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Graphical Abstract

Microwave-Promoted, Catalyst-Free, Multi-Component Reaction of Proline, Aldehyde, 1,3-Diketone: One Pot Synthesis of Pyrrolizidines and Pyrrolizinones

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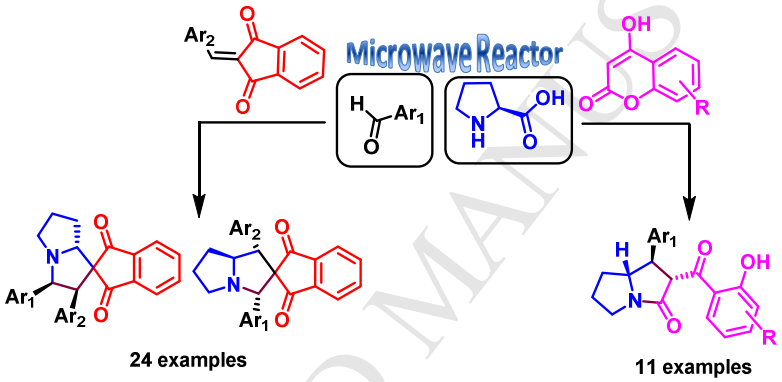

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ABSTRACT

One-pot, three-component preparation of the pyrrolizidine and pyrrolizinone derivatives in moderate to good yield is reported. The synthesis is facilitated by microwave irradiation of proline, aromatic aldehyde, and 1,3-diketone such as 2-arylmethylene-indene-1,3-dione and 4-hydroxycoumarin in 1,4-dioxane or xylene. This method provides a quick access to the multi-functionalized pyrrolizidines and pyrrolizinones.

1. Introduction

Pyrrolizidines (hexahydro-1*H*-pyrrolizine) are heterocyclic systems that consist of two fused five-membered rings with one ring junction carbon replaced by a nitrogen atom.[1] Hundreds of pyrrolizidine-containing alkaloids are biosynthesized by plants to function as a defense mechanism against herbivores.[2] Many naturally occurring pyrrolizidine and pyrrolizinone alkaloids have been discovered to exhibit diverse biological and pharmacological activities. To name a few, mitomycin C, for instance, was found to be useful as a chemotherapeutic agent by virtue of its antitumor activity (Figure 1).[3] Alexines represent polyhydroxylated carbohydrate-mimetic pyrrolizidine alkaloids exhibiting antiviral, anti-HIV, and anti-cancer properties.[4] Rhynchophylline and formosanine are pyrrolizidines with a fused six-membered ring in their structures, which are known for their anti-hypertensive and anti-inflammatory activities.[5] CJ-16,264 is a class of well-known antibiotics containing a pyrrolizinone skeleton.[6] UCS1025A is also an alkaloid with a pyrrolizinone core that exhibits antimicrobial and anti-proliferative properties as well as telomerase inhibitory activity.[7]

In light of their unique structural features along with the important biological activities, the preparations of pyrrolizidines and pyrrolizinones have drawn considerable attention to synthetic chemists in recent years. While a number of methods for the synthesis of pyrrolizidine and pyrrolizinone derivatives have been documented in the literature,[8] the development of new routes for efficient construction of the pyrrolizidines/pyrrolizinone core with diverse functionalized structures remains highly desired. Utilization of the azomethine

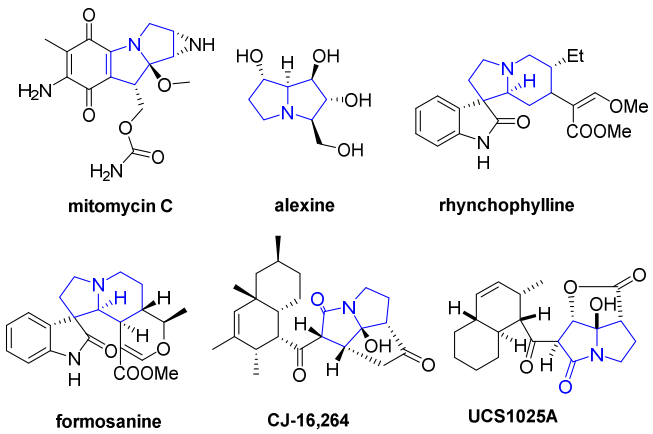
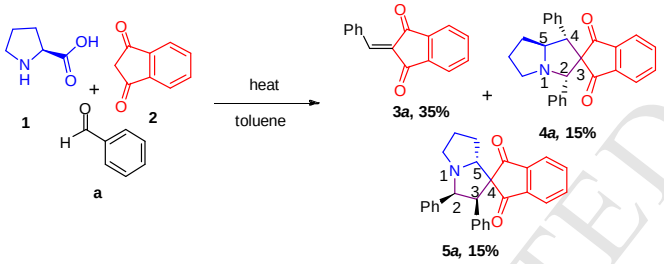


Fig 1. Some biologically important molecules containing a pyrrolizidine or pyrrolizinone core.

ylides-mediated [3+2] cycloaddition[9] and C-H functionalizations of α-amino acids[10] such as proline represent two most common ways used to synthesize pyrrolizidine or pyrrolizinone derivatives. In our continuing efforts[11] toward the preparation of molecules with novel molecular skeletons via multi-component reactions[12] (MCRs) and α,β-difunctionlization of proline by virtue of azomethine ylides, herein we wish to report a microwave-promoted, three-component coupling of proline, aromatic aldehyde, and 2-arylmethylene-indene-1,3-dione or 4-hydroxycoumarin to generate multi-functionalized pyrrolizidine or pyrrolizinone derivatives. The scope of this synthetic methodology and its limitation were explored and the possible mechanisms for the product formation were proposed.

2. Results and Discussion

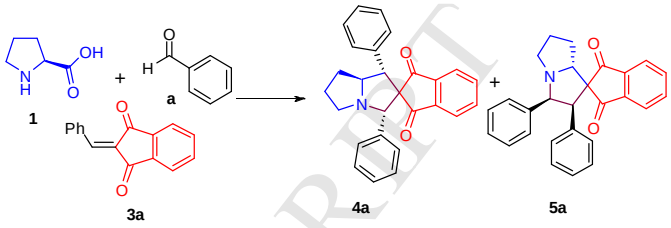
The present study began with the model reaction comprising of proline (**1**, 1.0 equiv), benzaldehyde (**a**, 2.2 equiv), and 1,3-indanedione (**2**, 1.1 equiv). Simple heating of these mixtures in toluene under reflux conditions for 1 h afforded the 2-benzylidene-1*H*-indene-1,3(2*H*)-dione (**3a**), the spiropyrrolizidines **4a**, and **5a** in 35, 15 and 15% yields (with respect to **2**), respectively (Scheme 1). Obviously, the added proline mainly serves as an organocatalyst to catalyze the condensation between benzaldehyde (**a)** and 1,3-indanedione (**2**) to give the α,β-unsaturated ketone **3a**, rather than functioning as a reactant to yield the desired spiropyrrolizidine derivatives. To enhance the conversion of all reactants into the spiropyrrolizidines **4a** and **5a**, the 1,3-indanedione (**2**) was subsequently replaced with 2-benzylidene-1*H*-indene-1,3(2*H*)-dione[13a] (**3a**) in forthcoming reactions. As expected, this change has brought much cleaner MCR profile and higher conversion of the reactants to the products. Further optimization of this one-pot, three-component reaction was performed and the results are summarized in Table 1. From the results, it is evident that xylene was found to be the most effective solvent (entries 5 and 6) and low boiling solvents (≤100 °C) gave poor product distributions (entries 1 and 3). Furthermore, prolonged reaction time did not increase the yields (entry 6). In quest of greener conditions, the reaction was further carried out under microwave irradiation in 1,4-dioxane. We observed that the microwave irradiation gave not only better yields but also cleaner reaction profiles, which compelled us to employ microwave irradiation conditions (entry 9) for all further reactions.



Scheme 1. Multicomponent model reaction of proline (**1**, 1.0 equiv), benzaldehyde (**a**, 2.2 equiv) and 1,3-indanedione (**2**, 1.1 equiv).

In order to evaluate the substrate scope of this MCR, various substrates were used to prepare the pyrrolizidine derivatives (Figure 2). Figures 3 and 4 depict the molecular structures and yields of the prepared spiropyrrolizidines **4a** and **5a**, respectively. The aromatic aldehydes with either electron-donating or -withdrawing group at the *para* position were found to be viable substrates, whereas the *ortho*-substituted aromatic aldehydes and aliphatic aldehydes generally gave complicated mixtures with lower yields. The synthesized compounds were all further characterized by spectroscopic data. In the ^{1}H NMR spectra, a characteristic singlet absorption peak of the *2-H* in the pyrrolizidine ring at the chemical shift between 4.57 and 4.67 ppm was observed for all prepared **4a**; whereas a small doublet (*J* = 5.7–6.0 Hz) absorption peak between 4.80 and 5.25 ppm, which again was assigned to the *2-H* in the pyrrolizidine ring, was observed for all prepared **5a** (see Scheme 1 for atom-numbering). Synthesized spiropyrrolizidines **4a** and **5a** were further characterized by the X-ray crystal analysis as shown in Figure 5.[14] This reaction was found to be stereospecific for 1,4-substituted spiropyrrolizidines **4**, since only *cis*-isomers were observed. While some *trans*-1,2-isomers **5** were detected in a trace amount during the isolation process, we did not isolate them due to their low yields. In addition to the formation of three C–C bonds and one C–N bond in the final product, this MCR creates a bicyclic system which contains three stereogenic centers.

