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Facile Three-Component Synthesis of Macrocyclane-Fused Pyrazolo[3,4-*b*]pyridine Derivatives

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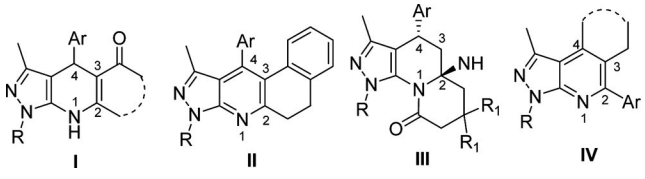
A series of new functionalized macrocyclane-fused pyrazolo[3,4-*b*]pyridine derivatives with an aryl group at the 2-position of the pyridine nucleus have been synthesized by microwave-assisted three-component reactions of aldehydes, aminopyrazole and cycloketones in HOAc using 1.0 equiv. of TFA as a promoter. The procedure is facile, avoiding time-consuming and costly syntheses, tedious work-ups and purifications of precursors as well as protection/deprotection of functional groups. This method is very efficient due to short reaction times and easy work-up and provides an efficient and promising synthetic strategy for the construction of the macrocyclane-fused pyrazolo[3,4-*b*]pyridine skeleton.

Introduction

The use of combinatorial chemistry has tremendously changed the theory and practice of the design and synthesis of new substances for pharmaceutical research. Great effort has been focused on synthesizing libraries of small heterocyclic molecules because of their high degree of structural diversity and widespread use as therapeutic agents.[1] However, the range of suitably functionalized heterocyclic building blocks for the synthesis of structurally diverse libraries is rather limited. The development of new, rapid and clean synthetic routes towards focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists.[2] Undoubtedly, synthetic strategies involving multicomponent reactions (MCRs) have manifested themselves as powerful tools for the rapid introduction and expansion of molecular diversity.[3] Consequently, the design and development of new MCR routes for the generation of heterocycles attracts ever increasing interest.[4,5]

Nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties. The pyrazolo[3,4-*b*]pyridine system as a key heterocycle represents the core skeleton of a pharmaceutically important class of heterocyclic compounds that possess a broad range of biological activities,[6] such as anxiolytic activity,[7] and can be used in the inhibition of xanthine oxidases[8] and cholesterol formation[9] and in the treatment of Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and alcohol withdrawal symptoms, drug addiction and infertility.[10] They have also been reported as potent and selective inhibitors of A1 adenosine receptors,[11] phosphodiesterase 4 (PDE4) inhibitors in immune and inflammatory cells,[12] glycogen synthase kinase-3 (GSK-3) inhibitors[13] and kinase inhibitors of p38 as anti-inflammatory drugs.[14] Because of the biological activities they exhibit, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. Thus, the preparation of these molecules has attracted considerable attention.[15] Many pyrazolo[3,4-*b*]pyridines have been synthesized through the reactions of 5-aminopyrazoles, aldehydes and appropriate cycloketones by various methods.[16] However, most of these compounds are pyrazolo[3,4-*b*]pyridines **I** or **II** (Figure 1) with the aryl group at the 4-position of pyridine ring. Recently, Chebanov and co-workers synthesized unexpected pyrazolopyridine **III** by similar three-component reactions under strong basic conditions.[17] In this reaction, the aryl group was also located at the 4-position of the pyridine ring (Figure 1). To the best of our knowledge, the regioselective construction of pyrazolopyridines of type **IV**, macrocyclane-fused pyrazolo[3,4-*b*]pyridines with an aryl group at the 2-position of the pyridine nucleus, has not been reported.



I II III IV

Figure 1. Different substituent patterns in the condensation of 5-aminopyrazoles, aldehydes and cycloketones.

In the past several years, our group and others have developed various multicomponent reactions (MCRs) that provide easy access to useful functionalized multiple ring

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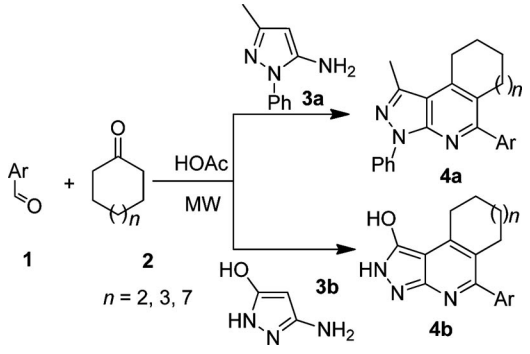
structures of chemical and pharmaceutical interest.[18–21] For example, a new four-component domino reaction has been established that provides an easy access to the synthesis of multifunctionalized quinazoline derivatives.[18a] The reaction is easily performed by simply mixing readily available starting materials, aromatic aldehydes, cyclopentanone and cyanoacetamide with K_2CO_3 in ethylene glycol, under microwave (MW) irradiation. When aliphatic aldehydes replaced their aromatic counterparts in the above multicomponent reaction, the reaction was found to proceed along another pathway leading to the formation of multifunctionalized tricyclo[6.2.2.0^{1,6}]dodecanes.[18b] Recently, we also found that the multicomponent reaction of Meldrum's acid, aromatic aldehydes and electron-rich heteroarylamines in aqueous solution under MW irradiation led to the multifunctionalized spiro{[1,3]dioxane-pyridine}-4,6-dione with high chemo-, regio- and stereoselectivity and good yields.[18d]

As a continuation of our research devoted to the development of multicomponent reactions,[18–20] we report herein another new three-component approach to the regioselective construction of macrocyclane-fused pyrazolo[3,4-*b*]pyridine derivatives that are of chemical and biomedical importance (Scheme 1). This reaction was achieved by reacting aromatic aldehydes, aminopyrazole and cycloketones as starting materials in acidic conditions under microwave irradiation.



Scheme 1. The synthesis of macrocyclane-fused pyrazolo[3,4-*b*]pyridines.

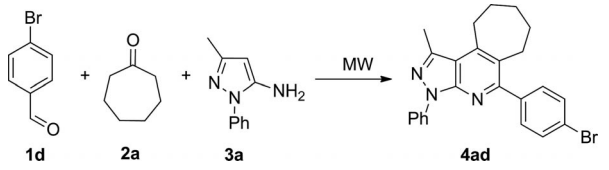
Results and Discussion

We started this study by treating 4-bromobenzaldehyde (**1d**) and cycloheptanone (**2a**) with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3a**) in the presence of 0.5 equiv. of trifluoroacetic acid (TFA) under microwave irradiation at 80 °C using different solvents, including acetonitrile, ethylene glycol, DMF and HOAc. Of these, HOAc proved to be the best solvent (Table 1, entry 4). Subsequently, the reaction was performed in HOAc and repeated many times at different temperatures in a sealed vessel under microwave irradiation for 15 min. The yield of the product **4ad** increased from 33 to 72% as the temperature was raised from 80 to 140 °C. When 1.0 equiv. of TFA was employed as a promoter in this reaction, the yield of the product **4ad** increased from 72 to 88% at 140 °C (Table 1, entry 8; Scheme 2).

Table 1. Optimization of the conditions for the synthesis of **4ad**.

Entry	Solvent	TFA [equiv.]	*T* [°C]	Time [min]	Yield [%][a]
1	CH_3CN	0.5	80	15	trace
2	DMF	0.5	80	15	11
3	ethylene glycol	0.5	80	15	19
4	HOAc	0.5	80	15	33
5	HOAc	0.5	100	15	47
6	HOAc	0.5	120	15	51
7	HOAc	0.5	140	15	72
8	HOAc	1.0	140	15	88

[a] Isolated yield.



Scheme 2. Synthesis of macrocyclane-fused pyrazolo[3,4-*b*]pyridines **4ad**.

With this result in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of structurally diverse aromatic aldehydes were investigated and a series of new macrocyclane-fused pyrazolo[3,4-*b*]pyridines were afforded in good yields, with

Table 2. Three-component synthesis of products **4aa**–**4az**.[a]

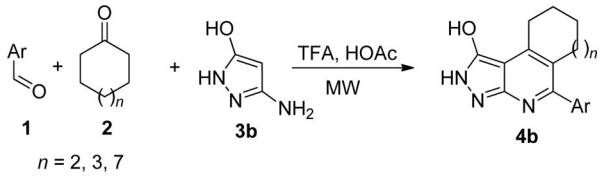
Entry	*n*	Product **4**	Ar	Time [min]	Yield [%][b]
1	2	**4aa**	phenyl (**1a**)	12	77
2	2	**4ab**	4-tolyl (**1b**)	14	80
3	2	**4ac**	4-methoxyphenyl (**1c**)	15	86
4	2	**4ad**	4-bromophenyl (**1d**)	11	80
5	2	**4ae**	2-chlorophenyl (**1e**)	12	70
6	2	**4af**	3,4,5-trimethoxyphenyl (**1f**)	14	88
7	2	**4ag**	4-nitrophenyl (**1g**)	12	70
8	2	**4ah**	2-thienyl (**1h**)	15	76
9	3	**4ai**	phenyl (**1a**)	13	76
10	3	**4aj**	2-chlorophenyl (**1e**)	12	75
11	3	**4ak**	3,4,5-trimethoxyphenyl (**1f**)	11	85
12	3	**4al**	2-thienyl (**1h**)	14	85
13	3	**4am**	2,3-dimethoxyphenyl (**1i**)	13	76
14	7	**4an**	phenyl (**1a**)	12	75
15	7	**4ao**	4-tolyl (**1b**)	11	70
16	7	**4ap**	4-methoxyphenyl (**1c**)	13	70
17	7	**4aq**	4-bromophenyl (**1d**)	12	88
18	7	**4ar**	2-chlorophenyl (**1e**)	11	72
19	7	**4as**	3,4,5-trimethoxyphenyl (**1f**)	12	88
20	7	**4at**	4-nitrophenyl (**1g**)	14	72
21	7	**4au**	2-thienyl (**1h**)	13	78
22	7	**4av**	2,3-dimethoxyphenyl (**1i**)	15	70
23	7	**4aw**	4-chlorophenyl (**1j**)	13	78
24	7	**4ax**	4-fluorophenyl (**1k**)	12	82
25	7	**4ay**	3,4-dimethoxyphenyl (**1l**)	13	80
26	7	**4az**	4-(dimethylamino)phenyl (**1m**)	14	80

[a] Reagents and conditions: TFA (1.0 equiv.), 140 °C, HOAc, microwaves. [b] Isolated yield.

the aryl group at the 2-position of the pyridine nucleus. As shown in Table 2, at the beginning, we explored the aldehyde substrate scope, using cycloheptanone (**2a**) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3a**) as model substrates (Table 2, entries 1–8). The results indicate that aromatic aldehydes bearing either electron-donating or -withdrawing functional groups, such as nitro, bromo, chloro or methoxy, were able to affect the synthesis of compound **4a**. Moreover, the heterocyclic aldehyde thiophene-2-carbaldehyde (Table 2, entry 8) still displayed high reactivity under the standard conditions. Note that this result is significant because there is no literature precedent for the synthesis of highly functionalized cyclohepta[*d*]pyrazolo[3,4-*b*]pyridines.

