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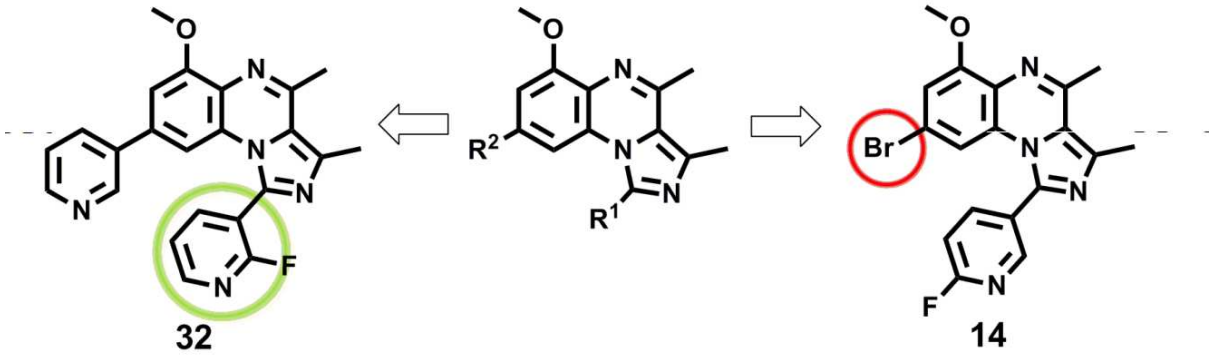

32

IC_{50} = 0.037 nM (PDE10A)
3.49 nM (PDE2A)

Highest PDE10A affinity

14

IC_{50} = 2.95 nM (PDE10A)
> 1000 nM (PDE2A)

Highest PDE10A selectivity

Development of highly potent phosphodiesterase 10A (PDE10A) inhibitors: Synthesis and *in vitro* evaluation of 1,8-dipyridinyl- and 1-pyridinyl-substituted imidazo[1,5-*a*]quinoxalines

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Development of highly potent phosphodiesterase 10A (PDE10A) inhibitors: Synthesis and *in vitro* evaluation of 1,8-dipyridinyl- and 1-pyridinyl-substituted imidazo[1,5-*a*]quinoxalines

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Abstract: Herein we report the synthesis of fluorinated inhibitors of phosphodiesterase 10A (PDE10A) which can be used potentially as lead structure for the development of a F-18 labeled PDE10A imaging agent for positron emission tomography. The use of ortho-fluoropyridines as residues could potentially enable the introduction of F-18 through nucleophillic substitution for radiolabeling purposes. 2-Fluoropyridines are introduced by a Suzuki coupling at different positions of the molecule. The reference compounds, 1,8-dipyridinylimidazo[1,5-*a*]quinoxalines and 1-pyridinylimidazo[1,5-*a*]quinoxalines, show inhibitory potencies at best in the subnanomolar range and selectivity factors greater than 38 against other PDE's. 1,8-Dipyridinylimidazo[1,5-*a*]quinoxalines are more potent inhibitors than 1-pyridinylimidazo[1,5-*a*]quinoxalines. Using 2-fluoro-3-pyridinyl as residue provided the most potent inhibitors **16** (IC_{50} = 0.12 nM), **17** (IC_{50} = 0.048 nM) and **32** (IC_{50} = 0.037 nM).

Keywords: PDE10A inhibitor, Imidazo[1,5-*a*]quinoxalines, PDE10A imaging agent.

1. Introduction

Phosphodiesterases (PDEs) represent a superfamily of enzymes capable of inactivating the second messengers cAMP or/and cGMP. These signaling molecules generated by cyclases regulate a wide range of physiological processes. By controlling cAMP/cGMP levels PDEs are key regulators of cellular signal transduction. So far 11 subfamilies of phosphodiesterases are known differing in structure, substrate specificity and inhibitor sensitivity. Classification by substrate specificity divides PDEs into cAMP-specific, cGMP-specific and dual substrate enzymes.

PDE10A is a dual substrate enzyme discovered in 1999 [1-4]. It is the only member of the PDE10 family. Across mammalian species PDE10A is primarily expressed in the striatum [5, 6], the main recipient of dopaminergic afferents from the substantia nigra [7]. Due to its high striatal expression PDE10A inhibitors are regarded as therapeutic approach in the treatment of diseases related to striatal dysfunction such as schizophrenia [8]. The antipsychotic-like effect of PDE10A inhibitors has been proven in animal models [9-11]. PDE10A inhibitors represent a new therapeutic treatment of negative, positive and cognitive symptoms of schizophrenia with a lower risk for side effects than traditional antipsychotics.

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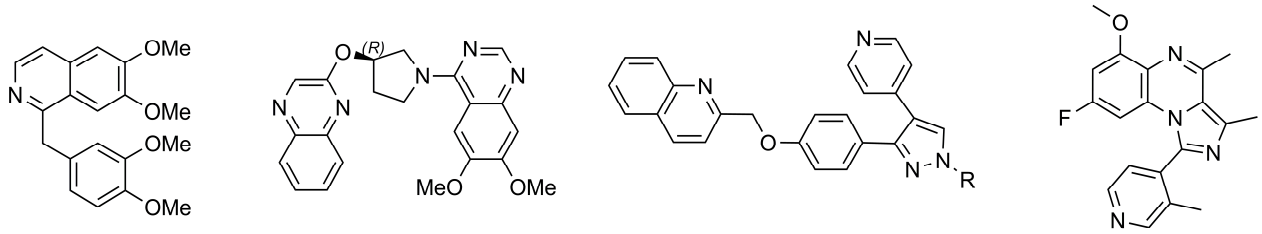
Therefore, the development of new PDE10A inhibitors is an increasing competitive field and a number of companies have established PDE10A research programs [12-15]. The natural alkaloid papaverine (**I**) is the first known PDE10A inhibitor. Structural optimizations lead to structures containing dialkoxyquinoxalines (e.g. PQ-10) similar to papaverine [16]. The discovery of TP-10 and MP-10 (Fig. 1) launched a new generation of inhibitors [9, 16, 17]. By exploring this new generation of inhibitors a novel binding mode was found [9]. The occupation of the so-called "selectivity pocket" is a specific feature of these highly affine and selective inhibitors. However, also inhibitors which do not occupy the selectivity pocket can be selective. For example compound **IV** is highly selective versus other PDEs [18]. Recently this new class of tricyclic imidazo[1,5-*a*]quinoxalines has been reported as potent and selective inhibitors [18].



I, Papaverine
PDE10A IC_{50}: 40 nM

II, PQ-10
(Pfizer 2007)
PDE10A IC_{50}: 6 nM

IIIa, MP-10 (PF-02545920, R=CH_3)
IIIb,TP-10 (R=CH_2CF_3)
(Pfizer 2008)
PDE10A IC_{50}: 0.18 nM (MP-10)
0.3 nM (TP-10)

IV
(BioCrea 2011)
PDE10A IC_{50}: 0.7 nM

Figure 1: Structure of different selective phosphodiesterase 10A inhibitors

As part of our ongoing interest in the development of PDE10A tracers for potential use in positron emission tomography (PET) [19, 20], we herein report the synthesis of several new fluorinated imidazo[1,5-*a*]quinoxalines. Fluorine substitution is commonly used in the design of drugs to improve metabolic stability, bioavailability and target interaction [21, 22]. Currently 20-25 % of newly developed pharmaceuticals contain at least one fluorine atom [21, 23]. Prospectively fluorination allows the development of ^{18}F-labeled (fluorine-18, $t_{½}$ = 109.7 min) PET tracers for use in diagnostic nuclear medicine and as *in vivo* pharmacological imaging tool in drug development as well as preclinical molecular imaging for pathophysiological studies.

Compound **IV** was chosen as lead compound for the development of a PDE10A tracer and modified with fluorine-containing groups to enable ^{18}F-labeling. Even though lead compound **IV** already possess a fluorine atom, which could be considered as position for an ^{18}F-label, this approach was not pursued. The nucleophilic aromatic ^{18}F-labeling via no-carrier-added (n.c.a.) [^{18}F]fluoride at this position is challenging due to the non-activated aromatic system [24, 25]. In another approach, introduction of the of fluoroalkoxy chains at position 6 has been demonstrated to diminish the inhibitory potency [18]. In addition fluoroalkoxy chains are often prone to dealkylation [26]. Therefore, we have chosen the 2-fluoropyridine moiety as aromatic, fluorine-bearing building block [24, 27, 28]. This structural element should facilitate a possible nucleophilic ^{18}F-labeling. The residues can be attached at position 1 and position 8 of the imidazo[1,5-*a*]quinoxalines (Fig. 2). In position 1 a pyridinyl residue is already present, whereas in position 8 a range of substituents is well tolerated [18].

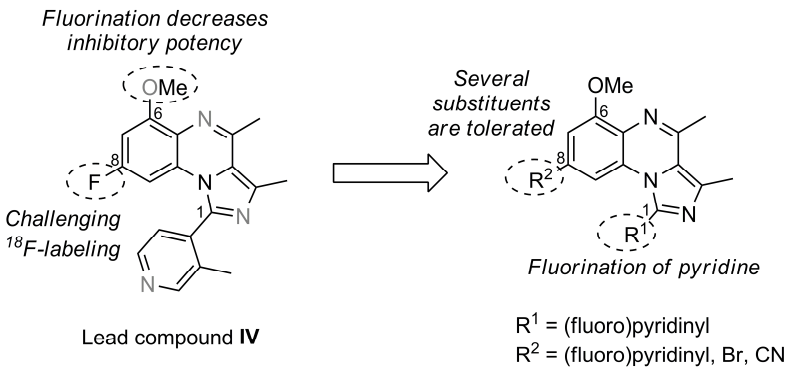


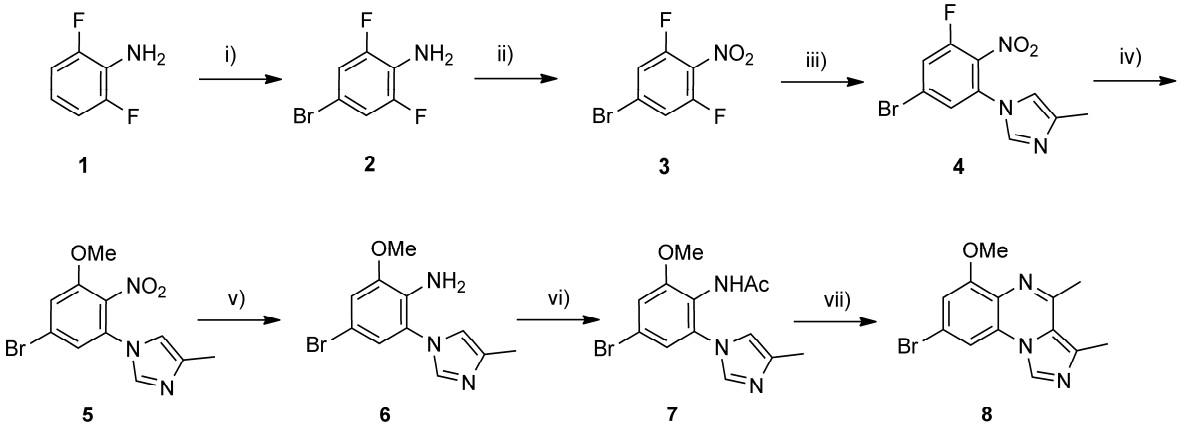
Figure 2: Planned modifications of lead compound IV in position 1 and 8, where different residues are tolerated [18]; important hydrogen bond acceptors in **IV** are grey colored

Structural modifications of the imidazo[1,5-*a*]quinoxaline scaffold were performed by introduction of different 2-fluoropyridinyl residues by a Pd-catalyzed Suzuki reaction which allows simple and quick variations in this last divergent synthetic step. Additionally the attachments at two positions (1 and 8) of the molecule (as R^1 or R^2) provide even more possibilities for variation.

