Application of the Modified Pictet−Spengler Cyclization Reaction for the Preparation of an Imidazopyrazine Ring: Synthesis of new Pyrido- and Pyrimido-imidazopyrazines

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An efficient and versatile method for the synthesis of imidazopyrazine ring using the modified Pictet−Spengler strategy has been reported. The two step strategy offers rapid assembly of druglike core templates pyridine or pyrimidine and imidazole into new annulated polycyclic skeletons: pyrido- and pyrimido-imidazopyrazines. The rate of endo cyclization of aryl/heteroaryl-amine substrates has been compared with traditionally used aliphatic amine substrates, and results have been discussed in the light of the pK_a values of amines present in each substrate.

Introduction

In recent years there has been growing interest in using privileged heterocyclic structures[1] as the starting point for library design.[2] The application of the privileged structure concept in the design of libraries can play a crucial role for the identification of high-affinity ligands.[3] Out of several approaches applied for their generation, one way to design a library based on privileged structures is to construct new fused polycyclic structures. Almost unlimited combinations of annulated heterocyclic structures can be designed, resulting in novel polycyclic skeletons with the most diverse physical, chemical, and biological properties. In the literature, compounds based on these templates have been reported to be associated with wide range of biological activities[4] owing to their rigid conformation analogous to natural products. Therefore, development of an efficient method for the construction of fused polyheterocyclic ring systems in few steps is highly desirable, particularly in the field of medicinal chemistry.

A few years ago, we began to investigate the application of a modified Pictet−Spengler strategy[5] involving an aryl amine based substrate for the synthesis of fused *N*-polycyclic frameworks. The methodology involved condensation of carbonyls to aryl amine substrates linked to an activated heterocycle which proceeds through the intramolecular attack of a π nucleophilic carbon from the activated heterocycle onto the carbon of the iminium ion (π-cyclization). The efficacy of the strategy was successfully demonstrated by synthesizing both naturally occurring and privileged template-based polycyclic structures of biological interest either via 6- or 7-endo cyclization.

Though we successfully demonstrated the efficacy of our modified strategy on a host of activated and deactivated heterocyclic rings, the aryl amine component (in the form of tethered aniline) remained the same in all substrates. This prompted us to explore the affect of replacing the aryl amine with a heteroaryl amine derived from either pyridine or pyrimidine rings as this would expand the repertoire of our substrates amenable to the modified Pictet−Spengler reaction. Interestingly, both pyridine and pyrimidines belong to a class of heterocycles with proven utility (privileged structure) in drug discovery; therefore, our strategy may offer scope for the engineering of biheterocycle frameworks into "privileged hybrid polycyclic skeletons".

In order to explore the affect of heteroaryl amine on 6-endo cyclization, we proposed to replace the *N*-linked aryl amine moiety in one of our earliest reported imidazole-based substrates **1**[5a] with 2-amino pyridine and 5-aminopyrimidine moieties thereby furnishing new substrates **2** and **3** (Figure 1).

Since **1** after condensation with aldehydes furnished imidazoquinoxalines[5a] via the formation of imidazopyrazine ring, we envisaged that application of our modified Pictet−Spengler strategy to substrates **2** and **3** (with heteroaryl amines) would offer a general route to the synthesis of structurally diverse imidazopyrazine derivatives hitherto not reported.

In recent years the imidazo[1,5-*a*]pyrazine scaffold has drawn significant interest among organic, medicinal, and material scientists. The biheterocyclic system on the one hand has been found to be a ligand for the corticotropin releasing hormone receptor and for the human somatostatin receptor[6]

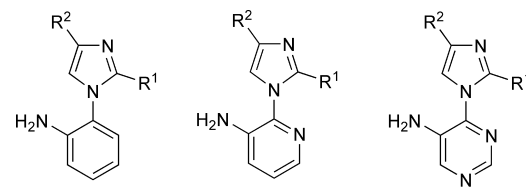

Figure 1. Aryl/heteroaryl amine-based substrates for the modified Pictet−Spengler strategy.

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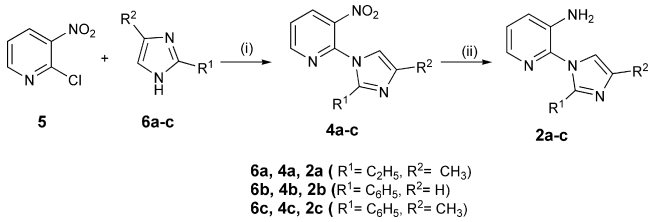
Scheme 1[a]



[a] Reagents and conditions: (i) DMF, 110 °C, 36 h. (ii) Fe, HCl/C_2H_5OH, reflux, 1 h.

Table 1. Optimization of Reaction Conditions for the Conversion of **2a** into **7a** via 6-Endo Cyclization

s. no.	**2a** + 4-ethoxybenzaldehyde + acidic protocols	isolated yield **7a** (%)
1	*p*-TsOH in toluene at reflux	35
2	10% AcOH in ethanol at reflux	26
3	5% TFA in CH_2Cl_2 at r.t. and DDQ	32
4	$Yb(OTf)_3$ in CH_3CN and DDQ	<20
5	1% TFA in toluene at reflux and DDQ	90

subtype 5; on the other hand, studies have established its efficacy for the treatment of acute ischemic stroke, as antioxidants,[7] and as inhibitors of insulin-like growth-factor-I receptor (IGF-IR),[8] gastric H^+/K^+-ATPase,[9] CDK,[10] and IgE synthesis.[11] Beside this, imidazo[1,2-*a*]pyrazine-3-ones have been isolated from a broad array of luminous marine organisms jellyfish (*Aequorea victoria*), sea pansy (*Renilla reniformis*), and squid (*Watasenia scintillans*).[12]

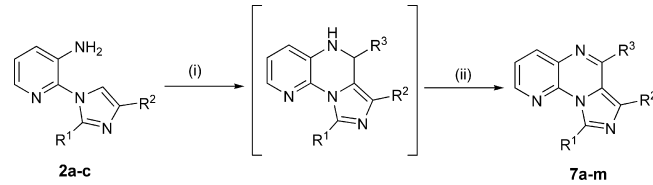
In the literature, synthesis of imidazo[1,5-*a*]pyrazine has been predominantly carried out either by the closure of the imidazole ring from substituted pyrazines[13] or by generating pyrazine ring on imidazole derivatives.[14] Other reports involve sequential ring closure of imidazole and pyrazine rings, respectively,[15] and a three component reaction involving 2-aminopyrimidine, aldehydes, and isonitrile using a nonpolar solvent.[16] In the present paper, we report an application of the modified Pictet−Spengler strategy to tethered biheterocyclic substrates **2** and **3** for the generation of new imidazopyrazine based polycyclic structures.

Result and Discussion

The substrate 2-imidazol-1-yl-pyridin-3-ylamine **2**, required as a key intermediate for the Pictet−Spengler reaction, was synthesized in two steps as depicted in Scheme 1. The synthesis commenced with the formation of nitro intermediates **4** by treating 2-chloro-3-nitro-pyridine **5** with imidazole derivatives **6** in DMF at 110 °C. The resulting nitro derivatives **4a**−**c** was then treated with Fe in HCl/ethanol under reflux to give **2a**−**c** in excellent yield.

We next explored efficacy of **2** to undergo π-cyclizations with a variety of aldehydes and ketones. In the first instance, the substrate **2a** was subjected to the Pictet−Spengler reaction by treating it with 4-ethoxybenzaldehyde using several acidic protocols (Table 1). The best results were obtained when substrate **2a** was treated with 4-ethoxybenzaldehyde in 1% TFA in toluene at reflux. Initially, the product was obtained as a mixture of two components as evident by both HPLC and TLC. The two spots were then separated by column chromatography and characterized by

Scheme 2[a]



[a] Reagents and conditions: (i) R^3CHO, 1% TFA in toluene, 120 °C. (ii) DDQ, 10 min.

Table 2. Synthesis of Imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine **7a**−**m**

entry	substrate	R^3	product	time (h)	yield (%)[a]
1	**2a**	4-OC_2H_5−C_6H_4	**7a**	1	90
2	**2a**	2-OH-C_6H_4	**7b**	1	88
3	**2a**	4-OCH_3−C_6H_4	**7c**	1	92
4	**2a**	4−Cl-C_6H_4	**7d**	0.5	90
5	**2a**	4-NO_2−C_6H_4	**7e**	0.5	92
6	**2a**	H	**7f**	1	91
7	**2b**	4-CH_3−C_6H_4	**7g**	3	89
8	**2b**	4-$(CH_3)_2N$−C_6H_4	**7h**	5	83
9	**2b**	4-OCH_3−C_6H_4	**7i**	5	82
10	**2b**	C_6H_5	**7j**	4	88
11	**2b**	C_2H_5	**7k**	8	80
12	**2c**	4−Br−C_6H_4	**7l**	4	89
13	**2c**	4-NO_2−C_6H_4	**7m**	2	90

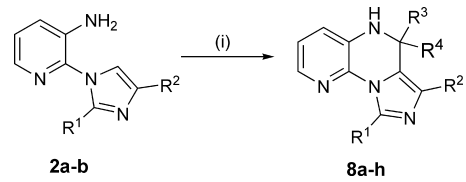
[a] Isolated yield.

ESMS and NMR. One of the major components with a lower R_f on TLC and with a mass of 335.3 Da was found to be dihydroimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine, and the second component with a higher R_f and a mass of 333.3 Da was identified as imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine **7a**, an oxidized product of the first component. Of these two, dihydroimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine had moderate stability, because even after purification, it had a tendency to undergo slow oxidation to **7a**. We therefore, used DDQ as an oxidizing agent in the final step after the Pictet−Spengler cyclization that furnished annulated polycyclic compound imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine **7a** as a single product. The annulation of the substrate **2a** occurred via C−C bond formation between C-5 of the electron-rich imidazole moiety and carbon of the imine (Scheme 2). A literature search revealed only one single report dealing with synthesis of compounds based on imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine framework associated with antiinflammatory activity.[17] The scope and limitation of this reaction was further studied by treating substraces **2a**−**c** with various aliphatic and aromatic aldehydes, and the results have been summarized in Table 2.

Substitution on substrates **2a**−**c** had no effect on the rate of endo cyclization and furnished cyclized products **7a**−**m** in excellent yield. Similarly, aldehydes with both electron-donating and -withdrawing groups underwent 6-endo cyclization within 1−5 h; however, reaction with propionaldehyde went at a slow pace (Table 2, entry 11).

