Synthesis of Novel Pyridobenzimidazoles Bonded to Indoleorbenzo[*b*]thiophenestructures

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Abstract: Pyridobenzimidazoles **6a-i**were synthesized in very good to excellent yields (81-96%) by the condensation of substituted *N*-phenyl-*o*-phenylenediamines **4a-d** with indole/benzo[*b*]thiophene-3-aldehydes **5a-t** inmethoxyethanol under reflux conditions. The diamines **4a-d** were prepared byfirst treating 2-chloro-3-nitropyridine (**1**)with suitably substituted anilines **2a-d** then reducing the resulting3-nitro-*N*-phenylpyridin-2-amines **3a-d** with tin(II)chloride using microwave heating in each case.

Keywords: Indole/benzo[*b*]thiophene-3-aldehydes, microwave irradiation, N^2-phenylpyridine-2,3-diamines, pyridobenzimidazoles, tin(II) chloride reduction.

INTRODUCTION

Benzimidazoles are priviledged structures [1] that are found in many commercial drugs such as Prilosec, Nexium, Protonix, Atacand, Famvir, and Vermax (shown in Fig **1**), and in numerous experimental drug candidates covering a wide range of therapeutical areas [2, 3]. Benzimidazoles are also widely used as ananthelminticin veterinary medicine [4] and display significant antiviral, [5-9] antiulcerative, anti-inflammatory, antihistaminic [10-12] and anticancer [13-14] activities. Therefore, it is not surprising that the synthesis of various types of benzimidazole has always been of great interest to organic chemists. During our continuing efforts directed toward novel drug discovery [15 a,b], we became interested in preparing pyridobenzimidazolescaffordanalogs by assembling pyridylbenzimidazoles toindole and benzo[*b*] thiophenes structures, since some pyridoimidazoles have been reported to behave as VLA-4 antagonists [15c]. Herein,we report a facile three step synthesis of some novel pyridobenzimidazoles attached to indole or benzo[*b*]thiophenestructures.

RESULTS AND DISCUSSION

Pyridobenzimidazoles (**6**) were prepared as shown in Scheme **1**. In the first step, 3-nitro-2-chloropyridine **1** and appropriate anilines (**2**) were converted to the corresponding 3-nitro-2-(*N*-phenylamino)pyridines (**3**) by a nucleophilic substitution reaction in nearly quantitative yields using microwave (MW) heating for 10 min at 110 °C under solvent-free conditions. Using conventional heating and dimethyl sulfoxide as solvent [16a], we obtained the nitro amines **3** in lower yields (60-70%) and significantlylonger reaction times were required (24h). Moreover these products were difficult to purify.

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In the second step, the microwave-assisted reduction of 3-nitro-*N*-phenylpyridin-2-amines (**3**) to the corresponding 3-amino-2-*N*-arylaminopyridines (**4**) was studied. Several novel reduction procedures have appeared recently in the literature (17 a-c) that use microwave heating and hydrogen transfer conditions as an alternative to conventional hydrogenation reductions that use highly inflammable hydrogen gas [17c]. The majority of these procedures use formate as the hydrogen transfer source. This microwave procedure, however, has the drawback of generating CO_2. This would increase the pressure to unsafe levels in the sealed microwave tube thus making removal of product tenuous at best. To avoid this potential hazard, we decided to substitute $SnCl_2$ in lieu of formate, since the former is airstable and easy to handle. To obtain optimum conditions for the $SnCl_2$-assisted reduction, several reactions using **3a** as a typical example were run under various experimental conditions. As shown in Table **1**, entry 7, the optimum conditions were found that involved microwave irradiation at 110 °C for 20 min in the presence of 5 equiv of $SnCl_2$ and in the absence of solvent. Compound **4a** was obtained in nearly quantitative yield (> 98%) and thus was readily purified. The remaining 5-amino compounds (**4b-d**) were prepared similarly in excellent yields (95-98%). The ^{1}H NMR and ^{13}C NMR spectra of **4a-d** were identical to those previously reported [16b]; all showed a broad singlet (equivalent to 2H) around δ 5.0 ppm. We also explored other hydrogenating agents (not listed in Table **1**) such as Pd/C –H_2 [16a], Raney Ni/NH_2NH_2 [15], Al/$NiCl_2$.6H_2O or Al/NH_4Cl [18], however, these reductions required sensitive and expensive chemicals and intractable mixture of products were obtained in all cases.

In the third step, the amines (**4**) were condensed with substituted indole/benzo[*b*]thiophene-3-aldehydes (**5**) at elevated temperature (~125 °C) in the presence of methoxyethanol [19] as a solvent (see Table **2**) to give the pyridobenzimidazoles **6** in good to excellent yields (81-96%). Our attempts to decrease the reaction time by use of

