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Progress toward a biomimetic synthesis of pegaharmaline A†

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Efforts towards a biomimetic synthesis of the alkaloid pegaharmaline A began with attempted validation of the putative biosynthesis described in the isolation report. The reaction between vasicinone-derived pyrroloquinazoline **1** and tryptamines **2** and **9** proceeded under aqueous conditions at ambient temperature, forming the 1,6,10-triazaspiro[4.5]dec-7-anes **7** and **8**. Alternative pyrroloquinazoline precursors were subsequently investigated; the reaction between dehydrodimethylisovasicinone (**10**) and tryptamine (**9**) led to the ring-opened product **13** that could not be converted into pegaharmaline A scaffold under Bischler–Napieralski conditions. The Pictet–Spengler reaction between a model isovasicinone (**22**) and tryptamine (**9**) was successful, but the resulting tetrahydro-β-carboline could not be converted into the natural product. These studies suggest an alternative biosynthetic pathway is potentially operating, while structural revision of the natural product cannot be ruled out at this time. As vasicinones and tryptamines are widely distributed throughout Nature, the novel scaffolds reported herein may be undiscovered natural products.

Introduction

Peganum harmala (Syrian rue, wild rue or harmal) is a plant found in semi-arid climates of the eastern Mediterranean, Middle East, North Africa and parts of China.[1,2] *P. harmala* is known to possess entheogenic properties[3–6] and the natural products present in this plant are interesting targets for study in the human central nervous system. In 2014, Wang and colleagues reported the isolation of (−)-pegaharmaline A from the seeds of *P. harmala*[7] (Fig. 1). Pegaharmaline A comprises β-carboline and vasicinone scaffolds fused *via* a spiroaminal, a rare example of a natural product that contains a single, enantioenriched spirocentre.[8]

The biosynthesis of pegaharmaline A was proposed by the isolation chemists[7] to commence with vasicinone undergoing a dehydration, oxidation and enzyme-mediated dimethylation sequence to form pyrroloquinazoline **1**, which could presumably also originate from isovasicinone (Scheme 1). From here, the union of **1** and 6-methoxytryptamine (**2**) generates pegaharmaline A, but mechanistic details for this final step were not provided. We propose that this reaction could proceed *via* two pathways, both commencing with attack of tryptamine onto C1 in **1**. In path A, an amidinium-type intermediate (**3**) undergoes a Pictet–Spengler type reaction to form pegaharmaline A. Alternatively, the initial C–N bond forming step triggers ring opening to enamide **4** that upon spirocyclisation forms the natural product (path B). As pegaharmaline A is chiral, an enzyme is likely to be involved during assembly of the spirocentre.

Results and discussion

The unique molecular architecture and intriguing biosynthesis of pegaharmaline A led us to embark on a biomimetic synthesis[9] in an effort to validate the proposal(s) outlined in Scheme 1. The pyrroloquinazoline **1** was readily prepared in a single step by stirring 2,3-dimethylmaleic anhydride (**5**) with anthranilamide (**6**) in acetic acid at elevated temperature (Scheme 2).

With **1** at hand, the biomimetic synthesis of pegaharmaline was attempted (Scheme 3A). Upon stirring **1** with 6-methoxy-

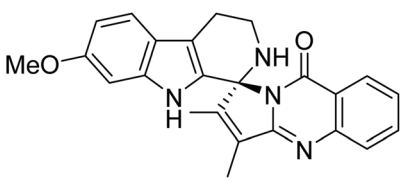

Fig. 1 (−)-Pegaharmaline A.

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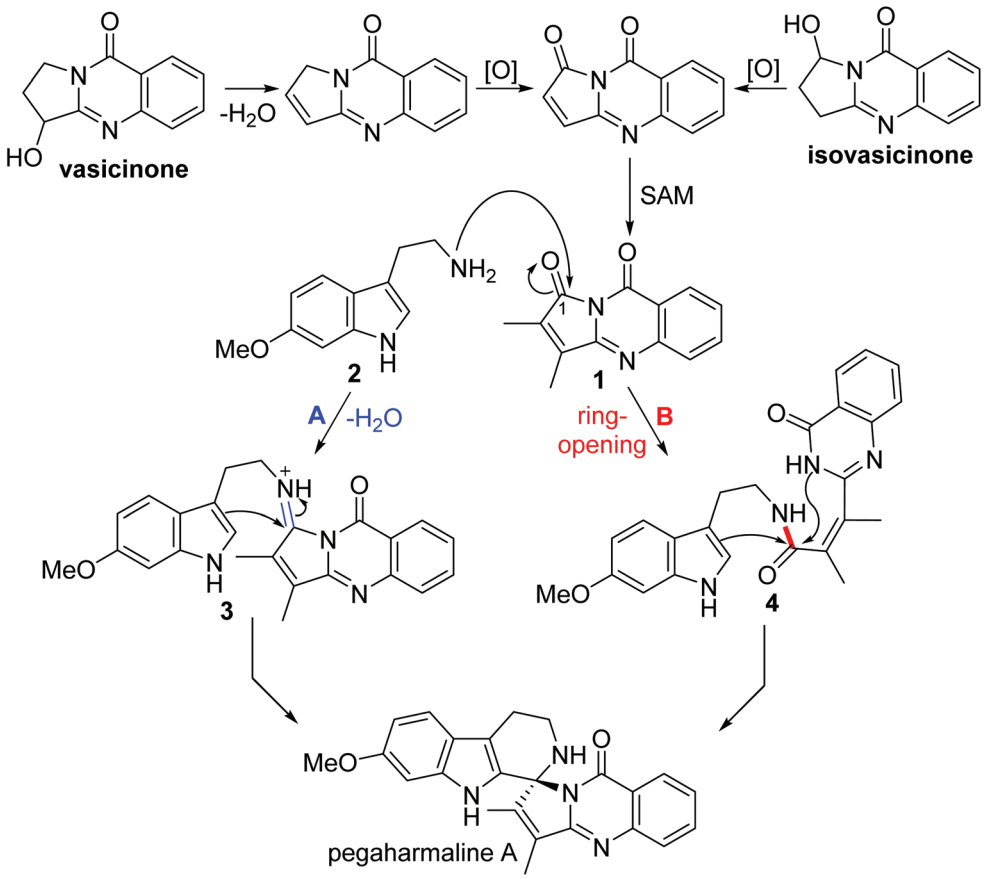
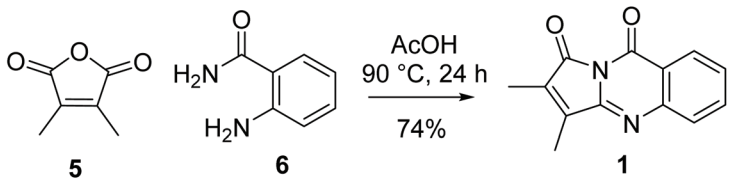
†Electronic supplementary information (ESI) available: NMR spectra for all novel compounds. CCDC 1859965 (**7**), 1859974 (**10**) and 2087701 (**23**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob02372a



