3-Methoxalylchromone – A Versatile Reagent for the Regioselective Synthesis of 1-Desazapurine

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Abstract: The reaction of 5-amino-1*H*-imidazoles with 3-methoxalylchromone provided a set of imidazo[4,5-*b*]pyridines (1-desazapurines) bearing the CO_2Me substituent at the α-position of the pyridine core. The corresponding acids were synthesized by subsequent hydrolysis of the ester function. Being typical purine isosteres, 1-desazapurines are considered to be potent pharmacophores, and are widely used in drug design and medicinal chemistry.

Key words: 3-methoxalylchromone, 5-aminoimidazoles, imidazo[4,5-*b*]pyridines, 1-desazapurines, cyclocondensations

The imidazopyridine moiety is an important pharmacophore that has proven to be useful for a number of biologically relevant targets.[1] Imidazo[4,5-*b*]pyridine, known as 1-desasapurine, is a common structural motif found in numerous molecules that display antiviral, antifungal, antibacterial, and antiproliferative activities. The potent biological activity and the prevalence of 1-desazapurines in both natural products and pharmaceuticals has inspired significant interest in the synthesis of these heterocycles.[2] Compounds that belong to the imidazo[4,5-*b*]pyridin-2-one class have been shown to be nonsteroidal anti-inflammatory and analgesic agents,[3–6] and to possess antidepressant,[4–7] antiphlogistic,[5–8] cardiotonic,[6–9] hypotensive and antiarrhythmic,[7–10] and antisecretory activity.[8–11] In addition, certain members of this class have post-emergence applications on broad-leaved plants.[9–12]

The parallel discovery of losartan and eprosartan, which are potent and orally active nonpeptide Ang II antagonists, has stimulated the design of a large number of congeners.[10] An outstanding position among the newly developed cogenders of losartan is occupied by the imidazo[4,5-*b*]pyridine moiety of compounds L-158,809 (Figure 1), L-158,338, and CR3210.[11,12] These congeners of losartan have been reported to show a subnanomolar AT1 receptor affinity about one order of magnitude higher than that of losartan and represents one of the most potent nonpeptide Ang II antagonists so far developed. Previously, the novel imidazo[4,5-*b*]pyridine derivative CCT 129202 had been reported to be a potent inhibitor of Aurora-A.[13]

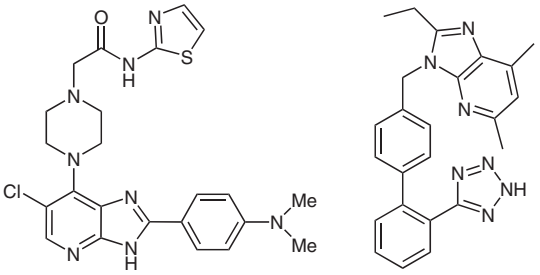

Figure 1 Pharmacologically relevant imidazo[4,5-*b*]pyridines

Being a core of purine-like scaffolds, imidazo[4,5-*b*]pyridines can serve as a base for the design and synthesis of potential adenosine deaminase (ADA) inhibitors.[14] On the other hand, pseudo-purines bearing a carbonyl function in the 2-position of the purine/pseudo-purine skeleton, are considered as platforms for the mechanism-based design and synthesis of potent inhibitors of inosine 5′-monophosphate dehydrogenase (IMPDH).[15]

It is known that 3-acylchromones **1**, and, especially, 3-formylchromones, can be considered as masked 1,3-dicarbonyl compounds, with a masked 2-hydroxybenzoyl fragment located at the 2-position, and they represent an important class of oxygen heterocyclic compounds. Because such chromones possess three electrophilic centers, their interaction with nucleophiles is sometimes difficult to predict.[16] Previously, a number of preparative methods for pyrimidine syntheses were elaborated on the basis of the mentioned 3-acylchromones and diverse amidines and guanidines.[17]

We have recently developed a synthesis of the new building block **2** and studied its application for the preparation of some fused pyridines (Scheme 1).[18] Here, we communicate our new results on the application of **2** for the assembly of functionalized 1-desazapurines bearing a carbonyl moiety located at the 2-position of the 1-desazapurine skeleton.

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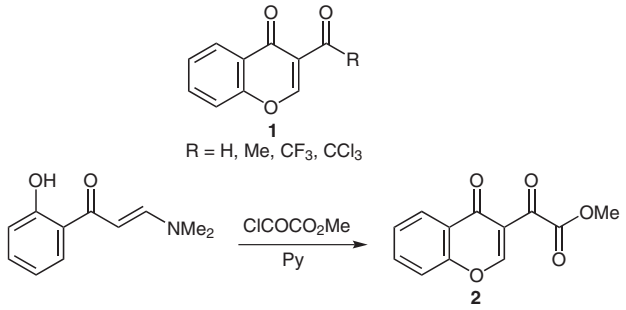


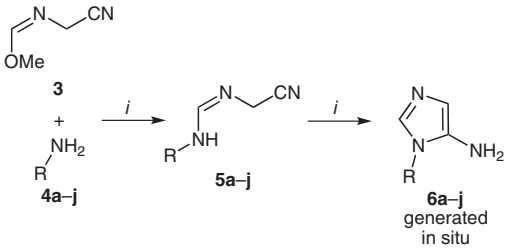
Scheme 1 Synthesis of 3-methoxalylchromone **2**

Continuing our research in the field of electron-enriched aminoheterocycles,[19] we focused our attention on 3-acylchromones as convenient intermediates in [3+3]-cyclocondensation reactions. Three available electrophilic centers (carbon atoms C-2 and C-4 of the chromone moiety and the methoxalyl carbonyl group), make these synthons versatile building blocks. The interaction of chromones with dinucleophiles usually leads to pyrone ring opening, with subsequent formation of a new cyclic structure.

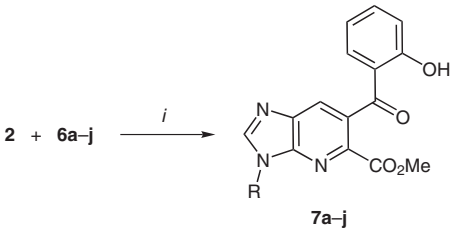
3-Acylchromones **1** are readily available by reaction of 3-(dimethylamino)-1-(2-hydroxyphenyl)propen-1-one with a number of electrophiles.[20] Recently, we have discovered a synthetic route to hitherto unknown 2-unsubstituted 3-methoxalylchromone (**2**) by reacting the corresponding enaminone with methyl 2-chloro-2-oxoacetate under basic conditions (Scheme 1). Obtained in such a way, **2** was led to react with a number of aminoheterocycles affording a set of fused α-carboxymethylpyridines.[18] Herein, we report a route to imidazo[4,5-*b*]pyridines containing a CO_2Me residue located at the α-position of the pyridine core and a 2-hydroxybenzoyl group at the β-position. Due to their electron-withdrawing properties, the latter can stabilize the γ-hydrated pyridine moiety, which mimics the transition state of adenosine mimetics and, thus, improves potential inhibition characteristics.