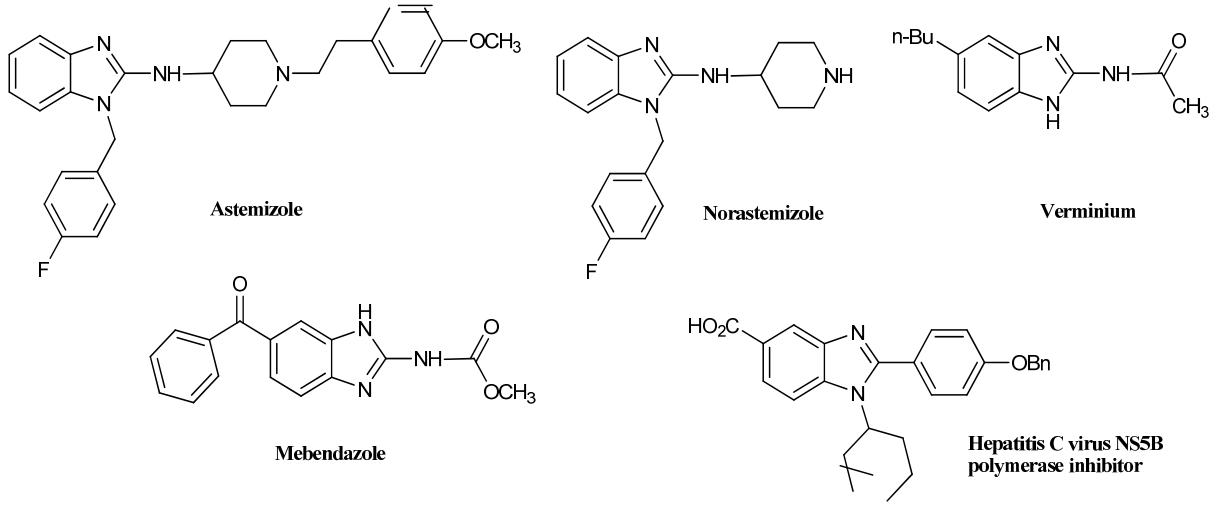
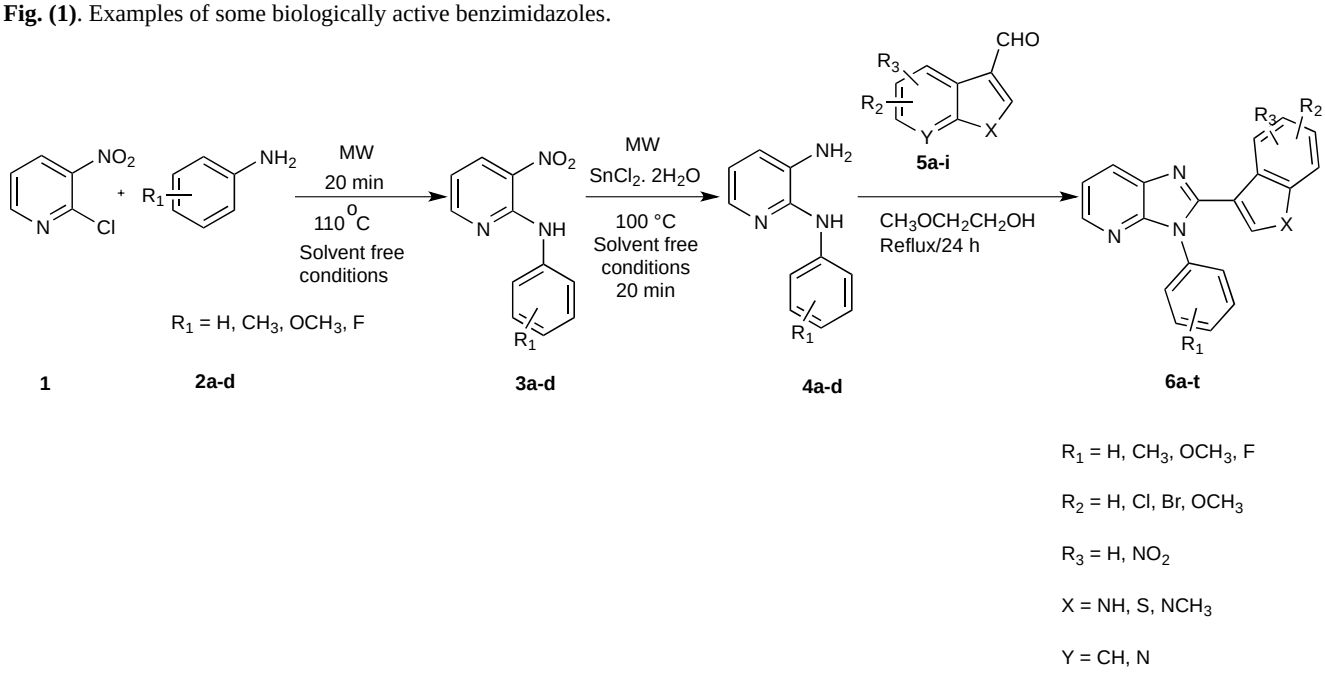


Fig. (1). Examples of some biologically active benzimidazoles.



Scheme 1. Schematic representation for the synthesis of pyridobenzimidazoles **6a-t.**

MW heating at different temperatures with various cyclization catalyst such as $ZrCl_4$ [16a] and silicotungstic acid (STA) [20] failed. In all cases, inseparable complex mixtures were obtained. The proposed structures of **6a-t** were confirmed, in part, by the absence of a NH_2 signal in the ^{1}H NMR spectra and the presence of two C=N signals around δ 144 ppm (indicative of an imidazole ring) in the ^{13}CNMR spectra.

Based on current state of knowledge on the mechanism of the formation of 2-arylbenzimidazoles from the condensation of *o*-phenylenediamines (*o*-PDS) with aryl aldehydes [21,22], two possible mechanism for the formation of compound **6** from **4** are shown in Scheme **2** are suggested. In pathway 1, the diamine **4** condenses with aldehyde **5** to give enamine **7** which then undergoes intramolecular cyclization to the dihydro intermediate **8** which is air oxidized to **6.**

Pathway 2, which was suggested by one of the reviewers,*N*-phenyl-2,3-diaminopyridine **4** first condenses with aldehyde (**5)** to give the corresponding amino alcohol **(9**), which subsequentlyloses hydroxide ion to give imine **(10**). Intermediate **10** then undergoes intramolecular cyclization tointermediate 2,3-diaryl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridine (**8**) which is readily air oxidized to corresponding pyridobenzimidazole (**6**) during workup. Attempts to isolate **9** were unsuccessful. Further work on the elucidation of the mechanism is underway and will be reported in due course.

CONCLUSIONS

In summary, we have successfully developed a synthetic method that provides ready access to novel biologically important pyridobenzimidazole scaffolds. Also, we have developed a novel, expedient synthetic route for the

Table 1. Screening of Solvents, Reaction Time and Temperature for the Typical Synthesis of 4a

Entry	Condition[a]	Temp (°C)	Time (min)	Yield [b] (%)
1	Methanol, 1 equiv $SnCl_2.2H_2O$	80	15	36
2	Methanol, 2 equiv $SnCl_2.2H_2O$	80	15	45
3	Methanol, 4 equiv $SnCl_2.2H_2O$	80	15	45
4	Methanol, 5 equiv $SnCl_2.2H_2O$	90	15	67
5	Methanol, 5 equiv $SnCl_2.2H_2O$	110	15	80
6	Methanol, 5 equiv $SnCl_2.2H_2O$	110	20	85
7	No solvent, 5 equiv $SnCl_2.2H_2O$	110	20	>98
8	Acetonitrile, 5 equiv $SnCl_2.2H_2O$	110	20	70
9	DMF, 5 equiv $SnCl_2.2H_2O$	110	20	71
10	Water, 5 equiv $SnCl_2.2H_2O$	110	20	63
11	Water + Methanol (50%, v/v), 5 equiv $SnCl_2.2H_2O$	110	20	51
12	DMF, 5 equiv $SnCl_2.2H_2O$	120-140	20	58
13	Toluene, 5 equiv $SnCl_2.2H_2O$	110	20	Trace
14	Isopropanol, 5 equiv $SnCl_2.2H_2O$	110	20	76
15	n-Butanol, 5 equiv $SnCl_2.2H_2O$	110	20	78

[a]All reactions were carried out in specially designed MW test tube at 250 psi pressure with 19 min ramping time. [b] Isolated yield

preparation of amines under solvent free conditions. We are currently attempting to extent this synthetic methodology to the synthesis of other pyridobenzimidazole based drugs Biological activity studies (antibacterial, antifungal, anticancer and neuroprotective kinase inhibitor activity) of these potentially important compounds are being carried out. Preliminary results indicate that some of these compounds may exhibit excellent neuroprotecting activities. The results of these biological studies will be reported in due course.

