), cyano (**2p**), and nitro (**2q**), were well tolerated in this reaction furnishing the desired products in very good yields. To our delight, heterocyclic aldehydes such as 2-furaldehyde (**2r**) and thiophenecarboxaldehydes (**2s** & **2t**) effectively participated under the optimized reaction conditions to furnish the desired products (**4ara–4ata**) in very good yields. Furthermore, polycyclic aldehydes such as 2-naphthaldehyde (**2u**) and pyran-carboxaldehyde (**2v**) smoothly underwent this reaction to give the desired products (**4aua** & **4ava**) in 86% and 85% yields, respectively.

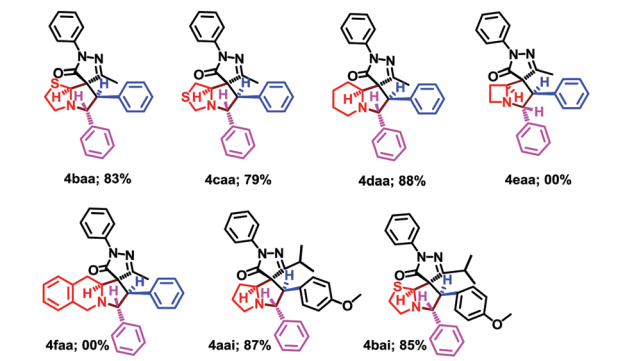
Afterwards, different unsaturated pyrazolones (**3a–3h**) containing electron-neutral (–H), electron-donating (–OMe), and



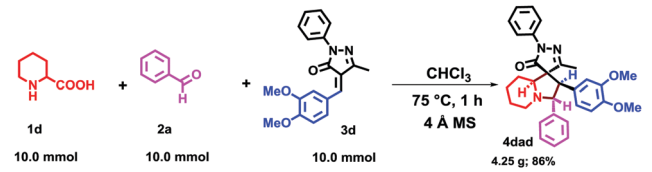
Scheme 2 Substrate scope with respect to various aldehydes. Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol); anhy. $CHCl_3$ (3.0 mL), 75 °C, 1 h, under nitrogen atmosphere.



Scheme 3 Different unsaturated alkylidenes. Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol) $CHCl_3$ (3.0 mL), 75 °C, 1 h; under N_2 atmosphere.



Scheme 4 Substrate scope with different cyclic α-amino acids. Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol) $CHCl_3$ (3.0 mL), 75 °C, 1 h; under N_2 atmosphere.



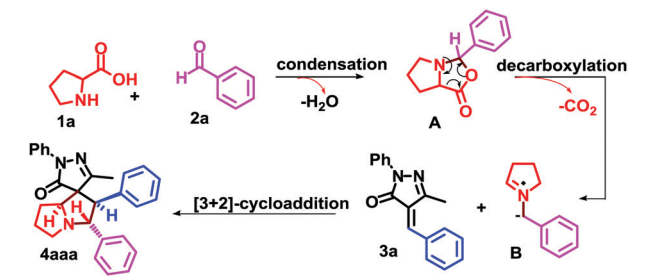
Scheme 5 Gram scale synthesis.

electron-withdrawing (Cl, $-NO_2$) groups on the aromatic rings smoothly participated under the optimized reaction conditions to furnish the desired aza-spirocyclic pyrazolones (**4aaa–4aah**) in very good to excellent yields (83–96%). Pleasingly, the unsaturated pyrazolones containing thiophenyl (**3i**) and naphthyl groups also participated in this reaction to form the desired 4aai and 4aah products in 83% and 84% yields, respectively.

Eventually, the substrate scope of the present methodology was evaluated with different cyclic α-amino acids (**1b–1f**) and the results are summarized in Scheme 4. Heteroatom substituted prolines such as thiazolidine-2-carboxylic acid (**1b**) and thiazolidine-4-carboxylic acid (**1c**) easily reacted with unsaturated pyrazolones (**3a–3i**) under the standard reaction conditions to give the desired functionalized aza-spirocyclic pyrazolones (**4baa–4eaa**, **4aai** & **4aai**) in very good yields. Furthermore, pipecolic acid (**1d**) under the optimized reaction conditions also furnished the corresponding product **4daa** in 88% yield. Unfortunately, azetidine-2-carboxylic acid (**1e**) and 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**1f**) failed to deliver the desired spirocyclic products.

Taking into consideration the potential importance of the aza-spirocyclic pyrazolones in medicinal and material chemistry, a gram scale synthesis for the present methodology was demonstrated, wherein **4dad** was prepared in 4.25 g, in 86% yield from pipecolic acid (**1d**), benzaldehyde (**1a**) and alkylidene pyrazolone (**3d**) under the optimized reaction conditions (Scheme 5). This result clearly indicates that there is not much loss of efficiency during the scale-up process.

Based on the previous literature reports, a possible reaction mechanism for this one-pot tandem reaction is given in Scheme 6.[15] The condensation reaction between L-proline (**1a**) and benzaldehyde (**2a**) gave lactone intermediate **A**. The lactone **A** undergoes decarboxylation to form the reactive azomethine ylide **B** which subsequently undergoes a [3+2]-cycloaddition



Scheme 6 Proposed reaction mechanism.

reaction with alkylidene pyrazolone (**3a**) to form the desired aza-spirocyclic product **4aaa**.

Conclusion

In summary, we have developed a three-component and highly diastereoselective synthesis of aza-spiropyrazolone from readily available α-amino acids, aromatic aldehydes and unsaturated pyrazolones. This reaction proceeds through a [3+2]-cycloaddition reaction between alkylidene pyrazolones and azomethine ylides generated *in situ* from α-amino acids and aldehydes by means of sequential condensation and decarboxylative annulation process cascades in one pot. In this methodology, different α-amino acids were reacted with variously substituted aldehydes and alkylidene pyrazolones to prepare a wide variety of functionalized aza-spiropyrazolones in excellent yields (up to 96%).

Experimental

All reagents were purchased from Sigma Aldrich, Alfa Aesar and local venders and were used without further purification. All experiments were carried out in a sealed tube. All the solvents used for the reaction were distilled before use. Product purification by column chromatography was accomplished using silica gel 100–200 mesh. Analytical TLC was performed with Merck silica gel 60 F254 plates, and the products were visualized by UV detection. ^{1}H and ^{13}C NMR and HRMS spectra were recorded on Bruker Avance III spectrometers at 400 MHz, 100 MHz and 376 MHz, respectively, using $CDCl_3$. In the Experimental section, the ^{1}H NMR chemical shift is expressed in the form of ppm (δ) relative to δ = 7.26 for $CDCl_3$, whereas the ^{13}C NMR chemical shift is expressed relative to δ = 77.00. Multiplicities in the ^{1}H NMR spectra are described as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet; coupling constants are reported in Hz. HRMS and electrospray ionization (ESI) (*m*/*z*) spectra were recorded on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS.

General procedure for the synthesis of unsaturated pyrazolones (3a–3h)

The starting materials (**3a–3h**) were prepared by the standard method reported in the literature.[12] To a solution of Edaravone (0.8 mmol, 1.1 equiv.) in acetic acid (2 mL) was added aldehydes (0.7 mmol, 1.0 equiv) and sodium acetate (0.07 g, 8.0 mmol, 1.1 equiv). The mixture was refluxed for 30 min and EtOAc (2 mL) was added for dilution. The solution was extracted with EtOAc (3 × 20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel) using petroleum ether/EtOAc (100 : 1) as the eluent, which offered compounds **3a–3h** in very good yields.

General experimental procedure for the synthesis of aza-spiropyrazolones (4aaa)

To a solution of alkylidene pyrazolone **3a** (1.0 mmol) in $CHCl_3$ (3.0 mL) was added L-proline **1a** (1.0 mmol) and benzaldehyde **2a** (1.0 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred in a 75 °C preheated oil bath for 1 h. The reaction mixture was then allowed to attain room temperature and the solvent was allowed to evaporate under reduced pressure to get the crude product (**4aaa**) which was purified by column chromatography using silica gel 100–200 mesh to furnish the desired **4aaa** in 96% yield as a white solid.