Based on our successful experiences mentioned above, we considered reacting 3-methoxalylchromone (**2**) with 5-aminoimidazoles to give the corresponding imidazo[4,5-*b*]pyridines. 5-Aminoimidazoles **6** were generated in situ according to our previously described procedure.[19h] Primary aliphatic amines reacted with *N*-(cyanomethyl)formimidate to give **5**, which could be transformed into 5-aminoimidazole by intramolecular cyclization (Scheme 2).

First attempts to obtain 1-deasapurine derivatives by simple addition of 3-methoxalylchromone to the reaction mixture and subsequent stirring under reflux resulted in formation of the desired product **7a** in 23% yield (Scheme 3). Further improvement of the procedure through preliminary cooling to 0 °C before the addition of the starting materials and stirring at 0 °C for 20 minutes before stirring under reflux, allowed the imidazo[4,5-*b*]pydridines to be isolated in moderate yields (Table 1).



Scheme 2 *Reagents and conditions*: (i) CH_2Cl_2, argon, reflux, 2 h.



Scheme 3 *Reagents and conditions*: (i) CH_2Cl_2, reflux, 5 h.

Table 1 Yields of Imidazo[4,5-*b*]pyridines **7a–j** and **10a–j**

7, **10**	R	**7** (%)	**10** (%)
a	*t*-Bu	48	69
b	allyl	44	75
c	*c*-Pr	47	86
d	*c*-Pent	46	82
e	*c*-Hex	51	87
f	4-$MeOC_6H_4CH_2$	50	88
g	4-$ClC_6H_4CH_2$	44	74
h	4-$MeOC_6H_4CH_2CH_2$	45	73
i	2-$MeOC_6H_4CH_2CH_2$	50	81
j	$PhCH_2CH_2$	54	90

All further attempts to achieve higher yields of the desired products (extension of the reaction time, evaporation of CH_2Cl_2 and heating of the residue in acetic acid) unfortunately failed.

The structure of product **7a** was independently confirmed by an X-ray crystal structure analysis (Figure 2).[21]

3-Dichloroacetylchromone (**8**) could also be synthesized by the same procedure used to generate 3-methoxalylchromone (using dichloroacetylchloride).[22] Following the previously described strategy, we attempted to react **8** with 5-aminoimidazoles to give the corresponding formyl-substituted 1-desazapurines. However, we could not isolate the 1-desazapurines **9a** or **9b** in more than 15% yield under any of the reaction conditions applied (Scheme 4).

The formation of products **7** can be explained by conjugate addition of the enamine carbon atom of **6** to the double bond of **2** to give intermediate **A**. Subsequent pyrone

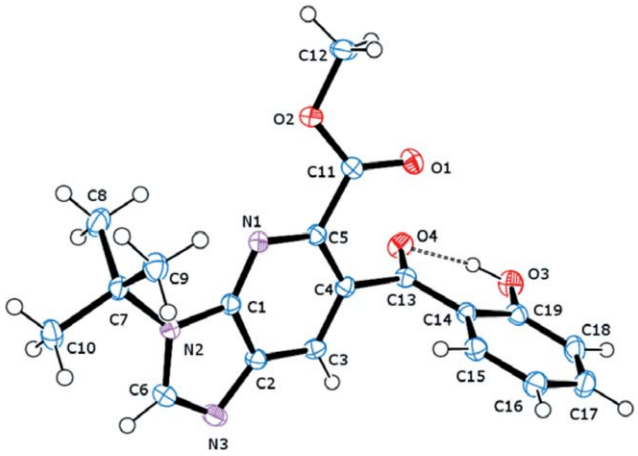
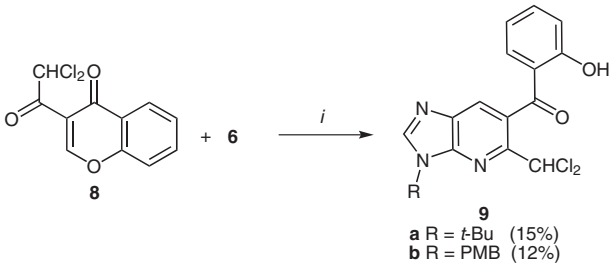
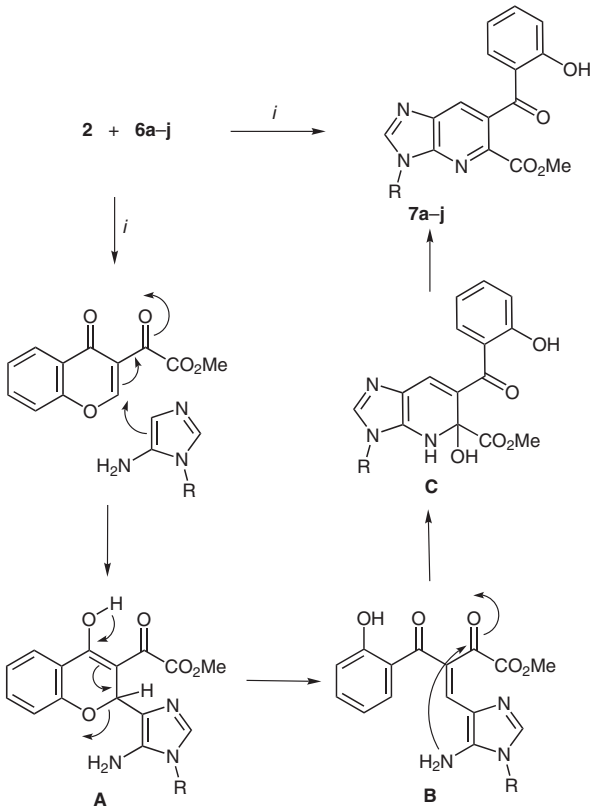


Figure 2 Molecular structure of compound **7a**



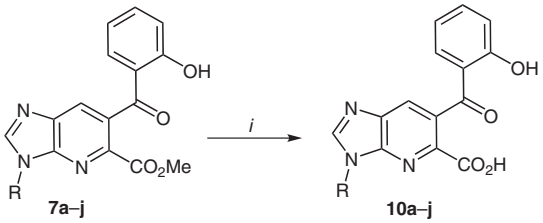
Scheme 4 *Reagents and conditions*: (i) CH_2Cl_2, reflux, 7 h.



Scheme 5 Proposed cyclization mechanism

ring opening delivers an intermediate of type **B**. Intramolecular attack of the amino group on the carbonyl group affords intermediate **C**, which undergoes elimination of water to give pyridines **7** (Scheme 5).

All isolated compounds **7a–j** were treated with a water/methanol solution of potassium hydroxide to give, after acidification with concentrated hydrochloric acid, the corresponding carboxylic acids **10a–j** (Scheme 6). Bearing an acidic proton, such carboxylic acid derivatives can have larger binding constants with ADA, which could result in improved inhibition properties.