Table 1. Optimization of reaction parameters for spiropyrrolizidines **4a** and **5a**.



entry	reaction conditions	time (h)	Yield (%)[a]	
			4a	5a
1	THF/ reflux	1	20	15
2	1,4-dioxane/ reflux	1	5	22
3	DCE/ reflux	1	10	27
4	toluene/ reflux	1	12	20
5	xylene/ reflux	1	20	25
6	xylene/ reflux	1	22	25
7	toluene/ 200 W, 150 °C	20 min	15	25
8	1,4-dioxane/ 150 W, 150 °C	20 min	20	28
9	1,4-dioxane/ 300 W, 275 °C	15 min	26	25
10	1,4-dioxane/ 300 W, 275 °C	20 min	30	31
11	1,4-dioxane/ 300 W, 275 °C	25 min	30	31
12	xylene/ 275 W, 250 °C	20 min	30	25

Note: (a) Proline (1.0 equiv), benzaldehyde (**a**, 2.2 equiv), and **3a** (1.1 equiv) were used. (b) Increase of the concentration of benzaldehyde (3-4 equiv) did not affect the product distributions. (c) Increase of the microwave irradiation time did not increase the yield. [a]Isolated yield.

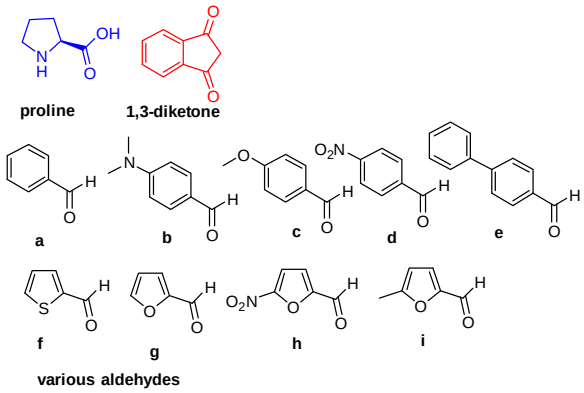


Fig 2. Substrate scope of the synthesis of spiropyrrolizidines **4** and **5**.

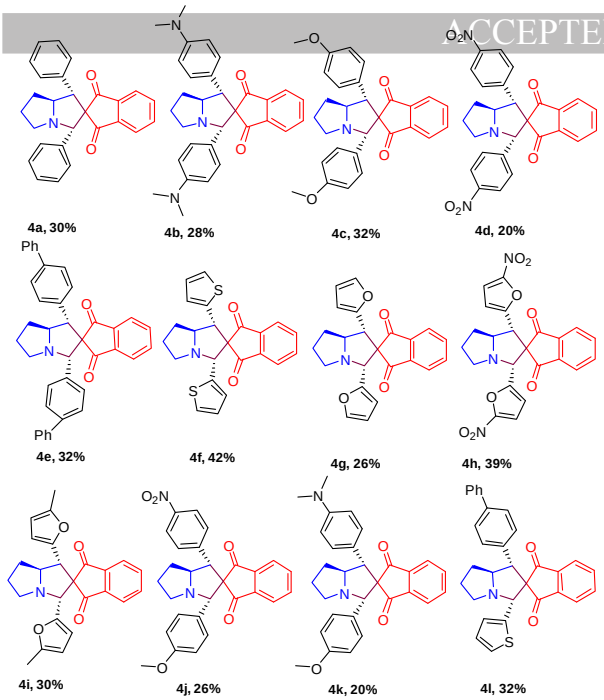


Fig 3. Structures of the prepared compounds **4a**–**l**.

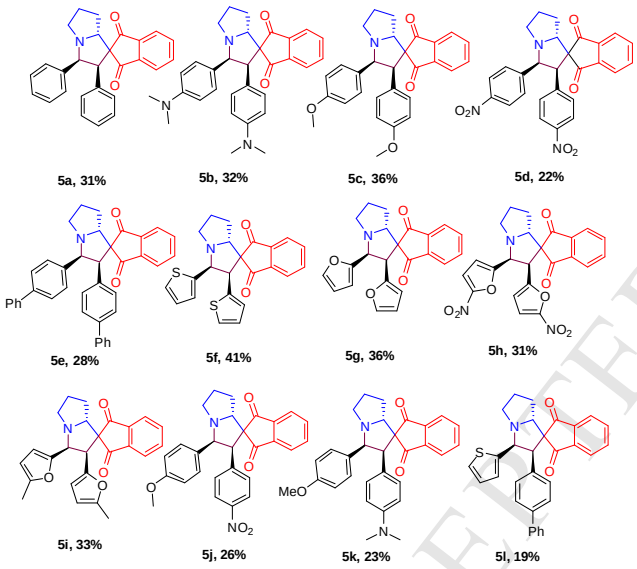


Fig 4. Structures of the prepared compounds **5a**–**l**.

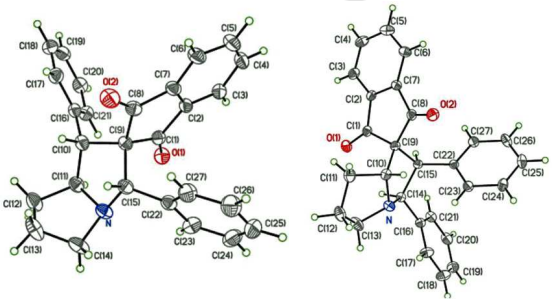
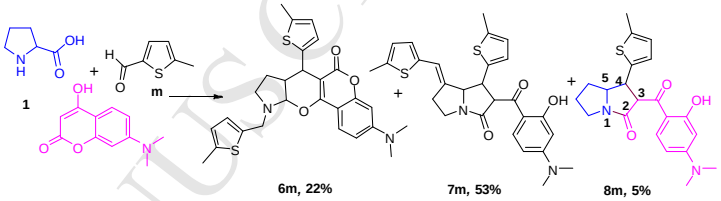


Fig 5. ORTEP crystal structures of **4a** (left) and **5a** (right).

In continuing our research in the preparation of pyrrolizinone derivatives, we have recently reported[11] a microwave-promoted, metal- and catalyst-free decarboxylative α,β-difunctionlization of secondary α-amino acids via a pseudo four-component coupling of proline, aldehyde, and 1,3-diketone to generate multi-functionalized pyrano[2,3-*b*]pyrrole **6m** and disubstituted pyrrolizinone **7m** derivatives (Scheme 2). Through careful purification of the product mixtures, we were able to identify the monosubstituted pyrrolizinone derivative **8m** as a minor product (5%) along with **6m** (22%) and **7m** (53%). This result promoted us to re-optimize the reaction conditions in favor of the formation of monosubstituted pyrrolizinone **8m** as the major product. Table 2 summarizes the results of our attempts to increase the yield of pyrrolizinone **8m** under various reaction parameters. To our delight, we were able to enhance the yield of the monosubstituted pyrrolizinone **8m** substantially and suppress the formation of **6m** and **7m** (entry 7). Changing the solvent from 1,4-dioxane to xylene, tuning the microwave irradiation conditions, and adding of a few drops of water brought much awaited changes in the product distributions.



Scheme 2. Multicomponent reaction of proline, aldehyde and substituted 4-hydroxycoumarin.

Table 2 Optimization of reaction parameters for **8m**.

entry	reaction conditions	time (h)	Yield (%)[b]		
			6m	7m	8m
1	toluene/ reflux	5	42	15	12
2	xylene/ reflux	5	45	20	18
3	toluene/ 150 W, 150 °C	15 min	36	17	20
4	toluene/ 200 W, 150 °C	20 min	35	20	20
5[a]	1,4-dioxane/ 200 W, 200 °C	20 min	30	24	28
6[a]	1,4-dioxane/ 250 W, 200 °C	20 min	15	26	35
7[a]	xylene/ 300 W, 275 °C	25 min	10	20	35
8[a]	xylene/ 300 W, 275 °C	30 min	10	12	42
9[a,c]	xylene/ 300 W, 275 °C	35 min	10	7	45

Note: Proline (**1**, 1.0 equiv), 5-methyl-2-thiophenecarboxaldehyde (**m**, 3.0 equiv), and 7-dimethylamino-4-hydroxycoumarin (**2**, 1.0 equiv) were used for optimization. [a] 3-4 drops of water were added. [b]Isolated yield. [c]Increase of the microwave irradiation time did not increase the yield.

The substrate scope of this MCR was further studied, and their molecular structures and the synthesized pyrrolizinones **8**–**12** are listed in Figures 6 and 7, respectively. Interestingly, the formation of the pyrrolizinone products **8**–**12** could only be observed for thiophene or furan carbaldehyde derivative substrates. Conversely, pyrrole carbaldehyde and its derivatives gave complex product distributions. Other aromatic aldehydes such as substituted benzaldehydes failed to yield any corresponding compounds **8**–**12**. While the electron-donating substituents on 4-hydroxycoumarin favored the product formation, the electron-withdrawing substituents resulted in lower yields or complex mixtures. In the ^{1}H NMR spectra, a large doublet (J = 10.5–11.1 Hz) absorption

peak at the chemical shift between 4.71 and 4.95 ppm, which was assigned to the 3-*H* in the pyrrolizinone ring, was observed for all compounds **8**–**12**. The synthesized compound **9o**, was further characterized by X-ray crystal analysis as shown in Figure 8. Note that the formation of **8**–**12** was found to be stereoselective, creating a bicyclic system that contains three stereogenic centers with *3-H* and *4-H trans* to each other (see **8m** in Scheme 2 for atom-numbering). Similar to the spiropyrrolizidines **4**–**5**, the bond formation during the construction of the pyrrolizinone scaffold is highly atom-economical, generating two C–C bonds and one C–N bond in the final product.