The compound **4aaa** (404 mg, yield = 96%, R_f = 0.50 (PE/EA = 7 : 3)) was isolated as a white solid; mp 209–211 °C; ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 7.4 Hz, 2H), 7.34 (dd, J = 8.2, 7.7 Hz, 2H), 7.25 (dd, J = 7.3, 6.0 Hz, 4H), 7.20 (t, J = 7.3 Hz, 1H), 7.19–7.14 (m, 3H), 7.12 (t, J = 7.3 Hz, 1H), 5.12 (d, J = 11.0 Hz, 1H), 4.43 (t, J = 7.0 Hz, 1H), 3.95 (d, J = 11.0 Hz, 1H), 3.06 (dd, J = 7.9, 4.9 Hz, 2H), 2.32 (s, 3H), 2.29–2.25 (m, 1H), 2.06–2.02 (m, 1H), 1.93–1.88 (m, 1H), 1.87–1.83 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.28, 159.09, 137.42, 133.26, 128.79, 128.62, 128.48, 128.42, 128.30, 127.91, 127.51, 127.38, 125.14, 119.27, 70.27, 68.72, 68.20, 63.02, 53.07, 28.18, 27.18, 13.75; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{28}N_3O$ [M + H] exact mass: 422.2227, found: 422.2219.

(2′*R*,4*S*,7a′*S*)-3-Methyl-1,2′-diphenyl-3′-(o-tolyl)-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1H)-one (4aba). The compound **4aba** (409 mg, yield = 94%, R_f = 0.48 (PE/EA = 8 : 2)) was isolated as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 3H), 7.34 (t, J = 7.9 Hz, 2H), 7.22–7.11 (m, 4H), 7.11–7.03 (m, 4H), 6.97 (d, J = 7.5 Hz, 1H), 5.39 (d, J = 11.0 Hz, 1H), 4.38 (t, J = 7.4 Hz, 1H), 4.00 (d, J = 11.0 Hz, 1H), 3.09–3.03 (m, 1H), 2.98–2.91 (m, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.24–2.17 (m, 1H), 2.01–1.94 (m, 1H), 1.89–1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.78, 159.35, 139.54, 137.52, 136.48, 133.49, 130.27, 128.68, 128.44, 128.24, 127.88, 127.14, 126.80, 126.21, 125.13, 119.24, 68.84, 68.73, 66.40, 63.81, 53.08, 28.23, 27.04, 19.57, 13.71; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{30}N_3O$ [M + H] exact mass: 436.2383, found: 436.2381.

(2′*R*,4*S*,7a′*S*)-3-Methyl-1,2′-diphenyl-3′-(*p*-tolyl) 2′,3′,5′,6′,7′,7a′-hexahydrospiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aca). The compound **4aca** (404 mg, yield = 94%, R_f = 0.47 (PE/EA = 6 : 4)) was isolated as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.9 Hz, 2H), 7.38–7.27 (m, 5H), 7.19–7.12 (m, 5H), 7.08 (d, J = 7.7 Hz, 2H), 5.10 (d, J = 11.1 Hz, 1H), 4.38 (t, J = 7.2 Hz, 1H), 3.94 (d, J = 11.1 Hz, 1H), 3.07–3.04 (m, 2H), 2.33 (s, 3H), 2.30 (s, 3H), 2.28–2.21 (m, 1H), 2.07–1.98 (m, 1H), 1.95–1.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.31, 159.14, 138.47, 137.46, 136.75, 133.50, 128.93, 128.56, 128.48, 128.32, 128.20, 127.77, 127.16, 125.01, 119.20, 119.17, 69.96, 68.80, 68.09, 63.06, 53.07, 28.13, 27.23, 21.00, 13.68; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{30}N_3O$ [M + H] exact mass: 436.2383, found: 436.2385.

(2′*R*,3′*S*,4*S*,7a′*S*)-3′-(4-Isopropylphenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydro-spiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4ada). The compound **4ada** (425 mg, yield = 92%, R_f = 0.35 (PE/EA = 8 : 2)) was isolated as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.1 Hz, 1H), 7.31 (t, J = 7.8 Hz, 4H), 7.25 (d, J = 7.9 Hz, 2H), 7.17–7.07 (m, 7H), 5.08 (d, J = 11.2 Hz, 1H), 4.35 (t, J = 7.5 Hz, 1H), 3.93 (d, J = 11.0 Hz, 1H), 3.06–3.02 (m, 2H), 2.87–2.79 (m, 1H), 2.30 (s, 3H), 2.25–2.20 (m, 1H), 2.05–1.96 (m, 1H), 1.91–1.79 (m, 2H), 1.20 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.38, 159.14, 147.63, 138.87,

137.50, 133.68, 128.58, 128.54, 128.21, 127.76, 127.21, 127.10, 126.30, 126.16, 125.04, 119.62, 119.26, 69.83, 68.99, 68.18, 62.89, 53.27, 33.61, 28.19, 27.23, 23.86, 13.72; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{34}N_3O$ [M + H] exact mass: 464.2696, found: 464.2693.

(2′*R*,3′*S*,4*S*,7a′*S*)-3′-(3-Methoxyphenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydro-spiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aea). The compound **4aea** (405 mg, yield = 90%, R_f = 0.35 (PE/EA = 8 : 2)) was isolated as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 7.09–7.01 (m, 5H), 6.86 (d, *J* = 7.4 Hz, 2H), 6.65–6.60 (m, 1H), 4.97 (d, *J* = 10.9 Hz, 1H), 4.27 (t, *J* = 7.5 Hz, 1H), 3.79 (d, *J* = 11.0 Hz, 1H), 3.62 (s, 3H), 2.98–2.92 (m, 2H), 2.19 (s, 3H), 2.17–2.10 (m, 1H), 1.97–1.87 (m, 1H), 1.80–1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.39, 159.49, 159.13, 137.48, 133.55, 129.16, 128.62, 128.57, 128.30, 127.88, 125.10, 119.63, 119.28, 112.90, 112.51, 70.22, 68.86, 68.28, 63.22, 55.04, 53.16, 28.27, 27.15, 13.73; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{30}N_3O$ [M + H] exact mass: 452.2333, found: 452.2327.

(2′*R*,4*S*,7a′*S*)-3′-(4-(Benzyloxy)phenyl)-3-ethyl-,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4afa). The compound **4afa** (469 mg, yield = 89%, R_f = 0.45 (PE/EA = 7 : 3)) was isolated as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.40–7.31 (m, 9H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.23–7.13 (m, 4H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.09 (d, *J* = 11.1 Hz, 1H), 5.00 (s, 2H), 4.43 (t, *J* = 7.4 Hz, 1H), 4.03 (d, *J* = 11.1 Hz, 1H), 3.06–3.03 (m, 2H), 2.35 (s, 3H), 2.29–2.24 (m, 1H), 2.03–1.94 (m, 1H), 1.94–1.80 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.24, 159.25, 158.26, 137.41, 136.99, 133.27, 132.61, 128.62, 128.52, 128.44, 128.30, 127.90, 127.87, 127.49, 125.15, 119.32, 114.62, 69.91, 69.64, 68.55, 67.57, 62.21, 52.96, 28.03, 27.29, 13.76; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{34}N_3O_2$ [M + H] exact mass: 528.2646, found: 528.2649.

