RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2015, **5**, 35201

Metal free direct formation of various substituted pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amines and their further functionalization†

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Received 2nd March 2015
Accepted 8th April 2015

DOI: 10.1039/c5ra03703d

www.rsc.org/advances

Original substituted pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amines have been prepared following a Groebke–Blackburn–Bienaymé MCR combined with an N-deprotection and a spontaneous final cyclization step in moderate to good yields. The flexibility of the described method enables the introduction of diverse groups in the 6 and 7 positions on the resulting scaffold using commercially available starting materials. Furthermore, a Buchwald–Hartwig cross coupling with a wide range of aryl and hetaryl halides has been successfully reported using our heterocyclic primary amine derivatives.

Introduction

Nitrogen-fused polycyclic heterocyclic scaffolds, especially fused imidazo[1,2-*a*]heterocycles, are an important class of pharmacophores and exhibit a wide range of biological activities. Pyrido[1,2-*a*]imidazo[5,4-*b*]indoles (**I**) are potent anti-hypertensive agents,[1] pyrido[1,2-*e*]purines (**II**) are able to intercalate DNA and exhibit anti-cancer activity,[2] benzimidazo[2,1-*a*]-isoquinolines (**III**) are potent anti-tumor agent,[1b,3] and pyrido[2′,1′-2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones (**IV**) are described as potent PARP-1,[4] tubulin polymerization[5] and CDK[6] inhibitors (Fig. 1).

Furthermore, several drugs with an imidazo[1,2-*a*]pyridine scaffold provide already successful treatments such as zolpidem or alpidem, used against insomnia or anxiety respectively. This brief overview underlines the need of novel strategies to access straightforwardly original fused imidazo-pyridines to broaden the scope of candidates for biological tests. Recently, our interest focuses on the synthesis of substituted pyrido[2′,1′:2,3]-imidazo[4,5-*c*]isoquinolin-5-amines. This following scaffold has been scarcely described in the literature and was obtained in a low yield after a long synthetic sequence making tougher the possibility of introducing variation.[7] Based on our expertise in the synthesis of diverse polynitrogen containing heterocycles[8] and in the combination of multicomponent reactions (MCRs) with post modifications,[1c,9] we describe herein a Groebke–Blackburn–Bienaymé MCR reaction[10] introducing a cyano moiety, where after a N-deprotection step a nucleophilic cyclization can occur. This two-step metal free process gives access directly to original substituted pyrido[2′,1′:2,3]imidazo[4,5-*c*]-isoquinolin-5-amines from commercially available starting materials. The reactivity of the resulting aminated product will be next evaluated in standard Buchwald–Hartwig cross coupling[11] conditions to examine the scope of the modulation.

Results and discussion

The optimization of the MCR was initiated using the experimental conditions described by Maleki *et al.* with 2-aminopyridine and 2-formylbenzonitrile as model substrates using first trimethylsilyl cyanide as functional isonitrile equivalent (Table 1, entry 1).[12] Unfortunately, after 24 hours of heating at 80 °C, the unreacted starting materials were recovered. Using 1,4-dioxane to increase the reaction temperature with

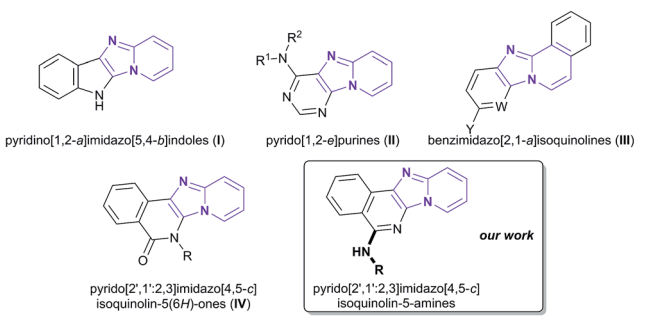

Fig. 1 Examples of fused imidazo-pyridines.

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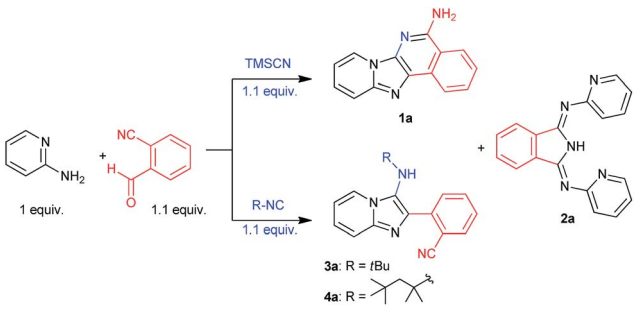
† Electronic supplementary information (ESI) available: Experimental procedures, spectral characterization, and copies of ^{1}H, ^{13}C, and ^{19}F spectra for all compounds. CCDC 1046891 and 1046892. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra03703d

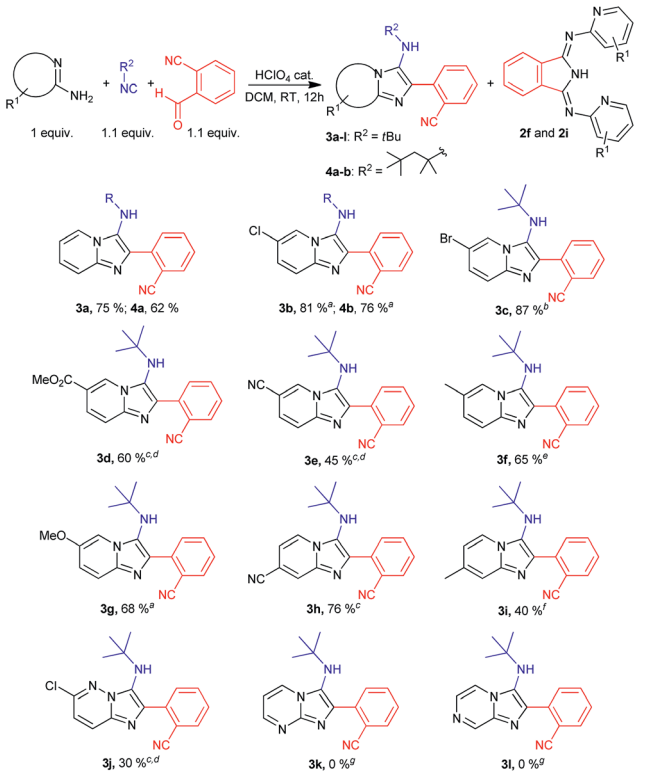
Table 1 Optimizing conditions



Entry	Reagent	Cat.[a]	Solvent	T (°C)	t (h)	Yield[b] x : 2a[c] (%)
1	TMSCN	—	MeCN	80	24	0 : 0[d]
2	TMSCN	—	1,4-Dioxane	120	24	0 : 0
3	TMSCN	—	1,4-Dioxane	140	10[e]	0 : 30
4	TMSCN	$HClO_4$	1,4-Dioxane	140	10[e]	0 : 38
5	—	$HClO_4$	1,4-Dioxane	140	10[e]	0 : 32
6	*t*BuNC	$HClO_4$	1,4-Dioxane	RT	4	60 : 6
7	*t*BuNC	$HClO_4$	THF	RT	4	58 : 7
8	*t*BuNC	$HClO_4$	MeCN	RT	4	40 : 25
9	*t*BuNC	$HClO_4$	MeOH	RT	4	10 : 25
10	*t*BuNC	$HClO_4$	PhMe	RT	12	68 : 7
11	*t*BuNC	$HClO_4$	DCM	RT	12	75 : 8
12	*t*BuNC	$HClO_4$	DCM	60	6	45 : 15
13	*t*BuNC	—	DCM	RT	24	0 : traces
14		$HClO_4$	DCM	RT	12	62 : traces

[a] Two or three drops of 70% solution in water (w/w). [b] Isolated yields. [c] x : **2a** referred to the isolated yields of **1a**, **3a** or **4a** along with **2a** depending on the cyanide or the isonitrile used for the reaction. [d] 2-Aminopyridine was recovered along with degradation. [e] Microwaves irradiation at 140 °C for 10 min.

