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Intramolecular arylation reactions: first efficient synthesis of novel fused pyridoimidazoquinolinones or pyridoimidazoazepinones libraries

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ABSTRACT

An efficient method for the synthesis of new polycyclic skeletons: pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones and pyrido[2′,1′:2,3]imidazo[5,4-*c*]azepin-7(6*H*)-ones libraries is described via Pd-catalyzed intramolecular arylation involving C(sp2)-H activation. This method permits the synthesis of polycyclic derivatives in good yield. The process tolerates a variety of aryl substituents as well as alkyl imidazo[1,2-*a*]pyridine-2-carboxamide structures. The resultant compounds, 10(11)-chloro-pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolinones or azepinones are functionalized under Suzuki cross-coupling conditions to give polyfunctional compounds.

1. Introduction

Significant efforts have been devoted to new synthetic methods regarding quinolinone and azepinone skeleton[1] because of many biologically active compounds of containing these ring systems.[1] For instance, carteolol has been used clinically as a β-adrenergic blocking agent.[1d] Paullone derivatives (Fig. 1) have been described as potent cyclin-dependent kinase as well as glycogen synthase kinase inhibitors.[2] Latondines **A** and **B** (Fig. 1) have been isolated from Indonesian sponge Stylissa carteri.[3] Recently, new compounds **I** (Fig. 1) were reported as most potent cytotoxic agents[4] and are described as potential Pfmrk inhibitors.[5] In 2005, compound **II** (Fig. 1), which was found to be an active molecule, induces S and G2/M arrests of cell cycle, leading to apoptosis.[6] Interestingly, all these compounds show a strong analogy with pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones and pyrido[2′,1′:2,3]imidazo[5,4-*c*]azepin-7(6*H*)-ones derivatives **III** (Fig. 1). Our protocol provides a more efficient alternative to the preparations of compounds **III**, using intramolecular C–H arylation of heteroaromatic compounds. The method reported herein opens up a modular access to pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones or pyrido[2′,1′:2,3]imidazo[5,4-*c*]azepin-7(6*H*)-ones.

The introduction of functionalized aryl moieties into heterocyclic compounds is also an important task in organic synthesis. Palladium-catalyzed direct coupling of (hetero)aryl halides offers an attractive alternative to cross-coupling reactions (Kumada, Negishi, Stille, Suzuki)[7] for the construction of complex polycyclic systems.[8]

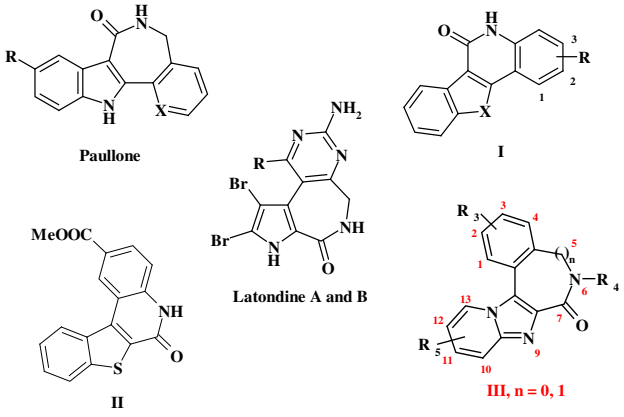

Figure 1. Some literature examples of active quinolinone and azepinone derivatives.

In this context, the overall goal of our research is to develop efficient synthesis of original imidazo[1,2-*a*]pyridine derivatives[9] to the design of therapeutic agents.[10] Some of our latest work in the area from the development of new synthetic methods includes direct and regioselective palladium-catalyzed intermolecular (hetero)arylation[11] and C–H alkenylation[12] at C-3 of imidazo[1,2-*a*]pyridines. Indeed we have described the first examples of one-pot Suzuki cross-coupling/direct arylation and one-pot cyclization/Suzuki cross-coupling/regioselective arylation.[13] These results prompted us to explore selective intramolecular arylation of *N*,*N*,di-substituted imidazo[1,2-*a*]pyridine-2-carboxamide for the synthesis of a library of pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones and pyrido[2′,1′:2,3]imidazo[5,4-*c*]azepin-7(6*H*)-ones

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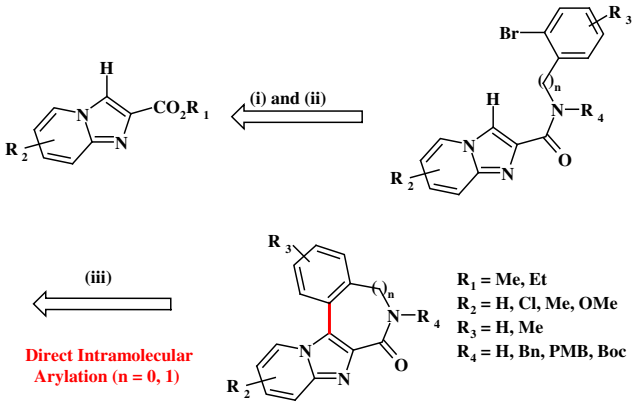
III (Fig. 1), which was then used in Suzuki palladium cross-coupling in order to access various polyfunctional compounds.

Recently, some examples of the formation of pyrido[2′,1′:2,3]imidazo[5,4-*c*]isoquinolin-5(6*H*)-one analogs by three-component reaction were reported in literature.[14] However, the synthesis of polyfunctional heteroaromatics **III** (Fig. 1) is very difficult using similar methodology. In order to prepare heterocyclic system **III** (Fig. 1), the application of intramolecular arylation reaction seems promising. As far as we know, this is the first example of intramolecular arylation of imidazo[1,2-*a*]pyridines as substrates. Such a strategy would furnish novel libraries of polycyclic frameworks derived from privileged structures that, in turn, could be used as a source for new chemical entities in medical and biological research.

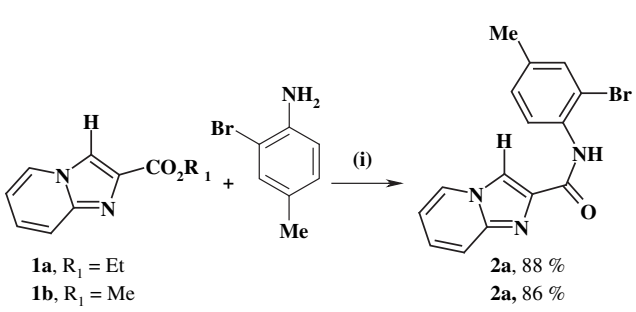
2. Results and discussion

The resulting original structures were obtained applying the retrosynthetic scheme shown in Scheme 1, in a few steps from alkylimidazo[1,2-*a*]pyridine-2-carboxylate derivatives and involved as key steps (i) condensation reaction with aniline derivatives, (ii) protection of the amide and (iii) palladium-catalyzed intramolecular arylation at C-3 imidazopyridine ring.



Scheme 1. Retrosynthetic scheme.

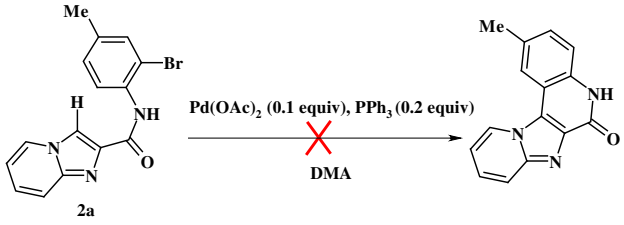
Our effort to design the cyclization precursor and the intramolecular palladium-catalyzed C–H arylation is described in Scheme 2. In the first case, we proposed the introduction of an aryl bromide on the imidazole moiety of the bicyclic ring to convert the alkylimidazo[1,2-*a*]pyridine-2-carboxylate structures into intramolecular arylation substrates and facilitate it. The precursor **2a**, required as key intermediate for the intramolecular arylation reaction, was carried out by treatment of ethyl and methyl imidazo[1,2-*a*]pyridine-2-carboxylates **1a** and **1b** with 2-bromo-4-methylaniline in the presence of Me_3Al[15] to afford the amide **2a** in 88 and 86% yield, respectively (Scheme 2).



Scheme 2. (i) Me_3Al, CH_2Cl_2, 0 °C then reflux, 4 h.

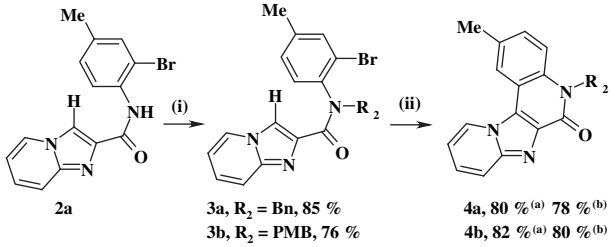
Then, a first attempt of the cyclization, carried out with amide **2a** using our conditions,[11] gave the starting material (entry 1, Table 1). Next, we used recently described various conditions[16,17] in order to avoid the protection of amide. Unfortunately, all these tests failed and resulted in the recovery of the starting material (entries 2 and 3, Table 1). The intramolecular CH arylation reaction conditions of **2a** are summarized in Table 1.

Table 1
Palladium-catalyzed cyclization of **2a**



Entry	Additives	Yield (%)
1	K_2CO_3, 100 °C, 48 h	0
2	CsOAc, NH(*i*Pr)$_2$, 100 °C, 48 h	0
3	MgO, CuI, 100 °C, 48 h	0

This failure was probably caused by the presence of the free NH group.[11,12,18] For this reason, we decided to perform the reaction using alkylated amide. Alkylation of the amide N-atom with benzyl and *p*-methoxybenzyl groups was done by the exposure of NaH and benzyl bromide or *p*-methoxybenzyl chloride, which afforded fully protected derivatives **3a** and **3b** in 85 and 76% yield, respectively. These intermediates were used as precursors for the intramolecular arylation reaction (Scheme 3).

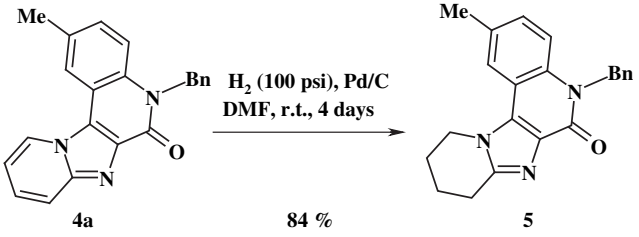


Scheme 3. (i) PMBCl or BnBr, NaH, THF, reflux, 24–36 h; (ii) (a) $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), K_2CO_3 (2 equiv), DMA, 100 °C, oil bath; (b) $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), K_2CO_3 (2 equiv), DMA, 130 °C, M.W.