2. Results and discussion

2.1.*Chemistry*

The 8-bromo substituted tricycle **8** as key intermediate was synthesized in seven steps starting from 2,6-difluoroaniline **1** as depicted in Scheme 1. Bromination of **1** using elemental bromine followed by the oxidation of the amino group with $NaBO_3 \cdot 4H_2O$ [29] afforded nitro compound **3**. Byproduct formation was minimized by slow addition of **2** to the oxidizing agents under high dilution conditions. Both fluorines of **3** could then be substituted subsequently by nucleophilic aromatic substitution. The amino-defluorination reaction of compound **3** with 0.8 equivalents of 4-methylimidazole provided four products as detected by TLC. Beside two monosubstituted regioisomers, products resulting from the substitution of the second fluorine were identified. Both monosubstituted regioisomers were formed in a ratio of ~4:1. Crystallization from ethanol provided the desired compound **4** (42% yield) as main isomer, whose structure was confirmed by NOE experiments.



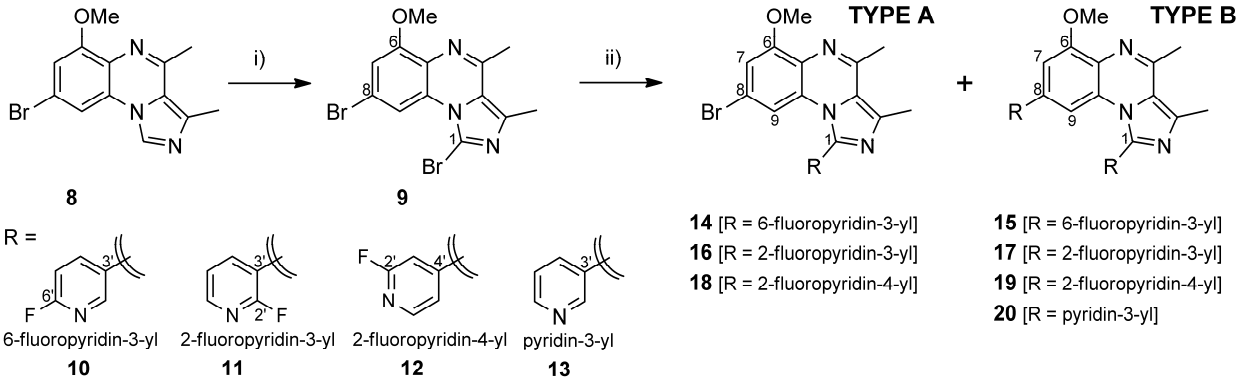
Scheme 1: Approach to key intermediate **8**. Reagents and conditions: i) Br_2, HOAc, rt, 84%; ii) $NaBO_3 4H_2O$, HOAc, 65℃, 2-3 d, 60%; iii) 4-Methylimidazol, K_2CO_3, DMF, rt, 18 h, 42%; iv) NaOMe, MeOH, rt, 1 h, 99%; v) Fe, HOAc/HOEt, reflux, 2 h, 92%; vi) Ac_2O, HOAc, rt, 16 h, 76%; vii) $POCl_3$, 115℃, 5d, 35%.

Substitution of the second fluorine in **4** with sodium methanolate afforded **5** in quantitative yield. Reduction of the nitro group by iron was followed by an acetylation with acetic anhydride to obtain

compound **7**. Cyclization of **7** by the use of phosphoryl chloride afforded the desired key intermediate **8** in moderate yield. The overall yield of the synthesis of compound **8** was 5%.

8-Bromo-1-pyridinylimidazo[1,5-a]quinoxalines and 1,8-dipyridinylimidazo[1,5-a]quinoxalines

For formation of 8-bromo-1-pyridinylimidazo[1,5-*a*]quinoxalines **14**, **16** and **18** key intermediate **8** was brominated using N-bromosuccinimide (NBS) in acetonitrile (22 ℃, 4 h) to provide the dibromo compound **9** in 82% yield (Scheme 2). Different *o*-fluoropyridinylboronic acids [$RB(OH)_2$] were coupled with **9** by the palladium catalyzed Suzuki reaction. In addition to the bromo derivatives (type A) also 1,8-dipyridinyl derivatives (type B), could be isolated in significant amounts. Formation of type B was expected as both bromine atoms are reactive.



Scheme 2: Approach to 1-pyridinyl-substituted and 1,8-dipyridinyl-substituted imidazo[1,5-*a*]quinoxalines. Reagents and conditions: i) NBS, MeCN, rt, 82%, 4 h, ii) $Pd(PPh)_4$, K_2CO_3, $R(B(OH)_2$ (**10**-**13**), dioxane/water (4/1), reflux.

However, due to the higher reactivity of the 1-bromo compared to the 8-bromo substituent in **9**, the mono-pyridinyl inhibitor of type A was preferably obtained. The results of conversion and product distribution for Suzuki coupling of **9** with three *o*-fluorinated pyridinylboronic acids are shown in Table 1.

Table 1: Yields of conversion and product distribution for Suzuki coupling of **9** with three o-fluorinated pyridinylboronic acids[a)]

entry	Boronic acid No	Equiv. boronic acid[b]	Type A Product No (yield%) [c)]	Type B Product No (yield%)[c)]	Recovered **9** (%)[c)]
1	**10** 6-F-pyridin-3-yl	1.3	**14** (39)	**15** (18)	(20)
2	**10** 6-F-pyridin-3-yl	1.5	**14** (58)	**15** (22)	(<5)
3	**11** 2-F-pyridin-3-yl	1.3	**16** (32)	**17** (9)	(38)
4	**12** 2-F-pyridin-4-yl	1.3	**18** (37)	**19** (16)	(25)
5	**13** pyridin-3-yl	2.3	n.d.	**20** (29)[d)]	n.d.

a) Conditions: 10mol% $Pd(Ph_3)_4$ in 1,4-dioxane/water (4/1) refluxed for 6 h.

b) Reaction with 1 equiv **9**

c) Yields of isolated pure products and calculated amounts of recovered **9**

d) Additional precipitation step after flash chromatography

When **9** was reacted with 1.3 equivalents of 6-fluoropyridin-3-ylboronic acid (**10**), the ratio of isolated type A inhibitor to type B was around ~2.2 (Table 1, entry 1). By the use of 1.5 equivalents of **10**, a full conversion of the starting material was achieved and no enhanced formation of **15** was detected (Table 1, entry 2, type A / type B-ratio: ~2.6). In the coupling reactions of 2-fluoropyridin-3-ylboronic acid a lower conversion and an improved type A / type B-ratio of ~3.6 was observed (Table 1, entry 3). A possible steric hindrance of the fluorine atom directly neighbored to the coupling position may explain these observations. To exploit the scope of the Suzuki coupling of **9**, we aimed to synthesize only type B inhibitors. Therefore, **9** was reacted with 2.3 equivalents of pyridin-3-ylboronic acid to yield compound **20** (Table 1, entry 5).

Interestingly enough inhibitor compounds containing a 2-fluoropyridin-3-yl moiety in position 1 such as **16** showed a through-space coupling of fluorine with the C-9 proton permitted through a short distance. This coupling possesses the same coupling constant as the H-H coupling between proton 7 and proton 9 ($^{7}J_{H,F}$ = 1.8 Hz, $^{4}J_{H,H}$ = 1.8 Hz) resulting in a triplet signal for the C-9 proton in ^{1}H-NMR. To our knowledge only a few through-space couplings of fluorine and protons have previously been reported [30, 31].

After characterization of the possible inhibitors by one- and two-dimensional NMR spectroscopy and HRMS the inhibitory potency of the compounds towards recombinant PDEs, expressed in a baculovirus-SF21 cell system, was estimated by measuring the degradation of [^{3}H]-cAMP. Values for IC_{50} (concentration in nM that inhibits 50%) were determined using the 2-parameter Hill model. Both types of compounds, bromo derivatives as well as their respective dipyridinyl-substituted analogs, are potent inhibitors (IC_{50} < 5 nM, Table 3).

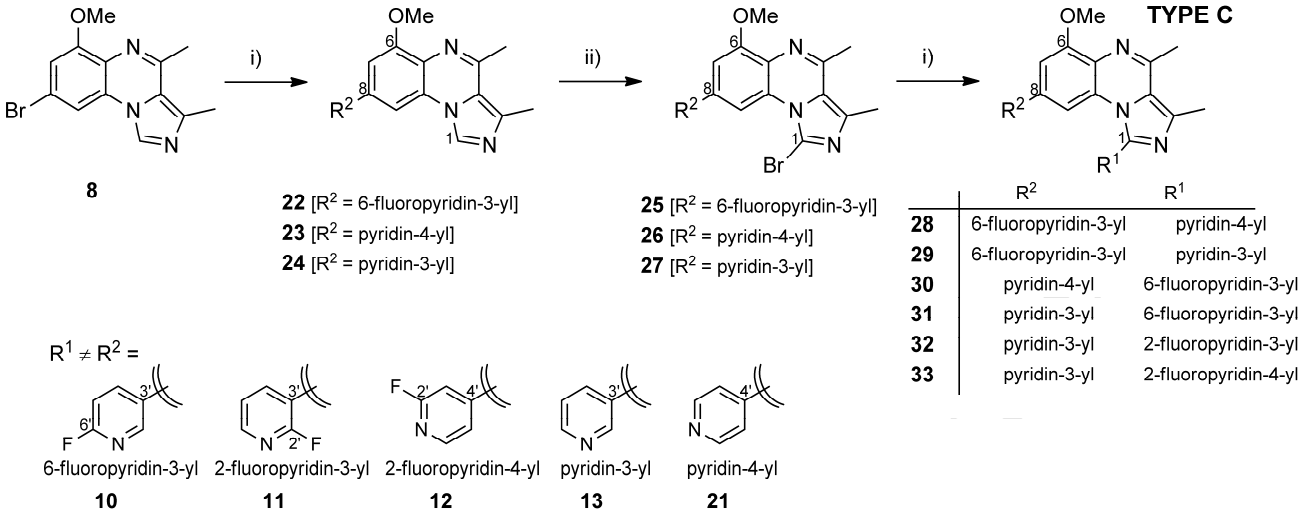
1,8-Dipyridinylimidazo[1,5-a]quinoxalines

Encouraged by the facile formation of the 1,8-dipyridinylimidazo[1,5-*a*]quinoxaline derivatives (Table 1, inhibitor type B) along with good preliminary binding data for PDE10A, a second synthetic route was conceived. In order to get access to tricyclic scaffolds bearing different pyridine moieties, an approach with derivatization in position 8 prior to position 1 was elaborated (Scheme 3). In that way different fluorine and non-fluorine containing pyridines could be introduced into the molecule as R^1 or R^2.

