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Design and synthesis of 2,6-disubstituted-8-amino imidazo[1,2a]pyridines, a promising privileged structure

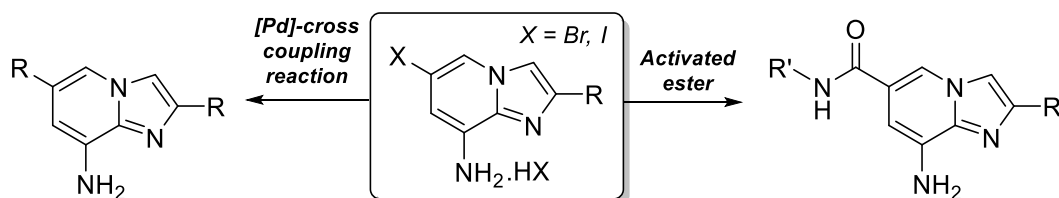
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Graphical abstract



Abstract

Imidazo[1,2a]pyridines have gained much interest in the field of medicinal chemistry research. In the aim of accessing new privileged structure, we decided to design and synthesize 8-aminated-imidazo[1,2a]pyridines substituted on positions 2 and 6. This scaffold, rarely found in the literature, was obtained *via* palladium-catalyzed coupling reactions (Suzuki reaction or *N*-hydroxysuccinimidyl activated ester method) and tested on adenosine receptor A_{2A}. We demonstrated how incorporation of an exocyclic amine enhanced affinity towards this receptor while maintaining low cytotoxicity.

Keywords: privileged structure, amino-imidazopyridine, A_{2A} receptor, palladium-catalyzed coupling reaction

1. Introduction

Among the various imidazopyridine isomers,[1] imidazo[1,2a]pyridines have gained much attention in the field of biological research[2] for their applications as antiprotozoal,[3] antimicrobial,[4] anti-inflammatory[5] and antitumor agents,[6–8] as well as their potential in the field of neurological and neurodegenerative disorders.[9,10] If the synthesis of substituted imidazo[1,2a]pyridines is well described and still leads to original chemical pathways,[11–13] studies describing access methods to 8-amino substituted imidazo[1,2a]pyridines are less common.[2,12,14–20] This class of heterocyclic amines constitutes a promising privileged structure as they are composed of a central scaffold that can be decorated by at least 3 substituents to explore diverse interactions. By integrating an exocyclic amine, they also offer the possibility to generate additional hydrogen bond that might be required for the interaction with their target. It constitutes an interesting challenge as it can find many applications in medicinal chemistry.[21,22] In this way, we aim to prepare 2,6-disubstituted-8-amino imidazo[1,2a]pyridines, a substitution pattern rarely found in the literature,[12,23,24] and to evaluate the effects of these modulations and the importance of the exocyclic amine on the affinity towards the adenosine receptor A_{2A}R, a very promising target in the field of neurodegenerative diseases.[25] This protein constitutes a target of interest in our group and promising antagonists compounds have been recently published.[26,27]. This receptor is widely expressed in the central nervous system. Expressed at different levels (neurons, astrocytes, microglial cells),[19,28–34] it acts at various levels of regulation.[35–39] Therefore, A_{2A}Rs are viewed as promising targets in various neurodegenerative diseases, mainly Parkinson's (PD) and Alzheimer's (AD) diseases.[40–42] In fact, many A_{2A}R's antagonists showed very promising results in cognitive impairments in both pathologies[42] through motor and neuroprotective effects. Some compounds reached clinical phases (Istradefylline, Preladenant, Tozadenant)[43,44] in the case of PD. In the case of AD, it is now well understood that A_{2A}R's blockade leads to improvement of spatial memory related to the decrease of A β amyloid burden, Tau hyper phosphorylation and neurotoxicity.[45,46]

Docking studies, based on the co-crystallized structure of A_{2A}R with the high affinity antagonist ZM-241385[47] confirmed the importance of the exocyclic amine. Additionally, these studies combined to results recently obtained by our group on benzoxazole derivatives[26,27] led us to explore various substitutions on position 6 of 8-amino-imidazo[1,2a]pyridines and therefore different chemical pathways to access these compounds. We describe here the functionalization of the position 6 using palladium catalyzed reaction and *N*-hydroxysuccinimidyl activated ester.[48]

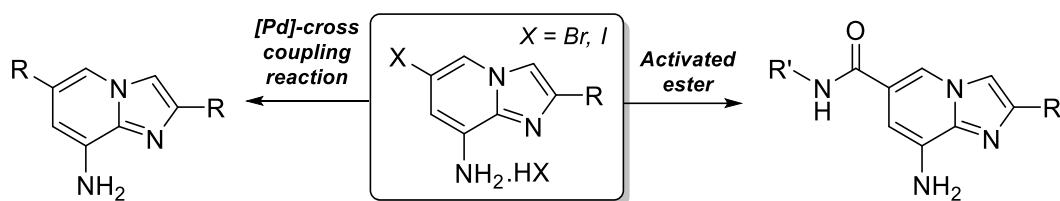


Figure 1.

2. Results and discussion

2.1. Modeling studies

Structure-based studies were performed using docking equipments into the orthosteric binding site of most recent crystal structure of A_{2A}R bound to the high affinity and selective antagonist ZM-241385.[49] Expecting the appropriate binding mode of *de novo* designed molecules, *in silico* process of docking was validated comparing position and interactions of reference ZM-241385 in both crystallized and docking structures (Figure 2). From this protocol, docking of amino-imidazopyridine **16** showed a position similar to ZM-241385, including hydrogen bonds with Glu¹⁶⁹ and Asn²⁵³.

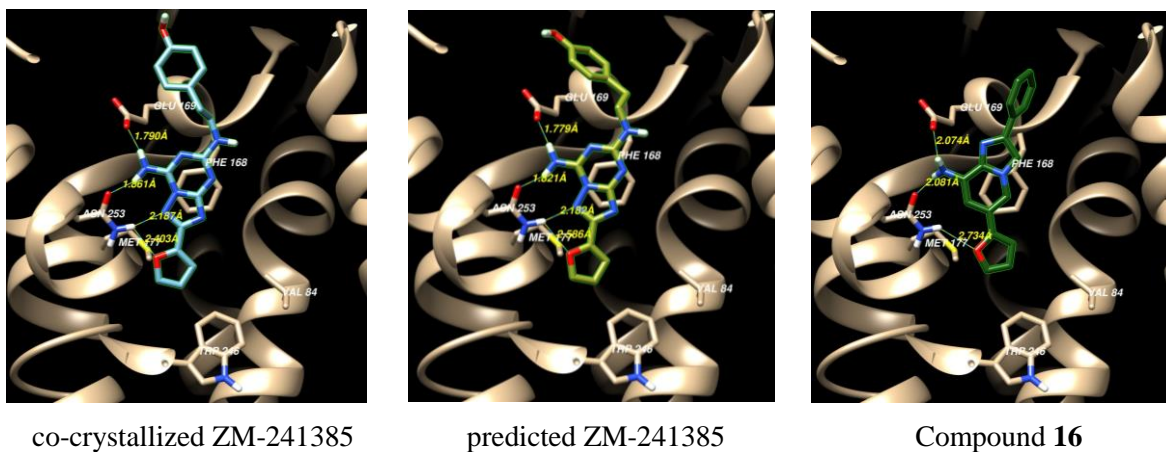
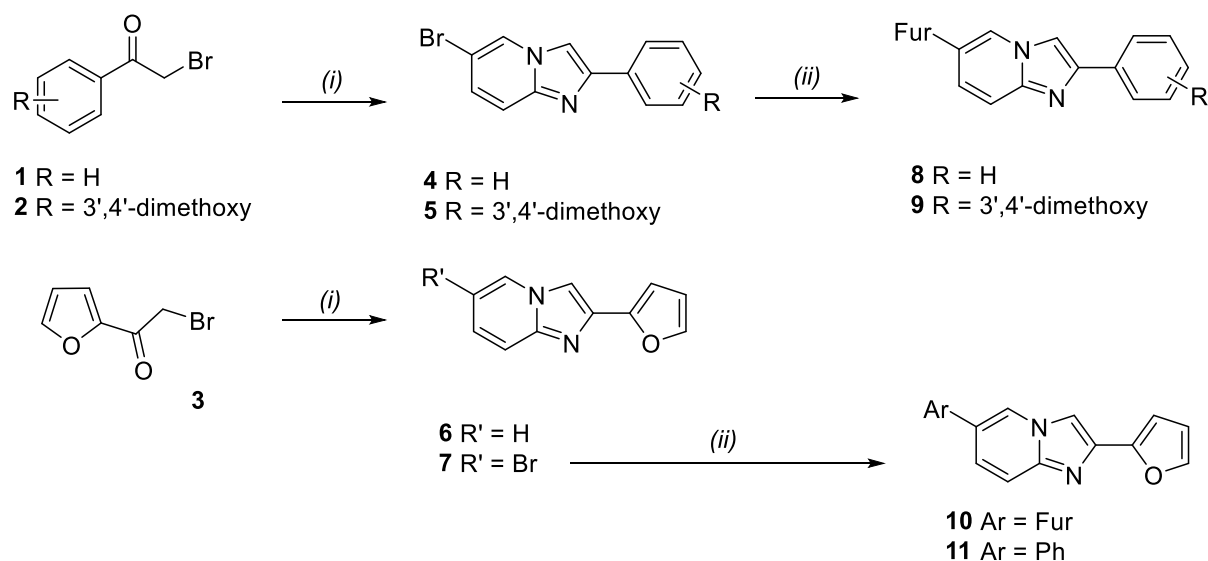


Figure 2. (i) A_{2A}R's crystal structure with high-affinity antagonist ZM-241385[49], (ii) predicted position of ZM-241385 in the docking model, (iii) predicted position of compound **16**. Distances are mentioned for each receptor-ligand hydrogen bond. Illustrations were performed with UCSF Chimera v1.12.[50]