Next, we examined the ability of substrate **2** to undergo endo cyclization with ketones (Scheme 3), which is traditionally known to be a sluggish reaction. Both aliphatic and aromatic ketones were subjected to the Pictet−Spengler reaction by treating substrates **2a**−**b** with ketones in the presence of 1% TFA in toluene and the results have been summarized in Table 3. Both the substrates underwent 6-endo

Scheme 3[a]



[a] Reagents and conditions: (i) R^3COR^4, 1% TFA in toluene, 120 °C.

Table 3. Synthesis of 5,6-Dihydroimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine **8a**−**h**

entry	substrate	R^3	R^4	product	time (h)	yield (%)[a]
1	**2a**	CH_3	C_6H_5	**8a**	9	72
2	**2a**	CH_3	C_2H_5	**8b**	1.5	83
3	**2a**	CH_3	CH_3	**8c**	1	86
4	**2a**	R^3 and R^4=C_6H_{10}		**8d**	1.5	85
5	**2a**	R^3 and R^4=C_5H_8		**8e**	1	84
6	**2b**	CH_3	CH_3	**8f**	4	94
7	**2b**	CH_3	C_2H_5	**8g**	6	88
8	**2b**	R^3 and R^4=C_6H_{10}		**8h**	6	93

[a] Isolated yield.

cyclization to furnish **8a**−**h** in excellent yield; however, the rate of cyclization was found to be comparatively less than that observed during condensation with aldehydes. Both the 6-endo cyclized products based on **7** and **8** are based on 6,6,5-fused tricyclic systems. Compounds based on 6,6,5-systems are widely distribute in nature[18] and have been reported to be useful drug leads for a variety of diseases.[19]

After successfully demonstrating the efficacy of our strategy on substrate **2**, we next examined the efficacy of the substrate **3** having *N*-linked pyrimidine amine toward endo cyclization. Synthesis of **3** was initially attempted by treating 4,6-dichloro-5-nitro pyrimidine **9** with the imidazole **6a**; however, the product was obtained as a mixture of both mono- and disubstituted pyrimidines. This led us to modify our strategy by selectively and sequentially replacing the chloro group at position 4 in **9** with diethyl amine followed by nucleophilic replacement of the chloro group at position 6 with the NH of imidazoles to furnish nitro derivatives **11a**−**b** (Scheme 4). Next, the nitro group in intermediate **11a**−**b** was reduced by treating with Fe/HCl to furnish the desired heteroarylamine substrates **3a**−**b**.

Finally, substrates **3a**−**b** were subjected to the Pictet−Spengler cyclization by treating with both aldehydes and ketones using 1% TFA in toluene as the condensation protocol. The condensation furnished 6,6,5-fused nitrogen containing pteridine derivatives, and the results have been summarized in Table 4. Thus, our methodology might be widely applicable to the 6,6,5-tricyclic systems from the corresponding substrate via the modified Pictet−Spengler reaction. In general **3b**, with disubstituted imidazole was found to be comparatively more reactive toward π-cyclization than the substrate **3a** having monosubstituted imidazole. Similarly, aldehydes with both electron-donating and -withdrawing groups successfully underwent 6-endo cyclization. This is in contrast to traditionally used aliphatic amine substrates (tryptophan/tryptamine) that are either adamant or sluggish to endo cyclization when treated with aldehydes having an electron-donating group (e.g., salicylaldehyde and *p*-*N*,*N*-dimethyl benzaldehyde). Cook et al.[20] attributed the electrophilicity of the imine double bond resulting from the condensation of amines and aldehydes as the limiting factor for the Pictet−Spengler cyclization and applied pK_a values of amines to compare the electrophilicities of the "imines". They argued that amines with comparatively lower pK_a values such as Trp (7.2) exhibit a higher order of reactivity toward endo cyclization than tryptamine with a relatively high pK_a value (10.2). Accordingly, we compared the reactivities of Trp-OMe and tryptamine with substrates **1**, **2**, and **3** toward endo cyclization when condensed with salicylaldehyde under similar reaction conditions, and the results have been summarized in Table 5. As expected, aliphatic amine derived substrates Trp-OMe and tryptamine were indeed sluggish toward endo cyclization; however, aryl/heteroaryl amine-based substrates (**1**, **2a**, and **3a**) underwent endo cyclization with relative ease and in high yields. This observation can be explained by comparing the pK_a values of the substrates (tryptamine 10.2, Trp-OMe 7.29, substrate **1** with the aniline 4.2, substrate **2** with 2-amino pyridine 6.82, and susbtrate **3** with 5-amino pyrimidine 2.83) which clearly suggests that the carbon−nitrogen double bond in the imines derived from substrates **1**−**3** due to the relatively higher electrophilicity than imines derived from Trp-OMe and tryptamine, undergo 6-endo cyclization with greater ease when condensed with salicyclaldehyde.

It is worth mentioning that substrates **2** and **3** have the heteroaryl moeity in "meta" relative to the nitrogen atom present in the heteroarene ring. This could be a relavant factor for the first step of the reaction that is imine formation since the meta position of an *N*-containing deactivated hetrocyclic compound (such as pyridine and pyrimidine) remains the only one not affected by the strong resonance effect of the endo cyclic pyridine-type nitrogen atom. As a consequence, an amino group meta could be much more nucleophilic than an amino group when present in ortho or para positions (where the lone pair of the amino goups is highly delocalized within the ring). Thus, the position of amino in substrate **2** and **3** may have contributed in facilitating π cyclization; however, this needs to be investigation by incorporating other aminopyridine and aminopyrimidine isomers.[21]

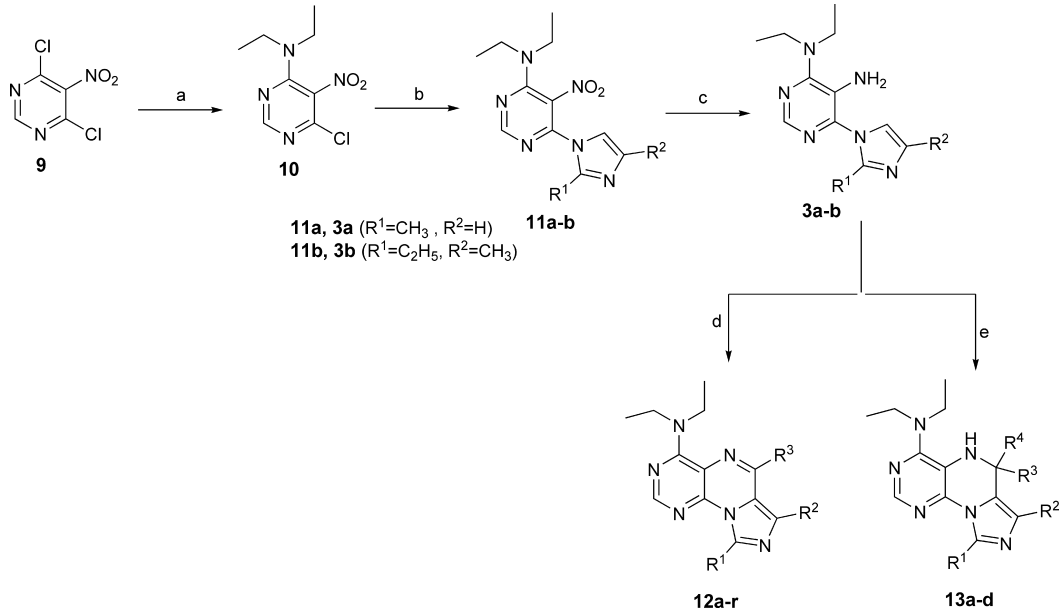
Conclusion

We have developed an efficient and versatile method for the preparation of pyridino- and-pyrimidino-imidazopyrazine derivatives based on 6,6,5-tricyclic systems using the modified Pictet−Spengler reaction. Extension of π-cyclization reactions from aryl amine-based substrates to heteroaryl amine-based substrates opens up new avenues for the synthesis of annulated polycyclic heterosystems from tethered biheterocyclic substrates in minimal steps. Currently studies are in progress to extend the modified Pictet−Spengler strategy to the synthesis of natural products and their derivatives.

Experimental Section

All solvents were commercially available and used without purification. All products were characterized by ^{1}H NMR, ^{13}C NMR, ESMS, and IR. Analytical TLC was performed using 2.5 × 5 cm plated coated with a 0.25 mm thickness

Scheme 4[a]



[a] Reagents and conditions: (a) Et_2NH, Et_3N, THF, 0 °C, 1 h. (b) imidazole, Et_3N, THF, 80 °C, 16 h. (c) Fe, HCl/C_2H_5OH, reflux, 1 h. (d) (i) R^3CHO, 1% TFA in toluene, 120 °C. (ii) DDQ, 10 min. (e) R^3COR^4, 1% TFA in toluene, 120 °C.

Table 4. Synthesis of Imidazo[5,1-*h*]pteridine **12a**−**r** and 5,6-Dihydroimidazo[5,1-*h*]pteridine **13a**−**d**

entry	substrate	R^3	R^4	product	time (h)	isolated yield (%)
1	**3a**	4-CH_3−C_6H_4		**12a**	7	74
2	**3a**	4-OC_2H_5−C_6H_4		**12b**	10	73
3	**3a**	4-OCH_3−C_6H_4		**12c**	9	75
4	**3a**	2-OH-C_6H_4		**12d**	8	70
5	**3a**	C_6H_5		**12e**	6	72
6	**3a**	4-NO_2−C_6H_4		**12f**	6	71
7	**3a**	4−Cl-C_6H_4		**12g**	6	70
8	**3a**	4−Br-C_6H_4		**12h**	6	73
9	**3a**	C_2H_5		**12i**	12	52
10	**3a**	CH_3	CH_3	**13a**	16	51
11	**3b**	4-OCH_3−C_6H_4		**12j**	1.5	75
12	**3b**	4-OH-C_6H_4		**12k**	2	73
13	**3b**	2-OH-C_6H_4		**12l**	5	68
14	**3b**	C_6H_5		**12m**	1.5	70
15	**3b**	4-CN-C_6H_4		**12n**	1	73
16	**3b**	4-NO_2−C_6H_4		**12o**	1	82
17	**3b**	4−Cl-C_6H_4		**12p**	1.5	73
18	**3b**	C_2H_5		**12q**	3	55
19	**3b**	CH_2−C_6H_5		**12r**	3	57
20	**3b**	CH_3	CH_3	**13b**	4	58
21	**3b**	CH_3	C_2H_5	**13c**	6	57
22	**3b**	CH_3	C_6H_5	**13d**	18	48

Table 5. Comparative Profile of the 6-Endo Cyclization of Aliphatic/Aryl Amine-Based Substrates with Salicylaldehyde Using 1% TFA in Toluene at 120 °C

entry	substrate	pK_a	time (h)	yield (%)[b]
1	Trp-OMe	7.2	24	45
2	tryptamine	10.2	24	19
3	**1**[a]	4.2	1	86
4	**2a**	6.8	1	88
5	**3a**	2.8	8	70

[a] $R^1 = C_2H_5$. $R^2 = CH_3$. [b] Isolated yield of 6-endo cyclized products.

of silica gel. 60F-254 and visualization was accomplished with UV light and iodine. Column chromatography was performed using silica gel (100−200 mesh). ^{1}H NMR spectra (200/300 MHz) are reported as follows: chemical shifts in parts per million downfield from TMS as internal standard (δ scale), multiplicity [br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, o = overlapped, integration and coupling constant (Hz)]. All ^{13}C NMR spectra (50/75 MHz) were recorded at 25 °C with complete proton decoupling and reported in parts per million except for compounds **7b**, **12f**, and **12k** which are insoluble at higher concentration. The purity and characterization of these compounds were further established using HR/EI mass spectroscopy. Elemental analyses were performed on microanalyzer or Elementar's Vario EL III microanalyzer. The microanalyses were performed at the Sophisticated Analytical Instrument Facility Division, CDRI. Mass spectra were recorded on a spectrometer and EI mass spectra were done on JEOL-600H at 70 eV. The melting points reported were uncorrected.