To further expand the scope of the reaction, different aldehydes and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3a**) were used as substrates with cyclooctanone (**2b**) and cyclododecanone (**2c**). In all these cases, the reactions proceeded smoothly to give the corresponding cycloocta- and cyclododeca[*d*]pyrazolo[3,4-*b*]pyridines in good yields of 70–88% (Table 2, entries 9–26). Indeed, the protocol provides a straightforward pathway for the construction of highly functionalized macrocyclane-fused pyrazolo[3,4-*b*]pyridines. The structures of cycloalka[*d*]pyrazolo[3,4-*b*]pyridines **4aa**–**4az** were deduced from their IR, ^{1}H NMR, ^{13}C NMR and mass spectra. Furthermore, the structure of **4ao** was further confirmed by single-crystal X-ray crystallography (Figure 2).[22]

To expand further the scope of the reaction, 3-amino-1*H*-pyrazol-5-ol (**3b**) was employed with cycloheptanone, cyclooctanone and cyclododecanone (Scheme 3). Under the above optimized conditions, all the reactions proceeded to generate the corresponding macrocyclane-fused pyrazolo[3,4-*b*]pyridin-1-ol derivatives **4ba**–**4br** in good-to-excellent yields (Table 3, entries 1–18).



Scheme 3. Synthesis of products **4ba**–**4br**.

Table 3. Three-component synthesis of products **4ba**–**4br**.[a]

Entry	*n*	Product	Ar	Time [min]	Yield [%][b]
1	2	**4ba**	4-tolyl (**1b**)	15	80
2	2	**4bb**	4-methoxyphenyl (**1c**)	13	86
3	2	**4bc**	4-bromophenyl (**1d**)	12	80
4	2	**4bd**	2-chlorophenyl (**1e**)	11	70
5	2	**4be**	2-thienyl (**1h**)	14	88
6	2	**4bf**	2,3-dimethoxyphenyl (**1i**)	13	70
7	2	**4bg**	4-(dimethylamino)phenyl (**1m**)	12	76
8	3	**4bh**	4-tolyl (**1b**)	11	76
9	3	**4bi**	4-methoxyphenyl (**1c**)	13	75
10	3	**4bj**	4-bromophenyl (**1d**)	12	85
11	3	**4bk**	2-chlorophenyl (**1e**)	11	85
12	3	**4bl**	2-thienyl (**1h**)	12	76
13	3	**4bm**	3,4-dimethoxyphenyl (**1l**)	14	75
14	7	**4bn**	4-tolyl (**1b**)	13	70
15	7	**4bo**	2-chlorophenyl (**1e**)	15	70
16	7	**4bp**	2-thienyl (**1h**)	13	80
17	7	**4bq**	2,3-dimethoxyphenyl (**1i**)	12	86
18	7	**4br**	3,4-dimethoxyphenyl (**1l**)	15	80

[a] Reagents and conditions: TFA (1.0 equiv.), 140 °C, HOAc, microwaves. [b] Isolated yield.

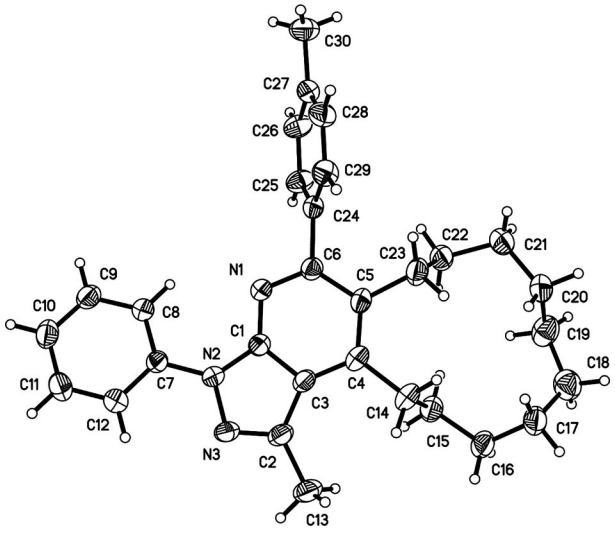
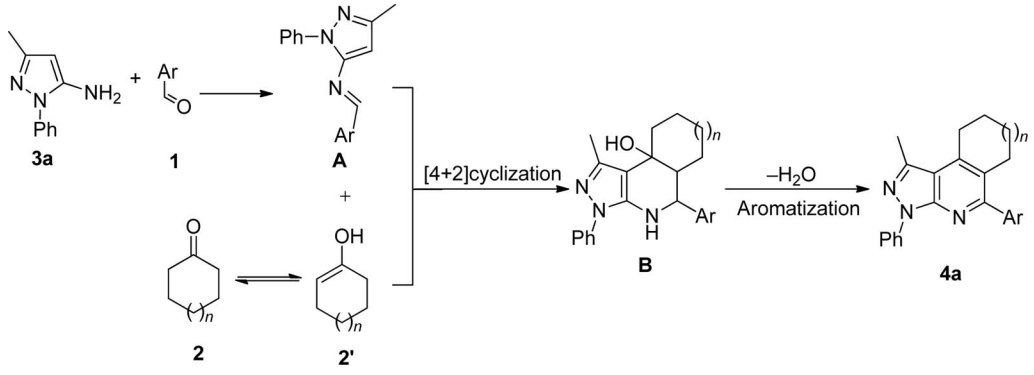


Figure 2. X-ray crystallographic structure of product **4ao**.



Scheme 4. Proposed mechanism for the formation of products **4a**.

The formation of pyrazolo[3,4-*b*]pyridines **I** or **II** by Knoevenagel-type condensation, intermolecular Michael addition and intramolecular cyclization has been reported previously.[16] Compared with compounds of type **I** or **II**, pyrazolo[3,4-*b*]pyridines **IV** with different aryl substitution patterns should be formed by another reaction process. Based on an analysis of the literature and experimental results, we reasoned that the reaction occurred by a [4+2] cycloaddition process. This type of [4+2] cycloaddition is well precedented.[23] Thus, a plausible mechanism for the formation of the type **IV** compounds is proposed in Scheme 4. Presumably, in the presence of HOAc, cycloketone **2** (cycloheptanone, cyclooctanone and cyclododecanone) is in equilibrium with the enol form **2′**. The condensed intermediate **A** undergoes a [4+2] cycloaddition with the enol form **2′** to form intermediate **B**. The subsequent dehydration of **B** and aromatization results in **4a**. This type of reaction is similar to the Povarov reaction.[24]

Conclusions

We have reported herein a one-pot three-component heterocyclization reaction (aminopyrazole, cyclic ketones and aldehydes) as an approach to the annulation of pyrazolo[3,4-*b*]pyridines with concomitant formation of three new σ bonds. The reaction proceeds by a selective [4+2] heterocyclization reaction to give pyrazolo[3,4-*b*]pyridines in good yields, which shows that the synthetic route allows us to build blocks of macrocyclane-fused pyrazolo[3,4-*b*]-pyridine derivatives with a wide range of substituents. This methodology is simple, practical and an alternative regioselective synthetic route to the formation of macrocyclane derivatives in good yields under microwave irradiation. This method is very efficient due to short reaction times and easy work-up.