Table 2 Scope of substrates



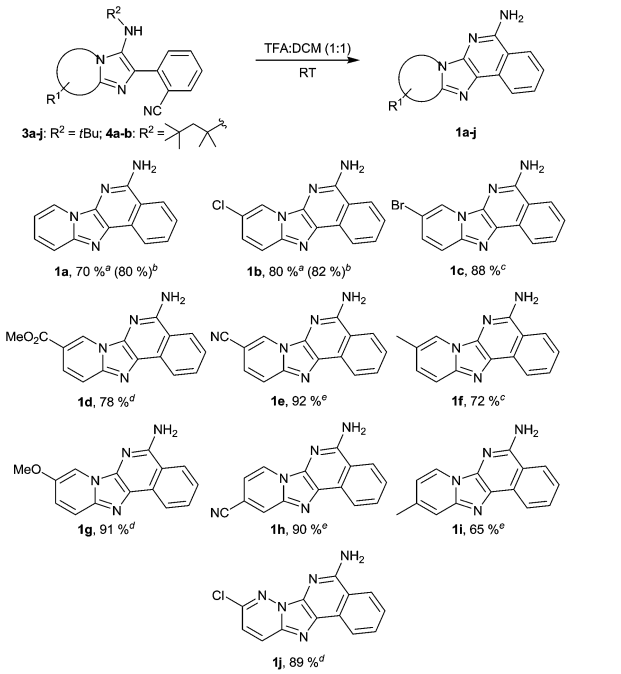
[a] Reaction time: 1 h. [b] Reaction time: 2 h. [c] Reaction time: 72 h. [d] The reaction was performed in a DCM/1,4-dioxane mixture and a small amount of 2-aminopyridine was recovered. [e] 10% of **2f** was isolated. [f] 25% of **2i** was isolated. [g] Degradation after 72 h of reaction.

conventional and microwave heating induced not significant change apart from the isolation of the compound **2a** as an undesired side product.[13] The formation of **2a** underlined the unsufficient reactivity of TMSCN toward the condensation between 2-aminopyridine and the cyano moiety. This lack of reactivity was confirmed when the reaction was carried out in the absence of TMSCN providing **2a** with same yield (entry 5). Facing this difficulty, we decided to perform the MCR with a conventional isonitrile, which can be removed in a second step generating a primary amine able to react with the cyano group. The optimization was then made with *tert*-butyl isocyanide. Several solvents were investigated and DCM appeared to give **3a** in the highest yield (75%) along with a minimum amount of **2a** when the reaction was performed at room temperature (entries 6–12). The need of a catalytic amount of acid to activate the reaction was next verified (entry 13). Since the removal of the *tert*-butyl group can be problematic, the more convertible 1,1,3,3-tetramethylbutyl isocyanide (Walborsky reagent)[14] was tried and **4a** was obtained in a moderate yield (entry 14). Hence the optimized reaction conditions were chosen as follows: 2-aminoheteroaryl (1 equiv.), 2-formylbenzonitrile (1.1 equiv.), *tert*-butyl isocyanide or 1,1,3,3-tetramethylbutyl isocyanide (1.1 equiv.) in DCM at room temperature.

In an endeavour to expand the scope of the methodology, the reactivity of various imidazoheterocycles was examined (Table 2). First various imidazo[1,2-*a*]pyridines substituted in positions 6, and 7 were synthetized with our optimized conditions. First, 1,1,3,3-tetramethylbutyl isocyanide was used with slightly less efficiency during the MCR but **4a** and **4b** were nevertheless obtained in good yields. We decided though to continue the scope of the reaction with the less expensive *tert*-butyl isocyanide. Electron donating groups (OMe, Me) along with weak electron withdrawing groups (Cl, Br) in position 6 provided the expected MCR product in moderate to good yields where moderate to strong electron withdrawing groups (CO_2Me and CN) required a significant longer reaction time to obtain **3d** and **3e** along with its respective unreacted 2-aminopyridine in 10% and 25% yield. Next, the same reactivity trend was observed with substituents in position 7. Fortunately, the product formed by the double condensation of the aminopyridine on 2-formylbenzonitrile was only observed with methyl substituents in position 4 and 5 (**2f** and **2i**) and always in a minor amount. Finally, 2-amino-pyridazine, -pyrimidine, and -pyrazine were tried and except for **3j** which was isolated in low yield, only degradation was observed.

With various MCR products in hand, the N-deprotection step was first tried with the conditions described by Guchhait *et al.*[15] In our case, a reaction between the solvent (*n*BuOH) and the

Table 3 Deprotection and cyclization



[a] Obtained from **3** after 12 h of reaction. [b] Obtained from **4** after 3 h of reaction. [c] Reaction time: 24 h. [d] Reaction time: 48 h. [e] Reaction time 72 h.

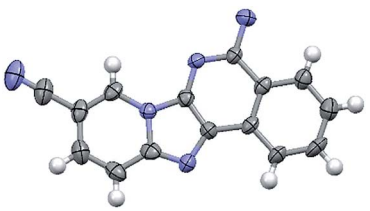
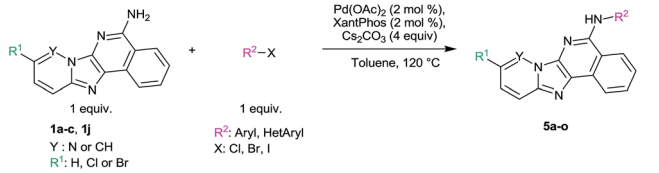


Fig. 2 ORTEP representation of **1e**. Thermal ellipsoids drawn at the 50% probability level.

cyano group was observed making us preferring the use of a 1/1 mixture of DCM/TFA at RT.[16] Under these acid conditions, the cyclisation takes place *via* an activation of the cyano group. The electrophilic carbon undergoes attack of the nitrogen and the concomitant N-deprotection allowed us to obtain desired aromatic product. Compound **1a** was then obtained from **3a** and **4a** in 70% and 80% yield respectively (Table 3).

The easier removal of 1,1,3,3-tetramethylbutyl group was confirmed by the reduced reaction time required to observe the completion of the reaction (4 hours *vs.* 12 hours). The same reactivity trend was noticed for **1b.** However the similar global yield for this two-step reaction starting from *tert*-butyl or 1,1,3,3-tetramethylbutyl isocyanide confirmed our choice to privileged the less expensive *tert*-butyl isocyanide. Our experimental conditions were next applied to our other imidazo[1,2-*a*]pyridines substituted in positions 6 and 7 and the corresponding pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amines **1c–i** were

Table 4 Buchwald–Hartwig cross coupling reaction



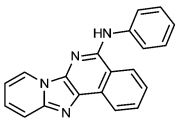
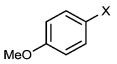
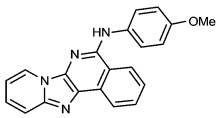
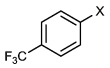
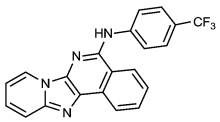
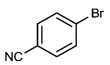
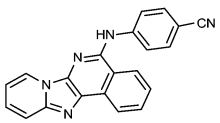
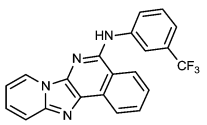
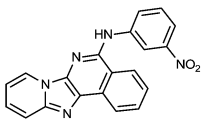
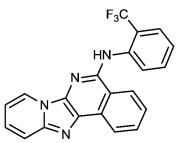
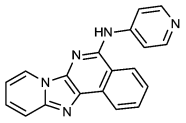
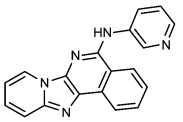
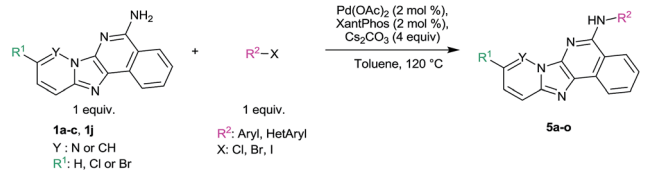
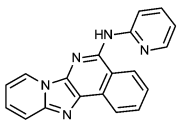
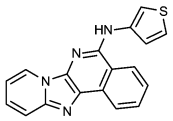
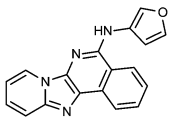
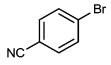
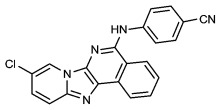
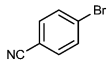
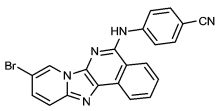
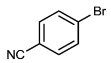
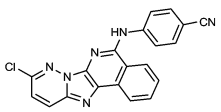
Entry	R^2–X	Product	Yield[a] (t)
1		 **5a**	83% (30)[b]
2		 **5b**	X = I, 65% (24)[b,c] X = Br, 60% (24)[b,c]
		 **5c**	X = I, 80% (1) X = Br, 75% (12) X = Cl, traces (48)[c]
3		 **5d**	90% (2)
4		 **5e**	85% (6)
5		 **5f**	66% (30)[d]
6		 **5g**	70% (24)
7		 **5h**	69% (12)
8		 **5i**	72% (12)

Table 4 (*Contd.*)



Entry	R^2–X	Product	Yield[a] (t)
9		 **5j**	70% (48)
10		 **5k**	0% (48)[c]
11		 **5l**	0% (48)[c]
12		 **5m**	74% (24)
13		 **5n**	72% (24)
14		 **5o**	68% (18)

[a] Reaction time in hours. [b] 1.5 equiv. of ArBr was used. [c] With $Pd(OAc)_2$ (10 mol%), Xantphos (10 mol%). [d] With $Pd(OAc)_2$ (5 mol%), Xantphos (5 mol%).

isolated in good to excellent yields. The presence of electron withdrawing groups in position 6 as well as any substitutions in position 7 tends to increase the reaction time up to 72 hours (**1e**, **1h** and **1i**). The structure of **1e** product was confirmed by a single-crystal X-ray study (Fig. 2). Finally, the imidazo[1,2-*b*]-pyridazine **3j** cleanly cyclized to form the original **1j** in 89% yield.