An additional water-mediated hydrogen bond between the pyridine residue of the inhibitor and the residues Thr623 and Leu625 of the binding pocket has been described for inhibitors with a pyridin-4-yl residue as R^1 [18]. Fluorination of this pyridine system may change the binding strength by the reduction of the hydrogen bond acceptor capacity of the pyridine nitrogen [32]. To maintain the strength of that interaction, it could be advantageous to introduce the fluoropyridinyl residue as R^2 while retaining the unsubstituted pyridine-4-yl residue as R^1.

Mixed 1,8-dipyridinyl-substituted imidazo[1,5-*a*]quinoxalines containing two different pyridines were synthesized according to Scheme 3. First a Suzuki coupling was used to exchange the bromine in **8** by a pyridine (Table 2, column 2). Subsequent bromination with NBS delivered 1-bromo compounds **25**, **26** and **27** in yields of 61%, 94% and 82%, respectively. In a second Suzuki step a number of five different

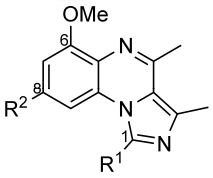
pyridinylboronic acids were coupled to form type C inhibitors (Table 2, column 3). This reaction sequence led to isomeric products with fluorine at one pyridinyl residue. No side product formation was detected.



Scheme 3: Approach to isomeric mono-fluorinated 1,8-dipyridinylimidazo[1,5-*a*]quinoxalines. Reagents and conditions: i) $R^2B(OH)_2$ (**10**, **13**, **21**), K_2CO_3, $Pd(PPh_3)_4$, dioxane/water (4/1), reflux, 3-8 h;ii) NBS, MeCN, rt, 2-6 h, iii) $R^2B(OH)_2$ (**10**-**13**, **21**), K_2CO_3, $Pd(PPh_3)_4$, dioxane/water (4/1), reflux, 3-120 h.

Yields employing different boronic acids at both possible positions of the molecule are summarized in Table 2. Couplings at the imidazole system (position 1/ R^1) afforded slightly higher (Table 2, row 1 and 2) yields compared to the benzene system (position 8/ R^2). Again, in the coupling of 2-fluoropyridin-3-ylboronic acid (entry 4) the yield was low, even after a reaction time of 5 days.

Table 2: Yields of Suzuki couplings with different o-fluoropyridinylboronic acids at both positions (1 and 8) of the molecule



Boronic acid No	R_2 Product No (yield%)	R_1 Product No (yield%)
10 6-fluoropyridin-3-yl	**22** (60)[a)]	**30/31** (82)[a)]/ (25)[c)]
21 pyridin-4-yl	**23** (66)[a),d)]	**28** (72)[b)]
13 pyridin-3-yl	**24** (69)[a),d)]	**29** (41)[c)]
11 2-fluoropyridin-3-yl	-	**32** (25)[c)]
12 2-fluoropyridin-4-yl	-	**33** (58)[c)]

a) Yield after flash chromatography;

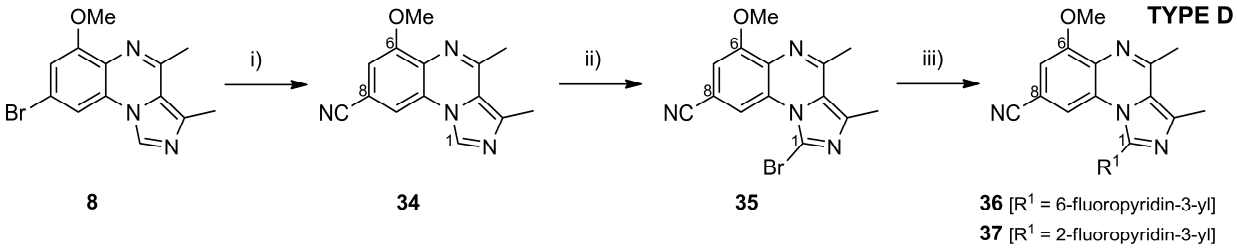
b) Yield after second flash chromatography

c) Yield after flash chromatography and precipitation from $CHCl_3$ by the addition of petroleum ether.

d) Average yield n=2 reactions.

8-Cyano-1-pyridinylimidazo[1,5-a]quinoxalines

After having substituted the bromine atoms on position 8 and position 1 by pyridines both in a simultaneous and sequential manner, we extended the sequential derivatization to other kinds of cross-coupling reactions (Scheme 4). The cyano group was selected as C-8 substituent, since it can be readily converted into other functional groups. In addition cyano may act as electron withdrawing group with pronounced hydrogen bond acceptor properties compared to the bromo substituent. To avoid stoichiometric amounts of CuCN, such as applied in the Rosenmund-von Braun reaction, the palladium-mediated procedure described by Anderson and co-workers was used for the nitrile-for-halide exchange [33]. Substoichiometric amounts of $Pd(PPh_3)_4$, CuI and stoichiometric amounts of NaCN were used in this procedure. Compound **34** could be isolated in a yield of 78%.



Scheme 4: Approach to nitrile substituted inhibitors. Reagents and conditions: i) NaCN (2 eq), $Pd(PPh_3)_4$ (10 mol%), CuI (20 mol%), MeCN, reflux, 3 h, 78%, ii) NBS, MeCN rt, 6 h, 75%; iii) $Pd(PPh)_4$, K_2CO_3, $R^1(BOH)_2$, dioxane/water (4/1), reflux, 3-72 h**.**

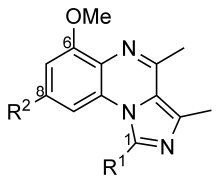
Bromination of compound **34** lead to **35** which is poorly soluble in various solvents. Due to the poor solubilty a standard characerization by ^{13}C NMR was omitted. In the last step two fluoropyridinylboronic acids were coupled to **35** by Suzuki reaction to obtain compounds **36** and **37** respectively in 57% and 37% yield.

2.2. *Inhibitory potency of PDE10A*

The inhibitory potencies of 17 tricyclic mono- or dipyridinyl compounds for PDE10A were investigated and summarized as shown in Table 3. All new inhibitors exhibited high inhibitory potencies (IC_{50} < 26 nM). Most of these derivatives possess also showed activity towards PDE2A. Therefore these IC_{50} values are additionally provided. Concurrent inhibition of PDE2A was also reported for the lead compound **IV** [18]. Crystal structure of PDE10A in complex with **IV** revealed a binding through the invariant Gln716 residue (see [18]) which is present throughout the binding pockets of all PDE families. However, the majority of residues in the active side of PDE10A and PDE2A are identical [34] and hence explaining the lack of selectivity. In contrast, binding in the selectivity pocket, which is not accessible in other PDEs, leads to highly selective inhibitors.

Nevertheless, all derivatives are at least 38-fold more selective towards PDE10A than to PDE2A. Compared to papaverine [35] and PQ-10 [19] they possess both a higher inhibitory potency and improved selectivity.

Table 3: IC_{50} values [nM] of compounds towards PDE10A and PDE2A



No	R^1	R^2	IC_{50} [nM] PDE2A	IC_{50} [nM] PDE10A	Selectivity factor IC_{50} (PDE10A) / IC_{50} (PDE2A)
14	6-fluoropyridin-3-yl	Br	> 1000	2.95	> 339
15	6-fluoropyridin-3-yl	6-fluoropyridin-3-yl	395	3.3	120
16	2-fluoropyridin-3-yl	Br	23.9	0.12	199
17	2-fluoropyridin-3-yl	2-fluoropyridin-3-yl	2.06	0.048	43
18	2-fluoropyridin-4-yl	Br	> 1000	3.18	> 312
19	2-fluoropyridin-4-yl	2-fluoropyridin-4-yl	481	1.57	306
20	pyridin-3-yl	pyridin-3-yl	10.9	0.11	99
22	H	6-fluoropyridin-3-yl	> 1000	26.3	> 38
25	Br	6-fluoropyridin-3-yl	> 1000	10.3	> 97
28	pyridin-4-yl	6-fluoropyridin-3-yl	65.7	0.41	160
29	pyridin-3-yl	6-fluoropyridin-3-yl	29.2	0.33	88
30	6-fluoropyridin-3-yl	pyridin-4-yl	162	0.99	164
31	6-fluoropyridin-3-yl	pyridin-3-yl	78.6	0.87	90
32	2-fluoropyridin-3-yl	pyridin-3-yl	3.49	0.037	94
33	2-fluoropyridin-4-yl	pyridin-3-yl	46.8	0.46	102
36	6-fluoropyridin-3-yl	CN	> 1000	20.4	> 49
37	2-fluoropyridin-3-yl	CN	98.6	1.69	58
IV	3-methylpyridin-4-yl	F	108	0.7 [18]	154
I	Papaverine			56.9 [35]	
II	PQ-10			16.0 [19]	
IIIa	MP-10			1.34 [35]	

Malamas and co-worker demonstrated that the methoxy group in position 6 is essential for good inhibitory potency [18], thus no structural modifications were carried out at this position. To maintain the contacts of the inhibitor and the Glycin residue, mediated by the methoxy group, only substituents at position 8 and 1 were altered.

Different substituents at position 8 have been employed. Comparison of bromo analogs (type A) with fluoropyridine analogs (type B) revealed a 2-fold increase of potency (**16** vs **17** and **18** vs **19**). For **14** and **15** no change in the potency of inhibiting PDE10A was observed. Pyridine analogs (type C) revealed a 3-fold increase of potency (**14** vs **30**/**31** and **16** vs **32**) compared to bromo analogs. In the case of **33** an even higher increase by a factor of 6 was found (**33** vs **18**). Notably, pyridinyl derivatives exhibit IC_{50} values in the subnanomolar range, comparable to the potency of lead compound **IV** [18] or MP-10 [35]. Replacement of the bulky bromine by the small and polar nitrile group (type D) resulted in a 15-20-fold loss of inhibitory potency for PDE10A. These observations are in accordance with the findings of Malamas et al. [18] that bulky substituents like morpholine and benzyl in position 8 lead to a very good inhibitory potency. An additional hydrophobic interaction of the bulky substituents and hydrophobic residues of the binding pocket might explain these observations.

We then turned our attention to position 1. Replacing the hydrogen of intermediate **22** by bromine (**25**) led to a 2-fold increase in potency. Further substitution of bromine by pyridinyl enhanced inhibitory activity at least 25-fold (**25** vs **28**/**29**). Substitution by 6-fluoropyridin-3-yl residue led to a 3-fold increase (**25** vs **15**) in inhibitory potency, whereas substitution of bromine in position 8 by 6-fluoropyridin-3-yl revealed no change (**14** vs **15**). Exchange of bromine in position 8 by pyridinyl increased potency slightly 3-fold (**14** vs **30**/**31**). This finding emphasizes that substitution effects at position 8 have minor impacts on inhibitory potency than at position 1, where a pyridinyl substituent is crucial for good potencies.

Next we explored the position of the fluorine. Fluorination of compound **20** at the pyridine (R^1) in the 2' position (**32**) increased the potency 3-fold (**32** vs **20**), whereas fluorination of the 6' position resulted in a 8-10-fold loss of potency (**31** vs **20**, **15** vs **29**). Interestingly fluorination of pyridine (R^2) in the 6' position (**29**) decreased the inhibitory potency towards PDE10A only 3-fold (**29** vs **20)**. Fluorination of both pyridinyl residues of **20** at the positions 6' and 6'' decreased the inhibitory potency 30-fold (**15** vs **20**). Contrary to this fluorination of the 2' and 2'' position increased the inhibitory activity 2-fold (**17** vs **20**). The reduction of inhibitory potency, when 6-fluoropyridin-3-yl residues were employed at position 1, might be caused by a steric conflict between the *para*-fluoro substituent and the residues at the wall of the binding pocket, as it has been assumed for *para*-methyl substituted derivatives [18].