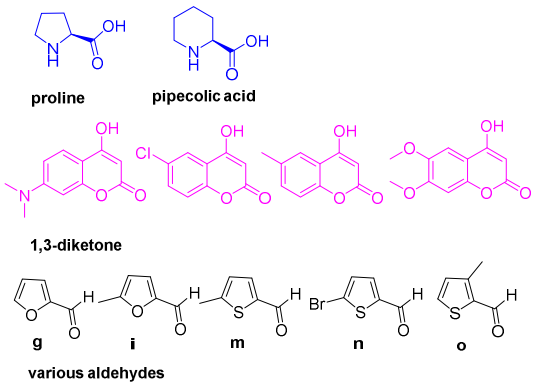


Fig 6. Substrate scope of the synthesis of pyrrolizinones **8**–**12**.

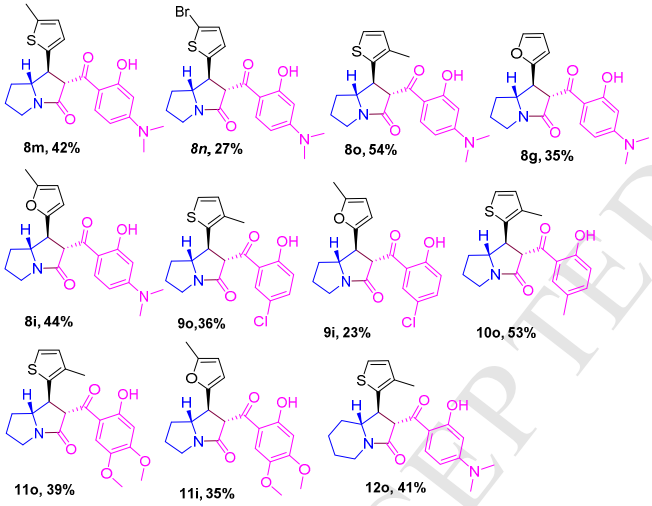


Fig 7. Structures of the prepared pyrrolizinones **8**–**12**.

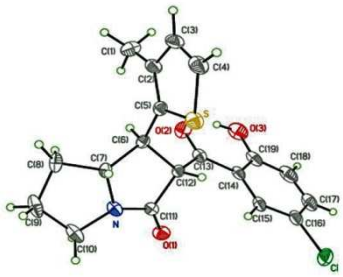
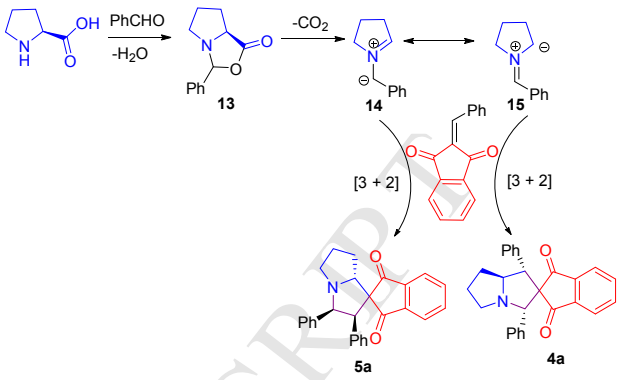


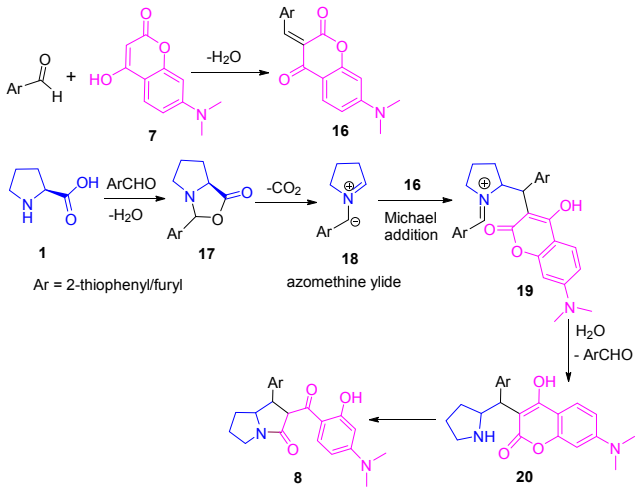
Fig 8. ORTEP crystal structure of **9o**.

Scheme 3 outlines the plausible mechanism for the formation of **4a** and **5a** from the three-component reaction. It begins with the condensation of proline with benzaldehyde to yield the oxazolidin-5-one **13**.[15] This known intermediate **13** then undergoes decarboxylation to form the azomethine ylide **14**. The resulting ylide **14** and its resonance contributing form **15** can further react with 2-benzylidene-1*H*-indene-1,3(2*H*)-dione **3a** via the [3+2] cycloaddition[16] to give the products **4a** and **5a**, respectively.



Scheme 3. Proposed mechanism for the formation of **4a** and **5a**.

Scheme 4 depicts the proposed mechanism for the formation of **8**. Similar to the formation of **4** and **5**, it also initiates with the condensation of proline with thiophene carbaldehyde to yield the oxazolidin-5-one **17**, and follows by decarboxylation to give the azomethine ylide **18**. The resulting ylide **18** can then undergo Michael addition[17] to α,β-unsaturated ketone **16** (generated *in situ* by condensation of thiophene-2-carbaldehyde and 7-*N*,*N*-dimethylamino-4-hydroxycoumarin) to afford the iminium **19**. The subsequent hydrolysis of the iminium **19** gives rise to the free amine **20**. Final intramolecular nucleophilic acyl substitution to open up the lactone ring on coumarin moiety by the amine nearby furnishes the product lactam **8**. This proposed mechanism can explain the observation of the increased yield of the product when some water is present in the reaction mixture, presumably by facilitating the hydrolysis of iminium **19**. Further, this mechanism is also supported by the fact that the formation of **8** is favored when a higher concentration of aldehyde is present in the reaction; that is, three equivalents of thiophene or furan carbaldehyde are required.



Scheme 4. Proposed mechanism for the formation of **8**.

Our study demonstrates that the azomethine ylide intermediates generated via microwave-promoted decarboxylative coupling of proline and aromatic aldehyde can react with 2-arylmethylene-indene-1,3-dione and 4-hydroxycoumarin in different mechanisms to afford the spiropyrrolizidines and pyrrolizinones, respectively. The mechanism of the former involves the typical [3+2] cycloaddition of azomethine ylide to 2-arylmethylene-indene-1,3-dione **3**, whereas the latter relates Michael addition of azomethine ylide to the α,β-unsaturated ketone **16**.

3. Conclusion

In summary, we have developed a catalyst-free synthesis of multi-functionalized spiropyrrolizidines **4**–**5** or pyrrolizinones **8**–**12** with moderate to good yield via a three-component coupling of proline, aromatic aldehyde, and 2-arylmethylene-indene-1,3-dione or 4-hydroxycoumarin in 1,4-dioxane or xylene under microwave irradiation. This MCR synthetic strategy provides a quick access to the biologically important pyrrolizidines and pyrrolizinones from readily available starting materials under environmentally benign conditions. Further studies on the application of this methodology to the synthesis of bioactive molecules are currently underway.

4. Experimental

4.1. Instrumentation

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. MS were performed with a JEOL JMS-SX/SX 102A spectrometer. Single-crystal structures were determined with a Bruker AXS SMART-1000 X-ray single-crystal diffractometer. Microwave reactions were performed using a CEM Discover unit (operating at 110 V, microwave irradiation of 2.45 GHz, maximum microwave output of 300 W) in 50 mL capacity open round-bottom flasks. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 150 MHz on a Varian VXR300 and Varian Unity Inovo-600 spectrometer respectively. All the NMR measurements were performed at room temperature. Chemical shifts were reported in parts per million on the δ scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Flash chromatography was performed in columns of various diameters with Merck silica gel (230-400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. Solvents, unless otherwise specified, were reagent grade and distilled once prior to use. All new compounds exhibited satisfactory spectroscopic and analytical data.

*4.2. Synthesis of α,β-unsaturated ketone derivatives of indanedione (**3a**–**3i**).*

The α,β-unsaturated ketone derivatives were synthesized by adopting the reported procedures.[13a] A mixture of 1,3-indanedione (100 mg, 0.68 mmol, 1.0 equiv), aldehyde (80 mg, 0.75 mmol, 1.1 equiv) and proline (24 mg, 10 mol%) in MeOH (20 mL) was stirred at room temperature for 15 h. The precipitate was then filtered-off, sequentially washed with MeOH (5 mL x 1) and hexane (10 mL x 3), and dried *in vacuo* to afford the condensation product.

4.2.1. ***3a***. R_f = 0.55 (20% EtOAc/hexanes); yellow solid; 127 mg; yield 79%; mp 150–152 °C (Lit.[13b] 152–153 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47–8.45 (m, 2H), 8.05–8.00 (m, 2H), 7.92 (s, 1H), 7.86–7.80 (m, 2H), 7.58–7.50 (m, 3H).

4.2.2. ***3b***. R_f =0.49 (40% EtOAc/hexanes); dark red solid; 149 mg; yield 78%; mp 204–206 °C (Lit.[13c] 208–210 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.54 (d, *J* = 8.7 Hz, 2H), 7.94–7.90 (m, 2H), 7.79 (s, 1H), 7.74–7.71 (m, 2H), 6.75 (d, *J* = 9.6 Hz, 2H), 3.16 (s, 6H).

4.2.3. ***3c***. R_f = 0.55 (30% EtOAc/hexanes); yellow solid; 140 mg; yield 77%; mp 153–155 °C (Lit.[13b] 156–157 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (dd, *J* = 7.2, 5.1 Hz, 2H), 8.01–7.97 (m, 2H), 7.85 (s, 1H), 7.80–7.78 (m, 2H), 7.02 (dd, *J* = 6.7, 1.8 Hz, 2H), 3.92 (s, 3H).