Then the reactivity of the resulted amino group was examined. The recent conditions described by Bogányi *et al.* was applied to our substrates.[17] Various aryl halides substituted in *para*, *meta* and *ortho* were successfully introduced in good to excellent yields (Table 4).

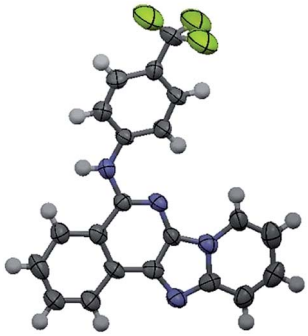


Fig. 3 ORTEP representation of **5c**. Thermal ellipsoids drawn at the 50% probability level.

Fortunately, the reaction can be performed either with aryl bromide or iodide (**5b**, **5c**). The loss of reactivity associated with the use of aryl bromide can be easily overcome by a longer reaction time. However no conversion was noticed with aryl chloride even after 48 hours (**5c**). The structure of **5c** was confirmed by a single-crystal X-ray study (Fig. 3).

Then we detected that the presence of electron-withdrawing groups generally facilitates the cross coupling reaction (**5c**, **5d** and **5e**), except for **5f** whose nitro group in *meta* position requires an additional amount of catalyst and exhibits a reduced reactivity, and **5g** where steric hindrance can explain the longer reaction time observed. Aryl halides with electron donating substituents such as OMe need 10 mol% of palladium and XantPhos to achieve good yields (**5b**). The difficulty to introduce π-electron rich aromatics is underlined when we tried to apply our experimental conditions to 3-bromothiophen and -furan where only traces of the expected products (**5k** and **5l**) were recovered. However reactivity was retrieved with π-electron deficient heteroaromatic rings. *Ortho*, *meta* or *para* halogenated pyridine is indeed cleanly cross-coupled in good yields (**5h**, **5i** and **5j**). Finally, compounds **5b**, **5c** and **5j** which have bromo and chloro moieties on their scaffold were submitted to the reaction condition with 4-bromobenzonitrile, no self-cross coupling was observed and the desired products were obtained in good yield.

Conclusions

In summary, we have developed an efficient method to obtain straightforwardly various pyrido[2′,1′:2,3]imidazo[4,5-*c*]-isoquinolin-5-amines by a two-step metal free process from commercially available starting materials. First a Groebke–Blackburn–Bienaymé MCR gave access to original imidazo[1,2-*a*]pyridines which were submitted to acidic conditions to induce a N-deprotection and a spontaneous cyclization of the amine on the cyano group previously introduced. Finally, known Buchwald–Hartwig conditions were successfully applied on the resulted primary amine widening the scope of substrates synthetized.

Experimental section

General information

The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60 (230–400.13 mesh, 0.040–0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. The infrared spectra of compounds were recorded on a Thermo Scientific Nicolet iS10 are given in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 250 (^{13}C, 62.9 MHz), Bruker avance II 250.13 (^{13}C, 63 MHz), Bruker avance 400.13 (^{13}C, 101 MHz), or on a Bruker avance III HD nanobay 400.13 (^{13}C, 101 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) as internal standard. Coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were performed on a Maxis Bruker 4G.

General Groebke–Blackburn–Bienaymé MCR procedure (3, 4)

To a solution of amine (1.06 mmol, 1 equiv.) in 1 ml dichloromethane, 2-cyanobenzaldehyde (1.16 mmol, 1.1 equiv.) and perchloric acid (2–3 drops, 70% in water) were added and left at room temperature for 1 hour, then isonitrile (1.16 mmol, 1.1 equiv.) was introduced. After completion of the reaction (controlled by TLC), the mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography on silica gel to provide the expected product.

2-(3-*tert*-Butylamino-imidazo[1,2-*a*]pyridin-2-yl)benzonitrile (3a). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-aminopyridine (100 mg, 1.06 mmol). (EA : PE : DCM: 1 : 7 : 2). Yellow solid (230 mg, 75%); mp 134–135 °C; IR (neat, cm^{-1}): 702, 1219, 1363, 1502, 2221 (CN), 2968; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 0.94 (s, 9H), 3.32 (s, 1H), 6.83 (t, $J = 6.8$ Hz, 1H), 7.21 (t, $J = 6.8$ Hz, 1H), 7.46 (t, $J = 7.9$ Hz, 1H), 7.55 (d, $J = 6.8$ Hz, 1H), 7.71 (t, $J = 7.9$ Hz, 1H), 7.75 (d, $J = 7.9$ Hz, 1H), 7.95 (d, $J = 7.9$ Hz, 1H), 8.35 (d, $J = 6.8$ Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 30.1 (3C), 55.7, 111.6, 111.8, 117.6, 120.1, 124.1, 125.1, 125.2, 128.0, 131.7, 133.0, 133.1, 137.5, 140.1, 142.7; HRMS (ESI) $[M + H]^+$ calcd for $C_{18}H_{19}N_4$: 291.1604, found: 291.1602.

1,3-Bis(2-pyridylimino)isoindole (BPI) (2a).[13] Yellow solid (25 mg, 8%); mp 179–180 °C (lit mp 181–183 °C); IR (neat, cm^{-1}): 686, 783, 1032, 1097, 1140, 1216, 1427, 1576, 1622, 3039, 3196; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 7.11 (ddd, $J = 7.4$, 4.9, 1.2 Hz, 2H), 7.45 (d, $J = 7.4$, 1.2 Hz, 2H), 7.61–7.67 (m, 2H), 7.76 (td, $J = 7.4$, 1.2 Hz, 2H), 8.05–8.09 (m, 2H), 8.61 (dd, $J = 4.9$, 1.2 Hz, 2H), 13.98 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 120.3 (2C), 122.7 (2C), 123.3 (2C), 131.8 (2C), 135.9 (2C), 138.2 (2C), 147.9 (2C), 153.8 (2C), 160.6 (2C); HRMS (ESI) $[M + H]^+$ calcd for $C_{18}H_{14}N_5$: 300.1244, found: 300.1245.

2-(3-(*tert*-Butylamino)-6-chloro-imidazo[1,2-*a*]pyridin-2-yl) benzonitrile (3b). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-amino-5-chloropyridine (136 mg, 1.06 mmol). (EA : PE : DCM: 2 : 6 : 2). Yellow solid (278 mg, 81%); mp 154–155 °C; IR (neat, cm^{-1}): 727, 907, 1322, 1498, 2221 (CN), 2968; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 0.94 (s, 9H), 3.34 (s, 1H), 7.17 (dd, $J = 9.5$, 2.1 Hz, 1H), 7.48 (td, $J = 7.8$, 1.3 Hz, 1H), 7.49 (d, $J = 9.5$ Hz, 1H), 7.72 (td, $J = 7.8$, 1.3 Hz, 1H), 7.75 (dd, $J = 7.8$, 1.3 Hz, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 8.37 (d, $J = 2.1$, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 30.1 (3C), 55.9, 111.6, 118.1, 120.0, 120.5, 122.0, 125.5, 126.7, 128.3, 131.6, 133.0, 133.2, 138.5, 139.5, 141.0; HRMS (ESI) $[M + H]^+$ calcd for $C_{18}H_{18}ClN_4$: 325.1215, found 325.1213.

2-(6-Bromo-3-(*tert*-butylamino)imidazo[1,2-*a*]pyridin-2-yl) benzonitrile (3c). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-amino-5-bromopyridine (183 mg, 1.06 mmol). (DCM : PE: 9 : 1). Beige solid (342 mg, 87%); mp 132–133 °C; IR (neat, cm^{-1}): 777, 848, 1215, 1322, 1496, 1600, 2221 (CN), 2954; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 0.94 (s, 9H), 3.33 (s, 1H), 7.27 (dd, $J = 9.4$ Hz, 2.1, 1H), 7.45 (d, $J = 9.4$ Hz, 1H), 7.49 (dd, $J = 7.9$, 1.2 Hz, 1H), 7.72 (td, $J = 7.9$, 1.2 Hz, 1H), 7.75 (d, $J = 7.9$ Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 1H), 8.47 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (101 MHz $CDCl_3$): δ 30.1 (3C), 55.9, 107.0, 111.6, 118.4, 120.0, 124.3, 125.4, 128.3, 128.7, 131.6, 133.0, 133.2, 138.3, 139.5, 141.1; HRMS (ESI) $[M + H]^+$ calcd for $C_{18}H_{18}BrN_4$: 369.0709 [^{79}Br], 371.0691 [^{81}Br], found: 369.0706 [^{79}Br], 371.0687 [^{81}Br].