General Procedure for the Synthesis of Nitro Derivative (4). A mixture of 2-chloro-3-nitro-pyridine **5** (790 mg, 5 mmol) and imidazole **6a** (1.10 g, 10 mmol) in DMF (1 mL) in a vessel was heated at 110 °C for 36 h. Upon completion of the reaction, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (100 mL). The solvent was washed with water (2 × 40 mL) and brine (40 mL) and finally dried over anhydrous Na_2SO_4. The organic layer was evaporated in vacuo to afford a crude residue which was purified by column chromatography on silica gel using hexane-ethyl acetate (35:65, v/v) to give the desired product **4a**.

2-(2-Ethyl-4-methyl-1*H*-imidazol-1-yl)-3-nitropyridine (4a). Yield: 67%. Yellow solid. mp 71−73 °C. R_f = 0.69 (1:9, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3019, 2975, 2851, 1594, 1536, 1351 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.80 (dd, J = 4.7, 1.7 Hz, 1 H, ArH), 8.36 (dd, J = 8.1, 1.7 Hz, 2 H, ArH), 7.62−7.56 (m, 1 H, ArH), 6.65 (d, J = 1.1 Hz, 1 H, ArH), 2.66 (q, J = 7.5 Hz, 2 H, CH_2), 2.24 (d, J = 1.1 Hz, 3 H, CH_3), 1.23 (t, J = 7.5 Hz, 3 H, CH_3). Mass (ES^+) *m*/*z*

233.3 [(M + 1)$^+$]. Anal. calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.78; H, 5.28; N, 24.18.

3-Nitro-2-(2-phenyl-1*H*-imidazol-1-yl)pyridine (4b). Yield: 52%. Yellow solid. mp 112−114 °C. R_f = 0.76 (1:9, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3021, 2922, 2862, 1594, 1528, 1346 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.83 (dd, J = 4.7, 1.7 Hz, 1 H, ArH), 8.24 (dd, J = 8.1, 1.7 Hz, 1 H, ArH), 7.62−7.56 (m, 1 H, ArH), 7.34−7.22 (m, 7 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.6, 153.0, 147.8, 143.8, 141.8, 134.5, 130.2, 129.2, 128.7, 128.5, 124.7, 121.0. Mass (ES$^+$) m/z 267.1 [(M + 1)$^+$]. Anal. calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.21; H, 3.64; N, 21.11.

2-(4-Methyl-2-phenyl-1*H*-imidazol-1-yl)-3-nitropyridine (4c). Yield: 46%. Yellow solid. R_f = 0.78 (1:9, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3020, 2983, 2849, 1578, 1378 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.79 (dd, J = 4.7, 1.5 Hz, 1 H, ArH), 8.20 (dd, J = 8.1, 1.5 Hz, 1 H, ArH), 7.56−7.52 (m, 1 H, ArH), 7.28−7.22 (m, 5 H, ArH), 7.06 (s, 1 H, ArH), 2.37 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.8, 152.7, 152.5, 147.0, 139.4, 138.1, 134.3, 129.3, 129.0, 128.6, 128.4, 124.1, 13.5. Mass (ES$^+$) m/z 281.2 [(M + 1)$^+$]. Anal. calcd for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.37; H, 4.45; N, 19.87.

General Procedure for the Synthesis of Amine Derivative (2). A solution of **4a** (1.16 g, 5 mmol) and Fe (1.10, 20 mmol) in acidic ethanol (1:4 HCl/EtOH) was refluxed under nitrogen atmosphere for 1 h. The reaction mixture was allowed to cool down and then poured into ice, and the pH is made slightly basic (pH 8) by addition of 5% aqueous $NaHCO_3$. The ethyl acetate (100 mL) was added to the mixture and filtered through a bed of Celitet. The organic layer was finally washed with water (2 × 50 mL), brine (2 × 50 mL), and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure. The crude product was purified on a silica gel column using hexane-ethyl acetate (20:80, v/v) as eluent to afford **2a**.

2-(2-Ethyl-4-methyl-1*H*-imidazol-1-yl)pyridin-3-amine (2a). Yield: 90%. White solid. mp 162−165 °C. R_f = 0.44 (1:9, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3184, 3116, 2937, 2875, 1643 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.96−7.93 (m, 1 H, ArH), 7.22 (d, J = 3.0 Hz, 2 H, ArH), 6.79 (s, 1 H, ArH), 4.15 (brs, 2 H, NH_2), 2.73 (q, J = 7.4 Hz, 2 H, CH_2), 2.34 (s, 3 H, CH_3), 1.25 (t, J = 7.4 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.8, 138.6, 138.5, 137.5, 136.7, 125.1, 123.9, 114.8, 20.6, 13.6, 12.3. Mass (ES$^+$) m/z 203.2 [(M + 1)$^+$]. Anal. calcd for $C_{15}H_{14}N_4$: C, 65.32; H, 6.98; N, 27.70. Found: C, 65.48; H, 6.87; N, 27.65.

2-(2-Phenyl-1*H*-imidazol-1-yl)pyridin-3-amine (2b). Yield: 74%. White solid. mp 147−150 °C. R_f = 0.51 (1:9, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3167, 3112, 3021, 1624 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.98 (dd, J = 4.5, 1.4 Hz, 1 H, ArH), 7.47−7.43 (m, 2 H, ArH), 7.32−7.17 (m, 6 H, ArH), 7.08 (dd, J = 8.0, 1.4 Hz, 1 H, ArH), 3.59 (brs, 2 H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.9, 138.7, 138.6, 137.1, 130.3, 129.9, 128.8, 128.5, 127.7, 125.6, 124.4, 121.4. Mass (ES$^+$) m/z 237.2 [(M + 1)$^+$]. Anal. calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.28; H, 5.06; N, 23.66.

2-(4-Methyl-2-phenyl-1*H*-imidazol-1-yl)pyridin-3-amine (2c). Yield: 68%. White solid. mp 145−147 °C. R_f = 0.53 (1:9, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3189, 3121, 3022, 2948, 2836, 1635 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96 (dd, J = 4.5, 1.6 Hz, 1 H, ArH), 7.45−7.40 (m, 2 H, ArH), 7.25−7.05 (m, 5 H, ArH), 6.89 (d, J = 0.9 Hz, 1 H, ArH), 3.62 (brs, 2 H, NH_2), 2.35 (d, J = 0.8 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.7, 138.5, 138.4, 136.9, 130.1, 129.7, 128.5, 128.2, 127.4, 125.3, 124.1, 121.1; 13.1. Mass (ES$^+$) m/z 251.2 [(M + 1)$^+$]. Anal. calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.89; H, 5.80; N, 22.31.

General Procedure for the Synthesis of Imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7). A mixture of amine **2a** (202 mg, 1 mmol) and 4-ethoxybenzaldehyde (150 μL, 1 mmol) was refluxed in 1% TFA in toluene until the disappearance of the starting material on TLC. Then, the reaction mixture was treated with DDQ (1.5 mmol) for 10 min at reflux. Toluene was evaporated in vacuo, and the residue so obtained was basified with aq $NaHCO_3$ and extracted with ethyl acetate (2 × 30 mL). The organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate was evaporated under reduced pressure to obtain residue that after column chromatography on silica gel using hexane-ethyl acetate (60:40 v/v) afforded **7a** as a white solid.

6-(4-Ethoxyphenyl)-9-ethyl-7-methylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7a). Yield: 90%. White solid. mp 146−147 °C. R_f = 0.64 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2930, 2849, 1607 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (dd, J = 4.5, 1.4 Hz, 1 H, ArH), 8.19 (dd, J = 7.9, 1.4 Hz, 1 H, ArH), 7.57 (d, J = 8.6 Hz, 2 H, ArH), 7.45−7.41 (m, 1 H, ArH), 7.04 (d, J = 8.6 Hz, 2 H, ArH), 4.14 (q, J = 7.0 Hz, 2 H, CH_2), 3.71 (q, J = 7.0 Hz, 2 H, CH_2), 2.20 (s, 3 H, CH_3), 1.53−146 (m, 6 H, 2 × CH_3). ^{13}C NMR (75 MHz, DMSO) δ = 149.6, 146.9, 143.5, 136.2, 135.9, 132.7, 131.9, 129.5, 128.0, 127.1, 124.2, 123.9, 122.6, 122.5, 51.2, 12.3. Mass (ES$^+$) m/z 333.3 [(M + 1)$^+$]. Anal. calcd for $C_{20}H_{20}N_4O$: C, 72.27; H, 6.06; N, 16.86. Found: C, 72.31; H, 6.11; N, 16.78.

2-(9-Ethyl-7-methylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazin-6-yl)phenol (7b). Yield: 88%. White solid. mp > 250 °C. R_f = 0.61 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2978, 2855, 1603 cm^{-1}. ^{1}H NMR (300 MHz, DMSO) δ = 9.73 (brs, 1 H, OH), 8.59 (dd, J = 4.6, 1.4 Hz, 1 H, ArH), 8.23 (dd, J = 7.9, 1.6 Hz, 1 H, ArH), 7.62−7.58 (m, 1 H, ArH), 7.39−7.34 (m, 1 H, ArH), 7.28 (dd, J = 7.4, 1.4 Hz, 1 H, ArH), 7.00−6.96 (m, 2 H, ArH), 3.57 (q, J = 7.4 Hz, 2 H, CH_2), 1.94 (s, 3 H, CH_3), 1.38 (t, J = 7.4 Hz, 3 H, CH_3). Mass (ES$^+$) m/z 305.3 [(M + 1)$^+$]. Anal. calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.14; H, 5.17; N, 18.32.

