A Facile Route to 1,3-Diazaheterocycle-Fused [1,2-*a*]Indole Derivatives via Acetic Acid Catalyzed Cyclocondensation Reactions

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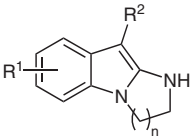
Abstract: A concise and efficient route for the synthesis of 1,3-diazaheterocycle-fused [1,2-*a*]indoles by simply refluxing a reaction mixture of different types of heterocyclic ketene aminals and 1,4-benzoquinones catalyzed by acetic acid was developed. This protocol provides an alternative method for application in combinatorial and parallel synthesis in drug discovery.

Key words: 1,3-diazaheterocycle-fused [1,2-a]indoles, heterocyclic ketene aminals, 1,4-benzoquinones, catalyst, acetic acid

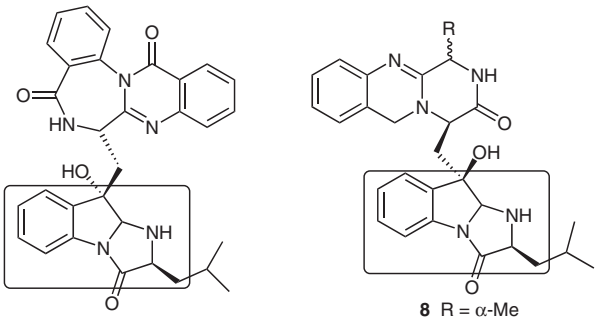
1,3-Diazaheterocycle-fused [1,2-*a*]indole and related compounds, such as 2,3-dihydro-1*H*-imidazo[1,2-*a*]indole (**4**), 1,2,3,4-tetrahydropyrimido[1,2-*a*]indole (**5**), and 2,3,4,5-tetrahydro-1*H*-[1,3]diazepino[1,2-*a*]indole (**6**) (Figure 1) are commonly found in nature and many alkaloids exist holding this kind of scaffold.[2] For instance, imidazoindoles are present as the key structural motif in the core structures of novel marine natural products and biologically active molecules, including the potent cholecystokinin antagonist asperlicin (**7**)[3] and the antifungal and moderately cytotoxic fumiquinazolines A (**8**) and B (**9**)[2a,b,4] (Figure 2). In addition, such 2-amino-substituted indoles are versatile building blocks for the total synthesis of natural products.[5] Because of their broad range of biological activities and their value as synthetic precursors for pharmaceutical compounds, 2-amino-substituted indole derivatives have received increasing interest over many years.[6] Mild and efficient methods to synthesize 2-amino-substituted indoles, such as transition metal-catalyzed procedures,[7] have been developed. However, such 2-amino-substituted indole moieties are difficult to access through traditional synthetic methods such as Fischer indole synthesis.[5,7–9] The introduction of multiple substituents into the indole ring often requires multistep reactions and complex experimental processes. Procedures to prepare highly functional and diverse 2-amino-substituted indoles are limited, hence a general and concise approach to this class of heterocycles that tolerates a wide variety of functional groups is highly desirable.

Heterocyclic ketene aminals (HKAs) are versatile intermediates for the synthesis of a wide variety of fused heterocyclic compounds.[10] These fused heterocyclic structures are frequently found in pharmacophores and play important roles in drug discovery and are also used as herbicides, pesticides,[11] antianxiety agents,[12] antileishmanial agents[13] and antibacterial drugs.[14]



4 n = 1
5 n = 2
6 n = 3

Figure 1 Chemical structures of 1,3-diazaheterocycle-fused [1,2-*a*]indoles



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8 R = α-Me
9 R = β-Me

Figure 2 Structures of natural products containing imidazoindole structural motif

Recently, we reported novel methods for the construction of a 1,3-diazaheterocycle-fused [1,2-*b*]isoquinolin-1(2*H*)-one library[15a] and a bicyclic pyridone library.[15b] Subsequent biological assays revealed that these kinds of compounds possess excellent cytotoxic activities against cancer cell lines.[15] This result prompted us to develop a methodology for the construction of a structurally similar and novel 1,3-diazaheterocycle-fused [1,2-*a*]indole library, with the expectation of finding better leading compounds in the biological assays. In this paper, we report a convenient approach for the synthesis of a library of 1,3-diazaheterocycle-fused [1,2-*a*]indoles based upon 1,4-Michael addition and cyclocondensation reaction of HKAs with 1,4-benzoquinones in good yields.

To examine the practicality of the projected synthetic route, we first evaluated the cyclocondensation reaction of highly functionalized 1,4-benzoquinone **1a** and ethyl 2-(imidazolidin-2-ylidene)acetate (**2a**). In earlier literature,

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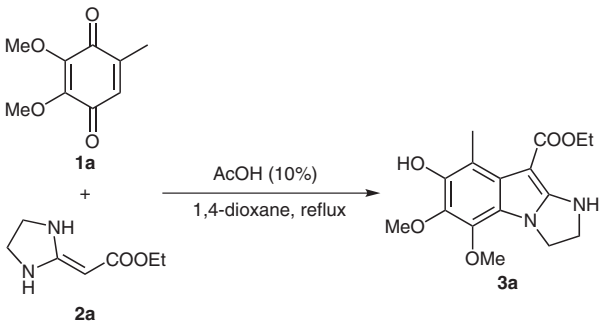
only one example of the reaction of 1,4-benzoquinone and heterocyclic ketene aminal has been examined; however, an exclusive tricyclic indole was obtained at a very low yield (9%).[16] The mixture in the present study was composed of a 1:1.1 ratio of **2a** to **1a** and was treated at reflux in various conditions (Scheme 1, Table 1, entries 1–10). Evaluation of the catalysts and solvents showed that the acid catalysts were better than the base catalysts, and that solvent reactions were superior to solvent-free conditions. Further screening of the solvents led to the identification of 1,4-dioxane as the most effective solvent for the transformation to the required product in a high isolated yield of 90%. Structural identification revealed that the compound obtained was the ethyl 2,3-dihydro-7-hydroxy-5,6-dimethoxy-8-methyl-1*H*-imidazo[1,2-*a*]indole-9-carboxylate (**3a**). Thus, we found that the optimum reaction condition for the formation of product **3a** was AcOH as the catalyst and 1,4-dioxane as the solvent (90%, Table 1, entry 8).