Having the *N*,*N*-di-substituted imidazo[1,2-*a*]pyridine-2-carboxamides **3a** and **3b** in hand, we next examined Pd-catalyzed intramolecular arylation. Gratifyingly, the compounds **3a** and **3b** could be efficiently functionalized at 3-position. The reaction was carried out in the presence of 10 mol % of $Pd(OAc)_2$/20 mol % PPh_3 and K_2CO_3 (2 equiv) in DMA.[11] The original 5-benzyl-2-methyl-pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-one derivatives **4a** and **4b** were isolated in excellent yield (Scheme 3). We next applied these last conditions [i.e., 10 mol % of $Pd(OAc)_2$/20 mol % PPh_3, K_2CO_3 (2 equiv), DMA] under microwave irradiation; after 1 h 30 min at 130 °C, the desired compound **4a** was isolated without any difficulty in 78% yield (Scheme 3). In order to complete our studies, each step was optimized in the presence of *p*-methoxybenzyl protecting group. Thus, compound **4b** was isolated in 80% yield (Scheme 3).

We then turned our attention to remove the *p*-methoxybenzyl and benzyl groups. Thus, exposure of 5-benzyl-2-methyl-pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-one **4a** to a catalytic

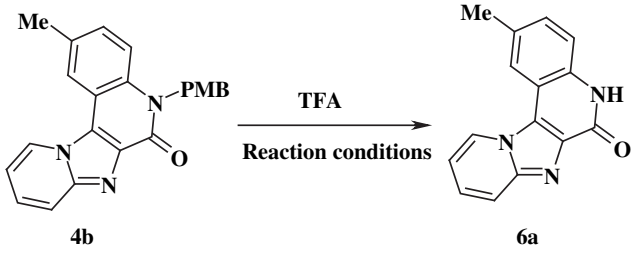
amount of Pd/C in DMF under an atmosphere of hydrogen resulted in clean reduction of the pyridine nucleus (Scheme 4). Under these conditions, corresponding **5** was obtained in 84% yield (Scheme 4). This result is comparable with literature.[19]



Scheme 4. Hydrogenation reaction (partial reduction) of **4a**.

The other assay performed with 5-(*p*-methoxybenzyl)-2-methylpyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones **4a** was realized in the presence of TFA under reflux for 48 h with conventional heating.[20] Unfortunately, only the starting material **4b** was recovered (entry 1, Table 2). Compound **6a** was obtained in 90% yield (entry 2, Table 2) using microwave irradiation at 130 °C for 2 h, under the same reaction conditions. Interestingly, when the irradiation time was increased to 3 h at 130 °C, the desired 2-methylpyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-one **6a** was isolated in excellent yield (entry 3, Table 2). Similar results were observed after two hours and 30 min at 150 °C (entry 4, Table 2).

Table 2
Deprotection of PMB group

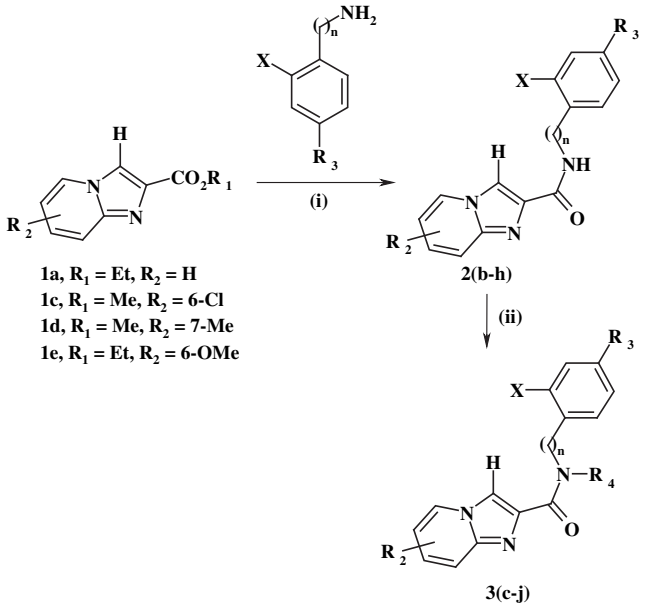


Entry	Reaction conditions	Yield (%)
1	Reflux, 48 h	0
2	M.W, 130 °C, 2 h	90
3	M.W, 130 °C, 3 h	98
4	M.W, 150 °C, 2 h 30 min	97

With these results in hand, we thought that this methodology could be extended to the synthesis of different pyrido[2′,1′:2,3]imidazo[5,4-*c*]heterocycles. Thus, starting material **1a**, **1**(**c**–**e**), treated with various amine derivatives in the presence of Me_3Al in the optimal conditions, led to the original compounds **2**(**b**–**h**) in good yield (entries 1–9, Table 3). Protection of the amide N-atom with benzyl, *p*-methoxybenzyl and Boc group gave functionalized substrates **3**(**c**–**j**) suitable for intramolecular coupling reactions (Table 3).

In order to explore the scope and limitation of the Pd-catalyzed intramolecular arylation method, we applied the optimized reaction conditions to precursor (**3c**–**3j**). The results (Table 4) showed that compounds (**3c**–**3j**) could be efficiently functionalized at position 3, the reaction being performed in dimethylacetamide (DMA) as solvent, with potassium carbonate as base and palladium(II) acetate/triphenylphosphine as catalyst under conventional heating. In this case, the novel pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-one derivatives **4**(**c**–**f**) were isolated in excellent yield ranging between 83 and 98% (entries 1–4, Table 4).

Table 3
Preparation of cyclization precursor



Entry	1	X	*n*	R_3	2	R_4	3
1	**1a**	Br	0	H	**2b**, 81%	PMB	**3c**, 85%[a]
2	**1c**	Br	0	Me	**2c**, 83%	PMB	**3d**, 79%[a]
3	**1d**	Br	0	Me	**2d**, 85%	PMB	**3e**, 82%[a]
4	**1e**	Br	0	Me	**2e**, 72%	PMB	**3f**, 74%[a]
5	**1a**	Br	1	H	**2f**, 72%	Bn	**3g**, 85%[a]
6	**1a**	Br	1	H	**2f**	PMB	**3h**, 83%[a]
7	**1a**	Br	1	H	**2f**	Boc	**3i**, 84%[b]
8	**1a**	H	1	OMe	**2g**, 80%	2-Br-Bn	**3h**, 83%[a]
9	**1c**	H	1	OMe	**2h**, 76%	2-Br-Bn	**3j**, 78%[a]

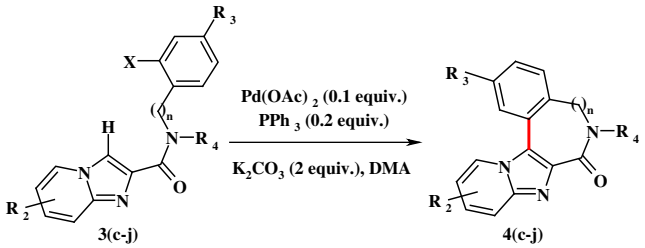
(i) Me_3Al, CH_2Cl_2, 0 °C—rt—reflux, 4–6 h; (ii) (a) PMBCl, BnBr or 2-Br-BnBr, NaH, THF, rt then reflux, 24–48 h; (b) DMAP, Et_3N, $(Boc)_2O$, THF, 0 °C-rt then reflux, 32 h.

Encouraged by these successful attempts with six-member libraries, we extended our studies to seven-membred ring of the azepinone by intramolecular arylation reaction. Our first attempt with **3g**, using conventional heating, afforded the desired pyrido[2′,1′:2,3]imidazo[5,4-*c*]benzazepin-7(6*H*)-one **4g** in 75% yield (entry 5, Table 4). Utilizing microwave irradiation at 130 °C for 1 h 30 min, under the same conditions gave compound **4g** in 87% yield (entry 6, Table 4). With these reaction conditions, we evaluated the scope and limitations of our method using various precursors **3** (Table 4).

The reaction with **3**(**h**–**j**) afforded the desired pyrido[2′,1′:2,3]imidazo[5,4-*c*]benzazepin-7(6*H*)-one **4**(**h**–**j**) in good yield (entries 7–9, Table 4). The reaction from **3j**, using microwave irradiation, afforded compound **4j** in 78% yield after two hours (entry 10, Table 4). Unfortunately, when using 20 mol % of $Pd(OAc)_2$ and 40 mol % of PPh_3 for 2 h, under the same reaction conditions, the coupling reaction of **3j** led to two different compounds **4j** and dehalogenated product **4h** in 51% and 25% yield, respectively (entry 11, Table 4). The intramolecular C–H arylation reaction of **3**(**c**–**j**) was summarized in Table 4.

We further expanded the diversity of derivatives using various 5-(*p*-methoxybenzyl)-pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-

Table 4
Palladium-catalyzed intramolecular CH arylation reaction of various cyclization precursors **3**



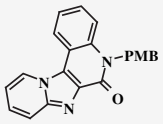
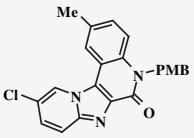
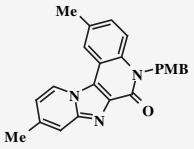
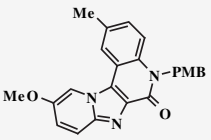
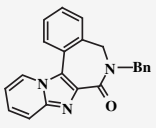
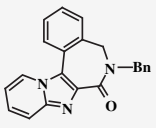
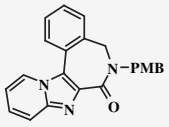
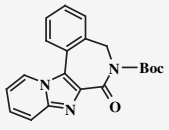
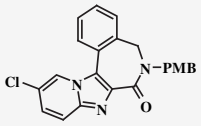
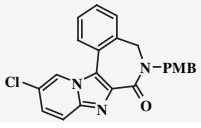
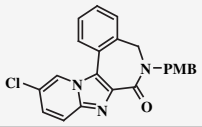
Entry	3	Reaction time	Product 4	Yield
1	**3c**	22 h[a]		**4c**, 95%
2	**3d**	30 h[a]		**4d**, 88%
3	**3e**	24 h[a]		**4e**, 98%
4	**3f**	36 h[a]		**4f**, 83%
5	**3g**	48 h[a]		**4g**, 75%[a]
6	**3g**	1 h 30 min[b]		**4g**, 87%[b]
7	**3h**	1 h 30 min		**4h**, 82%
8	**3i**	2 h[b]		**4i**, 75%
9	**3j**	48 h[a]		**4j**, 72%[a]
10	**3j**	2 h[b]		**4j**, 78%[b]