9-Ethyl-6-(4-methoxyphenyl)-7-methylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7c). Yield: 92%. Yellow solid. mp 156−158 °C. R_f = 0.35 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2978, 2855, 1603 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.49 (dd, J = 4.6, 1.7 Hz, 1 H, ArH), 8.18 (dd, J = 7.9, 1.7 Hz, 1 H, ArH), 7.58 (d, J = 8.8 Hz, 2 H, ArH), 7.45−7.39 (m, 1 H, ArH), 7.04 (d, J = 8.8 Hz, 2 H, ArH), 3.90 (s, 3 H, OCH_3), 3.69 (q, J = 7.4 Hz, 2 H, CH_2), 2.18

(s, 3 H, CH_3), 1.49 (t, $J = 7.4$ Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 161.2, 157.3, 148.2, 146.0, 140.1, 137.2, 136.6, 132.2, 130.4, 130.3, 122.7, 122.3, 114.0, 55.6, 24.7, 16.4, 12.6$. Mass ($ES^+$) m/z 319.4 [$(M + 1)^+$]. Anal. calcd for $C_{19}H_{18}N_4O$: C, 71.68; H, 5.70; N, 17.60. Found: C, 71.74; H, 5.62; N, 17.54.

6-(4-Chlorophenyl)-9-ethyl-7-methylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7d). Yield: 90%. Yellow solid. mp 193−195 °C. $R_f = 0.53$ (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3051, 2924, 2862, 1595 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 8.52$ (dd, $J = 4.7, 1.7$ Hz, 1 H, ArH), 8.19 (dd, $J = 8.0, 1.7$ Hz, 1 H,ArH), 7.60−7.41 (m, 5 H, ArH), 3.70 (q, $J = 7.4$ Hz, 2 H, CH_2), 2.15 (s, 3 H, CH_3), 1.49 (t, $J = 7.4$ Hz, 3 H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 156.5, 148.6, 146.7, 140.2, 137.4, 137.0, 136.6, 136.4, 132.2, 130.4, 129.2, 122.7, 25.0, 16.5, 12.8$. Mass ($ES^+$) m/z 323.3 [$(M + 1)^+$]. Anal. calcd for $C_{18}H_{15}ClN_4$: C, 66.98; H, 4.68; N, 17.36. Found: C, 66.82; H, 4.75; N, 17.44.

9-Ethyl-7-methyl-6-(4-nitrophenyl)imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7e). Yield: 92%. Yellow solid. mp 182−183 °C. $R_f = 0.45$ (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3080, 2923, 2858, 1594 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 8.56$ (dd, $J = 4.7, 1.7$ Hz, 1 H,ArH), 8.41 (d, $J = 8.8$ Hz, 2 H, ArH), 8.21 (dd, $J = 8.0, 1.7$ Hz, 1 H, ArH), 7.82 (d, $J = 8.8$ Hz, 2 H, ArH), 7.51−7.45 (m, 1 H, ArH), 3.72 (q, $J = 7.4$ Hz, 2 H, CH_2), 2.13 (s, 3 H, CH_3), 1.50 (t, $J = 7.4$ Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 169.1, 154.8, 148.6, 146.8, 143.7, 139.7, 136.8, 132.7, 131.5, 129.7, 128.1, 123.6, 122.4, 24.3, 15.9, 12.3$. Mass ($ES^+$) m/z 334.3 [$(M + 1)^+$]. Anal. calcd for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.77; H, 4.63; N, 21.11.

9-Ethyl-7-methylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7f). Yield: 91%. White solid. mp 99−101 °C. $R_f = 0.26$ (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3058, 2925, 2855, 1617 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.71$ (s, 1 H, ArH), 8.50 (dd, $J = 4.7, 1.7$ Hz, 1 H, ArH), 8.16 (dd, $J = 7.9, 1.7$ Hz, 1 H, ArH), 7.45−7.41 (m, 1 H, ArH), 3.65 (q, $J = 7.5$ Hz, 2 H, CH_2), 2.62 (s, 3 H, CH_3), 1.47 (t, $J = 7.5$ Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 148.1, 146.6, 146.2, 137.0, 136.8, 132.2, 123.8, 122.3, 24.5, 13.0, 12.5$. Mass ($ES^+$) m/z 213.3 [$(M + 1)^+$]. Anal. calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.87; H, 5.64; N, 26.49.

9-Phenyl-6-*p*-tolylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7g). Yield: 89%. White solid. mp 181−183 °C. $R_f = 0.58$ (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2918, 2844, 1606 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.31-8.28$ (m, 2 H, ArH), 8.03−7.88 (m, 5 H, ArH), 7.51−7.39 (m, 6 H, ArH), 2.49 (s, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 155.7, 145.9, 141.4, 138.8, 137.5, 134.3, 132.4, 132.2, 130.7, 130.2, 129.8, 129.1, 128.6, 127.6, 127.0, 123.2, 21.7$. Mass ($ES^+$) m/z 337.4 [$(M + 1)^+$]. Anal. calcd for $C_{22}H_{16}N_4$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.65; H, 4.64; N, 16.71.

***N*,*N*-Dimethyl-4-(9-phenylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazin-6-yl)aniline (7h).** Yield: 83%. Orange solid. mp 168−170 °C. $R_f = 0.54$ (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2918, 2856, 1607 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.26-8.21$ (m, 2 H, ArH), 8.07−8.02 (m, 3 H, ArH), 7.91−7.89 (m, 2 H, ArH), 7.49−7.39 (m, 4 H, ArH), 6.86 (d, $J = 7.7$ Hz, 2 H, ArH), 3.09 (s, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 155.2, 152.4, 145.5, 145.0, 138.7, 136.9, 132.7, 132.5, 130.7, 130.0, 129.2, 127.5, 127.0, 124.6, 123.0, 112.0, 109.7, 40.3$. Mass ($ES^+$) m/z 366.4 [$(M + 1)^+$]. Anal. calcd for $C_{23}H_{19}N_5$: C, 75.59; H, 5.24; N, 19.16. Found: C, 75.69; H, 5.19; N, 19.12.

6-(4-Methoxyphenyl)-9-phenylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7i). Yield: 82%. White solid. mp 169−170 °C. $R_f = 0.42$ (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3046, 2924, 2854, 1607 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 8.30-8.27$ (m, 1 H, ArH), 8.26 (s, 1 H, ArH), 8.07−8.03 (m, 3 H, ArH), 7.92−7.87 (m, 2 H, ArH), 7.51−7.41 (m, 4 H, ArH), 7.11 (d, $J = 8.8$ Hz, 2 H, ArH), 3.92 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 161.9, 154.9, 145.6, 138.6, 137.2, 132.3, 132.1, 130.6, 130.1, 129.4, 129.3, 129.2, 127.4, 126.8, 123.1, 114.3, 55.5$. Mass ($ES^+$) m/z 353.3 [$(M + 1)^+$]. Anal. calcd for $C_{22}H_{16}N_4O$: C, 74.98; H, 4.58; N, 15.90. Found: C, 74.82; H, 4.67; N, 15.84.

6,9-Diphenylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7j). Yield: 88%. Yellow solid. mp 141−142 °C. $R_f = 0.66$ (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3053, 2923, 2856, 1647 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 8.34-8.31$ (m, 1 H, ArH), 8.30 (s, 1 H, ArH), 8.08−8.02 (m, 3 H, ArH), 7.93−7.88 (m, 2 H, ArH), 7.62−7.59 (m, 3 H, ArH), 7.52−7.44 (m, 4 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 155.7, 146.1, 145.9, 138.8, 137,6, 137.1, 132.4, 132.2, 131.0, 130.7, 129.5, 129.4, 129.1, 128.6, 127.6, 127.0, 123.2$. Mass ($ES^+$) m/z 323.4 [$(M + 1)^+$]. Anal. calcd for $C_{21}H_{14}N_4$: C, 78.24; H, 4.38; N, 17.38. Found: C, 78.35; H, 4.43; N, 17.22.

6-Ethyl-9-phenylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7k). Yield: 80%. Yellow solid. mp 85−87 °C. $R_f = 0.46$ (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2978, 2855, 1603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.27$ (dd, $J = 4.6, 1.7$ Hz, 1 H, ArH), 8.20 (dd, $J = 8.0, 1.7$ Hz, 1 H, ArH), 7.95 (s, 1 H, ArH), 7.89−7.86 (m, 2 H, ArH), 7.49−7.41 (m, 4 H, ArH), 3.10 (q, $J = 7.6$ Hz, 6 H, CH_2), 1.50 (t, $J = 7.6$ Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 160.0, 145.7, 137.0, 132.2, 132.1, 130.7, 129.3, 127.5, 127.3, 127.2, 123.0, 28.8, 12.3$. Mass ($ES^+$) m/z 275.3 [$(M + 1)^+$]. Anal. calcd for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.37; H, 5.08; N, 20.55.

6-(4-Bromophenyl)-7-methyl-9-phenylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7l). Yield: 89%. Yellow solid. mp 220−221 °C. $R_f = 0.57$ (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2934, 2848, 1597 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.25$ (dd, $J = 4.6, 1.7$ Hz, 2 H, ArH), 8.20 (dd, $J = 7.9, 1.7$ Hz, 1 H, ArH), 7.87−7.84 (m, 2 H, ArH), 7.71 (d, $J = 8.4$ Hz, 1 H, ArH), 7.56 (d, $J = 8.4$ Hz, 2 H, ArH), 7.49−7.39 (m, 4 H, ArH), 2.22 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 156.4, 146.2, 144.5, 139.2, 138.8, 137.2, 136.8, 132.2, 132.0, 130.6, 130.5, 129.4, 127.6, 124.6, 123.2, 123.1, 16.5$. Mass ($ES^+$) m/z 415.3 [$(M + 1)^+$]. Anal. calcd for $C_{22}H_{15}BrN_4$: C, 63.63; H, 3.64; N, 13.49. Found: C, 63.56; H, 3.72; N, 13.37.

7-Methyl-6-(4-nitrophenyl)-9-phenylimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (7m). Yield: 90%. Yellow solid. mp 245−247 °C. $R_f = 0.64$ (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3022, 2926, 2857, 1592, 1519, 1351 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.44$ (d, $J = 8.7$ Hz, 2 H, ArH), 8.30 (dd, $J = 4.6, 1.7$ Hz, 1 H, ArH), 8.22 (dd, $J = 8.0, 1.7$ Hz,

1 H, ArH), 7.90−7.85 (m, 4 H, ArH), 7.50−7.43 (m, 4 H, ArH), 2.20 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.1, 148.9, 146.7, 144.8, 143.9, 139.1, 138.6, 137.4, 131.7, 130.6, 130.1, 129.6, 127.6, 124.0, 123.3, 122.9, 16.5. Mass (ES^+) *m/z* 382.2 [$(M + 1)^+$]. Anal. calcd for $C_{22}H_{15}N_5O_2$: C, 69.28; H, 3.96; N, 18.36. Found: C, 69.36; H, 3.85; N, 18.43.