2.2. Chemical synthesis

2.2.1. Aryl coupling

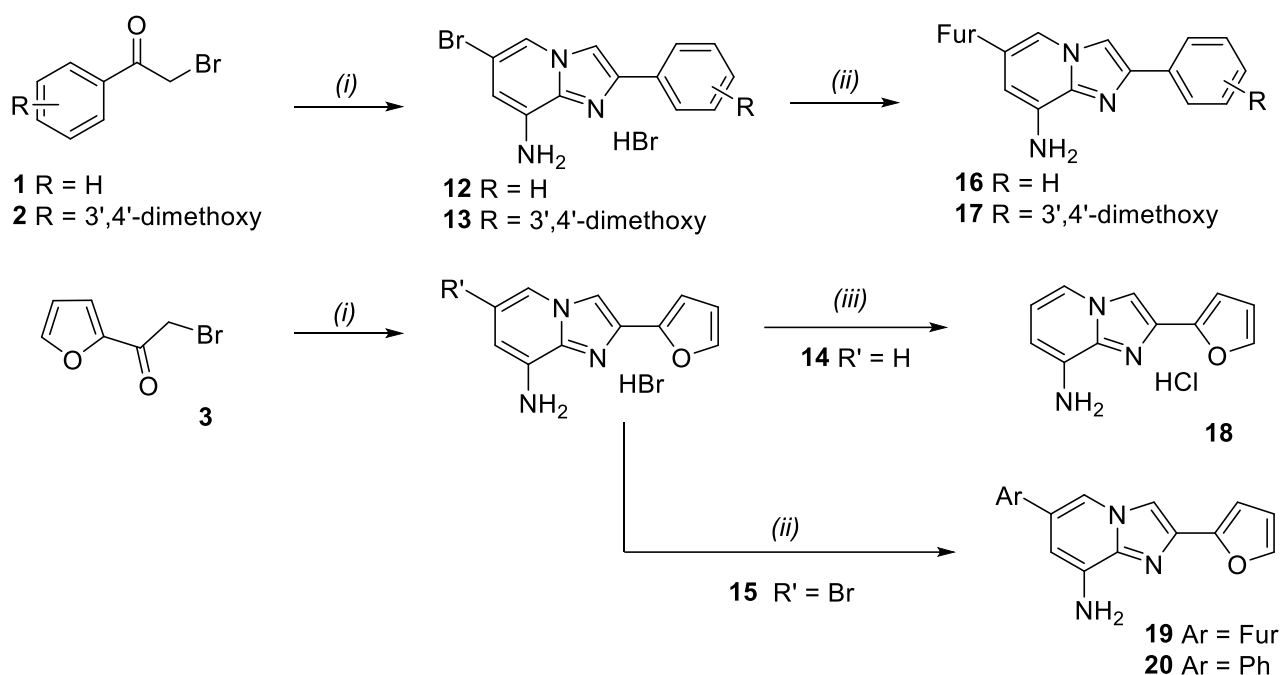
In order to first confirm the importance of the exocyclic amine of 8-amino imidazo[1,2a]pyridines, non aminated imidazopyridine analogs were prepared (Scheme 1). As commonly described in the literature, substituents on position 2 were chosen due to their capacity to interact with Trp²⁴⁶ in the bottom of the binding site.[47] Central imidazopyridine core (**4-7**) was obtained *via* reaction of brominated ketone (**1-3**) with 2-aminopyridine or 2-amino-5-bromopyridine in ethanol under reflux. While commercially available 2-bromoacetophenone was used, 2-bromo-3',4'-dimethoxyacetophenone **2** and 2-bromoacetylfuran **3** were prepared according to described procedures.[51] Suzuki coupling was achieved in DMF with appropriate boronic acid in the presence of aqueous K₃PO₄. Compounds **8-11** were obtained with yields from 22 to 80% depending on the difficulty to separate debrominated secondary product (reduction of **5** and **7**) from final expected compound.



Scheme 1. (i) 2-Amino-5-bromopyridine or 2-aminopyridine, ethanol, reflux, 18h, 29-57%. (ii) Boronic acid, aq. K₃PO₄, Pd(PPh₃)₄, DMF, 60°C, under N₂, 22-80%.

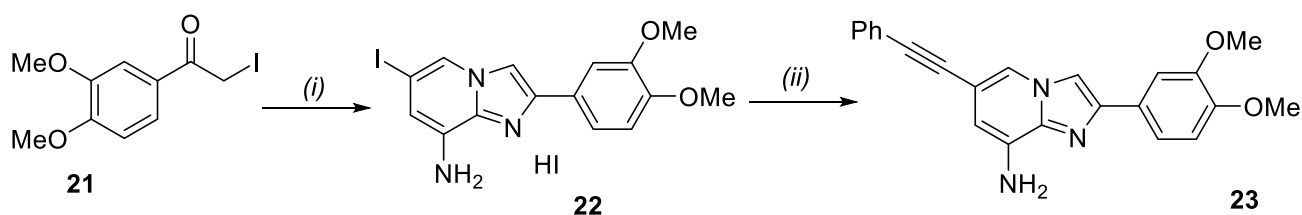
Functionalization of position 6 of 2-aryl-8-amino imidazo[1,2a]pyridines *via* Suzuki coupling has never been described, neither with *N*-protected amine nor with the free exocyclic amine. As described in Figure 1, Suzuki coupling was afforded from brominated intermediates **12**, **13** and **15**. These compounds were obtained as described in the literature[52] by cyclization of appropriate brominated ketone (**1-3**) with commercially available 2,3-diamino-5-bromopyridine in cyclohexanone (Scheme 2). Cyclization in cyclohexanone at 130°C afforded corresponding heterocycles **12-15** with yields from 43 to 90%.

Suzuki coupling was conducted in the same conditions as depicted in Scheme 1 for amino-imidazopyridines (Scheme 2) to afford compounds **16-17** and **19-20**. As observed for non-aminated compounds, variations of yields (9-80%) can be explained by the formation of secondary product resulting from the reduction of brominated intermediates **12**, **13** and **15**.



Scheme 2. (i) 2,3-Diamino-5-bromopyridine, cyclohexanone, 130°C, 18h, 43-90%. (ii) Boronic acid, aq. K₃PO₄, Pd(PPh₃)₄, DMF, 60°C, under N₂, 9-80%. (iii) HCl in diethyl ether.

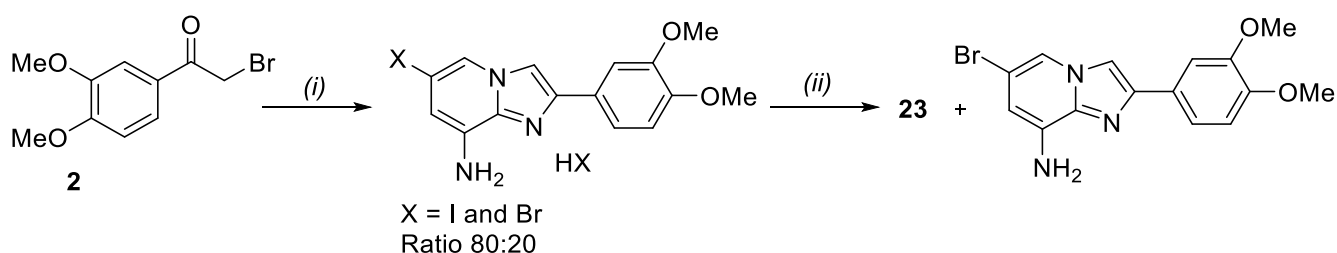
As depicted in table 1, by comparing compounds **8-11** and **16-20**, substitution with dimethoxyphenyl moiety on position 2 afforded best affinity constants and lower cytotoxic properties compared to furan substituent. Therefore, for the rest of the study, we decided to keep this substituent constant and to evaluate replacement of the 6-aryl moiety with a longer and more flexible chain. We therefore chose to connect a phenethyl moiety *via* a Sonogashira coupling and reduction step that has never been described on 8-amino-imidazo[1,2a]pyridines. Unfortunately, Sonogashira coupling starting from 6-bromo-8-amino-imidazo[1,2a]pyridine **13** did not go to completion. Therefore, more reactive iodinated imidazopyridine analog **22** derivative was prepared (Scheme 3) from corresponding iodinated ketone **21** as starting material. Sonogashira reaction was conducted under classical conditions, in the presence of copper iodide and bis(triphenylphosphine)palladium chloride under microwave heating. Conversion to compound **23** was complete.



Scheme 3. (i) 2,3-Diamino-5-iodopyridine,[53] cyclohexanone, 130°C, 18h, 53%. (ii)

Phenylacetylene, Et₃N, CuI, PdCl₂(PPh₃)₄, DMF, 100°C, 30 min, μ w, 95%.

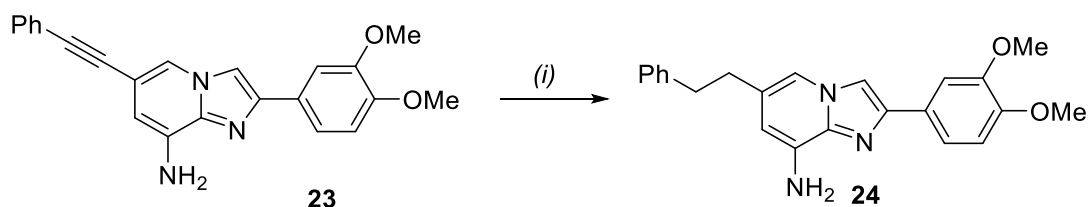
The use of iodinated ketone **21** instead of brominated derivative **2** was of main importance. Indeed, when using brominated ketone **2**, cyclization step partially led to the substitution of the iodine by the bromine of the 2,3-diamino-5-iodopyridine, giving a mixture of halogenated derivatives (iodo/bromo 80/20). Because bromo compound was not reactive enough, Suzuki step afforded a mixture of expected alkyne **23** and unreacted brominated derivative. Iodinated compound **22** was prepared as described in the literature[54] and reacted with 2,3-diamino-5-iodopyridine[47] to afford 6-iodo-8-amino-imidazo[1,2a]pyridine **23** (Scheme 4).



Scheme 4. (i) 2,3-Diamino-5-iodopyridine,[53] cyclohexanone, 130°C, 18h, 53%. (ii)

Phenylacetylene, Et₃N, CuI, PdCl₂(PPh₃)₄, DMF, 100°C, 30 min, μ w, 95%.

Alkyne derivative **23** was then reduced in the presence of ammonium formate in methanol (Scheme 5) to afford phenethyl-substituted amino-imidazopyridine **24**.

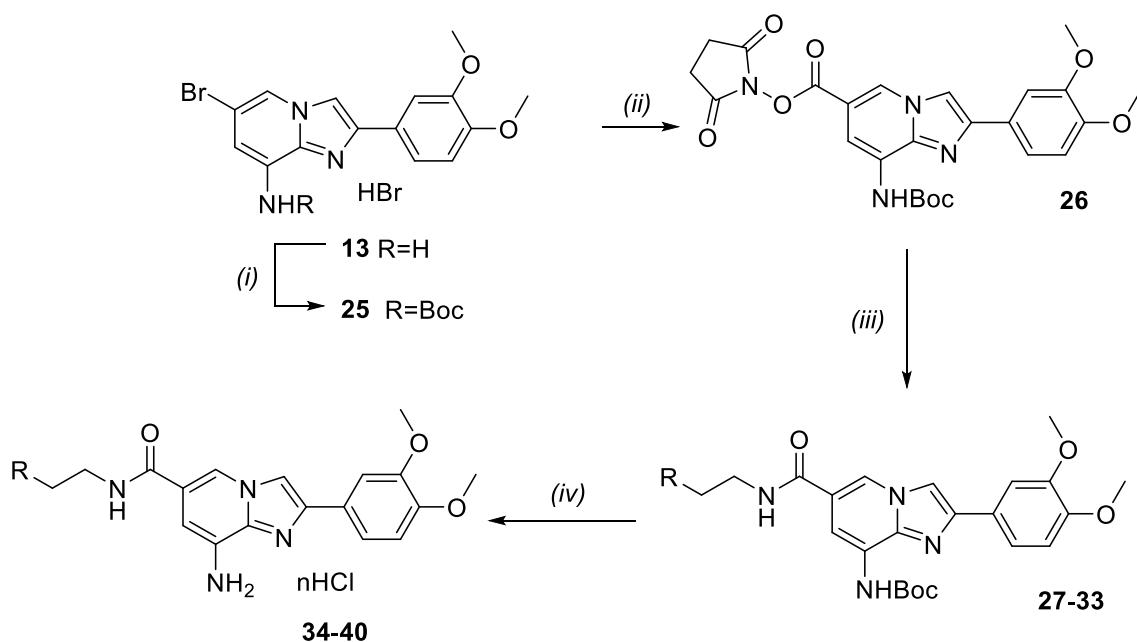


Scheme 5. (i) Ammonium formate, Pd(OH)₂, methanol, reflux, 2.5h, 20%.

Sonogashira coupling constitutes an interesting way to substitute 6-position with an alkyne, starting from non-protected 8-amino-imidazopyridine. If conversion was complete as shown by LC-MS analysis, yield was drastically impacted due to solubility issues of compound **24** during purification step.

