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Catalyst-free concise synthesis of imidazo[1,2-*a*]-pyrrolo[3,4-*e*]pyridine derivatives†

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An eco-benign and highly efficient aza–ene reaction for preparing imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridine derivatives from heterocyclic ketene aminals (HKAs) and 2,3-dioxopyrrolidines has been developed in environmentally benign solvent systems, as well as in the absence of any catalyst. The procedures feature excellent yields, short reaction times, a convenient one-pot method, and simple purification that not only minimise the generation of waste but also simplify the work-up procedure.

Introduction

The imidazo[1,2-*a*]pyridine derivatives and its analogues are some of the most important heterocycles as they are not only broadly used in material science[1] but also have widespread applications in medicinal chemistry; these compounds have a wide range of biologic activities such as insecticidal,[2] antituberculosis,[3] antiviral,[4] antiprotozoal,[5] antibacterial,[6] antiulcer,[7] and anti-inflammatory behaviours.[8] They have also been characterised as the inhibitors of β-amyloid plaques formation,[9] selective cyclin-dependent kinase,[10] and they constitute a novel class of orally active non-peptide bradykinin B2 receptor antagonists.[11] In addition to the before mentioned bio-activities, many marketed drugs including zolpidem,[12] zolimidine, olprinone[13] (Fig. 1), optically-active GSK812397 (Fig. 1) candidate[14] and saripidem[15] are derived from imidazo[1,2-*a*]pyridine core entities. Consequently, these have attracted considerable interest for synthetic chemists and stimulated the development of numerous methods for their preparation.[16]

On the other hand, the pyrrolin-2-ones core is featured in a number of natural products (*e.g.*, epolactaene[17] and UCS1025A[18]) (Fig. 1) and biologically active drug candidates.[19] Compounds carrying the pyrrolin-2-ones moiety exhibit anti-inflammatory[20] activities, and are found to inhibit cyclo-oxygenase-2,[21] vascular endothelial growth factor receptor (VEGF-R)[22] and protein kinase C.[23]

Further, the fused imidazo-pyrrolopyridines contain both imidazo-pyridine and pyrrole cores displaying a variety of biological activities. For example, AG110 (Fig. 1) displayed a strong antiviral activity against the bovine viral diarrhea virus.[24]

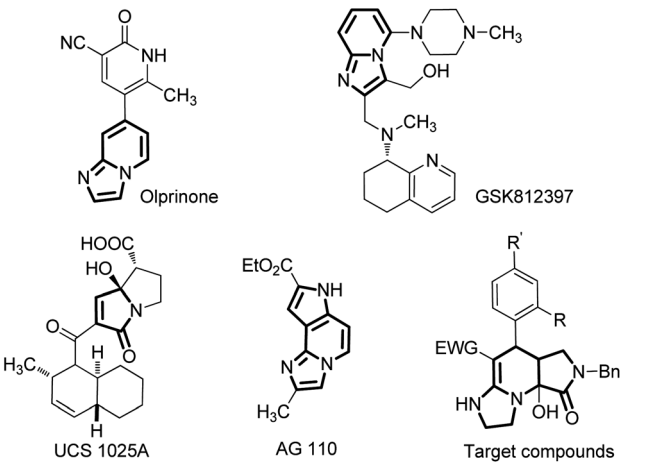

Fig. 1 Biologically active imidazo[1,2-*a*]pyridines, pyrrolin-2-one, imidazopyrrolopyridines and the target compounds.

Moreover, imidazo-pyrrolopyridines has used as the inhibitors of IκB-kinase (IKK)[25] and Janus protein tyrosine kinase (JAKs).[26] Numerous methods for the synthesis of imidazo[1,2-*a*]pyridine and pyrrolin-2-ones have been reported, but the preparation of fused imidazo-pyrrolopyridines are rarely.[27]

Heterocyclic ketene aminals (HKAs), as a type of versatile building block, are widely used for the synthesis of a variety of fused heterocyclic compounds, including anticancer agents,[28] herbicides, pesticides,[29] anti-anxious agents,[30] anti-leishmanial agents[31] and antibacterial and anti-therapeutic drugs.[32] Our group has been pursuing the diversified synthesis of natural product-like heterocycles[33] with potential bioactivities through one-pot reactions based on HKAs. This is part of our research program, which aims to develop new efficient and environmentally friendly methodologies for the preparation of heterocycles. Herein, we investigated a one-pot reaction of HKAs and 2,3-dioxopyrrolidines to afford a novel series of imidazo[1,2-*a*]-pyrrolo[3,4-*e*]pyridine derivatives.

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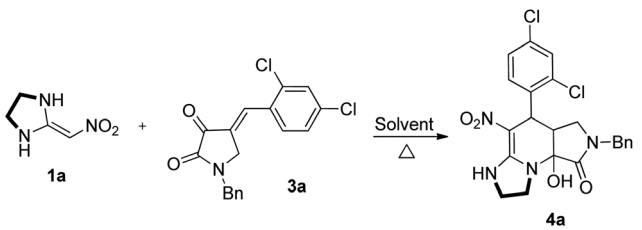
Results and discussion

The aza–ene reaction represents one of the most powerful methods for the formation of carbon–nitrogen bonds in organic synthesis, and has been applied to make a range of heterocycles. The aza–ene reactions of heterocyclic ketene aminals have recently been explored with a variety of bis-electrophilic reagents.[34]

In this paper, a series of imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridines **4–5** were easily prepared by a new aza–ene reaction of HKAs **1–2** and dioxopyrrolidines **3** in the absence of catalyst in ethanol with good to excellent yields (81–95%).

To test the success of our strategy, we first used the reaction of HKAs **1a** and dioxopyrrolidines **3a** as a representative to optimise the experimental conditions; and the results are summarized in Table 1. No reaction occurred in the solvent of ethanol at room temperature even for 12 h (Table 1, entry 1), but at 40 °C and 60 °C the product **4a** was obtained in 93% and 90% yields, respectively (Table 1, entries 2 and 3). We only obtain a final product with moderate yield in acetonitrile or 1,4-dioxane at 40 °C. However, the results indicate that the reaction could not proceed in water even at reflux temperature (Table 1, entry 6). The reaction temperature and solvents are key to product yields. It was realised that the ethanol was the best solvent for the reaction to furnish **4a**. The temperature of 40 °C is beneficial for the reaction. Inspired by these results, we continued to optimise reaction conditions to further improve the chemical yield; different basic and acidic catalysts such as TFA, HOAc, L-proline, *p*-TSA, piperidine, Et_3N, DABCO were added in ethanol, but the results showed that these catalysts could not promote this reaction efficiently (Table 1, entries 7–13). Thus, it was concluded that the optimum reaction conditions were the use of ethanol under catalyst-free conditions at 40 °C.

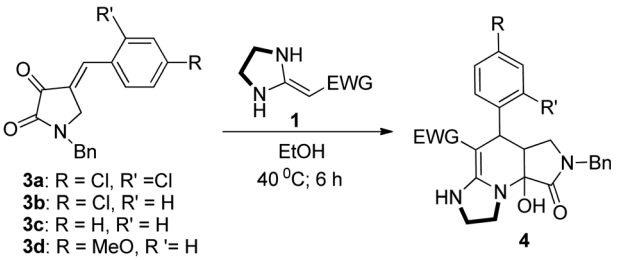
Table 1 Optimisation conditions for the formation of **4a**[a]



Entry	Solvent	Catalyst	*t* (°C)	Time/min	Yield[b] (%)
1	EtOH	—	rt	12	n.r.
2	EtOH	—	40	6	93
3	EtOH	—	60	6	90
4	CH_3CN	—	40	6	87
5	Dioxane	—	40	6	78
6	H_2O	—	Reflux	12	Trace
7	EtOH	TFA	40	6	77
8	EtOH	HOAc	40	6	81
9	EtOH	L-Proline	40	6	85
10	EtOH	*p*-TSA	40	6	83
11	EtOH	Piperidine	40	6	89
12	EtOH	Et_3N	40	6	89
13	EtOH	DABCO	40	6	79

[a] The reaction was performed with **1a** (1 mmol), **3a** (1.1 mmol) and the solvent (15 mL). [b] Isolated yields, isolated yield based on HKA **1a**. n.r. = no reaction.