Methyl 3-(*tert*-butylamino)-2-(2-cyanophenyl)imidazo[1,2-*a*]-pyridine-6-carboxylate (3d). Following the general Groebke–Blackburn–Bienaymé MCR procedure with methyl 6-aminopyridine-3-carboxylate (161 mg, 1.06 mmol). (EA : PE: 3 : 7). Yellow solid (221 mg, 60%); mp 120–121 °C; IR (neat, cm^{-1}): 759, 1125, 1293, 1415, 1716, 2227 (CN), 2948; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 0.96 (s, 9H), 3.40 (s, 1H), 3.98 (s, 3H), 7.50 (t, $J = 7.8$ Hz, 1H), 7.55 (d, $J = 9.4$ Hz, 1H), 7.73 (t, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 2H), 7.95 (d, $J = 7.8$ Hz, 1H), 9.10 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 30.1 (3C), 52.6, 55.9, 111.6, 116.1, 117.0, 119.9, 124.8, 126.2, 128.4, 128.4, 131.6, 133.1, 133.2, 139.0, 139.3, 143.1, 165.7; HRMS (ESI) $[M + H]^+$calcd for $C_{20}H_{21}N_4O_2$: 349.1659, found 349.1656.

3-(*tert*-Butylamino)-2-(2-cyanophenyl)imidazo[1,2-*a*]pyridine-6-carbonitrile (3e). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-amino-5-cyanopyridine (126 mg, 1.06 mmol). (EA : PE: 3 : 7). Beige solid (153 mg, 46%); mp 191–192 °C; IR (neat, cm^{-1}): 770, 1206, 1318, 1414, 1624, 2231 (CN), 2969, 3238; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 0.95 (s, 9H), 3.42 (s, 1H), 7.31 (d, $J = 9.2$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H), 7.62 (d, $J = 9.2$ Hz, 1H), 7.75 (t, $J = 7.9$ Hz, 1H), 7.78 (d, $J = 7.9$ Hz, 1H), 7.93 (d, $J = 7.9$ Hz, 1H), 8.79 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 30.1 (3C), 56.1, 98.3, 111.6, 117.0, 118.7, 119.8, 124.9, 126.3, 129.8, 130.6, 131.6, 133.1, 133.4, 138.7, 139.6, 141.6; HRMS (ESI) $[M + H]^+$: calcd for $C_{19}H_{18}N_5$: 316.1557, found: 316.1555.

2-(3-(*tert*-Butylamino)-6-methylimidazo[1,2-*a*]pyridin-2-yl) benzonitrile (3f). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-amino-5-methylpyridine (114 mg, 1.06 mmol). (EA : PE: 3 : 7). Beige solid (209 mg, 65%); mp 131–132 °C; IR (neat, cm^{-1}): 644, 727, 909, 1208, 1388, 1598, 1718, 2220 (CN), 2968; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 0.94 (s, 9H), 2.36 (s, 3H), 3.29 (s, 1H), 7.06 (d, $J = 9.1$ Hz, 1H), 7.45 (t, $J = 7.9$ Hz, 1H), 7.46 (d, $J = 9.1$ Hz, 1H), 7.68 (t, $J = 7.9$ Hz, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.94 (d, $J = 7.9$ Hz, 1H), 8.11 (s, 1H); ^{13}C NMR

(101 MHz, $CDCl_3$): δ 18.6, 30.1 (3C), 55.7, 111.5, 116.9, 120.2, 121.5, 121.7, 124.8, 127.9, 128.4, 131.6, 132.9, 133.1, 137.3, 140.2, 141.9; HRMS (ESI) $[M + H]^+$: calcd for $C_{19}H_{21}N_4$: 305.1761, found: 305.1758.

1,3-Bis(5-methyl-2-pyridylimino)isoindole (2f).[13] Yellow solid (35 mg, 10%); mp 213–215 °C (lit mp 215–216 °C); IR (neat, cm^{-1}): 654, 755, 810, 834, 1035, 1186, 1239, 1305, 1464, 1586, 1639, 3303; ^1H NMR (250.13 MHz, $CDCl_3$): δ 2.39 (s, 6H), 6.94 (d, $J = 5.2$ Hz, 2H), 7.29 (s, 2H), 7.60–7.67 (m, 2H), 8.03–8.09 (m, 2H), 8.46 (d, $J = 5.2$ Hz, 2H), 13.98 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.1 (2C), 121.5 (2C), 122.6 (2C), 123.8 (2C), 131.7 (2C), 136.0 (2C), 147.6 (2C), 149.3 (2C), 153.8 (2C), 160.6 (2C); HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{18}N_5$: 328.1557, found: 328.1556.

2-(3-(*tert*-Butylamino)-6-methoxyimidazo[1,2-*a*]pyridin-2-yl)-benzonitrile (3g). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-amino-5-methoxypyridine (131 mg, 1.06 mmol). (EA : PE: 3 : 7). Beige solid (230 mg, 68%); mp 133–135 °C; IR (neat, cm^{-1}): 707, 803, 1025, 1109, 1161, 1256, 1515, 1644, 2216 (CN), 2970, 3331; ^1H NMR (400.13 MHz, $CDCl_3$): δ 0.95 (s, 9H), 3.34 (s, 1H), 3.87 (s, 3H), 7.00 (d, $J = 9.6$ Hz, 1H), 7.42–7.46 (m, 2H), 7.69 (t, $J = 7.9$ Hz, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.87 (s, 1H), 7.93 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 30.1 (3C), 55.9, 56.2, 105.6, 111.4, 117.8, 120.2, 120.6, 125.8, 127.8, 131.5, 132.9, 133.1, 137.7, 139.9, 140.2, 149.0; HRMS (ESI) $[M + H]^+$: calcd for $C_{19}H_{21}N_4O$: 321.1710, found: 321.1711.

2-(3-(*tert*-Butylamino)-7-isocyanoimidazo[1,2-*a*]pyridin-2-yl) benzonitrile (3h). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-amino-4-cyanopyridine (126 mg, 1.06 mmol). (EA : PE : DCM: 2 : 7 : 1). Yellow light solid (254 mg, 76%); mp 220–221 °C; IR (neat, cm^{-1}): 636, 667, 792, 905, 1109, 1196, 1352, 1549, 2224 (CN), 2968, 3291; ^1H NMR (400.13 MHz, $CDCl_3$): δ 0.94 (s, 9H), 3.41 (s, 1H), 6.98 (d, $J = 7.1$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H), 7.75 (t, $J = 7.9$ Hz, 1H), 7.79 (d, $J = 7.9$ Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 1H), 7.96 (s, 1H), 8.43 (d, $J = 7.1$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 30.1 (3C), 56.3, 107.8, 111.6, 112.1, 117.9, 119.8, 124.0, 125.0, 127.3, 128.8, 131.6, 133.2, 133.4, 138.8, 140.3, 140.8; HRMS (ESI) $[M + H]^+$: calcd for $C_{19}H_{18}N_5$: 316.1557, found: 316.1558.

2-(3-(*tert*-Butylamino)-7-methylimidazo[1,2-*a*]pyridin-2-yl) benzonitrile (3i). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-amino-4-methylpyridine (114 mg, 1.06 mmol). (EA : PE : DCM: 2 : 6 : 2). Colorless oil (128 mg, 40%); IR (neat, cm^{-1}): 646, 729, 911, 1210, 1388, 1598, 1718, 2222 (CN), 2970; ^1H NMR (400.13 MHz, $CDCl_3$): δ 0.92 (s, 9H), 2.41 (s, 3H), 3.28 (s, 1H), 6.66 (d, $J = 7.1$ Hz, 1H), 7.29 (s, 1H), 7.44 (t, $J = 7.9$ Hz, 1H), 7.70 (t, $J = 7.9$ Hz, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.94 (d, $J = 7.9$ Hz, 1H), 8.21 (d, $J = 7.1$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.5, 30.1 (3C), 55.7, 111.5, 114.5, 115.9, 120.2, 123.4, 124.7, 127.8, 131.6, 132.9, 133.1, 136.1, 137.1, 140.3, 143.2; HRMS (ESI) $[M + H]^+$: calcd for $C_{19}H_{21}N_4$: 305.1761, found: 305.1758.