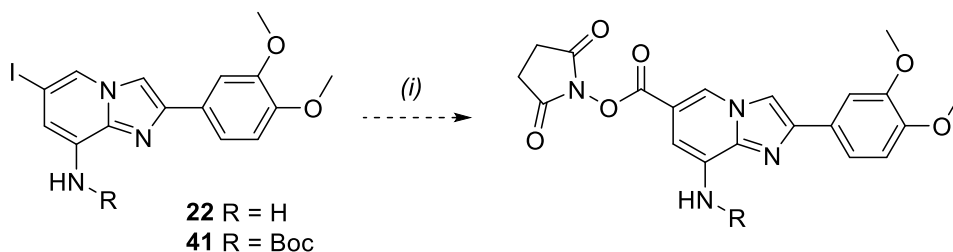
2.2.2. Amide linker

Studies in our group identified benzoxazole as a promising scaffold for A_{2A}R's antagonists.[26,27] More precisely, amide substitution gave interesting results. Therefore, we aim to synthesize amino-imidazopyridines substituted on position 6 with an amide moiety (Scheme 6) using the *N*-hydroxysuccinimidyl activated ester method.[48] Compound **13** first needed to be protected as conversion of unprotected compound to activated ester did not work. The amine group of substituted imidazopyridine **13** was protected using Boc₂O and a large excess of NaHMDS. Then, *N*-hydroxysuccinimidyl ester **26** is prepared to obtain desired amides **27** to **33**. This intermediate is formed from brominated derivative **25** and *N*-hydroxysuccinimidyl formate by a palladium-catalyzed carbonylative process.[48] The reaction was performed under a nitrogen atmosphere in a sealed tube in the presence of Pd(OAc)₂, Xantphos and triethylamine at 60°C in THF. The use of very dry NHS formate (NHSF) and a very small scale (less than 1 mmol in our hands) is required. NHS formate was prepared in good yield from hydroxysuccinimide and formic acid according to a procedure described in the literature.[48] Compound **26** was obtained with 40% yield. Unfortunately, all our efforts to optimize the yield of this step were unsuccessful: time of reaction had no impact on the conversion and use of compound **13** in its unprotected form, either as its acid or basic form, did not lead to the desired ester, only starting material was recovered. On another side, the use of the di-Boc-protected compound just gave degradation products. Finally, the resulting NHS ester **26** was reacted with various amines under mild conditions before amine deprotection to provide different substituted imidazopyridines as hydrochloride salts **35-40**. Compound **34** required the use of dioxane and heating at 50°C for 18h as mild conditions in dichloromethane were unsuccessful. Stoichiometry of chlorhydrate salts after HCl/dioxane exposure was determined using a silver nitrate titration in the presence of potassium chromate.



Scheme 6. (i) NaHMDS, Boc₂O, THF, r.t., 6h, 70%; (ii) NHSF, Xantphos, Pd(OAc)₂, Et₃N, THF, 60°C, 18h, 40%; (iii) Amine, CH₂Cl₂, RT or dioxane, 50°C, 18h, 51-95%; (iv) Dioxane HCl(4M), 60°C, 2h, 42-70%.

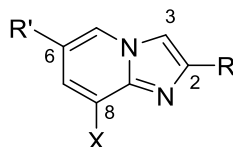
To optimize the reaction for carbonylation of halide derivative **25**, we evaluated replacement of bromide by iodide. The reaction was performed under the same conditions as described previously (Scheme 6) to afford iodinated compound **41**. To our delight, unprotected iodide compound **22** was totally converted into NHS ester as monitored by LC-MS (Scheme 7). However, this method suffers from several drawbacks such as the insolubility of corresponding ester and the formation of byproducts, making the isolation of pure NHS esters and then pure final amides difficult. Similarly, the use of *N*-Boc derivative **41** afforded the corresponding ester but also, many degradation products. Therefore, we chose to keep the brominated imidazopyridines synthesis pathway (Scheme 6) in which isolation of the products was much easier.



Scheme 7. (i) NHSF, Xantphos, Pd(OAc)₂, Et₃N, THF, 60°C, 18h.

2.3. Biological evaluation of 8-amino-imidazopyridine derivatives

Affinity of our compounds was evaluated on human A_{2A} receptor membranes stably expressed in HEK293 cells, by a competitive radioligand displacement assay using [³H]-ZM-241385 (Table 1).[56]



Cpd	R'	R	X	K _i (μM) ^a	CC ₅₀ (μM) ^b
6	/	Fur	H	>10	>100
18			NH ₂	>10	>100
11	Ph	Fur	H	>10	0.42
20			NH ₂	>10	0.5
10	Fur	Fur	H	1.63±0.24	3
19			NH ₂	>10	2.27
8	Fur	Ph	H	>10	>100
16			NH ₂	0.418±0.019	26
9	Fur	Ph(OMe) ₂	H	0.238±0.033	30
17			NH ₂	0.117±0.049	36.4
23	Ph—≡—	Ph(OMe) ₂	NH ₂	>10	66.7
24	Ph—CH ₂ —	Ph(OMe) ₂	NH ₂	>10	50.4

Table 1. ^aDisplacement of specific [³H]-ZM-241385 binding to hA_{2A} receptors stably expressed in HEK293 cells. A 10μM screening was first completed to select compounds of interest. Results are given with their standard deviation. K_i (inhibition constant at 50%) was calculated from two independent experiments. ^bCC₅₀: cytotoxic concentration *ie* compound concentration causing 50% of SY5Y cell death after 24 h treatment.

From table 1, it appears that exocyclic amine systematically improves imidazopyridines A_{2A}R's affinities. Substitution on position 6 is required as shown by compounds **6** and **18**. For aminated compounds, furane on position 2 leads to a better affinity than phenyl moiety (**20** and **19** vs entry **16**), which is in accordance with the fact that A_{2A}R's ligands commonly present a furane moiety, able to interact with Trp²⁴⁶ in the bottom of the binding pocket. Due to well known stability issues of the furane, we tried to replace it with 3,4-dimethoxyphenyl. As shown with compound **17**, this was successful as this latter compound exhibited a higher affinity. Therefore, we decided to keep 3,4-dimethoxyphenyle

on position 2 for the second series of compounds (Table 2). As previously identified in our group for benzoxazole scaffolds[26,27], amide substitution gave very promising results. Therefore, affinity of 6-amide substituted amino-imidazopyridine compounds was evaluated (Table 2).

Cpd	R	K _i (μM) ^a	CC ₅₀ (μM) ^b
34		>10	>100
35		>10	26.9
36		>10	>100
37		>10	>100
38		>10	49.6
39		>10	>100
40		>10	31.8

Table 2. ^aDisplacement of specific [³H]-ZM-241385 binding to hA_{2A} receptors stably expressed in HEK293 cells. A 10μM screening was first completed to select compounds of interest. Results are given with their standard deviation. K_i (inhibition constant at 50%) was calculated from two independent experiments. ^bCC₅₀: cytotoxic concentration *ie* compound concentration causing 50% of SY5Y cell death after 24 h treatment.

Unfortunately, unlike results obtained for benzoxazole series, no affinity for 6-amide substituted amino-imidazopyridines **34-40** was observed and amino-imidazopyridines substituted with small aromatic moieties (**9,16** and **17**, Table 1) remained the most promising compounds able to bind A_{2A}R.

3. Conclusion

This work describes new pathways to functionalize position 6 of 2-aryl-8-amino-imidazopyridine. Presented compounds exhibited moderate affinity towards A_{2A}R, however the low toxicity of most of them described in Tables 1 and 2 offers numerous possibilities to test them as ligands of interest in other fields. This scaffold therefore constitutes a promising easily approachable privileged structure[21,22] as an anchor point to orientate substituents in various positions enabling various pharmacomodulations. In addition, the exocyclic amine, rarely found on this type of imidazopyridine compound, brings interesting assets.

Experimental section

4.1. General information

Chemicals and solvents were obtained from commercial sources, and used without further purification unless otherwise noted. Reactions were monitored by TLC performed on Macherey-Nagel Alugram® Sil 60/UV254 sheets (thickness 0.2mm). Purification of products was carried out by either column chromatography or thick layer chromatography. Column chromatography was carried out on using Macherey-Nagel silica gel (230-400 mesh). NMR spectra were recorded on a Bruker DRX 300 spectrometer (operating at 300 MHz for ¹H and 75 MHz for ¹³C). Chemical shifts are expressed in ppm relative to either tetramethylsilane (TMS) or to residual proton signal in deuterated solvents. Chemical shifts are reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = double doublet, br = broad and m = multiplet), coupling constant (*J* in Hz), relative integral and assignment. The attributions of protons and carbons were achieved by analysis of 2D experiments (COSY, HSQC and HMBC). Mass spectra were recorded on a Varian triple quadrupole 1200W mass spectrometer equipped with a non-polar C₁₈ TSK-gel Super ODS (4.6 x 50 mm) column, using electrospray ionization and a UV detector (diode array). HRMS-ESI spectra were recorded on a Thermo Scientific Exactive spectrometer. The purity of final compounds was verified by two types of high pressure liquid chromatography (HPLC) columns: C₁₈ Interchrom UPTISPHERE and C₄ Interchrom UPTISPHERE. Analytical HPLC was performed on a Shimadzu LC-2010AHT system equipped with a UV detector set at 254 nm and 215 nm. Compounds were dissolved in 50 μL methanol and 950 μL buffer A, and injected into the system. The following eluent systems were used: buffer A (H₂O/TFA, 100:0.1) and buffer B (CH₃CN/H₂O/TFA, 80:20:0.1). HPLC retention times (HPLC t_R)

were obtained at a flow rate of 0.2 mL/min for 35 min using the following conditions: a gradient run from 100% of buffer A over 1 min, then to 100% of buffer B over the next 30 min. The melting point analyses were performed on Barnstead Electrothermal Melting Point Series IA9200 and are uncorrected. Preparative HPLC were performed using a Varian ProStar system using an OmniSphere 10 column C₁₈ 250 mm × 4.1 mm Dynamax from Varian, Inc. A gradient starting from 20% CH₃CN/80% H₂O/0.1% formic acid and reaching 100% CH₃CN/0.1% formic acid at a flow rate of 80 mL/min was used.

4.2. Protocols

2-bromo-3',4'-dimethoxyacetophenone (2). A solution of 3',4'-dimethoxyacetophenone (600 mg, 3.33 mmol) in CHCl₃ and EtOAc (6 mL, 1/1) was stirred for 10 minutes at RT. CuBr₂ (1.487 g, 2 eq) was added in one portion. The mixture was stirred at 60°C for 18 h. The reaction was filtered, 10 mL of water were added and the mixture was extracted twice with EtOAc. Organic layer was then washed once with NaCl saturated solution, dried over MgSO₄ and evaporated *in vacuo*. Flash chromatography (pure CH₂Cl₂) afforded compound **2** as a white solid (517.3 mg, 60%). ¹H NMR (CDCl₃, 300MHz), δ(ppm): 3.96 (s, 3H), 3.98 (s, 3H), 4.42 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.63 (dd, *J* = 8.4 and 2.1 Hz, 1H).[57]

2-bromo-acetylfuran (3). A solution of 2-acetylfuran (182 μL, 1.82 mmol) in CHCl₃ and EtOAc (3.3 mL, 1/1) was stirred for 10 minutes at RT. CuBr₂ (811 mg, 2 eq) was added in one portion. The mixture was stirred at 60°C for 18 h. The reaction was filtered, 10 mL of water were added and the mixture was extracted twice with EtOAc. Organic layer was then washed once with NaCl saturated solution, dried over MgSO₄ and evaporated *in vacuo*. Flash chromatography (pure CH₂Cl₂) afforded compound **3** as a dark yellow solid (199.4 mg, 58%). ¹H NMR (CDCl₃, 300MHz), δ(ppm): 4.33 (s, 2H), 6.59-6.64 (m, 1H), 7.35 (d, *J* = 2.9 Hz, 1H), 7.65 (s, 1H).[58]

General method A for the cyclization of imidazo[1,2-a]pyridines. To a solution of appropriate bromo acetylene derivative (1eq) in ethanol (4 mL/mmol), 2-aminopyridine or 2-amino-5-bromopyridine (1eq) was added in one portion. The mixture was stirred at 70°C overnight. The solvent was evaporated *in vacuum* and the crude product was dissolved in CH₂Cl₂, washed twice with NaOH 1M solution, once with water and dried over MgSO₄. The solvent was evaporated *in vacuo*. Compound was purified, if necessary, by flash chromatography.