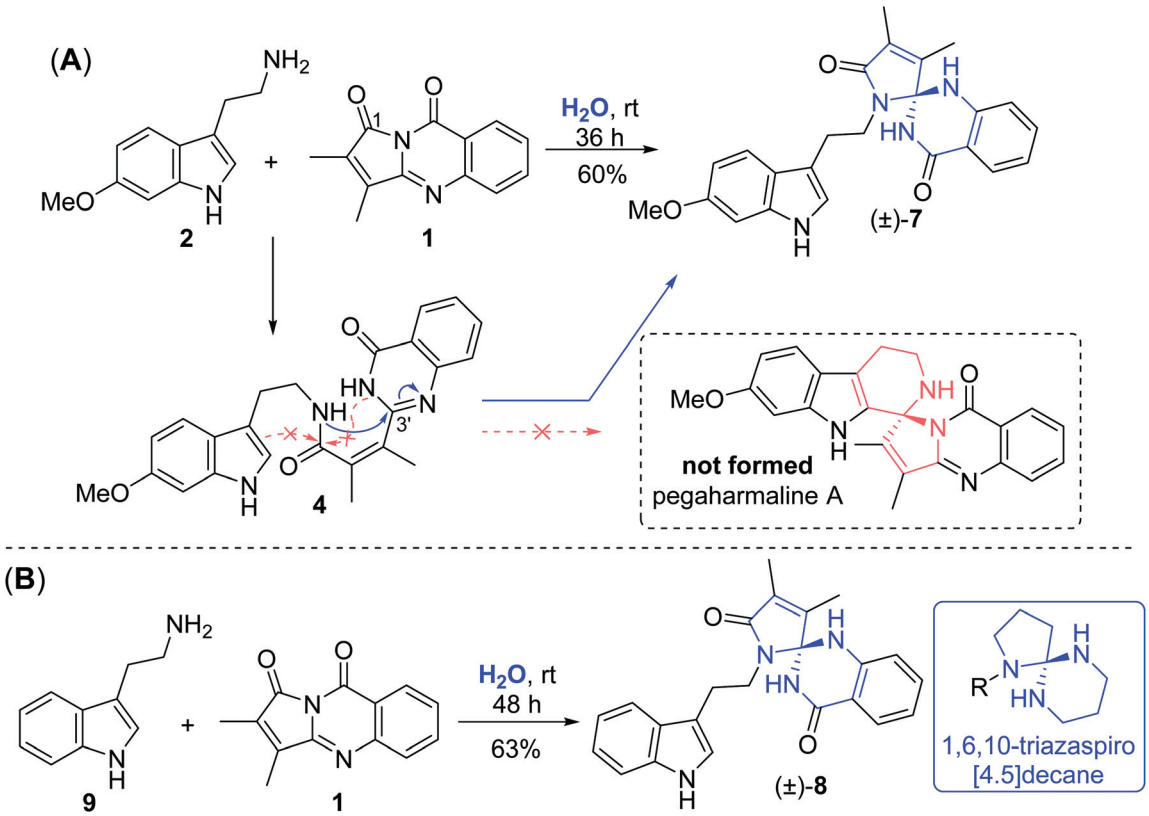
Scheme 1 Proposed biosynthesis of pegaharmaline A[7] (pathways A and B). SAM = *S*-adenosylmethionine.



Scheme 2 Synthesis of pyrroloquinazoline **1**.

tryptamine (**2**)[10] in the presence of several acids (TFA, HCl, *p*-TSA, AcOH) in water and organic solvents (THF, CH_2Cl_2, toluene), no reaction occurred, with more forcing conditions leading to degradation. However, upon performing the reaction in water at ambient temperature, compound (±)-**7** was formed. The same scaffold, (±)-**8**, was formed upon stirring tryptamine (**9**) and pyrroloquinazoline **1** in water (Scheme 3B), the structure of which was determined by X-ray crystallographic analysis, confirming the presence of a rare 1,6,10-triazaspiro[4.5]dec-7-ane[11] (Fig. 2). In these reactions, the ring-opened product **4** did not undergo the anticipated spirocyclisation to form pegaharmaline A (red arrows), but instead underwent a different cyclisation involving the amide attacking the adjacent quinazoline to install the triazaspiro[4.5]decane (blue arrows). While **1** is insoluble in water, tryptamines **2** and **9** are sparingly soluble, suggesting these reactions are mediated by a combination of in-water and on-water effects.[12–15] It is noteworthy that the ^{1}H and ^{13}C NMR spectroscopic data for **7** (and **8**) bear no resemblance to that reported for the natural product, ruling out structural reassignment at this stage. However, assuming that pyrroloquinazoline **1** is indeed present in *P. harmala*, its facile reaction with both tryptamines **2** and **9** under aqueous conditions at ambient temperature suggests **7** and **8** (or derivatives thereof) may be undiscovered natural products.