Generally, introduction of 2-fluoropyridin-3-yl residues (**16**, **32**, **37**) resulted in inhibitors with 12-20-fold higher inhibitory activity than corresponding 6-fluoropyridin-3-yl analogs (**14**, **31**, **36**). This increase was found for bromo, pyridine and nitrile analogs. The *ortho*-substituent of the 2-fluoropyridin-3-yl residue might lead to an orthogonal alignment of pyridinyl and imidazo[1,5-*a*]quinoxaline systems with consequent energetic gains for binding caused by the reduction of rotational freedom [36].

When 2-fluoropyridin-4-yl was introduced as R^1, in the case of 8-pyridine analogs the inhibitory activity was better than for the 6-fluoropyridin-3-yl residue (**33** vs **31**), whereas for 8-bromo analogs almost the same inhibitory potency was observed (**18** vs **14**). Use of pyridin-4-yl residues instead of pyridin-3-yl residues (**28** vs **29**, **30** vs **31**) did not change the inhibitory potency, but improved the selectivity (PDE10A/PDE2A) by a factor of 2.

Overall bromine containing compounds represent the most selective inhibitors with selectivity factors over 200. Among the others, only compound **19** (type B) showed a high selectivity factor of 306. In the class of dipyridinyl compounds (type C) pyridin-4-yl containing inhibitors showed the best selectivity. Nevertheless, all other 1,8-dipyridinylimidazo[1,5-*a*]quinoxalines were 43-fold more selective towards PDE10A rather than PDE2A.

Selectivity profiles of some of our new derivatives towards nine other PDE isoenzymes were screened and are presented in Table 4 as IC_{50} values. Compared to the inhibitory potency towards PDE2A, inhibitory potencies towards other PDEs were negligible. Only compound **30** possessed inhibitory potency towards PDE5A comparable to PDE2A. Out of the series, compound **14** in particular showed a high selectivity for inhibiting PDE10A.

Table 4: IC_{50} values [nM] of selected compounds towards different human phosphodiesterases

No	PDE isoenzyme										
	1B	2A	3A	4A	5A	6[a)]	7B	8A	9A	10A	11A
14	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	2.91	>1000
15	>1000	395	>1000	>1000	>1000	>1000	>1000	>1000	>1000	3.3	>1000
16	>1000	23.9	>1000	>1000	606	432	>1000	>1000	>1000	0.12	494
20	>1000	10.9	>1000	~1000	232	425	>1000	>1000	>1000	0.11	286
28	>1000	65.7	>1000	841	201	>1000	>1000	>1000	>1000	0.41	>1000
29	>1000	29.2	>1000	>1000	279	631	>1000	>1000	>1000	0.33	286
30	>1000	162	>1000	>1000	195	585	<1000	>1000	>1000	0.99	413
31	>1000	78.6	>1000	>1000	228	559	>1000	>1000	>1000	0.87	395
32	>1000	3.49	>1000	<1000	91.6	177	>1000	>1000	>1000	0.037	457

a) Bovine isoform

3. Conclusion

Several novel fluorinated PDE inhibitors have been synthesized in nine to ten steps using a diversity-oriented synthetic route. The inhibition potency towards different PDEs was measured. All compounds are very potent inhibitors of PDE10A and some possess an inhibitory potency comparable to MP-10 (Fig. 1) or lead compound **IV**. Even better potencies of PDE10A inhibition, down to the picomolar range, were achieved by using 2-fluoropyridin-3-yl residues. Some inhibitors, in particular those with pyridinyl substituents at position 1 and 8, show a lack of selectivity towards PDE2A. Bromo analogs were slightly less potent, but exhibited a high selectivity for PDE10A. Nitrile derivatives were less potent and selective. However, there was no selectivity problem towards other PDEs as demonstrated for representative compounds.

The introduction of 2-fluoropyridinyl residues enables ^{18}F-labeling and the use of these inhibitors as potential PET imaging agents for PDE10A, which is currently investigated in our laboratory.

4. Experimental Section

4.1. Chemistry

General: Chemicals were purchased in high quality from abcr, Aldrich, acros, Apollo scientific, fluorochem, Fluka and Merck and used without further purification. Air and moisture sensitive reactions were carried

out under a steam of argon. Solvents were purified according to standard procedures, if required. Pre-coated TLC-sheets POLYGRAM® SIL G/UV_{254} obtained from Macherey-Nagel were used for thin layer chromatography. Different zones were detected by UV irradiation (λ = 254 nm). Flash chromatography was performed on silica gel 60 (0.04-0.063 mm) from Merck. NMR spectra were recorded on Varian Mercury 300BB (300 MHz for ^{1}H, 75 MHz for ^{13}C, 282 MHz for ^{19}F) or Varian Mercury 400BB (400 MHz for ^{1}H, 101 MHz for ^{13}C). Chemical shifts δ are reported in ppm and referred to the solvent ($CHCl_3$: 7.26, $CDCl_3$: 77.16) as internal standard. Multiplicities of signals are indicated as follows: singlet (s), doublet (d), triplet (t), broad signal (br). Mass spectra were recorded on a ESQUIRE 3000 Plus (ESI, low resolution) and a 7 Tesla APEX II (ESI, high resolution) from Bruker Daltonics.

4-Bromo-2,6-difluoroaniline (2)

2,6-Difluoroaniline (20.0 g, 0.15 mol, 1.0 eq) was dissolved in of glacial acetic acid (70 mL). The mixture was cooled with an ice bath and bromine (27.6 g, 0.16 mol, 1.1 eq) dissolved in acetic acid (10 mL) was added dropwise. During the addition the product precipitated. After stirring for 2 h at room temperature Na_2SO_3-solution (1.3 g Na_2SO_3 in 400 mL water) was added. The product was filtered off, washed with water and dried to afford a colorless solid (27.7 g, 84%). **TLC** [Silica, DCM]: R_f = 0.71. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = = 7.08 – 6.89 (m, 2H), 3.73 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 151.9 (dd, *J* = 244.1, 8.6 Hz), 123.6 (t, *J* = 16.2 Hz), 115.1-114.6 (m), 107.2 (t, *J* = 11.7 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -131.1 (d, *J* = 7.1 Hz). **LRMS (ESI+):** *m/z* = 207.9 (calcd. 208.0 for $C_6H_5{}^{79}BrF_2N$ $[M+H]^+$).

4-Bromo-2,6-difluoronitrobenzene (3)

Sodiumperborate tetrahydrate (18.5 g, 0.12 mol, 5.0 eq) was suspended in glacial acetic acid (125 mL) and heated to 65 °C. 4-Bromo-2,6-difluoroanilline **2** (5.0 g, 24.0 mmol, 1.0 eq) dissolved in glacial acetic acid (50 mL) was added slowly through an funnel over 4 h. After the addition the reaction mixture was heated for 3 h additional hours before a second portion of $NaBO_3 \cdot 4\ H_2O$ (6.0 g, 30.0 mmol) was added. Then the mixture was stirred for 14 h and a third portion of oxidating agent (9.0 g, 45.0 mmol) was added. 9 h after the third addition full consumption of the starting material was indicated by TLC. After cooling the mixture to room temperature, the formed solid was removed by filtration. The filtrate was poured into ice-cold water (300 mL). The precipitated solid was filtered off and dried to give the product as yellow solid (3.40 g, 60%). **TLC** [Silica, hexane/$CHCl_3$ (5:1)]: R_f = 0.31. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.36 – 7.28 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 154.7 (dd, *J* = 265.7, 2.8 Hz), 126.4 (t, *J* = 11.0 Hz), 117.2 (dd, *J* = 22.7, 3.9 Hz), [*C*-NO_2 is not detected]. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -117.0 (d, *J* = 7.1 Hz). **LRMS (EI):** *m/z* = 237 (calcd. 237 for $C_6H_2{}^{79}BrF_2NO_2$ $[M]^+$).

4-Bromo-2-fluoro-6-(4-methyl-1H-imidazol-1-yl)nitrobenzene (4)

To a solution of 4-bromo-2,6-difluoronitrobenzene (8.0 g, 33.6 mmol, 1.3 eq) in of DMF (20 mL) potassium carbonate (7.4 g, 53.8 mmol, 2.0 eq) was added. The suspension was cooled to 4 °C and a solution of 4-methylimidazole (2.4 g, 26.9 mmol, 1.0 eq) in DMF (45 mL) was added over 5 h. After the addition the mixture was stirred an additional hour at 4°C and 1 7 h at room temperature. Half of the DMF was removed and the residue was poured into water (150 mL). The precipitate was filtered off. Ethyl acetate (25 mL)

was used to dissolve the solid and the organic layer was extracted with 1 N HCl (4 × 25 mL). During neutralization with Na_2CO_3- solution (pH 8) a precipitate was formed. It was filtered off and dried. Crystallization from ethanol (3 times) gave a pale yellow solid (3.40 g, 42%). **TLC** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.56. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 1.6 Hz, 1H), 7.53 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.42 (t, *J* = 1.8 Hz, 1H), 6.89 – 6.60 (m, 1H), 2.25 (d, *J* = 1.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 154.1 (d, *J* = 264.3 Hz), 140.8, 136.1, 131.8 (d, *J* = 1.4 Hz), 125.8, 125.7 (d, *J* = 3.7 Hz), 120.4 (d, *J* = 22.1 Hz), 115.9, 13.6, [*C*-NO_2 is not detected]. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = - 118.61 (dd, *J* = 8.3, 1.5 Hz). **LRMS (ESI+):** *m/z* = 322.0 (calcd. 322.0 for $C_{10}H_7{}^{79}BrF_2N_3NaO_2$ $[M+Na]^+$).

4-Bromo-2-methoxy-6-(4-methyl-1H-imidazol-1-yl)nitrobenzene (5)

Compound **4** (3.3 g, 11.0 mmol, 1.0 eq) was dissolved in methanol (20 mL). A 30 wt% solution of NaOMe in methanol (4 mL, 22.0 mmol, 2.0 eq) was added and the mixture was stirred at room temperature for 1.5 h. After the addition of 100 mL of water the mixture was extracted with ethyl acetate (3 × 25 mL). The organic phase was dried over $MgSO_4$. Evaporation of the solvent yielded **5** (3.5 g, 99%) as beige solid. **TLC** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.56. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 1.1 Hz, 1H), 7.22 (d, *J* = 1.7 Hz, 1H), 7.13 (d, *J* = 1.7 Hz, 1H), 6.76 (br s, 1H), 3.94 (s, 3H), 2.22 (d, *J* = 0.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.3, 140.3, 136.2, 131.1, 125.2, 121.2, 116.0, 115.8, 57.6, 13.6, [*C*-NO_2 is not detected]. **LRMS (ESI+):** *m/z* = 334.0 (calcd. 334.0 for $C_{11}H_{10}{}^{79}BrN_3NaO_3$ $[M+Na]^+$).