(2′*R*,4*S*,7a′*S*)-3-Methyl-1,2′-diphenyl-3′-(3,4,5-trimethoxy-phenyl)-2′,3′,5′,6′,7′,7a′-hexahydrospiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aga). The compound **4aga** (444 mg, yield = 87%, R_f = 0.48 (PE/EA = 7 : 3)) was isolated as a white solid; mp 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 6.6 Hz, 2H), 7.22–7.11 (m, 4H), 6.55 (s, 2H), 5.05 (d, *J* = 10.9 Hz, 1H), 4.35 (t, *J* = 7.5 Hz, 1H), 3.80 (d, *J* = 10.9 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 6H), 3.12–3.00 (m, 2H), 2.27 (s, 3H), 2.25–2.22 (m, 1H), 2.07–1.99 (m, 1H), 1.91–1.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.46, 159.18, 152.83, 137.46, 137.18, 136.66, 133.84, 128.79, 128.62, 128.30, 127.92, 125.11, 119.19, 103.62, 70.45, 68.74, 68.17, 63.38, 60.66, 55.82, 53.23, 28.30, 27.07, 13.73; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{34}N_3O_4$ [M + H] exact mass: 512.2544, found: 512.2542.

(2′*R*,4*S*,7a′*S*)-3′-(4-Fluorophenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aha). The compound **4aha** (387 mg, yield = 88%, R_f = 0.41 (PE/EA = 7 : 3)) was isolated as a white solid; mp 204–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.35–7.27 (m, 4H), 7.21 (d, *J* = 7.4 Hz, 2H), 7.17–7.11 (m, 4H), 6.90 (t, *J* = 8.6 Hz, 2H), 5.05 (d, *J* = 11.0 Hz, 1H), 4.34 (t, *J* = 7.5 Hz, 1H), 3.81 (d, *J* = 11.0 Hz, 1H), 3.01–2.98 (m, 2H), 2.27 (s, 3H), 2.24–2.17 (m, 1H), 2.05–1.95 (m, 1H), 1.90–1.85 (m, 1H), 1.85–1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.32, 160.80, 159.03, 137.44, 137.33, 133.26, 128.71, 128.63, 128.50, 128.36, 128.23, 127.98, 127.27, 125.13, 119.25, 115.13, 114.92, 69.68, 68.72, 68.20, 63.54, 53.04, 28.28, 27.16, 13.71; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{27}FN_3O$ [M + H] exact mass: 440.2133, found: 440.2131.

(2′*R*,4*S*,7a′*S*)-3-Methyl-1,2′-diphenyl-3′-(4-(trifluoromethyl)-phenyl)-2′,3′,5′,6′,7′,7a′-hexahydrospiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aia). The compound **4aia** (435 mg, yield = 89%, R_f = 0.47 (PE/EA = 8 : 2)) was isolated as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.55 (s, 4H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.25–7.17 (m, 4H), 5.22 (d, *J* = 10.9 Hz, 1H), 4.44 (t, *J* = 7.5 Hz, 1H), 3.89 (d, *J* = 10.9 Hz, 1H), 3.12–3.05 (m, 2H), 2.34 (s, 3H), 2.32–2.24 (m, 1H), 2.13–2.03 (m, 1H), 1.97–1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.31, 158.80, 146.23, 137.45, 133.01, 128.64, 128.53, 128.46, 128.17, 127.48, 125.18, 125.15, 125.11, 119.25, 69.97, 68.83, 68.46, 63.74, 53.08, 28.39, 27.03, 13.66; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{27}F_3N_3O$ [M + H] exact mass: 490.2101, found: 490.2097.

(2′*R*,4*S*,7a′*S*)-3′-(2-Chlorophenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aja). The compound **4aja** (395 mg, yield = 87%, R_f = 0.46 (PE/EA = 7 : 3)) was isolated as a white solid; mp 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.1 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.29 (dd, *J* = 10.1, 8.6 Hz, 4H), 7.19–7.11 (m, 5H), 5.76 (d, *J* = 11.1 Hz, 1H), 4.40 (t, *J* = 7.3 Hz, 1H), 4.14 (d, *J* = 11.1 Hz, 1H), 3.20–3.14 (m, 1H), 3.00–2.93 (m, 1H), 2.37 (s, 3H), 2.29–2.26 (m, 1H), 2.02–1.93 (m, 2H), 1.89–1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.21, 158.93, 138.61, 137.42, 134.30, 132.77, 129.65, 129.03, 128.62, 128.44, 128.17, 127.93, 127.11, 125.11, 119.26, 68.79, 68.31, 65.73, 62.43, 52.94, 27.93, 27.35, 13.75; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{27}ClN_3O$ [M + H] exact mass: 456.1837, found: 456.1837.

(2′*R*,4*S*,7a′*S*)-3′-(4-Chlorophenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aka). The compound **4aka** (386 mg, yield = 85%, R_f = 0.46 (PE/EA = 8 : 2)) was isolated as a white solid; mp 158–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 4H), 7.26–7.21 (m, 3H), 7.20–7.13 (m, 5H), 5.08 (d, *J* = 10.9 Hz, 1H), 4.37 (t, *J* = 7.5 Hz, 1H), 3.83 (d, *J* = 10.9 Hz, 1H), 3.04–3.00 (m, 2H), 2.29 (s, 3H), 2.27–2.21 (m, 1H), 2.07–1.98 (m, 1H), 1.93–1.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.27, 158.92, 140.20, 137.43, 133.10, 132.82, 128.62, 128.59, 128.49, 128.39, 128.37, 128.05, 125.15, 119.25, 69.75, 68.69, 68.25, 63.49, 53.01, 28.28, 27.10, 13.68; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{27}ClN_3O$ [M + H] exact mass: 456.1837, found: 456.1847.

(2′*R*,4*S*,7a′*S*)-3′-(2,3-Dichlorophenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydro-spiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4ala). The compound **4ala** (420 mg, yield = 86%, R_f = 0.40 (PE/EA = 8 : 2)) was isolated as a white solid; mp 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 3H), 7.33 (t, *J* = 8.2 Hz, 3H), 7.26–7.21 (m, 3H), 7.17–7.11 (m, 4H), 5.82 (d, *J* = 11.0 Hz, 1H), 4.41 (t, *J* = 7.2 Hz, 1H), 4.08 (d, *J* = 11.0 Hz, 1H), 3.17–3.10 (m, 1H), 2.99–2.91 (m, 1H), 2.34 (s, 3H), 2.30–2.22 (m, 1H), 2.00–1.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.17, 158.67, 137.40, 133.04, 132.58, 132.43, 129.45, 128.83, 128.66, 128.42, 128.30, 128.16, 127.42, 127.38, 127.03, 125.20, 119.28, 118.97, 68.73, 68.44, 66.58, 62.80, 52.90, 28.02, 27.22,

13.73; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{26}Cl_2N_3O$ [M + H] exact mass: 490.1447, found: 490.1445.

(2′*R*,4*S*,7a′*S*)-3′-(2-Bromophenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4ama). The compound **4ama** (434 mg, yield = 87%, R_f = 0.40 (PE/EA = 7 : 3)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.0 Hz, 3H), 7.06–6.99 (m, 4H), 6.98–6.92 (m, 1H), 5.64 (d, *J* = 11.1 Hz, 1H), 4.30 (t, *J* = 7.2 Hz, 1H), 4.03 (d, *J* = 11.1 Hz, 1H), 3.11–3.05 (m, 1H), 2.88–2.80 (m, 1H), 2.26 (s, 3H), 2.21–2.16 (m 1H), 1.87–1.79 (m, 2H) 1.76–1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.21, 158.91, 139.96, 137.45, 133.00, 132.71, 129.35, 128.87, 128.63, 128.57, 128.18, 127.96, 127.74, 127.19, 125.13, 124.79, 119.30, 118.97, 68.26, 68.01, 62.53, 52.76, 27.88, 27.41, 13.76; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{27}BrN_3O$ [M + H] exact mass: 500.1332, found: 500.1342.