As the reaction of the putative pyrroloquinazoline precursor **1** with tryptamines **2** and **9** in water led to 1,6,10-triazaspiro[4.5]dec-7-anes **7** and **8**, an alternative biosynthesis of pegaharmaline A under anhydrous conditions was considered (Scheme 4). Loss of water from the putative biosynthetic pre-



Scheme 3 Reaction of pyrroloquinazoline **1** with (A) 6-methoxytryptamine (**2**) and (B) tryptamine (**9**).

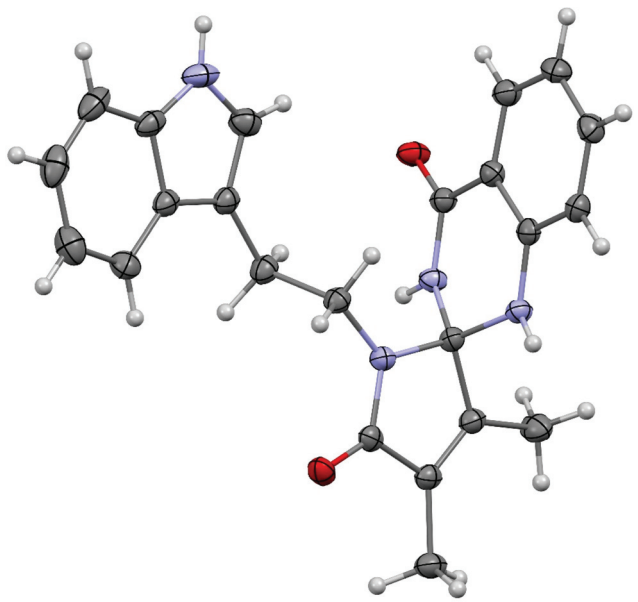
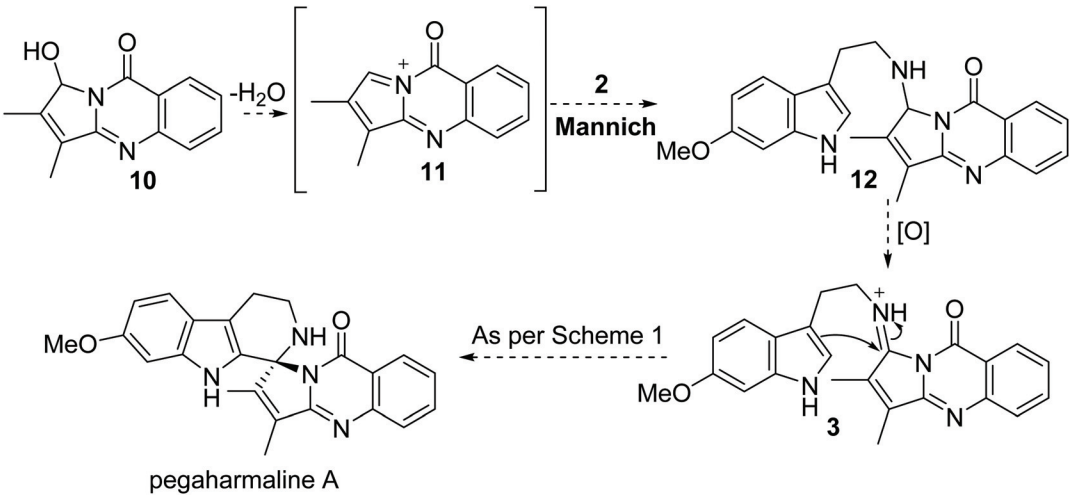


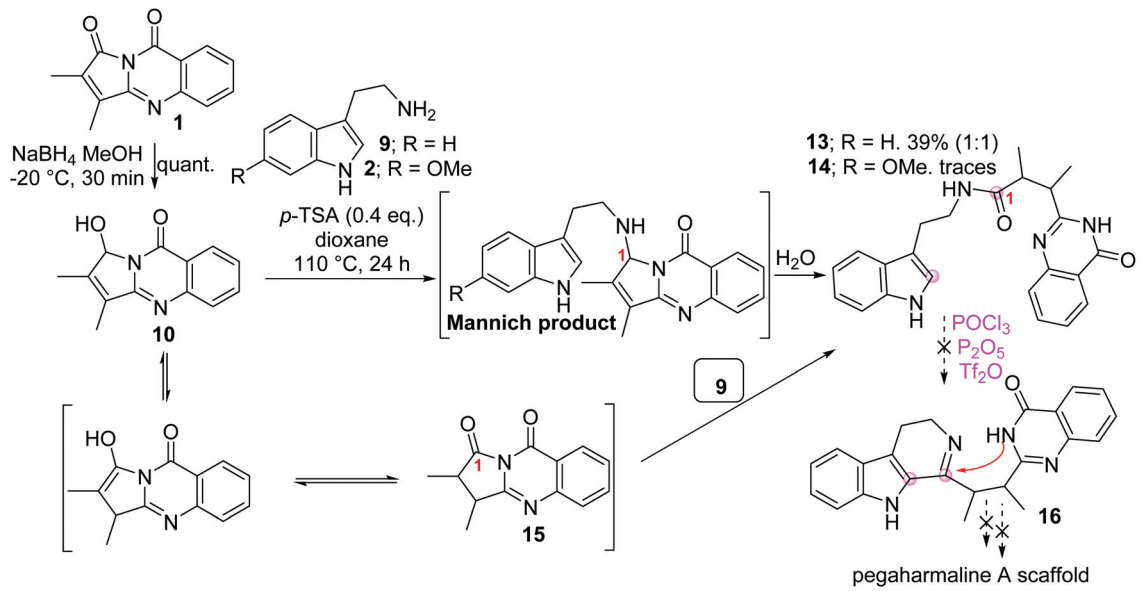
Fig. 2 Molecular structure of (±)-**8** (CCDC 1859965†). Atomic displacement parameters are drawn at 50% probability level.

cursor dehydrodimethylisovasicinone **10** would lead to *N*-acyliminium **11** that upon Mannich reaction with 6-methoxytryptamine (**2**) would give aminal **12**. From here, oxidation would form the same amidinium **3** invoked in the initial proposal (*cf.* Scheme 1).