Experimental Section

General: Microwave irradiation was carried out with a Biotage apparatus from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries. IR spectra were recorded with a FT-IR-Tensor 27 spectrometer using KBr pellets. The ^{1}H NMR spectra were recorded with a Bruker DPX 400 MHz spectrometer in $CDCl_3$ or [D_6]DMSO (^{13}C NMR, 100 MHz) with the chemical shifts (δ) given in ppm relative to TMS as internal standard. HRMS (ESI) were recorded with a microTOF-QII HRMS/MS instrument (Bruker). The X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

Typical Procedure for the Preparation of 5-(4-Bromophenyl)-1-methyl-3-phenyl-3,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo[3,4-*b*]-pyridine (4ad): In a 10 mL Emrys reaction vial, 4-bromobenzaldehyde (0.18 g, 1 mmol), cycloheptanone (0.12 g, 1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (0.17 g, 1 mmol), TFA (0.11 g, 1 mmol) and HOAc (2.0 mL) were mixed and stirred at room temperature for 3 min. Then the mixture was heated for 15 min at 140 °C under microwave irradiation. The automatic stirring mode helped to mix and uniformly heat the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The solid product was collected by Büchner filtration and subsequently washed with ethanol to give the pure white solid (yield: 0.38 g, 88%), m.p. 202–205 °C. IR (KBr): $\tilde{\nu}$ = 3079, 2980, 2918, 2850, 2843, 1582, 1507, 1414, 1382, 1305, 1252, 1205, 1136, 1108, 1070, 1008, 964, 839, 748, 685 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (d, J = 8.0 Hz, 2 H, ArH), 7.62 (d, J = 8.0 Hz, 2 H, ArH), 7.49–7.43 (m, 4 H, ArH), 7.23 (t, J = 7.2 Hz, 1 H, ArH), 3.36–3.33 (m, 2 H, CH_2), 2.96–2.93 (m, 2 H, CH_2), 2.82 (s, 3 H, CH_3), 1.98–1.93 (m, 2 H, CH_2), 1.86–1.80 (m, 2 H, CH_2), 1.72–1.63 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.1, 149.5, 149.1, 141.9, 140.7, 139.9, 31.2, 130.2, 128.9, 124.9, 122.2, 120.4, 115.1, 32.0, 30.1, 30.1, 27.8, 26.6, 16.4 ppm. HRMS (ESI): calcd. for $C_{24}H_{23}BrN_3$ 432.1070; found 432.1072.

1-Methyl-3,5-diphenyl-3,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo-[3,4-*b*]pyridine (4aa): White solid, m.p. 153–154 °C. IR (KBr): $\tilde{\nu}$ = 3056, 3028, 2979, 2927, 2856, 1584, 1508, 1492, 1441, 1411, 1380, 1295, 1204, 1141, 969, 756, 692 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.38–8.35 (m, 2 H, ArH), 7.59–7.56 (m, 2 H, ArH), 7.52–7.44 (m, 5 H, ArH), 7.23–7.20 (m, 1 H, ArH), 3.36–3.34 (m, 2 H, CH_2), 2.98–2.96 (m, 2 H, CH_2), 2.82 (s, 3 H, CH_3), 1.97–1.93 (m, 2 H, CH_2), 1.88–1.83 (m, 2 H, CH_2), 1.72–1.67 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.5, 149.6, 148.8, 141.9, 141.8, 140.0, 130.4, 129.5, 128.9, 128.0, 127.8, 124.8, 120.4, 114.9, 32.1, 30.1, 27.9, 26.6, 16.4 ppm. HRMS (ESI): calcd. for $C_{24}H_{24}N_3$ 354.1965; found 354.1961.

1-Methyl-3-phenyl-5-(*p*-tolyl)-3,6,7,8,9,10-hexahydrocyclohepta[*d*]-pyrazolo[3,4-*b*]pyridine (4ab): White solid, m.p. 184–186 °C. IR (KBr): $\tilde{\nu}$ = 2976, 2917, 2854, 1586, 1569, 1508, 1490, 1439, 1410, 1379, 1296, 1253, 1201, 1137, 1107, 964, 918, 828, 793, 759, 692 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.35–8.33 (m, 2 H, ArH), 7.46–7.41 (m, 4 H, ArH), 7.28 (d, J = 7.6 Hz, 2 H, ArH), 7.20–7.16 (m, 1 H, ArH), 3.33–3.30 (m, 2 H, CH_2), 2.96–2.94 (m, 2 H, CH_2), 2.79 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3), 1.94–1.90 (m, 2 H, CH_2), 1.84–1.79 (m, 2 H, CH_2), 1.69–1.64 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.3, 144.3, 143.5, 136.6, 134.8, 133.8, 132.3, 125.2, 124.2, 123.6, 123.5, 119.5, 115.1, 109.6, 26.9, 24.9, 22.6, 21.4, 16.1, 11.1 ppm. HRMS (ESI): calcd. for $C_{25}H_{25}N_3Na$ 390.1941; found 390.1938.

5-(4-Methoxyphenyl)-1-methyl-3-phenyl-3,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo[3,4-*b*]pyridine (4ac): White solid, m.p. 190–191 °C. IR (KBr): $\tilde{\nu}$ = 2973, 2915, 2855, 1583, 1509, 1414, 1370, 1299, 1251, 1174, 1028, 965, 836, 752, 645 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.37 (dd, J_1 = 1.2, J_2 = 8.0 Hz, 2 H, ArH), 7.53 (d, J = 8.8 Hz, 2 H, ArH), 7.49–7.45 (m, 2 H, ArH), 7.23–7.20 (m, 1 H, ArH), 7.03 (d, J = 4.8 Hz, 2 H, ArH), 3.91 (s, 3 H, OCH_3), 3.35–3.32 (m, 2 H, CH_2), 3.01–2.98 (m, 2 H, CH_2), 2.81 (s, 3 H, CH_3), 1.97–1.93 (m, 2 H, CH_2), 1.87–1.83 (m, 2 H, CH_2), 1.73–1.67 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.4, 158.2, 149.6, 148.8, 141.8, 140.0, 134.4, 130.9, 130.4, 128.9, 124.8, 120.4, 114.7, 113.5, 55.4, 32.1, 30.2, 30.1, 27.9, 26.7, 16.4 ppm. HRMS (ESI): calcd. for $C_{25}H_{26}N_3O$ 384.2071; found 384.2071.

5-(2-Chlorophenyl)-1-methyl-3-phenyl-3,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo[3,4-*b*]pyridine (4ae): White solid, m.p. 149–150 °C. IR (KBr): $\tilde{\nu}$ = 3057, 2970, 2923, 2854, 1583, 1507, 1440, 1412, 1383, 1297, 1209, 1135, 1115, 1052, 963, 753, 690, 675 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.32–8.30 (m, 2 H, ArH), 7.53–7.50 (m, 1 H, ArH), 7.47–7.43 (m, 2 H, ArH), 7.41–7.36 (m, 3 H, ArH), 7.23–7.19 (m, 1 H, ArH), 3.42–3.28 (m, 2 H, CH_2), 2.83 (s, 3 H, CH_3), 2.79–2.68 (m, 2 H, CH_2), 1.93–1.85 (m, 3 H, CH_2), 1.80–1.66 (m, 2 H, CH_2), 1.53–1.46 (m, 1 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.1, 149.4, 148.4, 141.9, 140.7, 139.8, 133.2, 131.1,

130.8, 129.4, 129.1, 128.9, 126.6, 125.0, 120.6, 115.5, 32.2, 30.2, 30.1, 27.5, 26.5, 16.4 ppm. HRMS (ESI): calcd. for $C_{24}H_{23}ClN_3$ 388.1566; found 388.1579.

1-Methyl-3-phenyl-5-(3,4,5-trimethoxyphenyl)-3,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo[3,4-*b*]pyridine (4af): White solid, m.p. 172–173 °C. IR (KBr): $\tilde{\nu}$ = 2982, 2919, 2849, 1584, 1508, 1456, 1413, 1384, 1237, 1170, 1130, 1006, 749, 689 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (d, J = 7.6 Hz, 2 H, ArH), 7.44 (t, J = 8.0 Hz, 2 H, ArH), 7.20 (t, J = 7.6 Hz, 1 H, ArH), 6.77 (s, 2 H, ArH), 3.93 (s, 3 H, OCH_3), 3.90 (s, 6 H, OCH_3), 3.34–3.32 (m, 2 H, CH_2), 2.99–2.96 (m, 2 H, CH_2), 2.79 (s, 3 H, CH_3), 1.98–1.93 (m, 2 H, CH_2), 1.86–1.82 (m, 2 H, CH_2), 1.73–1.62 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.2, 152.8, 149.3, 141.9, 139.8, 138.0, 137.1, 130.3, 128.9, 125.1, 120.7, 120.6, 115.0, 113.2, 106.8, 61.0, 56.2, 32.1, 30.2, 30.1, 27.9, 26.7, 16.3 ppm. HRMS (ESI): calcd. for $C_{27}H_{30}N_3O_3$ 444.2282; found 444.2268.

1-Methyl-5-(4-nitrophenyl)-3-phenyl-3,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo[3,4-*b*]pyridine (4ag): Light-yellow solid, m.p. 216–218 °C. IR (KBr): $\tilde{\nu}$ = 2972, 2917, 2850, 1581, 1515, 1507, 1412, 1343, 1205, 1134, 1103, 967, 843, 759, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.37–8.34 (m, 2 H, ArH), 8.32–8.29 (m, 2 H, ArH), 7.74–7.71 (m, 2 H, ArH), 7.49–7.45 (m, 2 H, ArH), 7.26–7.22 (m, 1 H, ArH), 3.38–3.36 (m, 2 H, CH_2), 2.94–2.91 (m, 2 H, CH_2), 2.83 (s, 3 H, CH_3), 2.00–1.95 (m, 2 H, CH_2), 1.89–1.84 (m, 2 H, CH_2), 1.73–1.67 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.8, 149.6, 149.4, 148.3, 147.5, 142.0, 140.6, 139.7, 130.5, 130.1, 129.0, 125.2, 123.3, 120.4, 115.5, 32.0, 30.1, 30.1, 27.8, 26.5, 16.3 ppm. HRMS (ESI): calcd. for $C_{24}H_{23}N_4O_2$ 399.1816; found 399.1819.

