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Article

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Design, Synthesis and Pharmacological Evaluation of 5,6-Disubstituted Pyridin-2(1*H*)-one Derivatives as Phosphodiesterase 10A (PDE10A) Antagonists

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ABSTRACT: We report the design and synthesis of novel 5,6-diarylated pyridin-2(1*H*)-one derivatives as pharmacophoric PDE10A inhibitors. This highly potent molecular scaffold was developed from an inactive diarylpyridine-2-amine derivative **3b** by extensive and systematic analogue synthesis and SAR analysis. Further optimization of the scaffold resulted in identification of pyridin-2(1*H*)-one **18b** as a lead compound with good potency (IC_{50}: 1.6 nM) and selectivity (> 6000 fold) over other related PDEs but with a poor pharmacokinetic profile. Careful metabolite profiling of **18b** revealed that poor systemic exposure in rats (C_{max}: 44 ng/mL; $AUC_{(0\text{-}t)}$: 359 ng.h/mL) at 10 mg/kg was due to the formation of *O*-glucuronide conjugate by phase 2 metabolism. The structure of the glucuronide metabolite was confirmed by retention time and LC-MS/MS fragmentation matching with the synthetic glucuronide **26**. The problem of low exposure of **18b** was effectively addressed by its conversion to an acetate

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prodrug **25b**, which upon oral dosing resulted in an improved pharmacokinetic profile (C_{max}: 359 ng.h/mL; $AUC_{(0-t)}$: 2436 ng.h/mL) and a desirable brain to plasma ratio of 1.2. The prodrug **25b** showed good efficacy in selected rodent models of psychosis.

INTRODUCTION

Phosphodiesterase 10A (PDE10A) is a dual substrate specific enzyme that hydrolyzes both 3′,5′-cyclic adenosine monophosphate (cAMP) and 3′,5′-cyclic guanosine monophosphate (cGMP) to the corresponding inactive phosphates.[1] It has a higher affinity for cAMP (K_m = 0.05 μM) than for cGMP (K_m = 3.0 μM).[2] PDE10A enzyme has been considered as a potential drugable target for the treatment of several central nervous system (CNS) disorders.[3] The enzyme is highly expressed in certain areas of the brain linked to CNS disorders including schizophrenia and Huntington's disease.[4] Schizophrenia is characterized by disordered thinking and behaviour and the patients, in general, suffer from delusions and hallucinations.[5] Huntington's disease is a neurodegenerative disease characterized by abnormalities mainly in cognition and movement.[6] The currently available therapy using typical antipsychotics (D2 receptor antagonists, e.g. haloperidol, fluphenazine) and atypical antipsychotics (D2/5HT2A antagonists, e.g. quetiapine, clozapine) are effective in treating only positive symptoms. These drugs are ineffective against negative symptoms and cognitive deficits of schizophrenia.[7] These drugs are also associated with unwanted side effects such as weight gain, diabetes and cardiovascular diseases. Recent studies have shown that PDE10A could modulate both dopaminergic and glutamatergic signaling pathways of the brain.[8] Thus, PDE10A inhibitors have the potential to address a high unmet medical need in treating negative and cognitive symptoms along with good efficacy on positive symptoms of the disease with fewer side effects.

In the previous studies with this target, we[9] and others[10] had identified diverse structural motifs that are efficient inhibitors of PDE10A. A large number of small molecule PDE10A inhibitors

are now reported in the literature and are in various stages of preclinical and clinical studies. Pfizer's well-studied molecule MP-10 (PF-02545920)[11] and Omeros' molecule OMS824[12] are currently in phase 2 clinical trials for treating positive and negative symptoms associated with schizophrenia and Huntington's disease. Omeros' proprietary molecule OMS824 has received fast track designation from US FDA for Huntington's disease. TAK-063 (Takeda)[13] and AMG-579 (Amgen)[14] are also presently in clinical trials.

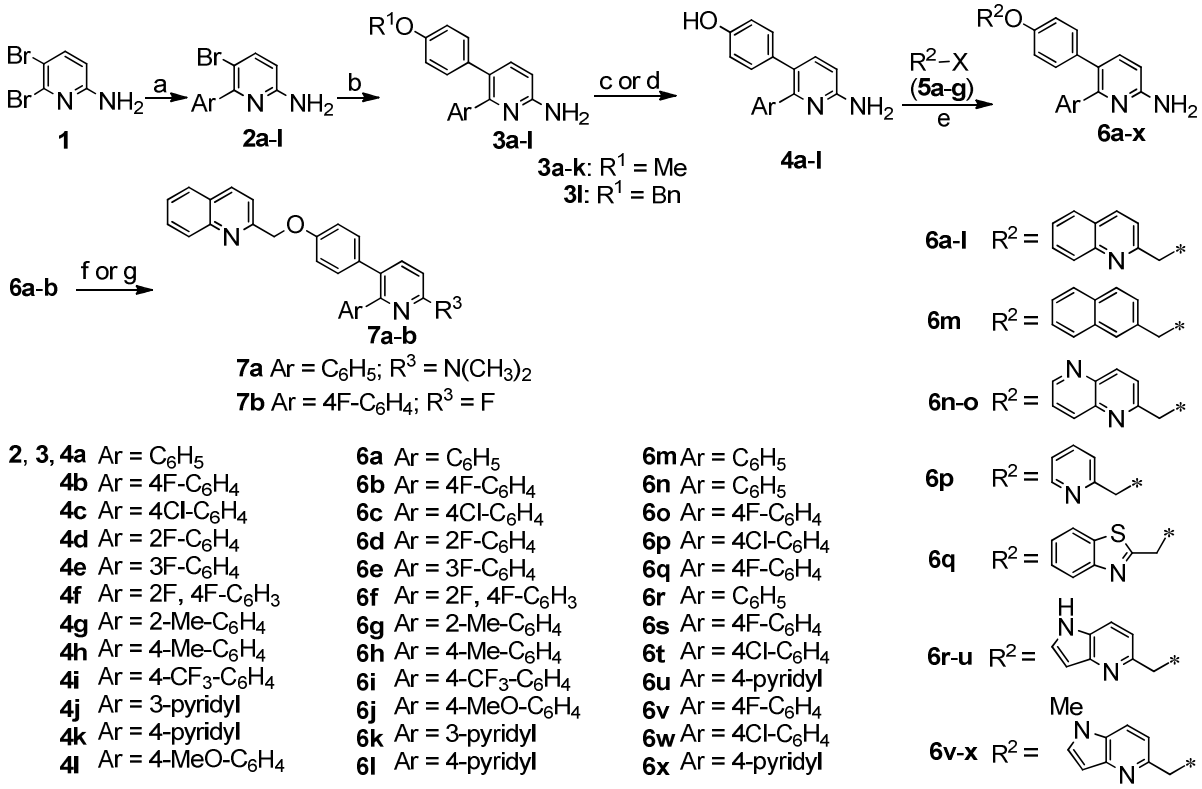
Despite enormous efforts to develop a PDE10A inhibitor by several pharmaceutical companies for more than a decade, so far no molecule has reached the market. This may be due to the complexity involved in co-optimizing and developing a drug for CNS indications such as Schizophrenia or Huntington's disease. There exists a need for developing and evaluating new PDE10A inhibitors with improved efficacy and safety profile. The objective of this study was to explore and generate a new chemical series of PDE10A inhibitors with good potency, selectivity and efficacy in relevant animal models.