Scheme 6 *Reagents and conditions*: (i) (a) MeOH, KOH, reflux, 2 h; (b) concd HCl.

The structure of compound **10b** was independently confirmed by X-ray structure analysis. Crystallized from *N*,*N*-dimethylformamide, it exists in the form of a hydrogen-bonded dimer (Figure 3).[21]

In summary, we have reported a convenient one-pot procedure that leads to previously unknown imidazo[4,5-*b*]pyridine derivatives. Bearing two electron-withdrawing groups, the products are of considerable interest as potent ADA inhibitors. The synthetic applications as well as a biological evaluation are currently being studied in our laboratories.

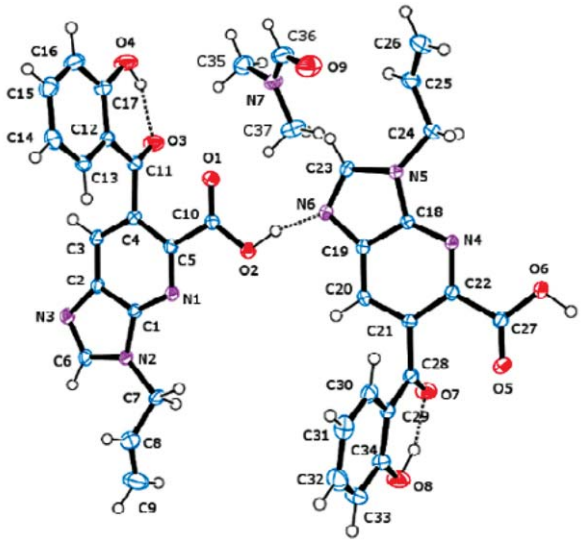


Figure 3 Molecular structure of compound **10b** and intermolecular interactions

Reactions were monitored by thin layer chromatography using UV light to visualize the course of the reaction. Purification of reaction products was carried out by flash chromatography on silica gel. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck 60F254 plates were used for TLC. Satisfactory microanalysis obtained C ±0.33; H ±0.45; N ±0.25.

Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker DPX-300 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad.

Synthesis of Compounds 7a–j; General Procedure

To a Schlenk flask fitted with a reflux condenser, CH_2Cl_2 (2.5 mL), primary amine (0.00345 mol), and methyl *N*-(cyanomethyl)formimidate (**1**; 0.338 g, 0.00345 mol) were added under an argon atmosphere at r.t. The reaction mixture was heated at reflux for 2 h then cooled down to r.t., and then to 0 °C with an ice bath. 3-Methoxalylchromone (0.800 g, 0.00345 mol) was added and the mixture was stirred at the same temperature for 15–20 min and then heated at reflux for 5 h. When product formation was complete, the solvent was evaporated to dryness and the residue was purified by column chromatography (EtOAc) to give **7a–j** as light-grey oily gum, which crystallized within a few hours in air.

Methyl 3-*tert*-Butyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7a)

Yield: 0.58 g (48%); light-grey solid; mp 196–198 °C; R_f = 0.68 (EtOAc).

IR (ATR): 1706, 1629, 1444, 1340, 1296, 1217, 1145, 911, 751, 626 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.84 (s, 9 H, *t*-Bu), 3.72 (s, 3 H, OCH_3), 6.91 (t, ^3J = 9.2 Hz, 1 H, H-4′), 7.02 (d, ^3J = 9.2 Hz, 1 H, H-2′), 7.36 (d, ^3J = 9.2 Hz, 1 H, H-5′), 7.55 (t, ^3J = 9.2 Hz, 1 H, H-3′), 8.28 (s, 1 H, H-4), 8.80 (s, 1 H, H-2), 11.20 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.5 (CH_3), 52.6 (OCH_3), 57.6 [$C(CH_3)_3$], 117.4 (C-4′), 119.2 (C-6′), 121.7 (C-2′), 127.1 (C-5), 131.1 (C-6), 132.1 (C-3′), 135.8 (C-5′), 137.1 (C-4), 139.8 (C-9), 146.8 (C-2), 147.6 (C-7), 160.0 (C-1′), 165.6 (*C*OOCH$_3$), 198.3 (C=O).

MS (GS): *m*/*z* (%) = 353 (11) [M]$^+$, 322 (10), 294 (81), 266 (20), 238 (95), 209 (10), 121 (11).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{19}H_{19}N_3O_4$: 353.1370; found: 353.1368.

Methyl 3-Allyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7b)

Yield: 0.51 g (44%); light-grey solid; mp 163–165 °C; R_f = 0.7 (EtOAc).

IR (ATR): 1709, 1628, 1608, 1483, 1445, 1374, 1280, 1255, 1235, 1203, 1145, 946, 907, 744, 672, 620 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.69 (s, 3 H, OCH_3), 5.01 (d, ^3J = 2.9 Hz, 2 H, CH_2), 5.08 (dd, $^3J_1$ = 15.3 Hz, $^2J_2$ = 2.1 Hz, 1 H, =CH_2(*trans*)), 5.25 (dd, $^3J_1$ = 8.7 Hz, $^2J_2$ = 2.1 Hz, 1 H, =CH_2(*cis*)), 6.15 (m, 1 H, CH=), 6.88 (t, ^3J = 9.1 Hz, 1 H, H-4′), 7.00 (d, ^3J = 9.1 Hz, 1 H, H-2′), 7.32 (d, ^3J = 9.1 Hz, 1 H, H-5′), 7.52 (t, ^3J = 9.1 Hz, 1 H, H-3′), 8.31 (s, 1 H, H-4), 8.78 (s, 1 H, H-2), 11.16 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.3 (CH_2), 52.6 (OCH_3), 117.5 (C-4′), 117.8 (=CH_2), 119.3 (C-6′), 121.7 (C-2′), 127.5 (C-5), 131.5 (C-6), 132.1 (C-3′), 132.9 (CH=), 135.7 (C-5′), 135.8 (C-4), 141.0 (C-9), 146.5 (C-2), 149.7 (C-7), 159.9 (C-1′), 165.56 (*C*OOCH$_3$), 198.2 (C=O).

MS (GS): *m*/*z* (%) = 337 (10) [M]$^+$, 305 (12), 278 (100), 250 (11), 41 (11).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_3O_4$: 338.1135; found: 338.114.

Methyl 3-Cyclopropyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7c)

Yield: 0.55 g (47%); light-grey solid; mp 172–174 °C; R_f = 0.68 (EtOAc).