(2′*R*,4*S*,7a′*S*)-3′-(3-Bromophenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4ana). The compound **4ana** (439 mg, yield = 88%, R_f = 0.43 (PE/EA = 7 : 3)) was isolated as a white solid; mp 209–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.36–7.30 (m, 3H), 7.24 (d, *J* = 7.2 Hz, 2H), 7.21–7.12 (m, 5H), 7.04 (t, *J* = 7.8 Hz, 1H), 5.07 (d, *J* = 10.9 Hz, 1H), 4.37 (t, *J* = 7.5 Hz, 1H), 3.83 (d, *J* = 10.9 Hz, 1H), 3.07–2.99 (m, 2H), 2.29 (s, 3H), 2.26–2.19 (m, 1H), 2.08–1.97 (m, 1H), 1.91–1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.28, 158.89, 144.28, 137.42, 133.01, 130.39, 129.91, 129.66, 128.64, 128.51, 128.42, 128.10, 126.28, 125.17, 122.60, 119.27, 69.86, 68.77, 68.34, 63.52, 53.04, 28.33, 27.06, 13.74; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{27}BrN_3O$ [M + H] exact mass: 500.1332, found: 500.1333.

(2′*R*,4*S*,7a′*S*)-3′-(4-Bromophenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aoa). The compound **4aoa** (424 mg, yield = 85%, R_f = 0.40 (PE/EA = 7 : 3)) was isolated as a white solid; mp 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.8 Hz, 2H), 7.36–7.29 (m, 4H), 7.27–7.19 (m, 4H), 7.19–7.15 (m, 2H), 7.14–7.11 (m, 2H), 5.05 (d, *J* = 10.9 Hz, 1H), 4.34 (t, *J* = 7.5 Hz, 1H), 3.80 (d, *J* = 10.9 Hz, 1H), 3.03–2.95 (m, 2H), 2.27 (s, 3H), 2.25–2.18 (m, 1H), 2.04–1.95 (m, 1H), 1.91–1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.26, 158.93, 140.86, 137.40, 133.08, 131.28, 128.94, 128.62, 128.48, 128.39, 128.05, 125.13, 120.93, 119.21, 69.76, 68.72, 68.25, 63.50, 53.02, 28.31, 27.09, 13.70; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{27}BrN_3O$ [M + H] exact mass: 500.1332, found: 500.1330.

(2′*R*,3′*S*,4*S*,7a′*S*)-3′-(3-Isocyanophenyl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydro-spiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (**4apa**)

The compound **4apa** (379 mg, yield = 85%, R_f = 0.40 (PE/EA = 8 : 2)) was isolated as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.67–7.61 (m, 2H), 7.45 (t, *J* = 8.8 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.28–7.22 (m, 3H), 7.21–7.13 (m, 4H), 5.12 (d, *J* = 10.9 Hz, 1H), 4.37 (t, *J* = 7.6 Hz, 1H), 3.76 (d, *J* = 10.9 Hz, 1H), 3.04–2.98 (m, 2H), 2.27 (s, 3H), 2.26–2.20 (m, 1H), 2.08–2.00 (m, 1H), 1.91–1.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.25, 158.68, 143.84, 137.39, 132.73, 131.90, 130.90, 130.68, 128.79, 128.65, 128.56, 128.48, 128.31, 125.21, 119.24, 119.04, 112.35, 69.75, 68.74, 68.48, 63.96, 53.00, 28.44, 26.95, 13.68; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{27}N_4O$ [M + H] exact mass: 447.2179, found: 447.2180.

(2′*R*,4*S*,7a′*S*)-3-Methyl-3′-(4-nitrophenyl)-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aqa). The compound **4aqa** (400 mg, yield = 86%, R_f = 0.44 (PE/EA = 8 : 2)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.25 (t, *J* = 7.9 Hz, 2H), 7.17–7.12 (m, 2H), 7.11–7.03 (m, 4H), 5.10 (d, *J* = 10.9 Hz, 1H), 4.29 (t, *J* = 7.6 Hz, 1H), 3.68 (d, *J* = 10.9 Hz, 1H), 2.96–2.89 (m, 2H), 2.19–2.11 (m, 4H), 1.99–1.89 (m, 1H), 1.83–1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.26, 158.63, 150.07, 147.28, 137.41, 132.70, 128.68, 128.62, 128.52, 128.40, 127.91, 125.27, 123.45, 119.26, 69.99, 68.72, 68.62, 64.05, 53.06, 28.50, 26.93, 13.68; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{27}N_4O_3$ [M + H] exact mass: 467.2078, found: 467.2076.

(2′*R*,4*S*,7a′*S*)-3′-(Furan-2-yl)-3-methyl-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4ara). The compound **4ara** (332 mg, yield = 81%, R_f = 0.33 (PE/EA = 6 : 4)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.26–7.18 (m, 3H), 7.15–7.07 (m, 4H), 7.06–7.01 (m, 2H), 6.14–6.07 (m, 2H), 5.10 (d, *J* = 11.3 Hz, 1H), 4.29–4.22 (m, 2H), 3.11–2.96 (m, 2H), 2.27 (s, 3H), 2.17–2.10 (m, 1H), 1.97–1.87 (m, 1H), 1.77–1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.09, 159.04, 153.15, 142.37, 137.32, 133.11, 128.62, 128.36, 127.95, 125.19, 119.30, 109.98, 107.81, 68.13, 67.56, 63.69, 58.27, 53.57, 27.96, 27.20, 13.79; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{26}N_3O_2$ [M + H] exact mass: 412.2020, found: 412.2017.

(2′*R*,4*S*,7a′*S*)-3-Methyl-1,2′-diphenyl-3′-(thiophen-2-yl)-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (**4asa**)

The compound **4asa** (350 mg, yield = 82%, R_f = 0.32 (PE/EA = 8 : 2)) was isolated as a white solid; mp 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.3 Hz, 2H), 7.20 (d, *J* = 6.9 Hz, 1H), 7.18–7.10 (m, 4H), 6.82–6.78 (m, 1H), 6.67 (d, *J* = 3.1 Hz, 1H), 5.38 (d, *J* = 10.8 Hz, 1H), 4.34 (t, *J* = 7.5 Hz, 1H), 3.90 (d, *J* = 10.8 Hz, 1H), 3.22–3.15 (m, 1H), 3.10–3.04 (m, 1H), 2.28 (s, 3H), 2.25–2.21 (m, 1H), 2.06–1.96 (m, 1H), 1.86–1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.16, 158.93, 137.41, 133.23, 128.64, 128.53, 128.41, 128.09, 126.83, 125.19, 124.10, 123.74, 119.31, 68.81, 67.81, 66.10, 63.13, 53.39, 28.10, 27.27, 13.76; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{26}N_3OS$ [M + H] exact mass: 428.1791, found: 428.1789.

(2′*R*,4*S*,7a′*S*)-3-Methyl-1,2′-diphenyl-3′-(thiophen-3-yl)-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4ata). The compound **4ata** (341 mg, yield = 80%, R_f = 0.33 (PE/EA = 8 : 2)) was isolated as a white solid; mp 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.39–7.30 (m, 4H), 7.27–7.17 (m, 6H), 6.99–6.96 (m, 1H), 5.25 (d, *J* = 11.0 Hz, 1H), 4.37 (t, *J* = 7.5 Hz, 1H), 3.98 (d, *J* = 11.0 Hz, 1H), 3.23–3.16 (m, 1H), 3.16–3.08 (m, 1H), 2.34 (s, 3H), 2.29–2.24 (m, 1H), 2.11–2.01 (m, 1H), 1.93–1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.25, 159.05, 143.16, 137.43, 133.68, 128.66, 128.59, 128.39, 128.37, 127.95, 126.24, 125.56, 125.50, 125.08, 123.17, 121.43, 119.24, 119.18, 68.66, 68.03, 66.14, 61.99, 53.57, 28.22, 27.14, 13.71; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{26}N_3OS$ [M + H] exact mass: 428.1791, found: 428.1791.