EXPERIMENTAL SECTION

General Information

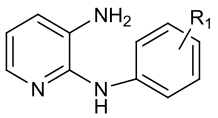
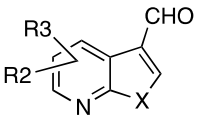
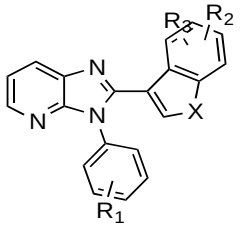
The ^1H and ^{13}CNMR spectra were recorded on a 500-MHz Jeol multinuclear NMR spectrometer. Chemical shifts (δ) are referenced to tetramethylsilane (TMS) as internal standard and J values are given in Hertz (Hz). Melting points were taken on a Meltemp apparatus. The microwave reactionswere carried out in a CEM Discover instrument. All chemicals and reagents were purchased from commercial sources. High-resolution mass spectra analyses were obtained from Washington University, St. Louis, MO. Column chromatographic separations were performed on a Combi-Flash instrument using pre-packed silica gel columns.

Microwave-assisted synthesis of 3-nitro-*N*-phenylpyridin-2-amines(3a-d). 2-Chloro-3-nitropyridine (**1**) (1mmol) and appropriate aniline (**2a-d)** (2 mmol) were mixed well then charged into a specially designed MW test tube. The filled test tube was sealed then subjected to microwave heating for 20 min at 110 °C and 250 psi pressure. Thereafter, the crude reaction mixture was purified by column chromatography using 25% ethylacetate-hexane mixture (v/v) as eluent. The ^1H NMR and ^{13}C NMR spectra of compounds **3a-d** were identical to those previously reported [16b].

Microwave-assisted synthesis of 3-amino-2-*N*-arylaminopyridines(4a-d). 3-Nitro-*N*-phenylpyridin-2-amines (**3a-d**) (1 mmol) and $SnCl_2.2H_2O$ (5 mmol) were mixed well in a mortar pestle then charged into a specially designed MW test tube, which was sealed then subjected to microwave irradiated for 20 min at 110 °C and 250-psi pressure. After cooling, the solid crude reaction mixture was crushed in a mortar and pestle then added to a 20 ml mixture containing equal volumes of ethyl acetate and water. The resulting mixture was treated with sodium bicarbonate then extracted with three 20 ml portions of ethyl acetate. The combined organic layers were dried (Na_2SO_4)and then concentrated to give a solid, which was purified by flash chromatography on silica gel. The NMR spectral data for compounds **4a-d** were identical to those previously reported [16b].

General synthesis of *2-(1H-Indol-3-yl)-3-phenyl-3H-imidazo[4,5-b]pyridines* (**6a-t**). Equimolar amounts of **3a-d** and suitably substituted indole/benzo[*b*]thiophene-3-aldehyde (**5a-i**) were placed in round bottom flask. Then 6 mL of methoxyethanol was added and the resulting mixture was refluxed for 24 h at 125 °C. Thereafter, the reaction mixture was kept overnight at 22 °C in an open vessel during which time the crude product precipitated in most cases. The crude product was collected by filtration then washed with 1:1 dichloromethane-hexane solution (v/v). In the exceptional cases where the product did not precipate upon

Table 2. Synthesis of Pyridobenzimidazoles (6a-t)

Entry	 **4**	 **5**	 **6**	Yield, %
1	**a.** R_1 = H	**a**.R_2 = R_3 = H, X = NH, Y =CH	**a**. R_1 = R_2 = R_3 = H, X = NH, Y =C	89
2	**a.** R_1 = H	**b**. R_2 = Br, R_3 = H, X =NH, Y = CH	**b.** R_1 =H, R_2 =OCH_3, R_3 = H, X = NH, Y =CH	96
3	**a.** R_1 = H	**c**. R_2 = OCH_3, R_3 = H, X = NH, Y =CH	**c.** R_1 =H, R_2 =OCH_3, R_3 = H, X = NH, Y =CH	86
4	**a**. R_1 = H	**d**. R_2 = R_3 = H, X = S, Y =CH	**d.** R_1 =R_2 = R_3 = H, X = S, Y=CH	85
5	**b**. R_1 = OCH_3	**a**. R_2 = R_3 = H, X = NH, Y =CH	**e.**R_1 =OCH_3, R_2 =R_3 = H, X = NH, Y =CH	91
6	**b**. R_1 = OCH_3	**d**.R_2 = R_3 = H, X = S, Y =CH	**f**. R_1 = OCH_3, R_2 = R_3 = H, X = S, Y =CH	83
7	**b**. R_1 = OCH_3	**e**. R_2 = Cl, R_3 = H, X = NH, Y =CH	**g.** R_1 = OCH_3, R_2 = Cl, R_3 = H, X = NH, Y =CH	85
8	**b**. R_1 = OCH_3	**f**. R_2 = R_3 = H, X = NH, Y = N	**h**. R_1 = OCH_3, R_2 = R_3 = H, X = NH, Y = N	88
9	**c**. R_1 = CH_3	**f**. R_2 = R_3 = H, X = NH, Y =N	**i**. R_1 = CH_3, R_2 = R_3 = H, X = NH, Y =N	89
10	**c**. R_1 = CH_3	**d**. R_2 = R_3 = H, X = S, Y =CH	**j**. R_1 = CH_3, R_2 = R_3 = H, X = S, Y =CH	83
11	**c**. R_1 = CH_3	**e**. R_2 = Cl, R_3 = H, X = NH, Y =CH	**k**. R_1 = CH_3, R_2 = Cl, R_3 = H, X = NH, Y =CH	85
12	**c**. R_1 = CH_3	**c**. R_2 = OCH_3, R_3 = H, X = NH, Y =CH	**l**. R_1 = CH_3, R_2 = OCH_3, R_3 = H, X = NH, Y =CH	90
13	**c**. R_1 = CH_3	**b**. R_2 = Br, R_3 = H, X = NH, Y =CH	**m.**R_1 = CH_3, R_2 = Br, R_3 = H, X = NH, Y =CH	93
14	**c**. R_1 = CH_3	**g**. R_2 = CN, R_3 = H, X = NH, Y =CH	**n.** R_1 = CH_3, R_2 = CN, R_3 = H, X = NH, Y =CH	82
15	**c**. R_1 = CH_3	**h**. R_2=H, R_3= NO_2, X=NH, Y =CH	**o.** R_1 = CH_3, R_2 = H, R_3 = NO_2, X = NH, Y =CH	92
17	**d**. R_1 = F	**b**. R_2 = Br, R_3 = H, X=NH, Y =CH	**q**.R_1 = F, R_2 = Br, R_3 = H, X = NH, Y =CH	93
18	**d**. R_1 = F	**g**. R_2 = CN, R_3 = H, X = NH, Y =CH	**r**.R_1 = F, R_2 = CN, R_3 = H, X = NH, Y =CH	81
19	**d**. R_1 = F	**i**. R_2 = R_3 = H, X = NH, Y = N	**s**.R_1 = F, R_2 = R_3 = H, X = NH, Y = N	95
20	**d**. R_1 = F	**a**. R_2 = R_3 = H, X = S, Y = CH	**t**.R_1 = F, R_2 = R_3 = H, X = S, Y = CH	91

[a] Isolated yield. All products were characterized by ^{1}HNMR, ^{13}CNMR, DEPT-135, IR and HRMS analysis.