4.2.1. ***3d***. R_f = 0.48 (30% EtOAc/hexanes); yellow solid; 169 mg; yield 89%; mp 231–233 °C (Lit.[13d] 225 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (d, *J* = 9.0 Hz, 2H), 8.34 (d, *J* = 8.7 Hz, 2H), 8.07 (dd, *J* = 5.7, 3.0 Hz, 2H), 7.90 (s, 1H), 7.89 (dd, *J* = 5.7, 3.0 Hz, 2H).

4.2.1. ***3e***. R_f = 0.63 (30% EtOAc/hexanes); yellow solid; 163 mg; yield 78%; mp 166–168 °C (Lit.[13e] 167–169 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (d, *J* = 8.4 Hz, 2H), 8.05–8.01 (m, 2H), 7.95 (s, 1H), 7.84–7.81 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 6.9 Hz, 1H), 7.52–7.39 (m, 4H).

4.2.1. ***3f***. R_f = 0.42 (20% EtOAc/hexanes); yellow solid; 90 mg; yield 54%; mp 173–175 °C (Lit.[13f] 177 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (dd, *J* = 3.6, 0.9 Hz, 1H), 8.03 (s, 1H), 8.01–7.97 (m, 2H), 7.89–7.87 (m, 1H), 7.81–7.78 (m, 2H), 7.25–7.24 (m, 1H).

4.2.1. ***3g***. R_f = 0.64 (30% EtOAc/hexanes); yellow solid; 131 mg; yield 86%; mp 206–208 °C (Lit.[13b] 209.5–211 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (d, *J* = 3.6 Hz, 1H), 7.99–7.97 (m, 2H), 7.81–7.76 (m, 3H), 7.77 (s, 1H), 6.74–6.72 (m, 1H).

4.2.1. ***3h***. R_f = 0.58 (40% EtOAc/hexanes); yellow solid; 147 mg; yield 80%; mp 218–219 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.61 (d, *J* = 4.2 Hz, 1H), 8.05 (dd, *J* = 5.6, 3.3 Hz, 2H), 7.88 (dd, *J* = 5.6, 3.3 Hz, 2H), 7.69 (s, 1H), 7.48 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.2, 188.1, 153.3, 151.5, 142.5, 140.6, 136.1, 136.0, 131.4, 126.1, 123.8, 123.6, 113.3; IR ν_{max} (KBr) 3144, 168, 1518, 1347, 1223, 1021, 827, 730 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_7NO_5$ [M^+] 269.0324, found 269.0319.

4.2.1. ***3i***. R_f = 0.63 (30% EtOAc/hexanes); yellow solid; 123 mg; yield 75%; mp 178–180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (d, *J* = 3.9 Hz, 1H), 7.95–7.92 (m, 2H), 7.77–7.74 (m, 2H), 7.69 (s, 1H), 6.39 (d, *J* = 3.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 190.5, 189.2, 161.3, 150.5, 142.2, 140.3, 134.9, 134.5, 129.1, 127.5, 122.9, 122.8, 122.7, 112.2, 14.5; IR ν_{max} (KBr) 3695, 2970, 1716, 1675, 1589, 1507, 1354, 1211, 1026, 734 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{10}O_3$ [M^+] 238.0630, found 238.0622.

*4.3. Synthesis of pyrrolizidine derivatives (**4a–l** and **5a–l**).*

A round bottomed flask charged with α,β-unsaturated ketone (100 mg, 0.43 mmol, 1.0 equiv), proline (98 mg, 0.85 mmol, 2.0 equiv) and an appropriate aldehyde (59 mg, 0.55 mmol, 1.3 equiv) in 1,4-dioxane (10 mL) was irradiated at 275 °C (300 W, open vessel standard conditions) for 25 minutes. Reaction flask was then allowed to cool down by compressed air and solvent was evaporated *in vacuo*. The crude reaction mixture was

purified by flash column chromatography to afford the desired compounds.

4.3.1. ***4a***. R_f = 0.45 (20% EtOAc/hexanes); light yellow solid; 51 mg; yield 30%; mp 186–187 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.58–7.51 (m, 1H), 7.48 (d, *J* = 3.9 Hz, 2H), 7.28–7.25 (m, 2H), 7.20–7.16 (m, 2H), 7.11–7.00 (m, 6H), 4.79–4.71 (m, 1H), 4.61 (s, 1H), 3.77 (d, *J* = 10.8 Hz, 1H), 3.12–3.04 (m, 1H), 2.74–2.67 (m, 1H), 2.18–1.95 (m, 3H) , 1.75–1.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.0, 199.2, 142.8, 141.8, 138.1, 135.5, 135.4, 135.0, 128.34, 128.30, 127.9, 127.5, 127.4, 127.2, 122.6, 122.5, 76.6, 73.3, 67.5, 58.7, 54.2, 31.7, 25.9; IR ν_{max} (KBr) 2924, 1734, 1701, 1593, 1358, 1257, 1100, 938, 765, 699 cm^{-1}; HRMS (EI) m/z calcd for $C_{27}H_{23}NO_2$ [M^+] 393.1729, found 393.1724.

4.3.2. ***4b***. R_f = 0.26 (40% EtOAc/hexanes); yellow solid; 49 mg; yield 28%; mp 210–211 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, *J* = 7.2 Hz, 1H), 7.56–7.48 (m, 3H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.44 (dd, *J* = 9.0, 4.8 Hz, 4H), 4.68–4.60 (m, 1H), 4.48 (s, 1H), 3.65 (d, *J* = 10.5 Hz, 1H), 3.06–2.98 (m, 1H), 2.783 (s, 6H), 2.780 (s, 6H), 2.72–2.66 (m, 1H), 2.13–1.88 (m, 2H) , 1.71–1.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.7, 200.1, 149.8, 149.5, 143.2, 142.1, 135.2, 134.7, 129.1, 128.1, 126.0, 123.4, 122.7, 122.4, 112.2, 112.0, 76.5, 73.4, 67.6, 58.4, 54.0, 40.4, 40.3, 31.7, 25.5; IR ν_{max} (KBr) 3695, 2869, 1733, 1702, 1613, 1524, 1355, 1254, 946, 810 cm^{-1}; HRMS (EI) m/z calcd for $C_{31}H_{33}N_3O_2$ [M^+] 479.2573, found 479.2579.

4.3.3. ***4c***. R_f = 0.34 (30% EtOAc/hexanes); white solid; 55 mg; yield 32%; mp 122–124 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.58–7.50 (m, 3H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.59 (t, *J* = 8.7 Hz, 5H), 4.67–4.62 (m, 1H), 4.51 (s, 1H), 3.69 (d, *J* = 10.5 Hz, 1H), 3.64 (s, 6H), 3.07–2.99 (m, 1H), 2.70–2.65 (m, 1H), 2.12–1.93 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.3, 199.7, 158.8, 158.6, 143.0, 141.9, 135.4, 134.9, 130.3, 129.4, 128.4, 127.7, 122.6, 122.5, 113.6, 113.3, 76.2, 73.4, 67.7, 58.2, 55.0, 54.3, 54.1, 31.7, 25.8; IR ν_{max} (KBr) 2932, 1739, 1705, 1610, 1513, 1250, 1180, 1031, 831 cm^{-1}; HRMS (EI) m/z calcd for $C_{29}H_{27}NO_4$ [M^+] 453.1940, found 453.1946.

4.3.4. ***4d***. R_f = 0.46 (30% EtOAc/hexanes); light orange solid; 35 mg; yield 20%; mp 186–188 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98–7.91 (m, 4H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 4.83–4.78 (m, 1H), 4.70 (s, 1H), 3.86 (d, *J* = 10.5 Hz, 1H), 3.11–3.05 (m, 1H), 2.73–2.65 (m, 1H), 2.19–2.02 (m, 3H), 1.74–1.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 199.7, 198.1, 147.4, 147.3, 145.8, 142.6, 142.3, 141.4, 136.5, 136.0, 129.3, 128.1, 123.6, 123.3, 123.01, 122.95, 75.7, 73.2, 67.8, 58.2, 54.2, 31.5, 26.4; IR ν_{max} (KBr) 2959, 1738, 1700, 1519, 1346, 1256, 1109, 859, 691 cm^{-1}; HRMS (EI) m/z calcd for $C_{27}H_{21}N_3O_6$ [M^+] 483.1430, found 483.1425.

4.3.5. ***4e***. R_f = 0.63 (30% EtOAc/hexanes); white solid; 56 mg; yield 32%; mp 219–220 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.59–7.47 (m, 3H), 7.44–7.40 (m, 4H), 7.37–7.32 (m, 10H), 7.29–7.24 (m, 4H), 4.82–4.77 (m, 1H), 4.67 (s, 1H), 3.83 (d, *J* = 10.2 Hz, 1H), 3.16–3.08 (m, 1H), 2.79–2.73 (m, 1H), 2.21–1.98 (m, 3H), 1.79–1.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.0, 199.3, 142.9, 141.9, 140.5, 140.3, 140.2, 140.0, 137.4, 135.6, 135.1, 134.7, 128.8, 128.63, 128.58, 127.7, 127.2, 127.1, 126.9, 126.8, 126.7, 126.6, 122.8, 122.6, 73.4, 67.7, 58.5, 54.3, 31.7, 26.0; IR ν_{max} (KBr) 2972, 1742, 1704, 1486, 1353, 1260, 764, 696 cm^{-1}; HRMS (EI) m/z calcd for $C_{39}H_{31}NO_2$ [M^+] 545.2355, found 545.2357.