6-bromo-2-phenyl-imidazo[1,2-a]pyridine (4). According to general procedure A, a solution of 0.217 g of 2-amino-5-bromopyridine (1.26 mmol) in ethanol and 0.250 g of 2-bromoacetophenone (1.26 mmol) were used. Compound **4** was isolated without any further purification as a light brown powder (173 mg, 45%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 7.23 (dd, *J* = 9.6 and 1.8 Hz, 1H), 7.31-7.37 (m, 1H), 7.45 (t, *J* = 7.1 Hz, 2H), 7.53 (d, *J* = 9.6 Hz, 1H), 7.81 (s, 1H), 7.91-7.97 (s, 1H), 8.25 (d, *J* = 0.7 Hz,

1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 107.0, 108.3, 118.1, 125.6, 126.1, 128.1, 128.3, 128.8, 133.2, 144.1, 146.7. MS (ESI⁺): m/z = 272.9/274.9 [M,H]⁺ found; C₁₃H₉N₂Br calculated m/z = 273.0/275.0 [M,H]⁺.

6-bromo-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridine (5). According to general procedure A, a solution of 192 mg of 2-bromo-1-(3,4-dimethoxyphenyl)ethan-1-one (0.783 mmol) in ethanol and 135 mg of 2-amino-5-bromopyridine (0.783 mmol) were used. Flash chromatography (CH₂Cl₂/MeOH, 95:5) afforded compound **5** as a gold yellow solid (100 mg, 57%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 3.89 (s, 3H), 3.94 (s, 3H), 7.03 (d, *J* = 8.4 Hz, 1H), 7.38-7.55 (m, 4H), 8.14 (s, 1H), 8.68 (q, *J* = 0.9 Hz, 1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 55.0, 106.7, 108.7, 109.5, 111.7, 116.2, 118.6, 126.7, 127.1, 127.6, 128.6, 145.0, 149.5. MS (ESI⁺): m/z = 332.9/334.9 [M,H]⁺ found; C₁₅H₁₃BrN₂O₂ calculated m/z = 333.0/335.0 [M,H]⁺.

2-(furan-2-yl)imidazo[1,2-a]pyridine (6). According to general procedure A, a solution of 389 mg of 2-bromo-1-(2-furyl)ethanone (2.06 mmol) in ethanol and 194 mg of 2-aminopyridine (2.06 mmol) were used. Flash chromatography (CH₂Cl₂-MeOH, 97:3) afforded compound **6** as a brown powder (110 mg, 29%). ¹H NMR (CDCl₃, 300 MHz), δ(ppm): 6.50 (m, 1H), 6.76 (dt, *J* = 6.8 et 1.0 Hz, 1H), 6.88 (m, 1H), 7.15 (m, 1H), 7.46 (m, 1H), 7.57 (d, *J* = 9.0 Hz, 1H), 7.78 (s, 1H), 8.06 (d, *J* = 9.2 Hz, 1H). ¹³C NMR (CDCl₃, 75 MHz), δ(ppm): 106.7, 107.9, 111.6, 112.6, 117.4, 125.0, 125.7, 138.0, 142.1, 145.6, 149.6. [59] HRMS (ESI⁺): m/z = 185.07147 [M,H]⁺ found; C₁₁H₉N₂O calculated m/z = 185.07094 [M,H]⁺. HPLC: C₄ column: t_R = 7.8 min, purity 96% C₁₈ column: t_R = 12.0 min, purity 98%.

6-bromo-2-(2-furyl)imidazo[1,2-a]pyridine (7). According to general procedure A, a solution of 100 mg of 2-bromo-1-(2-furyl)ethanone (0.529 mmol) in ethanol and 91.5 mg of 2-amino-5-bromopyridine (0.529 mmol) were used. Flash chromatography (CH₂Cl₂/EtOAc, 95:5) afforded compound **7** as a light brown solid (79 mg, 57%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 6.56 (dd, *J* = 3.4 and 1.8 Hz, 1H), 6.88 (d, *J* = 3.3 Hz, 1H), 7.44 (m, 2H), 7.58 (dd, *J* = 1.3 and 0.8 Hz, 1H), 8.02 (s, 1H), 8.68 (dd, *J* = 1.8 and 0.9 Hz, 1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 106.8, 106.9, 108.7, 111.2, 116.3, 126.8, 129.1, 137.6, 142.5, 143.8, 148.5. MS (ESI⁺): m/z = 262.9/264.9 [M,H]⁺ found; C₁₁H₇BrN₂O calculated m/z = 263.0/265.0 [M,H]⁺.

General method B for the cyclization of 8-amino imidazo[1,2a]pyridines. To a solution of appropriate diaminopyridine derivative (1eq) in cyclohexanone (1 mL/mmol of ketone), 2-bromoacetylene or 2-iodoacetylene derivative (1.2 eq) was added in one portion. The reaction was heated to 130°C overnight. TBME was added to the mixture. The precipitate was filtered and washed with TBME. The product was then dried further *in vacuo*. No further purification was performed.

(6-bromo-2-phenyl-imidazo[1,2-a]pyridin-8-yl)ammonium bromide (**12**). According to general procedure B, a solution of 0.250 g of 2,3-diamino-5-bromopyridine (1.33 mmol) in cyclohexanone and 0.318 g of 2-bromoacetophenone (1.6 mmol) were used. Compound **12** was obtained as a light brown powder (440 mg, 90%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 7.16 (d, *J* = 1.5 Hz, 1H), 7.55-7.68 (m, 3H); 7.86-7.93 (m, 2H), 8.34 (d, *J* = 1.5 Hz, 1H), 8.45 (s, 1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 111.4, 112.8, 113.5, 116.4, 125.9, 129.4, 130.6, 132.0, 133.9, 136.0. MS (ESI⁺): *m/z* = 287.9/289.9 [M,H]⁺ found; C₁₃H₁₀N₃Br calculated *m/z* = 288.0/290.0 [M,H]⁺.

6-bromo-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridin-8-amine hydrobromide (**13**). According to general procedure B, a solution of 464.4 mg of 2,3-diamino-5-bromopyridine (2.47 mmol) in cyclohexanone and 800 mg of 2-bromo-1-(3,4-dimethoxyphenyl)ethanone (3.01 mmol) were used. Compound **13** was obtained as a light brown powder (959 mg, 90%). ¹H NMR (dms_o-d₆, 300 MHz), δ(ppm): 4.07 (s, 3H), 4.12 (s, 3H), 7.15 (s br, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.74 (dd, *J* = 8.5 and 1.5 Hz, 1H), 7.77 (d, *J* = 1.5 Hz, 1H), 8.57 (s br, 1H), 8.72 (s br, 1H). ¹³C NMR (dms_o-d₆, 75 MHz), δ(ppm): 56.2, 56.5, 110.2, 111.1, 111.61, 112.1, 112.6, 115.8, 122.7, 132.3, 134.8, 136.5, 149.7, 150.9. MS (ESI⁺): *m/z* = 348.0/350.0 [M,H]⁺ found; C₁₅H₁₅N₃O₂Br calculated *m/z* = 348.0/350.0 [M,H]⁺.

2-(furan-2-yl)imidazo[1,2-a]pyridin-8-amine hydrochloride (**14,18**). According to general procedure B, a solution of 205 mg of 2,3-diamino-5-bromopyridine (1.88 mmol) in cyclohexanone and 425 mg of 2-bromo-1-(2-furanyl)-ethanone (2.25 mmol) were used. Product **14** was chorhydrated. Compound **18** was obtained as a light brown powder (161.7 mg, 43%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 6.71 (dd, *J* = 3.5 and 1.9 Hz, 1H), 7.07 (d, *J* = 9.1 Hz, 1H), 7.19 (d, *J* = 6.3 Hz, 1H), 7.26 (dd, *J* = 9.0 and 6.1 Hz, 1H), 7.80 (d, *J* = 1.5 Hz, 1H), 8.10 (d, *J* = 6 Hz, 1H), 8.36 (s, 1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 110.0, 110.8, 111.6, 112.1, 116.8, 118.7, 126.9, 133.0, 133.3, 141.5, 145.0. HRMS (ESI⁺): *m/z* = 200.08184 [M,H]⁺ found; C₁₁H₁₀N₃O calculated *m/z* = 200.08237 [M,H]⁺. Mp: 240.7°C. HPLC: C₄ column: *t_R* = 7.7 min, purity 99% C₁₈ column: *t_R* = 12.5 min, purity 99%.

[6-bromo-2-(2-furyl)imidazo[1,2-a]pyridin-8-yl]ammonium bromide (**15**). According to general procedure B, a solution of 414.5 mg of 2,3-diamino-5-bromopyridine (2.20 mmol) in cyclohexanone and 500 mg of 2-bromo-1-(2-furanyl)-ethanone (2.64 mmol) were used. Compound **15** was obtained as a light brown powder (560 mg, 71%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 6.73 (dd, *J* = 3.5 and 1.8 Hz, 1H), 7.13-7.18 (m, 2H), 7.83 (dd, *J* = 1.8 and 0.6 Hz, 1H), 8.31-8.36 (m, 2H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 110.0, 110.9, 112.1, 112.8, 113.7, 116.5, 127.3, 131.1, 133.8, 141.2, 145.2. MS (ESI⁺): *m/z* = 277.9/279.9 [M,H]⁺ found; C₁₁H₈N₃OBr calculated *m/z* = 277.9/279.9 [M,H]⁺.

General method C for Suzuki coupling. To a solution of appropriate 6-bromo-imidazopyridine derivative (1 eq) in DMF (2.5 mL/mmol of brominated derivative), boronic acid derivative (1.9 eq) and aqueous

K₃PO₄ (2M, 7.5 eq) solution were added. The mixture was stirred and flushed with nitrogen for 10 minutes. Then Pd(PPh₃)₄ (0.1 eq) was added. The mixture was stirred at 60°C overnight and then concentrated *in vacuo*. H₂O (6 mL/mmol of brominated starting material) was added, the product was extracted with EtOAc and dried over MgSO₄. The solvent was evaporated *in vacuo*. Flash chromatography was performed.

6-(2-furyl)-2-phenyl-imidazo[1,2-a]pyridine (8). According to general procedure C, a solution of 173 mg of 6-bromo-2-(phenyl)imidazo[1,2-a]pyridine (0.633 mmol) in DMF, 106 mg of 2-furanboronic acid (0.95 mmol), 2.42 mL of aqueous K₃PO₄ 2M solution and 73 mg of Pd(PPh₃)₄ (0.063 mmol) were used. Preparative HPLC purification (pH 9, acetonitrile/water) afforded compound **8** as a yellow solid (37 mg, 22%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 6.56 (dd, *J* = 3.4 and 1.8 Hz, 1H), 6.81 (d, *J* = 3.4 Hz, 1H), 7.30-7.35 (m, 1H), 7.40-7.45 (m, 2H), 7.51-7.56 (m, 1H), 7.59 (d, *J* = 1.5 Hz, 2H), 7.88-7.91 (m, 2H), 8.16 (s, 1H), 8.70 (d, *J* = 0.7 Hz, 1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 105.9, 109.6, 111.5, 115.8, 117.8, 120.9, 122.9, 125.6, 127.8, 128.4, 133.1, 142.5, 144.5, 145.4, 150.3. HRMS (ESI⁺): *m/z* = 261.10224 [M,H]⁺ found; C₁₇H₁₃N₂O calculated *m/z* = 261.10277 [M,H]⁺. Mp: 179.1°C. HPLC: C₄ column: *t_R* = 7.9 min, purity 99% C₁₈ column: *t_R* = 21.7 min, purity 99%.