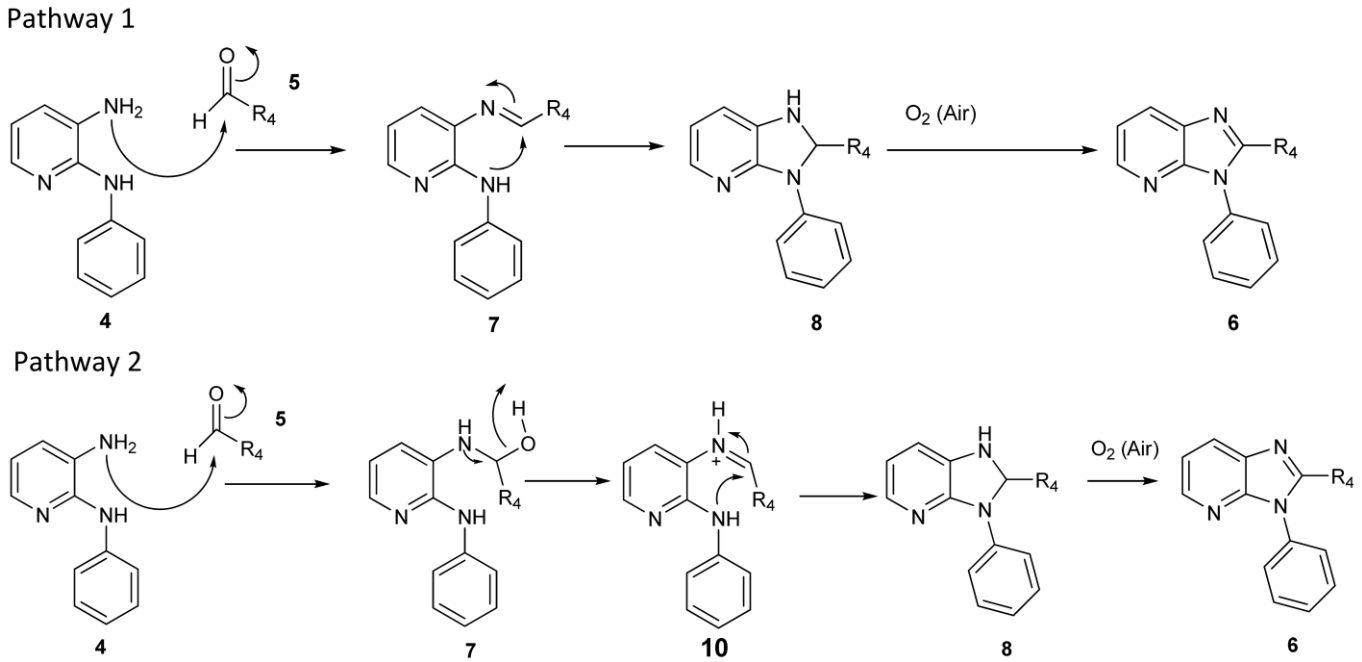
standing *i*,*e*, **6d**, **6f**, **6j**, the crude product was obtained by removing excess solvent under vacuum. In all cases, the imidazole[4,5-*b*]pyridines (**6a-t**) were purified by flash chromatography using 40% ethyl acetate-hexane as elutant.

2-(1H-Indol-3-yl)-3-phenyl-3H-imidazo[4,5-b]pyridines (6a)

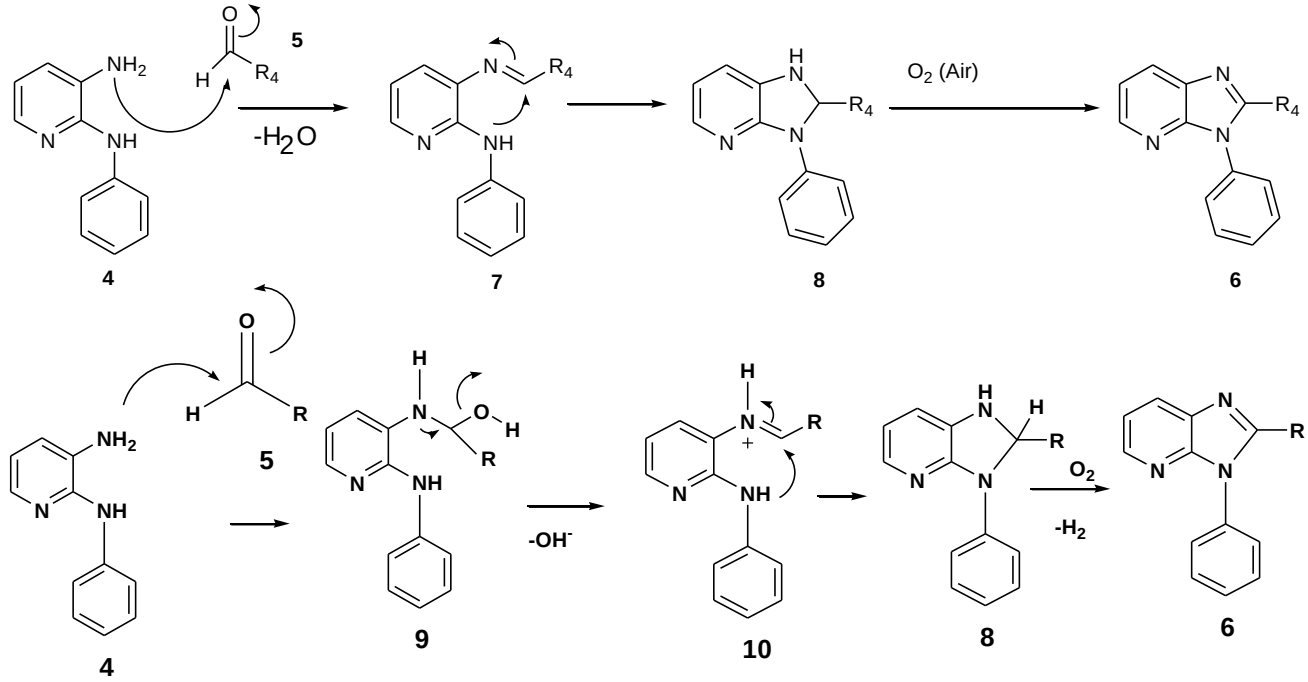
Compound **6a** was obtained as a light yellow crystals;mp 209-210 °C. ^{1}H NMR (DMSO-d_6): δ 11.91 (brs, 1H, NH), 8.87 (s, 1H, ArCH), 8.40 (d, *J* = 7.45 Hz, 1H, Ar-CH), 7.98 (dd, *J* = 1.7 Hz, 7.45 Hz, 1H, Ar-CH), 7.78 (d, *J* = 7.45 Hz, 2H, Ar-CH), 7.50-7.48 (m, 2H, Ar-CH), 7.27-7.25 (m, 4H, Ar-CH), 6.89 (dd, *J* = 7.45 Hz, 8.00 Hz, 1H, Ar-CH), 6.83-6.80 (m, 1H, Ar-CH).^{13}C NMR (DMSO-d_6): δ 156.5 (CH), 150.7 (C), 143.9 (C), 141.4 (C), 137.8 (C), 135.1 (CH), 129.2 (C), 125.3 (CH), 123.6, (CH) 123.0 (CH), 122.0 (CH), 121.2 (CH) 118.7 (CH), 115.5 (CH), 112.8 (CH), 104.6 (C); HRMS m/z : 311.1301 found (calculated for $C_{20}H_{14}N_4$, $[M+H]^+$ requires 311.1298).

