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Original article

Synthesis and biological evaluation of 2,3-diarylimidazo[1,2-*a*]pyridines as antileishmanial agents

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ABSTRACT

A novel series of 2,3-diarylimidazo[1,2-*a*]pyridines was synthesized and evaluated for their antileishmanial activities. Four derivatives exhibited good activity against the promastigote and intracellular amastigote stages of *Leishmania major*, coupled with a low cytotoxicity against the HeLa human cell line. The impact of compound lipophilicity on antiparasitic activities was investigated by Log *D* comparison. Although *Lm*CK1 could be the parasitic target for three compounds (**13**, **18**, **21**), the inhibition of another target is under study to explain the antileishmanial effect of the most promising compounds.

1. Introduction

Leishmaniasis remains a public health problem worldwide, affecting approximately 12 million people in 88 countries; 50,000 die of it each year. The disease is caused by *Leishmania*, obligate intracellular vector-borne parasites. In spite of its huge health impact on the populations in vast areas, leishmaniasis is one of the most neglected diseases [1–4]. The life cycle of *Leishmania* involves the transmission of flagellated promastigotes by phlebotomine sandfly bites that invade macrophages and rapidly transform into the infective form of the parasite (amastigote stage) which actively divides within the mononuclear phagocytes. In humans, the disease occurs in at least four major forms, depending on the parasite species and the cellular immune response of the patient, that are called cutaneous leishmaniasis (CL), diffuse cutaneous leishmaniasis (DCL), mucocutaneous leishmaniasis (MCL) and visceral leishmaniasis (VL) [5].

Concerning therapy, pentavalent antimonials remain the first-line leishmaniasis treatment although miltefosine, an orally active hexadecylphosphocholine, is now widely used for VL in all regions where antimonial resistance is widespread. Other drugs that may be used include pentamidine and amphotericin B. However these drugs display some limitations such as long-term parenteral administration, toxicity, high cost in endemic countries, resistance and a high rate of treatment failure in HIV co-infected patients [5]. Other drugs such as paromomycin, sitamaquine, azoles and azithromycin have been reported with variable cure rates [1–5]. Moreover, there is no effective vaccine to prevent leishmaniasis. Consequently there is still a real need for new active compounds that can provide therapeutic benefits but with fewer side effects.

Recently, selenocyanates and diselenides were described as a new class of potent antileishmanial agents [6]. 3,7-Disubstituted pyrazolo[4,3-*d*]pyrimidines also displayed promising inhibition

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activity against *Leishmania donovani* axenic amastigotes [7]. In addition, novel 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-amines exhibited good antileishmanial activity against the promastigote and amastigote forms of *Leishmania major* [8].

We previously discovered 3-imidazolylalkylindoles to be highly active against *Leishmania mexicana* amastigotes [9–11] and mechanism of action study suggested that the compounds interfere with the ergosterol synthesis leading to plasmatic membrane disruption [12]. We also evidenced that imidazolidin-2-one derivatives exhibited antileishmanial activity through inhibition of PKC activity and the parasite host cell invasion process [13], highlighting that *Leishmania* protein kinases could be relevant therapeutic target for the design of new antileismanial candidates [14]. Indeed, several other protein kinases namely cyclin-dependent kinases (CDKs) [7,15], mitogen-activated protein kinases (MAPKs) [16,17], casein kinase 1 (CK1) [18] or Aurora kinase [19], have been shown to be involved in parasite growth and survival.

The pharmacological interest of the imidazo[1,2-*a*]pyridine ring system has been well established [20]. In order to find new drugs with antileishmanial activity, we have synthesized and evaluated new 2,3-diarylimidazo[1,2-*a*]pyridine-based compounds against promastigote and amastigote forms of *L. major*. In addition, to explore putative mechanism of action of the most active compounds, kinase activity assessments were performed on *L. major* PKC (*Lm*PKC) and *L. major* CK1.2 (*Lm*CK1.2 (lmjF35.1010)).

2. Results and discussion

2.1. Chemistry

We were interested in preparing 2-arylimidazo[1,2-*a*]pyridines as intermediates for synthesizing target compounds. As recently described [21], our initial approach involved the preparation of imidazo[1,2-*a*]pyridin-2-yl triflate **1** from commercially available 2-aminopyridine in a two-step reaction (Scheme 1). A subsequent Suzuki cross-coupling reaction gave the desired products **2**–**10**. The results (Table 1) indicate that **1** can be effectively arylated with various arylboronic acids, although the yield is dependent on the nature of the arylboronic acid. Arylboronic acids with electron-donating groups gave better yields (compounds **8** and **9**) in comparison with their electron-withdrawing counterparts (compounds **6** and **7**). Surprisingly arylation occurred in very good yield in the presence of 2-fluoro derivative **4**. Indeed, even if both Suzuki couplings with 2-fluoro and 4-fluoro derivatives led to completion of the reaction, the difference of the yield (41% *vs* 97%) seems to result from a deficient extraction rate for compound **3**.

The direct arylation reaction at the 3-position was examined using 2-arylimidazo[1,2-*a*]pyridines **2**–**10** and aryl halides, applying optimized reaction conditions [21,22]. In the presence of $Pd(OAc)_2$ (2 mol %), $PCy_3 \cdot HBF_4$ (4 mol %), PivOH (0.3 equiv), K_2CO_3 (1.5 equiv), the reaction proceeded smoothly (10–48 h) in *N*,*N*-dimethylacetamide (DMA) at 100 °C and in a sealed tube. A variety of substituents are tolerated on aryl halide.

Bromobenzene, nitro-, cyano-, ethoxycarbonyl-, methoxyphenyl bromides, pyridyl and pyrimidyl bromides reacted efficiently with 2-phenylimidazo[1,2-*a*]pyridine **2** (Table 1, compounds **11**,**13**, **16**–**22**). 3-Bromothiophene was not able to undergo direct arylation in reasonable yield due to degradation of the reaction mixture. Using 4-bromotoluene and 4-iodophenyl acetate as reagents, compounds **12** and **14** were respectively obtained, but in moderate yields. For the last one, pivalic acid ester **15** was also isolated, resulting from a side reaction between phenol derivative **14**, obtained by *in situ* hydrolysis of acetate function, and pivalic acid in the reaction medium.

We thought that this methodology could be extended to the synthesis of various diarylimidazo[1,2-*a*]pyridines bearing substituted phenyl ring at the 2-position, thus providing diversity for structure–activity relationship study. As previously discussed in the literature [21], the desired products **24**–**36** were prepared in low to good yields, depending on electronic effects of substituted phenyl in position 2 of imidazo[1,2-*a*]pyridine scaffold.

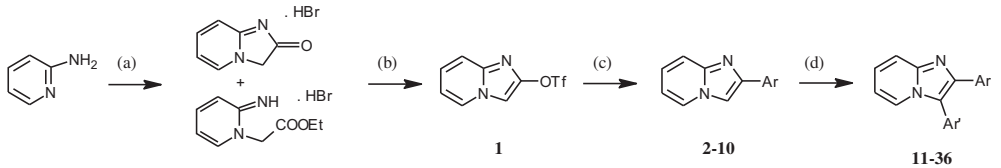
Finally, acetyl analogue **37** of compound **15** was synthesized by reaction between phenol derivative **14** and acetic anhydride in pyridine at room temperature (Scheme 2).

Hydrogenation of nitro derivative **16**, using a Raney-Nickel catalyst, led to the corresponding aromatic amine **38** in good yield. Amide analogue **39** was isolated by hydration of cyano precursor **17** in the presence of hydrogen peroxide and potassium carbonate in dimethyl sulfoxide at room temperature.

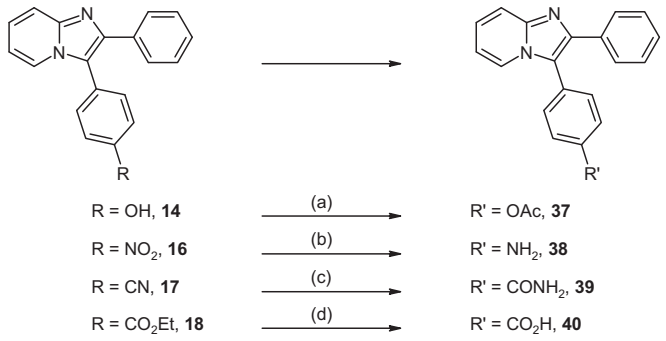
Table 1
Structures of 2-arylimidazo[1,2-*a*]pyridines **2**–**10** and 2,3-diarylimidazo[1,2-*a*]pyridines **11**–**36**.

Compd	Ar	Time	Yield[a] (%)	Compd	Ar′	Time	Yield[a] (%)
2	C_6H_5	7 h	43	**11**	C_6H_5	16 h	95
				12	4-MeC_6H_4	48 h	45
				13	4-$MeOC_6H_4$	24 h	81
				14	4-HOC_6H_4	12 h	53[b]
				15	4-$PivOC_6H_4$	12 h	6[c]
				16	4-$(NO_2)C_6H_4$	36 h	93
				17	4-$(CN)C_6H_4$	18 h	99
				18	4-$(CO_2Et)C_6H_4$	18 h	98
				19	3,5-$(Cl)_2C_6H_3$	12 h	68
				20	3-Pyridyl	48 h	90
				21	4-Pyridyl	16 h	85
				22	5-Pyrimidyl	12 h	73
				23	3-Thienyl	48 h	14
3	4-FC_6H_4	1 h	41	**24**	C_6H_5	15 h	60
				25	3-$(NO_2)C_6H_4$	16 h	92
				26	3-Pyridyl	15 h	56
4	2-FC_6H_4	1 h	97	**27**	C_6H_5	31 h	64
				28	3-Pyridyl	14 h	85
5	3-ClC_6H_4	6 h	45	**29**	C_6H_5	21 h	83
6	4-$(CO_2Et)C_6H_4$	45 min	9	**30**	C_6H_5	13 h	27
7	4-$(NO_2)C_6H_4$	4 h	26	**31**	C_6H_5	18 h	15
8	4-$MeOC_6H_4$	45 min	78	**32**	C_6H_5	10 h	81
				33	3-$(NO_2)C_6H_4$	21 h	67
9	2-$MeOC_6H_4$	1 h	94	**34**	C_6H_5	21 h	84
10	3,5-$(Cl)_2C_6H_3$	45 min	35	**35**	C_6H_5	18 h	83
				36	3-Pyridyl	15 h	69

[a] Isolated yields.
[b] Ar′X = 4-iodophenyl acetate.
[c] Side reaction from **14**.



Scheme 1. *Reagents and conditions*: (a) $BrCH_2CO_2Et$, 0 °C → rt, 15 min, then EtOH, reflux, 18 h; (b) $PhNTf_2$, Et_3N, toluene, reflux, 20 h, 67% (two steps); (c) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane/H_2O (2/1), sealed tube, 100 °C; (d) Ar′X (X = Br, I), $Pd(OAc)_2$, $PCy_3 \cdot HBF_4$, PivOH, K_2CO_3, DMA, sealed tube, 100 °C.



Scheme 2. *Reagents and conditions*: (a) Ac_2O, pyridine, r.t., 12 h, 63%; (b) H-Cube®, H_2 10 bar, Ni Raney, EtOH/THF (5/1), r.t., 81%; (c) H_2O_2, K_2CO_3, DMSO, r.t., 12 h, 66%; (d) 2 M NaOH, EtOH, reflux, 1.5 h, 19%.

Saponification of ester **18**, using classical conditions, afforded the desired carboxylic acid **40** but in a low yield.

2.2. Biological evaluation

2.2.1. In vitro antileishmanial activity against promastigotes

In this study, antileishmanial activity of thirty compounds was evaluated. Inhibitory concentrations 50 (IC_{50}) on *L. major* promastigote stage are reported in Table 2. Pentamidine was used as control drug. Eight compounds (**12**, **13**, **15**, **16**, **18**, **19**, **21** and **29**) displayed IC_{50} values less than 10 μM and could be considered as active as pentamidine.

Generally, most active compounds were obtained from 2-phenylimidazo[1,2-*a*]pyridine series (**11**–**23**, **37**–**40**), except compound **29**. The basic molecular structure 2,3-diphenylimidazo [1,2-*a*]pyridine **11** offered only moderate efficacy. Based on a comparison of compounds **13**, **16**, **18**, **19** (IC_{50} values of 7.2, 4.9, 5.2 and 7.7 μM, respectively) with analogues **32**, **31**, **30**, **35** (IC_{50} values of 26.6, 30.0, 40.0, 39.0 μM), switching substituents between positions 2 and 3 of the imidazo[1,2-*a*]pyridine ring led to decrease in activity. The presence of the atom of chlorine in meta position of 2-aryl seemed to influence markedly the antileishmanial activity against promastigotes (compounds **29** and **35**).

In the second series (**24**–**36**), consisting of imidazo[1,2-*a*]pyridines bearing a substituted phenyl in position 2 and a substituted or unsubstituted aryl ring in position 3, most of the compounds remained weakly active or inactive on promastigote form of *L. major* exhibiting IC_{50} values superior to 10 μM.

Considering structure–activity relationships (SARs) of 2-phenylimidazo[1,2-*a*]pyridines (**11**–**23**, **37**–**40**), 4-Me (**12**), 4-OMe (**13**), 4-OPiv (**15**) but also 4-NO_2 (**16**) or 4-CO_2Et (**18**) substitution pattern on the 3-phenyl ring was consistent with antileishmanial potency. Therefore, both electron-donating and electron-withdrawing groups could be tolerated. Hydrophilic groups seemed to be deleterious for the activity since 4-OH (**14**), 4-NH_2 (**38**) or 4-CO_2H (**40**) substitution produced only inactive compounds with the highest IC_{50} values. In addition, 4-CN derivative **17** and the corresponding amide **39** exhibited no activity. Finally, acetylated compound **37** (IC_{50} value of 16.0 μM) was less potent than its bulkier pivaloyl counterpart. One example of disubstituted compound **19** (3,5-diCl) provided interesting results with an IC_{50} value of 7.7 μM.

We also checked the influence, on biological activity, of the introduction of a heteroaryl moiety in position 3 of 2-phenylimidazo[1,2-*a*]pyridine scaffold. 5-Pyrimidyl analogue **22** was totally inactive, whereas 3-thiophenyl (**23**) and 3-pyridyl (**20**) derivatives displayed only moderate to low potency. Shifting of the nitrogen from meta to para position of the pyridyl appendage afforded a 3.5-fold more potent compound **21** with an IC_{50} value of 6.5 μM.

2.2.2. Cytotoxicity

Cytotoxicity on HeLa cell line was evaluated for compounds that exhibited good to moderate antileishmanial activity (i.e. $IC_{50} < 45$ μM) against promastigotes (Table 2) in order to identify drugs which were less toxic to human cells and as a prelude to selecting drugs for *in vitro* assay on relevant clinical *Leishmania* amastigote stage.

IC_{50} values ranged from 4 to 554 μM and most of drugs had IC_{50} less than 100 μM. The selectivity index (SI) was calculated as the ratio of cytotoxicity (IC_{50} value on HeLa cells) to activity (IC_{50} value on promastigotes). This *in vitro* therapeutic index showed that compounds **30** and **31**, belonging to the second series of 2,3-diarylimidazo[1,2-*a*]pyridines possessed the better selectivity profile (SI of 8.65 and 18.46, respectively). Concerning the first series, among the most active compounds on *L. major* promastigote stage, SI was better than that of pentamidine (3.13) for three molecules: **15**, **16** and **21** (SI = 5.43, 5.51 and 3.85, respectively). In contrast **12**, **13**, **18**, **19** and **29** showed a very low SI (less or equal to 2.34) explaining that they were less suitable for further investigation.