1-Methyl-3-phenyl-5-(2-thienyl)-3,6,7,8,9,10-hexahydrocyclohepta-[*d*]pyrazolo[3,4-*b*]pyridine (4ah): Grey solid, m.p. 126–127 °C. IR (KBr): $\tilde{\nu}$ = 3070, 2979, 2924, 2842, 1579, 1506, 1441, 1414, 1299, 1229, 1205, 1135, 958, 904, 838, 756, 704, 693, 659, 633 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.42–8.40 (m, 2 H, ArH), 7.53–7.51 (m, 1 H, ArH), 7.49–7.47 (m, 2 H, ArH, thienyl-H), 7.33 (dd, J_1 = 1.2, J_2 = 4.0 Hz, 1 H, thienyl-H), 7.27–7.23 (m, 1 H, ArH), 7.15 (dd, J_1 = 3.6, J_2 = 7.6 Hz, 1 H, thienyl-H), 3.35–3.32 (m, 2 H, CH_2), 3.31–3.21 (m, 2 H, CH_2), 2.79 (s, 3 H, CH_3), 2.01–1.96 (m, 2 H, CH_2), 1.87–1.76 (m, 4 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 150.9, 149.4, 149.3, 145.1, 141.9, 139.9, 130.0, 128.9, 127.5, 127.3, 127.2, 124.8, 120.1, 114.8, 32.0, 30.0, 29.7, 27.3, 26.7, 16.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{22}N_3S$ 360.1529; found 360.1527.

1-Methyl-3,5-diphenyl-6,7,8,9,10,11-hexahydro-3*H*-cycloocta[*d*]-pyrazolo[3,4-*b*]pyridine (4ai): White solid, m.p. 174–176 °C. IR (KBr): $\tilde{\nu}$ = 3059, 2959, 2917, 2850, 1601, 1579, 1506, 1413, 1380, 1251, 1136, 1080, 1030, 772, 748, 704, 688 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.35 (d, J = 8.0 Hz, 2 H, ArH), 7.54–7.43 (m, 7 H, ArH), 7.21 (t, J = 7.2 Hz, 1 H, ArH), 3.29–3.26 (m, 2 H, CH_2), 2.92–2.89 (m, 2 H, CH_2), 2.83 (s, 3 H, CH_3), 1.98–1.90 (m, 2 H, CH_2), 1.79–1.68 (m, 3 H, CH_2), 1.59–1.47 (m, 3 H, CH_2), 1.45–1.37 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.5, 149.6, 146.2, 142.2, 141.8, 139.9, 129.0, 128.9, 127.9, 127.9, 127.7, 124.9, 120.4, 114.8, 31.4, 31.2, 29.7, 27.9, 26.9, 26.3, 26.0, 15.7 ppm. HRMS (ESI): calcd. for $C_{25}H_{26}N_3$ 368.2122; found 368.2126.

5-(2-Chlorophenyl)-1-methyl-3-phenyl-6,7,8,9,10,11-hexahydro-3*H*-cycloocta[*d*]pyrazolo[3,4-*b*]pyridine (4aj): White solid, m.p. 149–150 °C. IR (KBr): $\tilde{\nu}$ = 3059, 2958, 2924, 2856, 1597, 1579, 1506, 1435, 1409, 1301, 1253, 1140, 1086, 1031, 755, 691, 635, 509 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.30 (d, J = 8.4 Hz, 2 H, ArH), 7.52 (d, J = 6.0 Hz, 1 H, ArH), 7.44 (t, J = 8.0 Hz, 2 H, ArH), 7.41–7.38 (m, 3 H, ArH), 7.21 (t, J = 7.2 Hz, 1 H, ArH), 3.38–3.32 (m, 1 H, CH_2), 3.26–3.20 (m, 1 H, CH_2), 2.83 (s, 3 H, CH_3), 2.73–2.67 (m, 1 H, CH_2), 2.03–1.81 (m, 2 H, CH_2), 1.71–1.31 (m, 7 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.9, 149.6, 146.3, 141.9, 140.6, 139.8, 133.1, 130.7, 129.5, 129.1, 128.9, 128.2, 126.4, 125.0, 120.6, 115.2, 31.2, 30.4, 27.9, 26.8, 26.3, 25.9, 15.7 ppm. HRMS (ESI): calcd. for $C_{25}H_{25}ClN_3$ 402.1732; found 402.1716.

1-Methyl-3-phenyl-5-(3,4,5-trimethoxyphenyl)-6,7,8,9,10,11-hexahydro-3*H*-cycloocta[*d*]pyrazolo[3,4-*b*]pyridine (4ak): White solid, m.p. 190–193 °C. IR (KBr): $\tilde{\nu}$ = 3059, 2958, 2924, 2856, 1597, 1579, 1506, 1409, 1380, 1301, 1253, 1140, 1119, 1086, 755, 691 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.35 (d, J = 8.0 Hz, 2 H, ArH), 7.46 (t, J = 8.0 Hz, 2 H, ArH), 7.22 (t, J = 7.2 Hz, 1 H, ArH), 6.75 (s, 2 H, ArH), 3.96 (s, 3 H, OCH_3), 3.91 (s, 6 H, OCH_3), 3.29–3.26 (m, 2 H, CH_2), 2.94–2.92 (m, 2 H, CH_2), 2.83 (s, 3 H, CH_3), 1.98–1.90 (m, 2 H, CH_2), 1.71–1.65 (m, 3 H, CH_2), 1.53–1.43 (m, 3 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.2, 152.8, 149.4, 146.4, 141.8, 139.9, 137.8, 137.6, 128.9, 128.0, 125.0, 120.5, 114.9, 106.6, 61.0, 56.3, 32.0, 31.1, 27.8, 27.2, 26.2, 15.7 ppm. HRMS (ESI): calcd. for $C_{28}H_{32}N_3O_3$ 458.2439; found 458.2432.

1-Methyl-3-phenyl-5-(2-thienyl)-6,7,8,9,10,11-hexahydro-3*H*-cycloocta[*d*]pyrazolo[3,4-*b*]pyridine (4al): Grey solid, m.p. 137–139 °C. IR (KBr): $\tilde{\nu}$ = 2920, 2850, 1594, 1574, 1505, 1408, 1297, 1252, 1138, 826, 753, 691, 647 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.38 (d, J = 8.0 Hz, 2 H, ArH), 7.54–7.50 (m, 3 H, 2× ArH, thienyl-H), 7.26 (d, J = 7.6 Hz, 1 H, thienyl-H), 7.21–7.18 (m, 1 H, ArH), 7.05 (d, J = 3.2 Hz, 1 H, thienyl-H), 3.21–3.18 (m, 2 H, CH_2), 2.87–2.84 (m, 2 H, CH_2), 2.07 (s, 3 H, CH_3), 2.00–1.89 (m, 2 H, CH_2), 1.75–1.58 (m, 2 H, CH_2), 1.54–1.37 (m, 4 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.7, 149.4, 142.6, 140.0, 136.6, 136.2, 130.0, 128.9, 128.1, 126.9, 126.2, 125.0, 120.6, 115.7, 36.2, 32.5, 31.3, 27.6, 26.6,26.1, 13.4 ppm. HRMS (ESI): calcd. for $C_{23}H_{23}N_3S$ 374.1686; found 374.1685.

5-(2,3-Dimethoxyphenyl)-1-methyl-3-phenyl-6,7,8,9,10,11-hexahydro-3*H*-cycloocta[*d*]pyrazolo[3,4-*b*]pyridine (4am): White solid, m.p. 168–171 °C. IR (KBr): $\tilde{\nu}$ = 2922, 2852, 1599, 1578, 1509, 1474, 1414, 1352, 1260, 1126, 1071, 1056, 1010, 795, 761, 695, 676 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.36 (d, J = 8.0 Hz, 2 H, ArH), 7.43 (t, J = 8.0 Hz, 2 H, ArH), 7.21–7.14 (m, 2 H, ArH), 7.03 (d, J = 7.6 Hz, 1 H, ArH), 6.91 (d, J = 7.2 Hz, 1 H, ArH), 3.96 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.36–3.30 (m, 1 H, CH_2), 3.25–3.18 (m, 1 H, CH_2), 2.83 (s, 3 H, CH_3), 2.80–2.73 (m, 2 H, CH_2), 2.03–1.85 (m, 2 H, CH_2), 1.64–1.54 (m, 1 H, CH_2), 1.51–1.32 (m, 5 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 151.6, 147.6, 144.4, 141.2, 140.4, 136.6, 134.8, 131.6, 123.6, 123.6, 119.5, 118.4, 17.0, 115.1, 109.8, 106.7, 56.1, 50.6, 26.0, 25.3, 22.6, 21.8, 21.0, 20.8, 10.4 ppm. HRMS (ESI): calcd. for $C_{27}H_{30}N_3O_2$ 428.2333; found 428.2336.

1-Methyl-3,5-diphenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4an): White solid, m.p. 186–187 °C. IR (KBr): $\tilde{\nu}$ = 2925, 2849, 1600, 1572, 1505, 1410, 1378, 1352, 1294, 1266, 1199, 1134, 1029, 909, 749, 699, 689, 671 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.33–8.31 (m, 2 H, ArH), 7.54–7.52 (m, 2 H, ArH), 7.50–7.42 (m, 5 H, ArH), 7.22–7.18 (m, 1 H, ArH), 3.21–3.16 (m, 2 H, CH_2), 2.84 (s, 1 H, CH_2), 2.82 (s, 3 H, CH_3), 2.80 (s, 1 H, CH_2), 1.94–1.85 (m, 2 H, CH_2), 1.72–1.62 (m, 5 H, CH_2), 1.59–1.50 (m, 3 H, CH_2), 1.49–1.39 (m, 4 H, CH_2), 1.35–1.27 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.4, 149.4, 146.0, 142.4, 141.8, 139.9, 128.9, 127.9, 127.7, 127.7, 124.9, 120.5, 115.5, 30.9, 30.4, 28.6, 28.3, 28.2, 27.8, 27.7, 27.1, 26.8, 22.5, 22.5, 15.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{34}N_3$ 424.2748; found 424.2740.