4-Bromo-2-methoxy-6-(4-methyl-1H-imidazol-1-yl)aniline (6)

4-Bromo-2-methoxy-6-(4-methyl-1H-imidazol-1-yl)nitrobenzene (**5**) (3.5 g, 11.0 mmol, 1.0 eq) was dissolved in a mixture of ethanol and acetic acid (80 mL, 1:1) under argon. Iron powder (3.1 g, 55.0 mmol 5.0 eq) was added to the solution and the reaction mixture was refluxed for 2 h. After filtration through a plug of celite the mixture was neutralized using a solution of Na_2CO_3 and extracted with ethyl acetate (3 × 25 mL). Combined organic layers were dried over $MgSO_4$. Evaporating the solvent under reduced pressure yielded the product as beige solid (2.9 g, 92%). **TLC** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.34. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 1.3 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.83 – 6.77 (m, 1H), 3.89 (s, 3H), 3.87 (s, 2H), 2.28 (d, *J* = 0.9 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 148.3, 139.3, 136.7, 131.7, 123.8, 121.6, 116.2, 113.5, 108.4, 56.4, 13.8. **LRMS (ESI+):** *m/z* = 282.0 (calcd. 282.0 for $C_{11}H_{13}{}^{79}BrN_3O$ $[M+H]^+$).

4-Bromo-2-methoxy-6-(4-methyl-1H-imidazol-1-yl)acetanilid (7)

Under a flush of argon 4-bromo-2-methoxy-6-(4-methyl-1H-imidazol-1-yl)aniline (**6**) (2.9 g, 10.2 mmol, 1.0 eq) was dissolved in acetic acid (28 mL). To this solution acetic acid anhydride (14 mL) and sulfuric acid (3 drops) were added. After stirring the solution at room temperature for 8 h it was neutralized (pH 8) using a solution of Na_2CO_3. The aqueous solution was extracted with DCM (3 × 20 mL) and combined organic layers were dried over $MgSO_4$. Purification by flash chromatography on silica using 5% of methanol in DCM as eluent afforded a colorless solid (2.5 g, 76%). **TLC** [Silica, $CHCl_3$/MeOH/30%

aqueous NH_3 (10:1:0.1)]: R_f = 0.38. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.84 (br s, 1H), 7.35 (s, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 6.75 (s, 1H), 3.86 (s, 3H), 2.16 (s, 3H), 2.04 (br s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9, 156.5, 138.4, 136.5, 136.1, 121.3, 121.0, 120.4, 116.2, 114.8, 56.7, 23.0, 13.5. **LRMS (ESI+):** *m/z* = 324.0 (calcd. 324.0 for $C_{13}H_{15}{}^{79}BrN_3O_2$ $[M+H]^+$).

8-Bromo-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (8)

Compound **7** (2.5 g, 7.6 mmol, 1.0 eq) was filled in a 50 mL thick-walled glass vessel and suspended in $POCl_3$ (20 mL). The vessel was closed and the reaction mixture was heated to 120 ℃ for 90 h. Half of the volume of the phosphoroxychloride was distilled off and the residue was poured in a solution of ice water/methanol (1:1). During the neutralization with KOH (50% solution) a solid precipitated. The solid was filtered of and dried. Flash chromatography of the solid using 3% of methanol in DCM as solvent yielded (0.8 g, 35%) of a colorless solid. **TLC** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.51. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.41 (s, 1H), 7.54 (s, 1H), 7.04 (s, 1H), 4.03 (s, 3H), 2.83 (s, 3H), 2.75 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.3, 153.5, 137.4, 127.6, 126.5, 125.6, 121.2, 121.1, 111.7, 109.4, 56.9, 24.5, 16.1. **LRMS (ESI+):** *m/z* = 328.0 (calcd. 328.0 for $C_{13}H_{12}{}^{79}BrN_3NaO$ $[M+Na]^+$).

1,8-Dibromo-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (9)

Compound **8** (360 mg, 1.14 mmol, 1.0 eq) was suspended in acetonitrile (8 mL). The suspension was protected against light and NBS (304 mg, 1.71 mmol, 1.5 eq) was added. After having stirred the reaction at room temperature for 4 h the solid was filtered off. The solid was taken up into $CHCl_3$ and the organic layer was washed with water. Organic layers were dried over $MgSO_4$. During the evaporation of solvent under reduced pressure a solid precipitated from solution. It was filtered off and dried to give the product as colorless solid (364 mg, 82%). **TLC** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.75. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.88 (d, *J* = 1.8 Hz, 1H), 7.13 (d, *J* = 1.8 Hz, 1H), 4.04 (s, 3H), 2.81 (s, 3H), 2.74 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.8, 152.8, 137.6, 127.6, 126.6, 124.6, 120.2, 112.3, 111.8, 110.6, 56.9, 24.6, 16.4. **LRMS (ESI+):** *m/z* = 385.9 (calcd. 385.9 for $C_{13}H_{12}{}^{79}Br^{81}Br\,N_3O$ $[M+H]^+$).

General procedure A for the Suzuki couplings of compound 9:

Compound **9**, fluoropyridinylboronic acid (1.3 or 1.6 eq) and K_2CO_3 (2 eq) were suspended in a mixture of 1,4-dioxane and water (4/1). The suspension was degassed and $Pd(PPh_3)_4$ (10 mol%) was added. After refluxing the mixture for 6 h (all components are soluble in heat) the solvent was removed and the residue portioned between $CHCl_3$ and water. The aqueous layer was twice extracted with $CHCl_3$ and combined organic layers were dried over $MgSO_4$. Solvents were removed under reduced pressure. Silica chromatography using $CHCl_3$/EtOAc as eluent afforded type A inhibitors (8-bromo derivatives). Type B inhibitors (1,8-dipyridinyl derivatives) were then eluted with $CHCl_3$/MeOH. Following products were isolated:

8-Bromo-1-(6-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (14) and **1,8-bis(6-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (15)**

According to the procedure A compound **9** (200 mg, 0.52 mmol, 1.0 eq), 6-fluoropyridin-3-ylboronic acid (109 mg, 0.78 mmol, 1.5 eq), K_2CO_3 (144 mg, 1.04 mmol, 2.0 eq), $Pd(PPh_3)_4$ (60 mg, 10 mol%) were

reacted in dioxane/water (10 mL). Silica chromatography using $CHCl_3$/EtOAc (5:1) as eluent afforded **14** (120 mg, 58%) as colorless solid. **15** was then eluted with $CHCl_3$/MeOH (8:1) to give a beige solid (48 mg, 22%).

8-Bromo-1-(6-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (14): TLC: [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.53. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 2.3 Hz, 1H), 8.07 (ddd, *J* = 8.4, 7.6, 2.5 Hz, 1H), 7.15 (dd, *J* = 8.4, 2.9 Hz, 1H), 7.07 (d, *J* = 1.8 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 4.03 (s, 3H), 2.88 (s, 3H), 2.80 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.3 (d, *J* = 244.0 Hz), 156.3, 153.7, 148.9 (d, *J* = 15.5 Hz), 142.3 (d, *J* = 8.3 Hz), 137.8, 137.2, 127.5, 126.8, 126.5 (d, *J* = 4.8 Hz), 123.3, 120.3, 109.9 (d, *J* = 37.8 Hz), 56.9, 24.7, 16.3. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -64.9 (dd, *J* = 7.1, *J* = 2.3 Hz). **HRMS (ESI+):** *m/z* = 401.0410 (calcd. 401.0408 for $C_{18}H_{15}{}^{79}BrFN_4O$ $[M+H]^+$).

1,8-Bis(6-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (15): TLC: [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.40. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 1.9 Hz, 1H), 8.18 (d, *J* = 1.9 Hz, 1H), 8.13 (ddd, *J* = 8.0, 8.0, 2.4 Hz, 1H), 7.67 (ddd, *J* = 8.1, 8.1, 2.6 Hz, 1H), 7.14 (dd, *J* = 8.4, 2.9 Hz, 1H), 7.05 (br s, 1H), 7.04 (br s, 1H), 6.96 (dd, *J* = 8.5, 2.9 Hz, 1H), 4.11 (s, 3H), 2.93 (s, 3H), 2.82 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.3 (d, *J* = 245.4 Hz), 163.6 (d, *J* = 241.4 Hz), 156.5, 154.0, 149.0 (d, *J* = 15.4 Hz), 145.9 (d, *J* = 15.0 Hz), 142.6 (d, *J* = 8.3 Hz), 139.6 (d, *J* = 8.0 Hz), 137.7, 137.4, 135.6, 134.0 (d, *J* = 4.7 Hz), 127.6, 127.4, 127.1 (d, *J* = 4.9 Hz), 123.5, 110.1 (d, *J* = 37.6 Hz), 110.0 (d, *J* = 37.6 Hz), 107.0, 106.8, 56.9, 24.8, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -64.8 (dd, *J* = 7.2, 2.6 Hz), -69.2 (dd, *J* = 6.9, 2.1 Hz). **HRMS (ESI+):** *m/z* = 418.1476 (calcd. 418.1474 for $C_{23}H_{18}F_2N_5O$ $[M+H]^+$).

8-Bromo-1-(2-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (16) and **1,8-bis(2-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (17)**

According to the procedure A compound **9** (192 mg, 0.50 mmol, 1.0 eq), 2-fluoropyridin-3-ylboronic acid (92 mg, 0.65 mmol, 1.3 eq), K_2CO_3 (128 mg, 1.00 mmol, 2.0 eq), $Pd(PPh_3)_4$ (58 mg, 10 mol%) were reacted in dioxane/water (8 mL). Flash chromatography on silica using $CHCl_3$/EtOAc (5:1) as eluent afforded **16** (65 mg, 32%) as colorless solid. **17** was then eluted with $CHCl_3$/MeOH (10:1) to give a beige solid (18 mg, 9%). 38% of starting material **9** was reisolated.

8-Bromo-1-(2-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (16): TLC: [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.51. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.47 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 8.14 (ddd, *J* = 9.3, 7.4, 2.0 Hz, 1H), 7.45 (ddd, *J* = 7.3, 4.9, 1.8 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 6.93 (dd, *J* = 1.8 Hz, $^7J_{H,F}$ = 1.8 Hz, 1H), 4.02 (s, 3H), 2.88 (s, 3H), 2.80 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.7 (d, *J* = 241.7 Hz), 156.0, 153.5, 149.9 (d, *J* = 14.5 Hz), 142.7 (d, *J* = 2.9 Hz), 137.1, 134.3 (d, *J* = 4.8 Hz), 127.6, 126.6, 123.2, 122.0 (d, *J* = 4.5 Hz), 120.4, 115.8 (d, *J* = 30.6 Hz), 111.9, 110.6, 56.9, 24.7, 16.3. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -65.4 (d, *J* = 9.0 Hz). **HRMS (ESI+):** *m/z* = 401.0411 (calcd. 401.0408 for $C_{18}H_{15}{}^{79}BrFN_4O$ $[M+H]^+$).