2.2.3. In vitro antileishmanial activity against amastigotes

In view to study antileishmanial activity against amastigotes, compounds were selected according to its high level of activity against promastigotes and/or its high selectivity index. For better understanding of SAR study, the direct analogues, at the positions 2 and 3 of diarylimidazo[1,2-*a*]pyridine heterocycle, were also preferably chosen for additional amastigote testing. Three biological profiles were observed. First profile concerns the compounds **12**, **13**, **15**, **16**, **19** and **29** that exhibit antileishmanial activity on both promastigote and amastigote stages of *L. major* as shown in Table 2 and Fig. 1A.

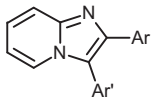
Among them, derivatives **15** and **16** displayed low cytotoxicity as noted above. Moreover, antileishmanial potency against promastigotes was not conserved on intracellular amastigote form for compounds **18** and **21**. Finally, weakly active compounds **11**, **30**, **31**, **32** and **35**, on promastigote form, were found to be very active on infected macrophages when treated at 10 μM (84–95% inhibition of amastigote burden). Interestingly, compound **35** remained active at only 1 μM coupled with low cytotoxicity on HeLa cells (IC_{50} value of 67 μM). Compounds **15**, **30** and **31** were also able to reduce percentage of infected macrophages (Fig. 1B).

2.2.4. Determination of compound lipophilicity

There are physical differences between the test systems on promastigote and amastigote forms of *L. major* which could give some explanations of the results obtained. Promastigote assay uses extracellular axenic parasite, making it more accessible than the intracellular amastigotes which are in mouse peritoneal macrophage phagolysosomes. Indeed, during the process of invasion, the parasite initiates the formation of a membrane, the so-called parasitophorous vacuole membrane, which surrounds the intracellular parasite. Penetration of the two membranes (i.e. plasmatic and vacuole) is therefore an important criterion for activity and can differ from a compound to the other, depending on its hydrophobic character.

In addition, in the macrophage system, the *L. major* amastigotes are in acidic phagolysosomal compartments (pH 4.7–5.2) [23], whereas the promastigote assays are performed at pH 7. This factor may also affect the biological results since physicochemical properties of the compound, associated with ionized molecule or not, are linked to its pK_a and pH value in culture medium.

Table 2
In vitro antileishmanial activities of 2,3-diarylimidazo[1,2-*a*]pyridines **11**–**40** against promastigotes and intracellular amastigotes of *L. major*, and cytotoxicity evaluation.



Compd	Ar	Ar′	IC_{50} ± SEM (μM)[a] *L. major* promastigotes	IC_{50} ± SEM (μM)[a] cytotoxicity on HeLa cells	Selectivity index cytotoxicity (IC_{50})/anti promastigotes activity (IC_{50})	% Inhibition[a] (conc. μM) *L. major* intracellular amastigotes
Pentamidine			4.8 ± 0.8	15 ± 0.2	3.13	99 (10)
11	C_6H_5	C_6H_5	22.5 ± 0.6	31 ± 3	1.38	84 (10)
12		4-MeC_6H_4	4.0 ± 0.4	4 ± 2	1.00	96 (10)
13		4-$MeOC_6H_4$	7.2 ± 0.3	14 ± 2	1.92	71 (10)
14		4-HOC_6H_4	40.0 ± 6.1	16 ± 6	0.40	n.d.
37		4-$AcOC_6H_4$	16.0 ± 6.1	40 ± 1	2.50	n.d.
15		4-$PivOC_6H_4$	7.0 ± 1.0	38 ± 7	5.43	95 (10)
16		4-$(NO_2)C_6H_4$	4.9 ± 0.2	27 ± 3	5.51	68 (10)
38		4-$(NH_2)C_6H_4$	43.0 ± 2.0	28.1 ± 8.7	0.65	n.d.
17		4-$(CN)C_6H_4$	>100	n.d.		n.d.
39		4-$(CONH_2)C_6H_4$	27.0 ± 3.2	27 ± 2	1.00	n.d.
18		4-$(CO_2Et)C_6H_4$	5.2 ± 1.0	5 ± 1	0.96	18 (10)
40		4-$(CO_2H)C_6H_4$	>100	n.d.		n.d.
19		3,5-$(Cl)_2C_6H_3$	7.7 ± 0.2	18 ± 3	2.34	79 (10)
20		3-Pyridyl	22.5 ± 6.0	4 ± 1	0.18	n.d.
21		4-Pyridyl	6.5 ± 1.6	25 ± 11	3.85	32 (10)
22		5-Pyrimidyl	>100	n.d.		n.d.
23		3-Thienyl	14.3 ± 2.2	35 ± 2	2.45	n.d.
24	4-FC_6H_4	C_6H_5	23 ± 4	72 ± 2	3.13	n.d.
25		3-$(NO_2)C_6H_4$	>100	n.d.		n.d.
26		3-Pyridyl	38.3 ± 7.4	87 ± 25	2.27	n.d.
27	2-FC_6H_4	C_6H_5	39.0 ± 1.0	18 ± 3	0.46	n.d.
28		3-Pyridyl	34.8 ± 1.9	29 ± 1	0.83	n.d.
29	3-ClC_6H_4	C_6H_5	4.4 ± 1.9	5 ± 1	1.14	94 (10)
30	4-$(CO_2Et)C_6H_4$	C_6H_5	40.0 ± 1.1	346 ± 174	8.65	86 (10)
31	4-$(NO_2)C_6H_4$	C_6H_5	30.0 ± 2.0	554 ± 48	18.46	84 (10)
32	4-$MeOC_6H_4$	C_6H_5	26.6 ± 1.5	48 ± 2	1.80	85 (10)
33		3-$(NO_2)C_6H_4$	14 ± 2	30 ± 2	2.14	n.d.
34	2-$MeOC_6H_4$	C_6H_5	18.2 ± 3.4	24 ± 14	1.32	n.d.
35	3,5-$(Cl)_2C_6H_3$	C_6H_5	39.0 ± 1.0	67 ± 2	1.71	71 (1)
36		3-Pyridyl	31.4 ± 2.8	28 ± 5	0.89	n.d.

SEM: standard error of the mean.
n.d.: not determined.
[a] Mean from at least three determinations.

To discuss this point of view, a pKa value close to 5.30 was calculated for the molecules depicted in Table 3, using pKa Plugin of MarvinSketch software from ChemAxon.

Lipophilicity was also determined by experimental procedure. In order to measure rapidly liquid–liquid partition coefficients, we used reversed-phase HPLC method, with standards and correlations [24]. Indeed, the logarithms of the retention factor of the solutes are linearly correlated with the logarithm of their partition coefficients as described first by Collander [25]. Logarithm of the distribution coefficient (Log *D*) of the compounds, between an organic phase (methanol) and an aqueous phase (buffer), was obtained at pH 4.5 and 7.5, near pH values of biological tests.

Variation of lipophilicity was observed between the two pH values, indeed, taking into account the pKa of 5.30, the molecules are not ionized at pH 7.5 and at pH 4.5 the protonated species are in majority in the medium. In conclusion, the physicochemical properties of the molecules can differ from testing conditions to the others. Considering Log *D* at pH 7.5, it seems that promastigote activity is not linked to lipophilicity of tested compounds since active and inactive molecules display the same Log *D* values (for example, compounds **19**: Log $D_{7.5} = 5.88$ and **35**: Log $D_{7.5} = 6.10$, Table 3).

Interestingly, as reported previously [26], very promising amastigote antileishmanial activities were correlated with a rise in lipophilicity as shown for compounds **15**, **16**, **19**, **29**, **30**, **31** and **35** (Log $D_{4.5}$ from 3.91 to 5.58). However, results observed for compounds **11**–**13**, **18** and **32** are not consistent with the previous observations. Indeed, other parameters are to be taken into account to explain more in depth the data, especially the variation of metabolite profiles of the tested compounds.

Finally, the target expression could differ between the two stages of the parasite, providing other hypothesis of the variability of the observed results.

2.2.5. Kinase inhibitory activities

To investigate mechanism of action, *Lm*CK1.2 inhibition study was performed for thirteen compounds as indicated in Table 4 [18]. Three compounds exhibited IC_{50} values inferior to 10 μM.

Taking into account the first results, antileishmanial activity against promastigotes seems to be only correlated with the inhibition of *Lm*CK1.2 for compounds **13**, **18** and **21**. However, no selectivity was observed against the *Leishmania* target since these same compounds were also able to inhibit porcine brain CK1 in the micromolar or submicromolar range. As noted for 4-pyridyl derivative **21**, the most active compound on CK1 kinases was one of the less active against amastigote form of *L. major*, and displayed the lowest lipophilicity (additional protonation of the pyridine nitrogen which could result in low cell permeability and thereby reduced biological effects). In a general approach, amastigote activity of the 2,3-diarylimidazo[1,2-*a*]pyridines was not correlated with *Lm*CK1.2 inhibition.

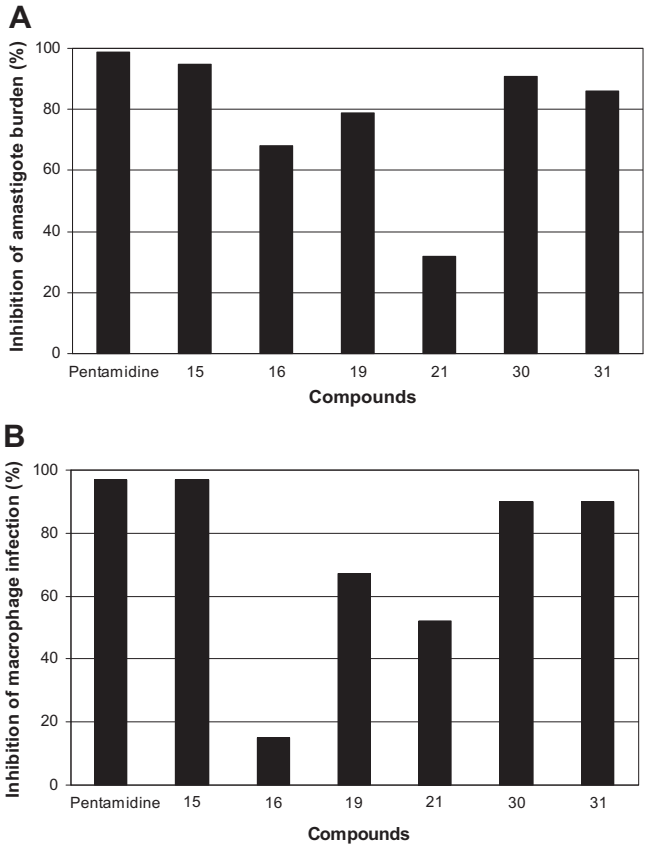


Fig. 1. *In vitro* activity against intramacrophage amastigotes of *L. major* at 10 μM.

Furthermore, compounds **15**, **30**, **31** and **35** were also tested for *L. major* PKC inhibition [13,14]. Nevertheless, none of them were able to reduce PKC activity.

Finally, it clearly appears that a different target has to be investigated to explain promising activities of these new anti-leishmanial agents.

3. Conclusion

We have developed a very promising 2,3-diarylimidazo[1,2-*a*]pyridine series, acting as antileishmanial agents. In addition, the synthetic pathway to achieve title compounds was also proved to be very easy and efficient. Among the thirty tested compounds against the promastigote form of *L. major*, thirteen were selected for anti-leishmanial testing against intracellular amastigotes. 2,3-Diarylimidazo[1,2-*a*]pyridines **15**, and especially, **30** and **31** exhibited very good antileishmanial activity against amastigotes and high therapeutic index. Analogue **35** was also of interest since its activity on intracellular amastigotes was conserved when testing at 1 μM-dose and its cytotoxicity was low on HeLa cells. An analysis of physicochemical properties demonstrated a link between lipophilicity and antiparasitic activity for the most promising compounds. Although *Lm*CK1.2 could be the parasitic target for three compounds (**13**, **18**, **21**), the inhibition of another target is under study to explain the antileishmanial effect of the most promising compounds.

4. Experimental protocols

4.1. Chemistry

All reactions were carried out under argon. All reactions were monitored by TLC analysis using Merck silica gel 60F-254 thin-layer plates. Column chromatography was carried out on silica gel Merck 60 (70–230 mesh ASTM). Melting points were determined on an Electrothermal IA 9000 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Paragon 1000 PC Perkin–Elmer spectrometer. ^{1}H and ^{13}C NMR spectra were performed in DMSO-d_6 using a Bruker AVANCE 400 MHz spectrometer. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane as internal standard and coupling constants (J) are given in hertz (Hz). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were recorded using an Electrospray Ionization Method with Waters ZQ 2000 spectrometer. Elemental analyses were performed on a Thermo Scientific Elemental Analyser Flash EA 1112 and were found within ±0.4% of the theoretical values.

4.1.1. Imidazo[1,2-a]pyridin-2-yl trifluoromethanesulfonate (*1*)

Compound **1** was synthesized according to previously described procedure [21].

4.1.2. Representative Suzuki coupling procedure for the synthesis of 2-arylimidazo[1,2-a]pyridines *2*–*10*

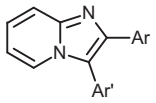
To a 10 mL vial with a magnetic stir bar were added imidazo[1,2-*a*]pyridin-2-yl trifluoromethanesulfonate **1** (400 mg, 1.5 mmol, 1 equiv), arylboronic acid (1.8 mmol, 1.2 equiv), sodium carbonate (382 mg, 3.6 mmol, 2.4 equiv) and tetrakis(triphenylphosphine) palladium(0) (87 mg, 5 mol %) in a mixture of 1,4-dioxane–water (13.5 mL, 2:1). The vial was sealed and purged with argon through the septum inlet for 5 min. The suspension was heated at 100 °C for 45 min to 7 h. After cooling, the resulting mixture was diluted with ethyl acetate, filtered through Celite® and washed with ethyl acetate. Water was added and the organic layer was extracted twice with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate as eluent. Trituration with diisopropylic ether afforded 2-arylimidazo[1,2-*a*]pyridine **2**–**10** (Fig. 2).

*4.1.2.1. 2-Phenylimidazo[1,2-a]pyridine (**2**).* Compound was obtained following the representative procedure, using imidazo[1,2-*a*]pyridin-2-yl trifluoromethanesulfonate **1** (400 mg, 1.5 mmol, 1 equiv), phenylboronic acid (368 mg, 3.0 mmol, 2 equiv), Na_2CO_3 (636 mg, 6.0 mmol, 4 equiv), $Pd(PPh_3)_4$ (87 mg, 5 mol %) and heating for 7 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (8/2) as eluent and to afford 2-phenylimidazo[1,2-*a*]pyridine **2** as a beige powder (125 mg, 43% yield).

Rf = 0.43 (petroleum ether/EtOAc: 6/4); Mp = 132–133 °C (lit. [27]: 130–132 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (d, 1H, ^{3}J = 6.6 Hz, H_5), 8.44 (s, 1H, H_3), 8.01 (d, 2H, ^{3}J = 7.2 Hz, H_a), 7.62 (d, 1H, ^{3}J = 8.4 Hz, H_8), 7.48 (dd, 2H, $^{3}J = {}^{3}J'$ = 7.2 Hz, H_b), 7.36 (t, 1H, ^{3}J = 7.2 Hz, H_c), 7.28 (ddd, 1H, ^{3}J = 8.4 Hz, ^{3}J = 7.0 Hz, ^{4}J = 0.8 Hz, H_7), 6.93 (ddd, 1H, ^{3}J = 7.0 Hz, ^{3}J = 6.6 Hz, ^{4}J = 0.4 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.99 (C), 144.52 (C), 134.09 (C), 128.87 ($2C_b$), 127.86 (C_c), 127.04 (C_5), 125.73 ($2C_a$), 125.10 (C_7), 116.81 (C_8), 112.43 (C_6), 109.26 (C_3). IR (KBr) cm^{-1}: 3043 ($\nu C{-}H_{ar}$), 1505, 1474 ($\nu C{=}C$ and $\nu C{=}N$). MS (ESI) m/z (%): 195.1 (100) $[M + H]^+$. Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.61; H, 5.28; N, 14.44.

