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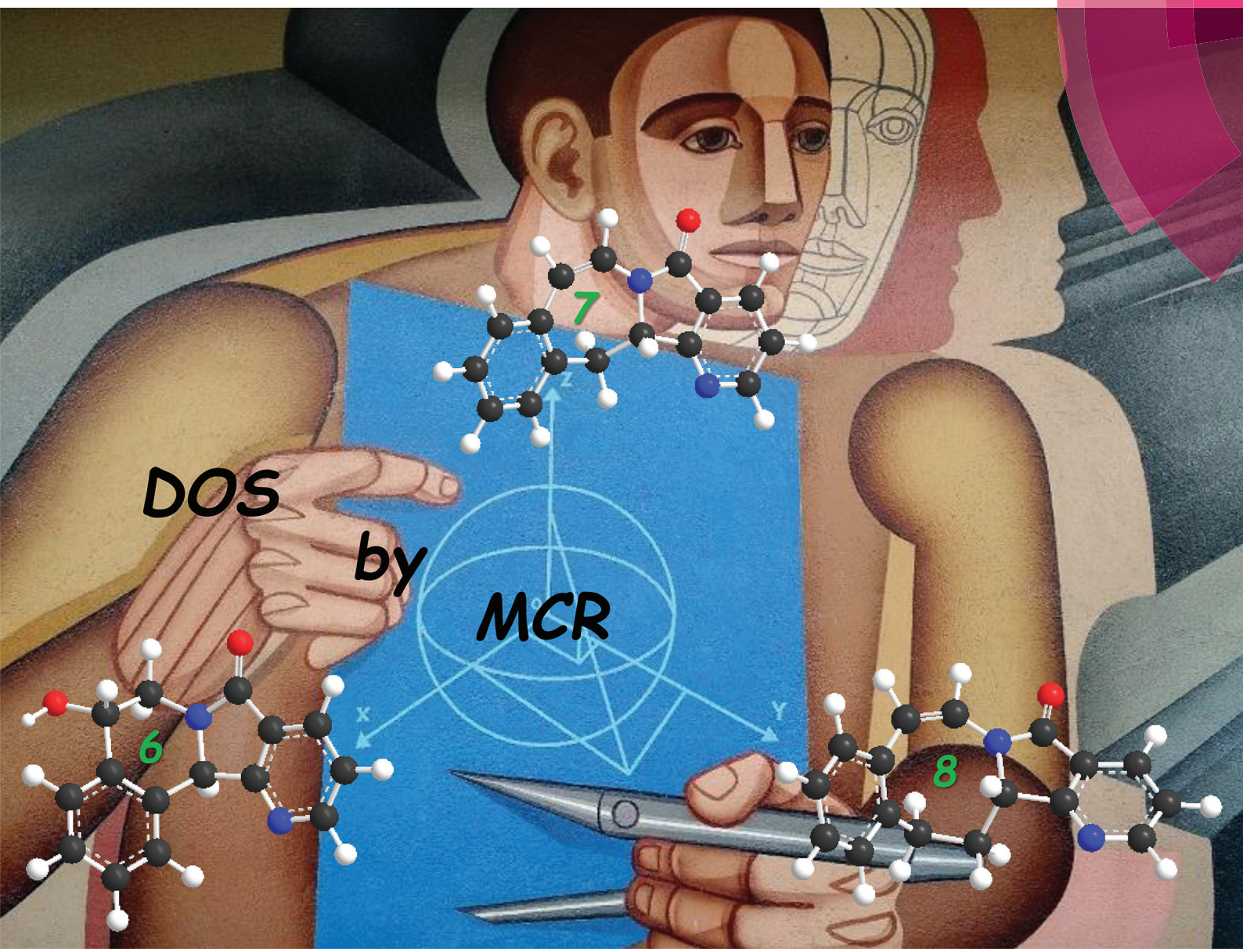


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PAPER

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# An efficient Ugi-3CR/aza Diels–Alder/Pomeranz–Fritsch protocol towards novel aza-analogues of (±)-nuevamine, (±)-lennoxamine and magallanesine: a diversity oriented synthesis approach†

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A rapid and efficient synthesis of a series of (±)-nuevamine, (±)-lennoxamine and magallanesine aza analogues is described. The synthetic strategy involves Ugi-3CR and two further condensation processes, aza-Diels–Alder cycloaddition and the Pomeranz–Fritsch reaction. The variation of the chain-size in aldehyde moieties provided structural diversity in only two operational reaction steps.

Amongst several heterocyclic alkaloids, natural products containing an isoindolin-1-one system such as (±)-nuevamine **1**,[1] (±)-lennoxamine **2**[2] and magallanesine **3**[3] (Fig. 1) are very important since their extensive occurrence in nature is known. Indeed, these nitrogen-containing heterocyclic compounds were first isolated from a plant native to South America known as michai (*Berberis darwinii Hook*).[3,4] These architecturally sophisticated structures include five-eight membered rings fused with different aromatic moieties and differently oxygenated substituents. Thus, analogues of these pentacyclic systems that incorporate an isoindolin[1,2-*a*]-5-one skeleton are of very high interest in pharmaceutical drug research due to their biological activity. Therefore, their unique structural features have recently attracted the attention of many organic research groups and various synthetic strategies have been carried out toward these attractive and synthetically challenging targets.