1-Methyl-3-phenyl-5-(*p*-tolyl)-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4ao): White solid, m.p. 203–204 °C. IR (KBr): $\tilde{\nu}$ = 2922, 2900, 2866, 2845, 1597, 1578, 1564, 1504, 1487, 1411, 1379, 1357, 1115, 812, 761, 692 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.30 (d, J = 7.6 Hz, 2 H, ArH), 7.43–7.39 (m, 4 H, ArH), 7.26 (s, 1 H, ArH), 7.24 (s, 1 H, ArH), 7.17 (t, J = 7.6 Hz, 1 H, ArH), 3.17–3.13 (m, 2 H, CH_2), 2.82–2.79 (m, 1 H, CH_2), 2.79 (s, 3 H, CH_3), 2.44 (s, 3 H, CH_3), 1.92–1.82 (m, 2 H, CH_2), 1.76–1.72 (m, 2 H, CH_2), 1.72–1.68 (m, 4 H, CH_2), 1.64–1.38 (m, 7 H, CH_2), 1.35–1.27 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.2, 144.1, 140.7, 136.5, 134.7, 134.2, 132.1, 123.6, 123.5, 123.4, 122.6, 119.6, 115.2, 112.7, 110.2, 25.1, 23.4, 23.1, 23.0, 22.6, 22.5, 21.8, 21.6, 17.4, 17.3, 16.1, 10.2 ppm. HRMS (ESI): calcd. for $C_{30}H_{36}N_3$ 438.2904; found 438.2919.

5-(4-Methoxyphenyl)-1-methyl-3-phenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4ap): White solid, m.p. 212–217 °C. IR (KBr): $\tilde{\nu}$ = 2933, 2919, 2864, 2844, 1575, 1519, 1506, 1411, 1380, 1291, 1251, 1175, 1032, 753, 688 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.30 (d, J = 7.6 Hz, 2 H, ArH), 7.46 (d, J = 7.6 Hz, 2 H, ArH), 7.42 (t, J = 7.6 Hz, 2 H, ArH), 7.18 (t, J = 6.8 Hz, 1 H, ArH), 6.98 (d, J = 7.2 Hz, 2 H, ArH), 3.89 (s, 3 H, OCH_3), 3.18–3.13 (m, 1 H, CH_2), 2.86–2.81 (m, 1 H, CH_2), 2.79 (s, 3 H, CH_3), 1.90–1.83 (m, 1 H, CH_2), 1.67–1.61 (m, 4 H, CH_2), 1.60–1.56 (m, 5 H, CH_2), 1.55–1.48 (m, 3 H, CH_2), 1.47–1.38 (m, 3 H, CH_2), 1.34–1.29 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.2, 145.9, 141.8, 139.9, 134.9, 130.1, 128.9, 27.9, 126.7, 124.8, 120.5, 115.4, 113.4, 55.3, 31.0, 30.4, 28.6, 28.3, 28.2, 27.8, 27.7, 27.0, 26.8, 22.6, 15.5 ppm. HRMS (ESI): calcd. for $C_{30}H_{36}N_3O$ 454.2853; found 454.2833.

5-(4-Bromophenyl)-1-methyl-3-phenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4aq): White solid, m.p. 218–220 °C. IR (KBr): $\tilde{\nu}$ = 2929, 2864, 2849, 1594, 1576, 1506, 1415, 1382, 1352, 1124, 1012, 752, 689, 619 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (d, J = 7.6 Hz, 2 H, ArH), 7.59 (d, J = 8.0 Hz, 2 H, ArH), 7.44–7.38 (m, 4 H, ArH), 7.19 (t, J = 7.6 Hz, 1 H, ArH), 3.18–3.14 (m, 2 H, CH_2), 2.79 (s, 3 H, CH_3), 2.79–2.76 (m, 1 H, CH_2), 1.90–1.82 (m, 2 H, CH_2), 1.74–1.61 (m, 6 H, CH_2), 1.57–1.29 (m, 9 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.0, 156.7, 149.2, 146.3, 141.8, 141.3, 139.8, 131.2, 130.6, 128.9, 127.6, 125.0, 122.0, 120.5, 115.7, 31.0, 30.4, 28.7, 28.3, 28.2, 27.8, 27.7, 27.0, 26.7, 22.5, 22.5, 15.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{33}BrN_3$ 502.1853; found 502.1828.

5-(2-Chlorophenyl)-1-methyl-3-phenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4ar): White solid, m.p. 183–184 °C. IR (KBr): $\tilde{\nu}$ = 2921, 2844, 1598, 1576, 1567, 1505, 1411, 1353, 1136, 1118, 757, 691 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.25 (d, J = 8.0 Hz, 2 H, ArH), 7.49–7.47 (m, 1 H, ArH), 7.43–7.37 (m, 5 H, ArH), 7.19–7.16 (t, J = 7.2 Hz, 1 H, ArH), 3.26–3.17 (m, 1 H, CH_2), 3.16–3.08 (m, 1 H, CH_2), 2.80 (s, 3 H, CH_3), 2.53–2.45 (m, 1 H, CH_2), 1.98–1.78 (m, 2 H, CH_2), 1.72–1.57 (m, 5 H, CH_2), 1.51–1.36 (m, 8 H, CH_2), 1.30–1.22 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.8, 149.2, 148.0, 146.0, 141.8, 140.6, 139.7, 133.0, 130.9, 129.4, 129.1, 128.9, 128.4, 126.4, 125.1, 120.7, 116.0, 31.0, 30.4, 28.5, 28.4, 28.1, 27.8, 27.2, 26.7, 22.4, 22.2, 15.4 ppm. HRMS (ESI): calcd. for $C_{29}H_{33}ClN_3$ 458.2358; found 458.2355.

1-Methyl-3-phenyl-5-(3,4,5-trimethoxyphenyl)-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4as): White solid, m.p. 205–208 °C. IR (KBr): $\tilde{\nu}$ = 2929, 2860, 2842, 1583, 1507, 1412, 1379, 1238, 1170, 1130, 1001, 826, 750, 691 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.30 (d, J = 8.0 Hz, 2 H, ArH), 7.43 (t, J = 8.0 Hz, 2 H, ArH), 7.19 (t, J = 7.6 Hz, 1 H, ArH), 6.73 (s, 2 H, ArH), 3.93 (s, 3 H, OCH_3), 3.88 (s, 6 H, OCH_3), 3.18–3.14 (m, 2 H, CH_2), 2.80 (s, 3 H, CH_3), 2.84–2.81 (m, 1 H, CH_2), 1.91–1.84 (m, 2 H, CH_2), 1.68–1.43 (m, 13 H, CH_2), 1.40–1.33 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.0, 152.8, 149.2, 146.2, 141.8, 139.8, 137.8, 128.9, 127.7, 125.0, 120.6, 120.6, 115.6, 113.2, 106.4, 61.0, 56.3, 31.0, 30.4, 29.1, 28.3, 28.3, 27.8, 27.7, 27.1, 22.6, 22.5, 15.5 ppm. HRMS (ESI): calcd. for $C_{32}H_{40}N_3O_3$ 514.3065; found 514.3060.

1-Methyl-5-(4-nitrophenyl)-3-phenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4at): Pale-yellow solid, m.p. 221–224 °C. IR (KBr): $\tilde{\nu}$ = 2928, 2857, 1599, 1578, 1571, 1507, 1416, 1347, 1132, 864, 854, 753, 691 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.36 (d, J = 8.8 Hz, 2 H, ArH), 8.26 (d, J = 8.8 Hz, 2 H, ArH), 7.71 (d, J = 8.8 Hz, 2 H, ArH), 7.45 (t, J = 8.0 Hz, 2 H, ArH), 7.23 (t, J = 7.2 Hz, 1 H, ArH), 3.22–3.18 (m, 2 H, CH_2), 2.83 (s, 3 H, CH_3), 2.81–2.78 (m, 1 H, CH_2), 1.94–1.85 (m, 2 H, CH_2), 1.72–1.63 (m, 4 H, CH_2), 1.63–1.49 (m, 5 H, CH_2), 1.48–1.44 (m, 2 H, CH_2), 1.41–1.37 (m, 2 H, CH_2), 1.35–1.30 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.7, 149.1, 148.8, 147.4, 146.8, 141.9, 139.6, 130.0, 128.9, 127.3, 125.2, 123.4, 120.5, 116.1, 31.0, 30.4, 28.8, 28.2, 28.1, 27.7, 27.7, 27.0, 26.6, 22.4, 15.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{33}N_4O_2$ 469.2599; found 469.2600.

1-Methyl-3-phenyl-5-(2-thienyl)-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4au): White solid, m.p. 180–181 °C. IR (KBr): $\tilde{\nu}$ = 2921, 2861, 2842, 1575, 1505, 1409, 1380, 1231, 1130, 905, 852, 751, 705, 691 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.38–8.36 (m, 2 H, ArH), 7.50–7.48 (m, 3 H, ArH), 7.46–7.44 (m, 2 H, thienyl-H), 7.24–7.20 (m, 1 H, ArH), 7.14–7.11 (m, 1 H, thienyl-H), 3.16–3.12 (m, 2 H, CH_2), 3.10–3.05 (m, 2 H, CH_2), 2.77 (s, 3 H, CH_3), 1.85–1.84 (m, 2 H, CH_2), 1.75–1.68 (m, 2 H, CH_2), 1.69–1.62 (m, 4 H, CH_2), 1.61–1.63 (m, 2 H, CH_2), 1.57–1.50 (m, 6 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 151.9, 149.0, 146.6, 145.8, 141.9, 139.8, 128.9, 127.6, 127.5, 127.2, 126.7, 124.9, 120.2, 115.6, 113.2, 30.1, 28.4, 28.2, 28.2, 27.8, 27.5, 27.4, 26.8, 22.5, 22.4, 15.4 ppm. HRMS (ESI): calcd. for $C_{27}H_{32}N_3$ 430.2312; found 430.2293.