RESULTS AND DISCUSSION

Synthetic Chemistry. A diverse set of diaryl pyridine and pyridone derivatives required for our study was prepared as shown in Schemes 1–7. A regioselective sequential double Suzuki coupling strategy was used for the synthesis of the desired compounds. The coupling reaction of 5,6-dibromopyridin-2-amine **1** with a suitable phenyl boronic acid in the presence of sodium carbonate under Suzuki reaction conditions exclusively gave the 6-aryl-5-bromo-2-aminopyridine **2a-l** (Scheme 1). The intermediates **2a–l** were then subjected to a second Suzuki coupling reaction with an appropriate aryl- or pyridyl boronic acid in the presence of cesium carbonate to yield the diaryl aminopyridines **3a**–**l** in good to excellent yield.[15] Demethylation of ethers **3a**–**k** using hydrogen bromide in glacial acetic acid gave the corresponding phenols **4a**–**k**.

The benzyl ether **3l** on hydrogenolysis using Pd/C gave **4l** in 65% yields. The phenols **4a**–**l** on coupling reaction with heterocylic halides or tosylates of the formula **5a–g** afforded ethers **6a**–**x**. Reductive alkylation of **6a** with formaldehyde in the presence of formic acid gave the dimethylaminopyridine **7a**. The compound **6b** on Balz–Schiemann reaction using *tert*-butyl nitrite in the presence of tetrafluoroboric acid afforded the 2-fluoropyridine derivative **7b** in good yield.[16]

Scheme 1. Synthesis of **2a**–**l**, **3a**–**l**, **4a**–**l**, **6a–x** and **7a**–**b**

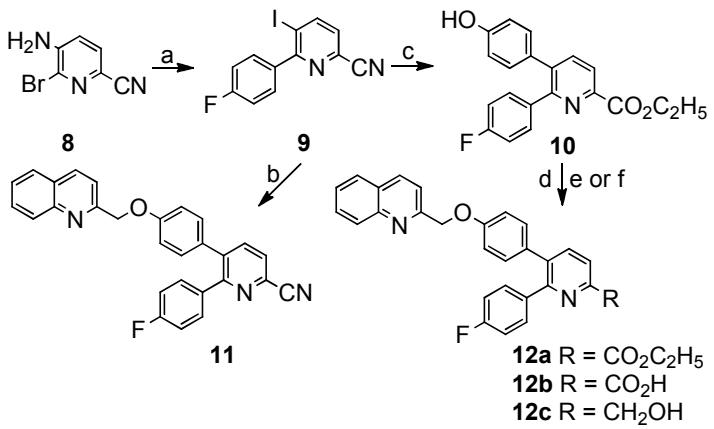


Reagents and conditions: (a) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, toluene, 110 °C, 16 h, 65–85%; (b) 4-Me-OPhB$(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3, dioxane, 100 °C, 16 h, 72–91%; (c) 33% HBr in glacial AcOH, 80 °C, 14 h, 61–82%; (d) H_2, 10% Pd/C, EtOH-THF (1:1), 50–60 psi, RT, 15 h, 65%; (e) Cs_2CO_3, DMF, 70 °C, 48 h, 67–95%; (f) HCHO, HCOOH, reflux, 15 h, 51%; (g) $(CH_3)_3CONO$, HBF_4, $CHCl_3$, RT, 18 h, 48%.

Analogous compounds bearing other functional groups such as an ester, carboxylic acid and a hydroxymethyl group at the 2-position of the pyridine ring were prepared as shown in Scheme 2. Thus, commercially available 5-amino-6-bromopyridine-2-carbonitrile **8** on coupling reaction with 4-fluorophenylboronic acid under Suzuki reaction conditions afforded the corresponding

aryl pyridine, which on diazotization with *tert*-butyl nitrite followed by treatment with iodine gave the 5-iodopicolinonitrile **9**. The iodide **9** on Suzuki coupling reaction with 4-hydroxyphenylboronic acid gave the phenol intermediate which on alkylation with 2-(chloromethyl)quinoline **5a** afforded compound **11**. The intermediate **10** required for the synthesis of compounds **12a**–**c** was prepared from **9** in three steps. Thus, Suzuki coupling reaction of **9** with 4-hydroxyphenylboronic acid followed by base hydrolysis and esterification of the resultant carboxylic acid yielded ester **10**. The compound **10** was then coupled with 2-(chloromethyl)quinoline to give ester **12a**. The ester **12a** on alkaline hydrolysis afforded the carboxylic acid **12b**. Lithium aluminum hydride mediated reduction of the ester functionality in **12a** afforded the hydroxylmethyl derivative **12c**.