2-(5-Bromo-1H-indol-3-yl)-3-phenyl-3H-imidazo[4,5-b]pyridine (6b)

Compound **6b** was obtained as a brownish yellow solid; mp 229-231°C. ^{1}HNMR (DMSO-d_6): δ 8.89 (s, 1H, Ar-CH), 8.57 (d, *J* = 7.50 Hz, 1H, AR-CH), 8.01 (dd, *J* = 1.9 H, 7.5 Hz, 1H, Ar-CH), 7.81 (d, *J* = 8.0 Hz, 2H, Ar-CH), 7.52 (dd, *J* = 1.9 Hz, 7.5 Hz, 1H, Ar-CH), 7.47 (d, *J* = 8.0 Hz, 1H, Ar-CH), 7.38 (dd, *J* = 2.0 Hz, 7.5 Hz, 1H, Ar-CH), 7.28 (dd, *J* = 7.5 Hz, 8.0 Hz, 2H, AR-CH), 6.83 (dd, *J* = 7.5 Hz, 8.0 Hz, 1H, Ar-CH), 6.82-6.81 (m, 1H, Ar-CH). ^{13}C NMR(DMSO-d_6): δ155.8 (CH), 150.8 (C), 144.2 (C), 141.5 (C), 136.5 (C), 134.1 (C), 129.2 (CH), 127.1 (C), 126.0 (CH), 124.3 (CH), 123.1 (CH), 121.2 (CH), 118.6 (CH), 115.5 (CH), 114.8 (CH), 109.4 (C).HRMS m/z : 389.0411 found (calculated for $C_{20}H_{13}BrN_4$, $[M+H]^+$ requires 389.0404).



Pathway 2(suggested by reviewer).



Scheme 2. Plausible mechanistic pathways for the formation of pyridobenzimidazoles.

2-(5-Methoxy-1H-indol-3-yl)-3-phenyl-3H-imidazo[4,5-b] pyridine(6c)

Compound **6c** was obtained as a yellowish solid; mp 169-171 °C. ^{1}H NMR (DMSO-d_6): δ 11.80 (brs, 1H, NH), 8.87 (s, 1H, Ar-CH), 8.05 (s, 1H, Ar-CH), 7.98 (dd, *J* = 2.5 Hz, 7.5 Hz, 1H, Ar-CH), 7.91 (d, *J* = 7.45 Hz, 1H, Ar-CH), 7.78 (d, *J* = 7.5 Hz, 2H, Ar-CH), 7.40 (d, *J* = 7.45 Hz, 1H, Ar-CH), 7.26 (dd, *J* = 7.5 Hz, 7.45 Hz, 2H, Ar-CH), 6.89-6.88 (m, 2H, Ar-CH), 6.88-6.81 (m, 1H, Ar-CH), 3.81 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): δ 156.4 (CH), 155.6 (CH), 150.7 (C), 143.8 (C), 135.2 (C), 134.6 (CH), 129.2 (C), 128.8 (C), 126.0 (CH), 122.9 (CH), 121.2 (CH), 118.6 (CH), 115.5 (CH), 113.5 (CH), 108.5 (CH), 103.7 (C).HRMS m/z : 341.1412 found (calculated for $C_{21}H_{16}N_4O$, $[M+H]^+$ requires 341.1404).

2-(Benzo[b]thiophen-3-yl)-3-phenyl-3H-imidazo[4,5-b]pyridine (6d)

Compound **6d** was isolated as a light yellow solid;mp 192-194 °C.^{1}H NMR ($CDCl_3$): δ 8.68 (d, *J* = 7.3 Hz, 1H, Ar-CH), δ 8.37 (dd, *J* = 2.5 Hz, 8.0 Hz, 1H, Ar-CH), 8.16 (s, 1H, Ar-CH), 7.79 (d, *J* = 7.5 Hz, 2H, Ar-CH), 7.44-7.42 (m, 4H, Ar-CH), 7.37-7.35 (m, 3H, Ar-CH), 7.27-7.25 (m, 1H,

Ar-CH). ^{13}C NMR ($CDCl_3$): δ 149.1 (CH), 148.8 (C), 144.8 (C), 140.7 (C), 139.5 (C), 139.4 (C), 137.5 (C), 129.9 (CH), 127.9 (CH), 127.6 (CH), 125.2 (CH), 125.0 (CH), 124.9 (CH), 123.6 (C), 122.4 (CH), 119.2 (CH); HRMS m/z : 328.0921 found (calculated for $C_{20}H_{13}N_3S$, $[M+H]^+$ requires 328.0910).

2-(1H-Indol-3-yl)-3-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine (6e)

Compound **6e** was isolated as a light brown solid; mp 253-255 °C. ^{1}H NMR (DMSO-d_6): δ 11.45 (brs, 1H, NH), 8.5 (s, 1H, Ar-CH), 8.10 (dd, *J* = 2.5 Hz, 7.5 Hz, 1H, Ar-CH), 8.07 (dd, *J* = 2.5 Hz, 7.5 Hz, 1H, Ar-CH), 7.42 (d, *J* = 8.0 Hz, 2H, Ar-CH), 7.25-7.23 (m, 3H, Ar-CH), 7.18-7.15 (m, 4H, Ar-CH), 3.81 (s, 3H, OCH_3). 13C NMR(DMSO-d_6): δ 160.2 (C), 151.4 (CH), 150. 2 (C), 143.1 (C), 138.3 (C), 136.1 (C), 130.5 (C), 127.2 (CH), 126.7 (CH), 126.0 (C), 125.8 (CH), 123.1 (CH), 121.7 (CH), 121.0 (CH), 118.8 (CH), 115.6 (CH),112.3 (CH), 105.3 (C), 55.8 (OCH_3).HRMS m/z : 341.1411 found (calculated for $C_{21}H_{16}N_4O$, $[M+H]^+$ requires 341.1404).