1,3-Bis(4-methyl-2-pyridylimino)isoindole (2i).[13] Yellow solid (86 mg, 25%); mp 163–165 °C (lit mp 165–166 °C); IR (neat, cm^{-1}): 654, 692, 755, 769, 835, 1117, 1219, 1407, 1587, 2918, 3210; ^1H NMR (250 MHz, $CDCl_3$): δ 2.39 (s, 6H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.58 (dd, $J = 8.2, 2.4$ Hz, 2H), 7.59–7.66 (m, 2H), 8.02–8.10 (m, 2H), 8.45 (d, $J = 2.4$ Hz, 2H), 13.95 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 18.3 (2C), 122.5 (2C), 122.7 (2C), 129.8 (2C), 131.5 (2C), 136.0 (2C), 138.8 (2C), 148.0 (2C), 153.3 (2C), 158.4 (2C); HRMS (ESI) $[M + H]^+$ calcd for $C_{20}H_{18}N_5$: 328.1557, found: 328.1556.

2-(3-(*tert*-Butylamino)-6-chloroimidazo[1,2-*b*]pyridazin-2-yl) benzonitrile (3j). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 6-chloropyridazin-3-amine (137 mg, 1.06 mmol). (acetone : PE: 1 : 9). Yellow solid (103 mg, 30%); mp 170–171 °C; IR (neat, cm^{-1}): 713, 801, 1092, 1192, 1296, 1519, 2221 (CN), 2973, 3099, 3296; ^1H NMR (400.13 MHz, $CDCl_3$): δ 1.01 (s, 9H), 3.53 (s, 1H), 7.02 (d, $J = 9.3$ Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 1H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.79 (d, $J = 7.8$ Hz, 1H), 7.87 (d, $J = 9.3$ Hz, 1H), 7.98 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 30.3 (3C), 57.0, 112.3, 118.4, 119.0, 127.4, 128.3, 130.2, 131.0, 132.5, 134.0, 134.5, 136.9, 138.5, 147.1; HRMS (ESI) $[M + H]^+$: calcd for $C_{17}H_{17}ClN_5$: 326.1167, found: 326.1166.

2-(3-(1,1,3,3-Tetramethylbutylamino)imidazo[1,2-*a*]pyridin-2-yl)benzonitrile (4a). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-aminopyridine (100 mg, 1.06 mmol), and 1,1,3,3-tetramethylbutyl isocyanide (1.16 mmol, 1.1 equiv.). (EA : PE : DCM: 1 : 7 : 2). Brown viscous oil (229 mg, 62%); IR (neat, cm^{-1}): 729, 756, 1221, 1383, 2220 (CN), 2952; ^1H NMR (400.13 MHz, $CDCl_3$): δ 0.88 (s, 1H, 6H), 0.98 (s, 9H), 1.47 (s, 2H), 3.42 (s, 1H), 6.89 (t, $J = 6.9$ Hz, 1H), 7.27 (t, $J = 6.9$ Hz, 1H), 7.49 (t, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 6.9$ Hz, 1H), 7.73 (t, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.95 (d, $J = 7.8$ Hz, 1H), 8.39 (d, $J = 6.9$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.8 (2C), 31.6, 31.9 (3C), 56.9, 60.0, 111.8, 112.4, 117.2, 119.9, 124.3, 125.1, 126.1, 128.4, 131.7, 133.0, 133.3, 136.6, 139.2, 142.2; HRMS (ESI) $[M + H]^+$ calcd for $C_{22}H_{27}N_4$: 347.2230, found 347.2234.

2-(6-Chloro-3-(1,1,3,3-tetramethylbutylamino)imidazo[1,2-*a*]-pyridin-2-yl)benzonitrile (4b). Following the general Groebke–Blackburn–Bienaymé MCR procedure with 2-amino-5-chloropyridine (136 mg, 1.06 mmol), and 1,1,3,3-tetramethylbutyl isocyanide (1.16 mmol, 1.1 equiv.). (EA : PE: 3 : 7). Beige solid (307 mg, 76%); mp 126–127 °C; IR (neat, cm^{-1}): 731, 910, 1217, 1320, 1320, 2220 (CN), 2963; ^1H NMR (400.13 MHz, $CDCl_3$): δ 0.88 (s, 6H), 0.97 (s, 9H), 1.47 (s, 2H), 3.42 (s, 1H), 7.17 (dd, $J = 9.5, 2.0$ Hz, 1H), 7.48 (td, $J = 7.9, 1.3$ Hz, 1H), 7.50 (d, $J = 9.5$ Hz, 1H), 7.72 (td, $J = 7.9, 1.3$ Hz, 1H), 7.76 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.90 (dd, $J = 7.9, 1.3$ Hz, 1H), 8.37 (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.8 (2C), 31.6, 31.9 (3C), 56.9, 60.0, 111.8, 118.1, 119.9, 120.5, 122.1, 125.5, 126.6, 128.3, 131.6, 132.9, 133.2, 138.7, 139.8, 141.0; HRMS (ESI) $[M + H]^+$ calcd for $C_{22}H_{26}ClN_4$ 381.1841, found 381.1838.

General N-deprotection-cyclization procedure (1)

To a solution of **3** or **4** (0.49 mmol, 1 equiv.) in dichloromethane (5 ml), TFA (5 ml) was added. After completion of the reaction (controlled by TLC), the mixture was concentrated and the residue was dissolved in water. The pH solution was adjusted at 8 and the resulting precipitate was collected by filtration,

washed with water and dried. The crude product was purified by crystallization with Et_2O.

Pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (1a).[7b] Following the general N-deprotection-cyclization procedure with **4a** (170 mg, 0.49 mmol). Yellow solid (91 mg, 80%); mp 253–255 °C (lit 254–256 °C); IR (neat, cm^{-1}): 628, 929, 1279, 1279, 1505, 1623, 3120, 3450; ^1H NMR (400.13 MHz, $CDCl_3$): δ 5.26 (s, 2H), 6.87 (t, J = 6.8 Hz, 1H), 7.30 (t, J = 6.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.71 (d, J = 6.8 Hz, 1H), 7.83 (t, J = 7.8 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 8.58 (d, J = 6.8 Hz, 1H), 8.68 (d, J = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.0, 118.0, 118.4, 123.0, 123.3, 124.0, 125.9, 126.4, 127.4, 131.0, 131.5, 134.1, 144.5, 152.5; HRMS (ESI) $[M + H]^+$: calcd for $C_{14}H_{11}N_4$: 235.0978, found: 235.0984.

9-Chloropyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (1b). Following the general N-deprotection-cyclization procedure with **4b** (187 mg, 0.49 mmol). Yellow solid (108 mg, 82%); mp 278–279 °C; IR (neat, cm^{-1}): 765, 1084, 1273, 1324, 1427, 1625, 3177, 3300, 3444; ^1H NMR (400.13 MHz, DMSO-d_6): δ 7.20 (s, 2H), 7.35 (dd, J = 9.6, 2.1 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 7.71 (d, J = 9.6 Hz, 1H), 7.86 (t, J = 7.7 Hz, 1H), 8.43 (dd, J = 7.7, 3.1 Hz, 2H), 8.57 (d, J = 2.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 118.0, 118.4, 118.4, 120.6, 120.6, 121.7, 125.6, 125.7, 126.1, 130.8, 130.9, 134.4, 140.8, 154.6; HRMS (ESI) $[M + H]^+$: calcd for $C_{14}H_{10}ClN_4$: 269.0589, found: 269.0587.

9-Bromopyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (1c). Following the general N-deprotection-cyclization procedure with **3c** (181 mg, 0.49 mmol). Yellow solid (135 mg, 88%); mp 285–286 °C; IR (neat, cm^{-1}): 777, 943, 1319, 1494, 1621, 3195, 3323, 3400; ^1H NMR (400.13 MHz, DMSO-d_6): δ 7.20 (s, 2H), 7.40 (d, J = 9.5 Hz, 1H), 7.58–7.67 (m, 2H), 7.85 (t, J = 7.7 Hz, 1H), 8.42 (dd, J = 7.7, 3.1 Hz, 2H), 8.61 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 104.8, 118.5, 118.6, 121.8, 122.7, 125.5, 125.6, 125.7, 128.1, 130.7, 130.8, 134.2, 141.0, 154.6; HRMS (ESI) $[M + H]^+$: calcd for $C_{14}H_{10}BrN_4$: 313.0083 [^{79}Br], 315.0064 [^{81}Br], found: 313.0080 [^{79}Br], 315.0062 [^{81}Br].