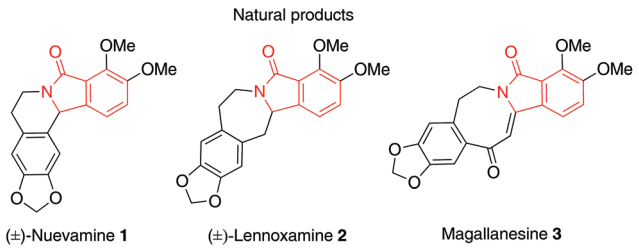


**Fig. 1** (±)-Nuevamine, (±)-lennoxamine and magallanesine.

(±)-Nuevamine (**1**) is the first naturally occurring isoindolo[1,2-*a*]isoquinolinone and therefore it is considered a single representative example of the category of isoquinoline alkaloids. The chemical structure of (±)-nuevamine (**1**) is very interesting from a pharmacological perspective, due to the potential and promising biological activity of many of its analogues, for example as anti-inflammatory, anti-microbial, anti-leukemic, and anti-tumoral properties.[5] Many synthetic approaches have been developed to obtain (±)-nuevamine (**1**) and its analogues.[6–8] For example, Ramanathan *et al.*[9] reported the activation of an imide carbonyl group with trifluoromethane sulfonic acid to synthesise (±)-nuevamine (**1**). Recently, Kim and Min[10] have used different oxazolidinediones prepared stepwise to synthesize (±)-nuevamine (**1**) and some analogues *via* intramolecular Friedel–Crafts acylation.

(±)-Lennoxamine (**2**) is biogenetically related to protoberberines and usually considered as isoquinoline-based alkaloids. The main structural feature is the isoindolo[1,2-*b*][3]benzazepine

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unit embedded in its skeleton. Interestingly, the chemical structure of (±)-lennoxamine is constructed from the 3*H*-3-benzazepine moiety which has shown very relevant biological activity,[11] and additionally incorporates an isoindole moiety (also related to biological properties). However, (±)-lennoxamine (**2**) does not exhibit pharmacological properties. Nevertheless, the analogues of (±)-lennoxamine (**2**) that show sophisticated chemical structures with varied-size membered rings fused with chemically and environmentally different aromatic moieties contiguously and the incorporation of many functional groups have significantly attracted the attention of the synthetic community to investigate many more synthetic methodologies. Some synthetic approaches toward these analogues are electrophilic alkylation and photochemical reactions using enamides and vinyl azides.[12] Lately, Fuwa and Sasaki[13] have employed a catalytic hydrosilane reduction of enol ethers and carbamates for the total synthesis of (±)-lennoxamine (**2**). Kise and co-workers[14] have synthesised (±)-lennoxamine (**2**) *via* an electro-reductive intermolecular approach. Finally, Wang *et al.*[15] developed a new strategy to synthesise different analogues of (±)-lennoxamine (**2**) *via* intramolecular condensations between tertiary enamides and aldehydes.

Magallanesine is the first known isoindolobenzazocine alkaloid[3,16] which was first isolated by Shamma *et al.*[16] Since the total synthesis of magallanesine (and its analogues) is rather challenging, only a few research groups have managed to report it.[17] This kind of azocine or azepine compounds have attracted the attention of many synthetic chemists because of their very interesting membered-ring cores as well as their biological applications.[18] It has been reported that compounds containing an isoindolobenzazocine unit exhibit significant pharmacological activities such as antiviral, antileukemic, anticancer, and antiulcer.[3,17a] Thus, only a few synthetic efforts have been carried out to design and synthesise magallanesine analogues.[6–8]

Thus, the analogues of natural heterocyclic alkaloids (±)-nuevamine (**1**), (±)-lennoxamine (**2**) and magallanesine (**3**) that incorporate the isoindolo[1,2-*a*]-5-one system are very attractive due to the sophistication of their intrinsic chemistry and the potential pharmaceutical applications. Not surprisingly, there is huge development on different synthetic strategies to obtain these pentacyclic systems.[19] Additionally, nitrogen-containing heterocyclic compounds are important pharmacophores in drug design and synthesis, particularly pyridine derivatives, which are among the most frequently cited heterocyclic compounds.[20] The synthesis of fused pyridines have often been rather cumbersome and lengthy even for the simplest fused pyridines.[21] The inclusion of a nitrogen atom in their aromatic rings can provide the opportunity to modulate both, the pharmacodynamic and kinetic properties of pyrrolopyridines.[22] Particularly, several modified analogues of (±)-nuevamine (**1**) and (±)-lennoxamine (**2**) have been synthesised to evaluate their biological properties.[23,24]

Recently, we have focused on the synthesis of the aza-analogues of important natural products like (±)-nuevamine (**1**) using multicomponent reactions such as the Ugi-3CR combined with further cyclization processes, such as free radical-mediated alkylation,[25] Pictet–Spengler,[26] the oxidative Ugi-type reaction,[27] and Pummerer cyclization.[28] We are also interested in the preparation of compound libraries of cyclic analogues toward relevant synthetic anticancer agents in medical chemistry.[29] In this context and as part of some of our goals, we are very interested in the design and development of novel synthetic methodologies toward new heterocyclic compounds containing the pyrrolo[3,4-*b*]pyridine-5-one core, since it is considered as the aza-analogue of the isoindolin-1-one moiety. Thus, we herein describe a straightforward two-step strategy to synthesize a series of new aza-analogues of nuevamine **4**, lennoxamine **5** and magallanesine **6** (Fig. 2), based on isocyanide multicomponent reactions (I-MCR) and two further condensation processes.