General Procedure for the Synthesis of 5,6-Dihydroimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (8). A mixture of amine **2a** (202 mg, 1 mmol) and acetophenone (120 μL, 1 mmol) was refluxed in 1% TFA in toluene until the disappearance of the starting material on TLC. The solvent was then evaporated, and the residue so obtained was basified with aq $NaHCO_3$. It was then extracted with ethyl acetate (2 × 30 mL), washed with brine (10 mL), and dried over anhydrous Na_2SO_4. The ethyl acetate was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (40:60 v/v) to afford **8a** as a white solid.

9-Ethyl-6,7-dimethyl-6-phenyl-5,6-dihydroimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (8a). Yield: 72%. White solid. mp 170−172 °C. R_f = 0.37 (1:19, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3019, 2975, 2934, 2858, 1589 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.86 (dd, *J* = 4.6, 1.6 Hz, 1 H, ArH), 7.43−7.40 (m, 2 H, ArH), 7.36−7.28 (m, 3 H, ArH), 7.03−6.93 (m, 2 H, ArH), 4.23 (brs, 1 H, NH), 3.40−3.31 (m, 2 H, CH_2), 1.90−189 (m, 6 H, 2 × CH_3), 1.38 (t, *J* = 7.4 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.8, 144.9, 138.3, 137.7, 131.2, 130.1, 128.6, 127.8, 126.7, 126.6, 122.0, 121.2, 57.1, 28.2, 24.1, 13.7, 12.5. Mass (ES^+) *m/z* 305.3 [$(M + 1)^+$]. Anal. calcd for $C_{19}H_{20}N_4$: C, 74.97; H, 6.62; N, 18.41. Found: C, 74.89; H, 6.74; N, 18.37.

6,9-Diethyl-6,7-dimethyl-5,6-dihydroimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (8b). Yield: 82%. White solid. mp 135−138 °C. R_f = 0.46 (1:19, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3021, 2927, 2866, 1592 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.82−7.81 (m, 1 H, ArH), 6.98−6.90 (m, 2 H, ArH), 3.66 (brs, 1 H, NH), 3.31 (q, *J* = 7.3 Hz, 2 H, CH_2), 2.29 (s, 3 H, CH_3), 1.70−1.63 (m, 2 H, CH_2), 1.55 (s, 3 H, CH_3), 1.35 (t, *J* = 7.3 Hz, 3 H, CH_3), 0.88 (t, *J* = 7.3 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.8, 137.8, 137.0, 131.5, 129.0, 125.8, 121.4, 121.2, 55.1, 34.8, 27.3, 24.2, 14.4, 12.6, 8.7. Mass (ES^+) *m/z* 257.2 [$(M + 1)^+$]. Anal. calcd for $C_{15}H_{20}N_4$: C, 70.28; H, 7.86; N, 21.86. Found: C, 70.34; H, 7.75; N, 21.91.

9-Ethyl-6,6,7-trimethyl-5,6-dihydroimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (8c). Yield: 82%. White solid. mp 141−143 °C. R_f = 0.39 (1:19, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3018, 2969, 2930, 2856, 1589 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.86−7.84 (m, 1 H, ArH), 6.98−6.95 (m, 2 H, ArH), 3.67 (brs, 1 H, NH), 3.31 (q, *J* = 7.5 Hz, 2 H, CH_2), 2.31 (s, 3 H, CH_3), 1.55 (s, 6 H, 2 × CH_3), 1.34 (t, *J* = 7.5 Hz, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.6, 138.0, 137.4, 131.3, 128.2, 127.2, 121.8, 121.2, 51.9, 29.4, 24.0, 14.3, 12.6. Mass (ES^+) *m/z* 243.3 [$(M + 1)^+$]. Anal. calcd for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12. Found: C, 69.44; H, 7.37; N, 23.19.

9′-Ethyl-7′-methyl-5′*H*-spiro[cyclohexane-1,6′-imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine](8d). Yield: 82%. Yellow−white solid. mp 188−190 °C. R_f = 0.47 (1:19, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3018, 2938, 2856, 1587 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.85−7.83 (m, 1 H, ArH), 7.05−7.02 (m, 1 H, ArH), 6.96−6.92 (m, 1 H, ArH), 4.44 (brs, 1 H, NH), 3.30 (q, *J* = 7.4 Hz, 2 H, CH_2), 2.35 (s, 3 H, CH_3), 1.94−1.17 (m, 8 H, CH_2), 1.48−1.26 (m, 5 H, CH_2, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.4, 138.6, 137.5, 130.6, 128.2, 127.9, 122.0, 121.1, 53.3, 35.0, 25.0, 24.1, 21.2, 15.1, 12.6. Mass (ES^+) *m/z* 283.3 [$(M + 1)^+$]. Anal. calcd for $C_{17}H_{22}N_4$: C, 72.31; H, 7.85; N, 19.84. Found: C, 72.24; H, 7.79; N, 19.97.

9′-Ethyl-7′-methyl-5′*H*-spiro[cyclopentane-1,6′-imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine] (8e). Yield: 82%. White solid. mp 175−177 °C. R_f = 0.38 (1:1, EtOAc/hexane). IR (KBr) ν_{max} 3020, 2934, 2876, 1587 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 7.87−7.83 (m, 1 H, ArH), 6.97−6.94 (m, 2 H, ArH), 3.92 (brs, 1 H, NH), 3.31 (q, *J* = 7.4 Hz, 2 H, CH_2), 2.29 (s, 3 H, CH_3), 2.24−2.18 (m, 2 H, CH_2), 1.87−1.82 (m, 6 H, 3 × CH_2), 1.34 (t, *J* = 7.4 Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 148.0, 139.0, 137.9, 131.7, 128.2, 127.3, 122.2, 121.3, 62.6, 39.7, 24.3, 24.2, 14.5, 12.9. Mass (ES^+) *m/z* 269.3 [$(M + 1)^+$]. Anal. calcd for $C_{16}H_{20}N_4$: C, C, 71.61; H, 7.51; N, 20.88. Found: C, 71.76; H, 7.48; N, 20.76.

6,6-Dimethyl-9-phenyl-5,6-dihydroimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (8f). Yield: 94%. White solid. mp 111−113 °C. R_f = 0.40 (1:1, EtOAc/hexane). IR (KBr) ν_{max} 3020, 2928, 2846, 1587 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.65−7.62 (m, 3 H, ArH), 7.38−7.36 (m, 3 H, ArH), 7.06 (dd, *J* = 7.7, 1.4 Hz, 1 H, ArH), 6.97−6.93 (m, 2 H, ArH), 3.86 (brs, 1 H, NH), 1.58 (s, 6 H, 2 × CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.1, 137.3, 137.0, 136.0, 132.4, 132.0, 129.7, 128.2, 127.2, 122.9, 122.1, 121.1, 51.2, 29.0. Mass (ES^+) *m/z* 277.3 [$(M + 1)^+$]. Anal. calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.27. Found: C, 73.82; H, 5.78; N, 20.40.

6-Ethyl-6-methyl-9-phenyl-5,6-dihydroimidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine (8g). Yield: 88%. White solid. mp 117−120 °C. R_f = 0.37 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3019, 2971, 2929, 2858, 1590 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ = 7.67−7.60 (m, 3 H, ArH), 7.39−7.36 (m, 3 H, ArH), 7.06 (dd, *J* = 7.9, 1.5 Hz, 1 H, ArH), 6.98−6.92 (m, 2 H, ArH), 3.91 (brs, 1 H, NH), 1.78 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.56 (s, 3 H, CH_3), 0.94 (t, *J* = 7.4 Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 145.4, 137.3, 134.8, 132.5, 132.2, 129.9, 128.5, 127.5, 122.8, 122.4, 54.6, 34.4, 26.5, 8.8. Mass (ES^+) *m/z* 291.3 [$(M + 1)^+$]. Anal. calcd for $C_{18}H_{18}N_4$; C, 74.46; H, 6.25; N, 19.30. Found: C, 74.34; H, 6.32; N, 19.34.

9′-Phenyl-5′*H*-spiro[cyclohexane-1,6′-imidazo[1,5-*a*]pyrido[3,2-*e*]pyrazine] (8h). Yield: 93%. White solid. mp 192−194 °C. R_f = 0.29 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3025, 2928, 2865, 1591 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.65−7.62 (m, 3 H, ArH), 7.38−7.36 (m, 3 H, ArH), 7.11 (dd, *J* = 7.7, 1.5 Hz, 1 H, ArH), 7.02 (s, 1 H, ArH), 6.98−6.94 (m, 1 H, ArH), 4.33 (brs, 1 H, NH), 1.93−1.72 (m, 6 H, 3 × CH_2), 1.60−1.41 (m, 4 H, 2 × CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.2, 137.7, 136.4, 132.4, 131.5,

129.8, 128.4, 127.4, 123.1, 122.1, 121.8, 52.9, 36.2, 24.9, 21.6. Mass (ES^+) *m/z* 317.3 [$(M + 1)^+$]. Anal. calcd for $C_{20}H_{20}N_4$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.86; H, 6.48; N, 17.66.

Synthesis of 6-Chloro-*N*,*N*-diethyl-5-nitropyrimidin-4-amine (10). To a solution of 4,6-dichloro-5-nitropyrimidine **9** (2.00 g, 10.4 mmol) in anhydrous THF (40 mL) was added dropwise a solution of diethylamine (879 μL, 8.5 mmol) and triethylamine (2.1 mL, 15.6 mmol) in anhydrous THF (20 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. After being warmed to room temperature, the solvent was concentrated in vacuo. The residue was dissolved in EtOAc (50 mL), washed with 1 N HCl (30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. The organic solvent was concentrated in vacuo, and the residue was purified by column chromatography on a silica gel column (hexane/EtOAc 20:1, v/v) which provided the desired product **10**.

6-Chloro-*N*,*N*-diethyl-5-nitropyrimidin-4-amine (10). Yield: 88%. Yellow oil. $R_f = 0.42$ (1:19, EtOAc/hexane). IR (Neat) ν_{max} 3020, 2938, 2851, 1530, 1354 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 8.35$ (s, 1 H, ArH), 3.49 (q, $J = 7.1$ Hz, 4 H, 2 × CH_2), 1.23 (t, $J = 7.1$ Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 156.2$, 152.9, 152.3, 44.2, 12.8. Mass (ES^+) *m/z* 231.2 [$(M + 1)^+$]. Anal. calcd for $C_8H_{11}ClN_4O_2$: C, 41.66; H, 4.81; N, 24.29. Found: C, 41.72; H, 4.69; N, 24.38.