4.3.6. ***4f***. R_f = 0.34 (20% EtOAc/hexanes); yellow solid; 31 mg; yield 42%; mp 210–211 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.69–7.58 (m, 3H), 7.01 (dd, *J* = 4.8, 1.2 Hz, 1H), 6.95 (dd, *J* = 4.8, 1.2 Hz, 1H), 6.78 (d, *J* = 3.3 Hz, 1H), 6.73 (t, *J* = 4.2 Hz, 1H), 6.65 (t, *J* = 4.2 Hz, 1H), 6.60 (d, *J* = 3.3 Hz, 1H), 4.79 (s, 1H), 4.69–4.62 (m, 1H), 3.97 (d, *J* = 9.9 Hz, 1H), 3.18–3.10 (m, 1H), 2.83–2.76 (m, 1H), 2.15–1.94 (m, 3H) , 1.79–1.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 200.1, 198.7, 143.1, 143.0, 142.1, 137.9, 135.7, 135.2, 126.7, 126.4, 125.7, 124.8, 124.3, 123.8, 122.9, 122.7, 72.3, 71.9, 69.4, 54.3, 53.4, 31.4, 25.4; IR ν_{max} (KBr) 2956,2380, 1733, 1700, 1591, 1367, 1354, 1257, 752, 710 cm^{-1}; HRMS (EI) m/z calcd for $C_{23}H_{19}NO_2S_2$ [M^+] 405.0857, found 405.0851.

4.3.7. ***4g***. R_f = 0.33 (30% EtOAc/hexanes); white solid; 44 mg; yield 26%; mp 154–155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, *J* = 7.5 Hz, 1H), 7.75–7.64 (m, 3H), 6.96–6.93 (m, 2H), 6.24 (d, *J* = 3.3Hz, 1H), 6.09–6.07 (m, 2H), 6.03 (d, *J* = 3.3 Hz, 1H), 4.56–4.49 (m, 2H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.17–3.09 (m, 1H), 2.82–2.75 (m, 1H), 2.16–1.95 (m, 3H), 1.82–1.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 200.8, 199.9, 153.7, 149.4, 142.4, 142.3, 142.2, 141.5, 135.64, 135.55, 123.2, 122.8, 110.0, 109.9, 107.6, 107.3, 70.5, 66.4, 65.5, 53.6, 52.8, 27.7, 26.7; IR ν_{max} (KBr) 2944, 1741, 1707, 1593, 1349, 1257, 1000, 795, 746, 730 cm^{-1}; HRMS (EI) m/z calcd for $C_{23}H_{19}NO_4$ [M^+] 373.1314, found 373.1319.

4.3.8. ***4h***. R_f = 0.18 (40% EtOAc/hexanes); brown solid; 68 mg; yield 39%; mp 204–206 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.85 (td, *J* = 8.1, 1.5 Hz, 1H), 7.75 (td, *J* = 8.1, 1.5 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 3.6 Hz, 1H), 7.03 (d, *J* = 3.6 Hz, 1H), 6.61 (d, *J* = 3.8 Hz, 1H), 6.27 (d, *J* = 3.8 Hz, 1H), 4.57 (s, 1H), 4.55–4.49 (m, 1H), 3.84 (d, *J* = 10.2 Hz, 1H), 3.22–3.15 (m, 1H), 2.86–2.79 (m, 1H), 2.22–2.03 (m, 3H), 1.89–1.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 197.2, 196.9, 156.0, 153.6, 151.30, 151.29, 141.6, 141.5, 136.54, 136.45,124.0, 123.1, 112.1, 112.0, 111.4, 110.9, 69.4, 69.1, 67.6, 54.8, 50.7, 31.2, 26.1 ; IR ν_{max} (KBr) 2971, 1741, 1703, 1498, 1353, 1237, 1012, 811, 738 cm^{-1}; HRMS (EI) m/z calcd for $C_{23}H_{17}N_3O_8$ [M^+] 463.1016, found 463.1012.

4.3.9. ***4i***. R_f = 0.34 (30% EtOAc/hexanes); brown oil; 59 mg; yield 30%; mp 183–185 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, *J* = 7.5 Hz, 1H), 7.76–7.65 (m, 3H), 6.07 (d, *J* = 3.0 Hz, 1H), 5.88 (d, *J* = 3.0 Hz, 1H), 5.63–5.25 (m, 2H), 4.52–4.44 (m, 1H), 4.42 (s, 1H), 3.70 (d, *J* = 10.2 Hz, 1H), 3.15–3.07 (m, 1H), 2.81–2.74 (m, 1H), 2.14–1.94 (m, 3H), 1.85 (s, 3H), 1.84 (s, 3H), 1.92–1.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 199.3, 198.1, 151.7, 151.6, 151.1, 148.5, 142.4, 141.9, 135.3, 134.8, 122.8, 122.7, 108.6, 107.6, 105.9, 105.8, 69.9, 69.2, 66.9, 54.4, 51.2, 31.5, 25.5, 13.1, 13.0; IR ν_{max} (KBr) 3359, 2923, 1744, 1706, 1633, 1260, 1021, 787, 749 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{23}NO_4$ [M^+] 401.1627, found 401.1632.

4.3.10. ***4j***. R_f = 0.2 (20% EtOAc/hexanes); orange solid; 43 mg; yield 26%; mp 152–154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.61 (td, *J* = 7.5, 1.8 Hz, 1H), 7.57–7.49 (m, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 4.80–4.73 (m, 1H), 4.54 (s, 1H), 3.85 (d, *J* = 10.5 Hz, 1H), 3.65 (s, 3H), 3.08–3.01 (m, 1H), 2.72–2.65 (m, 1H), 2.20–1.99 (m, 3H), 1.72–1.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 200.3, 198.9, 159.0, 147.1, 143.7, 142.7, 141.6, 135.9, 135.4, 129.4, 129.35, 128.3, 128.2, 123.5,

122.8, 122.7, 113.3, 73.4, 67.5, 57.4, 55.0, 53.9, 31.8, 26.1; HRMS (EI) m/z calcd for $C_{28}H_{24}N_2O_5$ [M^+] 468.1685, found 468.1688.

4.3.11. ***4k***. R_f = 0.2 (20% EtOAc/hexanes); white solid; 33 mg; yield 20%; mp 193–195 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (td, *J* =6.9, 1.2 Hz, 1H), 7.58–7.47 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 8.7 Hz, 2H), 6.44 (d, *J* = 8.7 Hz, 2H), 4.95 (m, 1H), 4.51 (s, 1H), 3.66 (d, *J* = 10.5 Hz, 1H), 3.64 (s, 3H), 3.07–2.99 (m, 1H), 2.79 (s, 6H), 2.72–2.63 (m, 1H), 2.14–1.90 (m, 2H), 1.72–1.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.8, 198.3, 157.6, 149.0, 142.3, 141.2, 135.5, 135.2, 132.8, 131.2, 128.6, 123.3, 123.2, 123.1, 113.0, 111.4, 72.7, 68.5, 67.0, 64.4, 55.0, 53.9, 40.3, 28.7, 26.9; IR ν_{max} (KBr) 3415, 1737, 1699, 1613, 1512, 1350, 1250, 1034, 948, 796 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{30}N_2O_3$ [M^+] 466.2256, found 466.2261.

4.3.12. ***4l***. R_f = 0.35 (20% EtOAc/hexanes); light yellow solid; 48 mg; yield 32%; mp 116–118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83–7.80 (m, 1H), 7.64–7.53 (m, 3H), 7.44–7.41 (m, 2H), 7.37–7.31 (m, 4H), 7.29–7.22 (m, 3H), 7.02 (dd, *J* = 5.1, 1.2 Hz, 2H), 6.67–6.61 (m, 2H), 4.85 (s, 1H), 4.82–4.76 (m, 1H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.21–3.14 (m, 1H), 2.87–2.79 (m, 1H), 2.14–1.97 (m, 3H) , 1.75–1.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.3, 198.8, 143.0, 142.8, 141.8, 140.0, 139.8, 135.4, 134.9, 134.2, 128.5, 128.4, 127.0, 126.7, 126.5, 126.1, 124.5, 123.7, 122.6, 122.4, 72.6, 72.1, 67.3, 58.0, 54.1, 31.3, 25.3, 22.4, 13.8; IR ν_{max} (KBr) 2939, 1736, 1702, 1365, 1257, 1230, 1216, 763, 719 cm^{-1}; HRMS (EI) m/z calcd for $C_{31}H_{25}NO_2S$ [M^+] 475.1606, found 475.1609.

4.3.13. ***5a***. R_f = 0.48 (20% EtOAc/hexanes); white solid; 52 mg; yield 31%; mp 188–189 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (d, *J* = 6.3 Hz, 1H), 7.88–7.75 (m, 3H), 7.29 (d, *J* = 7.8 Hz, 3H), 7.26 (s, 1H), 7.20–6.99 (m, 6H), 5.17 (d, *J* = 5.7 Hz, 1H), 4.63 (t, *J* = 7.8 Hz, 1H), 3.84 (d, *J* = 5.7 Hz, 1H), 3.28–3.21 (m, 1H), 2.89–2.81 (m, 1H), 2.26–2.16 (m, 1H), 2.11–2.02 (m, 1H), 1.75–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.8, 198.1, 142.2, 141.0, 140.4, 135.7, 135.5, 135.4, 130.5, 127.6, 127.5, 127.4, 127.3, 126.9, 125.9, 123.3, 123.2, 72.9, 69.1, 66.1, 64.3, 54.0, 28.8, 26.9; IR ν_{max} (KBr) 2818, 1698, 1595, 1280, 1248, 761, 699 cm^{-1}; HRMS (EI) m/z calcd for $C_{27}H_{23}NO_2$ [M^+] 393.1729, found 393.1722.