2-(Benzo[b]thiophen-3-yl)-3-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine (6f)

Compound **6f** was isolated as a light brown solid;mp 142-143 °C. ^{1}H NMR (DMSO-d_6): δ 8.59 (d, *J* = 7.5 Hz, 1H, Ar-CH), 8.30 (dd, *J* = 1.5 Hz, 7.5 Hz, 1H, Ar-CH), 8.22 (dd, *J* = 1.5 Hz, 7.5 Hz, 1H, Ar-CH), 8.01 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.47-7.38 (m, 6H, Ar-CH), 7.37-7.34 (m, 2H, Ar-CH), 3.81 (s, 3H, OCH_3). ^{13}C NMR (DMSO -d_6): δ159.9 (C), 149.6 (CH), 148.8 (C), 144.8 (C), 139.4 (C), 137.9 (C), 134.9 (C), 131.6 (CH), 129.9 (CH), 127.6 (CH), 125.6 (CH), 125.4 (CH), 125.2 (CH), 123.3 (CH), 119.6 (CH), 115.2 (CH). 55.7 (OCH_3). HRMS m/z : 358.1018 found (calculated for $C_{21}H_{15}N_3OS$, $[M+H]^+$ requires 358.1016).

2-(5-Chloro-1H-indol-3-yl)-3-(4-methoxyphenyl)-3H-imidazo[4,5-b]pyridine (6g)

Compound **6g** was isolated as a light yellow solid; mp 220-222 °C.^{1}H NMR (DMSO-d_6): δ11.60 (brs, 1H, NH), 8.61 (s, 1H, Ar-CH), 8.42 (dd, *J* = 2.5 Hz, 7.8 Hz, 1H, Ar-CH), 8.11 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.99 (s, 1H, Ar-CH), 7.66 (d, *J* = 7.8 Hz, 2H, Ar-CH), 7.44 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.24 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.14 (d, *J* = 7.5 Hz, 1H, Ar-CH), 6.86 (d, *J* = 7.8 Hz, 2H, Ar-CH), 3.85 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): δ 160.3 (C), 150.8 (CH), 150.1 (C), 143.1 (C), 138.7 (C), 134.7 (C), 130.4 (C), 129.9 (C), 128.5 (CH), 126.0 (C), 125.3 (CH), 123.1 (CH), 121.6 (CH), 121.0 (CH), 118.9 (CH), 115.6 (CH), 114.1 (CH), 105.1 (C), 55.6 (OCH_3).HRMS m/z :375.1019 found (calculated for $C_{21}H_{15}ClN_4O$, $[M+H]^+$ requires 375.1014).

3-(4-Methoxyphenyl)-2-(1H-pyrrolo[2,3-b]pyridin-3-yl)-3H-imidazo[4,5-b]pyridine (6h)

Compound **6h** was isolated as a light brown solid; mp 296-298 °C. ^{1}HNMR (DMSO-d_6): 12.03 (brs, 1H, NH), δ 8.82 (d, *J* = 7.45 Hz, 1H, Ar-CH), 8.30 (d, *J* = 7.9 Hz, 1H, Ar-CH), 8.16 (d, *J* = 7.9 Hz, 1H, Ar-CH), 8.08 (d, *J* = 8.0 Hz, 1H, Ar-CH), 7.45 (d, *J* = 8.0 Hz, 2H, Ar-CH), 7.27-7.22 (m, 2H, Ar-CH), 7.15 (d, *J* = 8.0 Hz, 2H, Ar-CH), 6.67 (s, 1H, Ar-CH), 3.85 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): δ 160.0 (C), 150.5 (C), 148.6 (C), 144.8 (CH), 143.4 (C), 142.4 (CH), 135.5 (C), 130.8 (C), 130.5 (CH), 128.6 (CH), 127.2 (CH), 126.2 (CH), 119.0 (C), 117.7 (CH), 115.6 (CH), 104.4 (C), 56.0 (OCH_3); HRMS m/z : 342.1369 found (calculated for $C_{20}H_{15}N_5O$, $[M+H]^+$ requires 342.1357).

2-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-3-p-tolyl-3H-imidazo[4,5-b]pyridine (6i)

Compound **6i** was isolated as a light yellow solid; mp 241-242 °C. ^{1}H NMR (DMSO-d_6): δ 12.41 (brs, 1H, NH), 8.82 (s, 1H, Ar-CH), 8.77 (dd, *J* = 2.1 Hz, 7.8 Hz, 1H, Ar-CH), 8.33 (dd, *J* = 2.1 Hz, 7.8 Hz, 1H, Ar-CH), 7.97 (dd, *J* = 2.5 Hz, 7.8 Hz, 1H, Ar-CH), 7.66 (d, *J* = 7.8 Hz, 2H, Ar-CH), 7.45 (dd, *J* = 2.1 Hz, 7.5 Hz, 1H, Ar-CH), 7.28 (dd, *J* = 7.5 Hz, 7.8 Hz, 1H, Ar-CH), 7.06 (d, *J* = 7.8 Hz, 2H, Ar-CH), 6.77 (dd, *J* = 7.5 Hz, 7.8 Hz, 1H, Ar-CH), 2.22 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 156.3 (CH), 150.9 (C), 150.0 (C), 144.8 (C), 144.3 (CH), 138.9 (C), 135.0 (C), 134.4 (C), 130.6 (CH), 130.1 (CH), 129.5 (CH), 123.8 (CH), 123.3 (CH), 119.3 (C), 115.1 (CH), 103.5 (C), 20.9 (CH_3). HRMS m/z : 326.1410 found (calculated for $C_{20}H_{15}N_5$, $[M+H]^+$ requires 326.1407).

2-(Benzo[b]thiophen-3-yl)-3-p-tolyl-3H-imidazo[4,5-b]pyridine (6j)

Compound **6j** was isolated as a bright yellow solid; mp 141-142 °C. ^{1}H NMR (DMSO-d_6): δ 9.01 (s, 1H, Ar-CH), 8.86 (d, *J* = 7.3 Hz, 1H, Ar-CH), 8.64 (s, 1H, Ar-CH), 8.09 (d, *J* = 7.3 Hz, 1H, Ar-CH), 8.03-8.02 (m, 2H, Ar-CH), 7.64 (d, *J* = 7.5 Hz, 2H, Ar-CH), 7.47 (dd, *J* = 7.3 Hz, 7.5 Hz, 1H, Ar-CH), 7.06 (d, *J* = 7.5 Hz, 2H, Ar-CH), 6.81 (dd, *J* = 7.3 Hz, 7.5 Hz, 1H, Ar-CH), 2.22 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ156.4 (CH), 150.8 (C), 145.5 (C), 140.2 (C), 139. 3(C), 138.2 (C), 138.1 (C), 137.3 (C), 135.1 (C), 129.4 (CH), 126.0 (CH), 125.1 (CH), 125.0 (CH), 123.6 (CH), 123.0 (CH), 122.9 (CH), 119.6 (CH), 20.9 (CH_3).HRMS m/z : 342.1070 found (calculated for $C_{21}H_{15}N_3S$, $[M+H]^+$ requires 342.1067).