General Procedure for the Synthesis of Nitro Derivative (11). To a solution of 6-chloro-*N*,*N*-diethyl-5-nitropyrimidin-4-amine **10** (1.15 g, 5 mmol) and triethylamine (1.04 mL, 7.5 mmol) in anhydrous THF (25 mL) was added a solution of 2-methyl-1*H*-imidazole (410 mg, 5 mmol) in anhydrous THF (5 mL) at rt. The reaction mixture was refluxed for 16 h. After being cooled to room temperature, the solvent was concentrated in vacuo. The residue was dissolved in ethyl acetate (80 mL), washed water (2 × 30 mL) and brine (2 × 30 mL), and dried over anhydrous Na_2SO_4. The organic solvent was concentrated in vacuo and the residue was purified by column chromatography on a silica gel column using neat chloroform to afford the desired product **11a**.

***N*,*N*-Diethyl-6-(2-methyl-1*H*-imidazol-1-yl)-5-nitropyrimidin-4-amine (11a).** Yield: 68%. Yellow oil. $R_f = 0.47$ (1:19, MeOH/$CHCl_3$). IR (Neat) ν_{max} 3020, 2926, 2846, 1589, 1532, 1358 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta =$ 8.55 (s, 1 H, ArH), 6.98−6.96 (m, 2 H, ArH), 3.52 (q, $J =$ 7.1 Hz, 4 H, 2 × CH_2), 2.38 (s, 3 H, CH_3), 1.26 (t, $J = 7.1$ Hz, 6 H, 2 × CH_3). ^{13}C NMR (75 MHz, DMSO) $\delta = 157.5$, 153.3, 150.1, 144.9, 128.0, 127.4, 120.4, 44.0, 13.0, 12.3. Mass (ES^+) *m/z* 277.1 [$(M + 1)^+$]. Anal. calcd for $C_{12}H_{16}N_6O_2$: C, 52.16; H, 5.84; N, 30.42. Found: C, 52.22; H, 5.72; N, 30.56.

***N*,*N*-Diethyl-6-(2-ethyl-4-methyl-1*H*-imidazol-1-yl)-5-nitropyrimidin-4-amine (11b).** Yield: 66%. Yellow oil. $R_f =$ 0.50 (1:19, MeOH/$CHCl_3$). IR (Neat) ν_{max} 3029, 2926, 2852, 1528, 1351 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 8.52$ (s, 1 H, ArH), 6.64 (d, $J = 1.0$ Hz, 1 H, ArH), 3.52 (q, $J = 7.1$ Hz, 4 H, 2 × CH_2), 2.68 (q, $J = 7.6$ Hz, 2 H, CH_2), 2.20 (d, $J = 1.0$ Hz, 3 H, CH_3), 1.29 × 1.21 (m, 9 H, 3 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 157.1$, 153.5, 150.5, 150.1, 137.7, 115.7, 44.3, 20.9, 13.5, 12.7, 12.2. Mass (ES^+) *m/z* 305.3 [$(M + 1)^+$]. Anal. calcd for $C_{14}H_{20}N_6O_2$: C, 55.25; H, 6.62; N, 27.61. Found: C, 55.31; H, 6.68; N, 27.72.

General Procedure for the Synthesis of Amine Derivative (3). A solution of **11a** (552 mg, 2 mmol) and Fe (440 mg, 8 mmol) in acidic ethanol (1:4 HCl/EtOH) was refluxed under nitrogen atmosphere for 1 h. The solution was allowed to cool down and then poured into ice, and the pH is made slightly basic (pH 8) by addition of 5% aqueous $NaHCO_3$. The ethyl acetate (50 mL) was added to the mixture and filtered through a bed of Celite. The organic layer was finally washed with water (50 mL) and brine (50 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness under reduced pressure. The crude product was purified on a silica gel column using chloroform-methanol (19:1, v/v) as eluent to afford **3a**.

***N*^{4},*N*^{4}-Diethyl-6-(2-methyl-1*H*-imidazol-1-yl)pyrimidine-4,5-diamine (3a).** Yield: 85%. White solid. mp 114−115 °C. $R_f = 0.29$ (1:19, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3342, 3208, 2927, 2848, 1631 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 8.26$ (s, 1 H, ArH), 7.08−7.05 (m, 2 H, ArH), 3.49−3.38 (m, 6 H, 2 × CH_2, NH_2), 2.37 (s, 3 H. CH_3), 1.18 (t, $J =$ 7.1 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.9, 147.8, 145.6, 141.2, 128.6, 126.0, 118.9, 43.1, 13.4. Mass (ES^+) *m/z* 247.4 [$(M + 1)^+$]. Anal. calcd for $C_{12}H_{18}N_6$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.41; H, 7.41; N, 34.18.

***N*^{4},*N*^{4}-Diethyl-6-(2-ethyl-4-methyl-1*H*-imidazol-1-yl)pyrimidine-4,5-diamine (3b).** Yield: 83%. White solid. mp 92−93 °C. $R_f = 0.38$ (1:19, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3349, 3205, 2968, 2927, 2849, 1631 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 8.27$ (s, 1 H, ArH), 6.77 (d, $J = 1.0$ Hz, 1H, ArH), 3.5−3.39 (m, 6 H, 2x CH_2, NH_2), 2.67 (q, $J =$ 7.6 Hz, 2 H, CH_2), 2.25 (d, $J = 1.0$ Hz, 3 H, CH_3), 1.27−1.16 (m, 9 H, 3 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 157.7$, 149.8, 147.7, 141.4, 137.7, 126.0, 114.8, 43.0, 20.8, 13.6, 13.3, 12.3. Mass (ES^+) *m/z* 275.3 [$(M + 1)^+$]. Anal. calcd for $C_{14}H_{22}N_6$: C, 61.29; H, 8.08; N, 30.63. Found: C, 61.34; H, 8.13; N, 30.53.

General Procedure for the Synthesis of Imidazo[5,1-*h*]pteridine (12). A mixture of amine **3a** (246 mg, 1 mmol) and 4-methylbenzaldehyde (120 μL, 1 mmol) was refluxed in 1% TFA in toluene until the disappearance of the starting material on TLC. Then, the reaction mixture was treated with DDQ (1.5 mmol) for 10 min at reflux. Toluene was evaporated in vacuo, and the residue so obtained was basified with aq $NaHCO_3$ and extracted with ethyl acetate (2−30 mL). The organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate was evaporated under reduced pressure to obtain residue that after column chromatography on silica gel using hexane-ethyl acetate (60:40 v/v) afforded **12a** as a white solid.

***N*,*N*-Diethyl-9-methyl-6-*p*-tolylimidazo[5,1-*h*]pteridin-4-amine (12a).** Yield: 74%. Yellow solid. mp 121−122 °C. $R_f = 0.60$ (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3037, 2984, 2930, 2852, 1550 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta =$ 8.40 (s, 1 H, ArH), 7.86 (d, $J = 8.2$ Hz, 2 H, ArH), 7.74 (s, 1 H, ArH), 7.34 (d, $J = 8.2$ Hz, 2 H, ArH), 4.03 (q, $J = 6.9$ Hz, 4 H, 2 × CH_2), 3.22 (s, 3 H. CH_3), 2.46 (s, 3 H, CH_3),

1.36 (t, J = 6.9 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 158.1, 153.9, 149.5, 144.2, 144.1, 140.5, 135.0, 129.5, 128.1, 125.9, 125.6, 116.2, 45.8, 21.6, 18.6, 13.7. Mass (ES^+) m/z 347.4 [$(M + 1)^+$]. Anal. calcd for $C_{20}H_{22}N_6$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.28; H, 6.53; N, 24.19.

6-(4-Ethoxyphenyl)-*N*,*N*-diethyl-9-methylimidazo[5,1-*h*]pteridin-4-amine (12b). Yield: 73%. Yellow solid. mp 117−119 °C. R_f = 0.60 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3022, 2976, 2929, 2848, 1589 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.40 (s, 1 H, ArH), 7.92 (d, J = 8.9 Hz, 2 H, ArH), 7.75 (s, 1 H, ArH), 7.03 (d, J = 8.9 Hz, 2 H, ArH), 4.19−3.99 (m, 6 H, 3 × CH_2), 3.22 (s, 3 H CH_3), 1.47 (t, J = 7.0 Hz, 3 H,CH_3), 1.36 (t, J = 7.0 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 160.8, 158.0, 153.7, 149.0, 144.1, 130.1, 129.9, 129.6, 125.8, 125.4, 116.2, 114.6, 63.8, 45.8, 18.6, 15.0, 13.8. Mass (ES^+) m/z 377.3 [$(M + 1)^+$]. Anal. calcd for $C_{21}H_{24}N_6O$: C, 67.00; H, 6.43; N, 22.32. Found: C, 67.14; H, 6.31; N, 22.23.

***N*,*N*-Diethyl-6-(4-methoxyphenyl)-9-methylimidazo[5,1-*h*]pteridin-4-amine (12c).** Yield: 75%. Yellow solid. mp 129−130 °C. R_f = 0.38 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3050, 2926, 2857, 1607 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.40 (s, 1 H, ArH), 7.93 (d, J = 8.9 Hz, 2 H, ArH), 7.74 (s, 1 H, ArH), 7.05 (d, J = 8.9 Hz, 2 H, ArH), 4.04 (q, J = 7.0 Hz, 6 H, 3 × CH_2), 3.90 (s, 3 H CH_3), 3.22 (s, 3 H CH_3), 1.36 (t, J = 7.0 Hz, 3 H, CH_3), 1.36 (t, J = 7.0 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 161.4, 158.0, 153.8, 149.0, 130.3, 129.7, 125.8, 125.5, 116.2, 114.2, 55.6, 45.8, 18.7, 13.8. Mass (ES^+) m/z 363.4 [$(M + 1)^+$]. Anal. calcd for $C_{20}H_{22}N_6O$: C, 66.28; H, 6.12; N, 23.19. Found: C, 66.16; H, 6.24; N, 23.25.

2-(4-(Diethylamino)-9-methylimidazo[5,1-*h*]pteridin-6-yl)phenol (12d). Yield: 70%. Yellow solid. mp 154−156 °C. R_f = 0.47 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3458, 2978, 2927, 2859, 1598 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 10.96 (brs, 1 H, OH), 8.45 (s, 1 H, ArH), 8.03−7.93 (m, 3 H, ArH), 7.47−7.38 (m, 1 H, ArH), 7.14−7.01 (m, 3 H, ArH), 3.96 (q, J = 7.0 Hz, 4 H, 2 × CH_2), 3.23 (s, 3 H, CH_3), 1.36 (t, J = 7.0 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 158.2, 157.6, 154.1, 144.7, 133.0, 132.4, 129.4, 129.0, 128.2, 125.4, 119.9, 119.7, 118.1, 117.9, 45.4, 18.9, 13.5. Mass (ES^+) m/z 349.3 [$(M + 1)^+$]. Anal. calcd for $C_{19}H_{20}N_6O$: C, 65.50; H, 5.79; N, 24.12. Found: C, 65.41; H, 5.86; N, 24.21.