*4.1.2.2. 2-(4-Fluorophenyl)imidazo[1,2-a]pyridine (**3**).* Compound was obtained following the representative procedure, using 4-fluorophenylboronic acid (252 mg, 1.8 mmol, 1.2 equiv) and heating for 1 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (8/2) as eluent to

Table 3
In vitro antileishmanial activities of 2,3-diarylimidazo[1,2-*a*]pyridines against promastigotes and intracellular amastigotes of *L. major*, and lipophilicity determination.



Compd	Ar	Ar′	IC_{50} ± SEM (μM)[a] *L. major* promastigotes	% Inhibition[a] (conc. μM) *L. major* amastigotes	Log *D*[b] pH 7.5	Log *D*[b] pH 4.5
Pentamidine			4.8 ± 0.8	99 (10)		
11	C_6H_5	C_6H_5	22.5 ± 0.6	84 (10)	4.50	2.15
12		4-MeC_6H_4	4.0 ± 0.4	96 (10)	5.13	2.61
13		4-$MeOC_6H_4$	7.2 ± 0.3	71 (10)	4.58	2.31
15		4-$PivOC_6H_4$	7.0 ± 1.0	95 (10)	5.90	4.04
16		4-$(NO_2)C_6H_4$	4.9 ± 0.2	68 (10)	4.35	3.29
18		4-$(CO_2Et)C_6H_4$	5.2 ± 1.0	18 (10)	5.19	3.59
19		3,5-$(Cl)_2C_6H_3$	7.7 ± 0.2	79 (10)	5.88	4.53
21		4-Pyridyl	6.5 ± 1.6	32 (10)	2.87	2.03
29	3-ClC_6H_4	C_6H_5	4.4 ± 1.9	94 (10)	5.25	3.91
30	4-$(CO_2Et)C_6H_4$	C_6H_5	40.0 ± 1.1	86 (10)	5.46	4.26
31	4-$(NO_2)C_6H_4$	C_6H_5	30.0 ± 2.0	84 (10)	4.65	4.20
32	4-$MeOC_6H_4$	C_6H_5	26.6 ± 1.5	85 (10)	4.59	2.04
35	3,5-$(Cl)_2C_6H_3$	C_6H_5	39.0 ± 1.0	71 (1)	6.10	5.58

SEM: standard error of the mean.
[a] Mean from at least three determinations.
[b] Lipophilicity determined by RP-HPLC method.

afford 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **3** as a white powder (131 mg, 41% yield).

Rf = 0.24 (petroleum ether/EtOAc: 7/3); Mp = 159–160 °C (lit. [27]: 158–160 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.56 (d, 1H, ^3J = 6.8 Hz, H_5), 8.42 (s, 1H, H_3), 8.04 (dd, 2H, ^3J = 8.8 Hz, ^4J = 5.2 Hz, H_a), 7.61 (d, 1H, ^3J = 8.4 Hz, H_8), 7.34–7.26 (m, 3H, H_7 and H_b), 6.94 (ddd, 1H, ^3J = 7.2 Hz, ^3J = 6.8 Hz, ^4J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.01 (d, ^1J = 242 Hz, C–F), 145.02 (C), 143.64 (C), 130.68 (d, ^4J = 3 Hz, C), 127.69 (d, ^3J = 9 Hz, $2C_a$), 127.09 (C_5), 125.22 (C_7), 116.79 (C_8), 115.77 (d, ^2J = 22 Hz, $2C_b$), 112.51 (C_6), 109.13 (C_3). IR (KBr) cm^{-1}: 3069 (νC–H_{ar}), 1595, 1435 (νC=C and νC=N), 1217 (νC–F). MS (ESI) *m*/*z* (%): 213.2 (100) $[M + H]^+$. Anal. Calcd for $C_{13}H_9FN_2$: C, 73.57; H, 4.27; N, 13.20. Found: C, 73.71; H, 4.43; N, 13.29.

*4.1.2.3. 2-(2-Fluorophenyl)imidazo[1,2-a]pyridine (**4**).* Compound was obtained following the representative procedure, using 2-fluorophenylboronic acid (252 mg, 1.8 mmol, 1.2 equiv) and heating for 1 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (8/2) as eluent to afford 2-(2-fluorophenyl)imidazo[1,2-*a*]pyridine **4** as a beige powder (309 mg, 97% yield).

Rf = 0.40 (petroleum ether/EtOAc: 7/3); Mp = 112–113 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 (d, 1H, ^3J = 6.8 Hz, H_5), 8.39 (s, 1H, H_3), 8.32 (ddd, 1H, ^3J = 9.6 Hz, ^3J = 7.6 Hz, ^4J = 2 Hz, H_b), 7.65 (d, 1H, ^3J = 9.2 Hz, H_8), 7.43–7.30 (m, 4H, H_7, H_a, H_c and H_d), 6.96 (ddd, 1H, ^3J = 7.6 Hz, ^3J = 6.8 Hz, ^4J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.75 (d, ^1J = 247 Hz, C–F), 144.32 (C), 137.91 (C), 129.36 (d, ^3J = 9 Hz, C_d), 128.62 (d, ^3J = 3 Hz, C_b), 127.28 (C_5), 125.63 (C_7), 124.94 (C_c), 121.60 (d, ^2J = 13 Hz, C), 116.78 (C_8), 116.02 (d, ^2J = 22 Hz, C_a), 112.60 (C_6), 112.49 (C_3). IR (KBr) cm^{-1}: 3051 (νC–H_{ar}), 1546, 1483 (νC=C and νC=N), 1210 (νC–F). MS (ESI) *m*/*z* (%): 213.0 (100) $[M + H]^+$. Anal. Calcd for $C_{13}H_9FN_2$: C, 73.57; H, 4.27; N, 13.20. Found: C, 73.51; H, 4.59; N, 13.56.

*4.1.2.4. 2-(3-Chlorophenyl)imidazo[1,2-a]pyridine (**5**).* Compound was obtained following the representative procedure, using 3-chlorophenylboronic acid (282 mg, 1.8 mmol, 1.2 equiv) and heating for 6 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (8/2) as eluent to

Table 4
Inhibition of *L. major* CK1 and porcine brain CK1 activities.

Compd	Ar	Ar′	IC_{50} (μM)[a] *L. major* CK1.2	IC_{50} (μM)[a] native porcine brain CK1δ/ε	IC_{50} ± SEM (μM)[a] *L. major* promastigotes	% Inhibition[a] (concentration μM) *L. major* amastigotes
11	C_6H_5	C_6H_5	>10	>10	22.5 ± 0.6	84 (10)
12		4-MeC_6H_4	>10	>10	4.0 ± 0.4	96 (10)
13		4-$MeOC_6H_4$	1.20	0.63	7.2 ± 0.3	71 (10)
15		4-$PivOC_6H_4$	>10	>10	7.0 ± 1.0	95 (10)
16		4-$(NO_2)C_6H_4$	>10	>10	4.9 ± 0.2	68 (10)
18		4-$(CO_2Et)C_6H_4$	4.00	7.10	5.2 ± 1.0	18 (10)
19		3,5-$(Cl)_2C_6H_3$	>10	>10	7.7 ± 0.2	79 (10)
21		4-Pyridyl	0.30	0.25	6.5 ± 1.6	32 (10)
29	3-ClC_6H_4	C_6H_5	>10	>10	4.4 ± 1.9	94 (10)
30	4-$(CO_2Et)C_6H_4$	C_6H_5	>10	>10	40.0 ± 1.1	86 (10)
31	4-$(NO_2)C_6H_4$	C_6H_5	>10	>10	30.0 ± 2.0	84 (10)
32	4-$MeOC_6H_4$	C_6H_5	>10	>10	26.6 ± 1.5	85 (10)
35	3,5-$(Cl)_2C_6H_3$	C_6H_5	>10	>10	39.0 ± 1.0	71 (1)

SEM: standard error of the mean.
[a] Mean from at least two or three determinations.

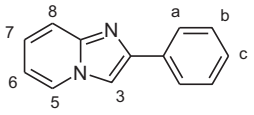


Fig. 2. 2-Arylimidazo[1,2-*a*]pyridines numbering for ^{1}H and ^{13}C NMR assignments.

afford 2-(3-chlorophenyl)imidazo[1,2-*a*]pyridine **5** as a beige powder (155 mg, 45% yield).

Rf = 0.34 (petroleum ether/EtOAc: 7/3); Mp = 109–110 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (d, 1H, ^{3}J = 6.8 Hz, H_5), 8.54 (s, 1H, H_3), 8.05 (dd, 1H, $^{4}J = {}^{4}J'$ = 2.0 Hz, H_a), 7.97 (ddd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 2.0 Hz, ^{4}J = 1.0 Hz, H_b), 7.63 (d, 1H, ^{3}J = 8.4 Hz, H_8), 7.51 (dd, 1H, $^{3}J = {}^{3}J'$ = 8.0 Hz, H_c), 7.42 (ddd, 1H, ^{3}J = 8.0 Hz, ^{4}J = 2.0 Hz, ^{4}J = 1.0 Hz, H_d), 7.31 (ddd, 1H, ^{3}J = 8.4 Hz, ^{3}J = 7.4 Hz, ^{4}J = 1.2 Hz, H_7), 6.96 (ddd, 1H, ^{3}J = 7.4 Hz, ^{3}J = 6.8 Hz, ^{4}J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.04 (C), 142.95 (C), 136.30 (C), 133.75 (C–Cl), 130.84 (C_c), 127.58 (C_d), 127.21 (C_5), 125.55 (C_7), 125.29 (C_a), 124.26 (C_b), 116.94 (C_8), 112.74 (C_6), 110.16 (C_3). IR (KBr) cm^{-1}: 3035 (νC–H_{ar}), 1601, 1568 (νC=C and νC=N), 746 (νC–Cl). MS (ESI) *m*/*z* (%): 229.0 (100) $[M + H]^+$, 231.0 (45) $[M + H + 2]^+$. Anal. Calcd for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.42; H, 4.13; N, 12.09.

*4.1.2.5. Ethyl 4-(imidazo[1,2-a]pyridin-2-yl)benzoate (**6**).* Compound was obtained following the representative procedure, using 4-ethoxycarbonylphenylboronic acid (350 mg, 1.8 mmol, 1.2 equiv) and heating for 45 min. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (8/2) as eluent to afford ethyl 4-(imidazo[1,2-*a*]pyridin-2-yl)benzoate **6** as a beige powder (36 mg, 9% yield).

Rf = 0.24 (petroleum ether/EtOAc: 7/3); Mp = 141–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60–8.59 (m, 2H, H_3 and H_5), 8.15 (d, 2H, ^{3}J = 8.4 Hz, H_b), 8.07 (d, 2H, ^{3}J = 8.4 Hz, H_a), 7.64 (d, 1H, ^{3}J = 9.0 Hz, H_8), 7.32 (dd, 1H, ^{3}J = 9.0 Hz, ^{3}J = 6.8 Hz, H_7), 6.97 (dd, 1H, $^{3}J = {}^{3}J'$ = 6.8 Hz, H_6), 4.37 (q, 2H, ^{3}J = 7.0 Hz, CH_2), 1.38 (t, 3H, ^{3}J = 7.0 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.74 (C=O), 145.23 (C), 143.22 (C), 138.66 (C), 129.86 ($2C_a$), 128.87 (C), 127.28 (C_5), 125.77 ($2C_b$), 125.67 (C_7), 117.03 (C_8), 112.82 (C_6), 110.81 (C_3), 60.86 (CH_2), 14.39 (CH_3). IR (KBr) cm^{-1}: 3042 (νC–H_{ar}), 1708 (νC=O), 1270 (νC–O). MS (ESI) *m*/*z* (%): 267.0 (100) $[M + H]^+$. Anal. Calcd for $C_{15}H_{11}N_2O_2$: C, 71.70; H, 4.41; N, 11.15. Found: C, 71.61; H, 4.73; N, 11.45.

*4.1.2.6. 2-(4-Nitrophenyl)imidazo[1,2-a]pyridine (**7**).*
Compound was obtained following the representative procedure, using 4-nitrophenylboronic acid (301 mg, 1.8 mmol, 1.2 equiv) and heating for 4 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent to afford 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine **7** as a yellow powder (93 mg, 26% yield).

Rf = 0.14 (petroleum ether/EtOAc: 7/3); Mp = 265–266 °C (lit. [28]: 266–267 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (s, 1H, H_3), 8.61 (d, 1H, ^{3}J = 6.8 Hz, H_5), 8.35 (d, 2H, ^{3}J = 8.6 Hz, H_b), 8.27 (d, 2H, ^{3}J = 8.6 Hz, H_a), 7.67 (d, 1H, ^{3}J = 8.6 Hz, H_8), 7.35 (dd, 1H, ^{3}J = 8.6 Hz, ^{3}J = 6.8 Hz, H_7), 6.99 (dd, 1H, $^{3}J = {}^{3}J'$ = 6.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 146.67 (C), 145.44 (C), 142.17 (C), 140.70 (C), 127.45 (C_5), 126.48 ($2C_a$), 126.11 (C_7), 124.37 ($2C_b$), 117.18 (C_8), 113.11 (C_6), 111.88 (C_3). IR (KBr) cm^{-1}: 3070 (νC–H_{ar}), 1513 ($\nu_{as}NO_2$), 1336 ($\nu_{sy}NO_2$); 854 (νC–N). MS (ESI) *m*/*z* (%): 240.0 (100) $[M + H]^+$. Anal. Calcd for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.02; H, 3.83; N, 17.64.

*4.1.2.7. 2-(4-Methoxyphenyl)imidazo[1,2-a]pyridine (**8**).* Compound was obtained following the representative procedure, using 4-methoxyphenylboronic acid (274 mg, 1.8 mmol, 1.2 equiv) and heating for 45 min. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent to afford 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine **8** as a beige powder (263 mg, 78% yield).

Rf = 0.14 (petroleum ether/EtOAc: 7/3); Mp = 135–136 °C (lit. [27]: 133–134 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.53 (d, 1H, ^{3}J = 6.8 Hz, H_5), 8.32 (s, 1H, H_3), 7.93 (d, 2H, ^{3}J = 8.8 Hz, H_a), 7.58 (d, 1H, ^{3}J = 8.6 Hz, H_8), 7.25 (ddd, 1H, ^{3}J = 8.6 Hz, ^{3}J = 7.4 Hz, ^{4}J = 1.2 Hz, H_7), 7.04 (d, 2H, ^{3}J = 8.8 Hz, H_b), 6.90 (ddd, 1H, ^{3}J = 7.4 Hz, ^{3}J = 6.8 Hz, ^{4}J = 1.2 Hz, H_6), 3.83 (s, 3H, OMe). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.19 (C–O), 144.90 (C), 144.62 (C), 127.04 ($2C_a$), 126.86 (C_5), 126.71 (C), 124.78 (C_7), 116.56 (C_8), 114.30 ($2C_b$), 112.20 (C_6), 108.18 (C_3), 55.30 (OMe). IR (KBr) cm^{-1}: 3070 (νC–H_{ar}), 1612, 1482 (νC=C and νC=N), 1248 (νC–O). MS (ESI) *m*/*z* (%): 225.0 (100) $[M + H]^+$. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.69; H, 5.56; N, 12.79.