2-(3,4-dimethoxyphenyl)-6-(2-furyl)imidazo[1,2-a]pyridine (9). According to general procedure C, a solution of 103 mg of 6-bromo-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridine (0.308 mmol) in DMF, 50 mg of 2-furanboronic acid (0.447 mmol), 1.5 mL of aqueous K₃PO₄ 2M solution and 80 mg of Pd(PPh₃)₄ (0.024 mmol) was used. Flash chromatography (CH₂Cl₂/EtOAc – 80:20) afforded compound **9** as a beige powder (100 mg, 52%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 3.89 (s, 3H), 3.95 (s, 3H), 6.57 (dd, *J* = 3.4 and 1.8 Hz, 1H), 6.84 (d, *J* = 3.3 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 8.3 and 2.0 Hz, 1H), 7.52-7.66 (m, 3H), 7.65 (dd, *J* = 9.4 and 1.7 Hz, 1H), 8.18 (s, 1H), 8.73-8.78 (m, 1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 55.1, 105.8, 108.9, 109.4, 111.5, 111.7, 115.6, 117.7, 118.5, 120.8, 122.7, 126.2, 142.5, 144.4, 145.5, 149.3, 150.3. HRMS (ESI⁺): *m/z* = 321.12389 [M,H]⁺ found; C₁₉H₁₇N₂O₃ calculated *m/z* = 321.12389 [M,H]⁺. Mp: 159.6°C. HPLC: C₄ column: *t_R* = 18.0 min, purity 97% C₁₈ column: *t_R* = 24.0 min, purity 96%.

2,6-bis(2-furyl)imidazo[1,2-a]pyridine (10). According to general procedure C, a solution of 105 mg of 6-bromo-2-(furan-2-yl)imidazo[1,2-a]pyridine (0.399 mmol) in DMF, 66 mg of 2-furanboronic acid (0.59 mmol), 1.5 mL of aqueous K₃PO₄ 2M solution and 46 mg of Pd(PPh₃)₄ (0.04 mmol) were used. Flash chromatography (CH₂Cl₂) afforded compound **10** as a yellow solid (80 mg, 80%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 6.53-6.57 (m, 2H), 6.88 (dd, *J* = 12.2 and 5.4 Hz, 2H), 7.52 (d, *J* = 9.4 Hz, 1H), 7.53-7.60 (m, 2H), 7.65 (dd, *J* = 9.4 and 1.7 Hz, 1H), 8.08 (s, 1H), 8.76 (s, 1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 105.9, 106.5, 109.0, 111.1, 111.4, 115.6, 117.9, 121.0, 123.3, 137.4, 142.3, 142.5, 144.4, 148.8, 150.2. HRMS (ESI⁺): *m/z* = 251.08150 [M,H]⁺ found; C₁₅H₁₁N₂O₂ calculated *m/z* =

251.08203 [M,H]⁺. Mp: 118.2°C. HPLC: C₄ column: t_R = 16.1 min, purity 97% C₁₈ column: t_R = 22.0 min, purity 96%.

2-(2-furyl)-6-phenyl-imidazo[1,2-a]pyridine (11). According to general procedure C, a solution of 79 mg of 6-bromo-2-(2-furyl)imidazo[1,2-a]pyridine (0.300 mmol) in DMF, 54.9 mg of phenylboronic acid (0.45 mmol), 1.15 mL of K₃PO₄ 2M solution and 34.7 mg of Pd(PPh₃)₄ (0.030 mmol) were used. Preparative HPLC purification (pH 9, acetonitrile/water) afforded compound **11** as a brown solid (36 mg, 46%). ¹H NMR (CDCl₃, 300 MHz), δ(ppm): 6.51 (dd, *J* = 3.4 and 1.8 Hz, 1H), 6.92 (d, *J* = 3.3 Hz, 1H), 7.42-7.65 (m, 2H), 7.43-7.45 (m, 1H), 7.45-7.49 (m, 2H), 7.52-7.56 (m, 2H), 7.68 (d, *J* = 12.0 Hz, 1H), 7.80 (s, 1H), 8.24 (s, 1H). ¹³C NMR (CDCl₃, 75 MHz), δ(ppm): 107.0, 108.3, 111.7, 117.1, 122.9, 126.0, 126.9, 128.0, 129.1, 137.1, 138.2, 142.2, 144.8, 149.4. HRMS (ESI⁺): *m/z* = 261.10224 [M,H]⁺ found; C₁₅H₁₂N₃O₂ calculated *m/z* = 261.10277 [M,H]⁺. Mp: 108.4°C. HPLC: C₄ column: t_R = 7.8 min, purity 99% C₁₈ column: t_R = 17.7 min, purity 99%.

6-(2-furyl)-2-phenyl-imidazo[1,2-a]pyridin-8-amine (16). According to general procedure C, a solution of 154 mg of (6-bromo-2-phenyl-imidazo[1,2-a]pyridin-8-yl)ammonium bromide (0.417 mmol) in DMF, 90 mg of 2-furanboronic acid (0.804 mmol), 2.04 mL of aqueous K₃PO₄ 2M solution and 0.08 mg of Pd(PPh₃)₄ (0.041 mmol) were used. Flash chromatography (CH₂Cl₂/EtOAc, 95:5) afforded compound **16** brown solid (95 mg, 83%). ¹H NMR (300 MHz, MeOD) δ 6.52 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.70 (dd, *J* = 3.4, 0.6 Hz, 1H), 6.74 (d, *J* = 1.5 Hz, 1H), 7.28-7.36 (m, 1H), 7.40-7.50 (m, 2H), 7.55 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.3 Hz, 2H), 8.08 (s, 1H), 8.14 (d, *J* = 1.5 Hz, 1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 99.8, 105.1, 110.3, 110.6, 111.2, 119.1, 125.5, 127.6, 128.4, 133.4, 136.0, 137.2, 142.5, 143.8, 151.3. HRMS (ESI⁺): *m/z* = 276.11314 [M,H]⁺ found; C₁₇H₁₄N₃O calculated *m/z* = 276.11370 [M,H]⁺. Mp: 82.6°C. HPLC: C₄ column: t_R = 18.1 min, purity 95% C₁₈ column: t_R = 24.4 min, purity 97%.

2-(3,4-dimethoxyphenyl)-6-(2-furyl)imidazo[1,2-a]pyridin-8-amine (17). According to general procedure C, a solution of 100 mg of 6-bromo-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridin-8-amine (0.233 mmol) in DMF, 39 mg of 2-furanboronic acid (0.35 mmol), 0.89 mL of K₃PO₄ 2M solution and 26.9 mg of Pd(PPh₃)₄ (0.023 mmol) were used. Flash chromatography (CH₂Cl₂-EtOAc, 90:10) afforded compound **17** as a brown solid (59 mg, 69%). ¹H NMR (dmsO-d₆, 300 MHz), δ(ppm): 6.54 (dd, *J* = 3.2 and 1.7 Hz, 1H), 6.72 (d, *J* = 3.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 1.5 Hz, 1H), 7.35 (dd, *J* = 8.4 and 2.1 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.82 (s, 1H), 7.95 (d, *J* = 1.3 Hz, 1H). ¹³C NMR (dmsO-d₆, 75 MHz), δ(ppm): 55.9, 56.2, 106.5, 107.8, 109.2, 109.3, 110.1, 111.1, 112.1, 118.2, 119.1, 123.0, 131.9, 133.4, 137.6, 143.4, 148.7, 149.6, 150.8. HRMS (ESI⁺): *m/z* = 336.13427 [M,H]⁺ found; C₁₉H₁₈N₃O₃ calculated *m/z* = 336.13480 [M,H]⁺. Mp: 124.7°C. HPLC: C₄ column: t_R = 15.9 min, purity 97% C₁₈ column: t_R = 23.9 min, purity 99%.

2,6-bis(2-furyl)imidazo[1,2-a]pyridin-8-amine (19). According to general procedure C, a solution of 60 mg of 6-bromo-2-(furyl)imidazo[1,2-a]pyridine (0.167 mmol) in DMF, 28 mg of 2-furanboronic acid (0.251 mmol), 0.638 mL of K₃PO₄ 2M solution and 19.3 mg of Pd(PPh₃)₄ (0.017 mmol) were used. Preparative HPLC purification (pH 9, acetonitrile/water) afforded compound **19** as a beige solid (37 mg, 9%). ¹H NMR (CDCl₃, 300 MHz), δ(ppm): 6.54 (dd, *J* = 3.4 and 1.9 Hz, 1H), 6.58 (dd, *J* = 3.4 and 1.8 Hz, 1H), 6.75 (dd, *J* = 3.4 and 0.5 Hz, 1H), 6.85 (d, *J* = 1.4 Hz, 1H), 6.88 (dd, *J* = 3.4 and 0.6 Hz, 1H), 7.57 (dd, *J* = 1.3 and 0.7 Hz, 1H), 7.61 (dd, *J* = 1.8 and 0.7 Hz, 1H), 8.01 (s, 1H), 8.18 (d, *J* = 1.4 Hz, 1H). ¹³C NMR (CDCl₃, 75 MHz), δ(ppm): 101.2, 105.7, 106.7, 109.8, 110.9, 111.3, 111.4, 119.8, 134.5, 135.4, 137.5, 142.4, 142.5, 147.8, 150.8. HRMS (ESI⁺): *m/z* = 266.09240 [M,H]⁺ found; C₁₅H₁₂N₃O₂ calculated *m/z* = 266.09298 [M,H]⁺. Mp: 124.7°C. HPLC: C₄ column: *t_R* = 8.3 min, purity 95% C₁₈ column: *t_R* = 17.4 min, purity 99%.

2-(2-furyl)-6-phenyl-imidazo[1,2-a]pyridin-8-amine (20). According to general procedure C, a solution of 150 mg of 6-bromo-2-(furyl)imidazo[1,2-a]pyridine (0.418 mmol) in DMF, 76.4 mg of phenylboronic acid (0.627 mmol), 1.60 mL of K₃PO₄ 2M solution and 48.3 mg of Pd(PPh₃)₄ (0.042 mmol) were used. Preparative HPLC purification (pH 9, acetonitrile/water) afforded compound **20** as a beige solid (34 mg, 30%). ¹H NMR (CD₃OD, 300 MHz), δ(ppm): 6.53 (dd, *J* = 3.4 and 1.8 Hz, 1H), 6.69 (d, *J* = 1.6 Hz, 1H), 6.81 (dd, *J* = 3.5 and 0.6 Hz, 1H), 7.28-7.33 (m, 1H), 7.35-7.41 (m, 2H), 7.50-7.52 (m, 1H), 7.53-7.54 (m, 2H), 7.88 (s, 1H), 7.92 (d, *J* = 1.5 Hz, 1H). ¹³C NMR (CD₃OD, 75 MHz), δ(ppm): 103.6, 105.8, 109.5, 111.1, 112.8, 126.4, 127.3, 128.5, 128.7, 135.7, 137.8, 138.5, 142.0, 149.0. HRMS (ESI⁺): *m/z* = 276.11314 [M,H]⁺ found; C₁₇H₁₄N₃O calculated *m/z* = 276.1137 [M,H]⁺. Mp: 150.0°C. HPLC: C₄ column: *t_R* = 8.3 min, purity 99% C₁₈ column: *t_R* = 18.7 min, purity 99%.