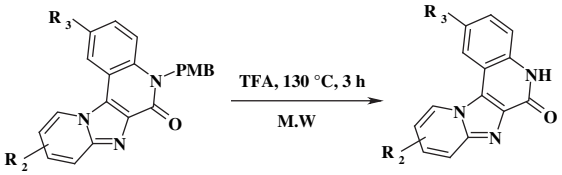
Table 4 (*continued*)

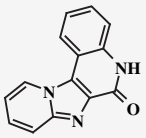
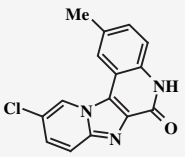
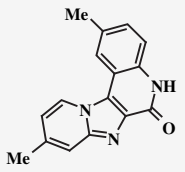
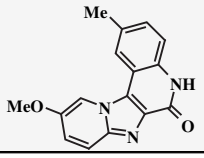
Entry	3	Reaction time	Product 4	Yield
11	**3j**	2 h[c]		51% (**4j**)+25% (**4h**)[c]

[a] 100 °C, oil bath.
[b] 130 °C, M.W.
[c] $Pd(OAc)_2$ (0.2 equiv), PPh_3 (0.4 equiv), K_2CO_3 (2 equiv), DMA 130 °C, M.W.

ones. Thus, the treatment of compounds **4**(**c**–**f**) with TFA under microwave irradiation at 130 °C for 3 h afforded the desired pyrido[2′,1′:2,3]imidazo[5,4-*c*] quinolin-6(5*H*)-ones **6**(**b**–**e**) in good yield (entries 1–4, Table 5).

Table 5
Deprotection of PMB group of various 10-(*p*-methoxybenzyl)pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones **4**

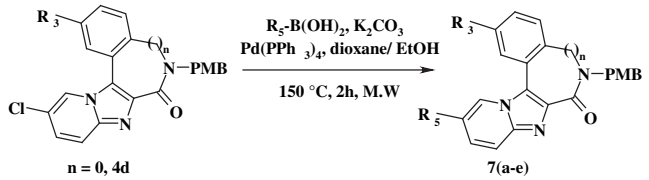


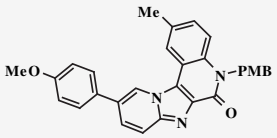
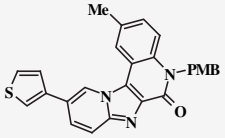
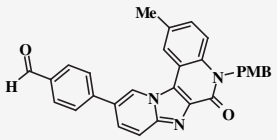
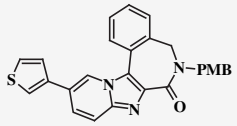
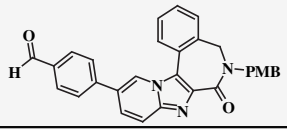
Entry	Reagent 4	Product 6	Yield
1	**4c**		**6b**, 88%
2	**4d**		**6c**, 81%
3	**4e**		**6d**, 85%
4	**4f**		**6e**, 94%

In this work, we have demonstrated the compatibility of the intramolecular arylation conditions with the presence of a chloro substituent at position 10 and 11, which could be used to introduce various substitutions using Suzuki cross-coupling reaction. The potential of this approach was explored: After optimization studies, we found the best reaction conditions:[11,13,21] Thus, 10-chloro-2-methyl-5-(*p*-methoxybenzyl)-pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-one **4d** and 11-chloro-6-(*p*-methoxybenzyl)-pyrido[2′,1′:2,3]imidazo[5,4-*c*]azepin-7(6*H*)-one **4j** were reacted with various aryl boronic acids (1.2 equiv), $Pd(PPh_3)_4$ (0.1 equiv), and K_2CO_3 (2 equiv) in a mixture of dioxane/EtOH (3/1: v/v) under

microwave irradiation at 150 °C for 2 h. These conditions afforded polysubstituted pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones and pyrido[2′,1′:2,3]imidazo[5,4-*c*]azepin-7(6*H*)-ones **7**(**a**–**e**) in good yield (Table 6).

Table 6
Suzuki cross-coupling of 10(11)-chloro-pyrido[2′,1′:2,3]imidazo[5,4-*c*]heterocycles **4d** and **4j** under microwave irradiation



Entry	Reagent **4**	Product **7**	Yield
1	**4d**		**7a**, 88%
2	**4d**		**7b**, 97%
3	**4d**		**7c**, 88%
4	**4j**		**7d**, 82%
5	**4j**		**7e**, 85%

3. Conclusion

We developed a straightforward preparation of original pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones and pyrido-[2′,1′:2,3]imidazo[5,4-*c*]azepin-7(6*H*)-ones library via palladium-catalyzed intramolecular arylation at the C-3 imidazopyridinic position. This method can be used with a wide range of cyclization precursors allowing the synthesis of novel pyrido[2′,1′:2,3]-imidazo[5,4-*c*]heterocycles. We also reported the compatibility of the synthesis with the presence of chloro groups, which was used to the synthesis of polyfunctional compounds. Additional studies are in progress to apply this method for the design of potent bioactive molecules.

4. Experimental section

4.1. General method

All reagents were purchased from Sigma–Aldrich, Acros Organics, and Alfa Aesar and used without further purification. Microwave-assisted reactions were carried out in a Biotage Initiator microwave synthesis instrument and temperatures were measured by an IR sensor. Melting points were determined with a Büchi SMP-20 melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR were recorded on a Bruker Avance DPX 250 spectrometer (250.19 MHz ^{1}H, 62.89 MHz ^{13}C) and DPX-400 spectrometer (400 MHz ^{1}H, 100.6 MHz ^{13}C) using TMS as the internal standard, multiplicities were determined by the DEPT 135 sequence. HRMS were recorded with a TOF spectrometer (ESI mode) or with a Finnigan MAT 95 XL (CI mode) at the Regional Center of Physical Measurement University Blaise Pascal, Clermont Ferrand. All commercial solvents were used without further purification. Column chromatography was carried out using Silica gel 60N (spherical, neutral, 40–63 mm, Merck). TLC was carried out on Merck silica gel 60F_{254} precoated plates and visualized with UV light.

4.2. *N*-substituted imidazo[1,2-*a*]pyridine-2-carboxamides (2); General procedure

Under N_2 atmosphere at −5–0 °C, Me_3Al (2 M soln in toluene, 2 equiv) was added to a soln of 2-bromoaniline or *p*-methoxybenzylamine (1.5 equiv) in anhyd CH_2Cl_2 (20 ml) was added dropwise at −5 °C, and the mixture was stirred for 30 min at this temperature. The mixture was then slowly warmed to 0 °C over 30 min, and a soln of **1** (1 g, 1 equiv) in anhyd CH_2Cl_2 (10 ml) was added dropwise. The mixture was stirred for 4–6 h at reflux, and then carefully quenched with 1 N aq HCl (10 ml) at 0 °C. The mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc–PE) to give the desired product **2**.

*4.2.1. N-(2-Bromo-4-methylphenyl)-imidazo[1,2-a]pyridine-2-carboxamide (**2a**).* White solid (88%); mp=215–217 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.32 (s, 3H, CH_3), 6.83–6.89 (m, 1H, H_{Ar}), 7.16 (d, 1H, $H_{5'}$, J=8.5 Hz), 7.24–7.30 (m, 1H, H_{Ar}), 7.41 (s, 1H, $H_{3'}$), 7.63–7.67 (m, 1H, H_{Ar}), 8.15–8.18 (m, 1H, H_{Ar}), 8.21 (s, 1H, H_3), 8.44 (d, 1H, $H_{6'}$, J=8.5 Hz), 9.79 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 20.7(CH_3), 113.7 (CH), 114.7 (CH), 118.7 (CH), 121.5 (CH), 126.2 (CH), 126.5 (CH), 129.0 (CH), 132.8 (CH), 133.5 (C), 135.1 (C), 140.2 (C), 144.8 (C), 160.7 (CO); HRMS: m/z $[M]^+$ calcd for $C_{15}H_{13}N_3OBr$: 330.0233, found 330.0242.

*4.2.2. N-(2-Bromophenyl)-imidazo[1,2-a]pyridine-2-carboxamide (**2b**).* Yellow solid (81%); mp=177–178 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.84–6.88 (m, 1H, H_{Ar}), 6.97–7.02 (m, 1H, H_{Ar}), 7.24–7.28 (m, 1H, H_{Ar}), 7.34–7.38 (m, 1H, HAr), 7.58–7.66 (m, 2H, H_{Ar}), 8.14–8.16 (m, 1H, H_{Ar}), 8.22 (s, 1H, H_3), 8.58–8.61 (m, 1H, H_{Ar}), 9.72 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 113.7 (CH), 113.8 (CH), 114.7 (C), 118.7 (CH), 121.6 (CH), 125.0 (CH), 126.2 (CH), 126.5 (CH), 128.4 (CH), 132.5 (CH), 136.1 (C), 140.1 (C), 144.6 (C), 160.9 (CO); SM (IS): m/z $[M+H]^+$=316 [^{79}Br], 318 [^{81}Br].

*4.2.3. N-(2-Bromo-4-methylphenyl)-6-chloroimidazo[1,2-a]pyridine-2-carboxamide (**2c**).* White solid (83%); mp>250 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.32 (s, 3H, CH_3), 7.17 (d, 1H, $H_{5'}$, J=8.2 Hz), 6.21–6.23 (m, 1H, H_7), 7.41 (s, 1H, $H_{3'}$), 7.60 (d, 1H, H_8, J=9.7 Hz), 8.19–8.23 (m, 2H, H_3, H_5), 8.43 (d, 1H, $H_{6'}$, J=8.2 Hz), 9.74 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 20.6 (CH_3), 113.6 (C), 114.8 (CH), 119.0 (CH), 121.4 (CH), 122.0 (C), 124.2 (CH), 127.8 (CH), 128.9 (CH), 132.7 (CH), 133.3 (C), 135.2 (C), 141.0 (C), 142.9 (C), 160.2 (CO); SM (IS): m/z $[M+H]^+$=365 [^{35}Cl], 367 [^{37}Cl], 364 [^{79}Br], 366 [^{81}Br].