Synthetic efforts towards the alternative biomimetic proposal are shown in Scheme 5. Chemoselective reduction of pyrroloquinazoline **1** was achieved with sodium borohydride at −20 °C, affording dehydrodimethylisovasicinone **10**, as confirmed by X-ray crystallographic analysis (Fig. 3). The reaction between **10** and tryptamine (**9**) required forcing conditions to proceed; *p*-TSA in dioxane at elevated temperature formed **13** (dr 1 : 1), not the Mannich product invoked in Scheme 4. Reaction of **10** with 6-methoxytryptamine (**2**) gave trace amounts of **14** (^{1}H NMR spectroscopy) due to the instability of **2** under the harsh reaction conditions. The formation of **13** mirrors the results obtained during the first approach; the C1–N bond is labile and the Mannich product undergoes facile hydrolysis. It is also plausible 13 forms *via* isomerisation-tautomerism of **10** to **15** followed by reaction with tryptamine (**9**) and C1–N cleavage. Attempts to cyclise **13** to the dihydro-β-carboline **16** under Bischler–Napieralski conditions ($POCl_3$, P_2O_5, Tf_2O) were unfortunately unsuccessful, with rapid degradation occurring in all cases. Although this cyclisation failed, the proposed spirocyclisation of a dihydro-β-carboline formed the basis of a third biosynthesis postulate (Scheme 6). A Pictet–Spengler reaction between dimethylisovasicinone **17** and 6-methoxytryptamine (**2**) would form the tetrahydro-β-carboline **18**. From here, oxidation to the dihydro-β-carboline



Scheme 4 Alternative biosynthetic proposal.



Scheme 5 Mannich reaction between **10** and tryptamines **9** (successful) and **2** (unsuccessful).

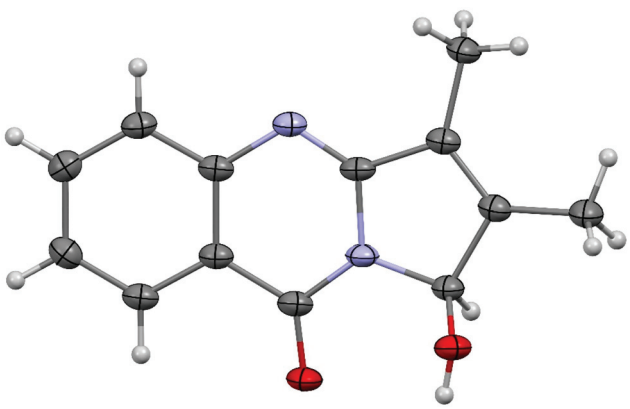
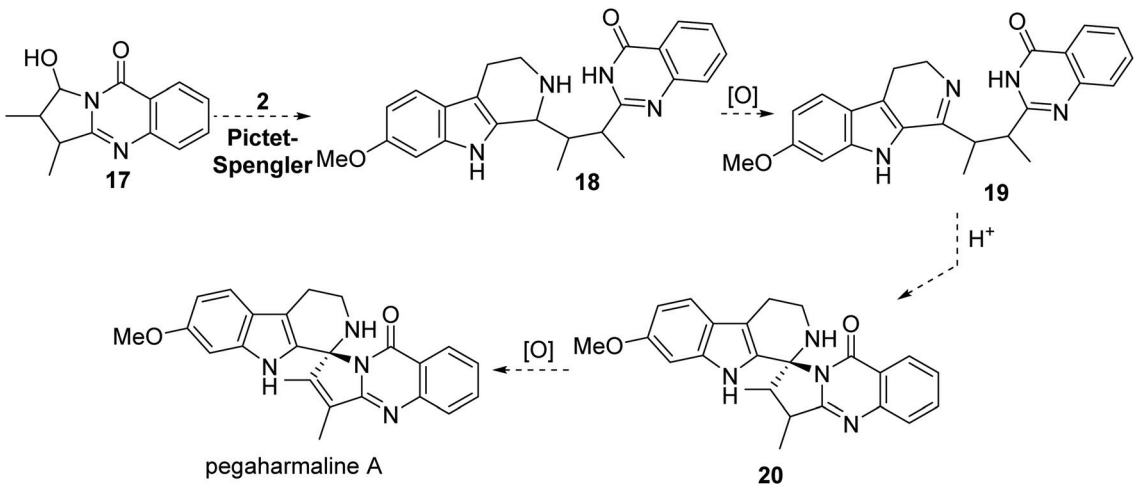


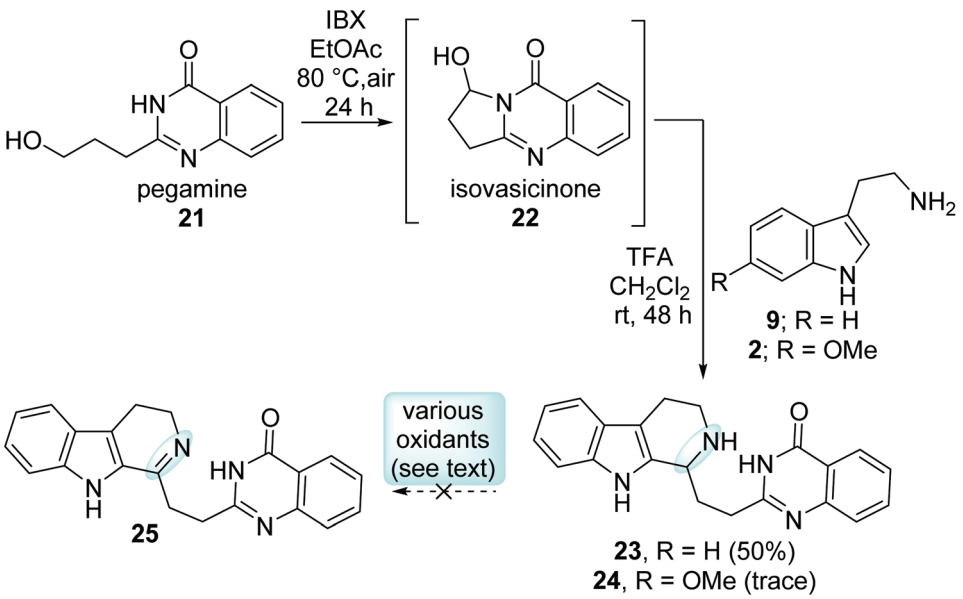
Fig. 3 Molecular structure of **10** (CCDC 1859974†). Atomic displacement parameters are drawn at 50% probability level.