The synthetic strategy (Scheme 1) involved a sequence of five processes in two operational reaction steps: Ugi-3CR; inter-

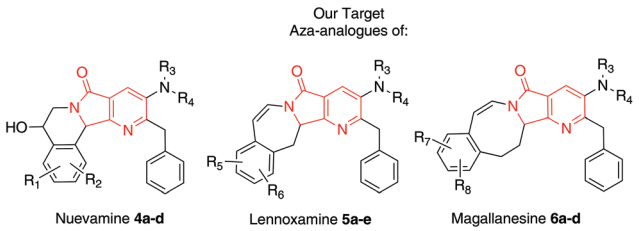
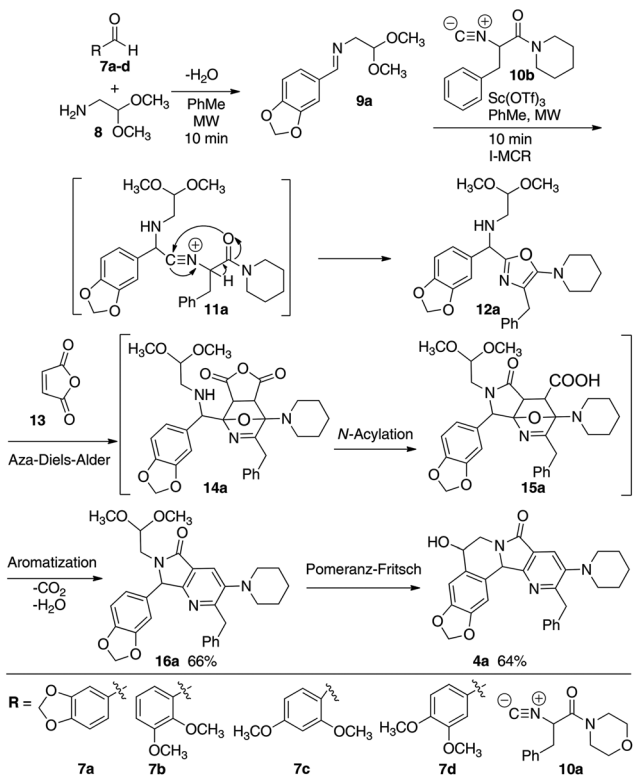



**Fig. 2** Aza-analogues of nuevamine, lennoxamine and magallanesine.




**Scheme 1** Synthesis of nuevamine aza-analogues **4a–d**.

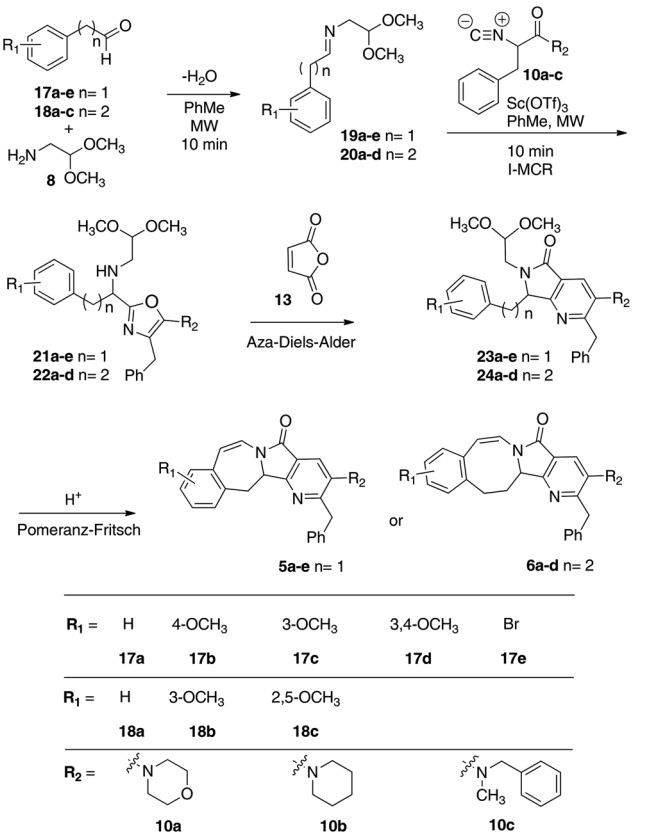
molecular aza-Diels–Alder; *N*-acylation; aromatization and Pomeranz–Fritsch cyclization. This strategy is based on the preparation of the isoindolo[1,2-*a*]-5-one system as an intermediate key for Pomeranz–Fritsch cyclization.