*4.1.2.8. 2-(2-Methoxyphenyl)imidazo[1,2-a]pyridine (**9**).* Compound was obtained following the representative procedure, using 2-methoxyphenylboronic acid (274 mg, 1.8 mmol, 1.2 equiv) and heating for 1 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (8/2) as eluent to afford 2-(2-methoxyphenyl)imidazo[1,2-*a*]pyridine **9** as a beige powder (317 mg, 94% yield).

Rf = 0.24 (petroleum ether/EtOAc: 7/3); Mp = 89–90 °C (lit. [29]: 95–97 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (d, 1H, ^{3}J = 6.4 Hz, H_5), 8.44 (s, 1H, H_3), 8.34 (d, 1H, ^{3}J = 7.6 Hz, H_d), 7.60 (d, 1H, ^{3}J = 8.2 Hz, H_8), 7.35 (dd, 1H, ^{3}J = 8.0 Hz, ^{3}J = 7.6 Hz, H_b), 7.26 (dd, 1H, ^{3}J = 8.2 Hz, ^{3}J = 6.4 Hz, H_7), 7.17 (d, 1H, ^{3}J = 8.0 Hz, H_a), 7.09 (dd, 1H, $^{3}J = {}^{3}J'$ = 7.6 Hz, H_c), 6.90 (dd, 1H, $^{3}J = {}^{3}J'$ = 6.4 Hz, H_6), 4.01 (s, 3H, OMe). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.63 (C–O), 143.67 (C), 140.16 (C), 128.75 (C_b), 128.18 (C_d), 127.04 (C_5), 124.99 (C_7), 122.28 (C), 120.71 (C_c), 116.53 (C_8), 112.86 (C_3), 111.97 (C_6), 111.61 (C_a), 55.64 (OMe). IR (KBr) cm^{-1}: 3065 (νC–H_{ar}), 1631, 1487 (νC=C and νC=N), 1239 (νC–O). MS (ESI) *m*/*z* (%): 225.1 (100) $[M + H]^+$. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.13; H, 5.77; N, 12.80.

*4.1.2.9. 2-(3,5-Dichlorophenyl)imidazo[1,2-a]pyridine (**10**).* Compound was obtained following the representative procedure, using 3,5-dichlorophenylboronic acid (344 mg, 1.8 mmol, 1.2 equiv) and heating for 45 min. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent to afford 2-(3,5-dichlorophenyl)imidazo[1,2-*a*]pyridine **10** as a white powder (138 mg, 35% yield).

Rf = 0.64 (petroleum ether/EtOAc: 7/3); Mp = 142–143 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (s, 1H, H_3), 8.57 (d, 1H, ^{3}J = 6.8 Hz, H_5), 8.04 (d, 2H, ^{4}J = 2.0 Hz, H_a), 7.64 (d, 1H, ^{3}J = 8.6 Hz, H_8), 7.58 (t, 1H, ^{4}J = 2.0 Hz, H_b), 7.33 (ddd, 1H, ^{3}J = 8.6 Hz, ^{3}J = 7.2 Hz, ^{4}J = 1.2 Hz, H_7), 6.97 (ddd, 1H, ^{3}J = 7.2 Hz, ^{3}J = 6.8 Hz, ^{4}J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.09 (C), 141.59 (C), 137.72 (C), 134.75 (2C–Cl), 127.34 (C_5), 127.00 (C_b), 125.89 (C_7), 124.09 ($2C_a$), 117.04 (C_8), 112.99 (C_6), 111.02 (C_3). IR (KBr) cm^{-1}: 3071 (νC–H_{ar}), 1600, 1574 (νC=C and νC=N), 800, 754 (νC–Cl). MS (ESI) *m*/*z* (%): 263.0 (100) $[M + H]^+$, 265.0 (88) $[M + H + 2]^+$, 267.0 (16) $[M + H + 4]^+$. Anal. Calcd for $C_{13}H_8Cl_2N_2$: C, 59.34; H, 3.06; N, 10.65. Found: C, 58.96; H, 3.22; N, 11.02.

*4.1.3. Representative direct arylation procedure for the synthesis of 2,3-diarylimidazo[1,2-a]pyridines **11**–**36***

To a 10 mL vial with a magnetic stir bar was added 2-arylimidazo[1,2-*a*]pyridine (1.5 mmol, 1 equiv), (hetero)aryl halides (1.5 mmol, 1 equiv), palladium(II) acetate (7 mg, 2 mol %), tricyclohexylphosphine tetrafluoroborate (22 mg, 4 mol %), pivalic

acid (46 mg, 0.45 mmol, 0.3 equiv) and potassium carbonate (318 mg, 2.3 mmol, 1.5 equiv) in dimethylacetamide (6.0 mL). The vial was sealed and purged with argon through the septum inlet for 10 min. The suspension was heated at 100 °C for 10–48 h. After cooling, the resulting mixture was diluted with ethyl acetate. Water was added and the organic layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine and water, dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography. Trituration with appropriate solvent afforded 2,3-diarylimidazo[1,2-*a*]pyridine **11**–**36** (Fig. 3).

*4.1.3.1. 2,3-Diphenylimidazo[1,2-a]pyridine (**11**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), bromobenzene (158 μL, 1.5 mmol, 1 equiv) and heating for 16 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (7/3) as eluent to afford 2,3-diphenylimidazo[1,2-*a*]pyridine **11** as a beige powder (397 mg, 95% yield).

Rf = 0.58 (petroleum ether/EtOAc: 7/3); Mp = 149–150 °C (lit. [30]: 150 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, 1H, ^3J = 6.8 Hz, H_5), 7.71 (d, 1H, ^3J = 9.2 Hz, H_8), 7.65–7.59 (m, 5H, H_a, H_e and H_f), 7.54 (dd, 2H, ^3J = 6.4 Hz, ^4J = 1.6 Hz, H_d), 7.38–7.27 (m, 4H, H_7, H_b and H_c), 6.93 (ddd, 1H, ^3J = 7.6 Hz, ^3J = 6.8 Hz, ^4J = 0.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.15 (C), 141.42 (C), 134.38 (C), 130.86 (2C_d), 129.84 (2C_e), 129.56 (C), 129.25 (C_f), 128.44 (2C_b), 127.62 (2C_a), 127.58 (C_c), 125.37 (C_7), 123.88 (C_5), 120.88 (C), 117.09 (C_8), 112.89 (C_6). IR (KBr) cm^{-1}: 3061 (νC–H_{ar}), 1508, 1443 (νC=C and νC=N). MS (ESI) *m*/*z* (%): 271.1 (100) [M + H]$^+$. Anal. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.21; H, 5.20; N, 10.52.

*4.1.3.2. 3-(4-Methylphenyl)-2-phenylimidazo[1,2-a]pyridine (**12**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 4-bromotoluene (185 μL, 1.5 mmol, 1 equiv) and heating for 48 h. The crude product was purified by silica gel chromatography using cyclohexane as eluent and trituration with petroleum ether afforded 3-(4-methylphenyl)-2-phenylimidazo[1,2-*a*]pyridine **12** as a beige powder (192 mg, 45% yield).

Rf = 0.48 (petroleum ether/EtOAc: 7/3); Mp = 136–137 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, 1H, ^3J = 7.0 Hz, H_5), 7.69 (d, 1H, ^3J = 9.2 Hz, H_8), 7.65 (d, 2H, ^3J = 6.8 Hz, H_a), 7.46–7.40 (m, 4H, H_d and H_e), 7.36–7.26 (m, 4H, H_7, H_b and H_c), 6.92 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, H_6), 2.47 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.14 (C), 141.29 (C), 138.78 (C), 134.49 (C), 130.74 (2C_e), 130.51 (2C_d), 128.48 (2C_b), 127.62 (2C_a), 127.58 (C_c), 126.56 (C), 125.32 (C_7), 123.91 (C_5), 120.92 (C), 117.08 (C_8), 112.85 (C_6), 21.22 (CH_3). IR (KBr) cm^{-1}: 3039 (νC–H_{ar}), 1513, 1478 (νC=C and νC=N). MS (ESI) *m*/*z* (%): 285.1 (100) [M + H]$^+$. Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.61; H, 5.78; N, 10.37.

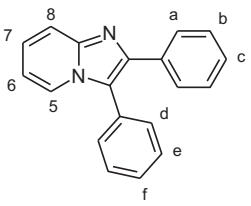


Fig. 3. 2,3-Diarylimidazo[1,2-*a*]pyridines numbering for ^{1}H and ^{13}C NMR assignments.

*4.1.3.3. 3-(4-Methoxyphenyl)-2-phenylimidazo[1,2-a]pyridine (**13**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 1-bromo-4-methoxybenzene (194 μL, 1.5 mmol, 1 equiv) and heating for 24 h. The crude product was purified by silica gel chromatography using cyclohexane/ethyl acetate (8/2) as eluent and trituration with petroleum ether afforded 3-(4-methoxyphenyl)-2-phenylimidazo[1,2-*a*]pyridine **13** as a beige powder (376 mg, 81% yield).

Rf = 0.36 (petroleum ether/EtOAc: 7/3); Mp = 129–130 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, 1H, ^3J = 6.8 Hz, H_5), 7.69–7.65 (m, 3H, H_8 and H_a), 7.45 (d, 2H, ^3J = 8.6 Hz, H_d), 7.36–7.26 (m, 4H, H_7, H_b and H_c), 7.19 (d, 2H, ^3J = 8.6 Hz, H_e), 6.91 (ddd, 1H, ^3J = 7.6 Hz, ^3J = 6.8 Hz, ^4J = 0.8 Hz, H_6), 3.89 (s, 3H, OMe). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.86 (C–O), 143.96 (C), 141.13 (C), 134.53 (C), 132.31 (2C_d), 128.43 (2C_b), 127.45 (2C_a), 127.43 (C_c), 125.15 (C_7), 123.92 (C_5), 121.37 (C), 120.73 (C), 117.01 (C_8), 115.32 (2C_e), 112.72 (C_6), 55.42 (OMe). IR (KBr) cm^{-1}: 3040 (νC–H_{ar}), 1609, 1509 (νC=C and νC=N), 1240 (νC–O). MS (ESI) *m*/*z* (%): 301.1 (100) [M + H]$^+$. Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.23; H, 5.69; N, 9.34.

*4.1.3.4. 4-(2-Phenylimidazo[1,2-a]pyridin-3-yl)phenol (**14**).* Comp ound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 4-iodophenyl acetate (394 mg, 1.5 mmol, 1 equiv) and heating for 12 h. The crude product was purified by silica gel chromatography using petroleum ether/dichloromethane (1/1) as eluent to afford 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)phenol **14** as a white powder (228 mg, 53% yield).

Rf = 0.21 (petroleum ether/EtOAc: 7/3); Mp = 296–297 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H, OH), 7.99 (d, 1H, ^3J = 6.2 Hz, H_5), 7.68–7.66 (m, 3H, H_8 and H_a), 7.34–7.27 (m, 6H, H_7, H_b, H_c and H_d), 7.01 (d, 2H, ^3J = 8.4 Hz, H_e), 6.91 (dd, 1H, ^3J = $^3J'$ = 6.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.31 (C–O), 143.90 (C), 140.94 (C), 134.64 (C), 132.29 (2C_d), 128.45 (2C_b), 127.45 (2C_a), 127.43 (C_c), 125.11 (C_7), 123.98 (C_5), 121.18 (C), 119.61 (C), 117.00 (C_8), 116.77 (2C_e), 112.69 (C_6). IR (KBr) cm^{-1}: 1607, 1483 (νC=C and νC=N), 1275, 1234 (νC–O). MS (ESI) *m*/*z* (%): 287.0 (100) [M + H]$^+$. Anal. Calcd for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.99; H, 4.66; N, 9.59.

*4.1.3.5. 4-(2-Phenylimidazo[1,2-a]pyridin-3-yl)phenyl 2,2-dimethylpropanoate (**15**).* By-product 4-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl) phenyl 2,2-dimethylpropanoate **15** was obtained from the purification of compound **14** by silica gel chromatography as a beige powder (33 mg, 6% yield).

Rf = 0.41 (petroleum ether/EtOAc: 7/3); Mp = 184–185 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, 1H, ^3J = 6.8 Hz, H_5), 7.71 (d, 1H, ^3J = 9.2 Hz, H_8), 7.63 (d, 2H, ^3J = 7.2 Hz, H_a), 7.59 (d, 2H, ^3J = 8.4 Hz, H_d), 7.39–7.28 (m, 6H, H_7, H_b, H_c and H_e), 6.95 (dd, 1H, ^3J = $^3J'$ = 6.8 Hz, H_6), 1.39 (s, 9H, 3 × CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.47 (C=O), 151.34 (C–O), 144.30 (C), 141.67 (C), 135.84 (C), 134.32 (C), 132.20 (2C_d), 131.76 (C), 128.58 (2C_b), 127.73 (2C_a), 126.95 (C_c), 125.59 (C_7), 123.98 (C_5), 123.26 (2C_e), 120.14 (C), 117.14 (C_8), 113.07 (C_6), 26.98 (3 × CH_3). IR (KBr) cm^{-1}: 3040 (νC–H_{ar}), 1750 (νC=O), 1509, 1478 (νC=C and νC=N), 1203 (νC–O). MS (ESI) *m*/*z* (%): 371.1 (100) [M + H]$^+$. Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.04; H, 6.11; N, 8.03.

*4.1.3.6. 3-(4-Nitrophenyl)-2-phenylimidazo[1,2-a]pyridine (**16**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 1-bromo-4-nitrobenzene (304 mg, 1.5 mmol, 1 equiv)

and heating for 36 h. The crude product was purified by silica gel chromatography using cyclohexane/ethyl acetate (8/2) as eluent to afford 3-(4-nitrophenyl)-2-phenylimidazo[1,2-*a*]pyridine **16** as an orange powder (441 mg, 93% yield).

Rf = 0.24 (petroleum ether/EtOAc: 7/3); Mp = 141–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (d, 2H, ^3J = 9.0 Hz, H_e), 8.29 (d, 1H, ^3J = 7.2 Hz, H_5), 7.84 (d, 2H, ^3J = 9.0 Hz, H_d), 7.76 (d, 1H, ^3J = 9.2 Hz, H_8), 7.59 (d, 2H, ^3J = 6.4 Hz, H_a), 7.45–7.35 (m, 4H, H_7, H_b and H_c), 7.01 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 147.29 (C), 145.00 (C), 143.11 (C), 136.45 (C), 133.86 (C), 131.89 ($2C_d$), 128.68 ($2C_b$), 128.16 ($2C_a$), 128.08 (C_c), 126.27 (C_7), 124.79 ($2C_e$), 124.17 (C_5), 118.96 (C), 117.27 (C_8), 113.41 (C_6). IR (KBr) cm^{-1}: 3024 (νC–H_{ar}), 1516 ($\nu_{as}NO_2$), 1345 ($\nu_{sy}NO_2$), 854 (νC–N). MS (ESI) *m*/*z* (%): 316.1 (100) $[M + H]^+$. Anal. Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 72.27; H, 4.25; N, 13.56.

*4.1.3.7. 4-(2-Phenylimidazo[1,2-a]pyridin-3-yl)benzonitrile (**17**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 4-bromobenzonitrile (274 mg, 1.5 mmol, 1 equiv) and heating for 18 h. The crude product was purified by silica gel chromatography using cyclohexane/ethyl acetate (8/2) as eluent and trituration with diisopropylic ether afforded 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)benzonitrile **17** as a beige powder (439 mg, 99% yield).