*4.2.4. N-(2-Bromo-4-methylphenyl)-7-methylimidazo[1,2-a]pyridine-2-carboxamide (**2d**).* Yellow solid (85%); mp=198–199 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.31 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.66 (dd, 1H, H_6, J=1.5, 7 Hz), 7.15 (dd, 1H, $H_{5'}$, J=1.2, 8.5 Hz), 7.26–7.40 (m, 2H, $H_{3'}$ and H_8), 8.01 (d, 1H, H_5, J=7 Hz), 8.12 (s, 1H, H_3), 8.42 (d,

1H, $H_{6'}$, J=8.5 Hz), 9.76 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 20.7(CH_3), 21.5(CH_3), 113.6 (C), 114.1 (CH), 116.4 (CH), 116.7 (CH), 121.4 (CH), 125.6 (CH), 128.9 (CH), 132.7 (CH), 133.6 (C), 135.0 (C), 137.2 (C), 139.9 (C), 145.1 (C), 160.9 (CO); SM (IS): m/z $[M+H]^+$=344 [^{79}Br], 346 [^{81}Br].

*4.2.5. N-(2-Bromo-4-methylphenyl)-6-methoxyimidazo[1,2-a]pyridine-2-carboxamide (**2e**).* Brown solid (72%); mp=125–127 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.32 (s, 3H, CH3), 3.83 (s, 3H, OCH_3), 7.05 (dd, 1H, H_7, J=2.25, 9.76 Hz), 7.16 (d, 1H, $H_{5'}$, J=8.5 Hz), 7.41 (s, 1H, $H_{3'}$), 7.60 (d, 1H, H_8, J=9.76 Hz), 7.64 (d, 1H, H_5, J=2 Hz), 8.17 (s, 1H, H_3), 8.43 (d, 1H, $H_{6'}$, J=8.5 Hz), 9.72 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 20.7 (CH_3), 20.7 (OCH_3), 107.5 (CH), 113.7 (C), 115.6 (CH), 118.8 (CH), 121.5 (CH), 122.1 (CH), 129.0 (CH), 132.8 (CH), 133.6 (C), 135.0 (C), 140.0 (C), 141.9 (C), 150.1 (C), 160.9 (CO); HRMS: m/z $[M]^+$ calcd for $C_{16}H_{15}N_3O_2Br$: 330.0348, found 360.0336.

*4.2.6. N-(2-Bromobenzyl)-imidazo[1,2-a]pyridine-2-carboxamide (**2f**).* Yellow solid (72%); mp=179–182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.75 (d, 2H, CH_2, J=6.4 Hz), 6.83 (t, 1H, H_{Ar}, J=6.8 Hz), 7.10–7.15 (m, 1H, H_{Ar}), 7.21–7.29 (m, 2H, H_{Ar}), 7.47 (d, 1H, H_{Ar}, J=7.2 Hz), 7.46–7.56 (m, 2H, H_{Ar}), 7.84 (t, 1H, NH, J=6.4 Hz), 8.12–8.16 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 43.5 (CH_2), 113.5 (CH), 114.4 (CH), 118.3 (CH), 123.8 (C), 126.1 (CH), 126.5 (CH), 127.7 (CH), 129.1 (CH), 130.1 (CH), 132.8 (CH), 137.4 (C), 139.9 (C), 144.6 (C), 162.7 (CO); HRMS: m/z $[M]^+$ calcd for $C_{15}H_{13}N_3OBr$: 330.0242, found 330.0241.

*4.2.7. N-(4-Methoxybenzyl)–imidazo[1,2-a]pyridine-2-carboxamide (**2g**).* Yellow solid (80%); mp=121–123 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.79 (s, 3H, OCH_3), 4.60 (d, 2H, CH_2, J=6.0 Hz), 6.80–6.89 (m, 3H, H_{Ar}, $H_{4'}$, $H_{6'}$), 7.18–7.33 (m, 3H, H_{Ar}, $H_{3'}$, $H_{7'}$), 7.52 (dd, 1H, H_{Ar}, J=0.8, 9.3 Hz), 7.66 (t, 1H, NH, J=6.0 Hz), 8.12–8.17 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 42.8 (CH_2), 55.4 (CH_3), 113.4 (CH), 114.1 (2×CH), 114.4 (C), 118.2 (CH), 126.1 (CH), 126.5 (CH), 129.4 (2×CH), 130.4 (CH), 140.1 (C), 144.6 (C), 159.1 (C), 162.6 (CO); SM (IS): m/z $[M+H]^+$=282.

*4.2.8. 6-Chloro-N-(4-methoxybenzyl)-imidazo[1,2-a]pyridine-2-carboxamide (**2h**).* Yellow solid (76%); mp=151–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 3H, OCH_3), 4.58 (d, 2H, CH_2, J=5.6 Hz), 6.84 (d, 2H, $H_{4'}$, $H_{6'}$, J=8.4 Hz), 7.15 (d, 2H, H_7, J=9.6 Hz), 7.27 (d, 2H, $H_{3'}$, $H_{7'}$, J=8.4 Hz), 7.42 (d, 1H, H_8, J=9.6 Hz), 7.71 (t, 1H, NH, J=5.6 Hz), 8.14 (s, 1H, H_3), 8.19 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 42.7 (CH_2), 55.3 (CH_3), 114.0 (2×CH), 114.6 (CH), 118.4 (CH), 121.6 (C), 124.3 (CH), 127.5 (CH), 129.2 (2×CH), 130.3 (C), 140.8 (C), 142.8 (C), 159.0 (C), 162.1 (CO); SM (IS): m/z $[M+H]^+$=316.

*4.2.9. N,N-di-substituted imidazo[1,2-a]pyridine-2-carboxamides (**3**); General procedure.* At 0 °C and under N_2 atmosphere, NaH (60% dispersion in oil; 2 equiv) was added to a stirred soln of **2** (0.4 g, 1 equiv) in anhyd THF (10 ml). The mixture was stirred for 30 min at 0 °C, and a soln of benzyl bromide, 2-bromobenzyl bromide or *p*-methoxybenzyl chloride (1.4 equiv) in anhyd THF (10 ml) was added dropwise. The mixture was stirred for 4–6 h at reflux, for 24–48 h, and then the mixture was cooled to rt and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc–PE) to afford the desired product **3**.

*4.2.10. N-Benzyl-N-(2-bromo-4-methylphenyl)-imidazo[1,2-a]pyridine-2-carboxamide (**3a**).* Yellow solid (85%); mp=134–135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 3H, CH_3), 4.26 (d, 1H, CH_2, J=8.7 Hz), 5.86 (d, 1H, CH_2, J=8.7 Hz), 6.76–6.73 (m, 2H, H_{Ar}), 6.9 (d, 1H, $H_{5'}$, J=5 Hz), 7.04 (s, 1H, $H_{3'}$), 7.06–7.10 (m, 1H, H_{Ar}), 7.23–7.33 (m, 5H, H_{Ar}), 7.43–7.49 (m, 2H, H_3, H_{Ar}), 7.86 (d, 1H, $H_{6'}$, J=5 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 20.9 (CH_2), 52.6 (CH_3), 113.2 (CH), 114.1 (CH), 118.9 (CH), 123.6 (C), 125.2 (CH), 126.0 (CH), 127.6 (CH), 128.4 (CH), 128.8 (CH), 129.7 (CH), 131.8 (CH), 134.0 (C), 136.9 (C), 138.8 (CH), 140.0 (C), 144.2 (C), 163.9 (CO); HRMS: m/z $[M]^+$ calcd for $C_{22}H_{19}N_3OBr$: 420.0711, found 420.0722.

*4.2.11. N-(2-Bromo-4-methylphenyl)-N-(4-methoxybenzyl)-imidazo[1,2-a]pyridine-2-carboxamide (**3b**).* Brown oil (76%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.31 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.21 (d, 1H, CH_2, J=9 Hz), 5.78 (d, 1H, CH_2, J=9 Hz), 6.67–6.69 (m, 2H, H_{Ar}), 6.76–7.79 (m, 2H, H_{Ar}), 6.91 (d, 1H, H_{Ar}, J=5 Hz), 7.02 (s, 1H, $H_{3'}$), 7.06–7.10 (m, 1H, H_{Ar}), 7.22–7.24 (m, 2H, H_{Ar}), 7.43–7.49 (m, 2H, H_3, H_{Ar}), 7.85 (d, 1H, $H_{6'}$, J=5 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 21.0(CH_3), 51.9(CH_2), 55.3(CH_3), 113.2 (CH), 113.8 (2×CH), 114.1 (CH), 118.9 (CH), 123.6 (C), 125.2 (CH), 126.0 (CH), 128.9 (CH), 129.2 (C), 131.1 (2×CH), 131.9 (CH), 133.9 (CH), 138.7 (C), 139.6 (C), 139.9 (C), 144.2 (C), 159.1 (C), 163.9 (CO); HRMS: m/z $[M]^+$ calcd for $C_{23}H_{21}N_3O_2Br$: 450.0817, found 450.0811.

*4.2.12. N-(2-Bromophenyl)-N-(4-methoxybenzyl)-imidazo[1,2-a]pyridine-2-carboxamide (**3c**).* Yellow oil (85%); mp=122–124 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.73 (s, 3H, OCH_3), 4.27 (d, 1H, CH_2, J=14.3 Hz), 5.78 (d, 1H, CH_2, J=14.3 Hz), 6.63 (t, 1H, H_{Ar}, J=6.6 Hz), 6.76 (d, 2H, $H_{4''}$, $H_{6''}$, J=8.5 Hz), 6.84 (dd, 1H, H_{Ar}, J=2.4, 7.1 Hz), 6.99–7.11 (m, 2H, H_{Ar}), 7.13–7.18 (m, 2H, H_{Ar}), 7.22 (d, 2H, $H_{3''}$, $H_{7''}$, J=8.5 Hz), 7.40 (d, 1H, H_{Ar}, J=9.3 Hz), 7.57–7.61 (m, 1H, H_{Ar}), 7.83 (d, 1H, H_{Ar}, J=6.6 Hz); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 51.5(CH_2), 55.9 (OCH_3), 112.9 (CH), 113.4 (2×CH), 114.0 (CH), 118.2 (CH), 123.7 (C), 125.0 (CH), 125.77 (CH), 127.8 (CH), 128.6 (C), 129.3 (CH), 130.7 (2×CH), 131.9 (CH), 133.2 (CH), 139.1 (C), 141.0 (C), 143.8 (C), 158.8 (C), 163.4 (CO); SM (IS): m/z $[M+H]^+$=436 [^{79}Br], 438 [^{81}Br].