4.3.14. ***5b***. R_f =0.49 (40% EtOAc/hexanes); light yellow solid; 55 mg; yield 32%; mp 186–187 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, *J* = 7.5 Hz, 1H), 7.84–7.79 (m, 1H), 7.76 (d, *J* = 3.9 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 8.7 Hz, 2H), 6.44 (d, *J* = 8.7 Hz, 2H), 4.97 (d, *J* = 5.7 Hz, 1H), 4.59 (t, *J* = 7.8 Hz, 1H), 3.67 (d, *J* = 5.7 Hz, 1H), 3.20–3.14 (m, 1H), 2.84 (s, 6H), 2.82 (s, 6H), 2.79–2.72 (m, 1H), 2.22–2.14 (m, 1H), 2.07–1.97 (m, 1H), 1.77–1.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.8, 198.4, 149.0, 148.8, 142.3, 141.2, 135.4, 135.1, 131.2, 128.7, 128.4, 123.6, 123.2, 123.1, 112.1, 111.4, 72.7, 68.2, 67.1, 64.5, 53.9, 40.7, 40.3, 28.7, 26.9; IR ν_{max} (KBr) 2801, 2326, 1738, 1699, 1614, 1520, 1348, 816, 789 cm^{-1}; HRMS (EI) m/z calcd for $C_{31}H_{33}N_3O_2$ [M^+] 479.2573, found 479.2577.

4.3.15. ***5c***. R_f = 0.46 (30% EtOAc/hexanes); light orange solid; 62 mg; yield 36%; mp 88–90 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, *J* = 7.5 Hz, 1H), 7.86–7.82 (m, 1H), 7.81–7.76 (m, 2H), 7.18 (d, *J* = 13.8 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.63 (dd, *J* = 13.8, 8.7 Hz, 4H), 5.04 (d, *J* = 6.0 Hz, 1H), 4.59 (t, *J* = 3.9 Hz, 1H), 3.71 (d, *J* = 6.0 Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 3.21–3.14 (m, 1H), 2.85–2.77 (m, 1H), 2.23–2.15 (m, 1H), 2.07–1.98 (m, 1H), 1.75–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.7, 198.2, 158.1, 157.7, 142.2, 141.1, 135.6, 135.4, 132.4, 131.6, 128.5, 127.7, 123.3, 123.2, 113.0, 112.7, 72.6, 68.7, 66.5, 64.0, 55.0, 54.8, 53.8, 28.7, 27.0; IR ν_{max} (KBr) 2970, 1739, 1702, 1611, 1512, 1247, 1179, 1031, 789 cm^{-1}; HRMS (EI) m/z calcd for $C_{29}H_{27}NO_4$ [M^+] 453.1940, found 453.1945.

4.3.16. ***5d***. R_f = 0.30 (30% EtOAc/hexanes); light yellow solid; 39 mg; yield 22%; mp 143–145 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.91 (t, *J* = 7.4 Hz, 1H), 7.84 (t, *J* = 6.9 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 5.34 (d, *J* = 6.0 Hz, 1H), 4.59 (t, *J* = 7.5 Hz, 1H), 3.99 (d, *J* = 6.0 Hz, 1H), 3.28–3.21 (m, 1H), 2.87–2.79 (m, 1H), 2.26–2.05 (m, 2H), 1.80–1.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.2, 197.4, 147.6, 146.9, 146.5, 142.6, 141.9, 141.0, 136.4, 136.2, 131.2, 128.0, 123.6, 123.5, 123.3, 123.0, 72.3, 70.0, 64.8, 62.5, 53.8, 28.8, 27.0; IR ν_{max} (KBr) 2970, 1739, 1702, 1517, 1345, 1245, 1108, 859, 716 cm^{-1}; HRMS (EI) m/z calcd for $C_{27}H_{21}N_3O_6$ [M^+] 483.1430, found 483.1427.

4.3.17. ***5e***. R_f = 0.41 (30% EtOAc/hexanes); white solid; 50 mg; yield 28%; mp 207–208 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, *J* = 7.5 Hz, 1H), 7.89–7.84 (m, 1H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 4H), 7.36–7.31 (m, 10H), 7.26–7.20 (m, 4H), 5.22 (d, *J* = 5.7 Hz, 1H), 4.68 (t, *J* = 7.5 Hz, 1H), 3.90 (d, *J* = 5.7 Hz, 1H), 3.31–3.24 (m, 1H), 2.93–2.85 (m, 1H), 2.28–2.20 (m, 1H), 2.14–2.05 (m, 1H), 1.78–1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.7, 198.0, 142.2, 141.1, 140.9, 140.7, 139.5, 139.2, 138.7, 135.8, 135.5, 134.6, 130.9, 128.51, 128.45, 128.0, 126.9, 126.85, 126.84, 126.83, 126.3, 126.1, 123.34, 123.28, 72.8, 69.1, 66.2, 64.0, 54.0, 28.8, 26.9; IR ν_{max} (KBr) 2961, 1740, 1700, 1487, 1349, 1272, 1250, 745, 694 cm^{-1}; HRMS (EI) m/z calcd for $C_{39}H_{31}NO_2$ [M^+] 545.2355, found 545.2359.

4.3.18. ***5f***. R_f = 0.41 (20% EtOAc/hexanes); white solid; 30 mg; yield 41%; mp 177–179 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, *J* = 6.9 Hz, 1H), 7.88–7.80 (m, 3H), 7.14 (t, *J* = 3.3 Hz, 1H), 7.04 (dd, *J* = 4.8, 1.2 Hz, 1H), 6.88–6.79 (m, 4H), 5.28 (d, *J* = 5.4 Hz, 1H), 4.64 (t, *J* = 7.2 Hz, 1H), 4.04 (d, *J* = 5.4 Hz, 1H), 3.24–3.17 (m, 1H), 2.96–2.89 (m, 1H), 2.22–2.13 (m, 1H), 2.07–1.96 (m, 1H), 1.73–1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 200.9, 197.2, 144.0, 142.0, 141.0, 136.5, 135.9, 135.6, 128.6, 126.1, 126.0, 125.4, 124.8, 124.2, 123.40, 123.37, 68.9, 68.3, 65.7, 58.5, 53.3, 28.0, 26.9; IR ν_{max} (KBr) 2962, 1739, 1697, 1592, 1263, 1234, 699 cm^{-1}; HRMS (EI) m/z calcd for $C_{23}H_{19}NO_2S_2$ [M^+] 405.0857, found 405.0851.

4.3.19. ***5g***. R_f = 0.47 (30% EtOAc/hexanes); light yellow solid; 60 mg; yield 36%; mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03–8.00 (m, 1H), 7.87–7.81 (m, 3H), 7.39 (d, *J* = 1.2 Hz, 1H), 7.21 (d, *J* = 1.2 Hz, 1H), 6.23–6.20 (m, 2H), 6.10 (d, *J* = 3.0 Hz, 1H) , 5.99 (d, *J* = 2.4 Hz, 1H) , 5.02 (d, *J* = 6.3 Hz, 1H), 4.65 (t, *J* = 7.5 Hz, 1H), 3.98 (d, *J* = 6.0 Hz, 1H), 3.27–3.20 (m, 1H), 2.96–2.88 (m, 1H), 2.17–1.99 (m, 2H), 1.76–1.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.5, 197.7, 153.7, 149.9, 142.2, 142.1, 141.4, 141.2, 135.9, 135.7, 123.4, 123.3, 109.93, 109.92, 109.7, 106.8, 70.1, 66.9, 65.4, 54.2, 53.7, 28.3, 26.6; IR ν_{max} (KBr) 2965, 2802, 1742, 1699, 1594, 1350, 1271, 1151, 782, 742 cm^{-1}; HRMS (EI) m/z calcd for $C_{23}H_{19}NO_4$ [M^+] 373.1314, found 373.1319.

4.3.20. ***5h***. R_f = 0.36 (40% EtOAc/hexanes); brown solid; 54 mg; yield 31%; mp 99–101 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, *J* = 7.2 Hz, 1H), 7.92–7.88 (m, 3H), 7.17 (t, *J* = 3.6 Hz, 2H),

6.64 (d, *J* = 3.3 Hz, 1H), 6.44 (d, *J* = 3.3 Hz, 1H), 5.21 (d, *J* = 5.7 Hz, 1H), 4.49 (t, *J* = 6.9 Hz, 1H), 4.19 (d, *J* = 6.0 Hz, 1H), 3.22–3.15 (m, 1H), 2.91–2.83 (m, 1H), 2.15–2.04 (m, 2H), 1.75–1.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 200.2, 196.5, 157.3, 152.9, 151.7, 151.6, 141.8, 141.1, 136.6, 136.5, 123.7, 123.6, 113.8, 112.5, 112.4, 111.5, 70.8, 66.1, 63.8, 53.8, 52.7, 28.4, 26.5; IR ν_{max} (KBr) 2928, 1701, 1495, 1354, 1241, 1019, 810, 740 cm^{-1}; HRMS (EI) m/z calcd for $C_{23}H_{17}N_3O_8$ [M$^+$] 463.1016, found 463.1021.

4.3.21. ***5i***. R_f = 0.48 (30% EtOAc/hexanes); brown oil; 65 mg; yield 33%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (d, *J* = 5.7 Hz, 1H), 7.86–7.80 (m, 3H), 5.96 (dd, *J* = 15.5, 3.3 Hz, 2H), 5.81–5.79 (m, 2H), 4.90 (d, *J* = 6.3 Hz, 1H), 4.61 (t, *J* = 6.9 Hz, 1H), 3.91 (d, *J* = 6.3 Hz, 1H), 3.25–3.18 (m, 1H), 2.97–2.88 (m, 1H), 2.24 (s, 3H), 2.17 (s, 3H), 2.10–2.00 (m, 2H), 1.75–1.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.5, 197.6, 151.9, 151.0, 150.7, 147.8, 142.3, 141.2, 135.8, 135.4, 123.13, 123.11, 110.4, 107.7,106.0, 105.8, 69.6, 66.7, 65.8, 54.1, 54.0, 28.0, 26.4, 13.6, 13.4; IR ν_{max} (KBr) 3426, 2948, 1740, 1702, 1594, 1328, 1263, 1163, 1020, 783, 734 cm^{-1}; HRMS (EI) m/z calcd for $C_{25}H_{23}NO_4$ [M$^+$] 401.1627, found 401.1629.