(2′*R*,4*S*,7a′*S*)-3-Methyl-3′-(naphthalen-1-yl)-1,2′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aua). The compound **4aua** (405 mg, yield = 86%, R_f = 0.35 (PE/EA = 7 : 3)) was isolated as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 7.4 Hz, 2H), 7.61–7.53 (m, 3H), 7.36–7.28 (m, 3H), 7.24 (t, J = 7.8 Hz, 2H), 7.06 (d, J = 7.2 Hz, 3H), 6.92–6.87 (m, 3H), 5.80 (d, J = 11.0 Hz, 1H), 4.41 (t, J = 7.2 Hz, 1H), 4.21 (d, J = 11.0 Hz, 1H), 3.07–3.04 (m, 1H), 2.86–2.80 (m, 1H), 2.24 (s, 3H), 2.20–2.10 (m, 1H), 1.91–1.73 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.72, 159.30, 137.54, 136.95, 133.92, 133.47, 132.18, 128.74, 128.68, 128.25, 128.20, 127.96, 127.75, 125.50, 125.47, 125.17, 123.44, 119.36, 68.94, 68.34, 63.02, 53.28, 28.25, 27.24, 13.78; HRMS (ESI) m/z calcd for $C_{32}H_{30}N_3O$ [M + H] exact mass: 472.2383, found: 472.2379.

(2′*R*,4*S*,7a′*S*)-3-Methyl-1,2′-diphenyl-3′-(pyren-1-yl)-2′,3′,5′,6′,7′,7a′-hexahydrospiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4ava). The compound **4ava** (463 mg, yield = 85%, R_f = 0.50 (PE/EA = 5 : 5)) was isolated as a white solid; mp 215–218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 9.4 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.14 (t, J = 7.5 Hz, 2H), 8.07 (d, J = 9.3 Hz, 1H), 8.02 (s, 2H), 7.97 (t, J = 7.6 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.26 (d, J = 7.3 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 7.00 (t, J = 7.3 Hz, 2H), 6.95 (d, J = 7.2 Hz, 1H), 6.33 (d, J = 10.9 Hz, 1H), 4.61 (t, J = 7.1 Hz, 1H), 4.42 (d, J = 10.9 Hz, 1H), 3.29–3.21 (m, 1H), 2.99–2.94 (m, 1H), 2.41 (s, 3H), 2.39–2.33 (m, 1H), 2.10–2.01 (m, 2H), 1.98–190 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.76, 159.30, 137.56, 134.96, 133.25, 131.27, 130.63, 130.47, 129.63, 128.69, 128.28, 128.20, 127.78, 127.34, 127.11, 127.05, 125.67, 125.25, 125.21, 124.90, 124.83, 124.66, 122.69, 119.37, 68.98, 68.54, 63.90, 53.10, 28.15, 27.38, 13.76; HRMS (ESI) m/z calcd for $C_{38}H_{32}N_3O$ [M + H] exact mass: 546.2540, found: 546.2540.

(2′*R*,4*S*,7a′*S*)-2′-(4-Methoxyphenyl)-3-methyl-1,3′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aab). The compound **4aab** (419 mg, yield = 93%, R_f = 0.48 (PE/EA = 7 : 3)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2 Hz, 2H), 7.39–7.29 (m, 4H), 7.25–7.16 (m, 3H), 7.14 (d, J = 8.2 Hz, 3H), 6.66 (d, J = 8.4 Hz, 2H), 5.02 (d, J = 11.0 Hz, 1H), 4.36 (t, J = 7.5 Hz, 1H), 3.88 (d, J = 11.0 Hz, 1H), 3.66 (s, 3H), 3.05–3.00 (m, 2H), 2.28 (s, 3H), 2.24–2.17 (m, 1H), 2.03–1.93 (m, 1H), 1.90–1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.50, 159.31, 158.99, 141.44, 137.55, 129.60, 128.63, 128.23, 127.34, 127.28, 125.45, 125.07, 119.24, 113.67, 70.54, 68.88, 68.07, 62.53, 55.00, 53.14, 28.20, 27.20, 13.72; HRMS (ESI) m/z calcd for $C_{29}H_{30}N_3O$ [M + H] exact mass: 452.2333, found: 542.2331.

(2′*R*,4*S*,7a′*S*)-2′-(2,4-Dimethoxyphenyl)-3-methyl-1,3′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydro-spiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aac). The compound **4aac** (437 mg, yield = 91%, R_f = 0.43 (PE/EA = 7 : 3)) was isolated as a white solid; mp 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.60 (m, 3H), 7.41 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.25 (t, J = 7.4 Hz, 2H), 7.20–7.10 (m, 2H), 6.36 (dd, J = 8.6, 2.0 Hz, 1H), 6.22 (d, J = 2.0 Hz, 1H), 5.00 (d, J = 11.2 Hz, 1H), 4.59 (d, J = 11.2 Hz, 1H), 4.36 (t, J = 7.5 Hz, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 3.05–3.00 (m, 2H), 2.31 (s, 3H), 2.26–2.17 (m, 1H), 2.03–1.95 (m, 1H), 1.91–1.85 (m, 1H), 1.84–1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.73, 160.75, 159.81, 158.35, 141.85, 137.67, 129.91, 128.55, 128.14, 127.47, 127.09, 124.86, 119.31, 114.34, 104.24, 98.11, 70.59, 68.35, 68.19, 55.07, 55.05, 53.45, 53.35, 28.05, 27.33, 13.83; HRMS (ESI) m/z calcd for $C_{30}H_{32}N_3O_3$ [M + H] exact mass: 482.2436, found: 482.2438.

(2′*R*,4*S*,7a′*S*)-2′-(3,4-Dimethoxyphenyl)-3-methyl-1,3′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydro-spiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aad). The compound **4aad** (437 mg, yield = 91%, R_f = 0.45 (PE/EA = 7 : 3)) was isolated as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2H), 7.36–7.29 (m, 4H), 7.24–7.11 (m, 4H), 6.89 (s, 1H), 6.62–6.55 (m, 2H), 4.99 (d, J = 11.0 Hz, 1H), 4.34 (t, J = 7.5 Hz, 1H), 3.82 (d, J = 11.0 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.04–2.99 (m, 2H), 2.25 (s, 3H), 2.23–2.17 (m, 1H), 2.06–1.97 (m, 1H), 1.89–1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.75, 159.43, 148.48, 148.44, 141.57, 137.64, 128.67, 128.21, 127.25, 127.19, 126.03, 125.03, 121.34, 118.83, 111.04, 110.57, 70.77, 68.87, 68.24, 63.26, 55.72, 55.54, 53.12, 28.27, 27.09, 13.68; HRMS (ESI) m/z calcd for $C_{30}H_{32}N_3O_3$ [M + H] exact mass: 482.2436, found: 482.2436.

(2′*R*,4*S*,7a′*S*)-2′-(4-Chlorophenyl)-3-methyl-1,3′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aae). The compound **4aae** (409 mg, yield = 90%, R_f = 0.34 (PE/EA = 8 : 2)) was isolated as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.1 Hz, 2H), 7.34 (t, J = 8.1 Hz, 4H), 7.26–7.19 (m, 3H), 7.19–7.15 (m, 3H), 7.11 (d, J = 8.4 Hz, 2H), 5.02 (d, J = 11.0 Hz, 1H), 4.36 (t, J = 7.5 Hz, 1H), 3.88 (d, J = 11.0 Hz, 1H), 3.03–2.98 (m, 2H), 2.27 (s, 3H), 2.23–2.17 (m, 1H), 2.03–1.94 (m, 1H), 1.89–1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.22, 158.97, 141.07, 137.42, 133.75, 132.12, 129.92, 128.72, 128.56, 128.35, 127.50, 127.28, 125.27, 119.19, 70.55, 68.64, 68.33, 62.39, 53.09, 28.19, 27.23, 13.70; HRMS (ESI) m/z calcd for $C_{28}H_{27}ClN_3O$ [M + H] exact mass: 456.1837, found: 456.1836.