*4.2.13. N-(2-Bromo-4-methylphenyl)-6-chloro-N-(4-methoxybenzyl)-imidazo[1,2-a]pyridine-2-carboxamide (**3d**).* Yellow solid (79%); mp=122–125 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.32 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.23 (d, 1H, CH_2, J=14.2 Hz), 5.76 (d, 1H, CH_2, J=14.2 Hz), 6.69 (d, 1H, H_{Ar}, J=8.0 Hz), 6.79 (d, 2H, $H_{4''}$, $H_{6''}$, J=8.5 Hz), 6.69 (d, 1H, H_6, J=7.2 Hz), 7.01–7.08 (m, 2H, H_{Ar}), 7.23 (d, 2H, $H_{3''}$, $H_{7''}$, J=8.5 Hz), 7.41–7.44 (m, 2H, H_{Ar}), 7.93 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 20.9(CH_3), 51.9 (CH_2), 55.3 (OCH_3), 113.7 (2×CH), 114.3 (CH), 119.1 (CH), 121.4 (C), 123.5 (C), 123.7 (CH), 126.8 (CH), 128.9 (C), 128.9 (CH), 131.1 (2×CH), 131.7 (CH), 133.9 (CH), 138.4 (C), 140.1 (C), 140.4 (C), 142.5 (C), 159.1 (C), 163.3 (CO); HRMS: m/z $[M]^+$ calcd for $C_{23}H_{20}N_3O_2BrCl$: 484.0427, found 484.0423.

*4.2.14. N-(2-Bromo-4-methylphenyl)-N-(4-methoxybenzyl)-7-methylimidazo[1,2-a]pyridine-2-carboxamide (**3e**).* Brown oil (82%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.26 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.21 (d, 1H, CH_2, J=14.5 Hz), 5.76 (d, 1H, CH_2, J=14.5 Hz), 6.47 (d, 1H, H_6, J=6.8 Hz), 6.69 (d, 1H, H_{Ar}, J=8.0 Hz), 6.76 (d, 2H, H_{Ar}, $H_{4''}$, $H_{6''}$, J=8.8 Hz), 6.86–6.91 (m, 1H, H_{Ar}), 7.20–7.34 (m, 3H, H_{Ar}, $H_{3''}$, $H_{7''}$), 7.41 (s, 1H, H_3), 7.70 (d, 1H, H_5, J=6.8 Hz); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 20.3 (CH_3), 21.1 (CH_3), 51.5 (CH_2), 54.91 (OCH3), 113.3 (CH), 113.4 (2×CH), 115.7 (CH), 116.3 (CH), 123.2 (C), 124.9 (CH), 128.6 (CH), 128.8 (C), 130.7 (2×CH), 131.5 (CH), 133.6 (CH), 135.9 (C), 138.3 (C), 138.8 (C), 139.7 (C), 144.3 (C), 158.7 (C), 163.6 (CO); SM (IS): m/z $[M+H]^+$=464 [^{79}Br], 466 [^{81}Br].

*4.2.15. N-(2-Bromo-4-methylphenyl)-N-(4-methoxybenzyl)-6-methoxyimidazo[1,2-a]pyridine-2-carboxamide (**3f**).* Brown solid (74%); mp=72–74 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.31 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.20 (d, 1H, CH_2, J=14.3 Hz), 5.76 (d, 1H, CH_2, J=14.3 Hz), 6.69 (d, 1H, H_{Ar}, J=8.5 Hz), 6.77 (d, 2H, $H_{4''}$, $H_{6''}$, J=8.5 Hz), 6.84–6.94 (m, 3H, H_{Ar}), 7.20–7.24 (m, 2H, H_{Ar}), 7.32–7.36 (m, 2H, H_{Ar}), 7.44 (s, 1H, H_5); ^{13}C NMR ($CDCl_3$,

100.6 MHz): δ 20.9 (CH_3), 51.8(CH_2), 55.2 (OCH_3), 56.1 (OCH3), 107.0 (CH), 113.6 (2×CH), 115.1 (CH), 118.8 (CH), 121.0 (CH), 123.5 (C), 128.8 (CH), 129.1 (C), 131.0 (2×CH), 131.8 (CH), 133.9 (CH), 138.6 (C), 139.2 (C), 139.8 (C), 141.3 (C), 149.7 (C), 159.0 (C), 163.7 (CO); SM (IS): m/z $[M+H]^+$=480 [^{79}Br], 482 [^{81}Br].

*4.2.16. N-Benzyl-N-(2-bromobenzyl)-imidazo[1,2-a]pyridine-2-carboxamide (**3g**).* Yellow solid (85%); mp=127–129 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 4.72 (s, 1H, CH_2), 4.80 (s, 1H, CH_2), 5.45 (s, 1H, CH_2), 5.50 (s, 1H, CH_2), 6.76–6.79 (m, 2H, H_{Ar}), 7.10–7.33 (m, 9H, H_{Ar}), 7.51–7.54 (m, 2H, H_{Ar}), 8.09–8.21 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 48.7 (CH_2), 51.3 (CH_2), 113.4 (CH), 113.9 (CH), 116.9 (CH), 118.6 (CH), 123.3 (C), 125.4 (CH), 126.0 (CH), 127.4 (CH), 127.7 (CH), 128.5 (CH), 128.6 (2×CH), 128.7 (CH), 128.9 (CH), 132.8 (CH), 136.0 (C), 137.0 (C), 137.6 (C), 140.8 (C), 144.1 (C), 165.0 (CO); m/z $[M+H]^+$=421.

*4.2.17. N-(2-Bromobenzyl)-N-(4-methoxybenzyl)-imidazo[1,2-a]pyridine-2-carboxamide (**3h**).* Yellow solid (83%); mp=125–127 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.76 (s, 3H, CH_3), 4.65 (s, 1H, CH_2), 4.78 (s, 1H, CH_2), 5.36 (s, 1H, CH_2), 5.46 (s, 1H, CH_2), 6.65–6.85 (m, 3H, H_{Ar}, $H_{4''}$, $H_{6''}$), 7.06–7.46 (m, 6H, H_{Ar}, $H_{3''}$, $H_{7''}$), 7.51–7.58 (m, 2H, H_{Ar}), 8.05–8.21 (m, 3H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 48.4 (CH_2), 51.0 (CH_2), 55.3 (CH_3), 113.4 (CH), 113.9 (2×CH), 116.7 (CH), 118.5 (CH), 123.6 (C), 125.4 (CH), 126.0 (CH), 127.6 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 129.9 (CH), 132.8 (CH), 136.0 (C), 137.0 (C), 140.9 (C), 144.1 (C), 159.0 (C), 164.8 (CO); m/z $[M+H]^+$=451.

*4.2.18. N-(2-Bromobenzyl)-6-chloro-N-(4-methoxybenzyl)-imidazo[1,2-a]pyridine-2-carboxamide (**3j**).* White solid (78%); mp=152–155 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.78 (s, 3H, CH_3), 4.63 (s, 1H, CH_2), 4.76 (s, 1H, CH_2), 5.31 (s, 1H, CH_2), 5.40 (s, 1H, CH_2), 6.81–6.86 (m, 2H, H_{Ar}), 7.10–7.18 (m, 3H, H_{Ar}), 7.24–7.34 (m, 3H, H_{Ar}), 7.42–7.54 (m, 2H, H_{Ar}), 8.11–8.19 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 48.2 (CH_2), 50.5 (CH_2), 55.0 (CH_3), 113.6 (2×CH), 116.8 (CH), 118.6 (CH), 121.4 (C), 123.3 (C), 123.4 (CH), 126.7 (CH), 127.3 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 129.6 (CH), 132.6 (CH), 135.6 (C), 136.6 (C), 141.5 (C), 142.1 (C), 158.7 (C), 164.1 (CO); HRMS: m/z $[M]^+$ calcd for $C_{23}H_{20}N_3O_2BrCl$: 484.0427, found 484.0432.

4.3. Procedure for synthesis of *tert*-butyl-*N*-(2-bromobenzyl)-{(imidazo[1,2-*a*]pyridinyl)carbonyl} carbamate (3i)

At rt and under N_2 atmosphere, DMAP (0.44 g, 3.63 mmol), Et_3N (0.51 ml, 3.63 mmol) were added to a stirred solution of amide (**2f**) (0.6 g, 1.8 mmol) in anhyd THF (10 ml). The mixture was stirred at rt, and a soln of $(Boc)_2O$ (0.59 g, 2.7 mmol) in anhyd THF (5 ml) was added dropwise. The mixture was stirred for 36 h at reflux, and then the mixture was cooled to rt and extracted with CH_2Cl_2 (3×). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc–PE) to give *tert*-butyl-*N*-(2-bromobenzyl)-{(imidazo[1,2-*a*]pyridinyl) carbonyl}carbamate (**3i**) as white solid (0.65 g, 84% yield).

Mp=157–159 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.21 (s, 9H, $OC(CH_3)_3$), 5.10 (s, 2H, CH_2), 6.84 (dt, 1H, H_{Ar}, J=3.4, 9.5 Hz), 7.10 (dt, 1H, H_{Ar}, J=3.9, 10.5 Hz), 7.20–7.32 (m, 2H, H_{Ar}), 7.45 (d, 1H, H_{Ar}, J=7.75 Hz), 7.53–7.63 (m, 2H, H_{Ar}), 8.07 (s, 1H, H_3), 8.13 (dt, 1H, H_{Ar}, J=1.06, 6.92 Hz); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 27.5 ($OC(CH_3)_3$), 49.5 (CH_2), 83.2 ($OC(CH_3)_3$), 113.6 (CH), 115.1 (CH), 118.8 (CH), 122.5 (C), 125.9 (CH), 126.3 (CH), 127.4 (CH), 127.7 (CH), 128.5 (CH), 132.7 (CH), 137.0 (C), 141.4 (C), 144.1 (C), 153.5 (CO), 168.1 (CO); HRMS: m/z $[M]^+$ calcd for $C_{20}H_{21}N_3O_3Br$: 430.0766, found 430.0773.

4.4. Pyrido[2′,1′:2,3]imidazo[5,4-*c*]heterocycles analogs (4); General procedure

By coventional heating: a mixture of *N*,*N*-di-substituted imidazo[1,2-*a*]pyridine-2-carboxamide (**3**) (200 mg, 1 equiv), K_2CO_3 (2 equiv), PPh_3 (0.2 equiv), and $Pd(OAc)_2$ (0.1 equiv) in DMA (2 mL) was heated to 100 °C. The reaction was stirred for 48 h, and then the mixture was cooled to rt and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc–PE) to give the desired product pyrido[2′,1′:2,3]imidazo[5,4-*c*]heterocycles analogs (**4**).