2-(5-Chloro-1H-indol-3-yl)-3-p-tolyl-3H-imidazo[4,5-b]pyridine (6k)

Compound **6k** was isolated as a greenish yellow solid; mp 229-230 °C. ^{1}H NMR (DMSO-d_6): δ 12.06 (brs, 1H, NH), 8.87 (s, 1H, Ar-CH), 8.41 (d, *J* = 7.8 Hz, 1H, Ar-CH), 8.10 (s, 1H, Ar-CH), 7.97 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.68 (d, *J* = 8.0 Hz, 2H, Ar-CH), 7.47 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.27 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.06 (d, *J* = 8.0 Hz, 2H, Ar-CH), 6.77 (dd, *J* = 7.5 Hz, 7.8 Hz, 1H, Ar-CH), 2.21 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ155.8 (CH), 150.9 (C), 144.2 (C), 139.0 (C), 136.2 (C), 135.9 (C), 134.0 (C), 130.0 (C), 129.6 (CH), 126.5 (CH), 125.0 (C), 125.3 (CH), 123.5 (CH), 123.0 (CH), 122.1 (CH), 121.3 (CH), 115.3 (CH), 105.1 (C), 20.8 (CH_3).HRMS m/z : 359.1071 found (calculated for $C_{21}H_{15}ClN_4$, $[M+H]^+$ requires 359.1065).

2-(5-Methoxy-1H-indol-3-yl)-3-p-tolyl-3H-imidazo[4,5-b] pyridine (6l)

Compound **6l** was isolated as a yellowish solid; mp 164-166 °C. ^{1}H NMR (DMSO-d_6): δ 11.81 (brs, 1H, NH), 8.86 (s, 1H, Ar-CH), 8.14 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.97 (dd, *J* = 2.5 Hz, 7.5 Hz, 1H, Ar-CH), 7.67 (d, *J* = 8.0 Hz, 2H, Ar-CH), 7.49-7.46 (m, 2H, Ar-CH), 7.40 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.07 (d, *J* = 8.0 Hz, 2H, Ar-CH), 6.78 (dd, *J* = 2.5 Hz, 7.5 Hz, 1H, Ar-CH), 3.81 (s, 3H, OCH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 156.3 (C), 155.6 (CH), 150.9 (C), 143.8 (C), 139.0 (C), 137.3 (C), 135.2 (C), 130.0 (CH), 129.6 (C), 129.2 (C), 126.3 (CH), 125.1 (CH), 123.7 (CH), 122.6 (CH), 115.5 (CH), 115.2 (CH), 113.5 (CH), 103.7 (C), 55.7 (OCH_3), 20.9 (CH_3).HRMS m/z : 355.1601 found (calculated for $C_{22}H_{18}N_4O$, $[M+H]^+$ requires 355.1561).

2-(5-Bromo-1H-indol-3-yl)-3-p-tolyl-3H-imidazo[4,5-b]p-yridine (6m)

Compound **6m** was isolated as a dark brown solid; mp 293-295 °C. ^{1}H NMR (DMSO-d_6): δ 11.63 (brs, 1H, NH), 8.73 (s, 1H, Ar-CH), 8.15-8.13 (m, 2H, Ar-CH), 7.43-7.39 (m, 5H, Ar-CH), 7.32 (dd, *J* = 2.1 Hz, 7.8 Hz, 1H, Ar-CH), 7.25 (dd, *J* = 7.5 Hz, 7.8 Hz, 1H, Ar-CH), 6.63 (s, 1H, Ar-CH), 2.22 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ150.5 (CH), 150.0 (C), 143.4 (C), 139.6 (C), 137.5 (C), 135.6 (C), 134.9 (C), 133.6 (C), 131.0 (CH), 129.0 (CH), 128.3 (CH), 126.2 (CH), 125.7 (CH), 124.5 (CH), 119.0 (C), 114.5 (CH), 114.0 (CH), 105.0 (C), 21.4 (CH_3); HRMS m/z : 403.0571 found (calculated for $C_{21}H_{15}BrN_4$, $[M+H]^+$ requires 403.0560).

3-(3-p-Tolyl-3H-imidazo[4,5-b]pyridin-2-yl)-1H-indole-5-carbonitrile (6n)

Compound **6n** was isolated as a greenish yellow solid; mp 170-172 °C. ^{1}H NMR (DMSO-d_6): δ 12.35 (brs, 1H, NH), 8.89 (s, 1H, Ar-CH), 8.29 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.98 (d, *J* = 2.5 Hz, 1H, Ar-CH), 7.68-7.67 (m, 3H, Ar-CH), 7.60 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.48 (dd, *J* = 2.5 Hz, 7.8 Hz, 1H, Ar-CH), 7.06 (d, *J* = 8.0 Hz, 2H, Ar-CH), 6.78-6.77 (m, 1H, Ar-CH), 2.22 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ155.7 (CH), 151.0 (C), 144.5 (C), 139.5 (C), 139.0 (C), 136.5 (C), 134.2 (C), 130.1 (C), 129.4 (CH), 127.5 (CH), 126.3 (CH), 125.2 (CH), 123.4 (CH), 123.0 (CH), 122.9 (CH), 118.2 (CN), 114.1 (CH), 103.9 (C), 101.2 (C), 20.9 (CH_3).HRMS m/z : 350.1409 found (calculated for $C_{22}H_{15}N_5$, $[M+H]^+$ requires 350.1407).

2-(4-Nitro-1H-indol-3-yl)-3-p-tolyl-3H-imidazo[4,5-b]py-ridine (6o)

Compound **6o** was isolated as a light brown solid; mp 330-331 °C. ^{1}H NMR (DMSO-d_6): δ 12.39 (brs, 1H, NH), 8.26 (s, 1H, Ar-CH), 8.08 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.92 (s, 1H, Ar-CH), 7.87-7.79 (m, 2H, Ar-CH), 7.31-7.29 (m, 2H, Ar-CH), 7.12-7.11 (m, 4H, Ar-CH), 2.21 (s, 3H, CH_3). ^{13}C NMR(DMSO-d_6): δ 151.0 (CH), 148.9 (C), 143.9 (C), 141.3 (C), 138.6 (C), 137.9 (C), 135.0 (C), 133.8 (C), 132.8 (C), 129.9 (CH), 127.8 (CH), 127.0 (CH), 125.3 (CH), 123.3 (CH), 121.8 (CH), 118.5 (CH), 118.2 (CH), 105.0 (C), 21.1 (CH).HRMS m/z :370.1310 found (calculated for $C_{21}H_{15}N_5O_2$, $[M+H]^+$ requires 370.1306).