Methyl 5-aminopyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carboxylate (1d). Following the general N-deprotection-cyclization procedure with **3d** (171 mg, 0.49 mmol). Yellow solid (112 mg, 78%); mp 296–297 °C; IR (neat, cm^{-1}): 760, 1099, 1275, 1418, 1643, 1716, 3184, 3315; ^1H NMR (400.13 MHz, DMSO-d_6): δ 3.93 (s, 3H), 7.31 (s, 2H), 7.58–7.75 (m, 3H), 7.87 (t, J = 7.8 Hz, 1H), 8.43 (d, J = 7.8 Hz, 2H), 9.12 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 52.4, 114.0, 117.0, 118.5, 121.8, 123.8, 125.6, 125.8, 125.9, 126.9, 130.7, 131.0, 134.8, 142.4, 154.9, 164.9; HRMS (ESI) $[M + H]^+$: calcd for $C_{16}H_{13}N_4O_2$: 293.1033, found: 293.1030.

5-Aminopyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-9-carbonitrile (1e). Following the general N-deprotection-cyclization procedure with **3e** (154 mg, 0.49 mmol). Yellow solid (117 mg, 92%); mp 318–319 °C; IR (neat, cm^{-1}): 765, 1141, 1258, 1326, 1419, 1520, 1623, 2221 (CN), 3327, 3456; ^1H NMR (400.13 MHz, DMSO-d_6): δ 7.30 (s, 2H), 7.51 (dd, J = 9.5, 1.6 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.78 (d, J = 9.5 Hz, 1H), 7.88 (t, J = 7.7 Hz, 1H), 8.45 (t, J = 7.7 Hz, 2H), 9.17 (d, J = 1.6 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 95.8, 117.4, 118.2, 118.6, 121.8, 124.6, 125.7, 125.9, 126.1, 130.6, 130.7, 131.1, 134.7, 141.3, 155.1; HRMS (ESI) $[M + H]^+$: calcd for $C_{15}H_{10}N_5$: 260.0931, found: 260.0928.

9-Methylpyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (1f). Following the general N-deprotection-cyclization procedure with **3f** (149 mg, 0.49 mmol). Yellow solid (87.6 mg, 72%); mp 247–248 °C; IR (neat, cm^{-1}): 787, 1026, 1324, 1416, 1508, 1624, 2920, 3176, 3330; ^1H NMR (400.13 MHz, DMSO-d_6): δ 2.37 (s, 3H), 7.03 (s, 2H), 7.20 (d, J = 9.4 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.58 (d, J = 9.4 Hz, 1H), 7.83 (t, J = 7.7 Hz, 1H), 8.33 (s, 1H), 8.41 (d, J = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 17.7, 116.8, 118.1, 120.1, 120.2, 121.6, 125.1, 125.1, 125.5, 128.8, 130.5, 130.9, 134.1, 142.0, 154.0; HRMS (ESI) $[M + H]^+$: calcd for $C_{15}H_{13}N_4$: 249.1135, found: 249.1132.

9-Methoxypyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (1g). Following the general N-deprotection-cyclization procedure with **3g** (157 mg, 0.49 mmol). Yellow-green solid (118 mg, 91%); mp 236–237 °C; IR (neat, cm^{-1}): 622, 793, 1242, 1322, 1429, 1512, 1623, 3151, 3300; ^1H NMR (400.13 MHz, DMSO-d_6): δ 3.88 (s, 3H), 7.09 (s, 2H), 7.13 (d, J = 9.4 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.60 (d, J = 9.4 Hz, 1H), 7.83 (t, J = 7.7 Hz, 1H), 8.00 (s, 1H), 8.40 (d, J = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 55.9, 103.5, 117.9, 118.0, 120.9, 121.5, 125.1, 125.5, 125.6, 130.6, 131.1, 135.0, 140.2, 147.7, 154.0; HRMS (ESI) $[M + H]^+$: calcd for $C_{15}H_{13}N_4O$: 265.1084, found: 265.1083.

5-Aminopyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-10-carbonitrile (1h). Following the general N-deprotection-cyclization procedure with **3h** (154 mg, 0.49 mmol). Yellow-orange solid (114 mg, 90%); mp 340–341 °C; IR (neat, cm^{-1}): 658, 765, 1306, 1437, 1557, 1570, 1647, 2224 (CN), 3318, 3444; ^1H NMR (400.13 MHz, DMSO-d_6): δ 7.17 (d, J = 7.1 Hz, 1H), 7.46 (s, 2H), 7.67 (t, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 8.38 (s, 1H), 8.46 (d, J = 7.7 Hz, 2H), 8.58 (d, J = 7.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 105.7, 110.7, 118.4, 118.9, 122.0, 123.8, 124.3, 125.7, 126.5, 127.5, 130.5, 131.2, 135.0, 140.1, 155.7; HRMS (ESI) $[M + H]^+$: calcd for $C_{15}H_{10}N_5$: 260.0931, found: 260.0931.

10-Methylpyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (1i). Following the general N-deprotection-cyclization procedure with **3i** (149 mg, 0.49 mmol). Yellow solid (79 mg, 65%); mp 237–238 °C; IR (neat, cm^{-1}): 761, 850, 1161, 1306, 1370, 1460, 1627, 3194, 3319; ^1H NMR (400.13 MHz, DMSO-d_6): δ 2.42 (s, 3H), 6.82 (d, J = 6.9 Hz, 1H), 7.02 (s, 2H), 7.42 (s, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.82 (t, J = 7.7 Hz, 1H), 8.39 (d, J = 7.7 Hz, 2H), 8.44 (d, J = 6.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 21.2, 113.7, 115.3, 117.9, 121.6, 122.3, 124.6, 125.0, 125.5, 130.4, 130.8, 134.2, 136.4, 143.2, 153.7; HRMS (ESI) $[M + H]^+$: calcd for $C_{15}H_{13}N_4$: 249.1135, found: 249.1132.

9-Chloropyridazino[6′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (1j). Following the general N-deprotection-cyclization procedure with **3j** (159 mg, 0.49 mmol). Yellow orange solid (100 mg, 89%); mp 299–300 °C; IR (neat, cm^{-1}): 708, 799, 1086, 1099, 1250, 1305, 1423, 1480, 1507, 3024, 3106, 3281; ^1H NMR (400.13 MHz, DMSO-d_6): δ 7.33 (d, J = 9.5 Hz, 1H), 7.47 (s, 2H), 7.67 (t, J = 7.7 Hz, 1H), 7.89 (t, J = 7.7 Hz, 1H), 8.24 (d, J = 9.5 Hz, 1H), 8.45 (t, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 118.6, 118.8, 121.6, 125.6, 126.1, 126.4, 127.9, 130.7, 131.2, 135.8, 135.8, 145.3, 156.0; HRMS (ESI) $[M + H]^+$: calcd for $C_{13}H_9ClN_5$: 270.0541, found: 270.0540.

General Buchwald–Hartwig cross-coupling procedure (5)

Under argon atmosphere, $Pd(OAc)_2$ (2 mg, 0.0085 mmol, 0.02 equiv.), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) (5 mg, 0.0085 mmol, 0.02 equiv.) were introduced in a round-bottomed flask and diluted in dry toluene (1 ml) and left at room temperature for 1 hour. Meanwhile, in a two-necked round-bottomed flask, aryl halide (0.426 mmol, 1.00 equiv.), **1** (100 mg, 0.426 mmol, 1.00 equiv.) and Cs_2CO_3 (558 mg, 1.70 mmol, 4.00 equiv.) were introduced in dry toluene (5 ml). To this suspension, the previously preformed Pd-catalyst was added. The resulting mixture was flushed with argon and heated at 120 °C. After completion of the reaction (controlled by TLC), toluene was removed under reduced pressure, water (10 ml) was added and the resulted aqueous phase was extracted with ethyl acetate. The combined organic layer were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

***N*-Phenylpyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (5a).**[7a] Following the general Buchwald–Hartwig cross-coupling procedure with iodobenzene (48 μL, 0.426 mmol). (DCM : EA: 7 : 3). Yellow solid (110 mg, 83%); mp 213–214 °C (lit 212–214 °C); IR (neat, cm^{-1}): 661, 764, 1241, 1315, 1344, 1421, 1495, 1544, 1598, 3048, 3324; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.90 (t, $J = 6.8$ Hz, 1H), 7.11 (t, $J = 7.5$ Hz, 1H), 7.31–7.38 (m, 2H), 7.43 (t, $J = 7.5$ Hz, 2H), 7.63 (t, $J = 7.9$ Hz, 1H), 7.72 (d, $J = 6.8$ Hz, 1H), 7.83–7.86 (m, 3H), 8.09 (d, $J = 7.9$ Hz, 1H), 8.63 (d, $J = 6.8$ Hz, 1H), 8.72 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.2, 117.9, 119.4, 119.7 (2C), 122.7, 122.8, 123.3, 123.6, 126.3, 126.8, 127.6, 129.1 (2C), 130.7, 131.7, 133.7, 140.7, 144.9, 147.9; HRMS (*m*/*z*) $[M + H]^+$: calcd for $C_{20}H_{15}N_4$: 311.1291, found: 311.1289.