Under microwave irradiation: to a soln of *N*,*N*-di-substituted imidazo[1,2-*a*]pyridine-2-carboxamide (**3**) (200 mg, 1 equiv) dissolved in DMA (2 mL) in a vial microwave tube was added, under argon, a stirrer bar, K_2CO_3 (2 equiv), PPh_3 (0.2 equiv), and $Pd(OAc)_2$ (0.1 equiv). The vial was sealed with a silicon septum and subjected to microwave irradiation [**4**(**a**–**h**): at 130 °C for 1 h 30 min; **4i** and **4j**: at 130 °C for 2 h] with stirring. The reaction vessel was allowed to cool to rt, diluted with CH_2Cl_2 (15 mL) and extracted (3×). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by column chromatography (silica gel, EtOAc–PE) to give the desired product.

*4.4.1. 5-Benzyl-2-methyl-pyrido[2′,1′:2,3]imidazo[5,4-c]quinolin-6(5H)-one (**4a**).* Yellow solid (80%); mp>250 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.48 (s, 3H, CH_3), 5.75 (s, 2H, CH_2), 7.11 (t, 1H, H_{Ar}, J=6.5 Hz), 7.18–7.27 (m, 6H, H_{Ar}), 7.34 (d, 1H, H_{Ar}, J=8.5 Hz), 7.45 (t, 1H, H_{Ar}, J=7.7 Hz), 7.90–7.94 (m, 2H, H_{Ar}), 8.90 (d, 1H, H_{Ar}, J=6.5 Hz); ^{13}C NMR ($CDCl_3$, 60.9 MHz): δ 21.2(CH_2), 46.3 (CH_3), 114.1 (CH), 114.2 (CH), 116.9 (CH), 120.1 (CH), 120.3 (CH), 125.1 (C), 126.6 (CH), 126.7 (CH), 127.2 (CH), 128.8 (CH), 128.9 (CH), 132.3 (C), 134.4 (C), 134.5 (C), 136.8 (CH), 147.7 (C), 158.9 (CO); HRMS: m/z $[M]^+$ calcd for $C_{22}H_{18}N_3OBr$: 340.1450, found 340.1457.

*4.4.2. 5-(4-Methoxybenzyl)-2-methylpyrido[2′,1′:2,3]imidazo [5,4-c] quinolin-6(5H)-one (**4b**).* Yellow solid (82%); mp>250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.50 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 5.70 (s, 2H, CH_2), 6.77–6.81 (m, 2H, H_{Ar}), 7.10–7.27 (m, 4H, H_{Ar}), 7.40–7.48 (m, 2H, H_{Ar}), 7.92–7.96 (m, 2H, H_{Ar}), 8.93 (d, 1H, H_{Ar}, J=7.2 Hz); ^{13}C NMR (CDCl3, 100.6 MHz): δ 21.24(CH_3), 45.8(CH_2), 55.36 (CH_3), 114.1 (CH), 114.2 (2×CH), 114.3 (C), 117.0 (CH), 120.1 (CH), 120.3 (CH), 125.1 (C), 126.6 (CH), 127.2 (CH), 128.1 (2×CH), 128.9 (C), 128.9 (CH), 132.2 (C), 134.4 (C), 134.6 (C), 147.7 (C), 158.8 (C), 159.0 (CO); HRMS: m/z $[M]^+$ calcd for $C_{23}H_{20}N_3O_2$: 370.1556, found 370.1552.

*4.4.3. 5-(4-Methoxybenzyl)-pyrido[2′,1′:2,3]imidazo[5,4-c] quinolin-6(5H)-one (**4c**).* Yellowish solid (95%); mp=242–244 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.54 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.70 (s, 2H, CH_2), 6.82 (d, 2H, $H_{4'}$, $H_{6'}$, J=8.8 Hz), 7.10 (dt, 1H, H_{Ar}, J=3.5, 9.5 Hz), 7.20 (d, 2H, $H_{3'}$, $H_{7'}$, J=8.8 Hz), 7.30–7.51 (m, 4H, H_{Ar}), 6.91 (d, 1H, H_{Ar}, J=9.5 Hz), 8.14 (dd, 1H, H_{Ar}, J=1.2, 8.0 Hz), 8.86 (d, 1H, H_{Ar}, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 45.8(CH_2), 55.3 (OCH_3), 114.2 (3×CH), 114.3 (C), 117.0 (CH), 120.0 (CH), 120.2 (CH), 122.6 (CH), 125.2 (C), 126.5 (CH), 127.3 (CH), 127.8 (CH), 128.1 (2×CH), 128.7 (C), 134.5 (C), 136.4 (C), 147.8 (C), 158.8 (C), 159.1 (CO); HRMS: m/z $[M]^+$ calcd for $C_{15}H_{13}N_3OBr$: 356.1404, found 356.1399.

*4.4.4. 10-Chloro-5-(4-methoxybenzyl)-2-methyl-pyrido[2′,1′:2,3] imidazo[5,4-c]quinolin-6(5H)-one (**4d**).* Yellowish solid (88%); mp>250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.54 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.70 (s, 2H, CH_2), 6.88–6.85 (m, 2H, $H_{4'}$, $H_{6'}$), 7.18–7.29 (m, 3H, H_{Ar}), 7.42–7.47 (m, 2H, $H_{3''}$, $H_{7''}$), 7.89–7.93 (m, 2H, H_{Ar}), 8.94 (s, 1H, H_{11}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 21.2(CH_3), 45.8(CH_2), 55.4 (OCH_3), 113.8 (C), 114.3 (2×CH), 117.1 (CH), 120.2 (C), 120.3

(CH), 120.4 (CH), 122.4 (C), 124.3 (CH), 125.3 (C), 128.1 (2×CH), 128.7 (CH), 129.5 (CH), 132.5 (C), 134.6 (C), 135.2 (C), 145.9 (C), 158.7 (C), 158.9 (CO); HRMS: m/z $[M]^+$ calcd for $C_{23}H_{19}N_3O_2Cl$: 404.1166, found 404.1167.

*4.4.5. 5-(4-Methoxybenzyl)-2,9-di-methyl-pyrido[2′,1′:2,3] imidazo [5,4-c]quinolin-6(5H)-one (**4e**).* Yellowish solid (98%); mp>250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.44 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.62 (s, 2H, CH_2), 6.77 (m, 2H, $H_{4'}$, $H_{6'}$, J=8.8 Hz), 6.86 (dd, 1H, H_6, J=1.2, 7.2 Hz), 7.13–7.17 (m, 3H, H_{Ar}, $H_{3'}$, $H_{7'}$), 7.32 (d, 1H, H_{Ar}, J=9.0 Hz), 7.59 (s, 1H, H_1), 7.80 (s, 1H, H_5), 8.67 (d, 1H, H_5, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 21.23 (CH_3), 21.69 (CH_3), 45.7 (CH_2), 55.4 (OCH_3), 114.2 (2×CH), 114.2 (C), 116.8 (CH), 116.9 (CH), 117.9 (CH), 120.1 (CH), 124.8 (C), 125.8 (CH), 128.1 (2×CH), 128.6 (CH), 129.0 (C), 132.1 (C), 134.2 (C), 134.6 (C), 138.5 (C), 148.2 (C), 158.8 (C), 159.0 (CO); HRMS: m/z $[M]^+$ calcd for $C_{24}H_{22}N_3O_2$: 384.1712, found 384.1710.

*4.4.6. 10-Methoxy-5-(4-methoxybenzyl)-2-methyl-pyrido [2′,1′:2,3]imidazo[5,4-c]quinolin-6(5H)-one (**4f**).* Yellow solid (83%); mp=242–244 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.49 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.0 (s, 3H, OCH_3), 5.64 (s, 2H, CH_2), 6.78 (d, 2H, $H_{4'}$, $H_{6'}$, J=8.5 Hz), 7.15–7.27 (m, 4H, H_{Ar}), 7.37 (d, 1H, H_{Ar}, J=8.8 Hz), 7.77–7.81 (m, 2H, H_{Ar}), 8.26 (d, 1H, H_{Ar}, J=2 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 21.4 (CH_3), 45.7 (CH_2), 55.3 (OCH_3), 55.6(OCH_3), 108.3 (CH), 114.2 (2×CH), 114.4 (C), 116.9 (CH), 119.9 (CH), 120.0 (CH), 122.6 (CH), 125.6 (C), 128.0 (2×CH), 128.7 (CH), 128.9 (C), 132.0 (C), 134.4 (C), 134.7 (C), 145.0 (C), 150.2 (C), 158.8 (C), 159.0 (CO); HRMS: m/z $[M]^+$ calcd for $C_{24}H_{22}N_3O_3$: 400.1661, found 400.1667.

*4.4.7. 6-(Benzyl)-pyrido[2′,1′:2,3]imidazo[5,4-c]benzazepin-7(6H)-one (**4g**).* Yellow solid (87%); mp=194–196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.08 (d, 1H, CH_2, J=14.8 Hz), 4.31 (d, 1H, CH_2, J=14.8 Hz), 4.60 (d, 1H, CH_2, J=14.8 Hz), 5.12 (d, 1H, CH_2, J=14.8 Hz), 6.97 (dt, 1H, H_{Ar}, J=2.2, 5.9 Hz), 7.13 (d, 1H, H_{Ar}, J=4.5 Hz), 7.27–7.36 (m, 7H, H_{Ar}), 8.63 (dt, 1H, H_{Ar}, J=2.4, 6.6 Hz), 7.82–7.84 (m, 2H, H_{Ar}), 8.6 (d, 1H, H_{Ar}, J=4.5 Hz); ^{13}C NMR ($CDCl_3$, 100.6 Hz): δ 50.4 (CH_2), 50.6 (CH_2), 114.0 (CH), 119.6 (CH), 123.9 (C), 124.3 (CH), 124.4 (CH), 126.5 (CH), 127.6 (C), 127.6 (CH), 128.4 (CH), 128.5 (CH), 128.6 (2×CH), 128.7 (2×CH), 128.9 (CH), 136.7 (C), 137.3 (C), 139.4 (C), 145.9 (C), 163.9 (CO); HRMS: m/z $[M]^+$ calcd for $C_{22}H_{18}N_3O$: 340.1450, found 340.1462.