1,8-Bis(2-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (17): TLC: [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.36. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 4.8 Hz,

1H), 8.25 – 8.05 (m, 2H), 7.71 (ddd, *J* = 9.6, 7.6, 1.8 Hz, 1H), 7.52 – 7.37 (m, 1H), 7.26 – 7.19 (m, 1H), 7.14 (br s, 1H), 7.09 (br s, 1H), 4.10 (s, 3H), 2.96 (s, 3H), 2.84 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 160.8 (d, *J* = 241.3 Hz), 160.1 (d, *J* = 240.8 Hz), 155.7, 154.0, 149.6 (d, *J* = 14.5 Hz), 147.1 (d, *J* = 15.0 Hz), 142.8 (d, *J* = 3.1 Hz), 140.5 (d, *J* = 4.0 Hz), 137.3, 132.8, 132.7, 127.6, 127.2, 123.4, 122.9 (d, *J* = 27.5 Hz), 122.2 (d, *J* = 4.4 Hz), 122.2 (d, *J* = 4.4 Hz), 116.2 (d, *J* = 30.5 Hz), 108.5 (d, *J* = 3.5 Hz), 108.0 (d, *J* = 3.1 Hz), 56.8, 24.8, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -65.2 (d, *J* = 9.0 Hz), -70.7 (d, *J* = 9.6 Hz). **HRMS (ESI+):** *m/z* = 418.1471 (calcd. 418.1474 for $C_{23}H_{18}F_2N_5O$ $[M+H]^+$).

8-Bromo-1-(2-fluoropyridin-4-yl)-6-methoxy-3,4-dimethylimidazo[1,50-*a*]quinoxaline (18) and **1,8-bis(2-fluoropyridin-4-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (19)**

According to the procedure A compound **9** (150 mg, 0.39 mmol, 1.0 eq), 2-fluoropyridin-4-ylboronic acid (71 mg, 0.51 mmol, 1.3 eq), K_2CO_3 (108 mg, 0.78 mmol, 2.0 eq), $Pd(PPh_3)_4$ (45 mg, 10 mol%) were reacted in dioxane/water (8 mL). Flash chromatography on silica using DCM/ethyl acetate (5/2) as eluent to afforded **18** (58 mg, 37 %) as colorless solid and **19** (26 mg, 16%) as yellow solid. 25% of starting material (**9**) was reisolated.

8-Bromo-1-(2-fluoropyridin-4-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (18): TLC: [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.51. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 4.7 Hz, 1H), 7.50-7.40 (m, 1H), 7.30 (s, 1H), 7.22 (s, 1H), 7.07 (s, 1H), 4.05 (s, 3H), 2.90 (s, 3H), 2.81 (s, 3H). Due to the low solubility of the compound no ^{13}C-NMR spectra could be obtained. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -65.8 (s). **HRMS (ESI+):** *m/z* = 401.0406 (calcd. 401.0408 for $C_{18}H_{15}{}^{79}BrFN_4O$ $[M+H]^+$).

1,8-Bis(2-fluoropyridin-4-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (19): TLC: [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.41. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 5.1 Hz, 1H), 8.23 (d, *J* = 5.3 Hz, 1H), 7.55 (dt, *J* = 5.1, 1.5 Hz, 1H), 7.36 (s, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.15 (d, *J* = 1.7 Hz, 1H), 7.05 (dt, *J* = 5.2, 1.6 Hz, 1H), 6.90 (s, 1H), 4.14 (s, 3H), 2.96 (s, 3H), 2.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.6 (d, *J* = 239.4 Hz), 164.1 (d, *J* = 241.1 Hz), 156.5, 154.5, 152.6 (d, *J* = 8.1 Hz), 148.7 (d, *J* = 15.1 Hz), 148,6 (d, *J* = 15.1 Hz), 145.2 (d, *J* = 8.4 Hz), 138.1, 138.0, 135.9, 128.7, 126.9, 123.8, 121.6 (d, *J* = 4.4 Hz), 119.2 (d, *J* = 4.1 Hz), 110.3 (d, *J* = 38.9 Hz), 107.6, 107.2 (d, *J* = 38.5 Hz), 106.7, 56.9, 24.8, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -65.5 (s), -67.3 (s). **HRMS (ESI+):** *m/z* = 418.1471 (calcd. 418.1474 for $C_{23}H_{18}F_2N_5O$ $[M+H]^+$).

1,8-Bis(pyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (20)

Compound **9** (140 mg, 0.36 mmol, 1.0 eq) and K_2CO_3 (120 mg, 0.83 mmol, 2.3 eq) were given into a 25 mL Duran container under Argon atmosphere. A 4:1 mixture of dioxane and water (10 mL) was added and degassed for 15 min. Pyridin-3-ylboronic acid (100 mg, 0.83 mmol, 2.3 eq) and $Pd(PPh_3)_4$ (40 mg, 10 mol%) were added to the suspension and heated to 100 °C for about 16 hours. Purification by column chromatography ($CHCl_3$:MeOH:TEA / 19:1:0.1) and crystallization from $CHCl_3$ and PE gave pure product (40 mg, 29%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.23.

^{1}H NMR (400 MHz, d_6-DMSO) δ = 8.58 (s, 1H), 8.47-8.42 (m 1H), 8.34 – 8.14 (m, 2H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.25 (m, 2H), 6.99 (s, 1H), 6.58 (s, 1H), 3.54 (s, 4H), 2.34 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (101 MHz, d_6-DMSO): δ = 155.3, 153.4, 149.7, 148.9, 145.4, 143.9, 138.7, 138.6,

138.1, 137.9, 135.9, 134.0, 128.4, 126.5, 125.6, 125.4, 124.2, 123.3, 107.5, 106.7, 56.5, 23.0, 15.8. **HRMS (ESI+):** *m/z* = 382.1660 (calcd. 382.1662 for $C_{23}H_{20}N_5O$ $[M+H]^+$).

General procedure B for the Suzuki couplings of mono-bromo derivatives 8, 25, 26, 27 and 35:
Brominated compound (1.0 eq), boronic acid (1.0-2.0 eq) and K_2CO_3 (1.0-3.0 eq) were suspended in a mixture of 1,4-dioxane and water (4:1) and the suspension was degassed. Then 5-10mol% $Pd(PPh_3)_4$ was added and the suspension was refluxed until the full conversion of starting material as indicated by TLC. All components dissolved under heating. After cooling to room temperature the solvent was removed, the residue was taken up in chloroform and the organic layer was washed with water. The organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Products were purified by flash chromatography using a mixture of methanol in DCM. Following products were isolated:

8-(6-Fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (22)
According to the procedure B compound **8** (100 mg, 0.33 mmol, 1.0 eq), 6-fluoropyridin-3-ylboronic acid (69 mg, 0.49 mmol, 1.5 eq), K_2CO_3 (135 mg,1.12 mmol, 3.0 eq) and $Pd(PPh_3)_4$ (19 mg, 5 mol%) were reacted in dioxane/water (5 mL). Flash chromatography was performed with DCM/MeOH (19/1) to yield **22** (64 mg, 60%) as colorless solid. **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.51. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.54 (s, 1H), 8.51 (d, *J* = 2.6 Hz, 1H), 8.06 (ddd, *J* = 8.4, 7.6, 2.6 Hz, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.12 – 6.91 (m, 2H), 4.12 (s, 3H), 2.88 (s, 3H), 2.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.6 (d, *J* = 240.9 Hz), 156.3, 153.7, 146.2 (d, *J* = 15.0 Hz), 140.0 (d, *J* = 8.0 Hz), 137.5, 136.7, 134.2 (d, *J* = 4.7 Hz), 127.6, 126.4, 126.3, 121.3, 109.9 (d, *J* = 37.6 Hz), 106.8, 104.8, 56.7, 24.5, 16.2. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -69.3 (d, J = 4.8 Hz). **LRMS (ESI+):** *m/z* = 345.1 (calcd. 345.1 for $C_{18}H_{15}FN_4NaO$ $[M+Na]^+$).

6-Methoxy-3,4-dimethyl-8-(pyridin-4-yl)imidazo[1,5-*a*]quinoxaline (23)
According to the procedure B compound **8** (300 mg, 0.98 mmol, 1.0 eq), pyridin-4-ylboronic acid (180 mg, 1.57 mmol, 2.0 eq), K_2CO_3 (406 mg, 2.94 mmol, 3.0 eq) and $Pd(PPh_3)_4$ (56 mg, 5 mol%) were reacted in dioxane/water (10 mL). Flash chromatography was performed in DCM/MeOH (10/1) to yield a yellow solid (185 mg, 62%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.18**. ^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 5.9 Hz, 2H), 8.56 (s, 1H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.58 (dd, *J* = 4.5, 1.7 Hz, 2H), 7.15 (d, *J* = 1.7 Hz, 1H), 4.12 (s, 3H), 2.88 (s, 3H), 2.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.2, 154.1, 150.6, 147.5, 138.1, 137.6, 127.6, 126.9, 126.3, 121.9, 121.3, 106.6, 104.8, 56.7, 24.5, 16.1. **LRMS (ESI+):** *m/z* = 327.1 (calcd. 327.1 for $C_{18}H_{16}N_4NaO$ $[M+Na]^+$).

6-Methoxy-3,4-dimethyl-8-(pyridin-3-yl)imidazo[1,5-*a*]quinoxaline (24)
According to the procedure B compound **8** (160 mg, 0.52 mmol, 1.0 eq), pyridin-3-ylboronic acid (96 mg, 0.78 mmol, 1.5 eq), K_2CO_3 (216 mg, 1.58 mmol, 3.0 eq) and $Pd(PPh_3)_4$ (56.0 mg, 10 mol%) were reacted in dioxane/water (10 mL). Flash chromatography was performed in DCM/MeOH (19/1) to yield **24** (110 mg, 70%) as a colorless solid. **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.20. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.93 (d, *J* = 2.3 Hz, 1H), 8.66 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.55 (s, 1H), 7.96 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.57 (d, *J* = 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.9, 4.8, 0.7 Hz, 1H), 7.11 (d, *J* = 1.7 Hz,

1H), 4.12 (s, 3H), 2.89 (s, 3H), 2.78 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.2, 153.6, 149.5, 148.5, 137.9, 137.4, 135.9, 134.7, 127.6, 126.4, 126.3, 123.8, 121.3, 106.8, 104.8, 56.7, 24.6, 16.2. **LRMS (ESI+):** *m/z* = 327.1 (calcd. 327.1 for $C_{18}H_{16}N_4NaO$ $[M+Na]^+$).

General procedure for bromination of compounds 22-24

Compound **22**/**23**/**24** (1.0 eq) was suspended in acetonitrile and the flask was protected against light. NBS (1.5 or 2.0 eq) was then added in one portion. The reaction mixture was stirred at room temperature until full conversion of starting material (TLC). Water was added and the aqueous layer was extracted with $CHCl_3$. Combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash chromatography gave following products:

1-Bromo-8-(6-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (25)

According to the general procedure for bromination compound **22** (70 mg, 0.22 mmol, 1.0 eq) and NBS (75 mg, 0.42 mmol, 2.0 eq) were reacted in MeCN (3 mL). DCM/MeOH (30/1) was used as eluent for flash chromatography providing **25** (80 mg, 90%) as a pale yellow solid. **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.65. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.91 (d, *J* = 1.7 Hz, 1H), 8.53 (d, *J* = 2.5 Hz, 1H), 8.07 (ddd, *J* = 8.4, 7.6, 2.6 Hz, 1H), 7.13 (d, *J* = 1.6 Hz, 1H), 7.07 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.12 (s, 3H), 2.86 (s, 3H), 2.75 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 163.6 (d, *J* = 240.8 Hz), 155.9, 153.0, 146.1 (d, *J* = 15.0 Hz), 139.8 (d, *J* = 8.1 Hz), 137.7, 135.3, 134.3 (d, *J* = 4.7 Hz), 127.5, 127.3, 124.7, 111.6, 110.0 (d, *J* = 37.6 Hz), 107.1, 106.1, 56.8, 24.7, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -69.4 (d, *J* = 5.1 Hz). **LRMS (ESI+):** *m/z* = 401.0 (calcd. 401.0 for $C_{18}H_{15}{}^{79}BrFN_4O$ $[M+H]^+$).