Dömling's amine **8** was chosen as a reagent containing a special functional group (protected aldehyde, 2,2-dimethoxyethylamine) to perform the final post-transformation processes *via* an intramolecular $S_NAr$ as Pomeranz–Fritsch cyclization. Then, the synthesis of the pyrrolo[3,4-*b*]pyridine-5-one series **16a–d** necessary to prepare the nuevamine aza-analogues was performed by three-component condensation of different benzaldehydes **7a–d**, Dömling's amine **8**, and two different isonitriles **10a–b** in dry toluene as a solvent, microwaves as a heat source and $Sc(OTf)_3$ as a catalyst. Stirring a solution containing benzo[*d*][1,3]dioxole-5-carbaldehyde **7a** and 2,2-dimethoxyethylamine **8** for 10 min at 65 °C in a sealed tube in a microwave reactor provided the imine intermediate **9a**, which reacted with the isonitrile **10b** to afford 5-amino-oxazole **12a** after ring-chain tautomerization. The Diels–Alder cycloaddition of **12a** as the aza-diene with maleic anhydride **13** as a dienophile provided, after 35 min in a microwave reactor, the pyrrolo[3,4-*b*]pyridine-5-one **16a** *via* the oxa-bridged intermediate **15a**, which spontaneously gave the desired compound in a triple cascade sequence: *N*-acylation, dehydration, and decarboxylation processes in a 66% overall yield, Scheme 1. In the second step, the pyrrolo[3,4-*b*]pyridine-5-one **16a** was cyclized in a good yield (64%) to the corresponding aza-analogue **4a** under the typical Pomeranz–Fritsch reaction conditions, under stirring (overnight) in strong acidic media (6 N of hydrochloric acid), Scheme 1. Three more examples (**4b–d**) were prepared in good yields (44, 45, 47% for the first step and 85, 73, 64% for the second step, respectively), using aldehydes **17b–d**, 2,2-dimethoxyethylamine **8** and the isonitrile **10a**, $Sc(OTf)_3$ and maleic anhydride **13**, Scheme 1.

The Diversity-Oriented Synthesis (DOS) has been a very important research area at the interface of organic synthesis and biochemical fields.[30] The essential point for DOS is that synthetic methods are needed to generate collections of small molecules with functional diversity and especially those having skeletons which can be found in natural products or drug-like molecules.[31] Perhaps the most promising and powerful methodology for the generation of new molecule collection by sequencing is multicomponent reactions[32–35] combined with appropriate subsequent transformations to increase molecular complexity and diversity.[36]

The scope of this methodology in DOS combining a MCR with intermolecular aza-Diels–Alder; *N*-acylation; aromatization and Pomeranz–Fritsch cyclization was evaluated by the inclusion of different series of 2-phenylacetaldehydes or 3-phenylpropanaldehydes as starting reagents instead of benzaldehydes to prepare the aza-analogues of lennoxamine **5a–e** and magallanesine **6a–d**, Scheme 2.

The synthesis of pyrrolo[3,4-*b*]pyridine-5ones series **23a–e** and **24a–d** was necessary to prepare the lennoxamine and magallanesine aza-analogues **5a–e** and **6a–d**. Thus, they reacted *via* condensation of different series of 2-phenylacetaldehydes or 3-phenylpropanaldehydes **17a–e** and **18a–c**, 2,2-dimethoxyethylamine **8**, $Sc(OTf)_3$, and the isonitriles series **10a–c** in dry toluene for 10 min at 65 °C (MW) in a sealed tube. First, it provided the imine intermediates **19a–e** and **20a–d**, which reacted with the isonitriles **10a–c** to afford the 5-amino-oxazole intermediates **21a–e** and **22a–d**, respectively, after heating for 30 min in a MW reactor. The aza Diels–Alder cycloaddition between the oxazoles **21a–e** and **22a–d**, and maleic anhydride **13** afforded, after heating for only 15 min in a MW reactor, the pyrrolopyridinones **23a–e** and **24a–d** in moderate yields (17–40% and 20–45%, respectively), Scheme 2.




**Scheme 2** Synthesis of lennoxamine and magallanesine aza-analogues **5a–e** or **6a–d**.

To prepare the targeted compounds **5a–e** and **6a–d**, the second step was achieved using the protocol for Pomeranz–Fritsch cyclization, employing sulphuric acid onto acetic acid as a solvent. The lennoxamine and magallanesine aza-analogues were prepared in moderate to good yields (30–74% and 62–80% yields, respectively), Scheme 2.

Finally, to evaluate the scope of this multicomponent process combined with intermolecular aza-Diels–Alder; *N*-acylation; aromatization and Pomeranz–Fritsch cyclization, we decided to include the second step in a full one-pot process to carry out the synthesis of the aza analogues of magallanesine **6a–d**. Under the established conditions that were previously applied for the two-step method, the aldehydes **18a–c**, 2,2-dimethoxyethylamine **8** and the isonitrile **10a**, and

$Sc(OTf)_3$ were placed in a MW tube using toluene as a solvent. Then, the mixture was irradiated for 30 min at 75 °C (MW). Maleic anhydride **13** was introduced and MW-irradiation was continued for additional 10 min at 85 °C. Then, the solvent was evaporated under reduced pressure and sulphuric acid onto acetic acid was added. The reaction mixture was stirred at room temperature for 60 min to afford the polyheterocycle series identified as the aza-analogues of magallanesine **6a–d** in moderate yields (14–20%) in a one-pot process (see ESI S30–S36† for further details). Only one example was prepared in the one-pot process in the case of the aza-analogues of lennoxamine (**5a**), with 8% of yield, using aldehyde **17a**, 2,2-dimethoxyethylamine **8**, isonitrile **10a**, $Sc(OTf)_3$ and maleic anhydride **13**.

As seen, we synthesized novel polyheterocycles, using a new combination, of known reactions: Ugi-3CR,[37] aza Diels–Alder (from 5-aminooxazoles),[38] aromatization (from *oxa*-bridged intermediates),[39] and Pomeranz–Fritsch cyclization (from masked aldehydes).[40] It is noteworthy that J. Zhu, H. Bienaymé and A. Dömling are the pioneers behind these processes.