Scheme 2. Synthesis of compounds **11** and **12a**–**c**

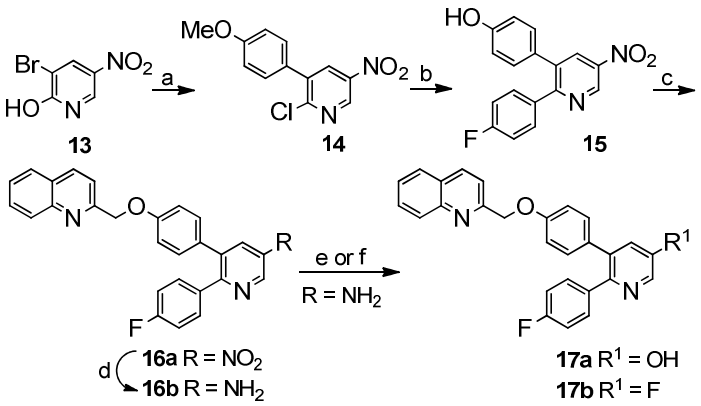


Reagents and conditions: (a) (i) 4F-PhB(OH)$_2$, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, MeOH, toluene, 110 °C, 16 h, 95%, (ii) Iodine, (CH$_3$)$_3$CONO, CHCl$_3$, RT, 1 h, 54%; (b) (i) 4-HO-PhB(OH)$_2$, Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$, dioxane, 100 °C, 16 h, 76%, (ii) 2-(chloromethyl)quinoline, K$_2$CO$_3$, DMF, 70 °C, 18 h, 69%; (c) (i) 4-HO-PhB(OH)$_2$, Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$, dioxane, 100 °C, overnight, 88%, (ii) 2N NaOH, EtOH, 1 h, RT, 81%, (iii) conc. H$_2$SO$_4$, EtOH, reflux, 16 h. 78%; (d) 2-(chloromethyl)quinoline, K$_2$CO$_3$, DMF, 40 °C, 18 h, 73%; (e) 2N NaOH, EtOH, 14 h, RT, 89%; (f) LAH, THF, 0 °C, 30 min, 86%.

An approach developed for the synthesis of compounds bearing selected functional groups such as nitro, amino, hydroxyl and fluorine at 3-position of the pyridine ring is shown in Scheme 3. Thus, Suzuki coupling reaction of 3-bromo-5-nitropyridin-2-ol **13** with 4-methoxyphenylboronic acid yielded 3-aryl-5-nitropyridin-2-ol derivative which on treatment with POCl$_3$ gave the 2-

chloropyridine derivative **14**. The intermediate **14** upon a second Suzuki coupling reaction with 4-(fluorophenyl)boronic acid followed by hydrogen bromide assisted demethylation gave the phenolic intermediate **15**. Alkylation of **15** with 2-(chloromethyl)quinoline **5a** gave compound **16a**. Reduction of **16a** with iron powder in the presence of aqueous ammonium chloride gave 3-aminopyridine derivative **16b**. Diazotization of **16b** using sodium nitrite in the presence of sulfuric acid gave the targeted 3-hydroxy pyridine derivative **17a**.[17] The 3-fluoropyridine derivative **17b** was prepared by treating **16b** with *tert*-butyl nitrite in the presence of tetrafluoroboric acid as described in Scheme 1.[16]

Scheme 3. Synthesis of pyridines **16a–b** and **17a**–**b**

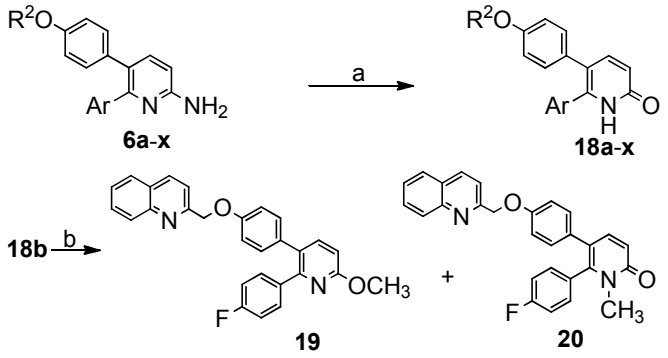


Reagents and conditions: (a) (i) 4-MeO-PhB(OH)$_2$, Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$, dioxane, 100 °C, 16 h, 61%, (ii) POCl$_3$, 120 °C, 2 h, 74%; (b) (i) 4F-PhB(OH)$_2$, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, MeOH, toluene, 110 °C, 16 h, 88%, (ii) BBr$_3$, dichloromethane, 0 °C–RT, 14 h, 63%; (c) 2-(chloromethyl)quinoline, Cs$_2$CO$_3$, DMF, 70 °C, 48 h, 72%; (d) Fe powder, aq. NH$_4$Cl, EtOH, RT, 30 min, 79%; (e) NaNO$_2$, aq. H$_2$SO$_4$, 0 °C, 10 min, 38%; (f) (CH$_3$)$_3$CONO, HBF$_4$, CHCl$_3$, RT, 16 h, 29%.

A diverse set of novel pyridones (pyridine-2(1*H*)-ones) **18a**–**x** was prepared by diazotization of the corresponding 2-aminopyridines **6a**–**x** followed by *in-situ* hydrolysis of the corresponding diazonium salts as shown in Scheme 4.[17] The desired 2-aminopyridine derivatives **6a**–**x** with pendent aryl or heteroaryl groups were prepared by late-stage coupling of advanced intermediates **4a**–**l** with an assorted set of electrophile components **5a**–**g** as described in Scheme 1. The details of Ar and R^2 groups of **6a**–**x** and **18a**–**x** are given in Table 3 (vide infra). The

targeted 6-methoxypyridine **19** and *N*-methylpyridone **20** required for structure activity relationship (SAR) analysis were prepared from pyridone **18b**. Thus, pyridone **18b** on alkylation with methyl iodide in the presence of anhydrous potassium carbonate in DMF afforded an easily separable mixture of 2-methoxypyridine **19** and *N*-methylpyridone **20**.

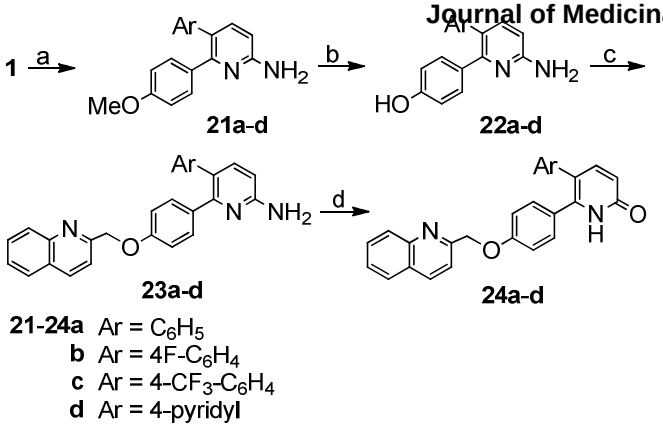
Scheme 4. Synthesis of **18a**–**x**, **19** and **20**



Reagents and conditions: (a) $NaNO_2$, 2.0 M H_2SO_4, 0 °C–RT, 10 min, 75–85%, (b) CH_3I, K_2CO_3, DMF, RT, 16 h (**19**: 44% and **20**: 51%).