4.3.22. ***5j***. R_f = 0.2 (20% EtOAc/hexanes); orange solid; 48 mg; yield 26%; mp 104–106 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, *J* = 7.2 Hz, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.89 (td, *J* = 7.5, 1.5 Hz, 1H), 7.83 (td, *J* = 7.5, 1.5 Hz, 1H), 7.77 (d, *J* = 6.6 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 5.19 (d, *J* = 6.0 Hz, 1H), 4.54 (t, *J* = 7.5 Hz, 1H), 3.86 (d, *J* = 5.7 Hz, 1H), 3.68 (s, 3H), 3.24–3.17 (m, 1H), 2.87–2.79 (m, 1H), 2.24–2.00 (m, 2H), 1.75–1.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.2, 198.0, 158.0, 146.7, 143.7, 141.9, 141.1, 136.1, 136.0, 131.5, 131.3, 128.3, 123.5, 123.4, 122.7, 113.3, 72.2, 69.6, 65.2, 63.2, 55.0, 53.7, 28.6, 27.2; IR ν_{max} (KBr) 2951, 1739, 1700, 1595, 1510, 1344, 1244, 1032, 857, 797 cm^{-1}; HRMS (EI) m/z calcd for $C_{28}H_{24}N_2O_5$ [M$^+$] 468.1685, found 468.1691.

4.3.23. ***5k***. R_f = 0.1 (20% EtOAc/hexanes); white solid; 38 mg; yield 23%; mp 135–137 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, *J* = 7.2 Hz, 1H), 7.85–7.78 (m, 1H), 7.76 (d, *J* = 3.6 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 8.7 Hz, 2H), 5.00 (d, *J* = 5.7 Hz, 1H), 4.60 (t, *J* = 8.1 Hz, 1H), 3.69 (s, 3H), 3.68 (d, *J* = 5.7 Hz, 1H), 3.21–3.14 (m, 1H), 2.84(s, 6H), 2.79–2.76 (m, 1H), 2.23–2.15 (m, 1H), 2.10–1.98 (m, 1H), 1.77–1.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.6, 199.9, 158.8, 149.6, 143.1, 142.1, 135.3, 134.8, 130.5, 129.1, 128.4, 123.3, 122.7, 122.5, 113.3, 112.3, 76.2, 73.5, 67.8, 58.4, 55.0, 54.1, 40.3, 25.7, 22.6; IR ν_{max} (KBr) 2957, 1737, 1702, 1510, 1251, 1029, 821 cm^{-1}; HRMS (EI) m/z calcd for $C_{30}H_{30}N_2O_3$ [M$^+$] 466.2256, found 466.2252.

4.3.24. ***5l***. R_f = 0.5 (20% EtOAc/hexanes); white solid; 29.2 mg; yield 19%; mp 207–209 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, *J* = 7.2 Hz, 1H), 7.88–7.82 (m, 1H), 7.80–7.78 (m, 2H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.41–7.35 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 3H), 6.97 (dd, *J* = 1.5, 1.2 Hz, 1H), 6.81 (d, *J* = 3.6 Hz, 1H), 6.76 (d, *J* = 5.1 Hz, 1H), 6.74 (d, *J* = 5.1 Hz, 1H), 5.33 (d, *J* = 6.0 Hz, 1H), 4.65 (t, *J* = 7.8 Hz, 1H), 3.77 (d, *J* = 3.0 Hz, 1H), 3.29–3.22 (m, 1H), 2.98–2.90 (m, 1H), 2.25–2.17 (m, 1H), 2.11–1.97 (m, 1H), 1.75–1.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.5, 197.7, 144.8, 142.2, 141.0, 140.7, 139.5, 135.9, 135.6, 134.3, 131.1, 128.5, 127.0, 126.9, 126.1, 126.06, 124.3, 123.9, 123.39, 123.36, 69.5, 68.9, 66.2, 64.0, 53.8, 28.4, 27.0; IR ν_{max} (KBr) 2807, 1699, 1489, 1345, 1248, 986, 721 cm^{-1}; HRMS (EI) m/z calcd for $C_{31}H_{25}NO_2S$ [M$^+$] 475.1606, found 475.1602.

*4.4. Synthesis of pyrrolizinone derivatives (**8-12**).*

A mixture of proline (0.87 mmol, 1.0 equiv), 4-hydroxycoumarin (0.87 mmol, 1.0 equiv), carbaldehyde (3.0 equiv) and a few drops of water in xylene (10 mL) was irradiated in a microwave reactor at 275 ^{o}C (300 W, open vessel standard conditions) for 25 minutes. After the heat was subsided by compressed air, the reaction mixture was concentrated *in vacuo* and purified over silica gel. The anticipated pyrrolizinone derivatives were isolated by flash chromatography as a major product.

4.4.1. ***8m***. R_f = 0.25 (40% EtOAc/hexanes); brown solid; 130 mg; yield 42%; mp 106–108 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.75 (s, 1H), 7.55 (d, *J* = 9.3 Hz, 1H), 6.63 (d, *J* = 3.3 Hz, 1H), 6.53–6.52 (m, 1H), 6.21 (dd, *J* = 6.6, 2.4 Hz, 1H), 6.05 (d, *J* = 2.4 Hz, 1H), 4.79 (d, *J* = 10.8 Hz, 1H), 4.22 (dd, *J* = 11.0, 8.5 Hz, 1H), 4.03 (td, *J* = 13.8, 8.5 Hz, 1H), 3.64 (dt, *J* = 11.4, 7.5 Hz, 1H), 3.19–3.14 (m, 1H), 3.03 (s, 6H), 2.40 (s, 3H), 2.24–2.10 (m, 3H), 1.73–1.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 195.1, 168.7, 165.4, 156.2, 140.1, 138.6, 133.0, 125.0, 124.6, 110.9, 104.3, 97.5, 66.4, 61.0, 45.9, 42.0, 39.9, 30.6, 26.8, 15.2; IR ν_{max} (KBr) 3357, 2923, 2852, 1632, 1364, 1217, 1132, 1019, 945, 732 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{24}N_2O_3S$ [M$^+$] 384.1508, found 358.1503.

4.4.2. ***8n***. R_f = 0.33 (40% EtOAc/hexanes); pale brown solid; 106 mg; yield 27%; mp 110–112 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.69 (s, 1H), 7.54 (d, *J* = 9.3 Hz, 1H), 6.84 (d, *J* = 3.6 Hz, 1H), 6.63 (dd, *J* = 3.9, 0.9 Hz, 1H), 6.23 (dd, *J* = 9.3, 2.4 Hz, 1H), 6.08 (d, *J* = 2.4 Hz, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 4.24 (dd, *J* = 11.1, 8.4 Hz, 1H), 4.01 (td, *J* = 8.4, 5.4 Hz, 1H), 3.64 (dt, *J* = 11.7, 7.5 Hz, 1H), 3.19–3.11 (m, 1H), 3.04 (s, 6H), 2.25–2.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 194.3, 168.6, 165.4, 156.2, 144.0, 133.0, 129.8, 125.3, 110.6, 110.6, 104.4, 97.4, 65.9, 60.8, 45.8, 42.0, 39.9, 30.6, 26.8; IR ν_{max} (KBr) 2885, 1692, 1693, 1526, 1384, 1213, 1146, 965, 789, 712 cm^{-1}; HRMS (EI) m/z calcd for $C_{20}H_{21}BrN_2O_3S$ [M$^+$] 448.0456, found 448.0452.

4.4.3. ***8o***. R_f = 0.55 (30% EtOAc/hexanes); brown solid; 180 mg; yield 54%; mp 154–156 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.77 (s, 1H), 7.47 (d, *J* = 9.6 Hz, 1H), 7.07 (d, *J* = 5.1 Hz, 1H), 6.73 (d, *J* = 5.1 Hz, 1H), 6.17 (dd, *J* = 9.3, 2.7 Hz, 1H), 6.02 (d, *J* = 2.7 Hz, 1H), 4.81 (d, *J* = 10.5 Hz, 1H), 4.34 (dd, *J* = 10.5, 8.4 Hz, 1H), 4.01 (td, *J* = 13.8, 8.4 Hz, 1H), 3.66 (dt, *J* = 11.7, 7.5 Hz, 1H), 3.21–3.13 (m, 1H), 3.01 (s, 6H), 2.16 (s, 3H), 2.11–2.05 (m, 3H), 1.71–1.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 195.4, 168.6, 165.4, 156.1, 136.1, 135.3, 132.8, 130.5, 122.26, 110.8, 104.3; 97.4, 67.6, 61.7, 44.3, 41.8, 39.9, 30.9, 26.8, 13.9; IR ν_{max} (KBr) 2925, 1694, 1622, 1529, 1377, 1254, 1146, 975, 828, 713 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{24}N_2O_3S$ [M$^+$] 384.1508, found 384.1506.