## Conclusions

Thirteen new heterocyclic-compound analogues of natural alkaloids (±)-nuevamine, (±)-lennoxamine and magallanesine were successfully synthesised in good yields. Remarkably, the structural complexity of the final products can lead to future investigations on the evaluation of their biological activity and thus, some pharmaceutical applications can be explored. The synthetic strategy to obtain these alkaloid analogues was carried out in a one-pot manner since Hayashi[41] emphasised that this approach is very effective because many synthetic conversions and bond-forming steps can be performed in a single pot, reducing reaction times, minimizing chemical waste and providing a superior category of chemical-design efficiency. This reaction is atom economical since seven chemical bonds and three rings were formed and, only water and $CO_2$ were lost in this multicomponent domino process: Ugi-3CR, Diels–Alder–Alder cyclization and two intramolecular ring closures (lactamization and Pomeranz–Fritsch cyclization). Finally, the operational versatility and simplicity of the synthetic methodology here presented, along with good chemical yields, made from these novel heterocycle syntheses, a highly attractive approach in the challenging diversity-oriented parallel synthesis field.

## Experimental section

All compounds were characterized by $^1$H NMR, $^{13}$C NMR, DEPT-135, COSY, HSQC, HMBC, NOESY, IR, and HRMS. $^1$H and $^{13}$C NMR spectra were acquired on either, Bruker Advance III (500 or 400 MHz) spectrometers. The solvent was deuterated chloroform ($CDCl_3$). Chemical shifts are reported in parts per million ($\delta$/ppm). The internal reference for $^1$H NMR spectra is with respect to TMS at 0.0 ppm. The internal reference for $^{13}$C NMR spectra is with respect to $CDCl_3$ at 77.0 ppm. Coupling constants are reported in hertz ($J$/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). IR spectra were acquired on a Perkin Elmer Spectrum 2000 and Perkin Elmer Spectrum 100. The absorbance peaks are reported in reciprocal centimeters ($\nu$/cm$^{-1}$). High resolution mass spectra were acquired on either, Bruker MicroTOF II (ESI) or Bruker Maxis Impact (ESI+) spectrometers. HRMS samples were ionized by ESI+ and recorded *via* the TOF method. Microwave assisted reactions were performed on a CEM Discover™ Synthesis Unit in a closed vessel mode. The reaction progress was monitored by TLC on precoated silica gel Kieselgel 60 F254 plates and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures of hexanes with AcOEt (v/v) as a mobile phase. The chromatography on silica-gel preparative plates was performed on precoated silica gel Kieselgel 60 F254 plates and the spots were visualized under UV light (254 or 365 nm). All starting materials were purchased from Sigma-Aldrich and were used without further purification. The solvents were distilled and dried according to standard procedures. See the ESI.†

### Synthesis of pyrrolo[3,4-*b*]pyridin-5-ones 16a–d, 23a–e, and 24a–d

**General procedure step 1 (GP-S1).** 2,2-Dimethoxyethan-1-amine (1.0 equiv.) and the corresponding aldehyde were placed in a 10 mL sealed CEM Discover™ microwave reaction tube and diluted in 1.0 mL of dry benzene or toluene. Then, the mixture was irradiated (MW, 65 °C, 55 W) for 20 min and $Sc(OTf)_3$ (0.03 equiv.) was added. The mixture was irradiated (MW, 65 °C, 55 W) for 15 min, and the corresponding isocyanide (1.2 equiv.) was added. The mixture was again irradiated (MW, 80 °C, 65 W) but, for 30 min and maleic anhydride (1.4 equiv.) was added. Finally, this reaction mixture was irradiated (MW, 80 °C, 65 W) for 30 min, and the solvent was removed until dryness. The crude was dissolved in $CH_2Cl_2$ (5.0 mL) and washed with a concentrated aq. solution of $NaHCO_3$ (3 × 25 mL) and with brine (3 × 25 mL). The organic layer was dried with $Na_2SO_4$, filtered using a Celite-pad and the solvent was removed under vacuum. The crude was purified by silica gel-flash chromatography (hexanes–EtOAc) to afford the corresponding pyrrolo[3,4-*b*]pyridin-5-ones.

### Synthesis of cyclic compounds 4a–d, 5a–e and 6a–e

**General procedure step 2 (GP-S2).** A solution of corresponding pyrrolo[3,4-*b*]pyridin-5-ones (1 mmol, 1eq.) was placed in a 10 mL round bottom flask and diluted in (1 : 2 v/v) dioxane : 6 N HCl solution or (1 : 2 v/v) acetic acid : sulphuric acid. Then, the mixture was allowed to stir overnight in the dark at room temperature under a $N_2$ atmosphere. The reaction mixture was neutralized by using a concentrated aq. solution of $NaHCO_3$ and extracted with EtOAc. The combined

EtOAc was washed with water and brine, dried over $Na_2SO_4$, and evaporated to get a pure cyclic product.