Table 2 Catalyst-free synthesis of imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridine derivatives **4**[a]



3a: R = Cl, R' =Cl
3b: R = Cl, R' = H
3c: R = H, R' = H
3d: R = MeO, R '= H

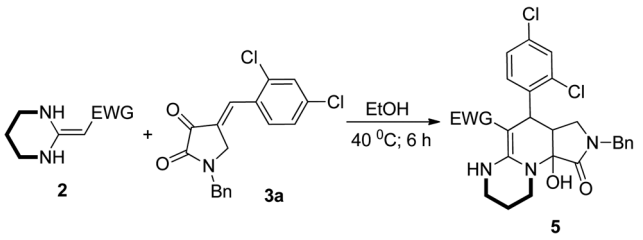
Entry	1/EWG	3	4	Yield[b] (%)
1	**1a** (NO_2)	**3a**	**4a**	93
2	**1a** (NO_2)	**3b**	**4b**	95
3	**1b** (*p*-FPhCO)	**3a**	**4c**	94
4	**1b** (*p*-FPhCO)	**3b**	**4d**	93
5	**1b** (*p*-FPhCO)	**3c**	**4e**	94
6	**1b** (*p*-FPhCO)	**3d**	**4f**	90
7	**1c** (*o*-FPhCO)	**3a**	**4g**	89
8	**1c** (*o*-FPhCO)	**3b**	**4h**	87
9	**1c** (*o*-FPhCO)	**3d**	**4i**	84
10	**1d** (*p*-ClPhCO)	**3a**	**4j**	94
11	**1d** (*p*-ClPhCO)	**3b**	**4k**	94
12	**1d** (*p*-ClPhCO)	**3c**	**4l**	92
13	**1d** (*p*-ClPhCO)	**3d**	**4m**	90
14	**1e** (PhCO)	**3a**	**4n**	94
15	**1e** (PhCO)	**3b**	**4o**	93
16	**1e** (PhCO)	**3c**	**4p**	90
17	**1e** (PhCO)	**3d**	**4q**	89
18	**1f** (*p*-MePhCO)	**3a**	**4r**	91
19	**1f** (*p*-MePhCO)	**3b**	**4s**	90
20	**1f** (*p*-MePhCO)	**3c**	**4t**	89
21	**1f** (*p*-MePhCO)	**3d**	**4u**	89
22	**1g** (*p*-MeOPhCO)	**3a**	**4v**	89
23	**1g** (*p*-MeOPhCO)	**3b**	**4w**	86
24	**1g** (*p*-MeOPhCO)	**3c**	**4x**	86
25	**1g** (*p*-MeOPhCO)	**3d**	**4y**	84

[a] The reaction was performed with **1** (1 mmol), **3** (1.1 mmol) and the solvent (15 mL). [b] Isolated yields, isolated yield based on HKA **1**.

With the optimised conditions, we investigated the scope of this aza–ene strategy for the construction of a library of imidazo [1,2-*a*]pyrrolo[3,4-*e*]pyridines (Table 2).

We first explored variations in the dioxopyrrolidines **3**; the results demonstrate that the reaction tolerates significant functionalisation of the dioxopyrrolidines both electron-donating and electron-withdrawing groups can be accommodated, and substituents *ortho* or *para* to the aromatic group can all be generated. It is observed that the substituents on the aromatic rings had slightly influence on the yields. The aromatics with electron-withdrawing groups *p*-chloro, 2,4-dichloro groups gave higher yields than those with electron-donating groups or no substituted ones (compare Table 2, entries 3, 4, 5 & 6).

Table 3 Catalyst-free synthesis of pyrimido[1,2-*a*]pyrrolo[3,4-*e*]-pyridines derivatives **5**[a]



Entry	2/EWG	5	Yield[b] (%)
1	**2a** (*p*-FPhCO)	**5a**	85
2	**2b** (*p*-ClPhCO)	**5b**	84
3	**2c** (PhCO)	**5c**	84
4	**2d** (*p*-MePhCO)	**5d**	84
5	**2e** (*p*-OMePhCO)	**5e**	81

[a] The reaction was performed with **2** (1 mmol), **3a** (1.1 mmol) and the solvent (15 mL). [b] Isolated yields, isolated yield based on HKA **2**.

Subsequently, the substrate **1** was also extended by using other five-membered HKAs; the similar reactions were observed (Table 2, entries 7–25). The results revealed that the five-membered HKAs, with various substituents, were all good substrates for the aza–ene reaction. Similarly, it was clearly shown that the electron-withdrawing aromatic rings of HKAs **1** can encourage the yield of the reaction (compare Table 2, entries 1, 3, 10, 14, 18, and 22). What is more, the HKAs with substituents at *para*-positions afforded higher yields than those counterparts at the *ortho*-positions (compare Table 2, entries 3 and 7).

In order to further investigate the scope of HKAs, the ring size was also examined in our work. Thus, five six-membered HKAs **2a–e** were also employed in this process; the corresponding products **5** were obtained (Table 3). On the whole, the six-membered HKAs provided lower yields than those of the five-membered HKAs (Table 3 *vs.* 2). It could be concluded that the ring size of HKAs can influence the yields of the reaction.

Compared with other aza–ene reactions, the present reaction showed the following attractive characteristics: (1) a high atom economy and ecologically benign process since no molecule was lost; (2) the environmentally friendly process which included green solvents, was catalyst-free, and used a mild reaction temperature; and (3) the convenient workup which only required simple filtration rather than column chromatography or recrystallisation.

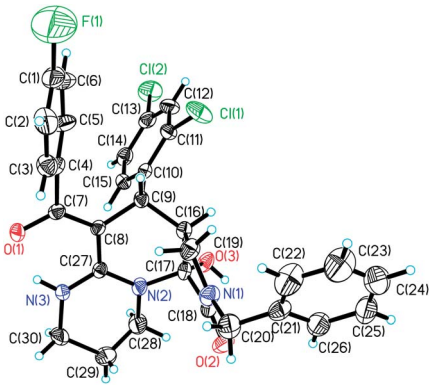
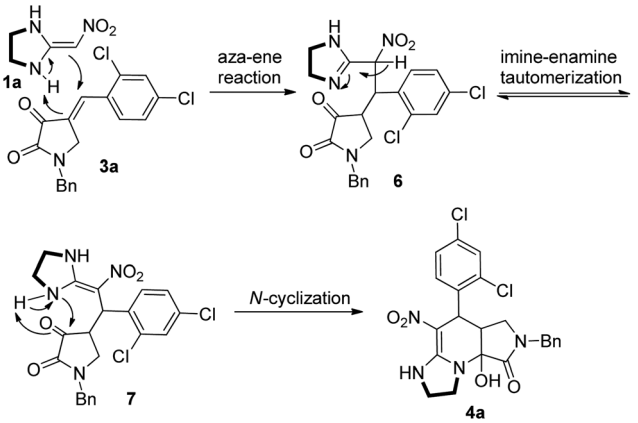


Fig. 2 X-ray crystal structures of **5a**; ellipsoids are drawn at the 30% probability level.



Scheme 1 The proposed mechanism of the reaction.