The synthesis of targeted regioisomeric pyridones **22a**–**d** bearing the alkoxyphenyl group on the carbon adjacent to pyridine nitrogen was accomplished by reversing the Suzuki coupling sequence as shown in Scheme 5. Thus, reaction of 5,6-dibromopyridin-2-amine **1** with 4-methoxyphenylboronic acid in the presence of sodium carbonate in a mixture of toluene and methanol afforded the 2-aryl pyridine, which was then subjected to the second Suzuki coupling reaction with aryl boronic acid to yield the diaryl 2-aminopyridines **21a**–**d**. Demethylation of **21a**–**d** using BBr_3 in dichloromethane yielded the corresponding phenol intermediates **22a**–**d**. Alkylation of **22a**–**d** with 2-(chloromethyl)quinoline **5a** gave the ethers **23a**–**d**. Finally, the pyridones **24a**–**d** were prepared by diazotization of amines **23a**–**d** and *in situ* hydrolysis of the corresponding diazonium salts.

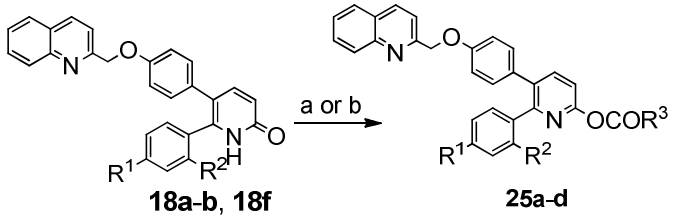
Scheme 5. Synthesis of isomeric pyridones **24a**–**d**



Reagents and conditions: (a) (i) 4-MeO-PhB(OH)$_2$, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, MeOH, toluene, 110 °C, 16 h, 78–86%, (ii) ArB(OH)$_2$, Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$, dioxane, 90 °C, 16 h, 90–95%; (b) BBr$_3$, CH$_2$Cl$_2$, 0 °C–RT, 14 h, 80–91%; (c) 2-(chloromethyl)quinoline, K$_2$CO$_3$, DMF, 70 °C, 16 h, 65–73%; (d) NaNO$_2$, H$_2$SO$_4$, 0 °C, 10 min, 67–75%.

The prodrugs required for our study were prepared from selected pyridones **18a**–**b** and **18f** (Scheme 6). The reaction of pyridones **18a**–**b**, and **18f** with acetic anhydride in presence of triethylamine afforded the corresponding pyridyl acetates **25a**–**c** in good yields. The reaction of **18b** with *N*,*N*-dimethylcarbamoyl chloride in the presence of potassium carbonate in THF afforded the carbamate **25d** in moderate yield.

Scheme 6. Synthesis of prodrugs **25a–d**



18a R^1 = R^2 = H
18b R^1 = F, R^2 = H
18f R^1 = R^2 = F

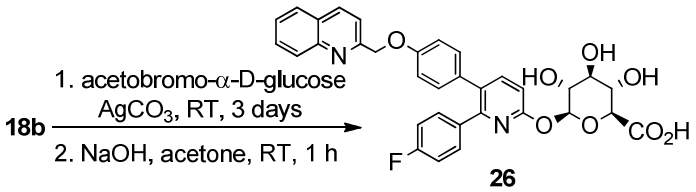
25a R^1 = R^2 = H, R^3 = Me
25b R^1 = F, R^2 = H, R^3 = Me
25c R^1 = R^2 = F, R^3 = Me
25d R^1 = F = R^2 = H, R^3 = N(Me)$_2$

Reagents and conditions: (a) (CH$_3$CO)$_2$O, Et$_3$N, THF, RT, 16 h, 81–88%; (b) (Me)$_2$NCOCl, K$_2$CO$_3$, THF, 70 °C, 15 h, 71%.

Finally, we targeted the conversion of pyridone **18b** to the corresponding *O*-glucuronide **26** and the synthetic approach developed has been delineated in Scheme 7. Thus, **18b** on reaction with

acetobromo-α-D-glucose using silver carbonate as a base smoothly afforded the corresponding acetyl glucuronide which on hydrolysis under basic conditions gave glucuronide **26** in 80% yield.[18] To the best of our knowledge, there have been no literature reports on the formation of glucuronide conjugates of pyridones *via* its enol tautomer.

Scheme 7. Synthesis of *O*-glucuronide **26**

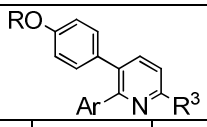


Reagents and conditions: (a) acetobromo-α-D-glucose, $AgCO_3$, RT, 3 days; (b) 1.0 M NaOH, acetone, RT, 1.0 h.

Structure activity relationship (SAR) analysis. Several structurally diverse molecules have been reported in the literature as PDE10A inhibitors. In an effort to discover new chemotypes, we compared structural and topographical similarities of a large number of molecules from our internal compound library with known PDE10A inhibitors reported in the literature. A number of molecules were selected for screening from our internal library based on structure and shape similarity, without considering their atom properties. Selected compounds **3a**–**c** were of particular interest to us due to their structural similarity with known PDE10A inhibitors reported by Pfizer.[11] These compounds were then screened against hPDE10A enzyme. The inhibitory activity of **3a–c** was measured using a scintillation proximity assay with [^{3}H]-cAMP as the substrate by measuring hydrolysis of cAMP to AMP using recombinant human PDE10A enzyme at 1.0 and 10 μM concentrations.[19] Unfortunately, these compounds did not show any activity at both the concentrations. We presumed that lack of activity of these compounds may be due to the absence of the critical binding interaction of these molecules with PDE10A enzyme. We hypothesized that replacing the methyl group in **3a**–**c** with a quinolinemethyl group may result in

the critical binding interaction with Tyr-683 of PDE10A enzyme.[11b] Thus, the quinolinemethyl ether derivative **6a** was prepared and screened against hPDE10A. As expected, **6a** showed significant inhibition of the enzyme at 1.0 and 10.0 μM concentrations of the compound (Table 1). It showed an IC_{50} of 2435.5 nM. The 5,6-diphenyl-2-aminopyridine derivatives **6b** and **6c**, prepared around the hit compound **6a** also showed similar binding affinity to PDE10A (Table 1). The fluoro derivative **6b** showed similar results while the corresponding chloro derivative **6c** showed significant improvement in potency (364.2 nM). The amino group in **6a** was then replaced by *N*,*N*-dimethylamino group as in the case of **7a**, which resulted in complete loss of binding affinity with the PDE10A enzyme. In another modification, the amino group in **6b** was replaced by a fluorine atom as in the case of **7b** to give a potency of 350.9 nM, which was comparable to the potency of **6c**.