***N*-(4-Methoxyphenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (5b).** Following the general Buchwald–Hartwig cross-coupling procedure with 4-iodoanisole (100 mg, 0.426 mmol). (DCM : EA: 9 : 1). Olive oil (95 mg, 65%); IR (neat, cm^{-1}): 745, 1032, 1228, 1409, 1504, 1707, 2929, 3342; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.86 (t, $J = 6.8$ Hz, 1H), 6.97 (d, $J = 8.9$ Hz, 2H), 7.33–7.25 (m, 2H), 7.59 (t, $J = 7.7$ Hz, 1H), 7.70 (d, $J = 6.8$ Hz, 1H), 7.72 (d, $J = 8.9$ Hz, 2H), 7.81 (t, $J = 7.7$ Hz, 1H), 8.05 (d, $J = 7.7$ Hz, 1H), 8.56 (d, $J = 6.8$ Hz, 1H), 8.69 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.8, 111.2, 114.4 (2C), 117.8, 119.3, 122.2 (2C), 123.0, 123.3, 123.6, 126.2, 126.7, 127.1, 130.7, 131.6, 133.8, 133.9, 144.7, 148.7, 155.7; HRMS (*m*/*z*) $[M + H]^+$: calcd for $C_{21}H_{17}N_4O_2$: 341.1397, found: 341.1397.

***N*-(4-(Trifluoromethyl)phenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinoline-5-amine (5c).** Following the general Buchwald–Hartwig cross-coupling procedure with 1-iodo-4-(trifluoromethyl)benzene (62 μL, 0.426 mmol). (DCM : EA: 7 : 3). Yellow solid (129 mg, 80%); mp 265–266 °C; IR (neat, cm^{-1}): 658, 768, 1064, 1110, 1319, 1522, 1626, 3333; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.06 (t, $J = 6.8$ Hz, 1H), 7.46 (t, $J = 6.8$ Hz, 1H), 7.67–7.79 (m, 4H), 7.93 (t, $J = 7.7$ Hz, 1H), 8.31 (d, $J = 8.9$ Hz, 2H), 8.56 (d, $J = 7.7$ Hz, 1H), 8.74 (d, $J = 7.7$ Hz, 1H), 8.80 (d, $J = 6.8$ Hz, 1H), 9.73 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 111.5, 117.3, 119.1 (2C), 119.3, 121.0 (q, C_q, $J_{CF_3} = 31.8$ Hz), 122.0, 123.7, 124.8 (q, C_q, $J_{CF_3} = 271.0$ Hz), 125.0, 125.7 (q, 2 × CH_{ar}, $J_{CF_3} = 3.8$ Hz), 126.1, 127.0, 127.2, 130.8, 132.6, 144.2, 145.0, 147.4 (2C_q); ^{19}F NMR (376 MHz, DMSO-d_6): δ −61.69; HRMS (ESI) $[M + H]^+$: calcd for $C_{21}H_{14}F_3N_4$: 379.1165, found: 379.1162.

4-(Pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-ylamino)benzonitrile (5d). Following the general Buchwald–Hartwig cross-coupling procedure with 4-bromobenzonitrile (77.5 mg, 0.426 mmol). (DCM : EA: 7 : 3). Yellow solid (128 mg, 90%); mp 279–280 °C; IR (neat, cm^{-1}): 650, 728, 810, 1170, 1244, 1320, 1404, 1496, 1506, 1600, 2209 (CN), 3360; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.11 (t, $J = 6.7$ Hz, 1H), 7.50 (t, $J = 6.7$ Hz, 1H), 7.73–7.84 (m, 4H), 7.97 (t, $J = 7.7$ Hz, 1H), 8.28 (d, $J = 8.9$ Hz, 2H), 8.59 (d, $J = 7.7$ Hz, 1H), 8.74 (d, $J = 7.7$ Hz, 1H), 8.82 (d, $J = 6.7$ Hz, 1H), 9.85 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 102.2, 111.6, 117.4, 119.0 (2C), 119.4, 119.7, 122.1, 123.8, 125.1, 126.2, 127.4, 127.4, 130.8, 131.0, 132.6 (2C), 133.0, 144.4, 145.7, 146.9; HRMS (*m*/*z*) $[M + H]^+$: calcd for $C_{21}H_{14}N_5$: 336.1244, found: 336.1241.

***N*-(3-(Trifluoromethyl)phenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]-isoquinoline-5-amine (5e).** Following the general Buchwald–Hartwig cross-coupling procedure with 1-iodo-3-(trifluoromethyl)benzene (61 μL, 0.426 mmol). (DCM : EA: 7 : 3). Yellow solid (127 mg, 79%); mp 233–235 °C; IR (neat, cm^{-1}): 695, 745, 789, 891, 1098, 1158, 1246, 1319, 1442, 1602, 2921, 3347; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.08 (t, $J = 6.8$ Hz, 1H), 7.35 (d, $J = 7.9$ Hz, 1H), 7.44 (t, $J = 6.8$ Hz, 1H), 7.62 (t, $J = 7.9$ Hz, 1H), 7.72 (d, $J = 6.8$ Hz, 1H), 7.73 (t, $J = 7.7$ Hz, 1H), 7.91 (t, $J = 7.7$ Hz, 1H), 8.45 (d, $J = 7.9$ Hz, 1H), 8.50 (s, 1H), 8.53 (d, $J = 7.7$ Hz, 1H), 8.59 (d, $J = 6.8$ Hz, 1H), 8.73 (d, $J = 7.7$ Hz, 1H), 9.67 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 111.6, 115.8 (q, CH_{ar}, $J_{CF_3} = 4.1$ Hz), 117.4, 117.5 (q, CH_{ar}, $J_{CF_3} = 3.9$ Hz), 119.1, 122.0, 122.9, 123.0, 124.5 (q, C_q, $J_{CF_3} = 272.4$ Hz), 124.8, 125.9, 126.7, 126.9, 129.2 (q, C_q, $J_{CF_3} = 31.2$ Hz), 129.6, 130.8, 130.8, 132.6, 142.0, 144.0, 147.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.18.; HRMS (ESI) $[M + H]^+$: calcd for $C_{21}H_{14}F_3N_4$: 379.1165, found: 379.1164.

***N*-(3-Nitrophenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (5f).** Following the general Buchwald–Hartwig cross-coupling procedure with 1-iodo-3-nitobenzene (106 mg, 0.426 mmol). (DCM : EA: 7 : 3). Red brick solid (100 mg, 66%); mp 276–277 °C; IR (neat, cm^{-1}): 716, 821, 877, 1242, 1323, 1482, 1518, 1595, 1627, 3033, 3431; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.05 (t, $J = 6.9$ Hz, 1H), 7.42 (t, $J = 6.9$ Hz, 1H), 7.60 (t, $J = 7.9$ Hz, 1H), 7.65–7.72 (m, 2H), 7.81 (d, $J = 7.9$ Hz, 1H), 7.88 (t, $J = 7.5$ Hz, 1H), 8.42–8.52 (m, 2H), 8.61 (d, $J = 6.9$ Hz, 1H), 8.67 (d, $J = 7.5$ Hz, 1H), 9.17 (s, 1H), 9.73 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 111.5, 113.4, 115.5, 117.4, 118.9, 122.0, 123.0, 124.7, 125.3, 125.9, 126.9, 127.0, 129.5, 130.7, 130.8, 132.3, 142.4, 144.1, 147.4, 147.9; HRMS (ESI) $[M + H]^+$: calcd for $C_{20}H_{14}N_5O_2$: 356.1142, found: 356.1140.

***N*-(2-(Trifluoromethyl)phenyl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]-isoquinoline-5-amine (5g).** Following the general Buchwald–Hartwig cross-coupling procedure with 1-iodo-2-(trifluoromethyl)benzene (60 μL, 0.426 mmol). (DCM : EA: 7 : 3). Yellow solid (113 mg, 70%); mp 180–181 °C; IR (neat, cm^{-1}): 645, 831, 1032, 1139, 1254, 1274, 1382, 1448, 1518, 1589, 1615, 2918, 3397; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.85 (t, $J = 6.8$ Hz, 1H),

7.13 (t, $J = 7.7$ Hz, 1H), 7.30 (t, $J = 6.8$ Hz, 1H), 7.56 (t, $J = 7.9$ Hz, 1H), 7.62 (t, $J = 7.7$ Hz, 1H), 7.63–7.73 (m, 3H), 7.83 (t, $J = 7.9$ Hz, 1H), 7.96 (d, $J = 7.7$ Hz, 1H), 8.53 (d, $J = 6.8$ Hz, 1H), 8.60 (d, $J = 7.9$ Hz, 1H), 8.70 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.2, 117.8, 118.6 (q, $J = 29.1$ Hz), 119.6, 121.8, 122.0, 122.6, 123.3, 123.4, 125.4 (q, C_q,$J_{CF_3} = 272.7$ Hz), 126.4 (q, CH_{ar},$J = 5.5$ Hz), 126.6, 127.0, 128.3, 130.8, 131.6, 132.6, 133.2, 139.0, 145.2, 146.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −61.57; HRMS (ESI) $[M + H]^+$: calcd for $C_{21}H_{14}F_3N_4$: 379.1165, found: 379.1161.