(2′*R*,3′*S*,4*S*,7a′*S*)-3-Methyl-2′-(4-nitrophenyl)-1,3′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aaf). The compound **4aaf** (424 mg, yield = 91%, R_f = 0.48 (PE/EA = 6 : 4)) was isolated as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 7.38–7.32 (m, 4H), 7.27–7.14 (m, 4H), 5.11 (d, J = 10.9 Hz, 1H), 4.40 (t, J = 7.4 Hz, 1H), 4.00 (d, J = 10.9 Hz, 1H), 3.03 (dd, J = 7.7, 4.9 Hz, 2H), 2.33 (s, 3H), 2.27–2.23 (m, 1H), 2.08–1.98 (m, 1H), 1.92–1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.87, 158.62, 147.52, 141.26, 140.76, 137.26, 129.64, 128.83, 128.55, 127.80, 127.19, 125.47, 123.56, 118.99, 70.67, 68.69, 68.59, 62.52, 53.11, 28.23, 27.33, 13.75; HRMS (ESI) m/z calcd for $C_{28}H_{27}N_4O_3$ [M + H] exact mass: 467.2078, found: 467.2084.

(2′*R*,4*S*,7a′*S*)-3-Methyl-1,3′-diphenyl-2′-(thiophen-2-yl)-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aag). The compound **4aag** (354 mg, yield = 83%, R_f = 0.37 (PE/EA = 8 : 2)) was isolated as a white solid; mp 205–207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.3 Hz, 2H), 7.26 (t, J = 7.9 Hz, 2H), 7.17 (t, J = 7.2 Hz, 2H), 7.14–7.10 (m, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.92 (d, J = 5.0 Hz, 1H), 6.74

(d, J = 3.3 Hz, 1H), 6.69–6.65 (m, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.23 (t, J = 7.5 Hz, 1H), 4.04 (d, J = 10.8 Hz, 1H), 2.93–2.88 (m, 2H), 2.16 (s, 3H), 2.12–2.07 (m, 1H), 1.93–1.84 (m, 1H), 1.78–1.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.33, 158.99, 141.41, 137.66, 135.96, 128.67, 128.24, 127.45, 127.31, 126.62, 126.30, 125.07, 124.82, 119.09, 72.29, 68.76, 68.33, 58.34, 53.09, 28.14, 27.30, 13.50; HRMS (ESI) m/z calcd for $C_{26}H_{26}N_3OS$ [M + H] exact mass: 428.1791, found: 428.1788.

(2′*R*,4*S*,7a′*S*)-3-Methyl-2′-(naphthalen-2-yl)-1,3′-diphenyl-2′,3′,5′,6′,7′,7a′-hexahydrospiro-[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aah). The compound **4aah** (395 mg, yield = 84%, R_f = 0.34 (PE/EA = 7 : 3)) was isolated as a white solid; mp 199–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.59 (m, 7H), 7.50 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 4.8 Hz, 3H), 7.29 (t, J = 7.8 Hz, 2H), 7.24–7.14 (m, 3H), 7.11 (t, J = 7.4 Hz, 1H), 5.24 (d, J = 10.9 Hz, 1H), 4.44 (t, J = 7.5 Hz, 1H), 4.08 (d, J = 10.9 Hz, 1H), 3.14–3.04 (m, 2H), 2.34 (s, 3H), 2.32–2.24 (m, 1H), 2.08–2.00 (m, 1H), 1.95–1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.53, 159.16, 141.69, 133.06, 132.88, 131.28, 128.58, 128.25, 128.11, 128.05, 127.84, 127.45, 127.20, 126.14, 125.88, 125.05, 119.20, 70.64, 68.97, 68.61, 63.66, 53.21, 28.32, 27.15, 13.78; HRMS (ESI) m/z calcd for $C_{32}H_{30}N_3O$ [M + H] exact mass: 472.2383, found: 472.2377.

(4*S*,5′*S*,6′*R*,7a′*S*)-3-Methyl-1,5′,6′-triphenyl-2′,3′,5′,6′-tetrahydro-7a′H-spiro[pyrazole-4,7′-pyrrolo[2,1-*b*]thiazol]-5(1*H*)-one (4baa). The compound **4baa** (364 mg, yield = 83%, R_f = 0.50 (PE/EA = 9 : 1)) was isolated as a white solid; mp 211–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.7 Hz, 2H), 7.45 (d, J = 7.0 Hz, 2H), 7.34–7.27 (m, 4H), 7.25–7.20 (m, 3H), 7.17–7.10 (m, 4H), 5.41 (s, 1H), 5.19 (d, J = 10.7 Hz, 1H), 3.78 (d, J = 10.7 Hz, 1H), 3.52–3.44 (m, 1H), 3.36–3.29 (m, 1H), 3.05–2.95 (m, 1H), 2.91–2.83 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.98, 157.66, 140.58, 137.44, 132.74, 128.90, 128.80, 128.74, 128.64, 128.59, 128.52, 128.45, 128.33, 127.99, 127.87, 127.78, 127.64, 125.22, 119.67, 119.02, 72.91, 70.19, 68.58, 59.97, 55.53, 32.37, 13.80; HRMS (ESI) m/z calcd for $C_{27}H_{26}N_3OS$ [M + H] exact mass: 440.1791, found: 440.1791.

(4*S*,5′*S*,6′*R*,7a′*R*)-3-Methyl-1,5′,6′-triphenyl-1′,5′,6′,7a′-tetrahydro-3′H-spiro[pyrazole-4,7′-pyrrolo[1,2-*c*]thiazol]-5(1*H*)-one (4caa). The compound **4caa** (346 mg, yield = 79%, R_f = 0.6 (PE/EA = 8 : 2)) was isolated as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, J = 8.4 Hz, 4H), 7.38–7.30 (m, 5H), 7.26–7.21 (m, 4H), 7.20–7.13 (m, 2H), 4.92 (d, J = 10.8 Hz, 1H), 4.20–4.10 (m, 3H), 3.90 (d, J = 10.8 Hz, 1H), 3.74 (dd, J = 11.5, 7.1 Hz, 1H), 2.97 (dd, J = 11.5, 7.8 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.58, 160.44, 139.32, 137.25, 133.22, 128.79, 128.56, 128.55, 128.15, 128.04, 127.87, 127.82, 125.07, 119.17, 70.12, 66.99, 65.10, 61.07, 55.92, 32.91, 13.72; HRMS (ESI) m/z calcd for $C_{27}H_{26}N_3OS$ [M + H] exact mass: 440.1791, found: 440.1791.

(1*S*,2*R*,3*S*,8a*S*)-3′-Methyl-1′,2,3-triphenyl-2,3,6,7,8,8a-hexahydro-5*H*-spiro[indolizine-1,4′-pyrazol]-5′(1′*H*)-one (4daa). The compound **4daa** (382 mg, yield = 88%, R_f = 0.5 (PE/EA = 9 : 1)) was isolated as a white solid; mp 174–175 °C; ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.54 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 7.5 Hz, 2H), 7.31–7.28 (m, 4H), 7.24 (t, J = 7.3 Hz, 1H), 7.23–7.20 (m, 4H), 7.17–7.15 (m, 1H), 7.10 (t, J = 7.3 Hz, 1H), 4.01 (d, J = 10.0 Hz, 1H), 4.01 (d, J = 10.0 Hz, 1H), 3.54 (d, J = 10.0 Hz, 1H), 3.54 (d, J = 10.0 Hz, 1H), 3.01 (dd, J = 11.5, 2.4 Hz, 1H), 2.94 (d, J = 11.0 Hz, 1H), 2.54 (s, 3H), 2.02 (td, J = 12.0, 2.3 Hz, 1H), 1.86 (d, J = 13.4 Hz, 1H), 1.67 (d, J = 13.4 Hz, 1H), 1.61 (d, J = 11.3 Hz, 1H), 1.59–1.49 (m, 2H), 1.38–1.30 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.31, 162.28, 139.73, 137.68, 134.96, 129.12, 128.57, 128.53, 127.98, 127.65, 127.38, 124.75, 118.97, 73.42, 72.53, 71.95, 69.82, 66.56, 59.22, 51.71, 51.62, 26.65, 24.96, 24.21, 15.98; HRMS (ESI) m/z calcd for $C_{29}H_{30}N_3O$ [M + H] exact mass: 436.2383, found: 436.2383.