19 followed by spirocyclisation would give the pegaharmaline scaffold **20**. Selective dehydrogenation would then lead to pegaharmaline A.

Synthetic efforts towards the third-generation biomimetic approach using the model isovasicinone (**22**) are shown in Scheme 7. The *P. harmala*-derived alkaloid pegamine (**21**)[16] underwent IBX-mediated oxidation to give isovasicinone (**22**; cyclic tautomer by ^{1}H NMR spectroscopy) that was used immediately in the subsequent Pictet–Spengler reaction with tryptamine (**9**), affording the tetrahydro-β-carboline **23**, as confirmed by XRD analysis (Fig. 4). The analogous Pictet–Spengler reaction of **22** and 6-methoxytryptamine (**2**) afforded trace amounts of **24**, again attributed to the instability of **2** under acidic conditions. With tetrahydro-β-carboline **23** in hand, its selective dehydrogenation to the dihydro-β-carboline **25** was



Scheme 6 Third-generation biomimetic approach.



Scheme 7 Pictet–Spengler reaction between isovasicinone and tryptamines **9** (successful) and **2** (unsuccessful).

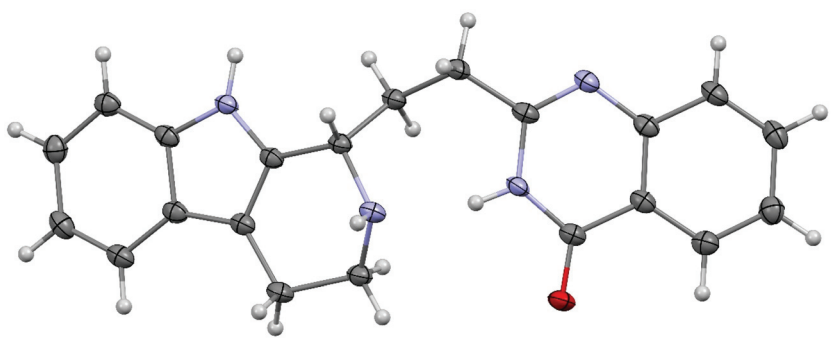


Fig. 4 Molecular structure of **23** (CCDC 2087701†). Atomic displacement parameters are drawn at 50% probability level.

attempted. A variety of oxidation conditions reported to selectively oxidise tetrahydro-β-carbolines to dihydro-β-carbolines were trialed, including diisopropyl azodicarboxylate,[17] *N*-bromosuccinimide (NBS),[18] CuCl–air,[19] I_2–H_2O_2,[20] IBX[21] but all resulted in either no reaction or degradation. Standard dehydrogenating agents including Pd/C, MnO_2 and DDQ were also attempted, but again with no success. Given we were unable to access the dihydro-β-carboline **25** (or **19**; *cf.* Scheme 6), the final spirocyclisation step could not be attempted.

Conclusions

In summary, we have described synthetic efforts to validate three distinct biomimetic proposals for pegaharmaline A. The first, proposed by the isolation chemists, involved reaction between pyrroloquinazoline **1** and tryptamines **2** and **9**, which led to the unique 1,6,10-triazaspiro[4.5]dec-7-ane scaffolds **7** and **8**, not pegaharmaline A. A second approach focused on a proposed Mannich reaction between tryptamine and the iminium ion-derived from dehydrodimethylisovasicinone **10**, led to the ring opened product **13**, suggesting the anticipated Mannich product was hydrolytically labile or the dehydrodimethylisovasicinone precursor underwent isomerisation-tautomerism prior to reaction with tryptamine. Attempts to convert the ring opened product **13** to the dihydro-β-carboline **16** using a Bischler–Napieralski reaction were unsuccessful. A final approach was based on the Pictet–Spengler reaction between isovasicinone (**22**) and tryptamine (**9**). While this was successful, the resulting tetrahydro-β-carboline **23** could not be dehydrogenated to the dihydro-β-carboline **25**. Overall, these biomimetic synthetic studies towards pegaharmaline A infer an alternative pathway may be operating, providing the foundations for ongoing biomimetic synthesis studies. Moreover, as tryptamines and (iso)vasicinones are abundant throughout Nature, the reactivity of vasicinone derivatives (**1**, **10**, **22**) towards tryptamines described herein suggests the resulting scaffolds (**7**, **8**, **13**, **23**; or derivatives thereof) may be undiscovered natural products.