Table 1. SAR of pyridines **3a**–**c**, **6a**–**c** and **7a**–**b**

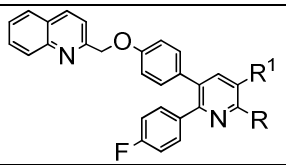


Compd	R	Ar	R^3	% Inhib[a,b]	hIC_{50} (nM)
3a	Me	Ph	NH_2	0.3/1	ND[c]
3b	Me	4F-Ph	NH_2	2/3	ND
3c	Me	4Cl-Ph	NH_2	0.2/3	ND
6a	Qu[d]	Ph	NH_2	33/79	2435.5 ± 86.2
6b	Qu	4F-Ph	NH_2	38/72	2740.1 ± 98.5
6c	Qu	4Cl-Ph	NH_2	71/83	364.2 ± 22.1
7a	Qu	Ph	$N(Me)_3$	7/12	ND
7b	Qu	4F-Ph	F	62/73	350.9 ± 29.5

[a]Percentage inhibition is measured at 1.0 and 10.0 μM concentrations of the compounds. [b]Values are mean of two independent experiments in duplicate. [c]ND refers to 'not determined'. [d]Qu represents quinolin-2-ylmethyl group.

Pyridine derivatives with cyano, ester, carboxylic acid and hydroxymethyl groups at 2-position of the pyridine ring were also studied and the results are shown in Table 2. The 2-cyanopyridine **11** showed poor enzyme inhibitory activity at 1.0 and 10 μM concentrations of the compound. The ester derivative **12a** and carboxylic acid **12b** also showed poor binding affinity. The hydroxymethyl derivative **12c** displayed a moderate potency of 120.1 nM. These results demonstrate that all the four functional groups at 2-position of the pyridine ring failed to give favourable binding interactions with the enzyme. With limited success in achieving good potency with **11** and **12a**–**c**, we profiled selected compounds with functional groups at 3-position of the pyridine ring. The novel 5,6-diarylpyridines bearing a nitro, amino, hydroxyl or a fluorine substitution at the 3-position of the pyridine ring were screened. The nitro pyridine **16a** showed poor inhibitory activity at 1.0 and 10 μM concentrations of the compound. The corresponding aminopyridine derivative **16b** showed a slightly better profile. A hydroxyl group or a fluorine atom at the 3-position of the pyridine ring as in the case of **17a** and **17b** resulted in moderate potency of 226.6 nM and 193.6 nM respectively.

Table 2. SAR of compounds **11**, **12a**–**c**, **16a**–**b** and **17a**–**b**



Compd	R	R^1	% Inhib[a,b]	hIC_{50} (nM)[c]
11	CN	H	12 / 23	ND[d]
12a	CO_2Et	H	3 / 39	ND
12b	CO_2H	H	47 / 87	ND
12c	CH_2OH	H	76 / 95	120.1 ± 9.7
16a	H	NO_2	7 / 23	ND
16b	H	NH_2	51 / 94	ND

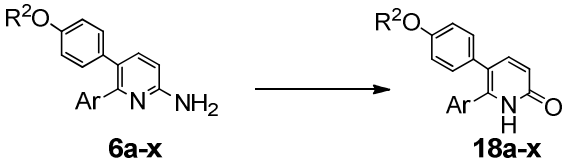
17a	H	OH	79 / 92	226.6 ± 15.1
17b	H	F	80 / 83	193.6 ± 16.2

[a]Percentage inhibition is measured at 1.0 and 10.0 μM concentrations of the compounds. [b]Percentage inhibition are mean of two independent experiments in duplicate. [c]IC_{50} values are mean ± SD of two independent experiments using 7 to 9-point concentration-response curve. [d]ND refers to 'not determined'.

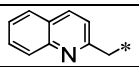
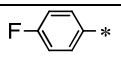
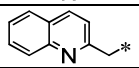
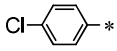
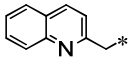
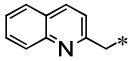
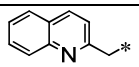
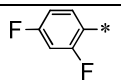
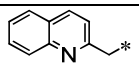
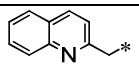
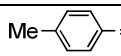
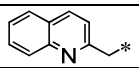
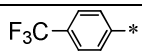
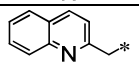
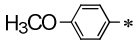
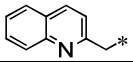
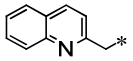
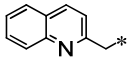
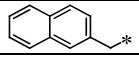
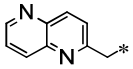
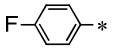
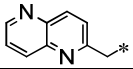
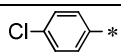
With limited success in achieving good potency in case of pyridine derivatives **6a**–**c** and **7a**–**b**, we further planned to evaluate the corresponding pyridine-2(1*H*)-ones. We were pleased to see that the conversion of H-bond donor amino group in **6a** with the H-bond acceptor carbonyl group as in the case of pyridone **18a** resulted in complete inhibition of the enzyme at 1.0 and 10.0 μM concentrations of the compound. It showed 2200 fold improvement in potency with IC_{50} value of 1.12 nM (Table 3). We then evaluated the *in vitro* potency of pyridone analogues with several quinoline ring replacement groups to derive reliable SAR for this series. Concurrent changes were also carried out with selected aryl group replacements at 6-position of the pyridone ring. The fluoro and chloro derivatives **18b** and **18c** also showed single digit nanomolar potency. The regioisomeric fluoro phenyl derivatives **18d** and **18e** also showed comparable potencies. The difluoro derivative **18f** also retained potency. While both **18g** and **18h** showed single digit nanomolar potency, the 4-methyl derivative **18h** was twice as potent as the 2-methyl derivative **18g**. The pyridone derivative with an electron withdrawing trifluoromethyl group at 4-position of the phenyl ring as in the case of **18i** resulted in significant loss of potency. The presence of electron donating methoxy group in **18j** resulted in retention of potency. Among the isomeric pyridine derivatives **18k** and **18l**, the 4-pyridyl derivative **18l** was found to be 10 fold more potent than the corresponding 3-pyridyl derivative **18k**. A topologically similar naphthyl derivative **18m**, which is devoid of the desired ring nitrogen resulted in complete loss of potency (3.5 and 5.8% at 1.0 and 10.0 μM concentration of the compound). Compounds **18n** and **18o** bearing 1,5-naphthyridine ring, wherein an additional ring nitrogen is present, showed loss of potency compared to the corresponding quinoline analogues **18a**–**b**. The compound **18p**,