2-(1-Methyl-1H-indol-3-yl)-3-p-tolyl-3H-imidazo[4,5-b]p-yridine (6p)

Compound **6p** was isolated as a greenish low melting solid.^{1}H NMR (DMSO-d_6): δ 8.56 (d, *J* = 7.5 Hz, 1H, Ar-CH), 8.12 (dd, *J* = 2.1 Hz, 7.8 Hz, 1H, Ar-CH), 7.95 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.74 (d, *J* = 8.0 Hz, 2H, Ar-CH), 7.40-7.39 (m, 3H, Ar-CH), 7.19 (d, *J* = 8.0 Hz, 2H, Ar-CH), 6.74-6.71 (m, 1H, Ar-CH), 3.61 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6):δ 154.2 (CH), 151.2 (C), 144.2 (C), 138.6 (C), 138.2 (C), 136.1 (C), 135.1 (C), 129.6 (CH), 129.2 (CH), 128.1 (C), 126.0 (CH), 123.7 (CH), 122.3 (CH), 122.2 (CH), 119.2 (CH), 119.1 (CH), 110.1 (CH), 105.3 (C), 33.3 (NCH_3), 20.9 (CH_3).HRMS m/z : 339.1621 found (calculated for $C_{22}H_{18}N_4$, $[M+H]^+$ requires 339.1611).

2-(5-Bromo-1H-indol-3-yl)-3-(4-fluorophenyl)-3H-imidazo [4, 5-b]pyridine (6q)

Compound **6q** was isolated as a bright yellow crystalline solid; mp 227-229 °C. ^{1}H NMR (DMSO-d_6): δ 12.06 (brs, 1H, NH), 8.86 (s, 1H, Ar-CH), 8.57 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.97 (dd, *J* = 2.5 Hz, 7.8 Hz, 1H, Ar-CH), 7.82-7.80 (m, 2H, Ar-CH), 7.49-7.46 (m, 2H, Ar-CH), 7.37 (dd, *J* = 2.5 Hz, 7.8 Hz, 1H, Ar-CH), 7.12-7.09 (m, 2H, Ar-CH), 6.80-6.79 (m, 1H, Ar-CH). ^{13}C NMR (DMSO-d_6): δ 158.2 (C), 155.9 (CH), 150.7 (C), 144.0 (C), 138.0 (C), 136.4 (C), 135.6 (C), 134.2 (C), 127.2 (CH), 126.0 (CH), 124.4 (CH), 123.3 (C), 120.6 (CH), 120.5 (CH), 115.6 (CH), 115.4 (CH), 114.7 (CH), 106.3 (C).HRMS m/z: 407.0409 found (calculated for $C_{20}H_{12}BrFN_4$, $[M+H]^+$requires 407.0309).

3-(3-(4-Fluorophenyl)-3H-imidazo[4,5-b]pyridin-2-yl)-1H -indole-5-carbonitrile (6r)

Compound **6r** was isolated as a light yellow solid; mp 221-223 °C. ^{1}H NMR(DMSO-d_6): δ 12.32 (brs, 1H, NH), 8.88 (s, 1H, Ar-CH), 8.30 (d, J = 7.5 Hz, 1H, Ar-CH), 7.98 (d, *J* = 2.5 Hz, 1H, Ar-CH), 7.80-7.77 (m, 2H, Ar-CH), 7.66-7.58 (m, 2H, Ar-CH), 7.47 (dd, *J* = 2.5 Hz, 7.8 Hz, 1H, Ar-CH), 7.10-7.07 (m, 2H, Ar-CH), 6.82-6.79 (m, 1H, Ar-CH). ^{13}C NMR (DMSO-d_6): δ155.9 (C), 150.7 (CH), 144.3 (C), 140.9 (C), 139.4 (C), 138.0 (C), 136.4 (C), 134.5(C) 127.7 (CH), 126.3 (CH) 125.2 (CH), 123.8 (CH), 121.1 (CH), 120.9 (CH), 116.0 (CN), 115.4 (CH), 115.3 (CH), 114.0 (CH), 103.8 (C).HRMS m/z: 354.1181 found (calculated for $C_{21}H_{12}FN_5$, $[M+H]^+$requires 354.1157).

3-(4-Fluorophenyl)-2-(1H-pyrrolo[2,3-b]pyridin-3-yl)-3H-imidazo[4,5-b]pyridine (6s)

Compound **6s** was isolated as a light brown solid,mp 250-252 °C. ^{1}H NMR (DMSO-d_6): δ 12.40 (brs, 1H, NH), 8.82 (s, 1H, Ar-CH), 8.73 (d, *J* = 7.8 Hz, 1H, Ar-CH), 8.33 (d, *J* = 7.5 Hz, 1H, Ar-CH), 8.23 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.96 (d, *J* = 7.8 Hz, 1H, Ar-CH), 7.79 (dd, *J* = 2.1 Hz, 7.8 Hz, 2H, Ar-CH), 7.45 (dd, *J*= 7.5 Hz, 7.8 Hz, 1H, Ar-CH), 7.27 (dd, *J* = 2.1 Hz, 7.8 Hz, 2H, Ar-CH), 6.81-6.80 (m, 1H, Ar-CH). ^{13}C NMR (DMSO-d_6): δ 156.4 (C), 155.7 (C), 150.7 (CH), 144.8 (C), 144.1 (C), 142.1 (CH), 138.5 (C), 135.0 (C), 130.8 (CH), 123.5 (CH), 1234.0 (CH), 121.1 (C), 121.0 (CH), 115.5 (CH), 115.3 (CH), 103.9 (C). HRMS m/z :

330.1261 found (calculated for $C_{19}H_{12}FN_5$, $[M+H]^+$ requires 330.1157).

2-(Benzo[b]thiophen-3-yl)-3-(4-fluorophenyl)-3H-imidazo [4,5-b]pyridine (6t)

Compound **6t** was isolated as a light yellow floppy solid; mp 147-148 ^oC.^1H NMR (DMSO-d_6): δ 8.86 (d, *J* = 7.4 Hz, 1H, Ar-CH), 8.16 (s, 1H, Ar-CH), 8.08 (d, *J* = 7.5 Hz, 1H, Ar-CH), 8.03 (d, *J* = 7.5 Hz, 1H, Ar-CH), 7.78-7.76 (m, 3H, Ar-CH), 7.57-7.54 (m, 2H, Ar-CH), 7.08 (d, *J* = 8.0 Hz, 2H, Ar-CH), 6.85-6.84 (m, 1H, Ar-CH). ^{13}C NMR (DMSO-d_6): δ 156.5 (C), 150.7 (CH), 145.3 (C),140.7 (C), 138.1 (C), 138.0 (C), 136.6 (C), 133.8 (C), 126.0 (CH), 124.3 (CH), 124.0 (CH), 123.5 (CH), 122.1 (CH), 121.4 (CH), 121.3 (CH), 115.5 (CH), 115.3 (CH). HRMS m/z : 346.0918 found (calculated for $C_{20}H_{12}FN_3S$, $[M+H]^+$ requires 346.0816).

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CONFLICT OF INTEREST

None declared.

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