Table 1 Optimizing the Reaction Conditions for **3a**

Entry	Catalyst (10%)	Solvent	Time (h)	Yield (%)[a]
1	AcOH	–	8	15
2	Et_3N	–	8	5
3	DBU	–	8	trace
4	AcOH	CH_2Cl_2	8	28
5	Et_3N	CH_2Cl_2	8	19
6	AcOH	THF	8	40
7	AcOH	MeCN	8	44
8	AcOH	1,4-dioxane	8	90
9	Et_3N	1,4-dioxane	8	48
10	AcOH	toluene	8	64

[a] Isolated yields based on HKAs **2a**.



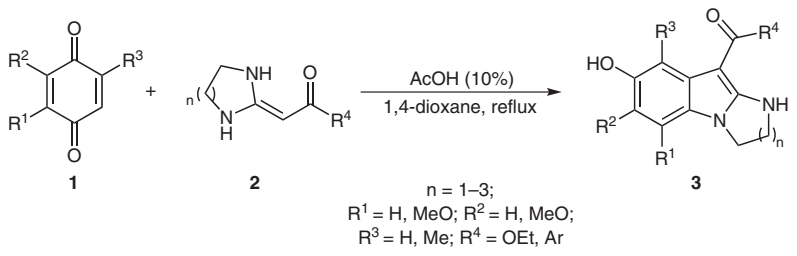
Scheme 1 Reaction of 1,4-benzoquinone **1a** with HKA **2a** in different conditions

Using the AcOH-catalyzed condition (10% AcOH, 1,4-dioxane), two 1,4-benzoquinones **1** reacted with various heterocyclic ketene aminals **2** to generate a number of 1,3-diazaheterocycle-fused [1,2-*a*]indoles **3**, as shown in Scheme 2 and Table 2 (entries 1–18). As a result, this methodology was found to be applicable to a diverse range of HKAs with various substituents and rings **2a**–**l** and 1,4-benzoquinones **1a**,**b**, producing the corresponding cyclocondensation products. The reactions usually took 6–8 hours at refluxing temperature in 1,4-dioxane under AcOH-catalyzed conditions for completion, and the yields were generally good.

The results in Table 2 demonstrate that HKAs, with various substituents (electron-withdrawing and -donating substituents on the aromatic backbone) and different ring-sizes **2a–l** were all good substrates for the reaction. The reactions were straightforward and gave very good to excellent overall yields. Notably, the structures of the HKAs **2** have an obvious influence on the reactivity and product yield. For example, the reactivity of **2** was increased by the electron-rich properties of the group on the aromatic ring (Table 2, entries 2–4, 7–10, 11–14, 15–18). Under the experimental conditions, the reactivity order of the six-membered HKAs was **2e > 2f > 2g > 2h**. The reactivity order of the seven-membered HKAs also showed the same tendency, that is, **2i = 2j > 2k > 2l**. Additionally, in terms of the ring-sizes of the HKAs **2**, the reactivity of five- and six-membered HKAs were superior to that of seven-membered HKAs. It is worth mentioning that the structure of the 1,4-benzoquinone **1** also had a noticeable influence on the reaction. The reactivity of **1** varied with the electron-rich properties of the groups R^1 to R^3, and the reactivity of 1,4-benzoquinone under the typical conditions was found to be **1a > 1b** (Table 2, entries 1–18).

To verify the structure of the 1,3-diazaheterocycle-fused [1,2-*a*]indole product, **3a** was selected as a representative compound and characterized by X-ray crystallography, as shown in Figure 3.[17]

A proposed mechanism of the acetic acid catalyzed cyclocondensation reaction is depicted in Scheme 3. The HKAs **2** react with 1,4-benzoquinone **1** possibly via an aza-ene



Scheme 2 Acetic acid catalyzed synthesis of 1,3-diazaheterocycle-fused [1,2-*a*]indoles **3**

addition mechanism[10a] to give the adduct **10** followed by imine–enamine tautomerization to form compound **11**, and subsequent condensation and elimination of H_2O resulted in the target product **3**.

In conclusion, this study offers a novel procedure for the facile synthesis of 1,3-diazaheterocycle-fused [1,2-*a*]indole derivatives. By simply refluxing a reaction mixture of different types of HKAs and 1,4-benzoquinones catalyzed by acetic acid, we obtained a novel library of 1,3-diazaheterocycle-fused [1,2-*a*]indoles. This protocol provides an alternative method for application in combinatorial and parallel syntheses in drug discovery.