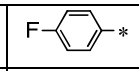
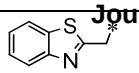
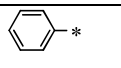
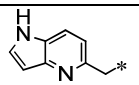
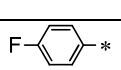
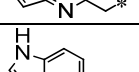
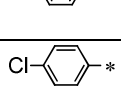
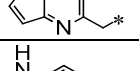
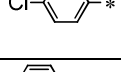
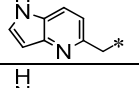
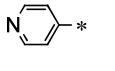
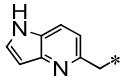
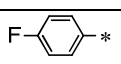
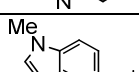
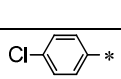
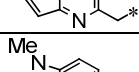
wherein the quinoline is replaced with a monocyclic pyridine ring resulted in 124 fold loss in potency, despite bearing suitably positioned nitrogen atom. Replacement of quinoline ring with 1,3-benzothiazol as in the case of **18q** resulted in around 570 fold loss in potency. The pyridines **18r**–**u** bearing 1*H*-pyrrolo[3,2-*b*]pyridine as the bicyclic core displayed sub-nanomolar potency. The 1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine **18v**–**x**, that are devoid of NH donor group also retained good potency except in the case of **18x**.

Table 3. SAR of **18a**–**x** and **19** and **20**



6a-x **18a-x**

Compd	Ar	R^2	hIC_{50} (nM)[a]
18a			1.12 ± 0.09
18b			1.62 ± 0.07
18c			1.11 ± 0.05
18d			2.71 ± 0.12
18e			1.23 ± 0.07
18f			1.41± 0.11
18g			5.02 ± 0.52
18h			1.85 ± 0.12
18i			6.46 ± 0.42
18j			1.90 ± 0.23
18k			18.62 ± 1.03
18l			1.22 ± 0.10
18m			ND[b]
18n			21.20 ± 1.01
18o			21.69 ± 1.15
18p			136.6 ± 8.36

18q			926.4 ± 60.2
18r			0.21 ± 0.01
18s			0.33 ± 0.03
18t			0.30 ± 0.02
18u			0.54 ± 0.05
18v			1.73 ± 0.10
18w			0.73 ± 0.07
18x			11.96 ± 0.65
19	-	-	> 10000[c]
20	-	-	2984.5 ± 192.2

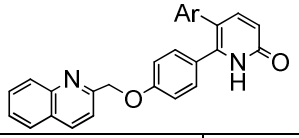
[a]IC_{50} values are mean ± SD of two independent experiments using 7 to 9-point concentration-response curve. [b]ND refers to IC_{50} value was not determined, showed 3% and 6% inhibition at 1.0 and 10.0 μM concentrations, respectively. [c]Compound **19** showed an inhibition of 21 and 28% at 1.0 and 10 μM concentrations, respectively.

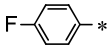
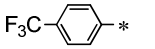
The 2-methoxypyridine **19** and the isomeric *N*-methylpyridone **20** were of special interest to us to understand the basis of high potency of most of the pyridones studied (Scheme 4 and Table 3) as compound **19** is devoid of the carbonyl functionality while compound **20** has locked or non-enolizable carbonyl functionality. Compound **19** showed nearly complete loss of potency (21% and 28% inhibition at 1.0 and 10 μM concentrations respectively). Compound **20** showed an IC_{50} value of 2984.5 nM, which is approximately 1840 fold reduction in potency relative to the parent pyridone **18b**. The loss of potency in **19** and **20** suggests the importance of having both enolizable carbonyl group and a free NH group to achieve good potency for this class of PDE10A inhibitors.

We then evaluated the binding affinity and potency of regioisomeric pyridones **24a**–**d** and the results are shown in Table 4. It was observed that transposition of the aryl groups at 5- and 6-position of the pyridone ring resulted consistent and significant reduction in potency. All the

compounds studied (**24a**–**d**) were less potent than the corresponding regioisomers **18a**–**b**, **18i** and **18l**. For example, **24a** is approximately 25 times less potent than the corresponding regioisomer **18a**. Similar trends were observed in the case of **24b** and **24c**, whereas the effect was less pronounced in the case of **24d**.

Table 4. SAR of isomeric pyridones **24a**–**d**



Compd	Ar	hIC_{50} (nM)[a]
24a		28.9 ± 2.1
24b		41.5 ± 4.7
24c		37.0 ± 3.3
24d		3.3 ± 0.24

[a]IC_{50} values are mean ± SD of two independent experiments using 7 to 9-point concentration-response curve.

The detailed SAR analysis discussed in Tables 1–4 clearly shows that pyridone derivatives, in general, were superior in potency compared to the related pyridine derivatives studied. Therefore, as a part of the lead optimization strategy, selected pyridones from Table 3 were screened against a broader panel of PDEs to assess the selectivity of this class of compounds and the results are given in Table 5. The PDE selectivity assay of compounds **18a**–**c**, **18f**, **18l**, **18r**, **18t** and **18v**–**w** was carried out using human recombinant PDEs 1–5, 7–9 and 11 at 1.0 and 10.0 μM concentrations of the compounds.[19] The *in vitro* radiometric assay results show that these compounds are at least 5800-fold more selective towards PDE10A enzyme over other related PDEs.

Table 5. PDE selectivity of compounds **18a–c**, **18f**, **18l**, **18r**, **8t** and **18v–w**

Compd	Percentage inhibition at 1.0 and 10.0 μM concentrations[a]								
	hPDE1	hPDE2	hPDE3	hPDE4	hPDE5	hPDE7	hPDE8	hPDE9	hPDE11
18a	3 / 10	15 / 30	3 / 5	2 / 14	3 / 36	29/ 35	3 / 8	1 / 1	13 / 19
18b	20 / 27	10 / 26	0.7 / 7	13 / 48	15 / 21	7/ 31	12 / 6	0 / 0	15 / 14
18c	11 / 26	12 / 34	1 / 3	0 / 9	8 / 25	14/ 36	0 / 0	12 / 18	1 / 13
18f	12 / 18	11 / 12	3 / 4	0 / 2	2 / 12	22/ 50	7 / 8	8 / 5	7 / 9
18l	ND[b]	16 / 43	2 / 9	0 / 15	3 / 34	9/ 40	2 / 8	10 / 13	7 / 15
18r	11 / 21	9 / 14	0.3 / 0	ND	8 / 7	12/ 17	3 / 0	0 / 13	0 /0
18t	29 / 30	16 / 18	1 / 0.8	ND	39 / 47	32/ 29	0 / 0	19 / 22	0 / 0
18v	40 / 35	11 / 10	0.5 / 0.9	ND	6 / 7	0/ 8	9 / 8	11 / 1	11 / 34
18w	29 / 31	32 / 37	9 / 16	ND	24 / 29	30/ 39	0 /0	16 / 16	0 / 0

[a]Percentage inhibition (1.0/10 μM) values are mean of two independent experiments run in duplicate for both concentrations. [b]ND refers to 'not determined'.