Rf = 0.26 (petroleum ether/EtOAc: 7/3); Mp = 186–187 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, 1H, ^3J = 6.8 Hz, H_5), 8.07 (d, 2H, ^3J = 8.4 Hz, H_e), 7.77–7.73 (m, 3H, H_8 and H_d), 7.58 (d, 2H, ^3J = 6.8 Hz, H_a), 7.43–7.31 (m, 4H, H_7, H_b and H_c), 6.98 (dd, 1H, $^3J = {}^3J'$ = 6.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.77 (C), 142.63 (C), 134.48 (C), 133.86 (C), 133.59 ($2C_e$), 131.66 ($2C_d$), 128.67 ($2C_b$), 128.08 ($2C_a$), 128.04 (C_c), 126.20 (C_7), 124.15 (C_5), 119.36 (CN), 118.82 (C), 117.18 (C_8), 113.37 (C_6), 111.45 (C–CN). IR (KBr) cm^{-1}: 3038 (νC–H_{ar}), 2226 (νC≡N), 1604, 1508 (νC=C and νC=N). MS (ESI) *m*/*z* (%): 296.1 (100) $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}N_3$: C, 81.34; H, 4.44; N, 14.23. Found: C, 81.51; H, 4.80; N, 14.48.

*4.1.3.8. Ethyl 4-(2-phenylimidazo[1,2-a]pyridin-3-yl)benzoate (**18**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), ethyl 4-bromobenzoate (245 μL, 1.5 mmol, 1 equiv) and heating for 18 h. The crude product was purified by silica gel chromatography using dichloromethane as eluent and trituration with diisopropylic ether afforded ethyl 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)benzoate **18** as a beige powder (504 mg, 98% yield).

Rf = 0.42 (petroleum ether/EtOAc: 7/3); Mp = 140–141 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (d, 1H, ^3J = 7.0 Hz, H_5), 8.16 (d, 2H, ^3J = 8.2 Hz, H_e), 7.74 (d, 1H, ^3J = 8.8 Hz, H_8), 7.70 (d, 2H, ^3J = 8.2 Hz, H_d), 7.60 (d, 2H, ^3J = 6.8 Hz, H_a), 7.42–7.32 (m, 4H, H_7, H_b and H_c), 6.97 (dd, 1H, $^3J = {}^3J'$ = 7.0 Hz, H_6), 4.41 (q, 2H, ^3J = 7.2 Hz, CH_2), 1.40 (t, 3H, ^3J = 7.2 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.58 (C=O), 144.68 (C), 142.32 (C), 134.36 (C), 134.09 (C), 131.07 ($2C_d$), 130.47 ($2C_e$), 130.14 (C), 128.63 ($2C_b$), 127.96 ($2C_a$), 127.92 (C_c), 125.93 (C_7), 124.08 (C_5), 119.86 (C), 117.23 (C_8), 113.26 (C_6), 61.20 (CH_2), 14.40 (CH_3). IR (KBr) cm^{-1}: 3035 (νC–H_{ar}), 1714 (νC=O), 1274 (νC–O). MS (ESI) *m*/*z* (%): 343.1 (100) $[M + H]^+$. Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.12; H, 5.48; N, 8.04.

*4.1.3.9. 3-(3,5-Dichlorophenyl)-2-phenylimidazo[1,2-a]pyridine (**19**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 1,3-dichloro-5-iodobenzene (410 mg, 1.5 mmol, 1 equiv) and heating for 12 h. The crude product was purified by silica gel chromatography using dichloromethane as eluent and trituration with methanol afforded 3-(3,5-dichlorophenyl)-2-phenylimidazo[1,2-*a*]pyridine **19** as a white powder (347 mg, 68% yield).

Rf = 0.60 (petroleum ether/EtOAc: 7/3); Mp = 210–211 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (d, 1H, ^3J = 6.8 Hz, H_5), 7.84 (t, 1H, ^4J = 1.6 Hz, H_e), 7.73 (d, 1H, ^3J = 9.2 Hz, H_8), 7.65 (d, 2H, ^4J = 1.6 Hz, H_d), 7.61 (d, 2H, ^3J = 7.2 Hz, H_a), 7.42–7.32 (m, 4H, H_7, H_b and H_c), 6.98 (dd, 1H, $^3J = {}^3J'$ = 6.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.55 (C), 142.40 (C), 135.27 (2C–Cl), 133.86 (C), 133.16 (C), 129.61 ($2C_d$), 128.87 (C_e), 128.64 ($2C_b$), 127.96 (C_c), 127.85 ($2C_a$), 125.96 (C_7), 124.43 (C_5), 118.18 (C), 117.05 (C_8), 113.16 (C_6). IR (KBr) cm^{-1}: 3036 (νC–H_{ar}), 1590, 1560 (νC=C and νC=N), 776, 750 (νC–Cl). MS (ESI) *m*/*z* (%): 339.0 (100) $[M + H]^+$, 341.0 (80) $[M + H + 2]^+$, 343.0 (15) $[M + H + 4]^+$. Anal. Calcd for $C_{19}H_{12}Cl_2N_2$: C, 67.27; H, 3.57; N, 8.26. Found: C, 67.50; H, 3.23; N, 7.98.

*4.1.3.10. 2-Phenyl-3-(pyridin-3-yl)imidazo[1,2-a]pyridine (**20**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 3-bromopyridine (221 μL, 2.3 mmol, 1.5 equiv) and heating for 48 h. The crude product was purified by silica gel chromatography using cyclohexane/ethyl acetate (7/3) as eluent to afford 2-phenyl-3-(pyridin-3-yl)imidazo[1,2-*a*]pyridine **20** as an orange powder (367 mg, 90% yield).

Rf = 0.07 (petroleum ether/EtOAc: 7/3); Mp = 128–129 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (d, 1H, ^3J = 3.2 Hz, H_g), 8.69 (s, 1H, H_d), 8.14 (d, 1H, ^3J = 6.4 Hz, H_5), 8.05 (d, 1H, ^3J = 7.2 Hz, H_e), 7.74 (d, 1H, ^3J = 8.8 Hz, H_8), 7.68–7.58 (m, 3H, H_a and H_f), 7.41–7.32 (m, 4H, H_7, H_b and H_c), 6.96 (dd, 1H, $^3J = {}^3J'$ = 6.4 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.31 (C_d), 150.02 (C_g), 144.68 (C), 142.62 (C), 138.63 (C_e), 134.07 (C), 128.60 ($2C_b$), 127.83 (C_c), 127.78 ($2C_a$), 125.90 (C), 125.84 (C_7), 124.63 (C_f), 124.12 (C_5), 117.72 (C), 117.13 (C_8), 113.13 (C_6). IR (KBr) cm^{-1}: 3028 (νC–H_{ar}), 1510, 1458 (νC=C and νC=N). MS (ESI) *m*/*z* (%): 272.1 (100) $[M + H]^+$. Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.83; H, 4.99; N, 15.12.

*4.1.3.11. 2-Phenyl-3-(pyridin-4-yl)imidazo[1,2-a]pyridine (**21**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 4-bromopyridine hydrochloride (292 mg, 1.5 mmol, 1 equiv) and heating for 16 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (6/4) as eluent and trituration with diisopropylic ether afforded 2-phenyl-3-(pyridin-4-yl)imidazo[1,2-*a*]pyridine **21** as a yellow powder (347 mg, 85% yield).

Rf = 0.08 (petroleum ether/EtOAc: 7/3); Mp = 181–182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (d, 2H, ^3J = 6.0 Hz, H_e), 8.30 (d, 1H, ^3J = 7.0 Hz, H_5), 7.75 (d, 1H, ^3J = 9.2 Hz, H_8), 7.60–7.56 (m, 4H, H_a and H_d), 7.44–7.33 (m, 4H, H_7, H_b and H_c), 6.99 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.98 ($2C_e$), 144.95 (C), 142.96 (C), 137.47 (C), 133.88 (C), 128.64 ($2C_b$), 128.12 ($2C_d$), 128.07 (C_c), 126.19 (C_7), 125.05 ($2C_a$), 124.21 (C_5), 118.36 (C), 117.25 (C_8), 113.37 (C_6). IR (KBr) cm^{-1}: 3043 (νC–H_{ar}), 1594, 1507 (νC=C and νC=N). MS (ESI) *m*/*z* (%): 272.1 (100) $[M + H]^+$. Anal. Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49. Found: C, 79.66; H, 4.89; N, 15.76.

*4.1.3.12. 2-Phenyl-3-(pyrimidin-5-yl)imidazo[1,2-a]pyridine (**22**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 5-bromopyrimidine (239 mg, 1.5 mmol, 1 equiv) and heating for 12 h. The crude product was purified by silica gel chromatography using cyclohexane/ethyl acetate (8/2) as eluent to

afford 2-phenyl-3-(pyrimidin-5-yl)imidazo[1,2-*a*]pyridine **22** as a beige powder (299 mg, 73% yield).

Rf = 0.07 (petroleum ether/EtOAc: 7/3); Mp = 154–155 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.37 (s, 1H, H_e), 9.02 (s, 2H, H_d), 8.32 (d, 1H, ^3J = 6.8 Hz, H_5), 7.76 (d, 1H, ^3J = 8.8 Hz, H_8), 7.58 (d, 2H, ^3J = 6.8 Hz, H_a), 7.44–7.32 (m, 4H, H_7, H_b and H_c), 6.99 (ddd, 1H, ^3J = 7.2 Hz, ^3J = 6.8 Hz, ^4J = 0.4 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.74 ($2C_d$), 158.35 (C_e), 145.15 (C), 143.73 (C), 133.73 (C), 128.75 ($2C_b$), 128.08 (C_c), 128.00 ($2C_a$), 126.30 (C_7), 124.73 (C), 124.55 (C_5), 117.12 (C_8), 114.62 (C), 113.27 (C_6). IR (KBr) cm^{-1}: 3040 (νC–H_{ar}), 1560, 1498 (νC=C and νC=N). MS (ESI) *m*/*z* (%): 273.1 (100) $[M + H]^+$. Anal. Calcd for $C_{17}H_{12}N_4$: C, 74.98; H, 4.44; N, 20.58. Found: C, 75.11; H, 4.17; N, 20.09.

*4.1.3.13. 2-Phenyl-3-(thiophen-3-yl)imidazo[1,2-a]pyridine (**23**).* Compound was obtained following the representative procedure, using 2-phenylimidazo[1,2-*a*]pyridine **2** (300 mg, 1.5 mmol, 1 equiv), 3-bromothiophene (216 μL, 2.3 mmol, 1.5 equiv) and heating for 48 h. The crude product was purified by silica gel chromatography using cyclohexane as eluent and trituration with diisopropylic ether afforded 2-phenyl-3-(thiophen-3-yl)imidazo [1,2-*a*]pyridine **23** as a beige powder (58 mg, 14% yield).

Rf = 0.40 (petroleum ether/EtOAc: 7/3); Mp = 130–131 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, 1H, ^3J = 6.8 Hz, H_5), 7.94 (s, 1H, H_d), 7.89 (d, 1H, ^3J = 4.4 Hz, H_e), 7.70–7.68 (m, 3H, H_8 and H_a), 7.39–7.29 (m, 4H, H_7, H_b and H_c), 7.25 (d, 1H, ^3J = 4.4 Hz, H_f), 6.96 (dd, 1H, $^3J = {}^3J'$ = 6.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.25 (C), 141.89 (C), 134.42 (C), 129.15 (C_f), 129.08 (C), 128.45 ($2C_b$), 128.19 (C_e), 127.65 (C_c), 127.50 ($2C_a$), 127.49 (C_d), 125.33 (C_7), 124.33 (C_5), 116.99 (C_8), 116.15 (C), 112.85 (C_6). IR (KBr) cm^{-1}: 3066 (νC–H_{ar}), 696 (νC–S). MS (ESI) *m*/*z* (%): 277.0 (100) $[M + H]^+$, 278.0 (25) $[M + H + 1]^+$, 279.0 (7) $[M + H + 2]^+$. Anal. Calcd for $C_{17}H_{12}N_2S$: C, 73.88; H, 4.38; N, 10.14. Found: C, 74.01; H, 4.56; N, 9.88.

*4.1.3.14. 2-(4-Fluorophenyl)-3-phenylimidazo[1,2-a]pyridine (**24**).* Compound was obtained following the representative procedure, using 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **3** (319 mg, 1.5 mmol, 1 equiv), bromobenzene (158 μL, 1.5 mmol, 1 equiv) and heating for 15 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with diisopropylic ether afforded 2-(4-fluorophenyl)-3-phenylimidazo[1,2-*a*]pyridine **24** as a yellow oil (260 mg, 60% yield).

Rf = 0.51 (petroleum ether/EtOAc: 7/3). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, 1H, ^3J = 7.0 Hz, H_5), 7.70 (d, 1H, ^3J = 8.4 Hz, H_8), 7.66–7.59 (m, 5H, H_a, H_d and H_e), 7.54 (dd, 2H, ^3J = 8.4 Hz, ^4J = 1.6 Hz, H_c), 7.36 (ddd, 1H, ^3J = 8.4 Hz, ^3J = 7.2 Hz, ^4J = 0.8 Hz, H_7), 7.19 (dd, 2H, $^3J = {}^3J'$ = 8.8 Hz, H_b), 6.94 (ddd, 1H, ^3J = 7.2 Hz, ^3J = 7.0 Hz, ^4J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.76 (d, ^1J = 243 Hz, C–F), 144.15 (C), 140.50 (C), 130.89 ($2C_c$), 130.84 (C), 129.91 ($2C_d$), 129.49 (d, ^3J = 8 Hz, $2C_a$), 129.35 (d, ^4J = 2 Hz, C), 129.34 (C_e), 125.49 (C_7), 123.93 (C_5), 120.70 (C), 117.05 (C_8), 115.41 (d, ^2J = 21 Hz, $2C_b$), 112.96 (C_6). IR (KBr) cm^{-1}: 3055 (νC–H_{ar}), 1603, 1477 (νC=C and νC=N), 1221 (νC–F). MS (ESI) *m*/*z* (%): 289.1 (100) $[M + H]^+$. Anal. Calcd for $C_{19}H_{13}FN_2$: C, 79.15; H, 4.54; N, 9.72. Found: C, 78.96; H, 4.37; N, 9.91.

*4.1.3.15. 2-(4-Fluorophenyl)-3-(3-nitrophenyl)imidazo[1,2-a]pyridine (**25**).* Compound was obtained following the representative procedure, using 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **3** (319 mg, 1.5 mmol, 1 equiv), 1-bromo-3-nitrobenzene (304 mg, 1.5 mmol, 1 equiv) and heating for 16 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with a mixture diisopropylic ether–petroleum ether afforded 2-(4-fluorophenyl)-3-(3-nitrophenyl)imidazo[1,2-*a*]pyridine **25** as a yellow powder (461 mg, 92% yield).