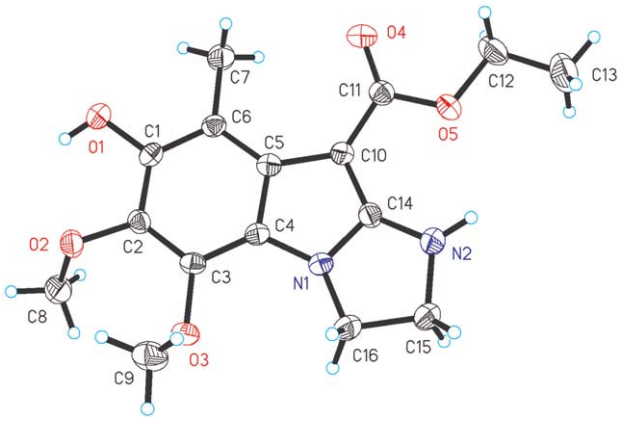


Figure 3 X-ray crystal structure of **3a**

Table 2 Synthesis of 1,3-Diazaheterocycle-Fused [1,2-*a*]Indoles **3**

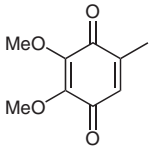
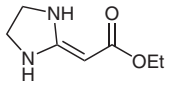
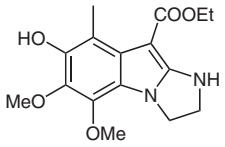
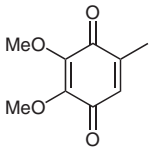
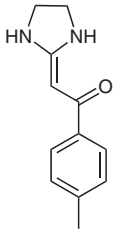
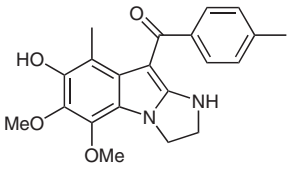
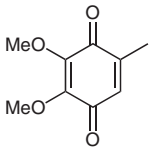
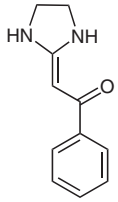
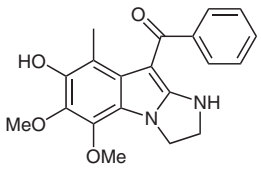
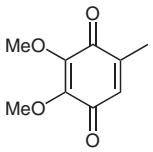
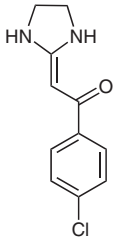
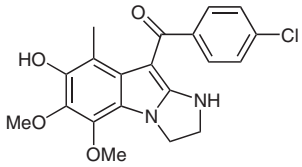
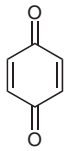
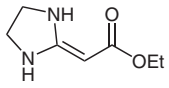
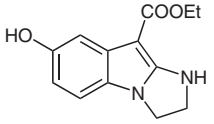
Entry	**1**		**2**		Product **3**		Yield (%)[a]
1	**1a**		**2a**		**3a**		90
2	**1a**		**2b**		**3b**		93
3	**1a**		**2c**		**3c**		92
4	**1a**		**2d**		**3d**		91
5	**1b**		**2a**		**3e**		78

Table 2 Synthesis of 1,3-Diazaheterocycle-Fused [1,2-*a*]Indoles **3** (continued)

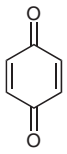
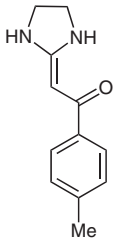
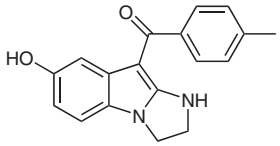
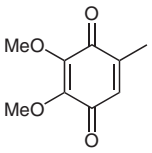
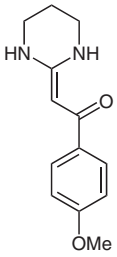
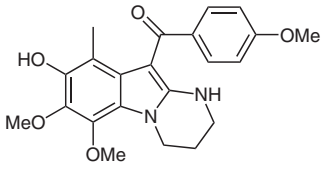
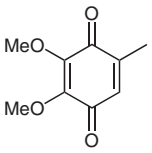
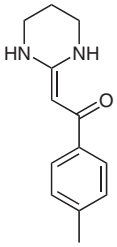
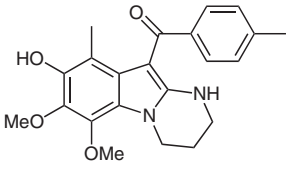
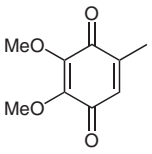
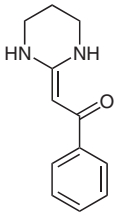
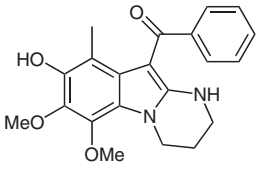
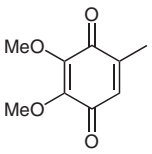
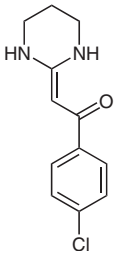
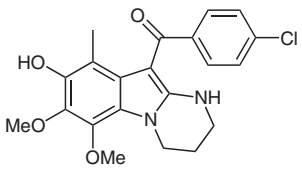
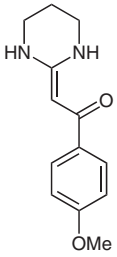
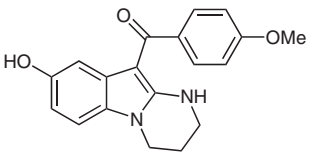
Entry	**1**		**2**		Product **3**		Yield (%)[a]
6	**1b**		**2b**		**3f**		86
7	**1a**		**2e**		**3g**		92
8	**1a**		**2f**		**3h**		90
9	**1a**		**2g**		**3i**		88
10	**1a**		**2h**		**3j**		87
11	**1b**		**2e**		**3k**		89

Table 2 Synthesis of 1,3-Diazaheterocycle-Fused [1,2-*a*]Indoles **3** (continued)