(2′*R*,3′*S*,4*S*,7a′*S*)-3-Isopropyl-2′-(4-methoxyphenyl)-1,3′-diphenyl-2′,3′,5′,6′,7′,7a′hexahydrospiro[pyrazole-4,1′-pyrrolizin]-5(1*H*)-one (4aai). The compound **4aai** (416 mg, yield = 87%, R_f = 0.34 (PE/EA = 9 : 1)) was isolated as a colourless oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 2H), 7.35 (t, J = 7.5 Hz, 4H), 7.25–7.20 (m, 3H), 7.18–7.16 (m, 3H), 6.66 (d, J = 8.6 Hz, 2H), 5.02 (d, J = 10.8 Hz, 1H), 4.50 (t, J = 7.4 Hz, 1H), 3.91 (d, J = 11.0 Hz, 1H), 3.67 (s, 3H), 3.08 (dd, J = 8.2, 4.2 Hz, 2H), 2.99–2.92 (m, 1H), 2.27–2.24 (m, 1H), 2.13–1.99 (m, 1H), 1.98–1.81 (m, 2H), 1.33 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.54, 166.66, 159.00, 141.88, 137.78, 130.06, 129.93, 129.55, 128.54, 128.13, 127.18, 127.11, 125.62, 124.92, 119.74, 119.27, 113.49, 70.57, 69.30, 67.85, 63.58, 54.93, 53.22, 28.50, 26.80, 26.77, 23.09, 20.46. HRMS (ESI) m/z calcd for $C_{31}H_{34}N_3O_2$ [M + H] exact mass: 480.2646, found: 480.2650.

(4*S*,5′*S*,6′*R*,7a′*S*)-3-Isopropyl-6′-(4-methoxyphenyl)-1,5′-diphenyl-2′,3′,5′,6′-tetrahydro-7a′*H*-spiro[pyrazole-4,7′-pyrrolo[2,1-*b*]thiazol]-5(1*H*)-one (4bai). The compound **4aai** (422 mg, yield = 85%, R_f = 0.36 (PE/EA = 9 : 1)) was isolated as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 7.1 Hz, 2H), 7.12 (t, J = 7.8 Hz, 2H), 7.08–6.97 (m, 3H), 6.92 (t, J = 8.0 Hz, 3H), 6.43 (d, J = 8.6 Hz, 2H), 5.30 (s, 1H), 4.91 (d, J = 10.4 Hz, 1H), 3.62–3.51 (m, 1H), 3.44 (s, 3H), 3.28–3.24 (m, 1H), 3.17–3.13 (m, 1H), 2.90–2.87 (m, 1H), 2.72–2.69 (m, 1H), 1.18 (d, J = 7.6 Hz, 3H), 1.15 (d, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.03, 165.27, 159.13, 137.68, 130.21, 128.62, 128.41, 127.72, 125.11, 119.67, 113.61, 72.42, 70.52, 69.28, 55.57, 55.04, 32.61, 27.12, 23.24, 20.98; HRMS (ESI) m/z calcd for $C_{30}H_{32}N_3O_2S$ [M + H] exact mass: 498.2210, found: 498.2216.

Gram scale synthesis of (1*S*,2*R*,3*S*,8a*S*)-2-(3,4-dimethoxyphenyl)-3′-methyl-1′,3-diphenyl-2,3,6,7,8,8a-hexa-hydro-5*H*-spiro-[indolizine-1,4′-pyrazol]-5′(1′*H*)-one (4dad). The compound **4dad** (1.16 g, yield = 86%, R_f = 0.48 (PE/EA = 7 : 3)) was isolated as a colourless oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.4 Hz, 2H), 7.33–7.27 (m, 4H), 7.25 (d, J = 7.8 Hz, 1H), 7.11 (t, J = 7.7 Hz, 1H), 6.74 (d, J = 7.0 Hz, 2H), 6.68 (d, J = 8.6 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.47 (d, J = 9.9 Hz, 1H), 2.99 (d, J = 9.1 Hz, 1H), 2.93 (d, J = 9.4 Hz, 1H), 2.52 (s, 3H), 2.00 (t, J = 10.4 Hz, 1H), 1.87–1.85 (m, 1H), 1.68–1.65 (m, 1H), 1.55–1.46 (m, 3H), 1.38–1.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.49, 162.49, 148.33, 148.21, 139.83, 137.83, 128.68, 128.57, 127.70, 127.66, 127.57, 124.79, 121.48, 118.86, 112.46, 110.46, 74.06, 72.06, 66.63, 59.09, 55.89, 55.65, 51.77, 26.70, 25.02, 24.28, 16.04; HRMS (ESI) m/z calcd for $C_{31}H_{34}N_3O_3$ [M + H] exact mass: 496.2595, found: 496.2624.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the Science and Engineering Research Board (SERB), New Delhi, for the financial support in the form of a Core Research Grant (File No. CRG/2020/000801). A.A. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi (India), for the award of a research fellowship. P.Y. thanks the University Grant Commission for the fellowship. A.A. and P.Y. gratefully acknowledge the Banaras Hindu University (BHU) for PhD registration. The authors thank the Director CBMR for infrastructure.

References

1 For selected reviews, see: (*a*) S. Fustero, M. Sanchez-Rosello, P. Barrio and A. Simon-Fuentes, *Chem. Rev.*, 2011, **111**, 6984; (*b*) X. Bao, B. Wang, L. Cui, G. Zhu, Y. He, J. Qu and Y. Song, *Org. Lett.*, 2015, **17**, 5168; (*c*) X. Jiang, L. Liu, P. Zhang, Y. Zhong and R. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 11329; (*d*) S. R. Yetra, S. Mondal, S. Mukherjee, R. G. Gonnade and A. T. Biju, *Angew. Chem., Int. Ed.*, 2016, **55**, 268; (*e*) D. Hack, A. B. Dürr, K. Deckers, P. Chauhan, N. Seling, L. Rübenach, L. Mertens, G. Raabe, F. Schoenebeck and D. Enders, *Angew. Chem., Int. Ed.*, 2016, **55**, 1797; (*f*) K. H. Chikhalia and K. R. Desai, *J. Inst. Chem.*, 1998, **70**, 142; (*g*) G. Saretzki, *Cancer Lett.*, 2003, **194**, 209.

2 (*a*) C. Pegurier, P. Collart, P. Danhaive, S. Defays, M. Gillard, F. Gilson, T. Kogej, P. Pasau, N. Van Houtvin, M. Van Thuyne and B. van Keulen, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4228; (*b*) A. Kimata, H. Nakagawa, R. Ohyama, T. Fukuuchi, S. Ohta, T. Suzuki and N. Miyata, *J. Med. Chem.*, 2007, **50**, 5053; (*c*) B. Schmidt, C. Scheufler, J. Volz, M. P. Feth, R.-P. Hummel, A. Hatzelmann, C. Zitt, A. Wohlsen, D. Marx, H.-P. Kley, D. Ockert, A. Heuser, J. A. M. Christiaans, G. J. Sterk and W. M. P. B. Menge, WO2008138939, Nycomed GmbH (Germany), 2010.

3 (*a*) Dipyrone, in *Martindale: The Complete Drug Reference*, ed. A. Brayfield, Pharmaceutical Press, 2014; (*b*) M. P. Clark, S. K. Laughlin, M. J. Laufersweiler, R. G. Bookland, T. A. Brugel, A. Golebiowski, M. P. Sabat, J. A. Townes, J. C. VanRens, J. F. Djung, M. G. Natchus, B. De, L. C. Hsieh, S. C. Xu, R. L. Walter, M. J. Mekel, S. A. Heitmeyer, K. K. Brown, K. Juergens, Y. O. Taiwo and M. J. Janusz, *J. Med. Chem.*, 2004, **47**, 2724; (*c*) M. A. Metwally, S. A. Bondock, S. I. El-Desouky and M. M. Abdou, *Int. J. Modern Org. Chem.*, 2012, **1**, 19; (*d*) M. S. Chande, P. A. Barve and V. Suryanarayan, *J. Heterocycl. Chem.*, 2007, **44**, 49.