1-Bromo-6-methoxy-3,4-dimethyl-8-(pyridin-4-yl)imidazo[1,5-*a*]quinoxaline (26)

According to the general procedure for bromination compound **23** (94 mg, 0.30 mmol, 1.0 eq) and NBS (80 mg, 0.45 mmol, 1.5 eq) were reacted in MeCN (3 mL). DCM/MeOH (10/1) was used as eluent for flash chromatography providing a yellow solid (70 mg, 61%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.31. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 9.03 (d, *J* = 1.7 Hz, 1H), 8.74 (br s, 2H), 7.59 (d, *J* = 5.4 Hz, 2H), 7.23 (d, *J* = 1.7 Hz, 1H), 4.13 (s, 3H), 2.86 (s, 3H), 2.76 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.9, 153.3, 150.7, 147.6, 137.8, 136.7, 128.0, 127.5, 124.7, 121.7, 111.7, 106.9, 106.2, 56.8, 24.7, 16.4. **LRMS (ESI+):** *m/z* = 383.0 (calcd. 383.1 for $C_{18}H_{16}{}^{79}BrN_4O$ $[M+H]^+$).

1-Bromo-6-methoxy-3,4-dimethyl-8-(pyridin-3-yl)imidazo[1,5-*a*]quinoxaline (27)

According to the general procedure for bromination compound **24** (100 mg, 0.33 mmol, 1.0 eq) and NBS (76 mg, 0.43 mmol, 1.3 eq) were reacted in MeCN (6 mL). DCM/MeOH (19/1) was used as eluent for flash chromatography providing of a beige solid (119 mg, 94%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.34. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.99-8.93 (m, 2H), 8.65 (dd, *J* = 4.6, 1.1 Hz, 1H), 7.97 (ddd, *J* = 7.9, 2.2, 1.7 Hz, 1H), 7.43 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.18 (d, *J* = 1.6 Hz, 1H), 4.11 (s, 3H), 2.85 (s, 3H), 2.75 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 155.8, 152.8, 149.8, 148.34, 137.6, 136.5, 136.1, 134.5, 127.5, 127.3, 124.7, 123.9, 111.6, 107.1, 106.2, 56.8, 24.7, 16.4. **LRMS (ESI+):** *m/z* = 405.0 (calcd. 405.0 for $C_{18}H_{15}{}^{79}BrN_4NaO$ $[M+Na]^+$).

8-(6-Fluoropyridin-3-yl)-6-methoxy-3,4-dimethyl-1-(pyridin-4-yl)imidazo[1,5-*a*]quinoxaline (28)

According to the procedure B compound **25** (60 mg, 0.15 mmol, 1.0 eq), pyridin-4-ylboronic acid (28 mg, 0.23 mmol, 1.5 eq), K_2CO_3 (31 mg, 0.23 mmol, 1.5 eq), $Pd(PPh_3)_4$ (17 mg, 10 mol%) were reacted in dioxane/water (5 mL). Flash chromatography was performed in DCM/MeOH (10/1) to yield a colorless solid (49 mg, 82%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.35. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.84 (s, 2H), 8.21 (d, *J* = 2.5 Hz, 1H), 7.68-7.58 (m, 3H), 7.16 (d, *J* = 1.7 Hz, 1H), 7.06 (d, *J* = 1.7 Hz, 1H), 4.12 (s, 3H), 2.94 (s, 3H), 2.83 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 163.6 (d, *J* = 241.2 Hz), 156.4, 154.0, 150.6, 145.9 (d, *J* = 15.1 Hz), 140.4, 139.5 (d, *J* = 8.0 Hz), 139.2, 137.6, 135.5, 133.8 (d, *J* = 4.7 Hz), 127.6, 127.2, 124.0, 123.6, 110.1 (d, *J* = 37.5 Hz), 107.5, 106.7, 56.9, 24.8, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -69.20 (dd, *J* = 6.9, 2.0 Hz). **HRMS (ESI+):** *m/z* = 400.1571 (calcd. 400.1568 for $C_{23}H_{19}FN_5O$ $[M+H]^+$).

8-(6-Fluoropyridin-3-yl)-6-methoxy-3,4-dimethyl-1-(pyridin-3-yl)imidazo[1,5-*a*]quinoxaline (29)

According to the procedure B compound **25** (70 mg, 0.18 mmol, 1.0 eq), pyridin-3-ylboronic acid (26 mg, 0.21 mmol, 1.2 eq), K_2CO_3 (30 mg, 0.21 mmol, 1.2 eq) and $Pd(PPh_3)_4$ (20 mg, 10 mol%) were reacted in dioxane/water (4 mL). Purification by column chromatography ($CHCl_3$:MeOH / 10:1) and subsequent crystallization gave the pure product (28 mg, 41%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.35. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.94 (d, *J* = 1.6 Hz, 1H), 8.81 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.13 (d, *J* = 2.6 Hz, 1H), 8.09 – 7.91 (m, 1H), 7.66 (ddd, *J* = 8.5, 7.5, 2.7 Hz, 1H), 7.51 (ddd, *J* = 7.9, 4.9, 0.8 Hz, 1H), 7.04 (d, *J* = 1.7 Hz, 1H), 7.02 (d, *J* = 1.7 Hz, 1H), 6.92 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.10 (s, 3H), 2.93 (s, 3H), 2.83 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 163.5 (d, *J* = 241.0 Hz), 156.3, 153.9, 151.0, 150.5, 145.8 (d, *J* = 15.0 Hz), 139.6 (d, *J* = 8.1 Hz), 138.8, 137.3, 137.1, 135.3, 133.9 (d, *J* = 4.7 Hz), 129.0, 127.5, 127.4, 123.6, 123.3, 109.9 (d, *J* = 37.6 Hz), 107.2, 106.5, 56.8, 24.8, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -69.5 (dd, *J* = 7.4, 2.6 Hz). **HRMS (ESI+):** *m/z* = 400.1565 (calcd. 400.1568 for $C_{23}H_{19}FN_5O$ $[M+H]^+$).

1-(6-Fluoropyridin-3-yl)-6-methoxy-3,4-dimethyl-8-(pyridin-4-yl)imidazo[1,5-*a*]quinoxaline (30)

According to the procedure B compound **26** (65 mg, 0.17 mmol, 1.0 eq), 6-fluoropyridin-3-ylboronic acid (38 mg, 0.27 mmol, 1.6 eq), K_2CO_3 (37 mg, 0.27 mmol, 1.6 eq), $Pd(PPh_3)_4$ (17 mg, 10 mol%) were reacted in dioxane/water (5 mL). Flash chromatography (twice) was performed with DCM/MeOH (19/1) to yield a yellow solid (49 mg, 72%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.28. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.68-8.56 (m, 3H), 8.14 (ddd, *J* = 8.4, 7.6, 2.5 Hz, 1H), 7.24 – 7.01 (m, 5H), 4.13 (s, 1H), 2.94 (s, 1H), 2.83 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.2 (d, *J* = 244.2 Hz), 156.3, 154.3, 150.6, 149.0 (d, *J* = 15.3 Hz), 147.2, 142.5 (d, *J* = 8.4 Hz), 137.7 (d, *J* = 1.0 Hz), 137.5, 136.9, 128.1, 127.3, 127.0 (d, *J* = 5.0 Hz), 123.4, 121.4, 110.1 (d, *J* = 37.5 Hz), 107.0, 106.5, 56.8, 24.8, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -65.0 (dd, *J* = 7.2, 2.4 Hz). **HRMS (ESI+):** *m/z* = 400.1568 (calcd. 400.1568 for $C_{23}H_{19}FN_5O$ $[M+H]^+$).

1-(6-Fluoropyridin-3-yl)-6-methoxy-3,4-dimethyl-8-(pyridin-3-yl)-imidazo[1,5-*a*]quinoxaline (31)

According to the procedure B compound **27** (110 mg, 0.30 mmol, 1.0 eq), K_2CO_3 (50 mg, 0.36 mmol, 1.2 eq), 6-fluoropyridin-3-ylboronic acid (50 mg, 0.36 mmol, 1.2 eq) and $Pd(PPh_3)_4$ (40 mg, 10 mol%) were

reacted in 6 mL of a 4:1 dioxane/water mixture. Purification by column chromatography ($CHCl_3$:MeOH / 10:1) and precipitation from $CHCl_3$/petroleum ether afforded the product (30 mg, 25%) as colorless solid. **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.22. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.59 (ddd, *J* = 6.7, 5.3, 1.9 Hz, 3H), 8.14 (td, *J* = 7.9, 2.5 Hz, 1H), 7.57 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.31 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.19 – 7.04 (m, 3H), 4.11 (s, 3H), 2.93 (s, 3H), 2.83 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.2 (d, *J* = 244.1 Hz), 156.3, 153.8, 149.4, 149.0 (d, *J* = 15.3 Hz), 148.1, 142.5 (d, *J* = 8.4 Hz), 137.6, 137.2, 136.7, 135.6, 134.2, 127.5, 127.3, 127.0 (d, *J* = 5.0 Hz), 123.9, 123.4, 109.9 (d, *J* = 37.6 Hz), 107.0, 106.8, 56.8, 24.7, 16.3. **^{19}F NMR** (282 MHz $CDCl_3$): δ = - 65.0 (dd, *J* = 7.5, 3.2 Hz). **HRMS (ESI+):** *m/z* = 422.1390 (calcd. 422.1388 for $C_{23}H_{18}FN_5NaO$ $[M+Na]^+$).

1-(2-Fluoropyridin-3-yl)-6-methoxy-3,4-dimethyl-8-(pyridin-3-yl)-imidazo[1,5-*a*]quinoxaline (32)

According to the procedure B 110 mg of **27** (110 mg, 0.30 mmol, 1.0 eq), K_2CO_3 (50 mg, 0.36 mmol, 1.2 eq), 2-fluoropyridin-3-ylboronic acid (50 mg, 0.36 mmol, 1.2 eq) and $Pd(PPh_3)_4$ (40 mg, 10 mol%) were reacted in dioxane/water mixture (6 mL). Thin layer chromatography showed remaining starting material after 2 days, so another portion of 2-fluoropyridin-3-ylboronic acid (13 mg, 0.09 mmol, 0.3 eq) and $Pd(PPh_3)_4$ (10 mg, 3 mol%) were added and the mixture was stirred for another 3 days. Purification by column chromatography ($CHCl_3$:MeOH / 30:1) and precipitation from $CHCl_3$/petroleum ether yielded the product (30 mg, 25%) as colorless solid. **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.26. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.57 (br s, 2H), 8.46 (ddd, *J* = 4.9, 1.8, 0.8 Hz, 1H), 8.17 (ddd, *J* = 9.3, 7.4, 2.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.40 (m, 1H), 7.35 – 7.27 (m, 1H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.02 (dd, *J* = 1.9 Hz, 1.9 Hz, 1H), 4.12 (s, 3H), 2.95 (s, 3H), 2.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.9 (d, *J* = 241.7 Hz), 156.1, 153.6, 149.7 (d, *J* = 14.4 Hz), 149.2, 148.1, 142.8 (d, *J* = 3.0 Hz), 137.2, 136.9, 135.8, 134.3, 127.5, 127.3, 123.8, 123.4, 134.3, 122.2 (d, *J* = 4.5 Hz), 116.4 (d, *J* = 30.5 Hz), 106.9, 106.2, 56.7, 24.7, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -64.7 (d, *J* = 9.1 Hz). **HRMS (ESI+):** *m/z* = 400.1570 (calcd. 400.1568 for $C_{23}H_{19}FN_5O$ $[M+H]^+$).