The structures of imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridines **4** and pyrimido[1,2-*a*]pyrrolo[3,4-*e*]pyridines **5** were identified by their IR, ^{1}H NMR, ^{13}C NMR and HRMS spectra. In order to further confirm the crystal structure of the product imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridine, **5a** was selected as a representative compound and characterized by X-ray crystallography, as shown in Fig. 2.[35]

A proposed mechanism for the aza–ene reaction is depicted in Scheme 1. First, HKA **1a** reacts with dioxopyrrolidine **3a** through an aza–ene reaction[36] to form the intermediate **6**, which undergoes a rapid imine–enamine tautomerisation to give **7**. Then, intra-molecular cyclisation of **7** forms imidazo[1,2-*a*]-pyrrolo[3,4-*e*]pyridines **4a**.

Conclusions

In conclusion, we developed an eco-benign, mild, and highly efficient method for the synthesis of fused tricyclic heterocycles containing imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridines & pyrimido [1,2-*a*]pyrrolo[3,4-*e*]pyridines *via* an aza–ene reaction of HKAs and dioxopyrrolidines. Our work presents a very simple reaction which is performed under neutral conditions without any catalyst in the green solvent ethanol. All products were easily isolated (filtration) and obtained in good to excellent yields. Features of this procedure include ease of execution, flexibility, and substantial minimisation of waste. Moreover, these special fused tricyclic heterocycles may be directly useful for drug design, discovery and development.

Experimental

General information

All compounds were fully characterised by spectroscopic data. The NMR spectra were recorded on Bruker DRX500 (^{1}H: 500

MHz, ^{13}C: 125 MHz) or Bruker AVIII-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz), chemical shifts (δ) are expressed in ppm, and J values are given in Hz, DMSO-d_6 was used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using a KBr pellet. The reactions were monitored by thin-layer chromatography (TLC) using silica gel GF_{254}. The melting points were determined on XT-4A melting point apparatus and are uncorrected. HRMs were performed on a Agilent LC/Msd TOF and Monoisotopic Mass instrument. All chemicals and solvents were used as received without further purification unless otherwise stated. The raw material **1–2** was synthesized according to the literature.[37] For the method of synthesis of compound **3** see the literature.[38]

General procedure

HKAs **1–2** (1 mmol), dioxopyrrolidines **3** (1.1 mmol), solvent EtOH (15 mL) were charged into a 25 mL round-bottom flask, and the mixture was stirred at 40 °C until the HKA **1–2** was completely consumed. The mixture was cooled to room temperature. Then the precipitation was filtered and successively washed by ethanol to afford the pure products **4–5** in a good yield (81–95%). The products were further identified by FT-IR, NMR and HRMS, being in good agreement with the assigned structures.

2-Benzyl-4-(2,4-dichlorophenyl)-9*a*-hydroxy-5-nitro-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4a). White solid; Mp 289–290 °C; IR (KBr): 3788, 3427, 1699, 1638, 1253, 1168, 735, 657 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.28 (br, 1H, NH), 7.57 (s, 1H, ArH), 7.32–7.41 (m, 2H, ArH), 7.28–7.34 (m, 2H, ArH), 7.19 (d, J = 7.1 Hz, 2H, ArH), 7.01 (d, J = 8.4 Hz, 1H, ArH), 6.90 (br, 1H, OH), 4.48 (d, J = 15.0 Hz, 1H, CH), 4.42 (AB, J = 15.0 Hz, 2H, $ArCH_2$), 3.73–3.84 (m, 2H, NCH_2), 3.60–3.68 (m, 2H, NCH_2), 3.38–3.48 (m, 1H, CH), 2.92–2.97 (m, 1H, NCH_2), 2.70–2.76 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.1, 155.8, 139.2, 136.5, 133.9, 132.1, 129.9, 129.3, 128.0, 127.8, 127.4, 102.2, 82.5, 46.7, 46.3, 44.9, 44.1, 43.2, 36.2; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{21}Cl_2N_4O_4$ [(M + H)$^+$], 475.0934; found, 475.0941.

2-Benzyl-4-(4-chlorophenyl)-9*a*-hydroxy-5-nitro-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4b). White solid; Mp 250–253 °C; IR (KBr): 3788, 3427, 1699, 1638, 1253, 1168, 735, 657 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.24 (br, 1H, NH), 7.35–7.39 (m, 2H, ArH), 7.26–7.32 (m, 3H, ArH), 7.18–7.28 (m, 4H, ArH), 6.85 (br, 1H, OH), 4.41 (AB, J = 14.9 Hz, 2H, $ArCH_2$), 4.24–4.28 (m, 1H, CH), 3.74–3.85 (m, 2H, NCH_2), 3.55–3.68 (m, 2H, NCH_2), 3.32–3.34 (m, 1H, CH), 2.82–2.90 (m, 2H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.3, 155.5, 142.3, 136.6, 131.0, 130.0, 129.2, 128.2, 128.0; 128.0; 103.5, 82.7, 47.0, 46.8, 46.2, 44.1, 43.1, 38.6; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{22}ClN_4O_4$ [(M + H)$^+$], 441.1324; found, 441.1320.

2-Benzyl-4-(2,4-dichlorophenyl)-5-(4-fluorobenzoyl)-9*a*-hydroxy-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]-pyrrolo[3,4-*e*]-pyridin-1-one (4c). White solid; Mp 225–227 °C; IR (KBr): 3329, 1703, 1599, 1512, 1142, 843, 536 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.48 (br, 1H, NH), 7.27–7.38 (m, 5H, ArH), 7.12–7.17 (m, 3H, ArH), 6.91–6.96 (m, 2H, ArH), 6.78–6.82 (m, 2H, ArH), 6.50 (br, 1H, OH), 4.47 (d, J = 15.0 Hz, 1H, $ArCH_2$), 4.32 (d, J = 15.0 Hz, 1H, $ArCH_2$), 3.76 (d, J = 10.3 Hz, 1H, CH), 3.66–3.74 (m, 2H, NCH_2), 3.54–3.60 (m, 2H, NCH_2), 3.27–3.31 (m, 1H, CH), 3.01–3.08 (m, 1H, NCH_2), 2.57–2.65 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.1, 169.7, 161.8 (d, J = 243.0 Hz), 159.9, 142.1, 139.4, 136.7, 133.0, 132.4, 131.6; 129.3, 128.5, 128.0, 127.3, 115.0 (d, J = 22.0 Hz), 114.8 (d, J = 22.0 Hz), 82.4, 82.2, 46.8, 46.2, 45.2, 43.4, 42.8, 36.2; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{25}Cl_2FN_3O_3$ [(M + H)$^+$], 552.1252; found, 552.1253.

2-Benzyl-4-(4-chlorophenyl)-5-(4-fluorobenzoyl)-9*a*-hydroxy-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4d). White solid; Mp 224–226 °C; IR (KBr): 3312, 1703, 1595, 1512, 1215, 837, 580 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.55 (br, 1H, NH), 7.35–7.40 (m, 2H, ArH), 7.28–7.33 (m, 1H, ArH), 7.20 (d, J = 7.7 Hz, 4H, ArH), 7.02 (d, J = 8.0 Hz, 2H, ArH), 6.93–6.99 (m, 2H, ArH), 6.87–6.92 (m, 2H, ArH), 6.42 (br, 1H, OH), 4.44 (d, J = 15.0 Hz, 1H, $ArCH_2$), 4.38 (d, J = 15.0 Hz, 1H, $ArCH_2$), 3.71–3.74 (m, 1H, CH), 3.66–3.90 (m, 2H, NCH_2), 3.58–3.62 (m, 2H, NCH), 3.34–3.37 (m, 1H, CH), 3.04 (t, J = 9.5 Hz, 1H, NCH_2), 2.74–2.80 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.0, 170.0, 162.0 (d, J = 242.0 Hz), 159.9, 145.5, 139.7, 136.8, 130.6, 130.2, 129.3, 128.6; 128.6, 128.1, 115.0 (d, J = 22.0 Hz), 114.8 (d, J = 22.0 Hz), 83.1, 82.7, 47.6, 47.1, 46.2, 43.4, 42.7, 40.6; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{26}ClFN_3O_3$ [(M + H)$^+$], 518.1641; found, 518.1645.