Rf = 0.24 (petroleum ether/EtOAc: 7/3); Mp = 213–214 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42–8.40 (m, 2H, H_c and H_f), 8.23 (d, 1H, ^3J = 6.8 Hz, H_5), 7.97 (d, 1H, ^3J = 7.6 Hz, H_d), 7.89 (dd, 1H, $^3J = {}^3J'$ = 7.6 Hz, H_e), 7.74 (d, 1H, ^3J = 8.6 Hz, H_8), 7.63 (dd, 2H, ^3J = 8.8 Hz, ^4J = 5.6 Hz, H_a), 7.41 (dd, 1H, ^3J = 8.6 Hz, ^3J = 6.8 Hz, H_7), 7.21 (dd, 2H, $^3J = {}^3J'$ = 8.8 Hz, H_b), 6.98 (dd, 1H, $^3J = {}^3J'$ = 6.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.72 (C), 161.92 (d, ^1J = 244 Hz, C–F), 148.85 (C), 144.60 (C), 141.56 (C), 137.64 (C_d), 131.42 (C_e), 131.00 (C), 130.40 (d, ^4J = 3 Hz, C), 129.86 (d, ^3J = 8 Hz, $2C_a$), 126.07 (C_7), 125.59 (C_c or C_f), 124.24 (C_5), 123.91 (C_c or C_f), 118.54 (C), 117.11 (C_8), 115.60 (d, ^2J = 22 Hz, $2C_b$), 113.22 (C_6). IR (KBr) cm^{-1}: 3063 (νC–H_{ar}), 1530 ($\nu_{as}NO_2$), 1346 ($\nu_{sy}NO_2$), 1222 (νC–F); 840 (νC–N). MS (ESI) *m*/*z* (%): 334.1 (100) $[M + H]^+$. Anal. Calcd for $C_{19}H_{12}FN_3O_2$: C, 68.46; H, 3.63; N, 12.61. Found: C, 68.57; H, 3.39; N, 12.71.

*4.1.3.16. 2-(4-Fluorophenyl)-3-(pyridin-3-yl)imidazo[1,2-a]pyridine (**26**).* Compound was obtained following the representative procedure, using 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **3** (319 mg, 1.5 mmol, 1 equiv), 3-bromopyridine (145 μL, 1.5 mmol, 1 equiv) and heating for 15 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with diisopropylic ether afforded 2-(4-fluorophenyl)-3-(pyridin-3-yl)imidazo[1,2-*a*]pyridine **26** as a beige powder (244 mg, 56% yield).

Rf = 0.11 (petroleum ether/EtOAc: 7/3); Mp = 125–126 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (dd, 1H, ^3J = 4.6 Hz, ^4J = 1.4 Hz, H_f), 8.70 (d, 1H, ^4J = 1.6 Hz, H_c), 8.14 (d, 1H, ^3J = 6.8 Hz, H_5), 8.05 (ddd, 1H, ^3J = 7.8 Hz, ^4J = 1.6 Hz, ^4J = 1.4 Hz, H_d), 7.73 (d, 1H, ^3J = 8.8 Hz, H_8), 7.67 (dd, 1H, ^3J = 7.8 Hz, ^3J = 4.6 Hz, H_e), 7.61 (dd, 2H, ^3J = 8.8 Hz, ^4J = 5.6 Hz, H_a), 7.40 (dd, 1H, ^3J = 8.8 Hz, ^3J = 6.8 Hz, H_7), 7.22 (dd, 2H, $^3J = {}^3J'$ = 8.8 Hz, H_b), 6.97 (dd, 1H, $^3J = {}^3J'$ = 6.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.89 (d, ^1J = 244 Hz, C–F), 151.31 (C_c), 150.12 (C_f), 144.66 (C), 141.70 (C), 138.67 (C_d), 130.58 (d, ^4J = 3 Hz, C), 129.72 (d, ^3J = 9 Hz, $2C_a$), 125.97 (C_7), 125.73 (C), 124.70 (C_e), 124.18 (C_5), 117.60 (C), 117.10 (C_8), 115.60 (d, ^2J = 21 Hz, $2C_b$), 113.20 (C_6). IR (KBr) cm^{-1}: 1508, 1465 (νC=C and νC=N), 1225 (νC–F). MS (ESI) *m*/*z* (%): 290.0 (100) $[M + H]^+$. Anal. Calcd for $C_{18}H_{12}FN_3$: C, 74.73; H, 4.18; N, 14.52. Found: C, 74.79; H, 4.00; N, 14.80.

*4.1.3.17. 2-(2-Fluorophenyl)-3-phenylimidazo[1,2-a]pyridine (**27**).* Compound was obtained following the representative procedure, using 2-(2-fluorophenyl)imidazo[1,2-*a*]pyridine **4** (319 mg, 1.5 mmol, 1 equiv), bromobenzene (189 μL, 1.8 mmol, 1.2 equiv) and heating for 31 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with diisopropylic ether afforded 2-(2-fluorophenyl)-3-phenylimidazo[1,2-*a*]pyridine **27** as a beige powder (277 mg, 64% yield).

Rf = 0.40 (petroleum ether/EtOAc: 7/3); Mp = 119–120 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 (d, 1H, ^3J = 6.8 Hz, H_5), 7.73 (d, 1H, ^3J = 9.2 Hz, H_8), 7.64 (ddd, 1H, ^3J = 8.8 Hz, ^3J = 7.8 Hz, ^4J = 1.6 Hz, H_b), 7.55–7.38 (m, 7H, H_7, H_d, H_e, H_f and H_g), 7.28 (ddd, 1H, ^3J = 7.8 Hz, ^3J = 7.2 Hz, ^4J = 0.8 Hz, H_c), 7.19 (ddd, 1H, ^3J = 9.2 Hz, ^3J = 8.8 Hz, ^4J = 0.8 Hz, H_a), 7.08 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 6.8 Hz, ^4J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.40 (d, ^1J = 247 Hz, C–F), 144.41 (C), 137.56 (C), 132.29 (d, ^3J = 3 Hz, C_b), 130.16 (d, ^3J = 8 Hz, C_d), 129.47 ($2C_e$), 129.33 ($2C_f$), 129.16 (C_g), 128.58 (C), 125.50 (C_7), 124.49 (C_c), 123.97 (C_5), 122.77 (C), 122.56 (d, ^2J = 15 Hz, C), 117.33 (C_8), 115.96 (d, ^2J = 22 Hz, C_a), 113.16 (C_6). IR (KBr) cm^{-1}: 3035 (νC–H_{ar}), 1507, 1478 (νC=C and νC=N), 1224 (νC–F). MS (ESI) *m*/*z* (%): 289.1 (100) $[M + H]^+$. Anal. Calcd for

$C_{19}H_{13}FN_2$: C, 79.15; H, 4.54; N, 9.72. Found: C, 78.87; H, 4.87; N, 9.55.

*4.1.3.18. 2-(2-Fluorophenyl)-3-(pyridin-3-yl)imidazo[1,2-a]pyridine (**28**).* Compound was obtained following the representative procedure, using 2-(2-fluorophenyl)imidazo[1,2-*a*]pyridine **4** (319 mg, 1.5 mmol, 1 equiv), 3-bromopyridine (145 μL, 1.5 mmol, 1 equiv) and heating for 14 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (6/4) as eluent and trituration with diisopropylic ether afforded 2-(2-fluorophenyl)-3-(pyridin-3-yl)imidazo[1,2-*a*]pyridine **28** as a beige powder (370 mg, 85% yield).

Rf = 0.07 (petroleum ether/EtOAc: 7/3); Mp = 133–134 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (dd, 1H, ^3J = 5.0 Hz, ^4J = 1.8 Hz, H_h), 8.57 (d, 1H, ^4J = 2.0 Hz, H_e), 8.37 (d, 1H, ^3J = 6.8 Hz, H_5), 7.96 (ddd, 1H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, ^4J = 1.8 Hz, H_f), 7.77 (d, 1H, ^3J = 8.8 Hz, H_8), 7.71 (ddd, 1H, ^3J = 8.6 Hz, ^3J = 8.0 Hz, ^4J = 1.6 Hz, H_b), 7.57 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 5.0 Hz, ^4J = 0.4 Hz, H_g), 7.46–7.41 (m, 2H, H_7 and H_d), 7.32 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 7.6 Hz, ^4J = 0.8 Hz, H_c), 7.19 (ddd, 1H, ^3J = 9.2 Hz, ^3J = 8.6 Hz, ^4J = 0.8 Hz, H_a), 7.03 (ddd, 1H, ^3J = 7.6 Hz, ^3J = 6.8 Hz, ^4J = 0.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.15 (d, ^1J = 246 Hz, C–F), 149.99 (C_e), 149.44 (C_h), 144.93 (C), 138.42 (C), 137.03 (C_f), 132.34 (d, ^3J = 6 Hz, C_b), 130.44 (d, ^3J = 7 Hz, C_d), 126.01 (C_7), 125.68 (C), 124.75 (C_c), 124.25 (C_g), 124.20 (C_5), 122.07 (d, ^2J = 12 Hz, C), 119.74 (C), 117.35 (C_8), 116.06 (d, ^2J = 19 Hz, C_a), 113.41 (C_6). IR (KBr) cm^{-1}: 3032 (νC–H_{ar}), 1562, 1491 (νC=C and νC=N), 1224 (νC–F). MS (ESI) *m*/*z* (%): 290.0 (100) $[M + H]^+$. Anal. Calcd for $C_{18}H_{12}FN_3$: C, 74.73; H, 4.18; N, 14.52. Found: C, 74.84; H, 4.23; N, 14.80.

*4.1.3.19. 2-(3-Chlorophenyl)-3-phenylimidazo[1,2-a]pyridine (**29**).* Compound was obtained following the representative procedure, using 2-(3-chlorophenyl)imidazo[1,2-*a*]pyridine **5** (344 mg, 1.5 mmol, 1 equiv), bromobenzene (158 μL, 1.5 mmol, 1 equiv) and heating for 21 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with diisopropylic ether afforded 2-(3-chlorophenyl)-3-phenylimidazo[1,2-*a*]pyridine **29** as a beige powder (380 mg, 83% yield).

Rf = 0.66 (petroleum ether/EtOAc: 7/3); Mp = 143–144 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, 1H, ^3J = 6.8 Hz, H_5), 7.72 (d, 1H, ^3J = 9.2 Hz, H_8), 7.68–7.60 (m, 4H, H_a, H_f and H_g), 7.55–7.51 (m, 3H, H_b and H_e), 7.40–7.35 (m, 3H, H_7, H_c and H_d), 6.95 (dd, 1H, ^3J = $^3J'$ = 6.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.22 (C), 139.70 (C), 136.55 (C), 133.28 (C–Cl), 130.89 ($2C_e$), 130.40 (C_c), 129.98 ($2C_f$), 129.59 (C_g), 129.10 (C), 127.37 (C_d), 127.09 (C_a), 125.88 (C_7), 125.82 (C_b), 124.08 (C_5), 121.53 (C), 117.20 (C_8), 113.20 (C_6). IR (KBr) cm^{-1}: 3069 (νC–H_{ar}), 1598, 1506 (νC=C and νC=N), 742 (νC–Cl). MS (ESI) *m*/*z* (%): 305.0 (100) $[M + H]^+$, 307.0 (36) $[M + H + 2]^+$. Anal. Calcd for $C_{19}H_{13}ClN_2$: C, 74.88; H, 4.30; N, 9.19. Found: C, 75.01; H, 4.39; N, 9.36.

*4.1.3.20. Ethyl 4-(3-phenylimidazo[1,2-a]pyridin-2-yl)benzoate (**30**).* Compound was obtained following the representative procedure, using ethyl 4-(imidazo[1,2-*a*]pyridin-2-yl)benzoate **6** (400 mg, 1.5 mmol, 1 equiv), bromobenzene (158 μL, 1.5 mmol, 1 equiv) and heating for 13 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with diisopropylic ether afforded ethyl 4-(3-phenylimidazo[1,2-*a*]pyridin-2-yl)benzoate **30** as an orange powder (139 mg, 27% yield).

Rf = 0.41 (petroleum ether/EtOAc: 7/3); Mp = 138–139 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (d, 1H, ^3J = 6.8 Hz, H_5), 7.91 (d, 2H, ^3J = 8.6 Hz, H_b), 7.77–7.72 (m, 3H, H_8 and H_a), 7.66–7.62 (m, 3H, H_f and H_g), 7.56 (dd, 2H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, H_e), 7.39 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, H_7), 6.97 (ddd, 1H, ^3J = 7.2 Hz, ^3J = 6.8 Hz, ^4J = 1.2 Hz, H_6), 4.33 (q, 2H, ^3J = 7.2 Hz, CH_2), 1.34 (t, 3H, ^3J = 7.2 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.62 (C=O), 144.36 (C), 140.12 (C), 139.02 (C), 130.81 ($2C_e$), 129.94 ($2C_f$), 129.51 (C_g), 129.32 ($2C_b$), 129.10 (C), 128.66 (C), 127.57 ($2C_a$), 125.87 (C_7), 124.09 (C_5), 122.12 (C), 117.26 (C_8), 113.23 (C_6), 60.80 (CH_2), 14.31 (CH_3). IR (KBr) cm^{-1}: 3047 (νC–H_{ar}), 1702 (νC=O), 1277 (νC–O). MS (ESI) *m*/*z* (%): 343.1 (100) $[M + H]^+$. Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.42; H, 4.88; N, 8.39.

*4.1.3.21. 2-(4-Nitrophenyl)-3-phenylimidazo[1,2-a]pyridine (**31**).* Compound was obtained following the representative procedure, using 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine **7** (360 mg, 1.5 mmol, 1 equiv), bromobenzene (189 μL, 1.8 mmol, 1.2 equiv) and heating for 18 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with diisopropylic ether afforded 2-(4-nitrophenyl)-3-phenylimidazo[1,2-*a*]pyridine **31** as a yellow powder (71 mg, 15% yield).

Rf = 0.40 (petroleum ether/EtOAc: 7/3); Mp = 157–158 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, 2H, ^3J = 8.8 Hz, H_b), 8.07 (d, 1H, ^3J = 7.0 Hz, H_5), 7.87 (d, 2H, ^3J = 8.8 Hz, H_a), 7.76 (d, 1H, ^3J = 8.6 Hz, H_8), 7.70–7.63 (m, 3H, H_d and H_e), 7.59 (dd, 2H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, H_c), 7.42 (ddd, 1H, ^3J = 8.6 Hz, ^3J = 7.2 Hz, ^4J = 1.2 Hz, H_7), 6.99 (ddd, 1H, ^3J = 7.2 Hz, ^3J = 7.0 Hz, ^4J = 0.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 146.45 (C), 144.53 (C), 141.11 (C), 139.03 (C), 130.87 ($2C_c$), 130.11 ($2C_d$), 129.81 (C_e), 128.77 (C), 128.19 ($2C_a$), 126.32 (C_7), 124.28 (C_5), 123.89 ($2C_b$), 123.01 (C), 117.39 (C_8), 113.54 (C_6). IR (KBr) cm^{-1}: 3093 (νC–H_{ar}), 1506 ($\nu_{as}NO_2$), 1337 ($\nu_{sy}NO_2$), 856 (νC–N). MS (ESI) *m*/*z* (%): 316.1 (100) $[M + H]^+$. Anal. Calcd for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33. Found: C, 72.31; H, 4.28; N, 13.15.

*4.1.3.22. 2-(4-Methoxyphenyl)-3-phenylimidazo[1,2-a]pyridine (**32**).* Compound was obtained following the representative procedure, using 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine **8** (337 mg, 1.5 mmol, 1 equiv), bromobenzene (158 μL, 1.5 mmol, 1 equiv) and heating for 10 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with diisopropylic ether afforded 2-(4-methoxyphenyl)-3-phenylimidazo[1,2-*a*]pyridine **32** as a beige powder (366 mg, 81% yield).