2-iodo-3',4'-dimethoxyacetophenone (21). 3',4'-dimethoxyacetophenone (2g, 11.1 mmol) was dissolved in MeOH (22 mL). I₂ (2.82 g, 1 eq) and CuO (0.882 g, 1 eq) were added. The mixture was heated at 65°C for 3 hours. Mixture was filtered on celite with EtOAc, washed with saturated NaHCO₃ and brine, dried on MgSO₄ and evaporated *in vacuo*. The crude solid was purified on flash chromatography (pure DCM) to afford compound as a brown solid (3 g, 88%). Flash chromatography (pure CH₂Cl₂) afforded compound **21** as a white solid (517.3 mg, 60%). ¹H NMR (CDCl₃, 300MHz), δ(ppm): 3.94 (s, 3H), 3.97 (s, 3H), 4.33 (s, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.62 (dd, *J* = 8.4 and 2.1 Hz, 1H). [60]

6-iodo-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridin-8-amine hydroiodide (22). According to general procedure B, a solution of 1 g of 2,3-diamino-5-iodopyridine (4.26 mmol) in cyclohexanone and 1.63 g of 2-iodo-1-(3,4-dimethoxyphenyl)ethanone (5.32 mmol) were used. Compound **22** was obtained as a light brown powder (1.19 g, 53%). ¹H NMR (dmsd-d₆, 300 MHz), δ(ppm): 3.83 (s, 3H), 3.88 (s, 3H), 7.06 (s, 1H), 7.17 (dd, *J* = 8.1, 1H), 7.44-7.49 (m, 2H), 8.36 (d, *J* = 1.7 Hz, 1H), 8.45 (s br, 1H). ¹³C

NMR (dmso- d_6 , 75 MHz), δ (ppm): 56.2, 56.4, 83.3, 110.1, 110.5, 112.7, 116.8, 119.5, 120.5, 132.6, 134.7, 136.0, 149.7, 150.9. MS (ESI⁺): m/z = 396.0 [M,H]⁺ found; C₁₅H₁₅IN₃O₂ calculated m/z = 396.0 [M,H]⁺.

2-(3,4-dimethoxyphenyl)-6-(phenylethynyl)imidazo[1,2-a]pyridin-8-amine (23). A mixture of 2-(3,4-dimethoxyphenyl)-6-iodoimidazo[1,2-a]pyridin-8-amine hydroiodide (0.3 g, 0.573 mmol) in DMF (2.29 mL) with Bis(triphenylphosphine)palladium(II) chloride (2 %, 8.05 mg, 0.0115 mmol) and Et₃N (2.29 mL) was degassed for 15 min. CuI (21.8 mg, 0.115 mmol) and phenylacetylene (69.3 μ L, 1.1 eq) were added. The mixture was heated under microwave at 100 °C for 30 min. The solvents were removed under reduced pressure. Water was added and the compound was extracted twice with CH₂Cl₂. The organic phase was then washed with brine, dried over MgSO₄ and evaporated under reduced pressure. Flash chromatography (CH₂Cl₂-EtOAc, 80 :20) afforded compound **23** as a brown solid (201 mg, 95%). ¹H NMR (CDCl₃, 300MHz), δ (ppm): 3.93 (s, 3H), 4.02 (s, 3H), 4.71 (s (br), 2H), 6.45 (s, 1H), 6.90 (d, J = 9.9 Hz, 1H), 7.36 (m, 4H), 7.53 (m, 2H), 7.56 (d, J = 2.0 Hz, 1H), 7.67 (s, 1H), 7.82 (s, 1H). ¹³C NMR (CDCl₃, 75MHz), δ (ppm): 55.9, 56.1, 86.3, 89.6, 105.2, 108.6, 109.3, 110.1, 111.1, 118.3, 118.7, 122.9, 126.3, 128.4, 128.5, 131.5, 135.0, 138.5, 144.8, 149.0, 149.2. HRMS (ESI⁺): m/z = 370.15500 [M,H]⁺ found; C₂₃H₂₀N₃O₂ calculated m/z = 370.15553 [M,H]⁺. Mp: 190°C. HPLC: C₄ column: t_R = 15.3 min, purity 99% C₁₈ column: t_R = 28.6 min, purity 99%.

2-(3,4-dimethoxyphenyl)-6-phenethylimidazo[1,2-a]pyridin-8-amine (24). 2-(3,4-dimethoxyphenyl)-6-(2-phenylethynyl)imidazo[1,2-a]pyridin-8-amine (50 mg, 0.135 mmol), ammonium formate 341 mg, 4 eq) and Pd(OH)₂ (19 mg, 1 eq) were dissolved in MeOH (2.03 mL) and heated under reflux for 2.5 h at 65 °C. The mixture was filtered through celite and washed with methanol. After evaporation of the filtrate under reduced pressure, flash chromatography (CH₂Cl₂-MeOH, 97:3) afforded compound **24** as a beige solid (10.1 mg, 20%). ¹H NMR (CDCl₃, 300 MHz), δ (ppm): 2.72-2.97 (m, 4H), 3.92 (s, 3H), 3.99 (s, 3H), 4.69 (s (broad), 1H), 6.24 (s, 1H), 6.91 (d, J = 8.4 Hz, 1H), 7.13-7.33 (m, 6H), 7.41 (dd, J = 8.4 and 1.9 Hz, 1H), 7.58 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz), δ (ppm): 34.9, 37.0, 55.9, 56.0, 105.2, 108.4, 109.3, 111.3, 113.7, 118.3, 126.1, 126.7, 127.3, 128.4, 128.5, 134.9, 138.4, 141.1, 143.6, 148.7, 149.2. HRMS (ESI⁺): m/z = 374.18630 [M,H]⁺ found; C₂₃H₂₄N₃O₂ calculated m/z = 374.18683 [M,H]⁺. Mp: 164°C. HPLC: C₄ column: t_R = 15.2 min, purity 99% C₁₈ column: t_R = 27.2 min, purity 99%.

Tert-Butyl N-[6-bromo-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridin-8-yl]carbamate (25). Into an oven dried flask and under nitrogen atmosphere were placed 6-bromo-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridin-8-amine hydrobromide **13** (3 g, 6.99 mmol) in dry THF (50 mL). NaHMDS (600 %, 1 M, 41.9 mL) was added at -10°C and the mixture was stirred at RT for 3h. Then, a solution of Boc₂O (4.58 g, 3 eq) dissolved in dry THF (40 mL) was added and the reaction mixture was stirred at RT for 3h. The mixture was quenched by saturated solution of ammonium chloride

(35 mL) and extracted 3 times by EtOAc, dried over MgSO₄, filtered and the solvent was evaporated. Flash chromatography (Cy/CH₂Cl₂, 50:50 to CH₂Cl₂) afforded compound **25** as brown crystals (2.2 g, 70%). ¹H NMR (CDCl₃, 300 MHz) δ(ppm): 1.57 (s, 9H), 3.93 (s, 3H), 4.00 (s, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.42 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.53 (s, 1H), 7.70 (s, 1H), 7.90 (d, *J* = 1.6 Hz, 1H), 7.96 (d, *J* = 4.4 Hz, 2H). MS (ESI⁺): *m/z* = 450.2 [M,H]⁺ found; C₂₀H₂₃N₃O₄Br calculated *m/z* = 450.2 [M,H]⁺.

2,5-dioxopyrrolidin-1-yl 8-[[*tert*-butoxy]carbonyl]amino}-2-(3,4-dimethoxyphenyl)imidazo [1,2-*a*]pyridine-6-carboxylate (**26**). In a dried sealed tube were placed *tert*-butyl N-[6-bromo-2-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridin-8-yl]carbamate **25** (300 mg, 0.669 mmol), 2,5-dioxopyrrolidin-1-yl formate (191 mg, 2 eq), Xantphos (9.68 mg, 0.025 eq), Pd(OAc)₂ (4.51 mg, 0.03 eq). The vial was evacuated and then purged three times with nitrogen. Then 4 mL of dry and degassed THF were added. The mixture was stirred at 60°C and NEt₃ (0.112 mL, 1.2 eq) was quickly added *via* a syringe. Fast gas evolution was observed and the reaction was left stirring for 18h at 60°C. The reaction mixture was diluted with EtOAc, filtered through celite and evaporated to dryness. The residue was taken up in dichloromethane, washed with water and brine. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. Flash chromatography (CH₂Cl₂ to CH₂Cl₂/EtOAc, 9:1) afforded compound **26** as yellow solid (137 mg, 40%). ¹H NMR (CDCl₃, 300 MHz) δ(ppm): 1.58 (s, 9H), 2.91 (s, 4H), 3.94 (s, 3H), 4.01 (s, 3H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.85 (s, 1H), 7.94 (s, 1H), 8.33 (s, 1H), 8.71 (d, *J* = 1.6 Hz, 1H). MS (ESI⁺): *m/z* = 511.2 [M,H]⁺ found; C₂₅H₂₇N₄O₈ calculated *m/z* = 511.2 [M,H]⁺.

Tert-Butyl-N-[2-(3,4-dimethoxyphenyl)-6-({4-[4-(2-methoxyethoxy)phenyl]piperazin-1-yl}carbonyl)imidazo[1,2-*a*]pyridin-8-yl]carbamate (**27**). 2,5-dioxopyrrolidin-1-yl-8-[[*tert*-butoxy]carbonyl]amino}-2-(3,4-dimethoxyphenyl)imidazo [1,2-*a*]pyridine-6-carboxylate **26** (65 mg, 0.127 mmol) was dissolved in dry dioxane (2 mL). 1-[4-(2-methoxyethoxy)phenyl]piperazine (30.1 mg, 1 eq) was added and the mixture was heated at 50°C for 18h. The reaction mixture was evaporated to dryness, taken up in CH₂Cl₂ and washed with water. The aqueous layer was extracted 5 times with CH₂Cl₂. The organics layers were washed with brine and dried over MgSO₄. The solvent was evaporated *under vacuum* and the crude product was purified by flash chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH, 98:2) to give the expected product **27** as white solid (53 mg, 66 %). ¹H NMR (CDCl₃, 300 MHz) δ(ppm): 1.57 (s, 9H), 3.12 (s, 4H), 3.45 (s, 3H), 3.74 (dd, *J* = 5.5, 3.9 Hz, 2H), 3.83 (s, 4H), 3.94 (s, 3H), 4.01 (s, 3H), 4.08 (dd, *J* = 5.5, 4.0 Hz, 2H), 6.87-6.92 (m, 4H), 6.95 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.80 (s, 1H), 7.87 (s, 1H), 7.98 (s, 1H), 8.04 (d, *J* = 1.4 Hz, 1H). MS (ESI⁺): *m/z* = 632.3 [M,H]⁺ found; C₃₄H₄₂N₅O₇ calculated *m/z* = 632.3 [M,H]⁺.