IR (ATR): 1704, 1628, 1485, 1443, 1337, 1298, 1265, 1237, 1141, 908, 759, 674, 628 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.22 (br m, 4 H, *c*-Pr), 3.74 (m, 4 H, OCH_3, *c*-Pr), 6.91 (t, ^3J = 9.1 Hz, 1 H, H-4′), 7.03 (d, ^3J = 9.1 Hz, 1 H, H-2′), 7.34 (d, ^3J = 9.1 Hz, 1 H, H-5′), 7.56 (t, ^3J = 9.1 Hz, 1 H, H-3′), 8.30 (s, 1 H, H-4), 8.79 (s, 1 H, H-2), 11.20 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.7 (CH_2), 25.6 (CH), 52.5 (OCH_3), 117.4 (C-4′), 119.2 (C-6′), 121.7 (C-2′), 127.3 (C-5), 131.6 (C-6), 132.0 (C-3′), 135.8 (C-5′), 136.2 (C-4), 140.8 (C-9), 147.8 (C-2), 149.6 (C-7), 159.9 (C-1′), 165.6 (*C*OOCH$_3$), 198.2 (C=O).

MS (GS): *m*/*z* (%) = 337 (12) [M]$^+$, 304 (14), 278 (97), 250 (16), 121 (10), 65 (10).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{15}N_3O_4$: 337.1057; found: 337.1050.

Methyl 3-Cyclopentyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7d)

Yield: 0.58 g (46%); light-grey solid; mp 161–163 °C; R_f = 0.71 (EtOAc).

IR (ATR): 2957, 1727, 1631, 1602, 1486, 1446, 1294, 1226, 1142, 910, 797, 754, 710 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.01 (br m, 8 H, *c*-Pent), 3.72 (s, 3 H, OCH_3), 5.12 (m, 1 H, CH), 6.90 (t, ^3J = 9.2 Hz, 1 H, H-4′), 7.03 (d, ^3J = 9.2 Hz, 1 H, H-2′), 7.34 (d, ^3J = 9.2 Hz, 1 H, H-5′), 7.55 (t, ^3J = 9.2 Hz, 1 H, H-3′), 8.31 (s, 1 H, H-4), 8.92 (s, 1 H, H-2), 11.18 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.6 (CH_2), 32.2 (CH_2), 52.5 (OCH_3), 55.4 (CH), 117.4 (C-4′), 119.2 (C-6′), 121.7 (C-2′), 127.3 (C-5), 131.4 (C-6), 132.1 (C-3′), 135.8 (C-5′), 136.1 (C-4), 140.6 (C-9), 146.6 (C-2), 148.1 (C-7), 160.0 (C-1′), 165.5 (*C*OOCH$_3$), 198.3 (C=O).

MS (GS): *m*/*z* (%) = 365 (14) [M]$^+$, 334 (10), 306 (97), 292 (11), 266 (21), 238 (34).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}N_3O_4$: 366.1448; found: 366.1456.

Methyl 3-Cyclohexyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7e)

Yield: 0.66 g (51%); light-grey solid; mp 143–145 °C; R_f = 0.72 (hexane–EtOAc, 1:1).

IR (ATR): 1715, 1630, 1605, 1447, 1377, 1295, 1252, 1240, 1214, 1141, 911, 796, 756, 674 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.74 (br m, 11 H, Cy), 3.72 (s, 3 H, OCH_3), 4.63 (m, 1 H, CH), 6.90 (t, ^3J = 9.3 Hz, 1 H, H-4′), 7.02 (d, ^3J = 9.3 Hz, 1 H, H-2′), 7.34 (d, ^3J = 9.3 Hz, 1 H, H-5′), 7.55 (t,^3J = 9.3 Hz, 1 H, H-3′), 8.30 (s, 1 H, H-4), 8.95 (s, 1 H, H-2), 11.18 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.7 (CH_2), 25.0 (CH_2), 32.4 (CH_2), 52.5 (OCH_3), 53.6 (CH), 117.4 (C-4′), 119.2 (C-6′), 121.7 (C-2′), 127.4 (C-5), 131.3 (C-6), 132.1 (C-3′), 135.8 (C-5′), 135.9

(C-4), 140.8 (C-9), 146.2 (C-2), 147.8 (C-7), 159.9 (C-1′), 165.6 (*C*OOCH$_3$), 198.2 (C=O).

MS (GS): *m*/*z* (%) = 379 (13) [M]$^+$, 346 (14), 320 (100), 302 (19), 266 (32), 238 (45), 207 (18).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_3O_4$: 380.1605; found: 380.1608.

Methyl 6-(2-Hydroxybenzoyl)-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7f)

Yield: 0.72 g (50%); light-grey solid; mp 165–166 °C; R_f = 0.68 (EtOAc).

IR (ATR): 1715, 1627, 1601, 1448, 1348, 1282, 1239, 1142, 1034, 904, 763 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3 H, OCH$_3$), 3.77 (s, 3 H, OCH$_3$), 5.56 (s, 2 H, CH$_2$), 6.92 (t, ^3J = 8.8 Hz, 1 H, H-4″), 6.98 (d, ^3J = 6.3 Hz, 2 H, H-2′, H-6′), 7.06 (d, ^3J = 8.8 Hz, 1 H, H-2″), 7.40 (m, 3 H, H-3′, H-5′, H-5“), 7.57 (t, ^3J = 8.8 Hz, 1 H, H-3″), 8.36 (s, 1 H, H-4), 8.92 (s, 1 H, H-2), 11.21 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.0 (CH$_2$), 52.9 (OCH$_3$), 55.1 (OCH$_3$), 114.1 (C-2′, C-6′), 117.4 (C-4″), 119.2 (C-6″), 121.6 (C-2″), 127.5 (C-5), 128.5 (C-4′), 129.3 (C-3′, C-5′), 131.5 (C-6), 132.2 (C-3″), 135.8 (C-5″), 135.8 (C-4), 141.0 (C-9), 146.5 (C-2), 149.5 (C-7), 158.9 (C-1′), 159.9 (C-1″), 165.5 (*C*OOCH$_3$), 198.2 (C=O).

MS (GS): *m*/*z* (%) = 385 (67), 358 (39), 281 (11), 207 (19), 121 (100), 77 (10).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}N_3O_5$: 418.1397; found: 418.1395.

Methyl 3-(4-Chlorobenzyl)-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7g)

Yield: 0.64 g (44%); light-grey solid; mp 130–132 °C; R_f = 0.68 (EtOAc).

IR (ATR): 1715, 1622, 1602, 1445, 1349, 1288, 1237, 1142, 904, 794, 752, 663 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76 (s, 3 H, OCH$_3$), 5.66 (s, 2 H, CH$_2$), 6.94 (t, ^3J = 8.9 Hz, 1 H, H-4″), 7.06 (d, ^3J = 8.9 Hz, 1 H, H-2″), 7.40 (d, ^3J = 8.9 Hz, 1 H, H-5″), 7.48 (m, 4 H, H-3′, H-2′, H-5′, H-6′), 7.60 (t, ^3J = 8.9 Hz, 1 H, H-3″), 8.39 (s, 1 H, H-4), 8.97 (s, 1 H, H-2), 11.21 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.7 (CH$_2$), 52.5 (OCH$_3$), 117.5 (C-4″), 119.2 (C-6″), 121.3 (C-2″), 126.8 (C-5), 128.7 (C-2′, C-6′), 129.5 (C-3′, C-5′), 131.2 (C-6), 132.3 (C-3″), 132.5 (C-4′), 135.4 (C-5″), 135.6 (C-1′), 136.1 (C-4), 141.8 (C-9), 146.2 (C-2), 149.6 (C-7), 160.0 (C-1″), 165.5 (*C*OOCH$_3$), 198.3 (C=O).