Experimental procedures

Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were used as supplied. Dioxane and DMSO were dried using an LC Technology Solutions Inc. SP-1 solvent purification system under an atmosphere of dry nitrogen. All reactions were routinely carried out in oven-dried glassware under a nitrogen atmosphere unless otherwise stated. Reactions that required heating were performed using a stainless-steel heating mantle. Analytical thin layer chromatography was performed using silica plates and compounds were visualized at 254 and/or 360 nm ultraviolet irradiation followed by staining ethanolic vanillin solution. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were obtained using a PerkinElmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). NMR spectra were recorded on a Bruker DRX400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/TMS solvent, or the residual methanol (δ 3.31 ppm), pyridine (δ 8.74, 7.58, 7.22 ppm), chloroform (δ 7.26 ppm) or DMSO (δ 2.50 ppm) peaks. The ^{13}C NMR values were referenced to the residual methanol (δ 49.0 ppm), pyridine (δ 150.3, 136.0, 124.0 ppm), chloroform (δ 77.1 ppm) or DMSO (δ 39.5 ppm) peaks. ^{13}C NMR values are reported as chemical shift δ and assignment. ^1H NMR shift values are reported as chemical shift δ, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), relative integral, coupling constant (J in Hz) and assignment. Assignments are made with the aid of COSY, NOESY, ROESY, HMBC and edited HSQC experiments. All experiments were conducted at 298 K. Conventional NMR tubes (5 mm diameter, Norell) using a sample volume of 500 μL were used. High resolution mass spectra were obtained on a Bruker microOTOF mass spectrometer, with electrospray ionisation using a capillary voltage of 4500 V for positive mode and 3200 V for negative mode. Samples were dissolved in an appropriate solvent (DMSO, DCM, MeOH or MeCN) and diluted to a nominal concentration of 3 μg mL^{-1} using either MeOH or MeCN, prior to direct infusion into the instrument. X-ray diffraction measurements of single crystals were performed on a Rigaku Oxford Diffraction XtaLAB-Synergy-S single-crystal diffractometer with a PILATUS 200 K hybrid pixel array detector using Cu Kα radiation (λ = 1.54184 Å). The data were processed with the SHELX2018-3 and Olex2 software packages.[22] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted at calculated positions or located directly and refined with a riding model or without restrictions. Mercury 2020.3.1[23] was used to visualize the molecular structure. Crystal growth for X-ray crystallographic analysis purposes was achieved using slow evaporation or slow vapour diffusion.

2,3-Dimethylpyrrolo[2,1-*b*]quinazoline-1,9-dione (1)

A solution of 2,3-dimethylmaleic anhydride (695 mg, 5.51 mmol) in glacial acetic acid (5.0 mL) was added dropwise to a stirred solution of anthranilamide (500 mg, 5.51 mmol) in glacial acetic acid (5.0 mL) and the reaction mixture stirred at 90 °C for 24 h. After cooling, water (5.0 mL) was added and the precipitate was collected by filtration, washed well with water and dried under vacuum to give the *title compound* (921 mg, 4.08 mmol, 74%) as a pale yellow solid; mp 183.1–184.3 °C; ν_{max} (neat)/cm^{-1} 1697, 1651, 1627, 1311, 1299; δ_H (400 MHz, DMSO-d_6) 8.15 (1 H, dd, J 7.9, 1.3, ArH), 7.83 (1 H, ddd, J 7.3, 1.5, ArH), 7.72 (1 H, d, J 8.0, ArH), 7.56 (1 H, td, J 7.8, 1.2, ArH), 2.14 (3 H, d, J 1.2, Me), 1.95 (3 H, d, J 1.2, Me); δ_C (100 MHz, DMSO-d_6) 167.0 (C), 155.9 (C), 153.5 (C), 146.3 (C),

142.5 (C═C), 135.3 (CH), 133.8 (C═C), 128.5 (CH), 128.4 (CH), 127.3 (CH), 122.4 (C), 9.1 (Me), 8.5 (Me); HRMS (ESI) $[M + Na]^+$ found: 249.0639 $[C_{13}H_{10}N_2O_2 + Na]^+$ requires: 249.0634.

(±)-1-(2-(6-Methoxy-1*H*-indol-3-yl)ethyl)-3,4-dimethyl-1′*H*-spiro[pyrrole-2,2′-quinazoline]-4′,5(1*H*,3′*H*)-dione (7)

To a solution of pyrroloquinazoline **1** (50.0 mg, 0.221 mmol) in water (2.5 mL) was added 6-methoxytryptamine[10] (50.5 mg, 0.265 mmol) and the reaction mixture was stirred at room temperature for 48 h. Water (5.0 mL) was added and the solution extracted with ethyl acetate (4 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was washed with cold dichloromethane and the solid collected to give the *title compound* (54.8 mg, 0.131 mmol, 60%) as an orange solid; mp 147.8–149.0 °C; ν_{max} (neat)/cm^{-1} 1651, 1623, 1608, 816, 756; δ_H (400 MHz, DMSO-d_6) 10.52 (1 H, br s, NH), 8.54 (1 H, d, *J* 1.6, NH), 7.75 (1 H, dd, *J* 8.0, 1.6, ArH), 7.52 (1 H, d, *J* 1.5, NH), 7.38–7.34 (1 H, m, ArH), 6.83–6.79 (2 H, m, 2 × ArH), 6.77 (2 H, dd, *J* 4.4, 2.2, 2 × ArH), 6.71 (1 H, d, *J* 8.6, ArH), 6.44 (1 H, dd, *J* 8.6, 2.3, ArH), 3.71 (3 H, s, OMe), 3.34–3.26 (1 H, m, ½ × CH$_2$ obscured by residual water peak), 3.17 (1 H, td, *J* 12.9, 5.2, ½ × CH$_2$), 2.84–2.76 (1 H, m, ½ × CH$_2$), 2.73–2.65 (1 H, m, ½ × CH$_2$), 1.88 (3 H, d, *J* 1.2, Me), 1.78 (3 H, d, *J* 1.2, Me); δ_C (100 MHz, DMSO-d_6) 168.0 (C), 162.9 (C), 155.4 (C), 148.9 (C), 146.2 (C), 136.8 (C), 134.0 (CH), 127.7 (C), 127.1 (CH), 121.11 (C), 121.10 (CH), 118.4 (CH), 117.3 (CH), 113.6 (CH), 111.2 (C), 111.1 (C), 108.5 (CH), 94.3 (CH), 86.7 (C), 55.1 (Me), 39.9 (CH$_2$ obscured by solvent peak, confirmed by DEPT135), 25.2 (CH$_2$), 9.9 (Me), 8.3 (Me); HRMS (ESI) $[M + Na]^+$ found: 439.1742 $[C_{24}H_{24}N_4O_3 + Na]^+$ requires: 439.1741.