General method D. 2,5-dioxopyrrolidin-1-yl-8-[[*tert*-butoxy]carbonyl]amino}-2-(3,4-dimethoxyphenyl)imidazo [1,2-*a*]pyridine-6-carboxylate **26** (1.0 eq) was dissolved in dry CH₂Cl₂ (2

mL). Amine (1.0 or 1.5 eq) was added and the mixture was stirred for 2h at RT. The reaction mixture was evaporated to dryness, taken up in CH₂Cl₂ and washed with water. The aqueous layer was extracted 5 times with CH₂Cl₂. The organics layers were washed with brine and dried over MgSO₄. The solvent was evaporated *under vacuum* and the crude product was purified by flash chromatography to give expected products.

tert-butyl N-[2-(3,4-dimethoxyphenyl)-6-{{2-(4-hydroxyphenyl)ethyl}carbamoyl}imidazo[1,2-a]pyridin-8-yl]carbamate (28). Compound **28** was obtained following the general procedure D from the activated ester **26** (110 mg, 0.21 mmol) and the tyramine (1.5 eq, 0.32 mmol) after stirring for 6h and purification by flash chromatography (CH₂Cl₂/MeOH, 98:2) as a white solid (76 mg, 66%). ¹H NMR (CDCl₃, 300 MHz) δ(ppm): 1.52 (s, 9H), 2.82 (t, *J* = 7.2 Hz, 2H), 3.62 (dd, *J* = 13.2, 6.8 Hz, 2H), 3.92 (d, *J* = 6.3 Hz, 6H), 6.68 (t, *J* = 5.6 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 7.38-7.46 (m, 1H), 7.51 (d, *J* = 1.4 Hz, 1H), 7.76 (s, 1H), 7.93 (s, 1H), 7.96 (s, 1H), 8.14 (s, 1H), 8.44 (s, 1H). MS (ESI⁺): *m/z* = 533.2 [M,H]⁺ found; C₂₉H₃₃N₄O₆ calculated *m/z* = 533.2 [M,H]⁺.

Tert-Butyl N-[2-(3,4-dimethoxyphenyl)-6-{{3-(morpholin-4-yl)propyl}carbamoyl}imidazo[1,2-a]pyridin-8-yl]carbamate (29). Compound **29** was obtained following the general procedure D from the activated ester **26** (70 mg, 0.14 mmol) and the N-(3-Aminopropyl)morpholine (1.0 eq, 0.14 mmol) after purification by flash chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH, 96:4) as a beige solid (70 mg, 95%). ¹H NMR (CDCl₃, 300 MHz) δ(ppm): 1.55 (s, 9H), 1.80 (s, 2H), 2.51 (d, *J* = 13.7 Hz, 8H), 3.58 (s, 2H), 3.72 (s, 4H), 3.92 (s, 3H), 3.98 (s, 3H), 6.93 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 6.8 Hz, 1H), 7.54 (s, 1H), 7.81 (d, *J* = 2.3 Hz, 1H), 7.87 (s, 1H), 8.06 (s, 2H), 8.52 (s, 1H). MS (ESI⁺): *m/z* = 540.3 [M,H]⁺ found; C₂₈H₃₇N₅O₆ calculated *m/z* = 540.3 [M,H]⁺.

Tert-Butyl N-[2-(3,4-dimethoxyphenyl)-6-{{3-(piperazin-1-yl)propyl}carbamoyl}imidazo[1,2-a]pyridin-8-yl]carbamate (30). Compound **30** was obtained following the general procedure D from the activated ester **26** (43 mg, 0.08 mmol) and the 3-(piperazin-1-yl)propan-1-amine (1.0 eq, 0.08 mmol) after purification by flash chromatography (CH₂Cl₂ (1% TEA) to CH₂Cl₂/MeOH, 9:1+1%TEA) as a white solid (23 mg, 51%). ¹H NMR (CDCl₃, 300 MHz) δ(ppm): 1.41-1.48 (m, 1H), 1.56 (s, 9H), 1.81 (dd, *J* = 12.4, 6.2 Hz, 2H), 2.49-2.56 (m, 6H), 2.84-3.02 (m, 4H), 3.56 (dd, *J* = 11.4, 5.8 Hz, 2H), 3.92 (s, 3H), 3.99 (s, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.83 (s, 2H), 8.03 (s, 1H), 8.05 (d, *J* = 1.1 Hz, 1H), 8.52 (d, *J* = 1.4 Hz, 1H). MS (ESI⁺): *m/z* = 539.4 [M,H]⁺ found; C₂₈H₃₉N₆O₅ calculated *m/z* = 539.4 [M,H]⁺.

Tert-Butyl N-[2-(3,4-dimethoxyphenyl)-6-{{3-(piperidin-1-yl)propyl}carbamoyl}imidazo[1,2-a]pyridin-8-yl]carbamate (31). Compound **31** was obtained following the general procedure D from the

activated ester **26** (70 mg, 0.14 mmol) and the 3-(piperidin-1-yl)propan-1-amine (1.0 eq, 0.14 mmol) after purification by flash chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH 96/4) as a white solid (50 mg, 68%). ¹H NMR (CDCl₃, 300 MHz) δ(ppm): 1.20-1.30 (m, 2H), 1.55 (s, 9H), 1.70-1.86 (m, 4H), 1.91-2.08 (m, 2H), 2.60-2.89 (m, 6H), 3.50-3.60 (m, 2H), 3.92 (s, 3H), 3.98 (s, 3H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.44 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.85 (s, 1H), 8.01 (s, 1H), 8.11 (s, 1H), 8.41 (s, 1H), 8.64 (s, 1H). MS (ESI⁺): *m/z* = 538.4 [M,H]⁺ found; C₂₉H₄₀N₅O₅ calculated *m/z* = 538.4 [M,H]⁺.

Tert-Butyl N-[2-(3,4-dimethoxyphenyl)-6-[[3-(4-methylpiperazin-1-yl)propyl]carbamoyl]imidazo[1,2-a]pyridin-8-yl]carbamate (32). Compound **32** was obtained following the general procedure D from the activated ester **26** (80 mg, 0.16 mmol) and the 3-(4-methylpiperazin-1-yl)propan-1-amine (1.0 eq, 0.16 mmol) after purification by flash chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH, 96:4) as a white solid (52 mg, 60%). ¹H NMR (CDCl₃, 300 MHz) δ(ppm): 1.52 (s, 9H), 1.75-1.87 (m, 2H), 2.27 (s, 3H), 2.44-2.79 (m, 10H), 3.54 (s, 2H), 3.90 (s, 3H), 3.94 (s, 3H), 6.90 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 1.5 Hz, 1H), 7.81 (s, 1H), 7.98-8.19 (m, 3H), 8.50 (s, 1H). MS (ESI⁺): *m/z* = 553.4 [M,H]⁺ found; C₂₉H₄₁N₆O₅ calculated *m/z* = 553.4 [M,H]⁺.

Tert-Butyl N-[2-(3,4-dimethoxyphenyl)-6-[(2-{4-[4-(2-methoxyethoxy)phenyl]piperazin-1-yl}ethyl)carbamoyl]imidazo[1,2-a]pyridin-8-yl]carbamate (33). Compound **33** was obtained following the general procedure D from the activated ester **26** (70 mg, 0.14 mmol) and the 2-{4-[4-(2-methoxyethoxy)phenyl]piperazin-1-yl}ethan-1-amine (1.0 eq, 0.14 mmol) after purification by flash chromatography (CH₂Cl₂ to CH₂Cl₂/MeOH, 96:4) as a beige solid (60 mg, 65 %). ¹H NMR (CDCl₃, 300 MHz) δ(ppm): 1.48 (s, 9H), 2.73 (s, 6H), 3.20 (s, 4H), 3.45 (dd, *J* = 3.4, 2.2 Hz, 3H), 3.61 (s, 2H), 3.68-3.77 (m, 2H), 3.93 (s, 3H), 3.99 (s, 3H), 4.07 (s, 2H), 6.90 (dt, *J* = 16.4, 5.5 Hz, 5H), 7.23-7.32 (m, 1H), 7.46 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.98 (s, 1H), 8.12 (s, 1H), 8.54 (s, 1H). MS (ESI⁺): *m/z* = 675.5 [M,H]⁺ found; C₃₆H₄₇N₆O₇ calculated *m/z* = 675.5 [M,H]⁺.

General method E. Intermediates **5** to **11** (0.10 mmol) was dissolved in dry dioxane HCl (4M) (2 mL) and heated at 60°C for 2h. Reaction was monitored by LCMS. The mixture was evaporated to dryness, dried several hours and washed by CH₂Cl₂ to afford expected products.

(8-amino-2-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyridin-6-yl)(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)methanone hydrochloride (34). Compound **34** was obtained following the general procedure E from the intermediate **27** (0.13 mmol) as a grey solid (30 mg, 63%). ¹H NMR (MeOD, 300 MHz) δ(ppm): 3.15 (s, 4H), 3.32 (s, 4H), 3.42 (s, 3H), 3.70-3.74 (m, 2H), 3.92 (s, 3H), 3.97 (s, 3H), 4.04-4.09 (m, 2H), 6.85-6.95 (m, 3H), 6.97-7.04 (m, 2H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.45-7.52 (m, 2H), 8.20 (d, *J* = 1.2 Hz, 1H), 8.38 (s, 1H). ¹³C NMR (MeOD, 75 MHz) δ(ppm): 49.0, 52.6, 56.6, 56.8, 59.2, 68.8, 72.3, 109.8, 110.8, 112.4, 113.3, 116.5, 116.6, 120.2, 120.5, 120.6, 128.5, 134.3, 135.1, 138.3,

145.7, 151.3, 152.8, 155.8, 167.9. HRMS (ESI⁺): m/z = 532.25686 [M,H]⁺ found; C₂₉H₃₄N₅O₅ calculated m/z = 532.25545 [M,H]⁺. Mp: 204.0°C. HPLC: C₄ column: t_R = 15.1 min, purity 99% C₁₈ column: t_R = 21.5 min, purity 97%.

8-amino-2-(3,4-dimethoxyphenyl)-N-(4-hydroxyphenethyl)imidazo[1,2-a]pyridine-6-carboxamide hydrochloride (35). Compound **35** was obtained following the general procedure E from the intermediate **28** (0.14 mmol) as a beige solid (38 mg, 57%). ¹H NMR (dmsd-d₆, 300 MHz) δ (ppm): 2.73 (t, J = 6.7 Hz, 2H), 3.40-3.50 (m, 2H), 3.83 (s, 3H), 3.90 (s, 3H), 6.68 (d, J = 7.9 Hz, 2H), 6.28-7.27 (m, 2H), 7.03 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 8.45 (s, 1H), 8.69 (s, 1H), 8.82 (s, 1H), 9.12 (s, 1H). ¹³C NMR (dmsd-d₆, 75 MHz) δ (ppm): 34.1, 41.3, 55.7, 56.1, 107.5, 110.0, 111.0, 112.1, 115.1, 115.5, 118.8, 119.3, 126.3, 129.3, 129.5, 132.7, 133.2, 135.9, 149.2, 150.3, 155.7, 163.3. HRMS (ESI⁺): m/z = 433.18829 [M,H]⁺ found; C₂₄H₂₅N₄O₄ calculated m/z = 433.18703 [M,H]⁺. Mp: 246.0°C. HPLC: C₄ column: t_R = 13.7 min, purity 99% C₁₈ column: t_R = 22.0 min, purity 98%.

8-amino-2-(3,4-dimethoxyphenyl)-N-(3-morpholinopropyl)imidazo[1,2-a]pyridine-6-carboxamide dihydrochloride (36). Compound **36** was obtained following the general procedure E from the intermediate **29** (0.13 mmol) as a beige solid (40 mg, 60%). ¹H NMR (dmsd-d₆, 300 MHz) δ (ppm): 1.89-2.05 (m, 2H), 2.95-3.19 (m, 4 H), 3.30-3.52 (m, 4H), 3.73-4.01 (m, 10H), 7.14 (d, J = 8.6 Hz, 1H), 6.46-7.59 (m, 2H), 7.20 (s, 1H), 7.70 (dd, J = 8.4, 2.0 Hz, 1H), 7.87 (d, J = 1.9 Hz, 1H), 8.56 (d, J = 1.0 Hz, 1H), 8.70 (s, 1H), 9.01 (s, 1H), 10.89 (s, 1H). ¹³C NMR (dmsd-d₆, 75 MHz) δ (ppm): 23.2, 36.6, 51.0, 53.9, 55.7, 56.2, 63.2, 107.4, 110.0, 110.9, 112.2, 115.7, 119.0, 119.3, 125.9, 133.0, 133.3, 136.3, 149.2, 150.3, 163.8. HRMS (ESI⁺): m/z = 440.23098 [M,H]⁺ found; C₂₃H₃₀N₅O₄ calculated m/z = 440.22923 [M,H]⁺. Mp: 216.0°C. HPLC: C₄ column: t_R = 13.5 min, purity 99% C₁₈ column: t_R = 19.1 min, purity 96%.