5-(2,3-Dimethoxyphenyl)-1-methyl-3-phenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4av): White solid, m.p. 180–181 °C. IR (KBr): $\tilde{\nu}$ = 2929, 2860, 2843, 1568, 1507, 1475, 1412, 1380, 1360, 1265, 1227, 1126, 1074, 1054, 1011, 748, 689 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.32–8.30 (m, 2 H, ArH), 7.42–7.38 (m, 2 H, ArH), 7.18–7.12 (m, 2 H, ArH), 7.01–6.99 (m, 1 H, ArH), 6.91–6.89 (m, 1 H, ArH), 3.94 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.24–3.07 (m, 2 H, CH_2), 2.80 (s, 3 H, CH_3), 2.77–2.73 (m, 1 H, CH_2), 2.64–2.54 (m, 1 H, CH_2), 1.90–1.82 (m, 2 H, CH_2), 1.67–1.37 (m, 12 H, CH_2), 1.27–1.25 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.9, 152.7, 149.4, 146.4, 145.4, 141.8, 140.0, 136.9, 129.0, 128.8, 124.8, 123.6, 122.6, 120.4, 115.8, 111.9, 61.4, 55.8, 30.4, 28.5, 28.4, 28.2, 27.8, 27.8, 27.2, 26.8, 22.4, 22.3, 15.5 ppm. HRMS (ESI): calcd. for $C_{31}H_{38}N_3O_2$ 484.2959; found 484.2958.

5-(4-Chlorophenyl)-1-methyl-3-phenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4aw): White solid, m.p. 225–226 °C. IR (KBr): $\tilde{\nu}$ = 2929, 2859, 1598, 1566, 1505, 1414, 1381, 1353, 1130, 1116, 747, 687, 619 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.27 (d, J = 8.0 Hz, 2 H, ArH), 7.47–7.40 (m, 6 H, ArH), 7.19 (t, J = 7.2 Hz, 1 H, ArH), 3.18–3.14 (m, 2 H, CH_2), 2.79 (s, 3 H, CH_3), 2.79–2.76 (m, 1 H, CH_2), 1.90–1.82 (m, 2 H, CH_2), 1.68–1.58 (m, 6 H, CH_2), 1.53–1.37 (m, 7 H, CH_2), 1.33–1.28 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.0, 149.3, 146.3, 141.8, 140.8, 139.8, 133.7, 130.3, 128.9, 128.2,

127.6, 125.0, 120.5, 115.7, 31.0, 30.4, 28.7, 28.3, 28.1, 27.8, 27.7, 27.0, 26.7, 22.5, 22.5, 15.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{33}ClN_3$ 458.2358; found 458.2342.

5-(4-Fluorophenyl)-1-methyl-3-phenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4ax): White solid, m.p. 173–174 °C. IR (KBr): $\tilde{\nu}$ = 2928, 2859, 2848, 1599, 1577, 1504, 1414, 1380, 1356, 1294, 1226, 1157, 1117, 845, 820, 746, 687 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.31–8.28 (m, 2 H, ArH), 7.53–7.49 (m, 2 H, ArH), 7.47–7.43 (m, 2 H, ArH), 7.23–7.14 (m, 3 H, ArH), 3.20–3.16 (m, 2 H, CH_2), 2.82 (s, 3 H, CH_3), 2.82–2.79 (m, 1 H, CH_2), 1.94–1.84 (m, 2 H, CH_2), 1.67–1.33 (m, 15 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.7, 161.2, 159.3, 149.3, 146.2, 141.8, 139.8, 138.4, 138.4, 130.6, 130.6, 128.9, 127.7, 125.0, 120.5, 115.6, 115.0, 114.8, 30.9, 30.4, 28.6, 28.3, 28.2, 27.8, 27.7, 27.0, 26.8, 22.5, 15.4 ppm. HRMS (ESI): calcd. for $C_{29}H_{33}FN_3$ 442.2654; found 442.2646.

5-(3,4-Dimethoxyphenyl)-1-methyl-3-phenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridine (4ay): White solid, m.p. 182–183 °C. IR (KBr): $\tilde{\nu}$ = 2927, 2902, 2864, 2842, 1600, 1576, 1566, 1508, 1412, 1381, 1354, 1255, 1230, 1167, 1138, 1021, 851, 814, 756, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.34 (d, J = 7.6 Hz, 2 H, ArH), 7.44 (t, J = 1.6 Hz, 2 H, ArH), 7.20 (t, J = 7.6 Hz, ArH), 7.13–7.09 (m, 2 H, ArH), 6.98 (d, J = 8.4 Hz, 2 H, ArH), 3.98 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.20–3.16 (m, 2 H, CH_2), 2.87–2.83 (m, 2 H, CH_2), 2.81 (s, 3 H, CH_3), 1.90–1.88 (m, 2 H, CH_2), 1.71–1.63 (m, 4 H, CH_2), 1.63–1.57 (m, 2 H, CH_2), 1.55–1.51 (m, 2 H, CH_2), 1.40–1.42 (m, 4 H, CH_2), 1.39–1.31 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.0, 149.3, 148.7, 148.3, 146.0, 141.8, 139.9, 135.2, 128.9, 127.8, 124.9, 121.3, 120.4, 115.4, 112.5, 110.7, 56.0, 56.0, 30.4, 28.8, 28.3, 27.8, 27.7, 27.1, 27.0, 22.5, 15.5 ppm. HRMS (ESI): calcd. for $C_{31}H_{38}N_3O_2$ 484.2959; found 484.2959.

***N*,*N*-Dimethyl-4-(1-methyl-3-phenyl-6,7,8,9,10,11,12,13,14,15-decahydro-3*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridin-5-yl)aniline (4az):** White solid, m.p. 246–249 °C. IR (KBr): $\tilde{\nu}$ = 2919, 2900, 2859, 2843, 1612, 1569, 1524, 1505, 1408, 1361, 1269, 1205, 1132, 1029, 815, 755, 692, 640 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.36 (dd, J_1 = 0.8, J_2 = 8.0 Hz, 2 H, ArH), 7.48 (dd, J_1 = 0.8, J_2 = 7.2 Hz, 2 H, ArH), 7.23–7.20 (m, 1 H, ArH), 7.14 (d, J = 8.0 Hz, 2 H, ArH), 6.82 (s, 2 H, ArH), 3.05 (s, 6 H, NCH_3), 3.00–2.95 (m, 2 H, CH_2), 2.69–2.65 (m, 2 H, CH_2), 2.11–2.04 (m, 2 H, CH_2), 1.94 (s, 3 H, CH_3), 1.66–1.60 (m, 2 H, CH_2), 1.57–1.50 (m, 4 H, CH_2), 1.48–1.42 (m, 6 H, CH_2), 1.33–1.27 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.5, 152.2, 142.6, 141.5, 140.5, 140.0, 138.2, 137.2, 134.8, 133.1, 131.7, 129.3, 129.3, 129.1, 129.0, 128.6, 125.1, 124.3, 120.8, 115.3, 31.0, 29.5, 26.8, 21.4, 21.4, 15.0 ppm. HRMS (ESI): calcd. for $C_{31}H_{39}N_4$ 467.3170; found 467.3164.

5-(*p*-Tolyl)-2,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo[3,4-*b*]-pyridin-1-ol (4ba): Pink solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3189, 3141, 3055, 2948, 2923, 2854, 2683, 1596, 1542, 1394, 1274, 1190, 960, 877, 819, 637 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.71 (s, 1 H, NH), 10.30 (s, 1 H, OH), 7.24 (d, J = 7.6 Hz, 2 H, ArH), 7.14 (d, J = 8.0 Hz, 2 H, ArH), 3.05–3.03 (m, 2 H, CH_2), 2.61–2.59 (m, 2 H, CH_2), 2.37 (s, 3 H, CH_3), 1.82–1.77 (m, 2 H, CH_2), 1.74–1.64 (m, 2 H, CH_2), 1.56–1.47 (m, 2 H, CH_2) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 164.6, 154.7, 151.3, 142.9, 136.6, 133.1, 129.1, 128.2, 127.1, 112.7, 101.2, 31.3, 28.2, 28.1, 26.5, 20.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{20}N_3O$ 294.1601; found 294.1609.

5-(4-Methoxyphenyl)-2,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo-[3,4-*b*]pyridin-1-ol (4bb): Light-yellow solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3136, 3052, 2926, 2853, 1595, 1543, 1518, 1442, 1394, 1290, 1249, 1189, 1035, 959, 877, 828, 814, 638, 589 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.70 (s, 1 H, NH), 7.19 (d, J = 8.8 Hz, 2 H, ArH), 7.00 (d, J = 8.8 Hz, 2 H, ArH), 3.82 (s, 3 H, OCH_3), 3.05–3.03 (m, 2 H, CH_2), 2.64–2.61 (m, 2 H, CH_2), 1.83–1.73 (m, 2 H, CH_2), 1.73–1.63 (m, 2 H, CH_2), 1.57–1.47 (m, 2 H, CH_2) ppm. HRMS (ESI): calcd. for $C_{18}H_{20}N_3O_2$ 310.1551; found 310.1550.

5-(4-Bromophenyl)-2,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo-[3,4-*b*]pyridin-1-ol (4bc): White solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3048, 2923, 2853, 1596, 1540, 1504, 1393, 1349, 1271, 1252, 1190, 1072, 1011, 961, 878, 820, 810, 634 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.77 (s, 1 H, NH), 10.41 (s, 1 H, OH), 7.64 (d, J = 8.4 Hz, 2 H, ArH), 7.22 (d, J = 8.4 Hz, 2 H, ArH), 3.06–3.04 (m, 2 H, CH_2), 2.59–2.57 (m, 2 H, CH_2), 1.83–1.73 (m, 2 H, CH_2), 1.72–1.68 (m, 2 H, CH_2), 1.57–1.47 (m, 2 H, CH_2) ppm. HRMS (ESI): calcd. for $C_{17}H_{17}BrN_3O$ 358.0550; found 358.0541.