MS (EI): *m*/*z* (%) = 421 (10) [M]$^+$, 390 (11), 362 (74), 125 (99), 89 (14), 65 (10).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{16}ClN_3O_4$: 422.0902; found: 422.0904.

Methyl 6-(2-Hydroxybenzoyl)-3-(4-methoxyphenethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7h)

Yield: 0.67 g (45%); light-grey solid; mp 149–151 °C; R_f = 0.65 (EtOAc).

IR (ATR): 1717, 1626, 1610, 1453, 1380, 1288, 1237, 1144, 1033, 908, 761, 618 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.19 (t, ^3J = 6.8 Hz, 2 H, CH$_2$), 3.71 (s, 3 H, OCH$_3$), 3.73 (s, 3 H, OCH$_3$), 4.59 (t, ^3J = 6.8 Hz, 2 H, CH$_2$), 6.83 (d, ^3J = 6.4 Hz, 2 H, H-2′, H-6′), 6.91 (t, ^3J = 9.1 Hz, 1 H, H-4″), 7.03 (d, ^3J = 9.1 Hz, 1 H, H-2″), 7.07 (d, ^3J = 6.4 Hz, 2 H, H-3′, H-5′), 7.31 (d, ^3J = 9.1 Hz, 1 H, H-5″), 7.55 (t, ^3J = 9.1 Hz, 1 H, H-3″), 8.29 (s, 1 H, H-4), 8.57 (s, 1 H, H-2), 11.22 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.9 (CH$_2$), 44.8 (CH$_2$), 52.5 (OCH$_3$), 54.9 (OCH$_3$), 113.8 (C-2′, C-6′), 117.4 (C-4″), 119.2 (C-6″), 121.6 (C-2″), 127.3 (C-5), 129.5 (C-3′, C-5′), 129.6 (C-4′), 131.3 (C-6), 132.0 (C-3″), 135.8 (C-5″), 135.8 (C-4), 140.7 (C-9), 146.6 (C-2), 149.6 (C-7), 157.9 (C-1′), 160.0 (C-1″), 165.5 (*C*OOCH$_3$), 198.3 (C=O).

MS (GS): *m*/*z* (%) = 431 (14) [M]$^+$, 429 (19), 372 (22), 310 (15), 134 (100), 91 (35), 65 (11).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{21}N_3O_5$: 432.1554; found: 432.1558.

Methyl 6-(2-Hydroxybenzoyl)-3-(2-methoxyphenethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7i)

Yield: 0.74 g (50%); light-grey solid; mp 138–140 °C; R_f = 0.75 (EtOAc).

IR (ATR): 1713, 1626, 1601, 1497, 1443, 1380, 1285, 1249, 1142, 1034, 898, 747, 630 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.19 (t, ^3J = 6.5 Hz, 2 H, CH$_2$), 3.67 (s, 3 H, OCH$_3$), 3.73 (s, 3 H, OCH$_3$), 4.61 (t, ^3J = 6.5 Hz, 2 H, CH$_2$), 6.78 (t, ^3J = 6.2 Hz, 1 H, H-4′), 6.91 (t, ^3J = 9.4 Hz, 1 H, H-4″), 6.93 (d, ^3J = 6.2 Hz, 1 H, H-2′), 6.94 (d, ^3J = 6.2 Hz, 1 H, H-5′), 7.03 (d, ^3J = 9.4 Hz, 1 H, H-2″), 7.18 (t, ^3J = 6.2 Hz, 1 H, H-3′), 7.27 (d, ^3J = 9.4 Hz, 1 H, H-5″), 7.55 (t, ^3J = 9.4 Hz, 1 H, H-3″), 8.25 (s, 1 H, H-4), 8.49 (s, 1 H, H-2), 11.22 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 30.2 (CH$_2$), 43.3 (CH$_2$), 52.5 (OCH$_3$), 55.0 (OCH$_3$), 110.5 (C-4′), 117.4 (C-4″), 119.2 (C-6″), 120.1 (C-6′), 121.6 (C-2″), 125.5 (C-2′), 127.0 (C-5), 128.1 (C-3′), 130.0 (C-5′), 131.1 (C-6), 132.0 (C-3″), 135.7 (C-5″), 135.8 (C-4), 140.5 (C-9), 146.7 (C-2), 149.6 (C-7), 157.2 (C-1′), 160.0 (C-1″), 165.5 (*C*OOCH$_3$), 198.4 (C=O).

MS (GS): *m*/*z* (%) = 431 (15) [M]$^+$, 400 (10), 372 (30), 134 (99), 119 (51), 91 (47), 65 (12).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{21}N_3O_5$: 432.1554; found: 432.1559.

Methyl 6-(2-Hydroxybenzoyl)-3-phenethyl-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylate (7j)

Yield: 0.75 g (54%); light-grey solid; mp 142–144 °C; R_f = 0.78 (EtOAc).

IR (ATR): 1716, 1628, 1609, 1453, 1379, 1292, 1242, 1142, 1123, 1056, 907, 759, 700, 618 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.27 (t, ^3J = 6.4 Hz, 2 H, CH$_2$), 3.73 (s, 3 H, OCH$_3$), 4.64 (t, ^3J = 6.4 Hz, 2 H, CH$_2$), 6.91 (t, ^3J = 8.7 Hz, 1 H, H-4′), 7.02 (d, ^3J = 8.7 Hz, 1 H, H-2′), 7.26 (br m, 6 H, PhH, H-5′), 7.55 (t, ^3J = 8.7 Hz, 1 H, H-3′), 8.29 (s, 1 H, H-4), 8.59 (s, 1 H, H-2), 11.21 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.8 (CH$_2$), 44.6 (CH$_2$), 52.5 (OCH$_3$), 117.5 (C-4″), 119.2 (C-6″), 121.7 (C-2″), 126.6 (C-4′), 127.3 (C-5), 128.4 (C-2′, C-6′), 128.6 (C-3′, C-5′), 131.3 (C-6), 132.1 (C-3″), 135.8 (C-5″), 135.9 (C-4), 137.8 (C-1′), 140.8 (C-9), 146.6 (C-2), 149.6 (C-7), 160.0 (C-1″), 165.5 (*C*OOCH$_3$), 198.3 (C=O).

MS (GS): *m*/*z* (%) = 401 (16) [M]$^+$, 370 (10), 342 (100), 238 (28), 207 (12), 104 (49), 91 (11).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd. for $C_{23}H_{19}N_3O_4$: 402.1448; found: 402.1455.