***N*,*N*-Diethyl-9-methyl-6-phenylimidazo[5,1-*h*]pteridin-4-amine (12e).** Yield: 72%. Yellow solid. mp 137−139 °C. R_f = 0.69 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2976, 2932, 2853, 1550 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (s, 1 H, ArH), 7.98−7.93 (m, 2 H, ArH), 7.76 (s, 1 H, ArH), 7.55 (m, 3 H, ArH), 4.04 (q, J = 6.8 Hz, 4 H, 2 × CH_2), 3.23 (s, 3 H, CH_3), 1.36 (t, J = 7.0 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 158.1, 154.2, 149.5, 144,4, 144.2, 137.7, 130.4, 128.9, 128.2, 126.0, 125.6, 116.2, 45.9, 18.7, 13.8. Mass (ES^+) m/z 333.3 [$(M + 1)^+$]. Anal. calcd for $C_{19}H_{20}N_6$: C, 68.65; H, 6.06; N, 25.28. Found: C, 68.48; H, 6.11; N, 25.41.

***N*,*N*-Diethyl-9-methyl-6-(4-nitrophenyl)imidazo[5,1-*h*]pteridin-4-amine (12f).** Yield: 71%. Red solid. mp 201−202 °C. R_f = 0.56 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2976, 2928, 2846, 1550, 1348 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.44−8.38 (m, 3 H, ArH), 8.13 (d, J = 8.7 Hz, 2 H, ArH), 7.74 (s, 1 H, ArH), 4.03 (d, J = 6.6 Hz, 4 H, 2 × CH_2), 3.24 (s, 3 H, CH_3), 1.36 (t, J = 6.8 Hz, 6 H, 2 × CH_3). Mass (ES^+) m/z 378.3 [$(M + 1)^+$]. Anal. calcd for $C_{19}H_{19}N_7O_2$: C, 60.47; H, 5.07; N, 25.98. Found: C, 60.32; H, 5.14; N, 25.81.

6-(4-Chlorophenyl)-*N*,*N*-diethyl-9-methylimidazo[5,1-*h*]pteridin-4-amine (12g). Yield: 70%. Yellow solid. mp 182−183 °C. R_f = 0.61 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 2977, 2927, 2861, 1634, 1548 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (s, 1H, ArH), 7.90 (d, J = 8.7 Hz, 2 H, ArH), 7.71 (s, 1 H, ArH), 7.51 (d, J = 8.7 Hz, 2 H, ArH), 4.02 (q, J = 6.8 Hz, 4 H, 2 × CH_2), 3.22 (s, 3 H. CH_3), 1.35 (t, J = 6.9 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 154.3, 148.2, 144.4, 136.3, 136.1, 129.4, 129.1, 125.7, 125.4, 116.0, 45.8, 18.6, 13.7. Mass (ES^+) m/z 367.4 [$(M + 1)^+$]. Anal. calcd for $C_{19}H_{19}ClN_6$: C, 62.21; H, 5.22; N, 22.91. Found: C, 62.33; H, 5.08; N, 22.82.

6-(4-Bromophenyl)-*N*,*N*-diethyl-9-methylimidazo[5,1-*h*]pteridin-4-amine (12h). Yield: 73%. Yellow solid. mp 180−181 °C. R_f = 0.56 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3037, 2984, 2926, 2864, 1586 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (s, 1 H, ArH), 7.83 (d, J = 8.7 Hz, 2 H, ArH), 7.71 (s, 1 H, ArH), 7.17 (d, J = 8.2 Hz, 2 H, ArH), 4.02 (q, J = 6.6 Hz, 4 H, 2 × CH_2), 3.22 (s, 3 H. CH_3), 1.35 (t, J = 6.9 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 158.1, 154.3, 148.3, 144.5, 144.4, 136.6, 132.1, 129.7, 125.6, 125.4, 124.7, 116.0, 45.9, 18.7, 13.8. Mass (ES^+) m/z 411.3 [$(M + 1)^+$]. Anal. calcd for $C_{19}H_{19}BrN_6$: C, 55.48; H, 4.66; N, 20.43. Found: C, 55.57; H, 4.71; N, 20.56.

***N*,*N*,6-Triethyl-9-methylimidazo[5,1-*h*]pteridin-4-amine (12i).** Yield: 52%. Yellow solid. mp 77−79 °C. R_f = 0.68 (1:9, MeOH/$CHCl_3$). IR (KBr) ν_{max} 2972, 2933, 2851, 1561 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.37 (s, 1 H, ArH), 7.56 (s, 1 H, ArH), 4.01 (q, J = 6.9 Hz, 4 H, 2 × CH_2), 3.16 (s, 3 H, CH_3), 2.95 (q, J = 7.4 Hz, 2 H, CH_2), 1.40−1.25 (m, 9 H, 3 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 157.9, 153.7, 153.5, 144.4, 143.8, 126.7, 123.3, 115.7, 45.7, 27.9, 18.4, 13.8, 11.0. Mass (ES^+) m/z 285.3 [$(M + 1)^+$]. Anal. calcd for $C_{15}H_{20}N_6$: C, 63.36; H, 7.09; N, 29.55. Found: C, 63.43; H, 7.14; N, 29.43.

***N*,*N*,9-Triethyl-6-(4-methoxyphenyl)-7-methylimidazo[5,1-*h*]pteridin-4-amine (12j).** Yield: 75%. Yellow solid. mp 129−130 °C. R_f = 0.57 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3032, 2978, 2927, 2849, 1553 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.37 (s, 1 H, ArH), 7.55 (d, J = 8.7 Hz, 2 H, ArH), 7.00 (d, J = 8.8 Hz, 2 H, ArH), 3.96 (q, J = 7.0 Hz, 4 H, 2 × CH_2), 3.89 (s, 3 H, CH_3), 3.66 (q, J = 7.4 Hz, 2 H, CH_2), 2.24 (s, 3 H. CH_3), 1.45 (t, J = 7.4 Hz, 3 H, CH_3), 1.30 (t, J = 6.9 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 160.9, 158.1, 153.8, 151.4, 147.7, 144.2, 134.6, 131.0, 130.5, 122.5, 116.0, 113.7, 55.6, 45.8, 24.8, 16.5, 13.8, 13.3. Mass (ES^+) m/z 391.4 [$(M + 1)^+$]. Anal. calcd for $C_{22}H_{26}N_6O$: C, 67.67; H, 6.71; N, 21.52. Found: C, 67.76; H, 6.59; N, 21.68.

4-(4-(Diethylamino)-9-ethyl-7-methylimidazo[5,1-*h*]pteridin-6-yl)phenol (12k). Yield: 73%. Yellow solid. mp 226−227 °C. R_f = 0.47 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3407, 2977, 2929, 2856, 1558 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 9.13 (brs, 1 H, OH), 8.36 (s, 1 H, ArH), 7.46 (d, J = 8.7 Hz, 2 H, ArH), 6.96 (d, J = 8.7 Hz, 2 H, ArH), 3.97 (q, J = 6.8 Hz, 4 H, 2 × CH_2), 3.66 (q, J = 7.4 Hz, 2 H, CH_2), 2.25 (s, 3 H, CH_3), 1.45 (t, J = 7.4 Hz, 3 H, CH_3), 1.30 (t, J = 6.9 Hz, 6 H, 2 × CH_3). Mass (ES^+) m/z 377.4 [$(M + 1)^+$]. Anal. calcd for $C_{21}H_{24}N_6O$: C, 67.00; H, 6.43; N, 22.32. Found: C, 67.12; H, 6.54; N, 22.56.

2-(4-(Diethylamino)-9-ethyl-7-methylimidazo[5,1-*h*]pteridin-6-yl)phenol (12l). Yield: 68%. Yellow solid. mp 183−185 °C. R_f = 0.60 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3415, 3020, 2975, 2930, 2851, 1580 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.88 (brs, 1 H, OH), 8.38 (s, 1 H, ArH), 7.42−7.35 (m, 2 H, ArH), 7.10−7.00 (m, 2 H, ArH), 3.92 (q, J = 7.0 Hz, 4 H, 2 × CH_2), 3.65 (q, J = 7.3 Hz, 2 H, CH_2), 2.27 (s, 3 H. CH_3), 1.44 (t, J = 7.4 Hz, 3H, CH_3), 1.29 (t, J = 7.0 Hz, 6H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 157.9, 155.6, 154.1, 150.5, 148.0, 144.5, 135.6, 131.5, 130.8, 123.1, 122.5, 119.5, 116.9, 115.4, 45.8, 24.7, 15.9, 13.6, 13.2. Mass (ES^+) m/z 377.3 [$(M + 1)^+$]. Anal. calcd for $C_{21}H_{24}N_6O$: C, 67.00; H, 6.43; N, 22.32. Found: C, 67.12; H, 6.31; N, 22.36.

***N*,*N*,9-Triethyl-7-methyl-6-phenylimidazo[5,1-*h*]pteridin-4-amine (12m).** Yield: 70%. Yellow solid. mp 80−82 °C. R_f = 0.68 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3021, 2979, 2929, 2861, 1559 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ= 8.39 (s, 1 H, ArH), 7.61−7.57 (m, 2 H, ArH), 7.51−7.47 (m, 3 H, ArH), 3.97 (q, J = 6.9 Hz, 4 H, 2 × CH_2), 3.68 (q, J = 7.4 Hz, 2 H, CH_2), 2.18 (s, 3 H. CH_3), 1.46 (t, J = 7.4 Hz, 3 H, CH_3), 1.29 (t, J = 6.9 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 158.1, 154.0, 151.6, 147.7, 144.3, 138.4, 134.6, 129.5, 128.9, 128.2, 122.3, 115.9, 45.8, 24.7, 16.2, 13.7, 13.2. Mass (ES^+) m/z 361.4 [$(M + 1)^+$]. Anal. calcd for $C_{21}H_{24}N_6$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.81; H, 6.83; N, 23.23.