(±)-1-(2-(Indol-3-yl)ethyl)-3,4-dimethyl-1′*H*-spiro[pyrrole-2,2′-quinazoline]-4′,5(1*H*,3′*H*)-dione (8)

To a solution of **1** (50.0 mg, 0.220 mmol) in water (2.5 mL) was added tryptamine (42.5 mg, 0.270 mmol) and the reaction mixture was stirred at room temperature for 48 h. Water (5.0 mL) was added and the solution extracted with ethyl acetate (4 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo.* The crude material was washed with cold dichloromethane and the remaining solid collected to give the *title compound* (54.0 mg, 0.139 mmol, 63%) as a colourless solid; mp decomposed at 202.5 °C; ν_{max} (neat)/cm^{-1} 3233, 1695, 1636, 1611, 739; δ_H (400 MHz, DMSO-d_6) 10.74 (1 H, br s, NH), 8.55 (1 H, br s, NH), 7.77 (1 H, dd, *J* 8.0, 1.5, ArH), 7.54 (1 H, br s, NH), 7.37 (1 H, t, *J* 7.7, ArH), 7.26 (1 H, d, *J* 8.2, ArH), 6.99 (1 H, t, *J* 7.5, ArH), 6.92 (1 H, d, *J* 2.2, ArH), 6.87 (1 H, d, *J* 7.8, ArH), 6.83–6.77 (3 H, m, ArH), 3.37–3.29 (1 H, m, CH$_2$), 3.24–3.16 (1 H, m, CH$_2$), 2.90–2.82 (1 H, m, CH$_2$), 2.79–2.71 (1 H, m, CH$_2$), 1.89 (3 H, d, *J* 1.1, Me), 1.78 (3 H, d, *J* 1.1, Me); δ_C (100 MHz, DMSO-d_6) 168.0 (C), 162.9 (C), 148.9 (C), 146.2 (C), 136.1 (C), 134.0 (CH), 127.7 (C), 127.1 (CH), 126.7 (C), 122.6 (CH), 120.8 (CH), 118.2 (CH), 117.9 (CH), 117.3 (CH), 113.7 (CH), 111.3 (CH), 111.15 (C), 111.11 (C), 86.7 (C), 39.9 (CH$_2$ obscured by solvent peak), 25.2 (CH$_2$), 10.0 (Me), 8.4 (Me); HRMS (ESI) $[M + Na]^+$ found: 409.1631 $[C_{23}H_{22}N_4O_2 + Na]^+$ requires: 409.1635.

(±)-1-Hydroxy-2,3-dimethylpyrrolo[2,1-*b*]quinazolin-9(1*H*)-one (10)

To a solution of pyrroloquinazoline **1** (500 mg, 2.21 mmol) in methanol (50 mL) cooled to −20 °C was added sodium borohydride (125 mg, 3.32 mmol) and the reaction mixture stirred at this temperature for 30 min. The reaction was diluted with water (50 mL) and extracted with dichloromethane (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the *title compound* (502 mg, 2.20 mmol, 100%) as a colourless solid; mp 204.7 °C; ν_{max} (neat)/cm^{-1} 3077, 1676, 1600, 1080, 770; δ_H (400 MHz, DMSO-d_6) 8.14 (1 H, dd, *J* 7.9, 1.4, ArH), 7.80–7.76 (1 H, m, ArH), 7.66 (1 H, d, *J* 8.0, ArH), 7.48 (1 H, t, *J* 7.5, ArH), 7.10 (1 H, d, *J* 8.1, CHOH), 6.02 (1 H, d, *J* 8.1, CHOH), 2.00 (3 H, s, Me), 1.97 (3 H, s, Me); δ_C (100 MHz, DMSO-d_6) 158.5 (C), 157.5 (C), 149.1 (C), 148.9 (C), 134.2 (CH), 127.1 (CH), 127.0 (C), 126.2 (CH), 126.0 (CH), 120.9 (C), 84.1 (CHOH), 11.3 (Me), 8.3 (Me); HRMS (ESI) $[M + Na]^+$ found: 251.0790 $[C_{13}H_{12}N_2O_2 + Na]^+$ requires: 251.0791.

(±) *N*-(2-(Indol-3-yl)ethyl)-2-methyl-3-(4-oxo-3,4-dihydroquinazolin-2-yl)butanamide (13)

To a solution of pyrroloquinazolinone **10** (50.0 mg, 0.220 mmol) and tryptamine (42.1 mg, 0.260 mmol) in dioxane (2.5 mL) was added PTSA·H_2O (16.7 mg, 0.088 mmol). The reaction mixture was then heated under reflux for 24 h. The mixture was cooled to room temperature, diluted with water (5.0 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography eluting with ethyl acetate–petroleum ether (1 : 1) then increasing to 100% ethyl acetate gave the *title compound* (34 mg, 0.086 mmol, 39%) as a 1 : 1 mixture of diastereomers (**13A** and **13B**) that were separated by flash chromatography eluting with ethyl acetate–petroleum ether (1 : 1) for characterisation purposes. The relative stereochemistry of the individual diastereomers could not be unequivocally determined.

Diastereomer 13A: yellow solid; mp 181.3 °C; ν_{max} (neat)/cm^{-1} 3291, 3234, 1686, 1636, 1608; δ_H (400 MHz, DMSO-d_6) 12.23 (1 H, br s, NH), 10.79 (1 H, br s, NH), 8.19 (1 H, br t, *J* 5.6, NH), 8.09 (1 H, dd, *J* 7.9, 1.3, ArH), 7.76–7.80 (1 H, m, ArH), 7.58 (1 H, d, *J* 8.1, ArH), 7.55 (1 H, d, *J* 7.9, ArH), 7.46 (1 H, t, *J* 7.5, ArH), 7.33 (1 H, d, *J* 8.0, ArH), 7.15 (1 H, d, *J* 2.1, ArH), 7.06 (1 H, t, *J* 7.2, ArH), 6.98 (1 H, t, *J* 7.3, ArH), 3.34–3.47 (2 H, m, CH$_2$), 2.82–2.92 (3 H, m, 1 × CH$_2$ and 1 × CH), 2.71–2.75 (1 H, m, CH), 1.14 (3 H, d, *J* 6.7, Me), 0.91 (3 H, d, *J* 6.7, Me); δ_C (100 MHz, DMSO-d_6) 173.9 (C), 161.7 (C), 160.3 (C), 149.0 (C), 136.2 (C), 134.3 (CH), 127.2 (C), 126.8 (CH), 126.0 (CH), 125.8 (CH), 122.6 (CH), 120.9 (C), 120.9 (CH), 118.2 (CH), 118.2 (CH), 111.7 (C), 111.3 (CH), 44.1 (CH), 42.0 (CH), 39.3 (CH$_2$ obscured by solvent peak, confirmed by DEPT135),

25.2 (CH_2), 18.0 (Me), 16.6 (Me); HRMS (ESI) $[M + Na]^+$ found: 411.1793 $[C_{23}H_{24}N_4O_2 + Na]^+$ requires: 411.1791.