Synthesis of Compounds 9a,b; General Procedure

To a Schlenk flask, fitted with a reflux condenser, CH_2Cl_2 (2.5 mL), primary amine (0.00117 mol), and methyl *N*-(cyanometh-

yl)formimidate (**1**; 0.00117 mol) were added under an argon atmosphere at r.t. The reaction mixture was heated at reflux for 2 h then cooled to r.t. and then to 0 °C with an ice bath. 3-Dichloroacetylchromone (0.300 g, 0.00117 mol) was added and the mixture was stirred at the same temperature for 15–20 min and then heated at reflux for 7 h. The solvent was evaporated to dryness and the residue was purified by column chromatography (EtOAc) to give **9** as green crystals.

{3-*tert*-Butyl-5-(dichloromethyl)-3*H*-imidazo[4,5-*b*]pyridine-6-yl}(2-hydroxyphenyl)methanone (9a)
Yield: 0.067 g (15%); greenish solid; mp 189–191 °C; R_f = 0.62 (EtOAc).

IR (ATR): 2974, 1592, 1486, 1398, 1337, 1230, 1210, 1029, 803, 756, 644 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.88 (s, 9 H, *t*-Bu), 6.88 (t, ^3J = 9.2 Hz, 1 H, H-4′), 7.02 (d, ^3J = 9.2 Hz, 1 H, H-2′), 7.33 (s, 1 H, $CHCl_2$), 7.39 (d, ^3J = 9.2 Hz, 1 H, H-5′), 7.47 (t, ^3J = 9.2 Hz, 1 H, H-3′), 8.18 (s, 1 H, H-4), 8.88 (s, 1 H, H-2), 11.06 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.3 (CH_3), 56.6 [$C(CH_3)_3$], 76.6 ($CHCl_2$), 117.3 (C-4′), 119.2 (C-6′), 122.0 (C-2′), 125.3 (C-5), 131.0 (C-6), 131.9 (C-3′), 136.1 (C-5′), 137.0 (C-4), 139.8 (C-9), 145.1 (C-7), 146.9 (C-2), 160.0 (C-1′), 197.6 (C=O).

MS (GS): *m*/*z* (%) = 377 (11) $[M]^+$, 342 (61), 294 (80), 286 (19), 250 (47), 238 (93), 222 (41), 140 (11), 57 (10).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}N_3O_4$: 378.0771; found: 378.0769.

{3-(4-Methoxybenzyl)-5-(dichloromethyl)-3*H*-imidazo[4,5-*b*]pyridine-6-yl}(2-hydroxyphenyl)methanone (9b)
Yield: 0.062 g (12%); green solid; mp 172–175 °C; R_f = 0.66 (EtOAc).

IR (ATR): 1712, 1617, 1577, 1533, 1446, 1391, 1334, 1285, 1140, 1088, 1040, 918, 877 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.82 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 5.51 (s, 2 H, CH_2), 6.91 (t, ^3J = 9.0 Hz, 1 H, H-4″), 6.95 (d, ^3J = 5.7 Hz, 2 H, H-2′, H-6′), 7.06 (d, ^3J = 9.0 Hz, 1 H, H-2″), 7.36 (m, 3 H, H-3′, H-5′, H-5″), 7.42 (s, 1 H, $CHCl_2$), 7.60 (t, ^3J = 9.0 Hz, 1 H, H-3″), 8.11 (s, 1 H, H-4), 8.48 (s, 1 H, H-2), 10.47 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.4 (CH_2), 53.0 (OCH_3), 75.3 ($CHCl_2$), 114.1 (C-2′, C-6′), 117.2 (C-4″), 118.9 (C-6″), 121.6 (C-2″), 126.9 (C-5), 128.4 (C-4′), 129.1 (C-3′, C-5′), 130.0 (C-6), 132.4 (C-3″), 135.2 (C-4), 136.1 (C-5″), 141.7 (C-9), 146.5 (C-2), 148.2 (C-7), 157.9 (C-1′), 160.1 (C-1″), 198.0 (C=O).

MS (GS): *m*/*z* (%) = 443 (12) $[M]^+$, 408 (38), 360 (80), 238 (86), 221 (23), 121 (96), 83 (13).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd. for $C_{22}H_{17}Cl_2N_3O_3$: 444.3116; found: 444.3120.

Synthesis of Compounds 10a–j; General Procedure
To a solution of the corresponding ester (300 mg) in MeOH (20 mL), KOH (30% in H_2O, 2 equiv) was added. The mixture was stirred at reflux temperature for 2 h then allowed to cool down. Concentrated HCl was added dropwise until the mixture became acidic. The precipitate formed was filtered and washed with H_2O (3 × 7 mL), then dried to give **10a–j** as white crystals.

3-*tert*-Butyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10a)
Yield: 0.20 g (69%); colourless solid; mp 274–275 °C.

IR (ATR): 1689, 1682, 1609, 1469, 1345, 1295, 1210, 1149, 898, 750 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.83 (s, 9 H, *t*-Bu), 6.88 (t, ^3J = 9.2 Hz, 1 H, H-4′), 7.00 (d, ^3J = 9.2 Hz, 1 H, H-2′), 7.29 (d, ^3J = 9.2 Hz, 1 H, H-5′), 7.52 (t, ^3J = 9.2 Hz, 1 H, H-3′), 8.23 (s, 1 H, H-4), 8.76 (s, 1 H, H-2), 11.41 (s, 1 H, OH), 13.33 (s, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.5 (CH_3), 57.5 [$C(CH_3)_3$], 117.4 (C-4′), 119.2 (C-6′), 121.3 (C-2′), 126.7 (C-5), 130.9 (C-6), 132.3 (C-3′), 135.9 (C-5′), 136.9 (C-4), 140.6 (C-9), 146.5 (C-2), 147.3 (C-7), 160.5 (C-1′), 166.5 (COOH), 199.3 (C=O).

MS (GS): *m*/*z* (%) = 321 (80), 294 (88), 266 (63), 237 (74), 220 (26), 205 (92), 190 (68), 177 (10), 145 (24), 117 (15), 157 (46).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_3O_4$: 340.1292; found: 340.1296.

3-Allyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10b)
Yield: 0.22 g (75%); colourless solid; mp 249–250 °C.

IR (ATR): 1633, 1613, 1488, 1445, 1354, 1244, 1186, 1151, 901, 764, 674 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 5.05 (d, ^3J = 2.6 Hz, 2 H, CH_2), 5.10 (dd, $^3J_1$ = 15.2 Hz, $^2J_2$ = 2.1 Hz, 1 H, =CH_2 (*trans*)), 5.28 (dd, $^3J_1$ = 9.1 Hz, $^2J_2$ = 2.1 Hz, 1 H, =CH_2 (*cis*)), 6.20 (m, 1 H, CH=), 6.88 (t, ^3J = 9.4 Hz, 1 H, H-4′), 7.03 (d, ^3J = 9.4 Hz, 1 H, H-2′), 7.29 (d, ^3J = 9.4 Hz, 1 H, H-5′), 7.54 (t, ^3J = 9.4 Hz, 1 H, H-3′), 8.30 (s, 1 H, H-4), 8.79 (s, 1 H, H-2), 11.42 (s, 1 H, OH), 13.42 (s, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.2 (CH_2), 117.5 (C-4′), 117.9 (=CH_2), 119.2 (C-6′), 121.4 (C-2′), 127.0 (C-5), 131.4 (C-6), 132.3 (C-3′), 133.0 (CH=), 135.6 (C-5′), 135.9 (C-4), 141.7 (C-9), 146.2 (C-2), 149.4 (C-7), 160.5 (C-1′), 166.3 (COOH), 199.2 (C=O).