### Synthesis one-pot of cyclic compounds 5a and 6a–c

**General procedure 3 – ONE POT (GP3-OP).** 2,2-Dimethoxyethan-1-amine (0.90 equiv.) and the corresponding aldehyde (1.00 equiv.) were placed in a 10 mL sealed CEM Discover™ microwave reaction tube and diluted in dry PhMe (1.0 mL). Then, the mixture was MW-heated (65 °C, 55 W) for 15 minutes, and $Sc(OTf)_3$ (0.03 equiv.) was added. The mixture was MW-heated (65 °C, 55 W) for 10 minutes, and the corresponding isocyanide (1.20 equiv.) was added. The mixture was MW-heated (85 °C, 65 W) for 15 minutes, and maleic anhydride (1.20 equiv.) was added. Finally, the reaction mixture was MW-heated (65 °C, 65 W) for 15 minutes, cooled at room temperature and the solvent was removed until dryness. Then, the crude was diluted in $CH_3COOH/H_2SO_4$, 1/1, v/v (3.0 mL) and stirred overnight at room temperature. The reaction mixture was neutralized by using a concentrated aq. solution of $NaHCO_3$ (3 × 25 mL) and extracted with EtOAc (3 × 25 mL). The organic layer was washed with water brine (3 × 25 mL). Finally, it was dried with $Na_2SO_4$ and the solvent was evaporated to dryness. The crude was purified by silica gel column chromatography using mixtures of hexanes–EtOAc to afford the corresponding aza-analogue.

### Procedure for obtaining the aza-analogue of nuevamine 4a

**Synthesis of 7-(benzo[*d*][1,3]dioxol-5-yl)-2-benzyl-6-(2,2-dimethoxyethyl)-3-(piperidin-1-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one 16a.** According to GP-S1, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), piperonal (103.0 mg, 0.685 mmol), scandium triflate (10.1 mg, 0.021 mmol), 2-isocyano-3-phenyl-1-(piperidin-1-yl)propan-1-one (203.0 mg, 0.838 mmol), and maleic anhydride (94.0 mg, 0.959 mmol) were reacted together in PhMe (1.0 mL) to afford pyrrolo[3,4-*b*]pyridin-5-ones. **16a** (0.223 g, 66%) as a yellow gum; $R_f$ = 0.47 (hexanes–AcOEt = 2/1 v/v); FT-IR (ATR) $\nu_{max}/cm^{-1}$ 2116 (C≡C), 1690 (C═O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.76 (s, 1H), 7.19–7.15 (m, 2H), 7.13–7.09 (m, 2H), 7.08–7.04 (m, 1H), 6.72 (d, $J$ = 7.9 Hz, 1H), 6.67 (dd, $J$ = 8.0, 1.6 Hz, 1H), 6.40 (d, $J$ = 1.5 Hz, 1H), 5.87 (d, $J$ = 6.5 Hz, 2H), 5.53 (s, 1H), 4.46 (dd, $J$ = 6.6, 3.8 Hz, 1H), 4.24 (d, $J$ = 13.7 Hz, 1H), 4.11 (d, $J$ = 13.7 Hz, 1H), 4.04 (dd, $J$ = 14.4, 3.8 Hz, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 2.83 (dd, $J$ = 14.4, 6.6 Hz, 1H), 2.76–2.66 (m, 4H), 1.66–1.60 (m, 4H), 1.53–1.47 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$: 167.3, 162.0, 159.9, 149.3, 148.1, 147.9, 139.5, 129.2, 128.9, 128.1, 126.0, 123.7, 123.5, 122.5, 108.5, 107.9, 102.8, 101.2, 66.0, 54.8, 54.3, 53.9, 41.4, 39.8, 26.3, 23.9. HRMS: $m/z$ calcd for: $C_{30}H_{34}N_3O_5^+$ = 516.2993, found: 516.2996.

**Synthesis of (11-benzyl-5-hydroxy-10-(piperidin-1-yl)-5,12b-dihydro-[1,3]dioxolo[4,5-*g*]pyrido[2′,3′:3,4]pyrrolo[2,1-*a*]isoquinolin-8(6H)-one) 4a.** According to GP-S2, pyrrolo[3,4-*b*]pyridin-5-one **16a** (55.0 mg, 1 mmol) was dissolved in (1 : 2 v/v) dioxane : 6 N HCl solution (3 ml) and stirred overnight to afford the (±)-nuevamine aza-analog **4a** (32.1 mg, 64%) as an orange gum; FT-IR (ATR) $\nu_{max}/cm^{-1}$ 2116 (C≡C), 1690 (C═O); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 9.57 (s, 1H), 7.84 (s, 1H), 7.23 (d, $J$ = 7.1 Hz, 2H), 7.18 (t, $J$ = 7.3 Hz, 2H), 7.13 (t, $J$ = 7.9 Hz, 1H), 6.79 (d, $J$ = 7.9 Hz, 1H), 6.71 (d, $J$ = 7.9 Hz, 1H), 6.44 (s, 1H), 5.96 (d, $J$ = 6.0 Hz, 2H), 5.53 (s, 1H), 4.73 (d, $J$ = 18.9 Hz, 1H), 4.30 (d, $J$ = 13.7 Hz, 1H), 4.19 (d, $J$ = 13.7 Hz, 1H), 3.81 (d, $J$ = 18.9 Hz, 1H), 2.83–2.74 (m, 4H), 1.71 (m, 4H), 1.61–1.55 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$: 196.6, 167.6, 162.7, 159.5, 149.6, 148.4, 139.5, 128.9, 128.5, 128.1, 126.0, 123.4, 122.5, 108.6, 107.7, 101.4, 66.0, 54.3, 50.3, 39.9, 29.7, 26.4, 23.9; HRMS: $m/z$ calcd for: $C_{28}H_{28}N_3O_4$ = 470.2074, found: 470.2043.