5-(2-Chlorophenyl)-2,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo-[3,4-*b*]pyridin-1-ol (4bd): White solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3137, 2925, 2856, 1589, 1543, 1439, 1398, 1280, 1252, 1218, 1184, 1053, 959, 878, 815, 749, 637 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.76 (s, 1 H, NH), 10.31 (s, 1 H, OH), 7.57–7.54 (m, 1 H, ArH), 7.46–7.38 (m, 2 H, ArH), 7.26–7.24 (m, 1 H, ArH), 3.12–3.00 (m, 2 H, CH_2), 2.48–2.42 (m, 2 H, CH_2), 1.78–1.58 (m, 4 H, CH_2), 1.56–1.40 (m, 2 H, CH_2) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 164.6, 154.6, 153.5, 151.3, 139.5, 135.4, 132.0, 130.6, 129.4, 128.9, 127.2, 126.7, 101.4, 31.3, 28.5, 27.7, 26.4 ppm. HRMS (ESI): calcd. for $C_{17}H_{17}ClN_3O$ 314.1055; found 314.1062.

5-(2-Thienyl)-2,6,7,8,9,10-hexahydrocyclohepta[*d*]pyrazolo[3,4-*b*]-pyridin-1-ol (4be): Brown solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3109, 2924, 2854, 1590, 1541, 1451, 1386, 1268, 1250, 1174, 961, 876, 829, 795, 724, 709 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.83 (s, 1 H, NH), 10.39 (s, 1 H, OH), 7. 70 (dd, J_1 = 0.8, J_2 = 5.2 Hz, 1 H, thienyl-H), 7. 16 (dd, J_1 = 3.2, J_2 = 5.2 Hz, 1 H, thienyl-H), 7. 06 (dd, J_1 = 0.8, J_2 = 3.6 Hz, 1 H, thienyl-H), 3.07–3.04 (m, 2 H, CH_2), 2.73–2.71 (m, 2 H, CH_2), 1.84–1.74 (m, 2 H, CH_2), 1.72–1.62 (m, 2 H, CH_2), 1.59–1.50 (m, 2 H, CH_2) ppm. HRMS (ESI): calcd. for $C_{15}H_{16}N_3OS$ 286.1009; found 286.1008.

5-(2,3-Dimethoxyphenyl)-2,6,7,8,9,10-hexahydrocyclohepta[*d*]-pyrazolo[3,4-*b*]pyridin-1-ol (4bf): Pink solid, m.p. 262–263 °C. IR (KBr): $\tilde{\nu}$ = 3109, 2933, 2854, 1594, 1545, 1473, 1425, 1349, 1264, 1231, 1196, 1174, 1060, 1001, 958, 879, 813, 771 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.62 (s, 1 H, NH), 7.11–7.06 (m, 2 H, ArH), 6.63 (dd, J_1 = 2.4, J_2 = 6.4 Hz, 1 H, ArH), 3.85 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 3.10–2.98 (m, 2 H, CH_2), 2.50–2.47 (m, 2 H, CH_2), 1.81–1.67 (m, 3 H, CH_2), 1.66–1.57 (m, 1 H, CH_2), 1.55–1.45 (m, 1 H, CH_2), 1.43–1.35 (m, 1 H, CH_2) ppm. HRMS (ESI): calcd. for $C_{19}H_{22}N_3O_3$ 340.1656; found 340.1671.

5-[4-(Dimethylamino)phenyl]-2,6,7,8,9,10-hexahydrocyclohepta-[*d*]pyrazolo[3,4-*b*]pyridin-1-ol (4bg): Yellow solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3042, 2911, 2852, 1611, 1594, 1541, 1524, 1441, 1400, 1350, 1273, 1225, 1182, 959, 875, 837, 812, 728, 636 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.63 (s, 1 H, NH), 10.45 (s, 1 H, OH), 7.10 (d, J = 8.4 Hz, 2 H, ArH), 6.77 (d, J = 8.8 Hz, 2 H, ArH), 3.04–3.01 (m, 2 H, CH_2), 2.96 (s, 6 H, NCH_3), 2.68–2.66 (m, 2 H, CH_2), 1.83–1.74 (m, 2 H, CH_2), 1.72–1.64 (m, 2 H, CH_2), 1.59–1.51 (m, 2 H, CH_2) ppm. HRMS (ESI): calcd. for $C_{19}H_{23}N_4O$ 323.1867; found 323.1842.

5-(*p*-Tolyl)-6,7,8,9,10,11-hexahydro-2*H*-cycloocta[*d*]pyrazolo[3,4-*b*]pyridin-1-ol (4bh): Pink solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3124, 3052, 2932, 2853, 2682, 1594, 1542, 1475, 1396, 1358, 1275, 1252, 1211, 1162, 1135, 1072, 912, 839, 819, 802, 778, 691, 647 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.62 (s, 1 H, NH), 11.04 (s, 1

H, OH), 7.23 (d, J = 8.0 Hz, 2 H, ArH), 7.14 (d, J = 8.0 Hz, 2 H, ArH), 3.00–2.97 (m, 2 H, CH_2), 2.66–2.63 (m, 2 H, CH_2), 2.37 (s, 3 H, CH_3), 1.80–1.71 (m, 2 H, CH_2), 1.43–1.23 (m, 6 H, CH_2) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 162.7, 144.0, 136.4, 133.5, 128.5, 128.2, 125.0, 112.7, 102.4, 35.4, 31.3, 30.7, 26.0, 25.9, 25.3, 20.9 ppm. HRMS (ESI): calcd. for $C_{19}H_{21}N_3NaO$ 330.1577; found 330.1573.

5-(4-Methoxyphenyl)-6,7,8,9,10,11-hexahydro-2*H*-cycloocta[*d*]-pyrazolo[3,4-*b*]pyridin-1-ol (4bi): White solid, m.p. 283–284 °C. IR (KBr): $\tilde{\nu}$ = 3124, 2921, 2851, 1594, 1537, 1518, 1467, 1449, 1395, 1358, 1308, 1289, 1248, 1209, 1180, 1137, 1038, 838, 804, 648, 595 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.56 (s, 1 H, NH), 10.27 (s, 1 H, OH), 7.18 (d, J = 8.4 Hz, 2 H, ArH), 6.98 (d, J = 8.4 Hz, 2 H, ArH), 3.81 (s, 3 H, OCH_3), 3.00–2.97 (m, 2 H, CH_2), 2.75–2.65 (m, 2 H, CH_2), 1.80–1.70 (m, 2 H, CH_2), 1.43–1.24 (m, 6 H, CH_2) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 162.7, 158.5, 155.0, 152.1, 143.8, 129.9, 128.5, 125.1, 113.0, 102.6, 55.0, 35.5, 31.3, 30.7, 26.0, 26.0, 25.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{21}N_3NaO_2$ 346.1526; found 346.1520.

5-(4-Bromophenyl)-6,7,8,9,10,11-hexahydro-2*H*-cycloocta[*d*]-pyrazolo[3,4-*b*]pyridin-1-ol (4bj): Pink solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3049, 2928, 2854, 1595, 1541, 1492, 1395, 1358, 1276, 1208, 1163, 1136, 1075, 1012, 841, 821, 720, 683, 643 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.68 (s, 1 H, NH), 10.43 (s, 1 H, OH), 7.63 (d, J = 8.4 Hz, 2 H, ArH), 7.24 (d, J = 8.0 Hz, 2 H, ArH), 3.04–2.95 (m, 2 H, CH_2), 2.70–2.59 (m, 2 H, CH_2), 1.81–1.69 (m, 2 H, CH_2), 1.43–1.24 (m, 6 H, CH_2) ppm. ^{13}C NMR ([D$_6$]-DMSO, 100 MHz): δ = 162.9, 152.0, 142.4, 135.7, 130.9, 130.6, 124.7, 120.9, 112.7, 79.5, 35.4, 31.2, 30.7, 26.0, 25.9, 25.3 ppm. HRMS (ESI): calcd. for $C_{18}H_{19}BrN_3O$ 372.0706; found 372.0702.

5-(2-Chlorophenyl)-6,7,8,9,10,11-hexahydro-2*H*-cycloocta[*d*]-pyrazolo[3,4-*b*]pyridin-1-ol (4bk): Pink solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3066, 2933, 2856, 1655, 1589, 1541, 1473, 1437, 1395, 1275, 1249, 1207, 1167, 1130, 1078, 1053, 855, 835, 808, 759, 635 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.67 (s, 1 H, NH), 10.32 (s, 1 H, OH), 7.55–7.54 (m, 1 H, ArH), 7.44–7.41 (m, 2 H, ArH), 7.32–7.31 (m, 1 H, ArH), 3.05–2.98 (m, 2 H, CH_2), 2.68–2.61 (m, 1 H, CH_2), 1.82–1.71 (m, 2 H, CH_2), 1.46–1.24 (m, 7 H, CH_2) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 163.0, 140.6, 135.4, 134.2, 132.0, 130.5, 129.5, 128.9, 126.6, 124.8, 105.9, 102.4, 35.4, 30.8, 30.4, 26.3, 25.9, 25.3 ppm. HRMS (ESI): calcd. for $C_{18}H_{19}ClN_3O$ 328.1212; found 328.1196.