In vitro liver microsomal stability of selected compounds

The above potent pyridones were subjected to *in vitro* metabolic stability studies using pooled liver microsomal preparations of wistar rat, CD1 mouse, beagle dog, cynomolgus monkey and human. The metabolic stability results are shown in Table 6. Briefly, the compounds were incubated at a final concentration of 1.0 μM with 1.0 mg/mL of microsomal protein fortified with NADPH (2.4 mM) at 37 °C for 60 min. The *in vitro* metabolic stability of compounds was determined by measuring their disappearance using LC-MS/MS. Compound **18a** showed moderate stability in the rat, dog and human while it showed poor stability in mouse and monkey liver microsomes. The metabolic stability profile of 4-substituted derivatives **18b** and **18c** was substantially better in mouse and monkey liver microsomes compared to the corresponding unsubstituted phenyl derivative **18a**. The most potent pyridones **18r** and **18s** bearing the 1*H*-

pyrrolo[3,2-*b*]pyridine side chain showed poor stability across the species except in the dog suggesting extensive metabolism of this ring. Similarly, the corresponding *N*-methylpyrrolo[3,2-*b*]pyridine derivative **18v** also showed poor metabolic stability in all species except the dog. The 2,4-difluoroderivative **18f** showed good stability in mouse, rat, dog and human but moderate stability in monkey. The 4-methyl derivative **18h** showed good metabolic stability in the dog and human, but poor stability in rat, mouse and monkey liver microsomes. The pyridine derivative **18l** showed good metabolic stability in all species studied. Thus, in general, compounds bearing quinolinyl-2-ylmethyl side chain were more stable than the more potent analogues bearing 1*H*-pyrrolo[3,2-*b*]pyridine moiety.

Table 6. Metabolic stability data[a,b] of **18a–c**, **18f**, **18h**, **18l**, **18r–s**, **18v**

Compd	Rat	Mouse	Dog	Monkey	Human
18a	59.7	3.5	70.0	3.0	62.6
18b	48.1	54.0	99.0	49.0	74.0
18c	60.6	60.9	100.0	53.8	92.2
18f	75.6	77.0	98.3	35.0	66.4
18h	18.5	41.9	88.7	29.0	65.4
18l	67.1	72.0	91.1	72.5	77.7
18r	11.1	20.3	42.0	3.6	1.0
18s	15.5	0.8	42.1	6.6	0.6
18v	4.3	3.9	51.7	1.3	4.4

[a]Values are mean of three replicates. [b]Percentage remaining at 60 min in liver microsomal preparations.

Pharmacokinetics and *in vivo* metabolism of 18a–b, 18f and the prodrugs 25a–d[20]

After evaluation of potency, selectivity and *in vitro* metabolic stability data of several compounds, we decided to assess the *in vivo* pharmacokinetic (PK) profile of selected

compounds **18a–b** and **18f**. A single dose (10 mg/kg) oral PK study of **18a–b** and **18f** was initially performed in male Sprague Dawley (SD) rats and the PK parameters are shown in Table 7. Compounds **18a–b** and **18f** exhibited very poor pharmacokinetics, with C_{max} (9 – 73 ng/mL) and $AUC_{0\text{-}t}$ (38 – 370 ng.h/mL) upon oral dosing as a methylcellulose suspension. The poor systemic exposures of these compounds did not correlate with the moderate to high *in vitro* metabolic stability as shown in Table 7. It may be noted that these compounds have favourable physicochemical properties (Mol. Wt.: 404–440; cLogP: 4.46–4.77; tPSA: ~ 50.6) amenable for oral absorption. In a parallel artificial membrane permeability assay (PAMPA),[21] these compounds were found to be highly permeable (P_{app}: 2.9 – 3.6 x 10^{-6} cm/s). These physicochemical properties also appear to be favorable for crossing the blood brain barrier by passive diffusion. However, compounds **18a–b** and **18f** showed poor aqueous solubility (< 0.1 μg/mL) which may have been due to the high melting nature of these pyridone compounds (226–246 °C). To address the poor solubility profile of these compounds, we sought to prepare corresponding prodrugs **25a–d** (Scheme 6). Prodrugs **25a–d** exhibited favorable melting points (143–167 °C) but resulted in no improvement in aqueous solubility. However, unlike the pyridones, these compounds showed very good solubility in organic solvents.

Although the prodrug approach did not improve aqueous solubility of these compounds, we decided to study the oral PK profile of **25a–d** in SD rats. Following oral administration of acetate prodrugs, quantifiable levels of parent pyridones were found in the plasma samples up to 8 h post dose in all the animals (n = 3) studied. The prodrug levels were not detected in the plasma samples at any time points. The acetate prodrugs **25a–c** showed improved PK profile upon oral dosing at 11.04 mg/kg (equivalent to 10 mg/kg of the parent compounds) in SD rats as shown in Table 7. The carbamate prodrug **25d** failed to improve the PK profile. Among the prodrugs studied, the best PK profile was observed for **25b**. It showed a mean C_{max} of 248 ± 68

ng/mL and AUC_{0-t} of 2436 ± 390 ng.h/mL. Thus, the strategy to dose **18b** as its prodrug **25b** substantially improved the PK profile of the parent compound. Further, the brain to plasma ratio was determined for compounds **18a**–**b**, **18f** at 1 h post-dose. Compound **18a** and **18b** showed good brain to plasma ratio of 1.5 and 1.1 respectively, while **18f** showed a relatively poor value of 0.5. Based on the superior PK profile and other favourable data discussed above, pyridone **18b** as its acetate prodrug **25b** was selected as a lead compound for further profiling.