2-Benzyl-5-(4-fluorobenzoyl)-9*a*-hydroxy-4-phenyl-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4e). White solid; Mp 194–197 °C; IR (KBr): 3324, 1701, 1596, 1515, 1214, 1008, 739 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.57 (br, 1H, NH), 7.32–7.38 (m, J = 6.8 Hz, 2H, ArH), 7.29–7.34 (m, 1H, ArH), 7.20 (d, J = 6.8 Hz, 2H, ArH), 7.11–7.15 (m, 2H, ArH), 7.01–7.06 (m, 1H, ArH), 7.00 (d, J = 6.8 Hz, 2H, ArH), 6.86–6.96 (m, 4H, ArH), 6.36 (br, 1H, OH), 4.43 (s, 2H, $ArCH_2$), 3.72–3.75 (m, 1H, CH), 3.67–3.74 (m, 2H, NCH_2), 3.57–3.61 (m, 1H, NCH_2), 3.48–3.52 (m, 1H, NCH_2), 3.05 (t, J = 9.3 Hz, 1H, NCH_2), 2.78–2.83 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.9, 170.1, 161.5 (d, J = 232.0 Hz); 160.0, 146.4, 139.7, 136.8, 129.2, 128.6, 128.5, 128.3; 128.1, 128.0; 126.0; 114.8 (d, J = 21.0 Hz); 114.6 (d, J = 21.0 Hz), 83.4, 82.8, 47.6, 47.2, 46.2, 43.4, 42.6, 39.3; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{27}FN_3O_3$ [(M + Na)$^+$], 506.1850; found, 506.1859.

2-Benzyl-5-(4-fluorobenzoyl)-9*a*-hydroxy-4-(4-methoxy-phenyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo-[3,4-*e*]-pyridin-1-one (4f). White solid; Mp 215–218 °C; IR (KBr): 3462, 1696, 1599, 1511, 1240, 751, 649 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.59 (br, 1H, NH), 7.37–7.42 (m, 2H, ArH), 7.30–7.34 (m, 1H, ArH), 7.22 (d, J = 7.4 Hz, 2H, ArH), 6.92–7.00 (m, 6H, ArH), 6.74 (d, J = 8.3 Hz, 2H, ArH), 6.34 (br, 1H, OH), 4.43 (s, 2H, $ArCH_2$), 3.76–3.78 (m, 1H, CH), 3.70–3.76 (m, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.60–3.63 (m, 1H, CH), 3.50–3.54 (m, 1H, NCH_2), 3.03–3.06 (m, 1H, NCH_2), 2.78–2.83 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.8, 170.1, 160.5 (d, J = 234.0 Hz); 159.9, 157.6, 139.7, 138.2, 136.8, 129.2, 129.2, 128.6; 128.0; 114.8 (d, J = 21.0 Hz), 114.6 (d, J = 21.0 Hz); 113.5; 83.6, 82.7, 55.3, 47.8, 47.1, 46.2, 43.3, 42.6, 39.0; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{29}FN_3O_4$ [(M + H)$^+$], 514.2137; found, 514.2142.

2-Benzyl-4-(2,4-dichlorophenyl)-5-(2-fluorobenzoyl)-9*a*-hydroxy-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4g). White solid; Mp 251–254 °C; IR (KBr): 3333, 1703, 1602, 1516, 1018, 755, 541 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.34 (br, 1H, NH), 7.34–7.40 (m, 2H, ArH), 7.24–7.32 (m, 3H, ArH), 7.15–7.23 (m, 3H, ArH), 6.86–6.98 (m, 2H, ArH), 6.54–6.58 (m, 1H, ArH), 6.53 (br, 1H, OH), 4.47–4.53 (m, 1H, $ArCH_2$), 4.31–4.37 (m, 1H, $ArCH_2$), 3.84–3.88 (m, 1H, CH), 3.70–3.76 (m, 2H, CH_2), 3.59–3.63 (m, 1H, CH), 3.31–3.38 (m, 2H, NCH_2), 3.00–3.08 (m, 1H, NCH_2), 2.54–2.62 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 184.4, 169.7, 159.4, 141.7, 136.7, 133.0, 132.4, 131.4; 129.9, 128.0, 127.0, 124.4, 115.7 (d, J = 22.0 Hz), 115.5 (d, J = 22.0 Hz), 82.3, 82.4, 46.6, 46.2, 45.1, 43.3, 42.8, 35.6; HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{25}Cl_2FN_3O_3$ [(M + H)$^+$], 552.1252; found, 552.1250.

2-Benzyl-5-(2-fluorobenzoyl)-9*a*-hydroxy-4-phenyl-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4h). White solid; Mp 216–219 °C; IR (KBr): 3430, 1701, 1599, 1517, 1135, 748, 551 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.40 (br, 1H, NH), 7.36–7.41 (m, 2H, ArH), 7.28–7.33 (m, 1H, ArH), 7.16–7.24 (m, 3H, ArH), 6.95–7.08 (m, 4H, ArH), 6.84–6.91 (m, 3H, ArH), 6.58–6.64 (m, 1H, ArH), 6.43 (br, 1H, OH), 4.43 (AB, J = 15.0 Hz, 2H, $ArCH_2$), 3.71–3.77 (m, 2H, NCH_2), 3.60–3.63 (m, 1H, CH), 3.47–3.53 (m, 2H, NCH_2), 3.38–3.42 (m, 1H, CH), 3.06 (t, J = 9.5 Hz, 1H, NCH_2), 2.74–2.79 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 184.3, 170.0, 159.4; 145.9, 136.8, 130.9, 129.7, 129.2, 128.6, 128.2, 128.0; 127.8, 125.9; 124.1; 115.6; 115.4, 84.7, 82.6, 47.3, 47.0, 46.2, 43.3, 42.7, 39.3; HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{27}FN_3O_3$ [(M + H)$^+$], 484.2031; found, 484.2031.

2-Benzyl-5-(2-fluorobenzoyl)-9*a*-hydroxy-4-(4-methoxyphenyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo-[3,4-*e*]-pyridin-1-one (4i). White solid; Mp 221–224 °C; IR (KBr): 3435, 1700, 1599, 1513, 1244, 749, 547 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.39 (br, 1H, NH), 7.36–7.40 (m, 2H, ArH), 7.30–7.33 (m, 1H, ArH), 7.17–7.27 (m, 3H, ArH), 6.96–7.02 (m, 1H, ArH), 6.87–6.93 (m, 1H, ArH), 6.80 (d, J = 6.7 Hz, 2H, ArH), 6.60–6.68 (m, 3H, ArH), 6.40 (br, 1H, OH), 4.43 (s, 2H, $ArCH_2$), 3.70–3.74 (m, 1H, CH), 3.64–3.68 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.45–3.51 (m, 1H, CH), 3.36–3.46 (m, 2H, NCH_2), 3.01–3.08 (m, 1H, NCH_2), 2.62–2.68 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 184.3, 170.1, 159.3; 157.5, 137.9, 136.8, 129.6, 129.2, 129.1, 128.6, 128.0; 124.1; 115.5, 113.2; 84.9, 82.7, 55.3, 47.4, 47.0, 46.2, 43.3, 42.7, 38.7; HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{29}FN_3O_4$ [(M + H)$^+$], 514.2137; found, 514.2142.