1-(2-Fluoropyridin-4-yl)-6-methoxy-3,4-dimethyl-8-(pyridin-3-yl)imidazo[1,5-*a*]quinoxaline (33)

According to the procedure B compound **27** (115 mg, 0.30 mmol, 1.0 eq), 2-fluoropyridin-4-ylboronic acid (67 mg, 0.48 mmol, 1.6 eq), K_2CO_3 (132 mg, 0.96 mmol, 1.6 eq), $Pd(PPh_3)_4$ (34 mg, 10 mol%) were reacted in dioxane/water (8 mL). Flash chromatography was performed with DCM/MeOH (19/1). The product was further purified by precipitation from $CHCl_3$/PE to afford a greenish solid (70 mg, 58%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.27. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.70 (s, 1H), 8.65-8.60 (m, 1H), 8.45 (d, *J* = 4.9 Hz, 1H), 7.69 – 7.54 (m, 2H), 7.46 – 7.32 (m, 2H), 7.28 (s, 1H), 7.17 (s, 1H), 4.16 (s, 3H), 2.98 (s, 3H), 2.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.1 (d, *J* = 240.9 Hz), 156.3, 153.7, 149.2, 148.4 (d, *J* = 15.3 Hz), 147.9, 145.2 (d, *J* = 8.5 Hz), 137.9 (d, *J* = 3.8 Hz), 137.7, 136.9, 135.7, 134.4, 127.6, 126.8, 124.0, 123.8, 121.7 (d, *J* = 4.4 Hz), 110.3 (d, *J* = 38.9 Hz), 107.5, 107.0, 56.8, 24.7, 16.3. **^{19}F NMR** (377 MHz, $CDCl_3$): δ = -65.4 (s). **HRMS (ESI+):** *m/z* = 422.1389 (calcd. 422.1388 for $C_{23}H_{18}FN_5NaO$ $[M+Na]^+$).

8-Cyano-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (34)

A suspension of compound **8** (150 mg, 0.49 mmol, 1.0 eq) in MeCN (3.0 mL) was degassed prior to the addition of NaCN (48 mg, 0.98 mmol, 2.0 eq), CuI (19 mg, 20 mol%) and $Pd(PPh_3)_4$ (57 mg, 10 mol%). After refluxing the suspension for 4 h, the starting material was fully converted (TLC). Water was added to the mixture and extracted with $CHCl_3$ (3 × 15 mL). Combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash chromatography using DCM/MeOH (19/1) yielded a yellow solid (97 mg, 78%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.41. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.47 (br s, 1H), 7.70 (d, *J* = 1.5 Hz, 1H), 7.10 (d, *J* = 1.5 Hz, 1H), 4.07 (s, 3H), 2.88 (s, 3H), 2.77 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.6, 156.2, 138.6, 129.6, 128.2, 126.1, 121.1, 118.2, 110.8, 110.7, 110.5, 57.0, 24.6, 16.2. **LRMS (ESI+):** *m/z* = 253.1 (calcd. 253.1 for $C_{23}H_{18}FN_5NaO$ $[M+H]^+$).

1-Bromo-8-cyano-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (35)

Compound **34** (83 mg, 0.33 mmol, 1.0 eq) was suspended in MeCN (5 mL) and protected against light. NBS (76 mg, 0.43 mmol, 1.3 eq) was added and the suspension was stirred for 6 h at room temperature. Water (5 mL) and $CHCl_3$ (16 mL) were added. The aqueous layer was extracted with $CHCl_3$ (2 × 5 mL). Combined organic layers were washed with water and dried over $MgSO_4$. After removal of solvent, the crude product was absorbed on celite and purified by flash chromatography in DCM/MeOH (19/1). A beige solid (82 mg, 75%) was isolated. **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.62. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 9.06 (d, *J* = 1.3 Hz, 1H), 7.21 (d, *J* = 1.1 Hz, 1H), 4.09 (s, 3H), 2.87 (s, 3H), 2.77 (s, 3H). Due to the poor solubility in various solvents no ^{13}C-NMR was obtained.

8-Cyano-1-(6-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (36)

Following the general procedure B compound **35** (60 mg, 0.18 mmol, 1.0 eq) was reacted with (41 mg, 0.29 mmol, 1.6 eq) 6-fluoropyridin-3-ylboronic acid, K_2CO_3 (40 mg, 0.29 mmol, 1.6 eq) and $Pd(PPh_3)_4$ (21 mg, 10 mol%) in dioxane/water (7.5 mL). Purification by flash chromatography using DCM/MeOH (19/1) as solvent and precipitation from chloroform and petroleum ether afforded the product as colorless solid (36 mg, 57%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.49. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.55 (d, *J* = 2.5 Hz, 1H), 8.06 (ddd, *J* = 8.4, 7.4, 2.5 Hz, 1H), 7.26 (d, *J* = 1.3 Hz, 1H), 7.18 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.11 (d, *J* = 1.5 Hz, 1H), 4.08 (s, 3H), 2.94 (s, 3H), 2.82 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 164.5 (d, *J* = 244.9 Hz), 156.8, 156.2, 148.8 (d, *J* = 15.5 Hz), 142.0 (d, *J* = 8.5 Hz), 141.5 (d, *J* = 9.1 Hz) 138.4, 131.0, 127.1, 126.1 (d, *J* = 4.9 Hz), 123.2, 118.1, 112.4, 110.7, 110.5 (d, *J* = 38.3 Hz), 109.8, 57.1, 24.8, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -63.8 (dd, *J* = 7.1, 2.5 Hz). **HRMS (ESI+):** *m/z* = 370.1077 (calcd. 370.1075 for $C_{19}H_{14}FN_5NaO$ $[M+Na]^+$).

8-Cyano-1-(2-fluoropyridin-3-yl)-6-methoxy-3,4-dimethylimidazo[1,5-*a*]quinoxaline (37)

A suspension of **35** (120 mg, 0.36 mmol, 1.0 eq) and K_2CO_3 (100 mg, 0.72 mmol, 2.0 eq) in dioxane/water (7.5 mL) was degassed before 2-fluoropyridin-3-ylboronic acid (102 mg, 0.72 mmol, 2.0 eq) and $Pd(PPh_3)_4$ (41 mg, 10 mol%) was added. After the addition the reaction was heated to 100℃ for 7 h and to 60℃ fo r 21 h. An additional portion of boronic acid (40 mg, 0.28 mmol, 0.8 eq) und K_2CO_3 (40 mg, 0.29 mmol, 0.8 eq) was added and the mixture was heated to 100℃ for 2 h and at 60℃ for 42 h. A third portion of

boronic acid (50 mg, 0.35 mmol, 1.0 eq) und K_2CO_3 (50 mg, 0.36 mmol, 1.0 eq) was added and the reaction mixture was heated to 100℃ for another 5 h. After cooling the reaction mixture was portioned between $CHCl_3$ (10 mL) and water (5 mL). Aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash chromatography using DCM/MeOH (15/1) as eluent followed by solvation in hot chloroform and precipitation by the addition of petroleum ether yielded a pale yellow solid (46 mg, 37%). **TLC:** [Silica, $CHCl_3$/MeOH/30% aqueous NH_3 (10:1:0.1)]: R_f = 0.52. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.50 (dd, *J* = 4.0, 0.9 Hz, 1H), 8.27 – 7.96 (m, 1H), 7.60 – 7.39 (m, 1H), 7.12 (br s, 2H), 4.07 (s, 3H), 2.94 (s, 3H), 2.83 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 160.5 (d, *J* = 241.2 Hz), 156.6, 156.0, 150.3 (d, *J* = 14.7 Hz), 142.6 (d, *J* = 2.9 Hz), 138.4, 135.1, 130.8, 127.2, 123.2, 122.4 (d, *J* = 4.6 Hz), 118.2, 115.2 (d, *J* = 30.5 Hz), 111.8, 110.7, 110.0, 57.1, 24.8, 16.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -65.2 (d, *J* = 9.0 Hz). **HRMS (ESI+):** *m/z* = 348.1254 (calcd. 348.1255 for $C_{19}H_{15}FN_5O$ $[M+H]^+$).

4.2. Biology

In vitro PDE assays. PDE2A and PDE10A were produced from full length human recombinant clones. Enzyme activity was measured with [^{3}H]cAMP by scintillation proximity assay at varied compound concentrations and fixed enzyme amount.

Screening (PDE10A Inhibition). PDE10A1 DNA (AB 020593, 2340 bp) was synthesized and cloned into vector pCR4TOPO (Entelechon GmbH, Regensburg, Germany). After inserting the gene into a baculovirus vector and ligation with the baculovirus DNA, the protein was expressed in SF21 cells. Isolation of the protein was carried out as follows: cells were harvested by centrifugation at 500g, suspended in 50 mM Tris-HCl/1 mM EDTA/250 nM sucrose,buffer (pH 7.4) (Sigma, Deisenhofen, Germany; Merck, Darmstadt, Germany) and lysis by sonication (3 × 15 s, Labsonic U, Fa. Braun, Degersheim, Switzerland, level setting “high”). Cytosolic fraction of PDE10A enzyme was isolated in the supernatant after centrifugation at 48000g for 1 h. It was stored at -70℃. PDE10A activity was then determined in a one-step procedure. 50 mM Tris-HCl/5 mM MgCl2 buffer, 0.1 µM [^{3}H]cAMP (PerkinElmer, Waltham, MA) and the enzyme in a total volume of 100 µL were used. Reactions were initiated by the addition of cyclic nucleotide substrate and incubated at 37℃ for 30 min. After addition of 25 µL Ysi-SPA beads (PerkinElmer, Waltham, MA) enzymatic activity was stopped. The beads were allowed to settle for 1 h and the mixture was quantified in a scintillation counter for microtiter plates (Microbeta Trilux). For each enzyme preparation the optimal amount of enzyme to use in the assay was determined. Non-specific activity was determined by control measurements in the absence of enzyme. For determination of IC_{50} values the Hill plot two-parameter model was used.

For the test of PDE2A (NM002599) 1µM cGMP was used to activate the enzyme. The substrate concentration in the assay was 0.5µM [^{3}H]cAMP.

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Research Highlights:

- Novel fluorinated imidazo[1,5-*a*]quinoxaline derivatives were synthesized.
- The strategy allows a diversity oriented synthesis (DOS).
- Compounds were evaluated as potent inhibitors of PDE10A.
- 2-F-pyridin-3-yl as substituent lead to highly potent (picomolar IC_{50}) inhibitors.
- A high selectivity for PDE10A was found for bromine-containing analogs.