***N*-(Pyridin-4-yl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (5h).** Following the general Buchwald–Hartwig cross-coupling procedure with 4-iodopyridine (87 mg, 0.426 mmol). (DCM : MeOH: 95 : 5). Yellow solid (91 mg, 69%); mp 257–259 °C; IR (neat, cm^{-1}): 731, 827, 1212, 1251, 1349, 1504, 1538, 2923, 3078, 3304; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.00 (t, $J = 6.8$ Hz, 1H), 7.42 (t, $J = 6.8$ Hz, 1H), 7.52 (s, 1H), 7.70 (t, $J = 7.6$ Hz, 1H), 7.76–7.80 (m, 3H), 7.90 (t, $J = 7.6$ Hz, 1H), 8.12 (d, $J = 7.6$ Hz, 1H), 8.55 (d, $J = 5.3$ Hz, 2H), 8.71 (d, $J = 6.8$ Hz, 1H), 8.78 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.7, 112.9 (2C), 118.1, 119.6, 122.8, 123.5, 123.6, 126.7, 127.6, 128.7, 131.1, 131.6, 145.7, 146.1, 147.6, 150.6 (2C), 151.0; HRMS (ESI) $[M + H]^+$: masse calcd for $C_{19}H_{14}N_5$: 312.1244, found: 312.1243.

***N*-(Pyridin-3-yl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (5i).** Following the general Buchwald–Hartwig cross-coupling procedure with 3-bromopyridine (41 μL, 0.426 mmol). (DCM : MeOH: 99 : 1). Yellow solid (95 mg, 72%); mp 246–247 °C; IR (neat, cm^{-1}): 745, 930, 1251, 1348, 1415, 1521, 1582, 2930, 3080, 3314; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.90 (t, $J = 6.8$ Hz, 1H), 7.31–7.38 (m, 2H), 7.56 (s, 1H), 7.62 (t, $J = 7.7$ Hz, 1H), 7.71 (d, $J = 6.8$ Hz, 1H), 7.83 (t, $J = 7.7$ Hz, 1H), 8.13 (d, $J = 7.7$ Hz, 1H), 8.34 (d, $J = 5.8$ Hz, 2H), 8.59 (d, $J = 6.8$ Hz, 1H), 8.70 (d, $J = 7.7$ Hz, 1H), 9.07 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.4, 117.9, 119.2, 122.8, 123.4, 123.5, 123.6, 126.4, 126.5, 127.1, 127.8, 130.8, 131.5, 133.3, 137.5, 141.7, 143.4, 145.1, 147.3. HRMS (ESI) $[M + H]^+$: calcd for $C_{19}H_{14}N_5$: 312.1244, found: 312.1243.

***N*-(Pyridin-2-yl)pyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-amine (5j).** Following the general Buchwald–Hartwig cross-coupling procedure with 2-bromopyridine (41 μL, 0.426 mmol). (DCM : acetone: 9 : 1). Yellow solid (92 mg, 70%); mp 175–176 °C; IR (neat, cm^{-1}): 756, 771, 987, 1162, 1310, 1439, 1517, 1583, 3232; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.94 (t, $J = 6.7$ Hz, 1H), 7.00 (t, $J = 7.9$ Hz, 1H), 7.36 (t, $J = 6.7$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.75 (d, $J = 6.7$ Hz, 1H), 7.79 (t, $J = 7.9$ Hz, 1H), 7.87 (t, $J = 7.6$ Hz, 1H), 8.18 (d, $J = 7.6$ Hz, 1H), 8.23 (s, 1H), 8.34 (d, $J = 4.0$ Hz, 1H), 8.66 (d, $J = 6.7$ Hz, 1H), 8.70 (d, $J = 7.9$ Hz, 1H), 8.73 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 111.4, 112.7, 117.8, 118.0, 119.4, 123.0, 123.2, 123.4, 126.6, 127.0, 128.1, 130.9, 131.6, 133.3, 138.1, 145.2, 146.4, 148.2, 153.5; HRMS (ESI) $[M + H]^+$: calcd for $C_{19}H_{14}N_5$: 312.1244, found: 312.1243.

4-((9-Chloropyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-yl)-amino)benzonitrile (5m). Following the general Buchwald–Hartwig cross-coupling procedure with 4-bromobenzonitrile (77.5 mg, 0.426 mmol). (DCM : EA: 7 : 3). Yellow solid (116 mg, 74%); mp 319–320 °C; IR (neat, cm^{-1}): 661, 765, 1089, 1173, 1244, 1511, 2212 (CN), 3376; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.49 (d, $J = 9.5$ Hz, 1H), 7.76–7.83 (m, 4H), 7.96 (t, $J = 7.7$ Hz, 1H), 8.29 (d, $J = 8.9$ Hz, 2H), 8.54 (d, $J = 7.7$ Hz, 1H), 8.72 (d, $J = 7.7$ Hz, 1H), 8.88 (s, 1H), 9.83 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 102.5, 118.3, 118.6, 119.3 (2C), 119.5, 119.7, 121.6, 122.1, 125.1, 126.4, 127.9, 130.7, 131.2, 132.6, 133.0 (2C), 142.5, 145.4, 147.5, 147.7; HRMS (*m*/*z*) $[M + H]^+$: calcd for $C_{21}H_{13}ClN_5$: 370.0854, found: 370.0852.

4-((9-Bromopyrido[2′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-yl)-amino)benzonitrile (5n). Following the general Buchwald–Hartwig cross-coupling procedure with 4-bromobenzonitrile (77.5 mg, 0.426 mmol). (DCM : EA: 7 : 3). Yellow solid (127 mg, 72%); mp 320–321 °C; IR (neat, cm^{-1}): 707, 769, 833, 1241, 1407, 1517, 1595, 2219 (CN), 3340; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.58 (dd, $J = 9.5$, 1.9 Hz, 1H), 7.75 (d, $J = 9.5$ Hz, 1H), 7.79 (t, $J = 7.6$ Hz, 1H), 7.83 (d, $J = 8.7$ Hz, 2H), 7.98 (t, $J = 7.6$ Hz, 1H), 8.30 (d, $J = 8.7$ Hz, 2H), 8.57 (d, $J = 7.7$ Hz, 1H), 8.75 (d, $J = 7.7$ Hz, 1H), 8.97 (d, $J = 1.9$ Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 102.5, 105.5, 118.6, 119.3 (2C), 119.6, 119.7, 122.1, 123.6, 125.1, 126.5, 127.7, 130.1, 130.7, 131.3, 132.5, 133.0 (2C), 142.6, 145.4, 147.5; HRMS (*m*/*z*) $[M + H]^+$: calcd for $C_{21}H_{13}BrN_5$: 414.0349 [^{79}Br], 416.0331 [^{81}Br], found: 414.0350 [^{79}Br], 414.0349 [^{81}Br].

4-((9-Chloropyridazino[6′,1′:2,3]imidazo[4,5-*c*]isoquinolin-5-yl)amino)benzonitrile (5o). Following the general Buchwald–Hartwig cross-coupling procedure with 4-bromobenzonitrile (77.5 mg, 0.426 mmol). (DCM : EA: 7 : 3). Orange-yellow solid (92 mg, 68%); mp: 355–356 °C.; IR (neat, cm^{-1}): 756, 821, 1102, 1321, 1411, 1506, 1571, 1606, 2217 (CN), 3057, 3396; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 7.44 (d, $J = 9.5$ Hz, 1H), 7.77 (t, $J = 7.7$ Hz, 1H), 7.81 (d, $J = 8.9$ Hz, 2H), 7.93 (t, $J = 7.7$ Hz, 1H), 8.23 (d, $J = 8.9$ Hz, 2H), 8.27 (d, $J = 9.5$ Hz, 1H), 8.49 (d, $J = 7.7$ Hz, 1H), 8.68 (d, $J = 7.7$ Hz, 1H), 9.83 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 103.0, 119.5 (2C), 119.7, 120.5, 121.8, 125.1, 126.9, 127.7, 128.1, 130.6, 131.4, 132.9 (2C), 133.7, 137.5, 145.1, 145.8, 149.2.

HRMS (*m*/*z*) $[M + H]^+$: calcd for $C_{20}H_{11}ClN_6$: 370.0806, found: 370.0806.

Acknowledgements

We acknowledge the OMJ (Office Mediterranéen de la Jeunesse) for financial support of Zahira Tber.

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