*4.4.8. 6-(4-Methoxybenzyl)-pyrido[2′,1′:2,3]imidazo[5,4-c] benzazepin-7(6H)-one (**4h**).* Yellow oil (82%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.80 (s, 3H, CH_3), 4.08 (d, 1H, CH_2, J=15.0 Hz), 4.27 (d, 1H, CH_2, J=15.0 Hz), 4.52 (d, 1H, CH_2, J=15.0 Hz), 5.08 (d, 1H, CH_2, J=15.0 Hz), 6.84 (m, 2H, $H_{4'}$, $H_{6'}$), 7.13 (dt, 1H, H_{Ar}, J=4.8, 15.4 Hz), 7.15 (d, 1H, H_{Ar}, J=7.5 Hz), 7.27–7.36 (m, 4H, H_{Ar}), 7.46–7.52 (m, 1H, $\mathbf{H}_{Ar}$), 7.79–7.84 (m, 2H, H_{Ar}), 8.59 (d, 1H, H_{Ar}, J=7 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 49.7 (CH_2), 50.3 (CH_2), 55.4 (CH_3), 114.0 (2×CH), 114.0 (CH), 119.6 (CH), 123.8 (C), 124.3 (CH), 124.4 (CH), 126.5 (CH), 127.6 (C), 128.4 (CH), 128.5 (CH), 128.9 (CH), 129.4 (C), 130.0 (2×CH), 136.7 (C), 136.8 (C), 139.4 (C), 145.9 (C), 159.2 (C), 163.8 (CO); HRMS: m/z $[M]^+$ calcd for $C_{23}H_{20}N_3O_2$: 370.1556, found 370.1546.

*4.4.9. tert-Butyl-7-oxo-pyrido[2′,1′:2,3]imidazo[5,4-c] benzazepine-6-carboxylate (**4i**).* Yellow Solid (75%); mp=180–183 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.53 (s, 9H, $OC(CH_3)_3$), 4.28 (d, 1H, CH_2, J=14.8 Hz), 5.25 (d, 1H, CH_2, J=14.8 Hz), 6.97 (dt, 1H, H_{Ar}, J=3.5, 9.4 Hz), 7.34 (dt, 1H, H_{Ar}, J=2.2, 7.0 Hz), 7.38–7.65 (m, 3H, H_{Ar}), 7.81–7.91 (m, 2H, H_{Ar}), 8.63 (d, 1H, H_{Ar}, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 28.13 ($OC(CH_3)_3$), 48.1 (CH_2), 83.4 ($OC(CH_3)_3$), 114.4 (CH), 119.9 (CH), 124.4 (CH), 124.5 (C), 124.8 (CH), 126.9 (CH), 127.3 (C), 128.8 (2×CH), 129.7 (CH), 136.9 (C), 138.6 (C), 145.9 (C), 151.2 (CO), 162.6 (CO); HRMS: m/z $[M]^+$ calcd for $C_{20}H_{20}N_3O_3$: 350.1505, found 350.1513.

*4.4.10. 11-Chloro-6-(4-methoxybenzyl)-pyrido[2′,1′:2,3]imidazo [5,4-c]benzazepin-7(6H)-one (**4j**).* Brown solid (78%); mp=132–134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.80 (s, 3H, CH_3), 4.08 (d, 1H, CH_2, J=14.8 Hz), 4.26 (d, 1H, CH_2, J=14.8 Hz), 4.53 (d, 1H, CH_2, J=14.8 Hz), 5.03 (d, 1H, CH_2, J=14.8 Hz), 6.84 (d, 2H, $H_{4'}$, $H_{6'}$, J=8.3 Hz), 7.15 (d, 1H, H_{Ar}, J=7.5 Hz), 7.25–7.37 (m, 4H, H_{Ar}), 7.50–7.56 (m, 1H, H_{Ar}), 7.74–7.82 (m, 2H, H_{Ar}), 8.61 (s, 1H, H_{12}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 49.8 (CH_2), 50.3 (CH_2), 55.4 (CH_3), 114.1 (2×CH), 120.0 (CH), 122.2 (CH), 122.4 (C), 124.2 (C), 124.3 (CH), 127.1 (CH), 127.2 (C), 128.0 (CH), 128.8 (CH), 129.1 (CH), 129.2 (C), 130.1 (2×CH), 137.0 (C), 140.1 (C), 144.2 (C), 159.3 (C), 163.5 (CO); HRMS: m/z $[M]^+$ calcd for $C_{23}H_{19}N_3O_2Cl$: 404.1166, found 404.1158.

4.5. Procedure synthesis of 5-benzyl-2-methyl-8,9,10,11-tetrahydropyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-7(6*H*)-one (5)

A solution of compound (**4a**) in DMF was hydrogenated with 10% palladium on carbon under H_2 (100 psi) for four days. After the catalyst was filtered off, the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH) to give 2-methyl-8,9,10,11-tetrahydropyrido[2′,1′:2,3] imidazo[5,4-*c*]quinolin-7(6*H*)-one (**5**) yellow solid (84%); mp>250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.01–2.04 (m, 2H, CH_2, H_9), 5.18–2.24 (m, 2H, CH_2, H_{10}), 2.40 (s, 3H, CH_3), 3.13 (t, 2H, CH_2, H_8, J=3.8 Hz), 4.51 (t, 2H, CH_2, H_{11}, J=3.8 Hz), 5.61 (s, 2H, CH_2), 7.10–7.27 (m, 7H, H_{Ar}), 7.92 (s, 1H, H_1); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 19.8 (CH_2), 21.1 (CH_3), 23.2 (CH_2), 25.9 (CH_2), 45.8 (CH_2), 46.6 (CH_2), 114.3 (C), 116.6 (CH), 121.14 (CH), 126.61 (2×CH), 126.66 (C), 127.03 (2×CH), 128.67 (CH), 128.89 (CH), 130.56 (C), 131.35 (C), 132.54 (C), 135.03 (C), 137.14 (C), 150.15 (C), 150.18 (C), 158.23 (CO); HRMS: m/z $[M]^+$ calcd for $C_{22}H_{22}N_3O$: 344.1763, found 344.1765.

4.6. Deprotection of PMB group of various 10-(*p*-methoxybenzyl)pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-ones (6); General procedure

To a soln of 10-(*p*-methoxybenzyl)pyrido [2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-one **4** dissolved in TFA (5 mL) in a vial microwave tube was added, under argon. The vial was sealed with a silicon septum and subjected to microwave irradiation at 130 °C for 3 h, with stirring. The reaction vessel was allowed to cool to rt, concentrated in vacuo to dryness, water was added to the residue and then extracted with CH_2Cl_2 (15 mL). The organic layer was washed successively with saturated aqueous $NaHCO_3$, water and brine, and dried over $MgSO_4$. The solvent was concentrated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH) to give the desired product (**6**).

*4.6.1. 2-Methyl-pyrido[2′,1′:2,3]imidazo[5,4-c]quinolin-6-one (**6a**).* Yellowish solid (98%); mp>250 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.48 (s, 3H, CH_3), 7.27–7.35 (m, 2H, H_{Ar}), 7.46 (d, 1H, $H_{5'}$, J=8.5 Hz), 7.66–7.69 (m, 1H, H_{Ar}), 7.89–7.90 (m, 1H, H_{Ar}), 8.30 (s, 1H, $H_{3'}$), 9.48–9.49 (m, 1H, H_{Ar}), 11.92 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 20.56(CH_3), 99.45 (C), 111.8 (C), 114.5 (CH), 116.2 (CH), 117.8 (CH), 120.3 (CH), 128.5 (CH), 128.8 (CH), 128.9 (CH), 131.7 (C), 132.8 (C), 144.4 (C), 133.5 (C), 157.3 (CO); HRMS: m/z $[M]^+$ calcd for $C_{15}H_{12}N_3O$: 250.0980, found 250.0992.

*4.6.2. Pyrido[2′,1′:2,3]imidazo[5,4-c]quinolin-6-one (**6b**).* Brown solid (88%); mp>250 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 7.20–7.26

(m, 1H, H_{Ar}), 7.33–7.39 (m, 1H, H_{Ar}), 7.50–7.62 (m, 3H, H_{Ar}), 7.88 (d, 1H, H_{Ar}, J=7.5 Hz), 8.49–7.52 (m, 1H, H_{Ar}), 9.36–9.39 (m, 1H, H_{Ar}), 11.90 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 99.9 (C), 112.2 (C), 114.1 (CH), 116.3 (CH), 118.6 (CH), 120.6 (CH), 122.2 (CH), 127.4 (CH), 127.9 (CH), 128.0 (CH), 134.3 (C), 135.5 (C), 154.5 (C), 158.1 (CO); HRMS: m/z [M]$^+$ calcd for $C_{14}H_{10}N_3O$: 236.0824, found 236.0821.

*4.6.3. 10-Chloro-2-methylpyrido[2′,1′:2,3]imidazo[5,4-c] quinolin-6-one (**6c**).* Brown solid (81%); mp>250 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.50 (s, 3H, CH_3), 7.33 (d, 1H, H_{Ar}, J=8.5 Hz), 7.41–7.45 (m, 1H, H_{Ar}), 7.65–7.69 (m, 1H, H_{Ar}), 7.90–7.94 (m, 1H, H_{Ar}), 8.35 (s, 1H, H_1), 9.54 (s, 1H, H_{11}), 8.24 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 20.40(CH_3), 94.7 (C), 111.5 (C), 116.2 (CH), 119.6 (C), 120.6 (CH), 121.4 (CH), 122.2 (C), 127.8 (CH), 129.1 (CH), 129.4 (CH), 131.8 (C), 133.6 (C), 157.2 (CO); HRMS: m/z [M]$^+$ calcd for $C_{15}H_{11}N_3OCl$: 284.0591, found 284.0593.

*4.6.4. 2,9-Dimethyl-pyrido[2′,1′:2,3]imidazo[5,4-c]quinolin-6-one (**6d**).* Brown solid (85%); mp>250 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.48 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 7.33 (d, 1H, H_{10}, J=4.5 Hz), 7.37 (d, 1H, H_3, J=5.3 Hz), 7.46 (d, 1H, H_4, J=5.3 Hz), 7.73 (s, 1H, H_1), 8.27 (s, 1H, H_8), 9.44 (d, 1H, H_{11}, J=4.5 Hz), 12.19 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 20.5(CH_3), 21.1(CH_3), 111.0 (C), 113.6 (CH), 116.5 (CH), 118.5 (CH), 120.5 (CH), 125.8 (C), 128.1 (C), 128.4 (CH), 129.6 (CH), 132.3 (C), 133.7 (C), 144.2 (C), 155.4 (C), 158.3 (CO); HRMS: m/z [M]$^+$ calcd for $C_{16}H_{14}N_3O$: 264.1137, found 264.1150.