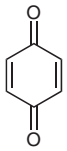
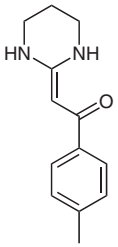
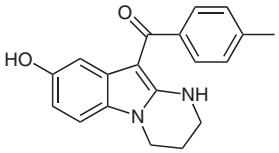
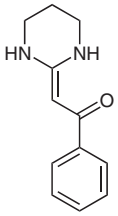
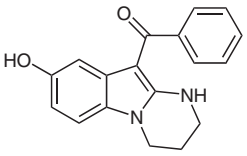
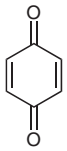
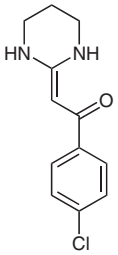
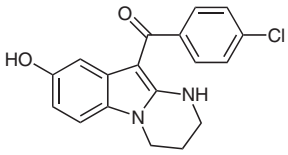
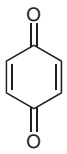
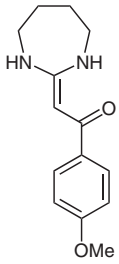
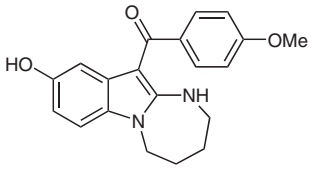
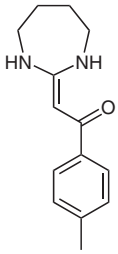
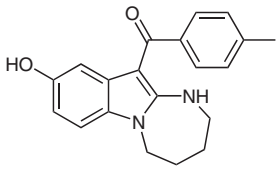
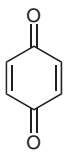
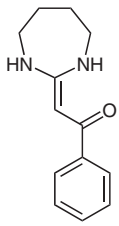
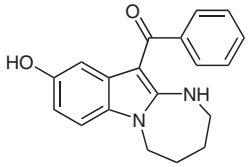
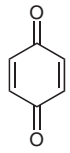
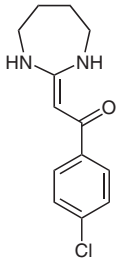
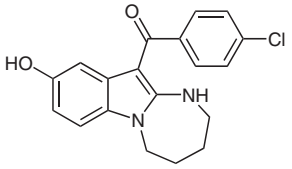
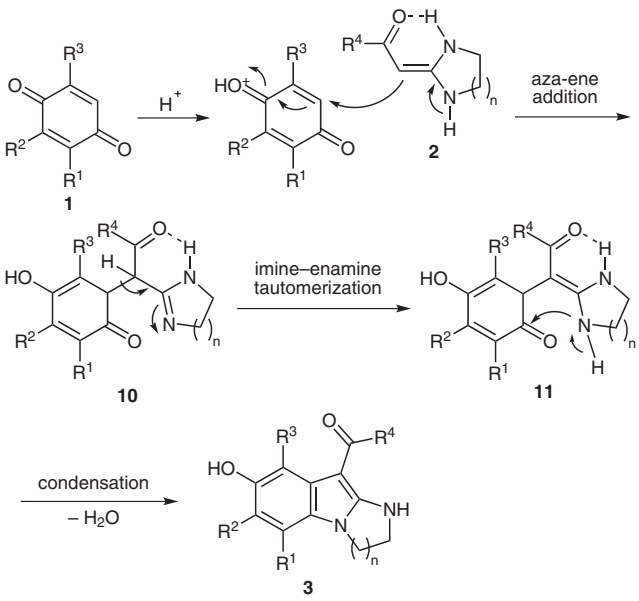
Entry	1		2		Product 3		Yield (%)[a]
12	**1b**		**2f**		**3l**		88
13	**1b**		**2g**		**3m**		85
14	**1b**		**2h**		**3n**		84
15	**1b**		**2i**		**3o**		86
16	**1b**		**2j**		**3p**		86
17	**1b**		**2k**		**3q**		80

Table 2 Synthesis of 1,3-Diazaheterocycle-Fused [1,2-*a*]Indoles **3** (continued)

Entry	1	2	Product 3	Yield (%)[a]
18	**1b** 	**2l** 	**3r** 	76

[a] Yield of isolated product from the reaction on a 1 mmol scale (based on HKAs **2**).



Scheme 3 Proposed mechanism for the acetic acid catalyzed cyclocondensation reaction of 1,4-benzoquinone **1** and HKAs **2**

All new compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 (^{1}H: 500 MHz, ^{13}C: 125 MHz), chemical shifts (δ) are expressed in ppm, and *J* values are given in Hz, and deuterated DMSO-d_6 or acetone-d_6 was used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellet. The reactions were monitored by TLC using silica gel GF_{254}. The melting points were determined on XT-4A melting point apparatus and are uncorrected. HRMS were performed on an Agilent LC/MSD TOF instrument.

All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh).

The material **2a** was synthesized according to the literature.[18]Compounds **2b–l** were prepared according to the literature.[19] Compounds **1a** and **1b** were purchased from Aldrich.

1,3-Diazaheterocycle-Fused [1,2-*a*]Indoles 3; General Procedure

In a 50 mL round-bottomed flask, 1,4-benzoquinone **1** (1.1 mmol) and HKA **2** (1.0 mmol) were mixed with 1,4-dioxane (10 mL) and AcOH (0.1 mmol) and the mixture was refluxed for 6–8 h until the HKA **2** was completely consumed (TLC monitoring). The mixture was diluted with EtOAc (20 mL) and quenched with H_2O (20 mL). The organic layer was washed with brine (20 mL), dried (Na_2SO_4), concentrated, and the residue purified by flash column chromatography to afford the required product.

Ethyl 2,3-Dihydro-7-hydroxy-5,6-dimethoxy-8-methyl-1*H*-imidazo[1,2-*a*]indole-9-carboxylate (3a)

Starting from 2,3-dimethoxy-5-methylcyclohexa-2,5-diene-1,4-dione (**1a**; 0.20 g, 1.1 mmol), ethyl 2-(imidazolidin-2-ylidene)acetate (**2a**; 0.16 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3a** was obtained as yellow crystals; yield: 0.29 g (90%); mp 180–182 °C.

IR (KBr): 3412, 2979, 2934, 2890, 1686, 1581, 1491, 1455, 1328, 1273, 1098, 1038, 852 cm^{-1}.

^{1}H NMR (500 MHz, acetone-d_6): δ = 6.96 (br s, 1 H, NH), 6.10 (br s, 1 H, OH), 4.30–4.26 (m, 2 H, NCH_2), 4.18 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.07–4.03 (m, 2 H, NCH_2), 3.92 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 2.65 (s, 3 H, ArCH_3), 1.31 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, acetone-d_6): δ = 165.2, 160.5, 144.6, 136.8, 136.2, 128.1, 119.8, 112.5, 84.4, 62.4, 61.7, 59.3, 49.8, 46.3, 15.6, 14.3.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{16}H_{21}N_2O_5$ [M + H$^+$]: 321.1445; found: 321.1445.

(2,3-Dihydro-7-hydroxy-5,6-dimethoxy-8-methyl-1*H*-imidazo[1,2-*a*]indol-9-yl)(*p*-tolyl)methanone (3b)

Starting from **1a** (0.20 g, 1.1 mmol), 2-(imidazolidin-2-ylidene)-1-*p*-tolylethanone (**2b**; 0.20 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3b** was isolated as a yellow solid (0.34 g, 93%); mp 271–272 °C.