5-(2-Thienyl)-6,7,8,9,10,11-hexahydro-2*H*-cycloocta[*d*]pyrazolo-[3,4-*b*]pyridin-1-ol (4bl): Brown solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3109, 2923, 2856, 1591, 1545, 1474, 1450, 1390, 1359, 1274, 1248, 1213, 1162, 1132, 1064, 840, 781, 698 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.81 (s, 1 H, NH), 7. 68 (d, J = 4.8 Hz, 1 H, thienyl-H), 7. 15 (t, J = 3.6 Hz, 1 H, thienyl-H), 7. 09 (d, J = 3.2 Hz, 1 H, thienyl-H), 3.01–2.98 (m, 2 H, CH_2), 2.78–2.75 (m, 2 H, CH_2), 1.80–1.71 (m, 2 H, CH_2), 1.58–1.48 (m, 2 H, CH_2), 1.41–1.28 (m, 4 H, CH_2) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 162.5, 154.3, 151.6, 136.1, 135.6, 128.2, 126.8, 126.7, 126.7, 102.7, 35.2, 32.1, 30.6, 26.6, 25.8, 25.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{18}N_3OS$ 300.1166; found 300.1159.

5-(3,4-Dimethoxyphenyl)-6,7,8,9,10,11-hexahydro-2*H*-cycloocta-[*d*]pyrazolo[3,4-*b*]pyridin-1-ol (4bm): Pink solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3100, 2929, 2852, 1600, 1545, 1518, 1463, 1415, 1382, 1359, 1324, 1260, 1233, 1212, 1170, 1140, 1028, 959, 855, 840, 797, 762, 694, 619 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 11.62 (s, 1 H, NH), 7.00 (d, J = 8.0 Hz, 1 H, ArH), 6.84 (s, 1 H, ArH), 6.79 (d, J = 8.0 Hz, 1 H, ArH), 3.81 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.00–2.97 (m, 2 H, CH_2), 2.75–2.65 (m, 2 H, CH_2), 1.82–1.71 (m, 2 H, CH_2), 1.48–1.26 (m, 6 H, CH_2) ppm. ^{13}C NMR ([D$_6$]-DMSO, 100 MHz): δ = 162.6, 148.1, 147.8, 128.7, 125.2, 121.1, 113.0, 110.9, 55.5, 55.4, 35.3, 31.6, 30.7, 26.3, 25.9, 25.5 ppm. HRMS (ESI): calcd. for $C_{20}H_{24}N_3O_3$ 354.1813; found 354.1798.

5-(*p*-Tolyl)-6,7,8,9,10,11,12,13,14,15-decahydro-2*H*-cyclododeca[*d*]-pyrazolo[3,4-*b*]pyridin-1-ol (4bn): White solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3198, 3147, 3055, 2921, 2861, 1598, 1537, 1519, 1475, 1410, 1320, 1077, 1206, 1179, 1129, 1020, 863, 815, 723 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.59 (s, 1 H, NH), 10.21 (s, 1 H, OH), 7.23 (d, J = 8.0 Hz, 2 H, ArH), 7.15 (d, J = 8.4 Hz, 2 H, ArH), 2.87–2.83 (m, 2 H, CH_2), 2.59–2.55 (m, 2 H, CH_2), 2.38 (s, 3 H, CH_3), 1.92–1.83 (m, 2 H, CH_2), 1.57–1.35 (m, 10 H, CH_2), 1.34–1.27 (m, 2 H, CH_2), 1.22–1.14 (m, 2 H, CH_2) ppm. HRMS (ESI): calcd. for $C_{23}H_{30}N_3O$ 364.2384; found 364.2382.

5-(2-Chlorophenyl)-6,7,8,9,10,11,12,13,14,15-decahydro-2*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridin-1-ol (4bo): White solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3100, 2931, 2846, 1601, 1539, 1505, 1284, 1254, 1208, 1052, 808, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.63 (s, 1 H, NH), 10.28 (s, 1 H, OH), 7.55 (d, J = 7.2 Hz, 1 H, ArH), 7.46–7.39 (m, 2 H, ArH), 7.33–7.31 (m, 1 H, ArH), 2.95–2.78 (m, 2 H, CH_2), 2.67–2.57 (m, 1 H, CH_2), 2.42–2.32 (m, 1 H, CH_2), 1.92–1.82 (m, 2 H, CH_2), 1.57–1.28 (m, 12 H, CH_2), 1.23–1.15 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.3, 151.8, 141.4, 135.4, 132.0, 130.7, 129.5, 128.9, 126.5, 125.2, 102.1, 32.8, 28.5, 27.7, 27.1, 26.7, 26.3, 25.8, 22.7, 22.3 ppm. HRMS (ESI): calcd. for $C_{22}H_{27}ClN_3O$ 384.1839; found 384.1841.

5-(2-Thienyl)-6,7,8,9,10,11,12,13,14,15-decahydro-2*H*-cyclododeca-[*d*]pyrazolo[3,4-*b*]pyridin-1-ol (4bp): Brown solid, m.p. >300 °C. IR (KBr): $\tilde{\nu}$ = 3118, 2927, 2845, 1596, 1537, 1473, 1442, 1271, 1196, 1128, 858, 820, 796, 695 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.79 (s, 1 H, NH), 10.32 (s, 1 H, OH), 7.67 (d, J = 5.2 Hz, 1 H, thienyl-H), 7.16–7.14 (m, 1 H, thienyl-H), 7.09 (d, J = 2.8 Hz, 1 H, thienyl-H), 2.87–2.83 (m, 2 H, CH_2), 2.70–2.67 (m, 2 H, CH_2), 1.91–1.82 (m, 2 H, CH_2), 1.52–1.36 (m, 12 H, CH_2), 1.27–1.23 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.0, 154.2, 151.4, 136.9, 135.8, 128.1, 127.0, 126.7, 126.6, 102.4, 32.8, 29.5, 27.7, 27.1, 26.9, 26.6, 26.4, 25.8, 22.8, 22.4 ppm. HRMS (ESI): calcd. for $C_{20}H_{26}N_3OS$ 356.1792; found 356.1793.

5-(2,3-Dimethoxyphenyl)-6,7,8,9,10,11,12,13,14,15-decahydro-2*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridin-1-ol (4bq): Yellow solid, m.p. 281–283 °C. IR (KBr): $\tilde{\nu}$ = 3118, 2934, 2854, 1641, 1595, 1536, 1475, 1427, 1267, 1234, 1194, 1099, 1061, 1008, 809, 743 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.54 (s, 1 H, NH), 10.40 (s, 1 H, OH), 7.11–7.06 (m, 2 H, ArH), 6.68 (dd, J_1 = 2.8, J_2 = 6.0 Hz, 1 H, ArH), 3.85 (s, 3 H, OCH_3), 3.47 (s, 3 H, OCH_3), 2.98–2.88 (m, 1 H, CH_2), 2.80–2.69 (m, 1 H, CH_2), 2.61–2.53 (m, 2 H, CH_2), 2.40–2.31 (m, 1 H, CH_2), 1.91–1.82 (m, 2 H, CH_2), 1.63–1.15 (m, 13 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.8, 152.0, 145.3, 141.6, 130.8, 125.9, 123.2, 121.8, 112.4, 102.7, 102.2, 59.5, 55.5, 32.8, 28.6, 27.7, 27.2, 26.8, 26.5, 26.5, 25.8, 22.8, 22.2 ppm. HRMS (ESI): calcd. for $C_{24}H_{32}N_3O_3$ 410.2439; found 410.2427.

5-(3,4-Dimethoxyphenyl)-6,7,8,9,10,11,12,13,14,15-decahydro-2*H*-cyclododeca[*d*]pyrazolo[3,4-*b*]pyridin-1-ol (4br): White solid, m.p. 284–285 °C. IR (KBr): $\tilde{\nu}$ = 3341, 2930, 2843, 1588, 1545, 1518, 1464, 1412, 1368, 1317, 1254, 1233, 1204, 1139, 1017, 849, 810, 762, 669 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.58 (s, 1 H, NH), 10.20 (s, 1 H, OH), 7.00 (d, J = 8.0 Hz, 1 H, ArH), 6.85 (s, 1 H, ArH), 6.80 (d, J = 9.6 Hz, 1 H, ArH), 3.81 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 2.89–2.82 (m, 2 H, CH_2), 2.67–2.59 (m, 2 H, CH_2), 1.92–1.82 (m, 2 H, CH_2), 1.52–1.32 (m, 12 H, CH_2), 1.26–1.18 (m, 2 H, CH_2) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.0, 151.8, 148.0, 147.7, 144.6, 128.8, 125.5, 121.1, 113.0, 110.8, 102.2,

55.5, 55.3, 32.8, 29.1, 27.7, 27.1, 27.0, 26.3, 26.2, 25.9, 22.8, 22.5 ppm. HRMS (ESI): calcd. for $C_{24}H_{32}N_3O_3$ 410.2439; found 410.2437.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of all the compounds.

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[22] Crystal data for **4ao**: $C_{30}H_{35}N_3$, colourless, crystal dimensions $0.18 \times 0.16 \times 0.07$ mm, monoclinic, space group $P2_1/c$, a = 10.8926(11), b = 21.927(2), c = 10.4954(14) Å, $\alpha = \gamma = 90$, β = 122.43(5)°, V = 4293(6) Å^3, M_r = 437.61, Z = 4, D_c = 1.180 Mg/m^3, λ = 0.71073 Å, μ(Mo-K_α) = 0.069 mm^{-1}, F(000) = 944, R = 0.0769, wR_2 = 0.1905, S = 1.013, largest diff. peak and hole: 0.203 and –0.173 e/Å^3. CCDC-813944 contains the supplementary crystallographic data for compound **4ao**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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