8-amino-2-(3,4-dimethoxyphenyl)-N-(3-(piperazin-1-yl)propyl)imidazo[1,2-a]pyridine-6-carboxamide trihydrochloride (37). Compound **37** was obtained following the general procedure E from the intermediate **30** (0.04 mmol) as a dark beige solid (14 mg, 60%). ¹H NMR (dmsd-d₆, 300 MHz) δ (ppm): 1.93-2.08 (m, 1H), 3.18-3.24 (m, 1H), 3.27-3.50 (m, 8H), 3.63-3.73 (m, 2H), 3.83 (s, 3H), 3.90 (s, 3H), 7.13 (d, J = 8.6 Hz, 1H), 6.90-7.41 (m, 2H), 7.21 (s, 1H), 7.71 (dd, J = 8.4, 1.9 Hz, 1H), 7.88 (d, J = 1.7 Hz, 1H), 8.57 (s, 1H), 8.71 (s, 1H), 9.00 (t, J = 5.2 Hz, 1H), 9.75 (s, 2H). ¹³C NMR (dmsd-d₆, 75 MHz) δ (ppm): 23.3, 39.5, 47.7, 53.6, 55.7, 56.2, 107.4, 110.0, 110.9, 112.2, 115.7, 118.9, 119.3, 126.0, 132.9, 133.3, 136.1, 149.2, 150.3, 163.7. HRMS (ESI⁺): m/z = 439.24652 [M,H]⁺ found; C₂₃H₃₁N₆O₃ calculated m/z = 439.24522 [M,H]⁺. Mp: 220.0°C. HPLC: C₄ column: t_R = 5.5 min, purity 98% (254 nm). C₁₈ column: t_R = 18.4 min, purity 96%.

8-amino-2-(3,4-dimethoxyphenyl)-N-(3-(piperidin-1-yl)propyl)imidazo[1,2-a]pyridine-6-carboxamide dihydrochloride (38). Compound **38** was obtained following the general procedure E from the intermediate **31** (0.09 mmol) as a grey solid (26 mg, 55%). ¹H NMR (dms_o-d₆, 300 MHz) δ(ppm): 1.65-1.80 (m, 6H), 1.92-2.03 (m, 2H), 2.80-2.90 (m, 2H), 3.00-3.15 (m, 2H), 3.39-3.45 (m, 4H), 3.83 (s, 3H), 3.90 (s, 3H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.89-7.37 (m, 2H), 7.19 (s, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.87 (s, 1H), 8.58 (s, 1H), 8.69 (s, 1H), 9.03 (s, 1H), 10.19 (s, 1H). ¹³C NMR (dms_o-d₆, 75 MHz) δ(ppm): 21.4, 22.3, 23.5, 36.7, 51.9, 53.7, 55.7, 56.2, 107.2, 110.0, 110.9, 112.1, 115.6, 119.0, 119.3, 125.8, 132.9, 133.4, 136.3, 149.2, 150.3, 163.7. HRMS (ESI⁺): *m/z* = 438.25008 [M,H]⁺ found; C₂₄H₃₂N₅O₃ calculated *m/z* = 438.24997 [M,H]⁺. Mp: 200.0°C. HPLC: C₄ column: *t_R* = 15.7 min, purity 96% C₁₈ column: *t_R* = 19.8 min, purity 97%.

8-amino-2-(3,4-dimethoxyphenyl)-N-(3-(4-methylpiperazin-1-yl)propyl)imidazo[1,2-a]pyridine-6-carboxamide trihydrochloride (39). Compound **39** was obtained following the general procedure E from the intermediate **32** (0.09 mmol) as a dark beige solid (22 mg, 42%). ¹H NMR (D₂O, 300 MHz) δ(ppm): 2.07-2.24 (m, 2H), 3.07 (s, 3H), 3.38-3.46 (m, 2H), 3.52 (t, *J* = 6.9 Hz, 2H), 3.65 (s, 3H), 3.71 (s, 3H), 3.74 (s, 8H), 6.65 (d, *J* = 8.6 Hz, 1H), 6.74 (s, 1H), 6.94 (t, *J* = 3.3 Hz, 2H), 7.91 (s, 1H), 8.12 (d, *J* = 1.0 Hz, 1H). ¹³C NMR (D₂O, 75 MHz) δ(ppm): 23.6, 36.9, 42.8, 48.8, 50.3, 54.6, 55.4, 55.7, 106.5, 108.1, 110.4, 110.9, 116.7, 116.9, 117.9, 124.8, 131.8, 132.1, 135.3, 147.9, 149.2, 165.2. HRMS (ESI⁺): *m/z* = 453.26160 [M,H]⁺ found; C₂₄H₃₃N₆O₃ calculated *m/z* = 453.26087 [M,H]⁺. Mp: 211.0°C. HPLC: C₄ column: *t_R* = 5.3 min, purity 95% (254 nm). C₁₈ column: *t_R* = 18.4 min, purity 98% (254 nm).

8-amino-2-(3,4-dimethoxyphenyl)-N-(2-(4-(4-(2-methoxyethoxy)phenyl)piperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-6-carboxamide dihydrochloride (40). Compound **40** was obtained following the general procedure E from the intermediate **33** (0.09 mmol) as a dark beige solid (40 mg, 70%). ¹H NMR (dms_o-d₆, 300 MHz) δ(ppm): 3.05-3.15 (m, 2H), 3.17-3.25 (m, 2H), 3.28 (s, 3H), 3.35-3.76 (m, 10H), 3.83 (s, 3H), 3.90 (s, 3H), 3.99-4.03 (m, 2H), 6.87 (d, *J* = 9.2 Hz, 2H), 6.97 (d, *J* = 9.2 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.27 (d, *J* = 1.2 Hz, 1H), 7.73 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.87 (d, *J* = 1.9 Hz, 1H), 8.70 (s, 1H), 8.74 (s, 1H), 9.27 (d, *J* = 5.5 Hz, 1H). ¹³C NMR (dms_o-d₆, 75 MHz) δ(ppm): 34.2, 46.8, 51.1, 54.8, 55.7, 56.2, 58.2, 67.2, 70.5, 107.8, 110.1, 111.1, 112.2, 115.1, 116.0, 118.1, 118.6, 119.5, 125.9, 132.7, 133.3, 136.0, 143.6, 149.3, 150.5, 153.1, 164.1. HRMS (ESI⁺): *m/z* = 575.29761 [M,H]⁺ found; C₃₁H₃₉N₆O₅ calculated *m/z* = 575.29764 [M,H]⁺. Mp: 190.0°C. HPLC: C₄ column: *t_R* = 15.4 min, purity 99% C₁₈ column: *t_R* = 21.4 min, purity 98%.

Tert-Butyl N-[2-(3,4-dimethoxyphenyl)-6-iodoimidazo[1,2-a]pyridin-8-yl]carbamate (41). Into an oven dried flask and under nitrogen atmosphere, were placed 2-(3,4-dimethoxyphenyl)-6-iodoimidazo[1,2-a]pyridin-8-amine (300 mg, 0.759 mmol) in dry THF (6 mL), NaHMDS (6.0 eq., 1 M, 4.55 mL) was added at -10°C and the mixture was stirred at room temperature for 3h. Then, a solution

of Boc₂O (3.0 eq, 497 mg) dissolved in dry THF (4 mL) was added and the reaction mixture was stirred at room temperature for 3h. The mixture was quenched by saturated solution of ammonium chloride (25 mL) and extracted 3 times by EtOAc, dried over MgSO₄, filtered and evaporated. The crude was used in the next step without purification. MS (ESI⁺): m/z = 496.2 [M,H]⁺ found; C₂₀H₂₃IN₃O₄ calculated m/z = 496.1 [M,H]⁺.

Displacement binding assays

Radioligands were obtained from the following source: [³H]-ZM241385 from American Radiolabeled Chemicals (ART 0884: 1 mCi/ml / 50 Ci/mmol). For A_{2A} receptor binding evaluation, the stock solution of compounds was prepared in DMSO (10mM). The final concentration of DMSO was no more than 3% for radioligand binding assay. Competition binding curves of the A_{2A} receptor antagonist [³H]-ZM-241385 by the designed A_{2A} antagonists described above, were performed as before[56] in Human HEK293 A_{2A}R membranes (PerkinElmer – RBHA2AM400UA – K_D = 1.5 nM). 160 µl of a membranes solution (96 wells: 19 mL buffer (pH 7.4, Tris 50 mM, MgCl₂ 10 mM); 48 µl of membranes; 2 µl of adenosine deaminase (Roche, Basel, Switzerland)) were incubated with [³H]-ZM-241385 (40 µl at 12 nM / 2 nM by well) and increasing concentrations of the designed A_{2A}R antagonists (40 µl at 0–600 nM) in a final volume of 240 µl. All samples were assayed in duplicate. Non-specific binding was determined for each assay in the presence of the antagonist ZM-241385 (8.3 nM). Microplates were incubated for 1 h at 30°C on a stirring plate and the reaction was stopped by *vacuum* filtration with a Skatron semi-automatic cell harvester with the buffer solution to filter mats 1.5 mm (Molecular Devices, Sunnyvale, CA). 30 µl by well of scintillation cocktail (OptiPhase “HiSafe” 2, PerkinElmer) were added and radioactivity bound to the filters was determined after 1h. Data were analysed using Graph Pad Prism, version 5.01 (San Diego, CA). Inhibition constants (K_i) were calculated from the IC₅₀ values by non-linear regression analysis, the Cheng and Prusoff equation and K_D value of 1.5 nM were used. Displacement reference curves were performed with ZM-241385 (Bio-Techne Europe, Lille, Ref: 1036) from 0 to 24 nM with a K_i of 4.2 nM in accordance with the literature. For K_i determination, a 10 µM screening first enabled us to select promising compounds. K_i of selected compounds (*ie* **9**, **10**, **16** and **17**) were measured using the following range of concentrations: from 6.10⁻⁹M to 3.6.10⁻⁴M.

Cell culture and cytotoxicity assay

The human neuroblastoma cell line (SY5Y) was cultured in Dulbecco's modified Eagle medium (DMEM) (Gibco, Waltham, MA) supplemented with 2mM L-glutamine, 100 mg/ml streptomycin, 100 IU/ml penicillin, 1mM non-essential amino acids and 10% (v/v) heat-inactivated foetal bovine serum (Sigma-Aldrich, Saint-Louis, MO), and grown at 37 °C in a humidified incubator with 5% CO₂. Cells were seeded at 10000 cells per well onto 96-well plates in DMEM medium. Cells were incubated in a culture medium that contained various concentrations of test compounds, each dissolved in less than

0.1% DMSO. After 72 h of incubation, cell growth was estimated by the colorimetric MTT (thiazolyl blue tetrazolium bromide) assay.

Docking process

Molecular docking was performed into 4EIY pdb structure[49] using Gold suite v5.2 within the Hermes v1.6 GUI (CCDC©). Thus after adding hydrogen atoms and removing water molecules, docking was performed in a 10 Å radius pocket around the co-crystallized ZM-241385. Early termination of 3 docking solutions within 1.5 Å was set up in order to highlight ligands converging toward a few binding modes, using GoldScore scoring function in a 100% automatic searching process. The best docking pose per ligand was selected as the best scored pose of the most populated pose cluster.

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