IR (KBr): 3333, 2934, 1601, 1522, 1455, 1407, 1279, 1212, 1091, 1058 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.99 (s, 1 H, NH), 7.49 (d, *J* = 7.9 Hz, 2 H, ArH), 7.24 (d, *J* = 7.9 Hz, 2 H, ArH), 6.34 (br s, 1 H, OH), 4.21 (t, *J* = 16.4 Hz, 2 H, NCH_2), 3.88 (t, *J* = 16.4 Hz, 2 H, NCH_2), 3.87 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 2.37 (s, 3 H, ArCH_3), 1.75 (s, 3H, ArCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.1, 159.3, 143.8, 140.7, 139.8, 136.2, 135.9, 129.1, 128.8, 127.2, 118.5, 111.7, 94.8, 62.1, 61.1, 49.0, 44.8, 21.4, 15.1.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{21}H_{23}N_2O_4$ [M + H$^+$]: 367.1652; found: 367.1654.

(2,3-Dihydro-7-hydroxy-5,6-dimethoxy-8-methyl-1*H*-imidazo[1,2-*a*]indol-9-yl)(phenyl)methanone (3c)

Starting from **1a** (0.20 g, 1.1 mmol), 2-(imidazolidin-2-ylidene)-1-phenylethanone (**2c**; 0.19 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3c** was isolated as a brown liquid (0.32 g, 92%).

IR (KBr): 3323, 2932, 1601, 1521, 1459, 1401, 1281, 1210, 1091, 1056, 738 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.01 (br s, 1 H, NH), 7.57 (d, *J* = 7.4 Hz, 2 H, ArH), 7.50 (d, *J* = 7.4 Hz, 1 H, ArH), 7.43 (dd, *J* = 7.4, 7.4 Hz, 2 H, ArH), 6.42 (br s, 1 H, OH), 4.22 (t, *J* = 16.5 Hz, 2 H, NCH_2), 3.90 (t, *J* = 16.5 Hz, 2 H, NCH_2), 3.87 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 1.71 (s, 3 H, ArCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.3, 159.5, 143.9, 142.6, 136.2, 135.9, 130.9, 128.6, 128.6, 127.0, 118.5, 111.8, 94.8, 62.1, 61.1, 49.1, 44.8, 15.1.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{20}H_{21}N_2O_4$ [M + H^+]: 353.1496; found: 353.1498.

(4-Chlorophenyl)(2,3-dihydro-7-hydroxy-5,6-dimethoxy-8-methyl-1*H*-imidazo[1,2-*a*]indol-9-yl)methanone (3d)

Starting from **1a** (0.20 g, 1.1 mmol), 1-(4-chlorophenyl)-2-(imidazolidin-2-ylidene)ethanone (**2d**; 0.22 g, 1.0 mmol) and AcOH (0.06 g, 0.1 mmol), **3d** was isolated as a yellow solid (0.35 g, 91%); mp 212–214 °C.

IR (KBr): 3325, 2975, 1599, 1519, 1455, 1399, 1279, 1213, 1091, 1017, 849 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.04 (br s, 1 H, NH), 7.59 (d, *J* = 8.3 Hz, 2 H, ArH), 7.49 (d, *J* = 8.3 Hz, 2 H, ArH), 6.49 (br s, 1 H, OH), 4.21 (t, *J* = 16.7 Hz, 2 H, NCH_2), 3.89 (t, *J* = 16.7 Hz, 2 H, NCH_2), 3.87 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 1.80 (s, 3 H, ArCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.6, 159.6, 144.0, 141.1, 136.4, 135.9, 135.6, 130.6, 128.7, 126.9, 118.6, 111.8, 94.6, 62.1, 61.1, 49.1, 44.8, 15.2.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{20}H_{20}ClN_2O_4$ [M + H^+]: 387.1106; found: 387.1108.

Ethyl 7-Hydroxy-2,3-dihydro-1*H*-imidazo[1,2-*a*]indole-9-carboxylate (3e)

Starting from cyclohexa-2,5-diene-1,4-dione (**1b**; 0.12 g, 1.1 mmol), **2a** (0.16 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3e** was isolated as a yellow solid (0.19 g, 78%); mp 214–216 °C.

IR (KBr): 3415, 3246, 2981, 2353, 1626, 1591, 1512, 1468, 1341, 1243, 1213, 1147, 1041, 870 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.63 (br s, 1 H, NH), 7.11 (s, 1 H, ArH), 6.91 (br s, 1 H, OH), 6.85 (d, *J* = 8.3 Hz, 1 H, ArH), 6.39 (dd, *J* = 8.3, 2.3 Hz, 1 H, ArH), 4.17 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.06–3.98 (m, 4 H, NCH_2CH_2N), 1.30 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.4, 158.4, 152.5, 150.1, 132.5, 125.4, 108.8, 107.7, 105.7, 58.2, 49.3, 42.7, 15.2.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{13}H_{15}N_2O_3$ [M + H^+]: 247.1077; found: 247.1081.

(2,3-Dihydro-7-hydroxy-1*H*-imidazo[1,2-*a*]indol-9-yl)(*p*-tolyl)methanone (3f)

Starting from **1b** (0.12 g, 1.1 mmol), **2b** (0.20 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3f** was isolated as a yellow solid (0.25 g, 86%); mp 271–272 °C.

IR (KBr): 3364, 3121, 2240, 1773, 1593, 1407, 1274, 1164, 1025, 806 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.64 (br s, 1 H, NH), 7.49 (d, *J* = 7.6 Hz, 2 H, ArH), 7.30 (d, *J* = 7.6 Hz, 2 H, ArH), 6.91 (s, 1 H, ArH), 6.88 (d, *J* = 8.4 Hz, 1 H, ArH), 6.73 (br s, 1 H, OH), 6.41 (d, *J* = 8.4 Hz, 1 H, ArH), 4.07 (t, *J* = 15.9 Hz, 2 H, NCH_2), 3.98 (t, *J* = 15.9 Hz, 2 H, NCH_2), 2.40 (s, 3 H, ArCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.1, 159.5, 152.5, 139.9, 139.7, 132.1, 129.2, 127.6, 125.7, 108.9, 108.3, 106.2, 93.5, 49.4, 42.5, 21.5.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{18}H_{17}N_2O_2$ [M + H^+]: 293.1285; found: 293.1285.