2-Benzyl-5-(4-chlorobenzoyl)-4-(2,4-dichlorophenyl)-9*a*-hydroxy-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4j). White solid; Mp 223–226 °C; IR (KBr): 3424, 1701, 1601, 1511, 1204, 841, 543 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.50 (br, 1H, NH), 7.31–7.40 (m, 5H, ArH), 7.17–7.25 (m, 5H, ArH), 6.80 (d, J = 7.1 Hz, 2H, ArH), 6.53 (br, 1H, OH), 4.42 (AB, J = 14.8 Hz, 2H, $ArCH_2$), 3.96–3.99 (m, 1H, CH), 3.70–3.78 (m, 2H, NCH_2), 3.59–3.63 (m, 1H, CH_2), 3.45–3.51 (m, 1H, NCH_2), 3.29–3.33 (m, 1H, CH), 3.04–3.09 (m, 1H, NCH_2), 2.63–2.67 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.0, 169.7, 159.9, 142.0, 141.6, 136.7, 133.0, 132.6, 132.4; 131.6, 129.3, 128.5, 128.1, 128.1, 128.0, 127.8, 127.3, 82.4, 82.2, 46.7, 46.2, 45.2, 43.4, 42.8, 36.2; HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{25}Cl_3N_3O_3$ [(M + H)$^+$], 568.0956; found, 568.0949.

2-Benzyl-5-(4-chlorobenzoyl)-4-(4-chlorophenyl)-9*a*-hydroxy-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4k). White solid; Mp 230–233 °C; IR (KBr): 3319, 1703, 1599, 1513, 1281, 827, 546 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.54 (br, 1H, NH), 7.35–7.40 (m, 2H, ArH), 7.28–7.32 (m, 1H, ArH), 7.17–7.23 (m, 6H, ArH), 7.03 (d, J = 7.9 Hz, 2H, ArH), 6.86 (d, J = 7.8 Hz, 2H, ArH), 6.43 (br, 1H, OH), 4.41 (AB, J = 15.1 Hz, 2H, $ArCH_2$), 3.72–3.74 (m, 1H, CH), 3.69–3.72 (m, 2H, CH_2), 3.59–3.62 (m, 1H, CH_2), 3.47–3.50 (m, 1H, NCH_2), 3.04 (t, J = 9.5 Hz, 1H, NCH), 2.74–2.80 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.6, 170.0, 159.9, 145.3, 141.9, 136.8, 132.6, 130.5, 130.1, 129.2, 128.2; 128.2, 128.1, 128.0, 82.9, 82.6, 47.5, 46.9, 46.2, 43.4, 42.7, 39.0; HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{26}Cl_2N_3O_3$ [(M + H)$^+$], 534.1346; found, 534.1348.

2-Benzyl-5-(4-chlorobenzoyl)-9*a*-hydroxy-4-phenyl-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4l). White solid; Mp 200–202 °C; IR (KBr): 3325, 1703, 1596, 1515, 1278, 1013, 751 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.57 (br, 1H, NH), 7.35–7.39 (m, 2H, ArH), 7.26–7.32 (m, 1H, ArH), 7.13–7.22 (m, 6H, ArH), 7.05–7.09 (m, 1H, ArH), 6.99–7.04 (m, 2H, ArH), 6.85 (d, J = 7.7 Hz, 2H, ArH), 6.37 (br, 1H, OH), 4.42 (AB, J = 15.4 Hz, 2H, $ArCH_2$), 3.74–3.77 (m, 1H, CH), 3.64–3.72 (m, 2H, CH_2), 3.57–3.62 (m, 1H, NCH_2), 3.49–3.53 (m, 1H, NCH_2), 3.05 (t, J = 9.4 Hz, 1H, NCH_2), 2.78–2.83 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.7, 170.1, 160.1, 146.4, 142.1, 136.9, 132.6, 129.3, 128.4, 128.2, 128.2, 128.0, 126.1, 83.4, 82.7, 47.7, 47.2, 46.2, 43.4, 42.7, 40.4; HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{27}ClN_3O_3$ [(M + H)$^+$], 500.1735; found, 500.1743.

2-Benzyl-5-(4-chlorobenzoyl)-9*a*-hydroxy-4-(4-methoxyphenyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4m). White solid; Mp 237–239 °C; IR (KBr): 3328, 1699, 1597, 1511, 1246, 1019, 833 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.55 (br, 1H, NH), 7.35–7.38 (m, 2H, ArH), 7.29–7.32 (m, 1H, ArH), 7.16–7.21 (m, 4H, ArH), 6.92 (d, J = 7.8 Hz, 2H, ArH), 6.87 (d, J = 7.8 Hz, 2H, ArH), 6.72 (d, J = 7.8 Hz, 2H, ArH), 6.32 (br, 1H, OH), 4.43 (AB, J = 15.0 Hz, 2H, $ArCH_2$), 3.68–3.72 (m, 1H, CH), 3.68 (s, 3H, OCH_3), 3.58–3.64 (m, 2H, CH_2), 3.50 (d, J = 7.6 Hz, 1H, CH), 3.02 (t, J = 9.3 Hz, 1H, NCH_2), 2.75–2.80 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.5, 170.1, 160.7; 157.6, 142.0, 138.2, 136.8, 132.6, 129.2, 129.2, 128.3, 128.0; 128.0, 113.5, 83.6, 82.7, 55.3, 47.8, 47.1, 46.2, 43.3, 42.6, 38.8; HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{29}ClN_3O_4$ [(M + H)$^+$], 530.1841; found, 530.1846.

5-Benzoyl-2-benzyl-4-(2,4-dichlorophenyl)-9*a*-hydroxy-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4n). White solid; Mp 222–225 °C; IR (KBr): 3283, 1703, 1602, 1513, 1208, 701, 600 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.53 (br, 1H, NH), 7.26–7.40 (m, 5H, ArH), 7.10–7.21 (m, 6H, ArH), 6.77 (d, J = 7.4 Hz, 2H, ArH), 6.52 (br, 1H, OH), 4.42 (AB, J = 15.0 Hz, 1H, $ArCH_2$), 3.98–4.02 (m, 1H, CH), 3.73–7.77 (m, 2H, CH_2), 3.59–3.63 (m, 1H, CH_2), 3.45–3.49 (m, 1H, NCH_2), 3.30 (t, J = 8.9 Hz, 1H, NCH_2), 3.06 (t, J = 9.8 Hz, 1H, CH), 2.64 (t, J = 8.9 Hz, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.3, 169.7, 160.0, 142.9, 142.2, 136.7, 133.1, 132.4, 131.5, 129.2,

128.8, 128.4, 128.0, 127.8, 127.4, 127.2, 125.8, 82.4, 82.1, 46.7, 46.2, 45.2, 43.4, 42.8, 36.3; HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{26}Cl_2N_3O_3$ [(M + H)$^+$], 534.1346; found, 534.1351.

5-Benzoyl-2-benzyl-4-(4-chlorophenyl)-9*a*-hydroxy-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4o). White solid; Mp 216–219 °C; IR (KBr): 3432, 1704, 1598, 1511, 1281, 1012, 694 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.56 (br, 1H, NH), 7.35–7.38 (m, 2H, ArH), 7.29–7.33 (m, 1H, ArH), 7.10–7.24 (m, 7H, ArH), 7.00–7.04 (m, 2H, ArH), 6.83–6.87 (m, 2H, ArH), 6.41 (br, 1H, OH), 4.41 (AB, J = 14.8 Hz, 2H, $ArCH_2$), 3.72–3.74 (m, 1H, CH), 3.68–3.72 (m, 2H, CH_2), 3.59–3.63 (m, 1H, CH_2), 3.46–3.50 (m, 1H, NCH_2), 3.05 (t, J = 8.7 Hz, 1H, NCH_2), 2.75–2.83 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.1, 170.0, 159.8, 145.5, 143.1, 136.8, 130.4, 130.1, 129.2, 128.0, 128.0, 128.0, 126.3, 82.9, 82.7, 47.5, 47.0, 46.2, 43.4, 42.6, 39.1; HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{27}ClN_3O_3$ [(M + H)$^+$], 500.1735; found, 500.1735.