### Procedure for obtaining the aza-analogue of lennoxamine 5a

**Synthesis of 2,7-dibenzyl-6-(2,2-dimethoxyethyl)-3-morpholino-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one 23a.** According to GP-S1, 2,2-dimethoxyethylamine (76.0 μL, 0.685 mmol), phenylacetaldehyde (98.6 mg, 0.822 mmol), scandium triflate (10.1 mg, 0.021 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (200.5 mg, 0.822 mmol), and maleic anhydride (93.9 mg, 0.959 mmol) were reacted together in Ph-H (2.0 mL) to afford pyrrolo[3,4-*b*]pyridin-5-ones. **23a** (133.4 mg, 40%) as a yellow oil; $R_f$ = 0.47 (hexanes/AcOEt, 2/1, v/v); FT-IR (ATR) $\nu_{max}/cm^{-1}$ 1683, 1122, 1053, 700; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 7.67 (s, 1H), 7.36–7.30 (m, 5H), 7.27–7.22 (m, 1H), 7.06–7.02 (m, 1H), 6.99–6.96 (m, 2H), 6.70 (d, $J$ = 8.0 Hz, 2H), 5.05–5.04 (m, 1H), 4.56–4.53 (m, 2H), 4.29 (dd, $J$ = 14.4, 3.7 Hz, 1H), 4.24 (d, $J$ = 13.8 Hz, 1H), 3.88–3.83 (m, 4H), 3.44 (s, 3H), 3.39–3.36 (m, 5H), 3.31–3.24 (m, 2H), 2.91–2.85 (m, 2H), 2.79–2.74 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 167.2, 161.2, 160.0, 147.3, 139.7, 134.8, 129.5, 129.0, 128.3, 127.9, 126.5, 126.3, 124.6, 123.4, 102.9, 67.1, 62.2, 55.1, 54.4, 53.1, 42.0, 40.0, 35.3; HRMS: $m/z$ calcd for: $C_{29}H_{33}N_3O_4$ = 487.2471, found: 487.2515.

**Synthesis of 2-benzyl-3-morpholino-13,13a-dihydro-5*H*-benzo[*d*]pyrido[2′,3′:3,4]pyrrolo[1,2-*a*]azepin-5-one 5a.** According to GP-S2, pyrrolo[3,4-*b*]pyridin-5-one **23a** (45 mg, 0.95 mmol) was dissolved in (1 : 2 v/v) acetic acid : sulphuric acid (3 ml) and stirred overnight to afford the (±)-lennoxamine aza-analog **5a** (11.7 mg, 30%) as a yellow solid, mp 110 °C; $R_f$ = 0.40 (AcOEt–hexanes = 3/1 v/v); FT-IR (film in $CH_2Cl_2$) $\nu_{max}/cm^{-1}$ 1710, 1637, 1440, 1358, 1107, 740; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.89 (s, 1H), 7.37–7.30 (m, 5H), 7.27–7.20 (m, 5H), 5.88 (d, $J$ = 10.3 Hz, 1H), 4.79 (d, 1H, $J$ = 9.4 Hz), 4.48–4.39 (m, 2H), 4.48–4.39 (m, 5H), 3.00 (dd, 1H, $J$ = 15.3, 9.9 Hz), 2.92–2.82 (m, 4H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 164.1, 162.9, 158.6, 148.3, 139.2, 135.9, 135.0, 131.0, 130.2, 128.8, 128.4, 127.2, 127.0, 126.4, 124.0, 123.2, 120.6, 110.6, 67.1, 61.5, 53.0, 40.2, 39.6.

### Procedure for obtaining the aza-analogue of magallanesine 6a

**Synthesis of 2-benzyl-6-(2,2-dimethoxyethyl)-3-morpholino-7-phenethyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one 24a.** According to GP-S1, 2,2-dimethoxyethan-1-amine (250.0 μL, 0.23 mmol), hydrocinnamaldehyde (270.0 μl, 0.206 mmol), scandium triflate (3.4 mg, 0.006 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (67.0 mg, 0.270 mmol), and maleic anhydride (22.0 mg, 0.270 mmol) were reacted together in PhMe (1.0 mL) to afford pyrrolo[3,4-*b*]pyridin-5-ones. **24a** (51.8 mg, 45%) as a yellow oil; $R_f$ = 0.53 (hexanes–AcOEt = 3/1

v/v); FT-IR (film in $CH_2Cl_2$) $\nu_{max}/cm^{-1}$ 2922, 2853, 1708, 1444); $^1$H-RMN (500 MHz, $CDCl_3$) $\delta$: 7.87 (s, 1H), 7.37–7.33 (m, 2H), 7.31–7.28 (m, 10H), 7.25–7.20 (m, 4H), 7.18–7.14 (m, 1H), 7.06–7.02 (m, 2H), 4.81–4.78 (m,1H), 4.56 (dd, $J$ = 6.2, 4.1 Hz, 1H), 4.46 (d, $J$ = 14.1 Hz, 1H), 4.32 (d, $J$ = 14.1 Hz, 1H), 4.24 (dd, $J$ = 14.4, 3.8 Hz, 1H), 3.89–3.86 (m, 4H), 3.44 (s, 3H), 3.37 (s, 1H), 3.18 (dd, $J$ = 14.4, 6.2 Hz, 1H), 2.92–2.85 (m, 4H), 2.59–2.53 (m, 1H), 2.48–2.42 (m, 1H), 2.22–2.17 (m, 2H); $^{13}$C-RMN (126 MHz, $CDCl_3$) $\delta$: 167.4, 161.4, 160.5, 147.4, 141.1, 139.6, 129.0, 128.4, 128.3, 125.9, 124.5, 123.5, 102.8, 67.2, 60.9, 54.8, 54.3, 53.1, 41.5, 39.9, 30.8, 29.1; HRMS: $m/z$ calcd for: $C_{30}H_{35}N_3O_4$ = 502.2628, found 502.2677.