(1,2,3,4-Tetrahydro-8-hydroxy-6,7-dimethoxy-9-methylpyrimido[1,2-*a*]indol-10-yl)(4-methoxyphenyl)methanone (3g)

Starting from **1a** (0.20 g, 1.1 mmol), 2-[tetrahydropyrimidin-2(1*H*)-ylidene]-1-(4-methoxyphenyl)ethanone (**2e**; 0.23 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3g** was isolated as a yellow solid (0.36 g, 92%); mp 237–238 °C.

IR (KBr): 3309, 2936, 1609, 1513, 1423, 1287, 1253, 1158, 1076, 1026, 836 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.09 (br s, 1 H, NH), 8.01 (br s, 1 H, OH), 7.41 (d, *J* = 8.4 Hz, 2 H, ArH), 6.92 (d, *J* = 8.4 Hz, 2 H, ArH), 4.29 (t, *J* = 11.2 Hz, 2 H, NCH_2), 3.97 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.40 (t, *J* = 11.2 Hz, 2 H, NCH_2), 2.07–2.11 (m, 2 H, CH_2), 1.35 (s, 3 H, ArCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.8, 161.1, 152.4, 144.0, 137.0, 136.5, 136.1, 130.3, 123.2, 119.9, 113.5, 109.9, 96.1, 62.0, 61.0, 55.6, 42.2, 38.0, 21.4, 15.7.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{22}H_{25}N_2O_5$ [M + H^+]: 397.1758; found: 397.1755.

(1,2,3,4-Tetrahydro-8-hydroxy-6,7-dimethoxy-9-methylpyrimido[1,2-*a*]indol-10-yl)(*p*-tolyl)methanone (3h)

Starting from **1a** (0.20 g, 1.1 mmol), 2-[tetrahydropyrimidin-2(1*H*)-ylidene]-1-*p*-tolylethanone (**2f**; 0.22 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3h** was isolated as a yellow solid (0.34 g, 90%); mp 211–212 °C.

IR (KBr): 3311, 2933, 1613, 1522, 1452, 1367, 1286, 1157, 1069, 843 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.20 (br s, 1 H, NH), 8.01 (br s, 1 H, OH), 7.34 (d, *J* = 7.8 Hz, 2 H, ArH), 7.18 (d, *J* = 7.8 Hz, 2 H, ArH), 4.29 (t, *J* = 11.5 Hz, 2 H, NCH_2), 3.87 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.41 (t, *J* = 11.5 Hz, 2 H, NCH_2), 2.34 (s, 3 H, ArCH_3), 2.10–2.06 (m, 2 H, CH_2), 1.28 (s, 3 H, ArCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.9, 153.1, 144.5, 141.8, 140.4, 137.5, 136.7, 129.3, 129.0, 123.6, 120.5, 110.5, 96.8, 62.5, 61.5, 42.7, 38.5, 21.9, 21.8, 16.2.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{22}H_{25}N_2O_4$ [M + H^+]: 381.1809; found: 381.1806.

(1,2,3,4-Tetrahydro-8-hydroxy-6,7-dimethoxy-9-methylpyrimido[1,2-*a*]indol-10-yl)(phenyl)methanone (3i)

Starting from **1a** (0.20 g, 1.1 mmol), 2-[tetrahydropyrimidin-2(1*H*)-ylidene]-1-phenylethanone (**2g**; 0.20 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3i** was isolated as a yellow solid (0.32 g, 88%); mp 229–230 °C.

IR (KBr): 3315, 2934, 1609, 1522, 1459, 1393, 1283, 1153, 1075, 807 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.29 (br s, 1 H, NH), 8.02 (br s, 1 H, OH), 7.45–7.36 (m, 5 H, ArH), 4.29 (t, *J* = 11.7 Hz, 2 H, NCH_2), 3.88 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.41–3.45 (m, 2 H, NCH_2), 2.07–2.11 (m, 2 H, CH_2), 1.24 (s, 3 H, ArCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.9, 153.3, 144.6, 144.6, 137.5, 136.8, 130.7, 128.9, 128.8, 123.5, 120.6, 110.6, 96.9, 62.5, 61.5, 42.7, 38.5, 21.8, 16.1.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{21}H_{23}N_2O_4$ [M + H^+]: 367.1652; found: 367.1651.

(4-Chlorophenyl)(1,2,3,4-tetrahydro-8-hydroxy-6,7-dimethoxy-9-methylpyrimido[1,2-*a*]indol-10-yl)methanone (3j)
Starting from **1a** (0.20 g, 1.1 mmol), 1-(4-chlorophenyl)-2-[tetrahydropyrimidin-2(1*H*)-ylidene]ethanone (**2h**; 0.24 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3j** was isolated as yellow crystals (0.35 g, 87%); mp 217–218 °C.

IR (KBr): 3307, 2964, 2349, 1613, 1522, 1392, 1284, 1157, 1078, 842 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.29 (br s, 1 H, NH), 8.06 (br s, 1 H, OH), 7.44–7.42 (m, 4 H, ArH), 4.29 (t, *J* = 11.5 Hz, 2 H, NCH_2), 3.88 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.41–3.45 (m, 2 H, NCH_2), 2.07–2.11 (m, 2 H, CH_2), 1.30 (s, 3 H, ArCH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 185.6, 153.0, 144.3, 142.7, 137.2, 136.4, 134.8, 130.3, 128.5, 122.7, 120.2, 109.9, 96.3, 62.0, 61.0, 42.2, 38.0, 21.2, 16.0.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{21}H_{22}ClN_2O_4$ [M + H$^+$]: 401.1263; found: 401.1257.