4.4.4. ***8g***. R_f = 0.25 (40% EtOAc/hexanes); brown solid; 108 mg; yield 35%; mp 123–125 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.71 (s, 1H), 7.55 (d, *J* = 9.3 Hz, 1H), 7.30–7.32 (m, 1H), 6.26 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.22 (dd, *J* = 9.3, 2.4 Hz, 1H), 6.08 (d, *J* = 3.3 Hz, 1H), 6.06 (d, *J* = 2.4 Hz, 1H), 4.92 (d, *J* = 10.5 Hz, 1H), 4.13–4.03 (m, 2H), 3.65 (dt, *J* = 11.7, 7.8 Hz, 1H), 3.18–3.10 (m, 1H), 3.04 (s, 6H), 2.23–2.04 (m, 3H), 1.75–1.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 195.1, 168.8, 165.4, 156.2, 152.5, 142.0, 133.0, 110.6, 110.3, 106.4, 104.3, 97.5, 63.7, 57.7, 43.5, 41.9, 39.9, 30.8, 26.7; IR ν_{max} (KBr) 3352, 2981, 1733, 1629, 1524, 1373, 1216, 1150, 1034, 787 cm^{-1}; HRMS (EI) m/z calcd for $C_{20}H_{22}N_2O_4$ [M$^+$] 354.1580, found 354.1584.

4.4.5. ***8i***. R_f = 0.28 (40% EtOAc/hexanes); brown solid; 142 mg; yield 44%; mp 136–138 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.74 (s, 1H), 7.57 (d, *J* = 9.0 Hz, 1H), 6.22 (dd, *J* = 9.3, 2.4 Hz, 1H), 6.06 (d, *J* = 2.4 Hz, 1H), 5.96 (d, *J* = 3.0 Hz, 1H), 5.82 (d, *J* = 3.0 Hz, 1H), 4.91 (d, *J* = 11.1 Hz, 1H), 4.06–4.02 (m, 2H), 3.64 (dt, *J* = 11.4, 7.5 Hz, 1H), 3.13–3.11 (m, 1H), 3.04 (s, 6H), 2.24 (s, 3H), 2.17–2.05 (m, 3H), 1.70–1.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 195.2, 168.8, 165.2, 156.0, 151.5, 150.5, 132.9, 110.5, 107.1, 106.1, 104.1, 97.3, 63.7, 57.6, 43.7, 41.8, 39.7, 30.7, 26.6, 13.4; IR ν_{max} (KBr) 2947, 1737, 1698, 1630, 1527, 1527, 1354, 1255, 1147, 893 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{24}N_2O_4$ [M^+] 368.1736, found 368.1730.

4.4.6. ***9o***. R_f = 0.40 (30% EtOAc/hexanes); brown solid; 127 mg; yield 36%; mp 186–188 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.91 (s, 1H), 7.72 (d, *J* = 2.7 Hz, 1H), 7.39 (dd, *J* = 5.7, 2.7 Hz, 1H), 7.11 (d, *J* = 5.7 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.75 (d, *J* = 5.1 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 4.36 (dd, *J* = 10.8, 8.7 Hz, 1H), 4.05 (td, *J* = 14.1, 8.4 Hz, 1H), 3.64 (td, *J* = 11.7, 7.5 Hz, 1H), 3.19 (td, *J* = 11.4, 8.7 Hz, 1H), 2.22 (s, 3H), 2.18–2.04 (m, 2H), 1.74–1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 199.3, 167.0, 161.2, 136.7, 135.5, 135.2, 130.8, 130.6, 123.8, 122.7, 120.6, 119.7, 67.5, 63.0, 44.0, 41.9, 30.8, 26.7, 13.9 ; IR ν_{max} (KBr) 2885, 1686, 1637, 1469, 1421, 1334, 1241, 1188, 985, 742 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{18}ClNO_3S$ [M^+] 375.0696, found 375.0693.

4.4.7. ***9i***. R_f = 0.25 (30% EtOAc/hexanes); brown solid; 72 mg; yield 23%; mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.94 (s, 1H), 7.76 (d, *J* = 2.7 Hz, 1H), 7.41 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 5.99 (d, *J* = 1.5 Hz, 1H), 5.84 (d, *J* = 3.0 Hz, 1H), 5.50 (d, *J* = 10.5 Hz, 1H), 4.15–3.97 (m, 2H), 3.65 (dt, *J* = 11.7, 7.2 Hz, 1H), 3.18–2.13 (m, 1H), 2.25 (s, 3H), 2.14–2.12 (m, 2H), 1.70–1.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 199.4, 167.4, 161.3, 152.1, 149.5, 136.7, 130.9, 123.8, 120.6, 119.8, 107.8, 106.2, 63.7, 59.0, 43.9, 42.1, 30.7, 26.7, 13.5; IR ν_{max} (KBr) 2924, 1678, 1639, 1513, 1422, 1365, 1217, 1113, 826, 713 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{18}ClNO_4$ [M^+] 359.0924, found 359.0919.

4.4.8. ***10o***. R_f = 0.48 (30% EtOAc/hexanes); light brown solid; 165 mg; yield 53%; mp 164–166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.87 (s, 1H), 7.50 (d, *J* = 1.2 Hz, 1H), 7.29 (d, *J* = 8.4, 1.2 Hz, 1H), 7.10 (d, *J* = 4.8 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 5.1 Hz, 1H), 4.97 (d, *J* = 11.1 Hz, 1H), 4.36 (dd, *J* = 8.4, 10.8 Hz, 1H), 4.05 (td, *J* = 8.4, 5.7 Hz, 1H), 3.66 (dt, *J* = 11.4, 7.5 Hz, 1H), 3.22–3.15 (m, 1H), 2.27 (s, 3H), 2.17 (s, 3H), 2.14–2.08 (m, 2H), 1.74–1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 199.9, 167.7, 160.8, 138.0, 135.6, 135.5, 131.2, 130.6, 128.1, 122.5, 67.6, 62.7, 44.2, 41.9, 30.8, 26.7, 20.5, 13.9; IR ν_{max} (KBr) 2970, 1739, 1691, 1633, 1481, 1365, 1216, 983, 831, 706 cm^{-1}; HRMS (EI) m/z calcd for $C_{20}H_{21}NO_3S$ [M^+] 355.1242, found 355.1240.

4.4.9. ***11o***. R_f = 0.55 (30% EtOAc/hexanes); brown solid; 135 mg; yield 39%; mp 156–158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.34 (s, 1H), 7.58 (s, 1H), 7.13 (d, *J* = 4.8 Hz, 1H), 6.85 (d, *J* = 5.1 Hz, 1H), 6.44 (s, 1H), 4.59–4.50 (m, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.55 (td, *J* = 11.7, 8.1 Hz, 1H), 3.15 (dt, *J* = 12.0, 6.6 Hz, 1H), 2.19 (s, 3H), 2.07–1.97 (m, 3H), 1.68–1.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 196.4, 168.0, 160.8, 157.1, 142.1, 135.6, 134.9, 130.0, 122.4, 112.5, 110.9, 100.1, 65.2, 65.1, 56.3, 56.2, 41.9, 39.7, 26.9, 25.7, 14.0; IR ν_{max} (KBr) 2970, 1738, 1625, 1512, 1365, 1263, 1154, 1000, 8427 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{23}NO_5S$ [M^+] 401.1297, found 401.1291.

4.4.10. ***11i***. R_f = 0.37 (30% EtOAc/hexanes); brown solid; 115 mg; yield 35%; mp 70–72 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.36 (s, 1H), 7.60 (s, 1H), 6.44 (s, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 5.91–5.90 (m, 1H), 4.54 (d, *J* = 1.8 Hz, 1H), 4.43 (td, *J* = 9.3, 6.9 Hz, 1H), 4.22 (dd, *J* = 6.9, 1.5 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.57 (td, *J* = 12.0, 8.1 Hz, 1H), 3.09 (dt, *J* = 12.0, 6.6 Hz, 1H), 2.28 (s, 3H), 2.24–2.09 (m, 1H), 2.01–1.94 (m, 2H), 1.78–1.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 196.3, 168.7, 160.8, 157.1, 152.0, 151.6, 142.1, 112.6, 110.9, 108.1, 106.0, 100.1, 64.7, 61.8, 56.4, 56.2, 41.1, 39.9, 26.7, 26.5, 13.6; IR ν_{max} (KBr) 2925, 1693, 1627, 1509, 1443, 1375, 1261, 1155, 1021, 784 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{23}NO_6$ [M^+] 385.1525, found 385.1528.

4.4.11. ***12o***. R_f = 0.25 (40% EtOAc/hexanes); brown solid; 142 mg; yield 41%; mp 85–87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.66 (s, 1H), 7.74 (d, *J* = 9.3 Hz, 1H), 7.07 (d, *J* = 5.1 Hz, 1H), 6.81 (d, *J* = 5.1 Hz, 1H), 6.25 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.05 (d, *J* = 2.4 Hz, 1H), 4.58–4.86 (m, 2H), 4.21–4.17 (m, 1H), 3.92–3.84 (m, 1H), 3.04 (s, 6H), 2.80–2.72 (m, 1H), 3.20 (s, 3H), 1.86–1.83 (m, 1H), 1.68–1.63 (m, 2H), 1.44–1.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 196.0, 168.7, 165.5, 156.2, 135.5, 135.1, 133.5, 130.1, 122.2, 110.1, 104.4, 97.5, 59.5, 57.0, 41.2, 39.9, 38.5, 28.0, 24.7, 23.6, 14.0; IR ν_{max} (KBr) 2925, 1688, 1626, 1526, 1370, 1275, 1147, 1006, 823, 717 cm^{-1}; HRMS (EI) m/z calcd for $C_{22}H_{26}N_2O_3S$ [M^+] 398.1664, found 398.1669.

Supplementary Material

^{1}H and ^{13}C NMR spectral copies and X-ray crystal structure details for **4a**, **5a** and **9o** (CIF) to this article can be found at http://dx.doi.org/xx.xxxx/j.tet.xxxx.xx.xxx.

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14. Crystallographic data (excluding structure factors) for **4a**, **5a** and **9o** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-1411138, -1411139 and -1411142, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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