**Synthesis of ((*Z*)-2-benzyl-3-morpholino-14,14a-dihydrobenzo[*e*]pyrido-[2′,3′:3,4]pyrrolo[1,2-*a*]azocin-5(13H)-one) 6a.** According to GP-S2, pyrrolo[3,4-*b*]pyridin-5-ones **24a** (51.0 mg, 0.1017 mmol) was dissolved in (1 : 1 v/v) acetic acid : sulphuric acid (1 ml) and stirred overnight to afford ((*Z*)-2-benzyl-3-morpholino-14,14a-dihydrobenzo[*e*]pyrido[2′,3′:3,4]pyrrolo [1,2-*a*]azocin-5(13H)-one) **6a** (26.7 mg, 60%) as a white solid mp; 172 °C $R_f$ = 0.40 (Hex–AcOEt 3 : 1 v/v); FT-IR (film in) $\nu_{max}/cm^{-1}$ 2922, 2853, 1708, 1444. $^1$H-RMN (500 MHz, $CDCl_3$) $\delta$: 7.92 (s, 1H), 7.35 (d, $J$ = 10.7 Hz, 1H), 7.28–7.16 (m, 9H), 5.84 (d, $J$ = 10.7 Hz, 1H), 4.70 (dd, $J$ = 11.5, 3.5 Hz, 1H), 4.36 (d, $J$ = 14.0 Hz, 1H), 4.32 (d, $J$ = 14.0 Hz, 1H), 3.86–3.79 (m, 4H), 3.18–3.10 (m, 1H), 3.01–2.95 (m, 1H), 2.88–2.78 (m, 4H), 2.55–2.47 (m, 1H), 1.71–1.64 (m, 1H); $^{13}$C-RMN (126 MHz, $CDCl_3$) $\delta$: 165.6, 162.6, 162.1, 147.9, 139.1, 137.0, 135.9, 129.5, 128.9, 128.7, 128.3, 127.6, 126.3 (2), 124.5, 123.5, 122.2, 107.9, 67.1, 58.5, 53.1, 40.2, 33.5, 30.9. HRMS: $m/z$ calcd for: $C_{28}H_{27}N_3O_2$ = 438.2182, found 438.2190.

**Synthesis ONE-POT of (*Z*)-2-benzyl-9-methoxy-3-morpholino-14,14a-dihydrobenzo[*e*]pyrido[2′,3′:3,4]pyrrolo[1,2-*a*]azocin-5(13H)-one 6b.** According to GP3-OP, 2,2-dimethoxyethan-1-amine (76.0 μL, 0.685 mmol), 3-methoxyhydrocinnamaldehyde (116.0 mg, 0.699 mmol), scandium triflate (11.0 mg, 0.0021 mmol), 2-isocyano-1-morpholino-3-phenylpropan-1-one (204.0 mg, 0.838 mmol), and maleic anhydride (96.0 mg, 0.978 mmol) were reacted together in PhMe (1.0 mL) to afford pyrrolo[3,4-*b*]pyridin-5-one **24b**. The crude was diluted in $CH_3COOH/H_2SO_4$, 1/1, v/v (3.0 mL) and stirred overnight at room temperature to afford the magallanesine aza-analogue **6b** (32.0 mg, 20%) as an orange gum; $R_f$ = 0.35 (AcOEt/hexanes, 3/1, v/v); FT-IR ($cm^{-1}$) $\nu_{max}$ 2922, 2853, 1708, 1444; $^1$H RMN (500 MHz, $CDCl_3$) $\delta$: 7.92 (s, 1H), 7.29–7.28 (m, 2H), 7.27–7.22 (m, 4H), 7.20–7.17 (m, 1H), 7.16 (d, $J$ = 8.6 Hz, 1H), 6.83 (d, $J$ = 2.7 Hz, 1H), 6.79 (dd, $J$ = 8.5, 2.7 Hz, 1H), 5.80 (d, $J$ = 9.8 Hz, 1H), 4.70 (dd, $J$ = 11.8, 3.8 Hz, 1H), 4.34 (q, $J$ = 14.1 Hz, 1H), 3.87 (s, 3H), 3.84–3.81 (m, 4H), 3.16–3.07 (m, 1H), 2.94–2.89 (m, 1H), 2.85–2.81 (m, 4H), 2.55–2.47 (m, 1H), 1.69–1.61 (m, 1H); $^{13}$C RMN (126 MHz, $CDCl_3$) $\delta$ 165.6, 162.5, 162.0, 159.2, 147.9, 139.2, 138.4, 130.2, 128.7, 128.5, 128.3, 126.3, 124.4, 122.6, 122.3, 114.5, 112.1, 107.7, 67.1, 58.5, 55.3, 53.1, 40.2, 33.6, 31.2; HRMS: $m/z$ calcd for: $C_{28}H_{27}N_3O_2$ = 438.2182, found: 438.2190.

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