(1,2,3,4-Tetrahydro-8-hydroxypyrimido[1,2-*a*]indol-10-yl)(4-methoxyphenyl)methanone (3k)
Starting from **1b** (0.12 g, 1.1 mmol), **2e** (0.23 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3k** was isolated as a yellow solid (0.29 g, 89%); mp 214–216 °C.

IR (KBr): 3178, 2957, 2866, 1607, 1531, 1468, 1408, 1309, 1255, 1170, 1018, 843 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.56 (br s, 1 H, NH), 8.42 (br s, 1 H, OH), 7.49 (d, *J* = 8.2 Hz, 2 H, ArH), 7.00 (d, *J* = 8.1 Hz, 2 H, ArH), 6.92 (d, *J* = 8.3 Hz, 1 H, ArH), 6.38 (d, *J* = 8.3 Hz, 1 H, ArH), 6.21 (s, 1 H, ArH), 3.92 (t, *J* = 11.0 Hz, 2 H, NCH_2), 3.84 (s, 3 H, OCH_3), 3.44–3.47 (m, 2 H, NCH_2), 2.07–2.10 (m, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.0, 160.7, 152.9, 152.5, 135.4, 129.3, 128.5, 126.9, 113.8, 108.3, 107.8, 104.7, 94.9, 55.6, 39.7, 39.6, 20.5.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{19}H_{19}N_2O_3$ [M + H$^+$]: 323.1390; found: 323.1392.

(1,2,3,4-Tetrahydro-8-hydroxypyrimido[1,2-*a*]indol-10-yl)(*p*-tolyl)methanone (3l)
Starting from **1b** (0.12 g, 1.1 mmol), **2f** (0.22 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3l** was isolated as a yellow solid (0.27 g, 88%); mp >300 °C.

IR (KBr): 3324, 3091, 2868, 1615, 1531, 1467, 1311, 1258, 1179, 1076, 839 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.57 (br s, 1 H, NH), 8.46 (br s, 1 H, OH), 7.41 (d, *J* = 7.8 Hz, 2 H, ArH), 7.29 (d, *J* = 7.8 Hz, 2 H, ArH), 6.91 (d, *J* = 8.4 Hz, 1 H, ArH), 6.38 (dd, *J* = 8.4, 1.8 Hz, 1 H, ArH), 6.12 (d, *J* = 1.8 Hz, 1 H, ArH), 3.91 (t, *J* = 11.1 Hz, 2 H, NCH_2), 3.45–3.48 (m, 2 H, NCH_2), 2.41 (s, 3 H, ArCH_3), 2.07–2.11 (m, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.9, 153.4, 153.0, 140.9, 139.8, 129.6, 129.1, 127.9, 127.3, 108.8, 108.4, 105.3, 95.5, 40.2, 40.1, 22.0, 21.0.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{19}H_{19}N_2O_2$ [M + H$^+$]: 307.1441; found: 307.1440.

(1,2,3,4-Tetrahydro-8-hydroxypyrimido[1,2-*a*]indol-10-yl)(phenyl)methanone (3m)
Starting from **1b** (0.12 g, 1.1 mmol), **2g** (0.20 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3m** was isolated as a yellow solid (0.25 g, 85%); mp 274–276 °C.

IR (KBr): 3320, 3074, 2869, 1617, 1536, 1480, 1312, 1172, 1078, 850 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.62 (br s, 1 H, NH), 8.50 (br s, 1 H, OH), 7.48–7.51 (m, 5 H, ArH), 6.89 (d, *J* = 8.3 Hz, 1 H, ArH), 6.39 (d, *J* = 8.3 Hz, 1 H, ArH), 6.03 (s, 1 H, ArH), 3.87–3.91 (m, 2 H, NCH_2), 3.43–3.47 (m, 2 H, NCH_2), 2.06–2.10 (m, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.9, 153.4, 153.0, 143.7, 130.2, 129.1, 129.1, 127.7, 127.3, 108.9, 108.5, 105.2, 95.6, 40.0, 38.5, 21.0.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{18}H_{17}N_2O_2$ [M + H$^+$]: 293.1285; found: 293.1285.

(4-Chlorophenyl)(1,2,3,4-tetrahydro-8-hydroxypyrimido[1,2-*a*]indol-10-yl)methanone (3n)
Starting from **1b** (0.12 g, 1.1 mmol), **2h** (0.24 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3n** was isolated as a yellow solid (0.27 g, 84%); mp 262–264 °C.

IR (KBr): 3319, 3085, 2868, 1616, 1528, 1468, 1313, 1256, 1170, 1083, 847 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.64 (br s, 1 H, NH), 8.47 (br s, 1 H, OH), 7.56 (d, *J* = 8.2 Hz, 2 H, ArH), 7.49 (d, *J* = 8.2 Hz, 2 H, ArH), 6.92 (d, *J* = 8.3 Hz, 1 H, ArH), 6.38 (dd, *J* = 8.3, 1.8 Hz, 1 H, ArH), 6.02 (d, *J* = 1.8 Hz, 1 H, ArH), 3.91 (t, *J* = 11.4 Hz, 2 H, NCH_2), 3.45–3.49 (m, 2 H, NCH_2), 2.07–2.11 (m, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.3, 153.4, 153.1, 142.3, 134.8, 129.7, 129.3, 129.1, 127.0, 109.1, 108.6, 105.0, 95.5, 40.2, 40.0, 20.9.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{18}H_{16}ClN_2O_2$ [M + H$^+$]: 327.0895; found: 327.0893.

(9-Hydroxy-2,3,4,5-tetrahydro-1*H*-[1,3]diazepino[1,2-*a*]indol-11-yl)(4-methoxyphenyl)methanone (3o)
Starting from **1b** (0.12 g, 1.1 mmol), 2-(1,3-diazepan-2-ylidene)-1-(4-methoxyphenyl)ethanone (**2i**; 0.25 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3o** was isolated as a yellow solid (0.29 g, 86%); mp 259–261 °C.

IR (KBr): 3166, 2927, 2845, 1754, 1587, 1542, 1457, 1311, 1247, 1170, 1036, 847 cm^{-1}.