Rf = 0.31 (petroleum ether/EtOAc: 7/3); Mp = 101–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, 1H, ^3J = 6.8 Hz, H_5), 7.67 (d, 1H, ^3J = 8.4 Hz, H_8), 7.66–7.52 (m, 7H, H_a, H_d, H_e and H_f), 7.33 (ddd, 1H, ^3J = 8.4 Hz, ^3J = 6.8 Hz, ^4J = 0.8 Hz, H_7), 6.93–6.90 (m, 3H, H_6 and H_b), 3.77 (s, 3H, OMe). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.90 (C–O), 144.06 (C), 141.43 (C), 130.87 ($2C_d$), 129.84 ($2C_e$), 129.76 (C), 129.15 (C_f), 128.84 ($2C_a$), 126.79 (C), 125.13 (C_7), 123.73 (C_5), 119.93 (C), 116.87 (C_8), 113.94 ($2C_b$), 112.69 (C_6), 55.23 (OMe). IR (KBr) cm^{-1}: 3047 (νC–H_{ar}), 1608, 1476 (νC=C and νC=N), 1250 (νC–O). MS (ESI) *m*/*z* (%): 301.0 (100) $[M + H]^+$. Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.22; H, 5.55; N, 9.26.

*4.1.3.23. 2-(4-Methoxyphenyl)-3-(3-nitrophenyl)imidazo[1,2-a]pyridine (**33**).* Compound was obtained following the representative procedure, using 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine **8** (337 mg, 1.5 mmol, 1 equiv), 1-bromo-3-nitrobenzene (304 mg, 1.5 mmol, 1 equiv) and heating for 21 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with methanol afforded 2-(4-methoxyphenyl)-3-(3-nitrophenyl)imidazo[1,2-*a*]pyridine **33** as an orange powder (348 mg, 67% yield).

Rf = 0.15 (petroleum ether/EtOAc: 7/3); Mp = 190–191 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41–8.39 (m, 2H, H_d and H_g), 8.22 (d,

1H, ^3J = 6.8 Hz, H_5), 7.96 (d, 1H, ^3J = 7.6 Hz, H_e), 7.88 (dd, 1H, $^3J = {}^3J'$ = 7.6 Hz, H_f), 7.71 (d, 1H, ^3J = 8.6 Hz, H_8), 7.53 (d, 2H, ^3J = 8.8 Hz, H_a), 7.38 (ddd, 1H, ^3J = 8.6 Hz, ^3J = 6.8 Hz, ^4J = 0.8 Hz, H_7), 6.97–6.92 (m, 3H, H_6 and H_b), 3.78 (s, 3H, OMe). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.13 (C–O), 148.84 (C), 144.56 (C), 142.50 (C), 137.69 (C_e), 131.42 (C), 131.37 (C_f), 129.15 (2C_a), 126.26 (C), 125.77 (C_7), 125.54 (C_d or C_g), 124.03 (C_5), 123.74 (C_d or C_g), 117.79 (C), 116.95 (C_8), 114.13 (2C_b), 112.98 (C_6), 55.26 (OMe). IR (KBr) cm^{-1}: 3052 (νC–H_{ar}), 1528 ($\nu_{as}NO_2$), 1348 ($\nu_{sy}NO_2$), 1257 (νC–O); 834 (νC–N). MS (ESI) *m*/*z* (%): 346.1 (100) [M + H]$^+$. Anal. Calcd for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17. Found: C, 69.62; H, 4.33; N, 12.36.

*4.1.3.24. 2-(2-Methoxyphenyl)-3-phenylimidazo[1,2-a]pyridine (**34**).* Compound was obtained following the representative procedure, using 2-(2-methoxyphenyl)imidazo[1,2-*a*]pyridine **9** (337 mg, 1.5 mmol, 1 equiv), bromobenzene (210 μL, 2.0 mmol, 1.3 equiv) and heating for 21 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with diisopropylic ether afforded 2-(2-methoxyphenyl)-3-phenylimidazo[1,2-*a*]pyridine **34** as a beige powder (379 mg, 84% yield).

Rf = 0.23 (petroleum ether/EtOAc: 7/3); Mp = 124–125 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, 1H, ^3J = 7.2 Hz, H_5), 7.69 (d, 1H, ^3J = 8.8 Hz, H_8), 7.53–7.47 (m, 3H, H_d and H_g), 7.43–7.33 (m, 5H, H_7, H_b, H_f and H_h), 7.03 (dd, 1H, $^3J = {}^3J'$ = 7.6 Hz, H_c), 6.98–6.96 (m, 2H, H_6 and H_a), 3.29 (s, 3H, OMe). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.58 (C–O), 144.01 (C), 140.33 (C), 131.78 (C_d), 130.27 (C), 129.55 (C_b), 129.00 (2C_f), 128.87 (2C_g), 127.99 (C_h), 124.75 (C_7), 123.89 (C), 123.63 (C_5), 122.30 (C), 120.42 (C_c), 117.17 (C_8), 112.78 (C_6), 111.61 (C_a), 54.62 (OMe). IR (KBr) cm^{-1}: 3070 (νC–H_{ar}), 1606, 1481 (νC=C and νC=N), 1246 (νC–O). MS (ESI) *m*/*z* (%): 301.0 (100) [M + H]$^+$. Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.70; H, 5.02; N, 9.39.

*4.1.3.25. 2-(3,5-Dichlorophenyl)-3-phenylimidazo[1,2-a]pyridine (**35**).* Compound was obtained following the representative procedure, using 2-(3,5-dichlorophenyl)imidazo[1,2-*a*]pyridine **10** (395 mg, 1.5 mmol, 1 equiv), bromobenzene (158 μL, 1.5 mmol, 1 equiv) and heating for 18 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent and trituration with diisopropylic ether afforded 2-(3,5-dichlorophenyl)-3-phenylimidazo[1,2-*a*]pyridine **35** as a beige powder (423 mg, 83% yield).

Rf = 0.78 (petroleum ether/EtOAc: 7/3); Mp = 155–156 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, 1H, ^3J = 6.8 Hz, H_5), 7.73 (d, 1H, ^3J = 8.6 Hz, H_8), 7.69–7.65 (m, 3H, H_d and H_e), 7.59 (dd, 2H, ^3J = 8.0 Hz, ^4J = 2.0 Hz, H_c), 7.55 (d, 2H, ^4J = 2.0 Hz, H_a), 7.54 (t, 1H, ^4J = 2.0 Hz, H_b), 7.41 (ddd, 1H, ^3J = 8.6 Hz, ^3J = 7.4 Hz, ^4J = 1.2 Hz, H_7), 6.98 (ddd, 1H, ^3J = 7.4 Hz, ^3J = 6.8 Hz, ^4J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.26 (C), 138.17 (C), 137.89 (C), 134.27 (2C–Cl), 130.90 (2C_c), 130.07 (2C_d), 129.87 (C_e), 128.64 (C), 126.86 (C_b), 126.20 (C_7), 125.58 (2C_a), 124.27 (C_5), 122.15 (C), 117.27 (C_8), 113.45 (C_6). IR (KBr) cm^{-1}: 3034 (νC–H_{ar}), 1588, 1561 (νC=C and νC=N), 802, 753 (νC–Cl). MS (ESI) *m*/*z* (%): 339.0 (100) [M + H]$^+$, 341.0 (83) [M + H + 2]$^+$, 343.0 (15) [M + H + 4]$^+$. Anal. Calcd for $C_{19}H_{12}Cl_2N_2$: C, 67.27; H, 3.57; N, 8.26. Found: C, 66.95; H, 3.68; N, 8.34.

*4.1.3.26. 2-(3,5-Dichlorophenyl)-3-(pyridin-3-yl)imidazo[1,2-a]pyridine (**36**).* Compound was obtained following the representative procedure, using 2-(3,5-dichlorophenyl)imidazo[1,2-*a*]pyridine **10** (395 mg, 1.5 mmol, 1 equiv), 3-bromopyridine (145 μL, 1.5 mmol, 1 equiv) and heating for 15 h. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (8/2) as eluent and trituration with diisopropylic ether afforded 2-(3,5-dichlorophenyl)-3-(pyridin-3-yl)imidazo[1,2-*a*]pyridine **36** as a beige powder (353 mg, 69% yield).

Rf = 0.18 (petroleum ether/EtOAc: 7/3); Mp = 161–162 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (dd, 1H, ^3J = 5.0 Hz, ^4J = 1.6 Hz, H_f), 8.76 (d, 1H, ^4J = 1.6 Hz, H_c), 8.15 (d, 1H, ^3J = 6.8 Hz, H_5), 8.10 (ddd, 1H, ^3J = 8.0 Hz, ^4J = 1.6 Hz, ^4J = 1.6 Hz, H_d), 7.76 (d, 1H, ^3J = 8.6 Hz, H_8), 7.71 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 5.0 Hz, ^4J = 0.8 Hz, H_e), 7.58 (t, 1H, ^4J = 2.0 Hz, H_b), 7.51 (d, 2H, ^4J = 2.0 Hz, H_a), 7.44 (ddd, 1H, ^3J = 8.6 Hz, ^3J = 7.4 Hz, ^4J = 1.2 Hz, H_7), 7.00 (ddd, 1H, ^3J = 7.4 Hz, ^3J = 6.8 Hz, ^4J = 1.2 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.35 (C_c), 150.61 (C_f), 144.74 (C), 139.38 (C), 138.84 (C_d), 137.61 (C), 134.38 (2C–Cl), 127.15 (C_b), 126.60 (C_7), 125.83 (2C_a), 125.08 (C), 124.74 (C_e), 124.48 (C_5), 118.96 (C), 117.31 (C_8), 113.66 (C_6). IR (KBr) cm^{-1}: 3020 (νC–H_{ar}), 1589, 1561 (νC=C and νC=N), 800, 739 (νC–Cl). MS (ESI) *m*/*z* (%): 340.0 (100) [M + H]$^+$, 342.0 (70) [M + H + 2]$^+$, 344.0 (12) [M + H + 4]$^+$. Anal. Calcd for $C_{18}H_{11}Cl_2N_3$: C, 63.55; H, 3.26; N, 12.35. Found: C, 63.69; H, 3.59; N, 12.54.

*4.1.4. 4-(2-Phenylimidazo[1,2-a]pyridin-3-yl)phenyl acetate (**37**)*

At room temperature, acetic anhydride (118 μL, 1.3 mmol) was added portionwise to a solution of 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)phenol **14** (300 mg, 1.0 mmol) in pyridine (1.0 mL). The reaction mixture was stirred for 12 h at room temperature. Water was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were successively washed with a saturated aqueous solution of sodium bicarbonate, dried over sodium sulfate, filtered and concentrated under vacuum. Trituration with methanol afforded 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)phenyl acetate **37** as a beige powder (218 mg, 63% yield).

Rf = 0.21 (petroleum ether/EtOAc: 7/3); Mp = 187–188 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, 1H, ^3J = 7.0 Hz, H_5), 7.71 (d, 1H, ^3J = 9.2 Hz, H_8), 7.63 (d, 2H, ^3J = 7.2 Hz, H_a), 7.59 (d, 2H, ^3J = 8.4 Hz, H_d), 7.40 (d, 2H, ^3J = 8.4 Hz, H_e), 7.37–7.28 (m, 4H, H_7, H_b and H_c), 6.95 (dd, 1H, $^3J = {}^3J'$ = 7.0 Hz, H_6), 2.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.21 (C=O), 151.01 (C–O), 149.79 (C), 144.21 (C), 141.66 (C), 134.32 (C), 132.11 (2C_d), 128.48 (2C_b), 127.67 (2C_a), 126.92 (C_c), 125.45 (C_7), 123.96 (C_5), 123.27 (2C_e), 120.08 (C), 117.09 (C_8), 112.95 (C_6), 21.12 (CH_3). IR (KBr) cm^{-1}: 3039 (νC–H_{ar}), 1752 (νC=O), 1200 (νC–O). MS (ESI) *m*/*z* (%): 329.1 (100) [M + H]$^+$. Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 77.10; H, 4.77; N, 8.57.

*4.1.5. 4-(2-Phenylimidazo[1,2-a]pyridin-3-yl)aniline (**38**)*

Using the H-Cube® system in controlled mode, 3-(4-nitrophenyl)-2-phenylimidazo[1,2-*a*]pyridine **16** (1.1 g, 3.5 mmol) was dissolved in a mixture ethanol–tetrahydrofuran (120 mL, 5:1) and passed through a cartridge of Raney nickel at room temperature with a flow rate of 0.8 mL/min at 10 bar. Afterwards, the solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography using petroleum ether/ethyl acetate (9/1) as eluent to afford 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)aniline **38** as an orange powder (806 mg, 81% yield).

Rf = 0.12 (petroleum ether/EtOAc: 7/3); Mp = 216–217 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, 1H, ^3J = 6.8 Hz, H_5), 7.72 (d, 2H, ^3J = 7.2 Hz, H_a), 7.64 (d, 1H, ^3J = 9.2 Hz, H_8), 7.35–7.24 (m, 4H, H_7, H_b and H_c), 7.13 (d, 2H, ^3J = 8.4 Hz, H_d), 6.89 (ddd, 1H, ^3J = 8.0 Hz, ^3J = 6.8 Hz, ^4J = 1.2 Hz, H_6), 6.78 (d, 2H, ^3J = 8.4 Hz, H_e), 5.53 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.67 (C), 143.68 (C), 140.54 (C), 134.86 (C), 131.53 (2C_d), 128.33 (2C_b), 127.33 (2C_a), 127.24 (C_c), 124.79 (C_7), 123.93 (C_5), 121.91 (C), 116.94 (C_8), 115.49 (C), 114.82 (2C_e), 112.43 (C_6). IR (KBr) cm^{-1}: 3321 and 3215 (νN–H), 1607, 1481 (νC=C and νC=N). MS (ESI) *m*/*z* (%): 286.1 (100) [M + H]$^+$. Anal. Calcd for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73. Found: C, 79.84; H, 5.56; N, 14.32.

*4.1.6. 4-(2-Phenylimidazo[1,2-a]pyridin-3-yl)benzamide (**39**)*

At room temperature, a solution of hydrogen peroxide in water (35%, 360 μL) and potassium carbonate (154 mg, 1.1 mmol) were added to a solution of 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl) benzonitrile **17** (150 mg, 0.51 mmol) in dimethyl sulfoxide (2.0 mL). The reaction mixture was stirred for 12 h at room temperature. Water was added and the precipitate was collected by filtration to give 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)benzamide **39** as a yellow powder (105 mg, 66% yield).

Rf = 0.14 (EtOAc/petroleum ether: 7/3); Mp = 277–278 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (s, 1H, NH_2), 8.14 (d, 1H, ^3J = 6.8 Hz, H_5), 8.10 (d, 2H, ^3J = 8.0 Hz, H_e), 7.72 (d, 1H, ^3J = 8.8 Hz, H_8), 7.64–7.60 (m, 4H, H_a and H_d), 7.56 (s, 1H, NH_2), 7.40–7.29 (m, 4H, H_7, H_b and H_c), 6.96 (dd, 1H, ^3J = $^3J'$ = 6.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.47 (C═O), 144.44 (C), 141.96 (C), 134.58 (C), 134.22 (C), 132.39 (C), 130.63 ($2C_d$), 128.86 ($2C_e$), 128.52 ($2C_b$), 127.81 ($2C_a$), 127.74 (C_c), 125.64 (C_7), 124.02 (C_5), 120.16 (C), 117.14 (C_8), 113.06 (C_6). IR (KBr) cm^{-1}: 3344 and 3150 (νN–H), 1670 (νC═O), 1390 (νC–N). MS (ESI) *m*/*z* (%): 314.1 (100) $[M + H]^+$. Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.87; H, 4.99; N, 13.16.