Diastereomer 13B: yellow solid; mp 79.7–81.0 °C; ν_{max} (neat)/cm^{-1} 3297, 2922, 1656, 1606; δ_H (400 MHz, DMSO-d_6) 12.20 (1 H, s, NH), 10.74 (1 H, s, NH), 8.07 (1 H, dd, *J* 7.9, 1.2, ArH), 7.95 (1 H, t, *J* 5.8, NH), 7.72–7.77 (1 H, m, ArH), 7.58 (1 H, d, *J* 7.7, ArH), 7.44 (1 H, ddd, *J* 8.1, 7.2, 1.1, ArH), 7.36 (1 H, d, *J* 7.9, ArH), 7.30 (1 H, d, *J* 8.1, ArH), 7.01–7.06 (2 H, m, ArH), 6.93 (1 H, ddd, *J* 7.9, 7.1, 1.0, ArH), 3.40–3.25 (1 H, m, CH_2), 3.12–3.21 (1 H, m, CH_2), 2.94–3.01 (1 H, m, CH), 2.80–2.85 (1 H, m, CH), 2.57–2.61 (2 H, m, CH_2), 1.21 (3 H, d, *J* 7.0, Me), 1.07 (3 H, d, *J* 7.0, Me); δ_C (100 MHz, DMSO-d_6) 174.6 (C), 161.7 (C), 160.4 (C), 148.9 (C), 136.2 (C), 134.2 (CH), 127.1 (C), 126.9 (CH), 125.9 (CH), 125.6 (CH), 122.4 (CH), 120.9 (CH), 118.1 (2 CH), 111.7 (C), 111.3 (CH), 43.0 (CH), 41.4 (CH), 39.2 (CH_2 obscured by solvent peak, confirmed by DEPT135), 25.2 (CH_2), 15.9 (Me), 14.9 (Me), 1 × quaternary C not observed; HRMS (ESI) $[M + Na]^+$ found: 411.1786 $[C_{23}H_{24}N_4O_2 + Na]^+$ requires: 411.1791.

(±)-2-(2-(2,3,4,9-Tetrahydropyrido[3,4-*b*]indol-1-yl)ethyl) quinazolin-4(3*H*)-one (23)

To a solution of pegamine **21**[16] (100 mg, 0.490 mmol) in ethyl acetate (3.5 mL) was added 2-iodoxybenzoic acid (411 mg, 1.50 mmol) and the reaction mixture was then heated at reflux for 24 h. Upon cooling, the reaction mixture was filtered, the filtrate collected and concentrated *in vacuo* to give isovasicinone (~100 mg) that was used immediately in the next step without further purification. A solution of crude isovasicinone **22** (100 mg, 0.490 mmol) and tryptamine (54.8 mg, 0.340 mmol) in TFA-dichloromethane (5% v/v, 0.83 mL) was stirred at room temperature for 48 h, followed by concentrating the reaction mixture *in vacuo*. Aqueous sodium hydroxide (1 M, 0.50 mL) was added and the solution extracted with dichloromethane (5 × 5.0 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography eluting with ammonium hydroxide : methanol : dichloromethane (0.5 : 5 : 94.5) to give the *title compound* (83.5 mg, 0.240 mmol, 50%) as a brown solid; mp decomposition at 210.2 °C; ν_{max} (neat)/cm^{-1} 3313, 1607, 1470, 1450, 742; δ_H (300 MHz, DMSO-d_6) 10.72 (1 H, br s, NH), 8.08 (1 H, dd, *J* 7.9, 1.3, ArH), 7.77 (1 H, ddd, *J* 8.5, 7.2, 1.5, ArH), 7.60 (1 H, d, *J* 8.0, ArH), 7.45 (1 H, t, *J* 7.5, ArH), 7.36 (1 H, d, *J* 7.6, ArH), 7.28 (1 H, d, *J* 7.9, ArH), 7.01 (1 H, t, *J* 7.0, ArH), 6.93 (1 H, t, *J* 7.4, ArH), 4.07 (1 H, d, *J* 6.6, CH), 3.16 (1 H, dt, *J* 12.3, 5.1, CH_2), 2.94–2.85 (1 H, m, CH_2), 2.81 (2 H, t, *J* 7.6, CH_2), 2.63–2.58 (2 H, m, CH_2), 2.37 (1 H, dtd, *J* 11.5, 7.6, 3.7, CH_2), 2.08 (1 H, td, *J* 16.5, 7.9, CH_2), 2 × NH not observed; δ_C (75 MHz, DMSO-d_6) 161.8 (C), 157.8 (C), 148.9 (C), 136.6 (C), 135.7 (C), 134.2 (CH), 127.0 (C), 126.6 (CH), 125.8 (CH), 125.7 (CH), 120.8 (C), 120.4 (CH), 118.1 (CH), 117.4 (CH), 110.9 (CH), 107.5 (C), 51.5 (CH), 41.3 (CH_2), 31.3 (CH_2), 30.9 (CH_2), 22.2 (CH_2); HRMS (ESI) $[M + Na]^+$ found: 367.1517 $[C_{21}H_{20}N_4O + Na]^+$ requires: 367.1529.

Conflicts of interest

There are no conflicts of interest to declare.

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