^1H NMR (500 MHz, acetone-d_6): δ = 8.99 (br s, 1 H, NH), 7.72 (br s, 1 H, OH), 7.60 (d, *J* = 8.5 Hz, 2 H, ArH), 7.10 (d, *J* = 8.5 Hz, 1 H, ArH), 7.02 (d, *J* = 8.5 Hz, 2 H, ArH), 6.54 (dd, *J* = 8.5, 2.3 Hz, 1 H, ArH), 6.39 (d, *J* = 2.3 Hz, 1 H, ArH), 4.09 (t, *J* = 10.5 Hz, 2 H, NCH_2), 3.90 (s, 3 H, OCH_3), 3.46–3.43 (m, 2 H, NCH_2), 2.08–1.99 (m, 4 H, CH_2CH_2).

^{13}C NMR (125 MHz, acetone-d_6): δ = 190.1, 162.6, 161.4, 153.7, 136.4, 131.1, 130.9, 128.9, 114.5, 110.7, 109.8, 106.2, 99.2, 56.3, 46.8, 46.5, 31.2, 28.4.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{20}H_{21}N_2O_3$ [M + H$^+$]: 337.1547; found: 337.1549.

(9-Hydroxy-2,3,4,5-tetrahydro-1*H*-[1,3]diazepino[1,2-*a*]indol-11-yl)(*p*-tolyl)methanone (3p)
Starting from **1b** (0.12 g, 1.1 mmol), 2-(1,3-diazepan-2-ylidene)-1-*p*-tolylethanone (**2j**; 0.23 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3p** was isolated as a yellow solid (0.28 g, 86%); mp 243–245 °C.

IR (KBr): 3165, 2842, 1583, 1539, 1462, 1421, 1369, 1312, 1261, 1204, 1168, 1043, 837 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.95 (br s, 1 H, NH), 8.72 (br s, 1 H, OH), 7.39 (d, *J* = 7.9 Hz, 2 H, ArH), 7.30 (d, *J* = 7.9 Hz, 2 H, ArH), 7.09 (d, *J* = 8.7 Hz, 1 H, ArH), 6.42 (dd, *J* = 8.7, 2.1 Hz, 1 H, ArH), 6.03 (d, *J* = 2.1 Hz, 1 H, ArH), 4.02 (t, *J* = 9.8 Hz, 2 H, NCH_2), 3.40–3.43 (m, 2 H, NCH_2), 2.40 (s, 3 H, ArCH_3), 1.95–1.88 (m, 4 H, CH_2CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 189.0, 159.8, 152.5, 139.8, 139.8, 129.5, 129.2, 127.5, 127.2, 110.1, 108.9, 104.8, 97.7, 45.5, 44.9, 29.1, 26.9, 21.5.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{20}H_{21}N_2O_2$ [M + H$^+$]: 321.1598; found: 321.1601.

(9-Hydroxy-2,3,4,5-tetrahydro-1*H*-[1,3]diazepino[1,2-*a*]indol-11-yl)(phenyl)methanone (3q)

Starting from **1b** (0.12 g, 1.1 mmol), 2-(1,3-diazepan-2-ylidene)-1-phenylethanone (**2k**; 0.22 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3q** was isolated as a yellow crystal (0.25 g, 80%); mp 267–269 °C.

IR (KBr): 3242, 2932, 2868, 1650, 1559, 1471, 1375, 1268, 1174, 1088, 842 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.02 (br s, 1 H, NH), 8.67 (br s, 1 H, OH), 7.54–7.47 (m, 5 H, ArH), 7.10 (d, *J* = 8.6 Hz, 1 H, ArH), 6.43 (dd, *J* = 8.6, 2.1 Hz, 1 H, ArH), 5.94 (d, *J* = 2.1 Hz, 1 H, ArH), 4.03 (t, *J* = 10.7 Hz, 2 H, NCH_2), 3.40–3.44 (m, 2 H, NCH_2), 1.96–1.89 (m, 4 H, CH_2CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 188.9, 159.9, 152.6, 142.8, 130.0, 129.5, 128.7, 127.3, 127.2, 110.1, 108.9, 104.7, 97.6, 45.5, 44.9, 29.1, 26.9.

HRMS (TOF ES$^+$): *m*/*z* calcd for $C_{19}H_{19}N_2O_2$ [M + H$^+$]: 307.1441; found: 307.1450.

(4-Chlorophenyl)(2,3,4,5-tetrahydro-9-hydroxy-1*H*-[1,3]diazepino[1,2-*a*]indol-11-yl)methanone (3r)

Starting from **1b** (0.12 g, 1.1 mmol), 1-(4-chlorophenyl)-2-(1,3-diazepan-2-ylidene)ethanone (**2l**; 0.25 g, 1.0 mmol), and AcOH (0.06 g, 0.1 mmol), **3r** was isolated as a yellow solid (0.26 g, 76%); mp 289–291 °C.

IR (KBr): 3254, 2931, 1641, 1583, 1529, 1469, 1357, 1176, 1089, 842 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.15 (br s, 1 H, NH), 9.05 (br s, 1 H, OH), 7.59 (d, *J* = 7.5 Hz, 2 H, ArH), 7.56 (d, *J* = 7.5 Hz, 2 H, ArH), 7.12 (dd, *J* = 8.5, 1.8 Hz, 1 H, ArH), 6.38 (d, *J* = 8.5 Hz, 1 H, ArH), 6.09 (s, 1 H, ArH), 3.57–3.60 (m, 2 H, NCH_2), 3.35–3.40 (m, 2 H, NCH_2), 2.07–2.11 (m, 2 H, CH_2), 1.74–1.78 (m, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.9, 166.8, 154.4, 142.9, 140.2, 135.3, 129.3, 128.9, 127.2, 110.7, 108.9, 104.7, 93.1, 41.6, 41.6, 27.1, 27.1.

HRMS (TOF ES$^-$): *m*/*z* calcd for $C_{19}H_{17}ClN_2O_2$ [M]: 340.0979; found: 340.0970.

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