*4.6.5. 10-Methoxy-2-methyl-pyrido[2′,1′:2,3]imidazo[5,4-c] quinolin-6-one (**6e**).* Yellowish solid (94%); mp>250 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 2.48 (s, 3H, CH_3), 4.0 (s, 3H, OCH_3), 7.28–7.32 (m, 1H, H_{Ar}), 7.39–7.44 (m, 2H, H_{Ar}), 7.46 (d, 1H, H_{Ar}, J=9.8 Hz), 8.16 (s, 1H, H_{Ar}), 8.60–8.62 (m, 1H, H_{Ar}), 11.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 60.9 MHz): δ 20.7(CH_3), 56.7(OCH_3), 109.3 (CH), 112.1 (C), 116.1 (CH), 118.9 (CH), 120.2 (CH), 122.9 (CH), 126.2 (CH), 128.5 (CH), 131.3 (C), 133.4 (C), 134.5 (C), 143.9 (C), 149.5 (C), 157.8 (CO); HRMS: m/z [M]$^+$ calcd for $C_{16}H_{14}N_3O_2$: 280.1086, found 280.1089.

*4.6.6. 10(11)-Aryl-pyrido[2′,1′:2,3]imidazo[5,4-c]heterocycles (**7**) under microwaves irradiation; general procedure.* To a soln of 10-chloro-5-(4-methoxybenzyl)-2-methyl-pyrido[2′,1′:2,3]imidazo[5,4-*c*]quinolin-6(5*H*)-one (**4d**) and 11-chloro-6-(4-methoxybenzyl)-pyrido[2′,1′:2,3] imidazo[5,4-*c*]benzazepin-7(6*H*)-one (**4j**) (0.1 g) dissolved in dioxane–EtOH (2:1, 2 mL) in a vial microwave tube were added under argon a stirrer bar, aryl boronic acid (1.2 equiv), K_2CO_3 (2 equiv), and $Pd(PPh_3)_4$ (0.1 equiv). The reaction vessel was sealed with a silicon septum and subjected to microwave irradiation at 150 °C for 2 h with stirring. The mixture was then allowed to cool to rt, diluted with CH_2Cl_2 (15 mL) and extracted (3×). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The crude material obtained was purified by column chromatography (silica gel, EtOAc–PE) to give the desired product (**7**).

*4.6.7. 10-(4-Methoxyphenyl)-5-(4-methoxybenzyl)-2-methyl-pyrido[2′,1′:2,3]imidazo[5,4-c]quinolin-6(5H)-one (**7a**).* Brown solid (88%); mp=134–136 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.50 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 5.67 (s, 2H, CH_2), 6.79 (d, 2H, H_{Ar}, J=9.8 Hz), 7.07–7.25 (m, 5H, H_{Ar}), 7.41 (d, 2H, H_{Ar}, J=8.8 Hz), 7.58–7.67 (m, 3H, H_{Ar}), 7.93–7.96 (m, 2H, H_{Ar}), 8.92 (s, 1H, H_{12}); NMR ^{13}C ($CDCl_3$, 62.9 MHz): δ 21.3(CH_3), 45.8 (CH_2), 55.3 (OCH_3), 55.6(OCH_3), 114.2 (2×CH), 114.3 (C), 115.0 (2×CH), 117.0 (CH), 119.6 (CH), 120.3 (CH), 123.0 (CH), 125.3 (C), 128.1 (2×CH), 128.5 (CH), 128.6 (2×CH), 128.8 (C), 129.0 (CH), 129.5 (C), 132.1 (C), 132.3 (C), 134.4 (C), 134.8 (C), 146.9 (C), 158.8 (C), 158.9 (C), 160.1 (CO); HRMS: m/z [M]$^+$ calcd for $C_{30}H_{26}N_3O_3$: 476.1974, found 476.1988.

*4.6.8. 5-(4-Methoxybenzyl)-2-methyl-10-(thiophen-3-yl)-pyrido[2′,1′:2,3] imidazo[5,4-c]quinolin-6(5H)-one (**7b**).* Yellow solid (97%); mp=241–243 °C; NMR ^{1}H ($CDCl_3$, 400 MHz): δ 2.46 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 5.60 (s, 2H, CH_2), 6.76 (d, 2H, $H_{4'}$, $H_{6'}$, J=8.8 Hz), 7.14 (d, 2H, $H_{3'}$ and $H_{7'}$, J=8.8 Hz), 7.17–7.18 (m, 1H, H_{Ar}), 7.32 (d, 1H, H_{Ar}, J=9.0 Hz), 7.42 (dd, 1H, H_{Ar}, J=1.2, 5.2 Hz), 7.42 (dd, 1H, H_{Ar}, J=3.0, 5.2 Hz), 7.58–7.63 (m, 2H, H_{Ar}), 7.83–7.87 (m, 2H, H_{Ar}), 8.90 (s, 1H, H_{12}); NMR ^{13}C ($CDCl_3$, 100.6 MHz): δ 21.1(CH_3), 45.4 (CH_2), 55.1 (OCH_3), 113.9 (C), 114.0 (2×CH), 116.7 (CH), 119.4 (CH), 119.9 (CH), 121.9 (CH), 122.6 (CH), 123.4 (C), 125.0 (C), 125.7 (CH), 127.5 (CH), 127.5 (CH), 127.8 (2×CH), 128.6 (C), 128.7 (CH), 132.0 (C), 134.2 (C), 134.7 (C), 137.5 (C), 146.6 (C), 158.5 (C), 158.6 (CO); HRMS: m/z [M]$^+$ calcd for $C_{27}H_{22}N_3O_2S$: 452.1433, found: 452.1450.

*4.6.9. {5-(4-Methoxybenzyl)-2-methyl-pyrido[2′,1′:2,3] imidazo [5,4-c]quinolin-6(5H)-on-10-yl}benzaldehyde (**7c**).* Yellow solid (88%); mp=241–243 °C; NMR ^{1}H ($CDCl_3$, 250 MHz): δ 2.49 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.63 (s, 2H, CH_2), 6.75–6.78 (m, 2H, H_{Ar}), 7.14–7.28 (m, 3H, H_{Ar}), 7.39 (d, 1H, H_{Ar}, J=10.0 Hz), 7.67 (d, 1H, H_{Ar}, J=7.5 Hz), 7.84–8.07 (m, 6H, H_{Ar}), 9.05 (s, 1H, H_{12}), 10.09 (s, 1H, CHO); NMR ^{13}C ($CDCl_3$, 60.9 MHz): δ 21.3(CH_3), 45.7(CH_2), 55.3(OCH_3), 114.0 (C), 114.16 (2×CH), 117.0 (CH), 120.0 (CH), 120.3 (CH), 124.5 (CH), 125.4 (C), 127.4 (C), 127.5 (CH), 128.0 (4×CH), 128.7 (C), 129.2 (CH), 130.7 (2×CH), 132.4 (C), 134.5 (C), 135.1 (C), 136.0 (C), 142.9 (C), 146.8 (C), 158.6 (C), 158.8 (CO), 191.5 (CHO); HRMS: m/z [M]$^+$ calcd for $C_{30}H_{24}N_3O_3$: 474.1818, found 474.1812.

*4.6.10. 6-(4-Methoxybenzyl)-11-(thiophen-3-yl)-pyrido[2′,1′:2,3] imidazo[5,4-c]benzazepin-7(6H)-one (**7d**).* Yellow solid (82%); mp=143–145 °C; NMR ^{1}H ($CDCl_3$, 250 MHz): δ 3.80 (s, 3H, OCH_3), 4.09 (d, 1H, CH_2, J=15.0 Hz), 4.30 (d, 1H, CH_2, J=15.0 Hz), 4.52 (d, 1H, CH_2, J=15.0 Hz), 5.06 (d, 1H, CH_2, J=15.0 Hz), 6.85 (d, 2H, $H_{4'}$ and $H_{6'}$, J=8.5 Hz), 7.16 (d, 1H, H_{Ar}, J=7.25 Hz), 7.27–7.37 (m, 4H, H_{Ar}), 7.44–7.61 (m, 4H, H_{Ar}), 7.81–7.89 (m, 2H, H_{Ar}), 8.75 (s, 1H, H_{12}); NMR ^{13}C ($CDCl_3$, 60.9 MHz): δ 49.7(CH_2), 50.3(CH_2), 55.4(CH_3), 114.0 (2×CH), 119.5 (CH), 120.7 (CH), 121.6 (CH), 123.5 (C), 124.2 (C), 124.4 (CH), 125.8 (CH), 127.0 (CH), 127.5 (CH), 127.6 (C), 128.4 (CH), 128.7 (CH), 129.0 (CH), 129.4 (C), 130.1 (2×CH), 136.8 (C), 137.8 (C), 139.8 (C), 145.1 (C), 159.2 (C), 163.7 (CO); HRMS: m/z [M]$^+$ calcd for $C_{27}H_{22}N_3O_2S$: 452.1433, found 452.1444.

*4.6.11. {6-(4-methoxybenzyl)-pyrido[2′,1′:2,3]imidazo[5,4-c]benzazepin-7(6H)-on-11-yl}benzaldehyde (**7e**).* Brown solid (85%); mp=241–243 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.80 (s, 3H, OCH_3), 4.11 (d, 1H, CH_2, J=15.0 Hz), 4.30 (d, 1H, CH_2, J=15.0 Hz), 4.54 (d, 1H, CH_2, J=15.0 Hz), 5.05 (d, 1H, CH_2, J=15.0 Hz), 6.83–6.86 (m, 2H, H_{Ar}), 7.18 (d, 1H, H_{Ar}, J=7.5 Hz), 7.27–7.39 (m, 3H, H_{Ar}), 7.52–7.64 (m, 2H, H_{Ar}), 7.74–7.77 (m, 2H, H_{Ar}), 7.87–7.93 (m, 2H, H_{Ar}), 7.99–8.02 (m, 2H, H_{Ar}), 8.81 (s, 1H, H_{12}), 10.07 (s, 1H, CHO); NMR ^{13}C ($CDCl_3$, 60.9 MHz): δ 49.8(CH_2), 50.3(CH_2), 55.4(CH_3), 114.0 (2×CH), 119.8 (CH), 122.3 (CH), 124.4 (CH), 126.7 (CH), 127.2 (C), 127.4 (C), 127.7 (2×CH), 128.7 (CH), 128.8 (CH), 129.1 (CH), 129.2 (C), 130.0 (2×CH), 130.6 (2×CH), 135.9 (C), 136.9 (C), 140.1 (C), 142.9 (C), 145.2 (C), 159.2 (C), 163.5 (C), 163.6 (CO), 191.5 (CHO); HRMS: m/z [M]$^+$ calcd for $C_{30}H_{24}N_3O_3$: 474.1818, found 474.1815.

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