4 X. J. Zhao, Z. H. Cui, R. L. Wang, X. Li, S. J. Fan and W. G. Chen, *Chin. Chem. Lett.*, 2015, **26**, 259.

5 (*a*) K. Wang, X. Fu, J. Liu, Y. Liang and D. Dong, *Org. Lett.*, 2009, **11**, 1015; (*b*) M. I. Konaklieva and B. Plotkin, *J. Curr. Med. Chem. Anti-Infect. Agents*, 2003, **2**, 287; (*c*) H. L. White, J. L. Howard, B. R. Cooper, F. E. Soroko, J. D. McDermed, K. J. Ingold and R. A. Maxwell, *J. Neurochem.*, 1982, **39**, 271.

6 (*a*) S. Hanessian, G. McNaughton-Smith, H. G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, **53**, 12789; (*b*) J. M. Brynaert and L. Ghosez, in *Recent Progress in the Chemical Synthesis of Antibiotics*, ed. G. Lukacs and M. Ohno, Springer, Berlin, 1990.

7 For a review, see: (*a*) A. Moyano and R. Rios, *Chem. Rev.*, 2011, **111**, 4703; (*b*) P. Chauhan, S. Mahajan and D. Enders, *Chem. Commun.*, 2015, **51**, 12890; (*c*) X. Xie, L. Xiang, C. Peng and B. Han, *Chem. Rec.*, 2019, **19**, 2209; (*d*) J. Zhou, W. J. Huang and G. F. Jiang, *Org. Lett.*, 2018, **20**, 1158; (*e*) J. Zheng, S.-B. Wang, C. Zheng and S. L. You, *Angew. Chem., Int. Ed.*, 2017, **56**, 4540; (*f*) C. Ni and X. Tong, *J. Am. Chem. Soc.*, 2016, **138**, 7872; (*g*) R. Maity, C. Gharui, A. K. Sil and S. C. Pan, *Org. Lett.*, 2017, **19**, 662; (*h*) S. R. Yetra, S. Mondal, E. Suresh and A. T. Biju, *Org. Lett.*, 2015, **17**, 1417.

8 (*a*) S. Gogoi, C. G. Zhao and D. Ding, *Org. Lett.*, 2009, **11**, 2249; (*b*) Z. G. Yang, Z. Wang, S. Bai, X. Liu, L. Lin and X. Feng, *Org. Lett.*, 2011, **13**, 596; (*c*) A. Zea, A. N. R. Alba, A. Mazzanti, A. Moyano and R. Rios, *Org. Biomol. Chem.*, 2011, **9**, 6519; (*d*) Z. Wang, Z. Yang, D. Chen, X. Liu, L. Lin and X. Feng, *Angew. Chem., Int. Ed.*, 2011, **50**, 4928; (*e*) Z. Wang, Z. Chen, S. Bai, W. Li, X. Liu, L. Lin and X. Feng, *Angew. Chem., Int. Ed.*, 2012, **51**, 2776; (*f*) S. B. Kale, P. K. Jori, T. Thatikonda, R. G. Gonnade and U. Das, *Org. Lett.*, 2019, **21**, 7736; (*g*) C. Zhao, K. Shi, G. He, Q. Gu, Z. Ru, L. Yang and G. Zhong, *Org. Lett.*, 2019, **21**, 7943; (*h*) U. Ursic, U. Groselj, A. Meden, J. Svete and B. Stanovnik, *Synthesis*, 2009, 217; (*i*) J. H. Li, H. Wen, L. Liu and D. M. Du, *Eur. J. Org. Chem.*, 2016, 2492; (*j*) E. M. Buev, V. S. Moshkin and V. Y. Sosnovskikh, *J. Org. Chem.*, 2017, **82**, 12827; (*k*) P. Chauhan, S. Mahajan, C. C. J. Loh, G. Raabe and D. Enders, *Org. Lett.*, 2014, **16**, 2954; (*l*) J.-Y. Liu, J. Zhao, J.-L. Zhang and P.-F. Xu, *Org. Lett.*, 2017, **19**, 1846; (*m*) D.-S. Ji, Y.-C. Luo, X.-Q. Hu and P.-F. Xu, *Org. Lett.*, 2020, **22**, 1028.

9 (*a*) L. Guideri, R. Noschese and F. Ponticelli, *J. Heterocycl. Chem.*, 2012, **49**, 297; (*b*) H. X. Wang, L. L. Wu, Y. M. Wang and Z.-H. Zhou, *RSC Adv.*, 2015, **5**, 42836; (*c*) R. Maity and S. C. Pan, *Org. Biomol. Chem.*, 2017, **15**, 8032; (*d*) D. F. Yue, J. Q. Zhao, Z. H. Wang, X. M. Zhang, X. Y. Xu and W. C. Yuan, *Org. Biomol. Chem.*, 2016, **14**, 1946.

10 (*a*) J. Agejas and L. Ortega, *J. Org. Chem.*, 2015, **80**, 6509; (*b*) B. B. Sun, J. B. Chen, J. Q. Zhang, X. P. Yang, H. P. Lv, Z. Wang and X. W. Wang, *Org. Chem. Front.*, 2020, **7**, 796; (*c*) C. Wang, D. Wen, H. Chen, Y. Deng, X. Liu, X. Liu, L. Wang, F. Gao, Y. Guo, M. Sun, K. Wang and W. Yan, *Org. Biomol. Chem.*, 2019, **17**, 5514.

11 N. Chen, L. Zhu, L. Gan, Z. Liu, R. Wang, X. Cai and X. Jiang, *Eur. J. Org. Chem.*, 2018, 2939.

12 A. Awasthi, P. Yadav, V. Kumar and D. K. Tiwari, *Adv. Synth. Catal.*, 2020, **362**, 4378–4383.

13 (*a*) D. K. Tiwari, J. Pogula, B. Sridhar, D. K. Tiwari and P. R. Likhar, *Chem. Commun.*, 2015, **51**, 13646; (*b*) M. Phanindrudu, D. K. Tiwari, B. Sridhar, P. R. Likhar and D. K. Tiwari, *Org. Chem. Front.*, 2016, **03**, 795; (*c*) D. K. Tiwari, M. Phanindrudu, V. K. Aravilli, B. Sridhar, P. R. Likhar and D. K. Tiwari, *Chem. Commun.*, 2016, **52**, 4675–4678; (*d*) M. Phanindrudu, D. K. Tiwari, V. K. Aravilli,

K. C. Bhadwaj, G. Sabapathi, P. R. Likhar and D. K. Tiwari, *Eur. J. Org. Chem.*, 2016, 4629; (*e*) D. K. Tiwari, R. A. Maurya and J. B. Nanubolu, *Chem. – Eur. J.*, 2016, **22**, 526; (*f*) D. K. Tiwari, M. Phanindrudu, S. B. Wakade, J. B. Nanubolu and D. K. Tiwari, *Chem. Commun.*, 2017, **53**, 5302; (*g*) S. B. Wakade, D. K. Tiwari, P. S. K. P. Ganesh, M. Phanindrudu, P. R. Likhar and D. K. Tiwari, *Org. Lett.*, 2017, **19**, 4948; (*h*) M. Phanindrudu, S. B. Wakade, D. K. Tiwari, P. R. Likhar and D. K. Tiwari, *J. Org. Chem.*, 2018, **83**, 9137.

14 Formation of the other diastereomer was not observed within detectable limits in ^{1}H NMR.

15 (*a*) A. Solderra, M. Askri, M. Knorr, Y. Rousselin, M. M. Kubicki, C. Golz and C. Strohmann, *J. Org. Chem.*, 2015, **80**, 9064; (*b*) N. T. Subasi, H. Yalcinkaya and A. S. Demir, *Tetrahedron*, 2017, **73**, 4329; (*c*) Y. K. Kang and D. Seidel, *Org. Lett.*, 2016, **18**, 4277; (*d*) D. Das and D. Seidel, *Org. Lett.*, 2013, **15**, 4358; (*e*) T. Khan, V. Kumar and O. Das, *Bull. Chem. Soc. Jpn*, 2016, **89**, 1331.