5-Benzoyl-2-benzyl-9*a*-hydroxy-4-phenyl-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4p). White solid; Mp 202–205 °C; IR (KBr): 3324, 1702, 1597, 1513, 1277, 1009, 698 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.60 (br, 1H, NH), 7.36–7.40 (m, 2H, ArH), 7.29–7.34 (m, 2H, ArH), 7.22–7.26 (m, 2H, ArH), 7.10–7.20 (m, 5H, ArH), 7.04–7.09 (m, 1H, ArH), 7.01 (d, J = 7.5 Hz, 2H, ArH), 6.85 (d, J = 7.5 Hz, 2H, ArH), 6.36 (br, 1H, OH), 4.42 (AB, J = 12.1 Hz, 2H, $ArCH_2$), 3.73–3.77 (m, 1H, CH), 3.68–3.74 (m, 2H, CH_2), 3.58–3.65 (m, 1H, CH_2), 3.38–3.53 (m, 1H, NCH_2), 3.32–3.36 (m, 1H, CH), 3.07 (t, J = 9.6 Hz, 1H, NCH_2), 2.81–2.85 (m, 1H, NCH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 189.5, 170.5, 160.4; 146.8, 143.7, 137.2, 129.6, 129.2, 128.7, 128.4, 128.4, 128.3; 126.8, 126.3, 83.7, 83.1, 48.0, 47.6, 46.6, 43.8, 43.1, 40.4; HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{28}N_3O_3$ [(M + H)$^+$], 466.2125; found,466.2132.

5-Benzoyl-2-benzyl-9*a*-hydroxy-4-(4-methoxyphenyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4q). White solid; Mp 217–220 °C; IR (KBr): 3431, 1698, 1598, 1511, 1245, 1021, 702 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.59 (br, 1H, NH), 7.35–3.40 (m, 2H, ArH), 7.28–7.32 (m, 1H, ArH), 7.16–7.22 (m, 3H, ArH), 7.11–7.15 (m, 2H, ArH), 6.92 (d, J = 8.4 Hz, 2H, ArH), 6.86 (d, J = 7.2 Hz, 2H, ArH), 6.71 (d, J = 8.4 Hz, 2H, ArH), 6.32 (br, 1H, OH), 4.41 (s, 2H, $ArCH_2$), 3.75 (d, J = 8.8 Hz, 1H, CH), 3.69–3.74 (m, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.57–3.61 (m, 1H, CH), 3.51 (t, J = 6.9 Hz, 1H, CH_2), 3.04 (t, J = 9.6 Hz, 1H, NCH_2), 2.77–2.83 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.0, 170.1, 160.7; 157.5, 143.3, 138.3, 136.8, 129.2, 129.2, 128.0, 127.9, 126.4, 113.4; 83.6, 82.8, 55.3, 47.8, 47.1, 46.2, 43.4, 42.6, 38.9; HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{30}N_3O_4$ [(M + H)$^+$], 496.2231; found, 496.2239.

2-Benzyl-4-(2,4-dichlorophenyl)-9*a*-hydroxy-5-(4-methylbenzoyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4r). White solid; Mp 234–237 °C; IR (KBr): 3788, 3427, 1699, 1638, 1253, 1168, 735, 657 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.58 (br, 1H, NH), 7.43 (s, 1H, ArH), 7.32–7.39 (m, 4H, ArH), 7.20–7.25 (m, 3H, ArH), 6.96 (d, J = 7.0 Hz, 2H, ArH), 6.70 (d, J = 7.0 Hz, 2H, ArH), 6.50 (br, 1H, OH), 4.51 (AB, J = 14.7 Hz, 2H, $ArCH_2$), 4.03–4.07 (m, 1H, CH), 3.70–3.78 (m, 2H, CH_2), 3.62 (d, J = 7.5 Hz, 1H, CH), 3.48 (d, J = 5.4 Hz, 1H, NCH_2), 3.31 (d, J = 7.9 Hz, 1H, NCH_2), 3.05 (t, J = 9.4 Hz, 1H, NCH_2), 2.68–3.73 (m, 1H, NCH_2), 2.23 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.1, 169.8, 160.0, 142.2, 140.1, 137.4, 136.7, 133.1, 132.4, 131.5, 129.2, 128.5, 128.0, 127.2, 125.9, 82.4, 82.0, 46.7, 46.2, 45.2, 43.4, 42.7, 36.4, 21.2; HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{28}Cl_2N_3O_3$ [(M + H)$^+$], 548.1502; found, 548.1500.

2-Benzyl-4-(4-chlorophenyl)-9*a*-hydroxy-5-(4-methylbenzoyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4s). White solid; Mp 228–230 °C; IR (KBr): 3312, 1703, 1595, 1512, 1215, 837, 580 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.58 (br, 1H, NH), 7.35–7.39 (m, 2H, ArH), 7.28–7.32 (m, 1H, ArH), 7.18–7.24 (m, 4H, ArH), 7.05 (d, J = 7.9 Hz, 2H, ArH), 6.95 (d, J = 7.4 Hz, 2H, ArH), 6.77 (d, J = 7.4 Hz, 2H, ArH), 6.37 (br, 1H, OH), 4.41 (AB, J = 15.3 Hz, 2H, $ArCH_2$), 3.74–3.78 (m, 1H, CH), 3.65–3.71 (m, 2H, CH_2), 3.56–3.60 (m, 1H, CH_2), 3.46–3.50 (m, 1H, NCH_2), 3.35–3.39 (m, 1H, CH), 3.03 (t, J = 9.5 Hz, 1H, NCH_2), 2.78–2.83 (m, 1H, NCH_2), 2.21 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.1, 170.0, 159.9, 145.5, 140.3, 137.4, 136.8, 130.4, 130.1, 129.2, 128.5, 128.0, 128.0, 126.4, 82.8, 82.7, 47.6, 47.0, 46.1, 43.4, 42.6, 39.1, 21.2; HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{29}ClN_3O_3$ [(M + H)$^+$], 514.1892; found, 514.1890.

2-Benzyl-9*a*-hydroxy-5-(4-methylbenzoyl)-4-phenyl-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4t). White solid; Mp 213–216 °C; IR (KBr): 3335, 1704, 1597, 1514, 1279, 907, 698 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.61 (br, 1H, NH), 7.35–7.40 (m, 2H, ArH), 7.25–7.29 (m, 1H, ArH), 7.10–7.25 (m, 4H, ArH), 7.02–7.08 (m, 3H, ArH), 6.92 (d, J = 7.6 Hz, 2H, ArH), 6.76 (d, J = 7.6 Hz, 2H, ArH), 6.30 (br, 1H, OH), 4.41 (s, 2H, $ArCH_2$), 3.73–3.77 (m, 1H, CH), 3.62–3.68 (m, 2H, CH_2), 3.57–3.61 (m, 1H, CH), 3.48–3.52 (m, 1H, NCH_2), 3.04 (t, J = 9.5 Hz, 1H, NCH_2), 2.82–2.88 (m, 1H, NCH_2), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.0, 170.1, 160.0; 146.5, 140.4, 137.3, 136.8, 129.2, 128.8, 128.4, 128.3; 128.1, 128.0; 127.8; 126.5; 126.0, 83.2, 82.7, 47.7, 47.1, 46.1, 43.4, 42.6, 39.3, 21.2; HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{30}N_3O_3$ [(M + H)$^+$], 480.2287; found, 480.2287.