MS (GS): *m*/*z* (%) = 305 (90), 276 (98), 260 (12), 250 (29), 237 (12), 156 (22), 92 (10), 41 (14).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{13}N_3O_4$: 324.0979; found: 324.0979.

3-Cyclopropyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10c)
Yield: 0.25 g (86%); colourless solid; mp 276–277 °C.

IR (ATR): 1682, 1627, 1485, 1450, 1343, 1297, 1234, 1148, 1028, 895, 760, 708 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.22 (br m, 4 H, *c*-Pr), 3.73 (m, 1 H, CH), 6.88 (t, ^3J = 8 Hz, 1 H, H-4′), 7.02 (d, ^3J = 8.8 Hz, 1 H, H-2′), 7.27 (d, ^3J = 8.8 Hz, 1 H, H-5′), 7.54 (t, ^3J = 8.8 Hz, 1 H, H-3′), 8.25 (s, 1 H, H-4), 8.76 (s, 1 H, H-2), 11.42 (s, 1 H, OH), 13.45 (s, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 5.6 (CH_2), 25.6 (CH), 117.5 (C-4′), 119.2 (C-6′), 121.4 (C-2′), 126.9 (C-5), 131.4 (C-6), 132.3 (C-3′), 135.9 (C-5′), 136.1 (C-4), 141.8 (C-9), 147.6 (C-2), 149.4 (C-7), 160.5 (C-1′), 166.5 (COOH), 199.3 (C=O).

MS (GS): *m*/*z* (%) = 305 (91), 278 (78), 249 (34), 221 (13), 65 (10).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{13}N_3O_4$: 324.0979; found: 324.0977.

3-Cyclopentyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10d)
Yield: 0.24 g (82%); colourless solid; mp 297–298 °C.

IR (ATR): 1693, 1626, 1486, 1453, 1344, 1293, 1227, 1148, 895, 763, 742, 670 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.02 (br m, 8 H, *c*-Pent), 5.12 (m, 1 H, CH), 6.88 (t, ^3J = 9.0 Hz, 1 H, H-4′), 7.00 (d, ^3J = 9.0 Hz, 1 H, H-2′), 7.33 (d, ^3J = 9.0 Hz, 1 H, H-5′), 7.55 (t, ^3J = 9.0 Hz, 1 H, H-3′), 8.27 (s, 1 H, H-4), 8.91 (s, 1 H, H-2), 11.43 (s, 1 H, OH), 13.32 (s, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.5 (CH_2), 32.1 (CH_2), 55.4 (CH), 117.4 (C-4′), 119.1 (C-6′), 121.4 (C-2′), 126.8 (C-5), 131.2 (C-6), 132.3 (C-3′), 135.9 (C-5′, C-4), 141.3 (C-9), 146.3 (C-7), 147.9 (C-2), 160.5 (C-1′), 166.4 (COOH), 199.3 (C=O).

MS (GS): *m*/*z* (%) = 351 (11) $[M]^+$, 332 (10), 292 (26), 282 (39), 171 (19), 69 (16).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{17}N_3O_4$: 352.1292; found: 352.1292.

3-Cyclohexyl-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10e)
Yield: 0.25 g (87%); colourless solid; mp >300 °C.

IR (ATR): 2930, 1627, 1607, 1488, 1447, 1353, 1295, 1225, 1184, 1148, 895, 743, 670 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.71 (br m, 11 H, Cy), 4.61 (m, 1 H, CH), 6.85 (t, ^3J = 8.9 Hz, 1 H, H-4′), 7.00 (d, ^3J = 8.9 Hz, 1 H, H-2′), 7.27 (d, ^3J = 8.9 Hz, 1 H, H-5′), 7.51 (t, ^3J = 8.9 Hz, 1 H, H-3′), 8.23 (s, 1 H, H-4), 8.90 (s, 1 H, H-2), 11.42 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.7 (CH_2), 25.1 (CH_2), 32.3 (CH_2), 53.4 (CH), 117.4 (C-4′), 119.1 (C-6′), 121.7 (C-2′), 127.6 (C-5), 131.4 (C-6), 132.1 (C-3′), 135.8 (C-5′), 135.9 (C-4), 140.8 (C-9), 146.3 (C-2), 147.6 (C-7), 160.0 (C-1′), 166.4 (COOH), 198.1 (C=O).

MS (GS): *m*/*z* (%) = 365 (10) $[M]^+$, 332 (11), 306 (22), 244 (35), 184 (10), 83 (16), 59 (10).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{19}N_3O_4$: 366.1448; found: 366.1452.

6-(2-Hydroxybenzoyl)-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10f)
Yield: 0.26 g (88%); colourless solid; mp 286–288 °C.

IR (ATR): 1714, 1606, 1511, 1456, 1295, 1238, 1142, 1032, 911, 772, 739 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.74 (s, 3 H, OCH_3), 5.54 (s, 2 H, CH_2), 6.87 (t, ^3J = 9.2 Hz, 1 H, H-4″), 6.94 (d, ^3J = 5.7 Hz, 2 H, H-2′, H-6′), 7.03 (d, ^3J = 9.2 Hz, 1 H, H-2″), 7.28 (d, ^3J = 9.2 Hz, 1 H, H-5″), 7.42 (d, ^3J = 5.7 Hz, 2 H, H-3′, H-5′), 7.55 (t, ^3J = 9.2 Hz, 1 H, H-3″), 8.29 (s, 1 H, H-4), 8.89 (s, 1 H, H-2), 11.40 (s, 1 H, OH), 13.43 (s, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.0 (CH_2), 55.1 (OCH_3), 114.1 (C-2′, C-6′), 117.5 (C-4″), 119.2 (C-6″), 121.4 (C-2″), 127.0 (C-5), 128.5 (C-4′), 129.3 (C-3′, C-5′), 131.4 (C-6), 132.4 (C-3″), 135.7 (C-5″), 135.9 (C-4), 141.6 (C-9), 146.2 (C-2), 149.3 (C-7), 158.9 (C-1′), 160.5 (C-1″), 166.3 (COOH), 199.2 (C=O).

MS (EI): *m*/*z* (%) = 403 (23) $[M]^+$, 385 (70), 370 (11), 358 (97), 342 (16), 121 (82), 91 (12), 77 (15).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{17}N_3O_5$: 404.1241; found: 404.1236.