*4.1.7. 4-(2-Phenylimidazo[1,2-a]pyridin-3-yl)benzoic acid (**40**)*

To a solution of ethyl 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl) benzoate **18** (200 mg, 0.58 mmol) in ethanol (10 mL) was added a 2 M sodium hydroxide aqueous solution (5 mL). After refluxing for 1.5 h, the solvent was removed under reduced pressure. Afterwards, the reaction mixture was neutralized by a saturated aqueous ammonium chloride solution, poured into water, extracted with ethyl acetate and washed with brine. The combined organic layers were successively dried over sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography using dichloromethane/ethanol (98/2) as eluent to give 4-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)benzoic acid **40** as a white powder (35 mg, 19% yield).

Rf = 0.14 (EtOAc/petroleum ether: 7/3); Mp = 341–342 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11–8.09 (m, 3H, H_5 and H_e), 7.70 (d, 1H, ^3J = 9.2 Hz, H_8), 7.63 (d, 2H, ^3J = 7.2 Hz, H_d), 7.47 (d, 2H, ^3J = 7.6 Hz, H_a), 7.37–7.28 (m, 4H, H_7, H_b and H_c), 6.93 (dd, 1H, ^3J = $^3J'$ = 6.8 Hz, H_6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.00 (C═O), 144.52 (C), 142.07 (C), 134.17 (C), 133.21 (C), 130.71 ($2C_e$), 130.56 ($2C_d$), 130.46 (C), 128.54 ($2C_b$), 127.85 ($2C_a$), 127.79 (C_c), 125.73 (C_7), 124.06 (C_5), 120.13 (C), 117.17 (C_8), 113.12 (C_6). IR (KBr) cm^{-1}: 3422 (νO–H), 1701 (νC═O), 1240 (νC–O). MS (ESI) *m*/*z* (%): 315.1 (100) $[M + H]^+$. Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.69; H, 4.44; N, 8.76.

4.2. Biological evaluation

Compounds were diluted in dimethyl sulfoxide (DMSO) in view to obtain stock solutions (10 mM). Dilutions of each compound were realized in medium in accordance with cell line culture and at a maximum final concentration of 1% DMSO.

4.2.1. In vitro antileishmanial activity

4.2.1.1. Strains. L. major (MHOM/IL/81/BNI) promastigotes were maintained in Schneider's insect medium (Sigma chemical Co. St Louis, Mo) supplemented with 13% heat-inactivated foetal bovine serum (FBS, Sigma–Aldrich), penicillin (100 UI/mL) and streptomycin (100 mg/mL) at 26 °C by passage every 7 days.

4.2.1.2. Antileishmanial activity against promastigote stage. Promastigote susceptibility testing was performed with a spectrofluorimetric micromethod previously described [31]. Briefly, 100 μL of a 10^6 promastigotes/mL suspension were placed into wells of a 96-well microplate (Nunc®). The cultures were exposed for 96 h at 26 °C to the drugs. Four hours before measurement, 10 μL of resazurin solution (700 μM) were added. Then fluorescence was measured at 590 nm with an excitation at 550 nm.

4.2.1.3. Antileishmanial activity against amastigote stage. Cytotoxicity against the intracellular amastigote stage of the parasite was determined after infection of Balb/c mice peritoneal macrophages (CE Janvier, Le Genest, France). 100 μL of a peritoneal macrophage suspension were placed into a 24-well plate (Nunc) on glass slides (10 mm diameter) at 1.5 × 10^5 cell/mL in RPMI 1640 with 15% FBS at 37 °C and 5% CO_2. Following a 24 h-incubation to allow attachment, macrophages were infected with 100 μL of a stationary phase promastigote suspension (1.5 × 10^5 promastigotes/mL in RPMI 1640 medium plus 15% FBS) and then incubated for a 24 h-period at 37 °C and 5% CO_2 for infection. Macrophage culture was washed and exposed to drugs at a concentration of 10 μM. Medium plus drugs were replaced after 48 h. After 2 days, cultures were fixed with methanol, stained with May-Grunwald–Giemsa and microscopically examined. The average number of amastigotes per macrophage was determined by counting the number of amastigotes in 100 randomly chosen macrophages in each duplicate well. Inhibitory percentages after a 10 μM treatment were calculated by using the values of the number of amastigotes per macrophage. Percentage of infected macrophages was also calculated [12].

4.2.2. Cytotoxicity assay

HeLa cells were subcultured every 4 days in RPMI 1640 medium supplemented with 10% SBF (Sigma–Aldrich). Cells were harvested after a 5 min incubation with trypsine solution (Sigma–Aldrich).

Hela cells were seeded in a 96-well microplate, 100 μL of a 10^5/mL suspension in each well. After a 24 h-incubation time at 37 °C and 5% CO_2, 100 μL of drugs concentrations were added in duplicate. After 96 h, 10 μL of resazurin solution (700 μM) were added. After a 3 h-incubation time at 37 °C, 5% CO_2, fluorescence was measured at 590 nm with an excitation at 550 nm.

4.2.3. Kinase inhibitory activities

4.2.3.1. PKC inhibition. The PKC activity was measured using the PKC kinase activity kit (Enzo Life Sciences). *L. major* promastigotes were cultured for 6 days at 26 °C. Then proteins were extracted with the following extraction buffer: Mammalian Protein Extraction Reagent M-PER (Thermo Scientifics), phosphatase inhibitor cocktail (Sigma–Aldrich), protease inhibitor cocktail (Sigma–Aldrich), Phenylmethylsulfonyl Fluoride (Sigma–Aldrich), leupeptin (Sigma–Aldrich), and aprotinin (Sigma–Aldrich) and conserved at −80 °C. The extracted proteins were assayed at a concentration of 0.2 mg/μL that was chosen after a preliminary study to demonstrate PKC activity in this species. A PKC inhibitor, RO32-04325 (Sigma–Aldrich), was used at 0.2 μM as inhibitor control. The positive control is achieved using active PKC supplied with the kit. Drugs were tested according to the protocol recommended by Enzo Life Sciences. Drugs concentrations (10 μM or 50 μM) were chosen according to their IC_{50} against *L. major* promastigotes.

4.2.3.2. CK1 and LmCK1.2 (lmjF35.1010) inhibition

4.2.3.2.1. Buffers. Buffer A: 60 mM β-glycerophosphate, 30 mM *p*-nitrophenylphosphate, 25 mM Mops (pH 7.2), 5 mM EGTA, 15 mM $MgCl_2$, 1 mM DTT, 0.1 mM sodium vanadate, 1 mM phenylphosphate.

4.2.3.2.2. Kinase preparations and assays. Kinase activities were assayed in Buffer A, at 30 °C, at a final ATP concentration of 15 μM. Blank values were subtracted and activities expressed in % of the maximal activity, i.e. in the absence of inhibitors. Controls were

performed with appropriate dilutions of DMSO. CK1 and *Lm*CK1 peptide substrates were obtained from Proteogenix (Oberhausbergen, France).

CK1δ/ε (porcine brain, native) was assayed in three-fold diluted buffer A, as previously described [32,33] but using 25 μM CKS peptide (RRKHAAIGpSAYSITA), a CK1-specific substrate [34]. Its kinase activity was assayed in buffer A, with 1 mg histone H1/mL, in the presence of 15 μM [γ-^{33}P] ATP (3000 Ci/mmol; 10 mCi/mL) in a final volume of 30 μL. After incubation for 30 min at 30 °C, the reaction was stopped by deposing 25 μL onto P81 phosphocellulose papers (Whatman) using a FilterMate harvester (Perkin–Elmer) and were washed in 1% phosphoric acid. Scintillation fluid was added and the radioactivity measured in a Perkin–Elmer counter.

*Lm*CK1.2 (LmjF35.1010, *L. major*, recombinant, His-fusion protein in *Escherichia coli*) [18a] was purified by affinity chromatography on cobalt beads and its kinase activity was assayed as described for CK1.

4.3. RP-HPLC method for lipophilicity determination

HPLC-grade methanol and de-ionised water were used to prepare the eluting solvents, which were degassed before use. All the chromatographic runs were performed on a Dionex Ultimate 3000 with a diode array detector to monitor signals at 210, 220 and 254 nm. Column temperature was fixed at 30 °C. The solutes were dissolved in the organic modifier (methanol). The injection volume was 0.5 μL. The flow rate was 0.2 mL/min. Data were collected using Chromeleon 7 software. The stationary phase consisted of XBridge C-18 column (75 × 2.1 mm i.d., 2.5 μm particle size, pore volume 0.70 cm^3/g). The mobile phase consisted of methanol and appropriate buffer (a solution of ammonium acetate 0.01 M for pH = 7.4 and a solution of acetic acid 0.01 M for pH = 4.5). For each compound, the retention factor expressed as $k = (t_R - t_0)/t_0$ was determined at different proportions of methanol (three points were used to plot Log k as a function of the percentage of methanol), and then extrapolated to 100% of water using a linear procedure to give Log k_w. In all cases, the square of the correlation coefficient was above 0.99. The dead time t_0 was measured by injection of thiourea (unretained organic substance). The dataset included 30 compounds of the 60 described as the reference substances in the guideline for testing chemicals of the Organization for Economic Co-operation and Development (OECD) [35]. For each reference substance, the logarithm of the extrapolated retention factor Log k_w was determined as described above, and then Log k_w was plotted as a function of Log D (values obtained in the chemical properties section of substance detail in SciFinder). We determined Log k_w of the library of imidazo [1,2-*a*]pyridines using the above described procedure. Finally, the distribution coefficient (Log D) was obtained by interpolation of the calculated Log k_w on the calibration graph for each pH.

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References

[1] T. Kobets, I. Grekov, M. Lipoldová, Curr. Med. Chem. 19 (2012) 1443–1474.
[2] T.S. Tiuman, A.O. Santos, T. Ueda-Nakamura, B.P. Dias Filho, C.V. Nakamura, Int. J. Infect. Dis. 15 (2011) e525–e532.
[3] S. Malik, S. Kumar, A. Choudhary, A. Kumar, A. Singh, G. Avasthi, J. Chem. Pharm. Res. 2 (2010) 70–91.
[4] J.V. Richard, K.A. Werbovetz, Curr. Opin. Chem. Biol. 14 (2010) 447–455.
[5] P. Le Pape, J. Enzyme Inhib. Med. Chem. 23 (2008) 708–718.
[6] D. Plano, Y. Baquedano, D. Moreno-Mateos, M. Font, A. Jiménez-Ruiz, J.A. Palop, C. Sanmartín, Eur. J. Med. Chem. 46 (2011) 3315–3323.
[7] R. Jorda, N. Sacerdoti-Sierra, J. Voller, L. Havlíček, K. Kráčalíková, M.W. Nowicki, A. Nasereddin, V. Kryštof, M. Strnad, M.D. Walkinshaw, C.L. Jaffe, Bioorg. Med. Chem. Lett. 21 (2011) 4233–4237.
[8] A. Tahghighi, S. Razmi, M. Mahdavi, P. Foroumadi, S.K. Ardestani, S. Emami, F. Kobarfard, S. Dastmalchi, A. Shafiee, A. Foroumadi, Eur. J. Med. Chem. 50 (2012) 124–128.
[9] P. Marchand, M. Le Borgne, Y.M. Na, F. Pagniez, H. Abdala, G. Le Baut, P. Le Pape, J. Enzyme Inhib. Med. Chem. 17 (2002) 353–358.
[10] Y.M. Na, N. Lebouvier, M. Le Borgne, F. Pagniez, N. Alvarez, P. Le Pape, G. Le Baut, J. Enzyme Inhib. Med. Chem. 19 (2004) 451–457.
[11] F. Giraud, C. Logé, F. Pagniez, D. Crepin, S. Barres, C. Picot, P. Le Pape, M. Le Borgne, J. Enzyme Inhib. Med. Chem. 24 (2009) 1067–1075.
[12] F. Pagniez, H. Abdala-Valencia, P. Marchand, M. Le Borgne, G. Le Baut, S. Robert-Piessard, P. Le Pape, J. Enzyme Inhib. Med. Chem. 21 (2006) 277–283.
[13] N. Alvarez, S. Robeldo, I.D. Velez, J.-M. Robert, G. Le Baut, P. Le Pape, J. Enzyme Inhib. Med. Chem. 17 (2002) 443–447.
[14] N. Alvarez-Rueda, M. Biron, P. Le Pape, PLoS ONE 4, 2009, pp. e7581 1–e7581 9.
[15] L.A.T. Cleghorn, A. Woodland, I.T. Collie, L.S. Torrie, N. Norcross, T. Luksch, C. Mpamhanga, R.G. Walker, J.C. Mottram, R. Brenk, J.A. Frearson, I.H. Gilbert, P.G. Wyatt, ChemMedChem 6 (2011) 2214–2224.
[16] P. Saravanan, S.K. Venkatesan, C.G. Mohan, S. Patra, V.K. Dubey, Eur. J. Med. Chem. 45 (2010) 5662–5670.
[17] M. Wiese, Int. J. Parasitol. 37 (2007) 1053–1062.
[18] (a) N. Rachidi, et al., in preparation; (b) J.J. Allocco, R. Donald, T. Zhong, A. Lee, Y.S. Tang, R.C. Hendrickson, P. Liberator, B. Nare, Int. J. Parasitol. 36 (2006) 1249–1259.
[19] K.M. Grant, Curr. Pharm. Des. 14 (2008) 917–924.
[20] C. Enguehard-Gueiffier, A. Gueiffier, Mini Rev. Med. Chem. 7 (2007) 888–899.
[21] S. Marhadour, M.-A. Bazin, P. Marchand, Tetrahedron Lett. 53 (2012) 297–300.
[22] B. Liégeault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, J. Org. Chem. 74 (2009) 1826–1834.
[23] J.-C. Antoine, E. Prina, C. Jouanne, P. Bongrand, Infect. Immun. 58 (1990) 779–787.
[24] A. Nasal, D. Siluk, R. Kaliszan, Curr. Med. Chem. 10 (2003) 381–426.
[25] R. Collander, Acta Chem. Scand. 5 (1951) 774–780.
[26] C.C. Musonda, G.A. Whitlock, M.J. Witty, R. Brun, M. Kaiser, Bioorg. Med. Chem. Lett. 19 (2009) 401–405.
[27] Y.Y. Xie, Z.C. Chen, Q.G. Zheng, Synthesis 11 (2002) 1505–1508.
[28] M. Ueno, H. Togo, Synthesis 16 (2004) 2673–2677.
[29] T. Mutai, H. Tomoda, T. Ohkawa, Y. Yabe, K. Araki, Angew. Chem. Int. Ed. 47 (2008) 9522–9524.
[30] C. Enguehard, J.L. Renou, V. Collot, M. Hervet, S. Rault, A. Gueiffier, J. Org. Chem. 65 (2000) 6572–6575.
[31] P. Le Pape, F. Pagniez, H. Abdala-Valencia, Acta Parasitol. 47 (2002) 79–81.
[32] S. Leclerc, M. Garnier, R. Hoessel, D. Marko, J.A. Bibb, G.L. Snyder, P. Greengard, J. Biernat, E.M. Mandelkow, G. Eisenbrand, L. Meijer, J. Biol. Chem. 276 (2001) 251–260.
[33] S. Bach, M. Knockaert, J. Reinhardt, O. Lozach, S. Schmitt, B. Baratte, M. Koken, S.P. Coburn, L. Tang, T. Jiang, D.C. Liang, H. Galons, J.F. Dierick, L.A. Pina, F. Meggio, F. Totzke, C. Schächtele, A.S. Lerman, A. Carnero, Y. Wan, N. Gray, L. Meijer, J. Biol. Chem. 280 (2005) 31208–31219.
[34] J. Reinhardt, Y. Ferandin, L. Meijer, Protein Expr. Purif. 54 (2007) 101–109.
[35] OECD, Guideline for Testing of Chemicals, vol. 117 (1989).http://www.oecd.org.