2-Benzyl-9*a*-hydroxy-4-(4-methoxyphenyl)-5-(4-methylbenzoyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4u). White solid; Mp 222–225 °C; IR (KBr): 3416, 1700, 1598, 1510, 1246, 1022, 758 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.60 (br, 1H, NH), 7.35–7.40 (m, 2H, ArH), 7.29–7.33 (m, 1H, ArH), 7.20 (d, J = 7.1 Hz, 2H, ArH), 6.91–6.97 (m, 4H, ArH), 6.79 (d, J = 7.9 Hz, 2H, ArH), 6.73 (d, J = 8.6 Hz, 2H, ArH), 6.26 (br, 1H, OH), 4.40 (s, 2H, $ArCH_2$), 3.65–3.69 (m, 1H, CH), 3.61–3.67 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.57–3.61 (m, 1H, CH), 3.48–3.52 (m, 1H, CH_2), 3.02 (t, J = 9.5 Hz, 1H, NCH_2), 2.80–2.84 (m, 1H, NCH_2), 2.21 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 189.0, 170.2, 160.7, 157.5, 140.5, 138.3, 137.3, 136.8, 129.2, 129.2, 128.4, 128.0, 126.5, 113.5, 83.5, 82.8, 55.3, 47.8, 47.1, 46.1, 43.4, 42.6, 38.9, 21.2; HRMS (ESI-TOF): *m*/*z* calcd for $C_{31}H_{32}N_3O_4$ [(M + H)$^+$], 510.2387; found, 510.2398.

2-Benzyl-4-(2,4-dichlorophenyl)-9*a*-hydroxy-5-(4-methoxybenzoyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo-[3,4-*e*]pyridin-1-one (4v). White solid; Mp 229–231 °C; IR (KBr): 3419, 1703, 1598, 1509, 1250, 838, 749 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.54 (br, 1H, NH), 8.29 (br, 1H, OH), 7.41 (s, 1H, ArH), 7.26–7.37 (m, 4H, ArH), 7.15–7.18 (m, 3H, ArH), 6.76 (d, J = 8.6 Hz, 2H, ArH), 6.66 (d, J = 8.6 Hz, 2H, ArH), 4.44 (AB,

J = 15.0 Hz, 1H, $ArCH_2$), 4.05–4.09 (m, 1H, CH), 3.67–3.71 (m, 2H, CH_2), 3.64 (s, 3H, OCH_3), 3.55–3.59 (m, 1H, CH), 3.43–3.47 (m, 1H, NCH_2), 3.26–3.30 (m, 1H, NCH_2), 2.98–3.02 (m, 1H, NCH_2), 2.64–2.68 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.6, 169.8, 160.1, 159.3, 142.2, 136.7, 135.3, 133.1, 132.3, 131.5, 129.2, 128.6, 128.6, 128.0, 127.6, 127.3, 113.3, 82.4, 82.0, 55.5, 46.7, 46.2, 45.3, 43.4, 42.7, 36.5; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{28}Cl_2N_3O_4$ [$(M + Na)^+$], 586.1271; found, 586.1270.

2-Benzyl-4-(4-chlorophenyl)-9*a*-hydroxy-5-(4-methoxybenzoyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo-[3,4-*e*]-pyridin-1-one (4w). White solid; Mp 230–232 °C; IR (KBr): 3420, 1705, 1597, 1510, 1249, 1017, 649 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.59 (br, 1H, NH), 7.35–7.40 (m, 2H, ArH), 7.28–7.33 (m, 1H, ArH), 7.19–7.24 (m, 4H, ArH), 7.08 (d, J = 8.1 Hz, 2H, ArH), 6.86 (d, J = 8.2 Hz, 2H, ArH), 6.69 (d, J = 8.2 Hz, 2H, ArH), 6.36 (br, 1H, OH), 4.41 (AB, J = 15.1 Hz, 2H, $ArCH_2$), 3.81–3.84 (m, 1H, CH), 3.72 (s, 3H, OCH_3), 3.67–3.71 (m, 2H, CH_2), 3.56–3.60 (m, 1H, CH), 3.46–3.50 (m, 1H, NCH_2), 3.03 (t, J = 4.8 Hz, 1H, NCH_2), 2.79–2.84 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.5, 170.0, 159.9, 159.3, 145.5, 136.8, 135.5, 130.4, 130.1, 129.2, 128.1, 128.0, 128.1, 113.2, 82.8, 82.7, 55.4, 47.6, 47.0, 46.1, 43.4, 42.6, 39.1; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{29}ClN_3O_4$ [$(M + H)^+$], 530.1841; found, 530.1840.

2-Benzyl-9*a*-hydroxy-5-(4-methoxybenzoyl)-4-phenyl-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridin-1-one (4x). White solid; Mp 192–194 °C; IR (KBr): 3328, 1705, 1594, 1247, 1023 694, 576 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.62 (br, 1H, NH), 7.35–3.40 (m, 2H, ArH), 7.28–7.32 (m, 1H, ArH), 7.15–7.22 (m, 4H, ArH), 7.05–7.08 (m, 3H, ArH), 6.86 (d, J = 8.1 Hz, 2H, ArH), 6.67 (d, J = 8.1 Hz, 2H, ArH), 6.28 (br, 1H, OH), 4.41 (s, 2H, $ArCH_2$), 3.80–3.84 (m, 1H, CH), 3.69–3.75 (m, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.56–3.60 (m, 1H, CH), 3.49–3.53 (m, 1H, NCH_2), 3.43–3.47 (m, 1H, NCH_2), 3.05 (t, J = 9.4 Hz, 1H, NCH_2), 2.84–2.89 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.5, 170.1, 160.1; 159.3, 146.5, 136.8, 135.6, 129.2, 128.3, 128.2, 128.2, 128.0, 126.0, 113.1, 83.2, 82.7, 55.4, 47.7, 47.2, 46.1, 43.4, 42.6, 39.4; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{30}N_3O_4$ [$(M + H)^+$], 496.2231; found, 496.2239.

2-Benzyl-9*a*-hydroxy-5-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-2,3,3*a*,4,6,7,8,9*a*-octahydro-1*H*-imidazo[1,2-*a*]pyrrolo[3,4-*e*]-pyridin-1-one (4y). White solid; Mp 216–219 °C; IR (KBr): 3431, 1698, 1599, 1510, 1246, 833, 408 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.62 (br, 1H, NH), 7.35–7.40 (m, 2H, ArH), 7.28–7.32 (m, 1H, ArH), 7.20 (d, J = 7.4 Hz, 2H, ArH), 6.97 (d, J = 8.4 Hz, 2H, ArH), 6.88 (d, J = 8.4 Hz, 2H, ArH), 6.74 (d, J = 8.4 Hz, 2H, ArH), 6.68 (d, J = 8.4 Hz, 2H, ArH), 6.25 (br, 1H, OH), 4.40 (s, 2H, $ArCH_2$), 3.74–3.78 (m, 1H, CH), 3.69 (s, 3H, OCH_3), 3.65–3.69 (m, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.61–3.65 (m, 1H, CH), 3.55–3.59 (m, 1H, CH_2), 3.48–3.52 (m, 1H, CH_2), 3.02 (t, J = 9.5 Hz, 1H, NCH_2), 2.81–2.86 (m, 1H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.4, 170.2, 160.0, 159.3, 157.5, 138.4, 136.8, 135.6, 129.2, 128.2, 128.0, 113.5, 113.1, 83.5, 82.8, 55.4, 55.3, 47.9, 47.1, 46.1, 43.4, 42.6, 39.0; HRMS (ESI-TOF): m/z calcd for $C_{31}H_{32}N_3O_5$ [$(M + H)^+$], 526.2336; found, 526.2344.