4-(4-(Diethylamino)-9-ethyl-7-methylimidazo[5,1-*h*]pteridin-6-yl)benzonitrile (12n). Yield: 73%. Yellow solid. mp 147−148 °C. R_f = 0.68 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3037, 2981, 2928, 2847, 2222, 1553 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (s, 1 H, ArH), 7.81 (d, J = 8.4 Hz, 2 H, ArH), 7.71 (d, J = 8.2 Hz, 2 H, ArH), 3.94 (q, J = 6.8 Hz, 4 H, 2 × CH_2), 3.67 (q, J = 7.4 Hz, 2 H, CH_2), 2.18 (s, 3 H, CH_3), 1.45 (t, J = 7.4 Hz, 3 H, CH_3), 1.29 (t, J = 6.9 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ =158.1, 154.6, 149.3, 148.2, 144.6, 142.7, 134.4, 132.2, 129.7, 121.9, 118.6, 115.7, 113.4, 45.9, 24.8, 16.4, 13.7, 13.2. Mass (ES^+) m/z 386.4 [$(M + 1)^+$]. Anal. calcd for $C_{22}H_{23}N_7$: C, 68.55; H, 6.01; N, 25.44. Found: C, 68.43; H, 6.06; N, 25.51.

***N*,*N*,9-Triethyl-7-methyl-6-(4-nitrophenyl)imidazo[5,1-*h*]pteridin-4-amine (12o).** Yield: 82%. Orange solid. mp 132−133 °C. R_f = 0.65 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3031, 2965, 2925, 2854, 1560, 1508, 1371 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (s, 1 H, ArH), 8.37 (d, J = 8.8 Hz, 2 H, ArH), 7.77 (d, J = 8.8 Hz, 2 H, ArH), 3.95 (q, J = 6.9 Hz, 4H, 2 × CH_2), 3.67 (q, J = 7.4 Hz, 2 H, CH_2), 2.19 (s, 3 H. CH_3), 1.45 (t, J = 7.4 Hz, 3 H, CH_3), 1.29 (t, J = 6.9 Hz, 6H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 158.1, 154.7, 148.9, 148.6, 144.6, 144.5, 134.4, 130.0, 123.7, 121.9, 115.7, 45.9, 24.8, 16.5, 13.7, 13.2. Mass (ES^+) m/z 406.3 [$(M + 1)^+$]. Anal. calcd for $C_{21}H_{23}N_7O_2$: C, 62.21; H, 5.72; N, 24.18. Found: C, 62.33; H, 5.81; N, 24.12.

6-(4-Chlorophenyl)-*N*,*N*,9-triethyl-7-methylimidazo[5,1-*h*]pteridin-4-amine (12p). Yield: 73%. Yellow solid. mp 112−114 °C. R_f = 0.73 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3046, 2984, 2928, 2849, 1552 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.39 (s, 1 H, ArH), 7.55−7.46 (m, 4 H, ArH), 3.95 (d, J = 6.6 Hz, 4 H, 2 × CH_2), 3.66 (q, J = 7.4 Hz, 2 H, CH_2), 2.21 (s, 3 H, CH_3), 1.45 (t, J = 7.4 Hz, 3 H, CH_3), 1.29 (t, J = 6.9 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 158.1, 154.2, 150.3, 147.9, 136.9, 135.7, 134.5, 130.4, 128.6, 122.2, 115.9, 45.8, 24.8, 16.4, 13.8, 13.3. Mass (ES^+) m/z 395.3 [$(M + 1)^+$]. Anal. calcd for $C_{21}H_{23}ClN_6$: C, 63.87; H, 5.87; N, 21.28. Found: C, 63.77; H, 5.72; N, 21.34.

***N*,*N*,6,9-Tetraethyl-7-methylimidazo[5,1-*h*]pteridin-4-amine (12q).** Yield: 55%. Yellow solid. mp 112−114 °C. R_f = 0.73 (3:7, EtOAc/hexane). IR (KBr) ν_{max} 3046, 2979, 2933, 2849, 1559 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.34 (s, 1 H, ArH), 4.01 (q, J = 6.9 Hz, 4 H, 2 × CH_2), 3.60 (q, J = 7.4 Hz, 2 H, CH_2), 3.04 (q, J = 7.4 Hz, 2 H, CH_2), 2.70 (s, 3 H, CH_3), 1.45−1.28 (m, 12 H, 4 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 157.8, 154.3, 153.6, 147.0, 144.6, 133.3, 122.9, 115.7, 45.7, 29.3, 24.7, 16.0, 13.9, 13.2, 11.3. Mass (ES^+) m/z 313.3 [$(M + 1)^+$]. Anal. calcd for $C_{17}H_{24}N_6$: C, 65.36; H, 7.74; N, 26.90. Found: C, 65.43; H, 7.81; N, 26.22.

6-Benzyl-*N*,*N*,9-triethyl-7-methylimidazo[5,1-*h*]pteridin-4-amine (12r). Yield: 57%. Yellow oil. R_f = 0.76 (2:3, EtOAc/hexane). IR (KBr) ν_{max} 3017, 2973, 2933, 2853, 1558 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.34 (s, 1 H, ArH), 7.27−7.25 (m, 5 H, ArH), 4.35 (s, 2 H, CH_2), 3.82 (q, J = 6.9 Hz, 4 H, 2 × CH_2), 3.61 (q, 2 H, J = 7.4 Hz, CH_2), 2.64 (s, 3 H. CH_3), 1.41 (t, J = 7.4 Hz, 3 H, CH_3), 1.14 (t, J = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 157.7, 154.2, 153.8, 151.7, 147.3, 144.6, 137.8, 133.6, 129.3, 128.7, 126.7, 123.2, 45.7, 42.2, 24.8, 16.1, 13.6, 13.3. Mass (ES^+) m/z 375.4 [$(M + 1)^+$]. Anal. calcd for $C_{22}H_{26}N_6$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.68; H, 7.14; N, 22.18.

General Procedure for the Synthesis of 5,6-Dihydroimidazo[5,1-*h*]pteridine (13). A mixture of amine **3a** (246 mg, 1 mmol) and acetone (58 μL, 1 mmol) was refluxed in 1% TFA in toluene until the disappearance of the starting material on TLC. The solvent was then evaporated, and the residue so obtained was basified with aq $NaHCO_3$. It was then extracted with ethyl acetate (2 × 30 mL), washed with brine (10 mL), and dried over anhydrous Na_2SO_4. The ethyl acetate was evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexane−ethyl acetate (45:55 v/v) to afford **13a** as a white solid.

***N*,*N*-Diethyl-6,6,9-trimethyl-5,6-dihydroimidazo[5,1-*h*]pteridin-4-amine (13a).** Yield: 51%. Brown solid. mp 97−99 °C. R_f = 0.62 (1:9, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3020, 2973, 2927, 2855, 1569 cm^{-1}. ^{1}H NMR (200 MHz,

$CDCl_3$) δ = 8.26 (s, 1 H, ArH), 6.69 (s, 1 H, ArH), 3.61 (brs, 1 H, NH), 3.30 (q, J = 7.1 Hz, 4H, 2 × CH_2), 2.82 (s, 3 H. CH_3), 1.51 (s, 6 H, 2 × CH_3), 1.11 (t, J = 7.1 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 156.4, 147.2, 144.7, 142.7, 133.7, 120.1, 119.3, 50.6, 43.7, 29.2, 17.2, 13.2. Mass (ES^+) m/z) 287.3 [$(M + 1)^+$]. Anal. calcd for $C_{15}H_{22}N_6$: C, 62.91; H, 7.74; N, 29.35. Found: C, 62.86; H, 7.82; N, 29.41.

***N*,*N*,9-Triethyl-6,6,7-trimethyl-5,6-dihydroimidazo[5,1-*h*]pteridin-4-amine (13b).** Yield: 58%. Yellow oil. R_f = 0.41 (1:1, EtOAc/hexane). IR (KBr) ν_{max} 3020, 2975, 2931, 2849, 1583 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.25 (s, 1 H, ArH), 3.56 (brs, 1 H, NH), 3.30 (q, J = 7.1 Hz, 6 H, 3 × CH_2), 2.31 (s, 3 H. CH_3), 1.55 (s, 2 H, 2 × CH_3), 1.35 (t, J = 7.4 Hz, 3 H, CH_3), 1.13 (t, J = 7.1 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 156.2, 148.3, 147.3, 142.7, 128.9, 127.1, 119.5, 51.9, 44.0, 29.4, 23.8, 14.2, 13.4, 12.7. Mass (ES^+) m/z 315.3 [$(M + 1)^+$]. Anal. calcd for $C_{17}H_{26}N_6$: C, 64.94; H, 8.33; N, 26.73. Found: C, 64.89; H, 8.24; N, 26.87.

***N*,*N*,6,9-Tetraethyl-6,7-dimethyl-5,6-dihydroimidazo[5,1-*h*]pteridin-4-amine (13c).** Yield: 57%. Yellow oil. R_f = 0.37 (1:1, EtOAc/hexane). IR (KBr) ν_{max} 3020, 2972, 2929, 2847, 1579 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.23 (s, 1 H, ArH), 3.64 (brs, 1 H, NH), 3.39−3.17 (m, 6 H, 3 × CH_2), 2.29 (s, 3 H, CH_3), 1.87−1.63 (m, 2 H, CH_2), 1.56 (s, 3 H, CH_3), 1.35 (t, J = 7.4 Hz, 3 H, CH_3), 1.12 (t, J = 7.1 Hz, 6 H, 2 × CH_3), 0.86 (t, J = 7.4 Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 155.7, 148.4, 146.7, 142.1, 129.7, 125.8, 120.1, 55.1, 43.9, 34.6, 27.2, 23.9, 14.2, 13.4, 12.6, 8.6. Mass (ES^+) m/z 329.4 [$(M + 1)^+$]. Anal. calcd for $C_{18}H_{28}N_6$; C, 65.82; H, 8.59; N, 25.59. Found: C, 65.95; H, 8.43; N, 25.62.

***N*,*N*,9-Triethyl-6,7-dimethyl-6-phenyl-5,6-dihydroimidazo[5,1-*h*]pteridin-4-amine (13d).** Yield: 48%. Yellow oil. R_f = 0.43 (1:19, MeOH/$CHCl_3$). IR (KBr) ν_{max} 3019, 2973, 2930, 2850, 1579 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.22 (s, 1 H, ArH), 7.26 (s, 5 H, ArH), 4.26 (brs, 1 H, NH), 3.40−3.16 (m, 6 H, 3 × CH_2), 2.06 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 1.36 (t, J = 7.5 Hz, 3 H, CH_3), 1.11 (t, J = 7.1 Hz, 6 H, 2 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 156.1, 148.5, 147.4, 144.9, 143.1, 131.0, 128.7, 127.9, 126.5, 126.0, 120.2, 57.6, 44.2, 28.9, 23.8, 13.9, 13.4, 12.5. Mass (ES^+) m/z 377.3 [$(M + 1)^+$]. Anal. calcd for $C_{22}H_{28}N_6$; C, 70.18; H, 7.50; N, 22.32. Found: C, 70.14; H, 7.38; N, 22.48.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra of the compounds (**7a**−**m**, **8a**−**h**, **12a**−**r**, and **13a**−**d**). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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