3-(4-Chlorobenzyl)-6-(2-hydroxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10g)
Yield: 0.21 g (74%); colorless solid; mp 299–300 °C.

IR (ATR): 1705, 1622, 1605, 1489, 1383, 1242, 1195, 1143, 910, 774, 740, 726 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.63 (s, 2 H, CH_2), 6.88 (t, ^3J = 9.0 Hz, 1 H, H-4″), 7.03 (d, ^3J = 9.0 Hz, 1 H, H-2″), 7.30 (d, ^3J = 9.0 Hz, 1 H, H-5″), 7.46 (m, 4 H, H-3′, H-2′, H-5′, H-6′), 7.54 (t, ^3J = 9.0 Hz, 1 H, H-3″), 8.31 (s, 1 H, H-4), 8.92 (s, 1 H, H-2), 11.40 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.7 (CH_2), 117.4 (C-4″), 119.1 (C-6″), 121.3 (C-2″), 127.1 (C-5), 128.7 (C-2′, C-6′), 129.6 (C-3′, C-5′), 131.6 (C-6), 132.3 (C-3″), 132.6 (C-4′), 135.6 (C-5″), 135.7 (C-1′), 135.9 (C-4), 141.7 (C-9), 146.4 (C-2), 149.4 (C-7), 160.5 (C-1″), 166.2 (COOH), 199.1 (C=O).

MS (EI): *m*/*z* (%) = 389 (50), 360 (37), 250 (10), 207 (19), 125 (100), 99 (10), 89 (22), 63 (12).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{14}ClN_3O_4$: 408.0746; found: 408.0746.

6-(2-Hydroxybenzoyl)-3-(4-methoxyphenethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10h)
Yield: 0.21 g, 73%); colorless solid; mp 252–255 °C.

IR (ATR): 1626, 1610, 1512, 1453, 1361, 1294, 1242, 1184, 1145, 1032, 893, 759, 713, 609 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.21 (t, ^3J = 6.3 Hz, 2 H, CH_2), 3.72 (s, 3 H, OCH_3), 4.61 (t , ^3J = 6.3 Hz, 2 H, CH_2), 6.84 (d, ^3J = 5.8 Hz, 2 H, H-2′, H-6′), 6.90 (t, ^3J = 9.0 Hz, 1 H, H-4″), 7.03 (d, ^3J = 9.0 Hz, 1 H, H-2″), 7.10 (d, ^3J = 5.8 Hz, 2 H, H-3′, H-5′), 7.27 (d, ^3J = 9.0 Hz, 1 H, H-5″), 7.55 (t, ^3J = 9.0 Hz, 1 H, H-3″), 8.26 (s, 1 H, H-4), 8.57 (s, 1 H, H-2), 11.46 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.9 (CH_2), 44.9 (CH_2), 54.9 (OCH_3), 113.8 (C-2′, C-6′), 117.5 (C-4″), 119.1 (C-6″), 121.3 (C-2″), 126.8 (C-5), 129.6 (C-3′, C-5′), 129.6 (C-4′), 131.2 (C-6), 132.3 (C-3″), 135.7 (C-5″), 135.9 (C-4), 141.3 (C-9), 146.3 (C-2), 149.4 (C-7), 157.9 (C-1′), 160.5 (C-1″), 166.3 (COOH), 199.4 (C=O).

MS (GS): *m*/*z* (%) = 390 (27), 282 (20), 247 (52), 224 (10), 162 (82), 135 (95), 58 (14).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{19}N_3O_5$: 418.1397; found: 418.1399.

6-(2-Hydroxybenzoyl)-3-(2-methoxyphenethyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10i)
Yield: 0.24 g (81%); colorless solid; mp 240–241 °C.

IR (ATR): 1632, 1485, 1453, 1296, 1235, 1181, 1147, 1035, 752, 710 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.19 (t, ^3J = 6.4 Hz, 2 H, CH_2), 3.67 (s, 3 H, OCH_3), 4.59 (t, ^3J = 6.4 Hz, 2 H, CH_2), 6.77 (t, ^3J = 6.0 Hz, 1 H, H-4′), 6.92 (br m, 4 H, H-4″, H-2′, H-5′, H-2″), 7.18 (m, 2 H, H-3′, H-5″), 7.53 (t, ^3J = 9.1 Hz, 1 H, H-3″), 8.21 (s, 1 H, H-4), 8.46 (s, 1 H, H-2), 11.43 (s, 1 H, OH), 13.37 (s, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 30.1 (CH_2), 43.2 (CH_2), 55.5 (OCH_3), 110.6 (C-4′), 117.5 (C-4″), 119.1 (C-6″), 120.1 (C-6′), 121.3 (C-2″), 125.5 (C-2′), 126.6 (C-5), 128.1 (C-2′), 130.0 (C-3′), 131.0 (C-6), 132.2 (C-3″), 135.6 (C-5″), 135.9 (C-4), 141.3 (C-9), 146.5 (C-2), 149.3 (C-7), 157.2 (C-1′), 160.5 (C-1″), 166.4 (COOH), 199.4 (C=O).

MS (GS): *m*/*z* (%) = 417 (12) $[M]^+$, 357 (61), 324 (15), 296 (20), 221 (13), 135 (96), 105 (18), 44 (10).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{19}N_3O_5$: 418.1397; found: 418.1400.

6-(2-Hydroxybenzoyl)-3-phenethyl-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic Acid (10j)
Yield: 0.26 g (90%); colorless solid; mp 229–231 °C.

IR (ATR): 1625, 1483, 1454, 1360, 1290, 1254, 1184, 1145, 894, 701, 611 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.29 (t, ^3J = 6.3 Hz, 2 H, CH_2), 4.66 (t, ^3J = 6.3 Hz, 2 H, CH_2), 6.89 (t, ^3J = 8.6 Hz, 1 H, H-4′), 7.05 (d, ^3J = 8.6 Hz, 1 H, H-2′), 7.25 (br m, 6 H, PhH, H-5′), 7.55 (t, ^3J = 8.6 Hz, 1 H, H-3′), 8.26 (s, 1 H, H-4), 8.59 (s, 1 H, H-2), 11.45 (s, 1 H, OH), 13.38 (s, 1 H, COOH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 34.8 (CH_2), 44.5 (CH_2), 117.5 (C-4″), 119.1 (C-6″), 121.3 (C-2″), 126.5 (C-4′), 126.8 (C-5), 128.4

(C-2′, C-6′), 128.6 (C-3′, C-5′), 131.2 (C-6), 132.3 (C-3″), 135.7 (C-5″), 135.9 (C-4), 137.8 (C-1′), 141.3 (C-9), 146.3 (C-2), 149.3 (C-7), 160.5 (C-1″), 166.3 (COOH), 199.3 (C=O).

MS (GS): *m*/*z* (%) = 369 (44), 237 (10), 104 (100), 91 (12).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{17}N_3O_4$: 388.1292; found: 388.1298

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