2-Benzyl-4-(2,4-dichlorophenyl)-5-(4-fluorobenzoyl)-10*a*-hydroxy-2,3,3*a*,4,6,7,8,9-octahydropyrrolo[3′,4′:5,6]pyrido-[1,2-*a*]pyrimidin-1(10*aH*)-one (5a). White solid; Mp 187–190 °C; IR (KBr): 3403, 1703, 1595, 1545, 1237, 841, 541 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.55 (br, 1H, NH), 7.17–7.40 (m, 8H, ArH), 6.90–6.96 (m, 2H, ArH), 6.68–6.74 (m, 2H, ArH), 6.46 (br, 1H, OH), 4.47 (d, J = 14.7 Hz, 1H, $ArCH_2$), 4.33 (d, J = 14.7 Hz, 1H, $ArCH_2$), 3.79–3.83 (m, 1H, CH), 3.41–3.54 (m, 2H, CH_2), 3.24–3.28 (m, 1H, CH), 3.12–3.18 (m, 1H, NCH_2), 2.64–2.72 (m, 1H, NCH_2), 1.79–1.99 (m, 2H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 185.8, 169.8, 157.5, 141.8, 139.8, 136.7, 133.0, 132.7, 131.5, 129.2, 128.8, 128.5, 128.0, 127.8, 127.4, 115.1 (d, J = 22.0 Hz), 114.9 (d, J = 22.0 Hz), 83.9, 83.2, 46.5, 46.3, 44.4, 40.6, 40.4, 38.5, 36.4, 20.7; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{27}Cl_2FN_3O_3$ [$(M + H)^+$], 566.1408; found, 566.1412.

2-Benzyl-5-(4-chlorobenzoyl)-4-(2,4-dichlorophenyl)-10*a*-hydroxy-2,3,3*a*,4,6,7,8,9-octahydropyrrolo[3′,4′:5,6]pyrido-[1,2-*a*]pyrimidin-1(10*aH*)-one (5b). White solid; Mp 193–196 °C; IR (KBr): 3402, 1703, 1593, 1547, 1244, 842, 517 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$-d_6): δ = 12.61 (br, 1H, NH), 7.25–7.29 (m, 3H, ArH), 7.17–7.21 (m, 1H, ArH), 7.12–7.16 (m, 2H, ArH), 7.05–7.11 (m, 2H, ArH), 7.03 (d, J = 8.1 Hz, 2H, ArH), 6.65 (d, J = 8.1 Hz, 2H, ArH), 4.35 (s, 2H, $ArCH_2$), 4.09 (s, 1H, CH), 3.82 (br, 1H, OH), 3.31–3.44 (m, 4H, CH_2), 3.09–3.18 (m, 2H, CH_2), 2.78 (t, J = 8.4 Hz, 1H, CH), 1.79–1.92 (m, 2H, NCH_2); ^{13}C NMR (100 MHz, $CDCl_3$-d_6): δ = 186.6, 169.7, 157.5, 140.6, 140.3, 134.9, 133.6, 133.3, 132.8, 131.1, 129.1, 128.3, 128.1, 127.9, 127.1, 127.0, 84.3, 82.9, 47.2, 46.7, 44.7, 39.8, 38.6, 36.1, 20.7; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{27}Cl_3N_3O_3$ [$(M + H)^+$], 582.1113; found, 582.1112.

5-Benzoyl-2-benzyl-4-(2,4-dichlorophenyl)-10*a*-hydroxy-2,3,3*a*,4,6,7,8,9-octahydropyrrolo[3′,4′:5,6]pyrido[1,2-*a*]pyrimidin-1(10*aH*)-one (5c). White solid; Mp 188–190 °C; IR (KBr): 3456, 1703, 1598, 1544, 1049, 700, 459 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.61 (br, 1H, NH), 7.33–7.41 (m, 5H, ArH), 7.09–7.31 (m, 6H, ArH), 6.65–6.61 (m, 2H, ArH), 6.44 (br, 1H, OH), 4.48 (d, J = 14.9 Hz, 1H, $ArCH_2$), 4.34 (AB, J = 15.0 Hz, 2H, $ArCH_2$), 3.55–3.61 (m, 2H, CH_2), 3.44–3.51 (m, 2H, CH_2), 3.25–3.29 (m, 1H, CH), 3.14–3.18 (m, 1H, NCH_2), 2.70–2.76 (m, 1H, NCH_2), 1.90–1.96 (m, 2H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 186.9, 169.9, 157.6, 143.3, 141.9, 136.7, 133.1, 132.6, 131.4; 129.2, 128.4, 128.1, 128.0, 127.6, 127.3, 125.6, 83.8, 83.3, 46.5, 46.3, 44.5, 40.6, 38.5, 36.5, 20.8; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{28}Cl_2N_3O_3$ [$(M + H)^+$], 548.1502; found, 548.1501.

2-Benzyl-4-(2,4-dichlorophenyl)-10*a*-hydroxy-5-(4-methylbenzoyl)-2,3,3*a*,4,6,7,8,9-octahydropyrrolo[3′,4′:5,6]pyrido-[1,2-*a*]-pyrimidin-1(10*aH*)-one (5d). White solid; Mp 195–197 °C; IR (KBr): 3422, 1702, 1545, 1247, 1123, 761, 703 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.72 (br, 1H, NH), 7.39–7.45 (m, 4H, ArH), 7.35–7.39 (m, 1H, ArH), 7.31–7.35 (m, 1H, ArH), 7.22–7.28 (m, 2H, ArH), 6.95 (d, J = 7.8 Hz, 2H, ArH), 6.62 (d, J = 7.8 Hz, 2H, ArH), 4.43 (AB, J = 15.0 Hz, 2H, $ArCH_2$), 3.88–3.92 (m, 1H, CH), 3.82 (br, 1H, OH), 3.59–3.64 (m, 4H, CH_2), 3.27–3.31 (m, 1H, CH), 3.13–3.17 (m, 1H, CH_2), 2.76 (t, J = 8.8 Hz, 1H, CH_2), 1.22 (s, 3H, CH_3), 1.83–1.93 (m, 2H, NCH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 186.9, 169.9, 157.6, 142.0, 140.5, 136.8, 136.7, 133.1, 132.6, 131.4, 129.2, 128.6, 128.0, 127.3, 125.6, 83.8, 83.3, 46.5, 46.3, 44.5, 39.3, 38.5, 36.6, 21.2, 20.8; HRMS (ESI-TOF): m/z calcd for $C_{31}H_{30}Cl_2N_3O_3$ [$(M + H)^+$], 562.1659; found, 561.1663.

2-Benzyl-4-(2,4-dichlorophenyl)-10*a*-hydroxy-5-(4-methoxybenzoyl)-2,3,3*a*,4,6,7,8,9-octahydropyrrolo[3′,4′:5,6]pyrido[1,2-*a*]-pyrimidin-1(10*aH*)-one (5e). White solid; Mp 179–182 °C; IR (KBr): 3408, 1700, 1596, 1544, 1244, 1041, 702 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 12.75$ (br, 1H, NH), 7.43 (s, 1H, ArH), 7.35–7.40 (m, 2H, ArH), 7.31–7.34 (m, 1H, ArH), 7.29–7.33 (m, 1H, ArH), 7.21–7.25 (m, 2H, ArH), 6.67–6.73 (m, 4H, ArH), 6.62 (br, 1H, OH), 4.34 (AB, $J = 14.9$ Hz, 2H, $ArCH_2$), 3.92–3.95 (m, 1H, CH), 3.64 (s, 3H, OCH_3), 3.42–3.49 (m, 2H, CH_2), 3.26–3.30 (m, 1H, CH), 3.10–3.19 (m, 1H, CH_2), 2.76 (t, $J = 8.8$ Hz, 1H, CH_2), 1.80–1.90 (m, 2H, NCH_2), 1.83–1.93 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 186.2$, 169.6, 158.5, 157.4, 141.7, 136.4, 135.5, 132.8, 132.3, 131.1; 128.9, 128.2, 127.7, 127.0, 126.9, 113.1, 83.5, 82.9, 55.1, 46.2, 46.0, 44.2, 40.2, 38.2, 36.4, 20.5; HRMS (ESI-TOF): *m*/*z* calcd for $C_{31}H_{30}Cl_2N_3O_4$ [$(M + H)^+$], 578.1608; found, 578.1615.

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