Table 7. PK data[a] of **18a**–**b**, **18f** when doses as such and as their prodrugs **25a**–**d**[b] in SD rats

Drug / Prodrug	C_{max} (ng/mL)	T_{max} (h)[c]	AUC_{0-t} (ng.h/mL)	B/P ratio
18a / **25a**	9 ± 3 / 372 ± 58	0.5 / 1.0	38 ± 20 / 1497 ± 615	1.5
18b / **25b**	44 ± 12 / 372 ± 128	0.5 / 1.0	359 ± 272 / 2436 ± 1025	1.1
18f / **25c**	73 ± 57 / 266 ± 50	4.0 / 2.0	370 ± 264 / 1764 ± 226	0.5
18b / **25d**	44 ± 12 / 42 ± 19	0.5 / 1.0	359 ± 272 / 182 ± 44	ND[d]

[a]Mean ± SD values (n = 3). [b]11.04 mg/kg dose of the prodrug is equivalent to 10 mg/kg of the parent. [c]T_{max} is median. [d]ND refers to 'not determined'.

The parent compound **18b** was also evaluated on selected panel of receptors, ion channels, transporters and enzymes (CEREP) at a concentration of 10 μM. In the binding assay experiments, compound **18b** showed no significant effect on a majority of the enzymes in the panel. It showed an IC_{50} of 6.7 nM on h5HT2b receptor binding assay. The compound showed relatively low binding affinity towards norepinephrine transporter, LTD4 receptor and dopamine receptor with IC_{50} values above 1200 nM. The follow-up studies were conducted for h5HT2b receptor to assess its functional modulation. Compound **18b** showed functional antagonism on h5HT2b receptor with an IC_{50} of 220 nM and therefore is 135-fold more selective towards PDE10A. Compound **18b** was then tested for its hERG potassium channel inhibition to evaluate its cardiovascular safety. It showed 42.4% inhibition at 10 μM concentration in hERG302-HEK

cells in a patch clamp electrophysiology assay and was classified as a low potency hERG channel blocker.

Characterization and quantification of phase 2 metabolite of pyridone 18b

We proposed that the low exposure of **18b** is due to the *O*-glucuronide conjugate formation through pyridine-2-ol tautomer. As discussed in the chemistry section, the pure (96% by HPLC) *O*-glucuronide **26** of pyridone **18b** was prepared and characterized to compare with the metabolites isolated from the *in vitro* liver and intestinal microsomal incubations. The *in vitro* microsomal incubations of **18b** were carried out in the presence of uridine 5'-diphospho-glucuronic acid (UDPGA) as cofactor. The phase 2 metabolite identification studies were carried on LC-MS/MS using a neutral loss (loss of 176 amu in positive ionization mode) scan. We observed that **18b** underwent *O*-glucuronidation in these incubations and it was confirmed by comparison of the metabolite with synthetic *O*-glucuronide **26**. Details of the experiment and characterization studies are given in the supporting information.

Additional *in vivo* studies were carried out for quantification of glucuronide metabolite **26** by dosing **18b** as its acetate prodrug **25b**. Plasma level of glucuronide conjugate was quantified using LC-MS/MS analysis. Prodrug **25b** was administered both orally (0.5% MC suspension) and intravenously (20% NMP + 20% ethanol + 10% PG + 50% premix of 3:2 of PEG 200 and water) to SD rat, beagle dog and cynomolgus monkey. As shown in Table 8, the percentage exposure of glucuronide metabolite to parent **18b** was approximately 3–9 times lower upon intravenous (i.v.) administration as compared to oral administration in all the three species studied. Systemic exposure of the glucuronide was found to be in the order monkey > dog > rat, upon oral administration of **25b**. These investigations revealed that poor oral PK profile of **18b** and other pyridone derivatives may partly be attributed to the significant first pass *O*-glucuronidation in liver as well as in intestine.

Table 8: PK data of **18b** after i.v. and oral administration of **25b**

Species	Route	Dose[a] (mg/Kg)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	CL (mL/min/kg)	T_{max} (h)	**26**/**18b**[b] ratio
Rat	i.v.	1.10	ND[c]	492	28	NA[d]	0.34
	oral	11.04	372	2436	ND	1.0	1.33
Dog	i.v.	1.10	ND	841	20	NA	0.25
	oral	11.04	49	555	ND	1.0	2.19
Monkey	i.v.	1.10	ND	1314	13	NA	1.32
	oral	11.04	38	345	ND	6.0	4.06

[a]Doses 1.10 mg/kg and 11.04 mg/kg of **25b** are equivalent to 1.0 and 10 mg/kg doses of the parent compound **18b**, respectively. [b]AUC ratio of **26** to **18b**. [c]ND refers to 'not determined'. [d]NA refers to 'not applicable'.

***In vivo* pharmacology:**

Having achieved good potency, selectivity and acceptable pharmacokinetics and drug metabolism (PKDM) profile for **18b**, we decided to study this compound in relevant rodent models of psychosis. The calculated physicochemical properties of **18b** (Mol. Wt.: 422; cLogP: 4.6; tPSA: 50.6) appeared to be favourable to achieve good brain levels and efficacy in animal models. To establish a reliable correlation between *in vitro* potency, pharmacokinetics (PK) and pharmacodynamics (PD), compound **18b** was also screened against the rat and mouse PDE10A enzyme. It showed an IC_{50} of 4.3 nM in rat and 2.6 nM in mouse, which is close to the human potency of 1.6 nM. As discussed above, **18b** is poorly bioavailable and therefore its acetate prodrug **25b** was selected for *in vivo* dosing. The compound was tested in rat and mouse models that are predictive of anti-psychotic activity in humans. The details of the studies are given in Fig 1, 2 and 3.

Firstly, compound **25b** was evaluated in apomorphine-induced compulsive climbing and sniffing behavior in male CD1 mice, a model constructed on dopaminergic hypothesis of

schizophrenia (Fig. 1).[22] Apomorphine (1.0 mg/kg, s.c.) treated vehicle control group exhibited robust climbing and sniffing behavior with cumulative scores of 43.1 ± 3.6 and 11.8 ± 0.6, respectively. The compound **25b** upon intraperitoneal administration at 0.3, 1, 3, 10, and 30 mg/kg produced dose-dependent inhibition of apomorphine induced climbing and sniffing behaviors with ED_{50} values of 3.76 mg/kg and 18.75 mg/kg respectively. These results show that the PDE10A inhibitor **25b** has an antipsychotic profile similar to a D_2 receptor antagonist in alleviating dopamine related dysfunction in psychosis. An ED_{50} ratio of around 5 for sniffing vs. climbing demonstrates selectivity of compound **25b** for limbic over striatal brain region, which predicts atypical anti-psychotic profile of this compound.

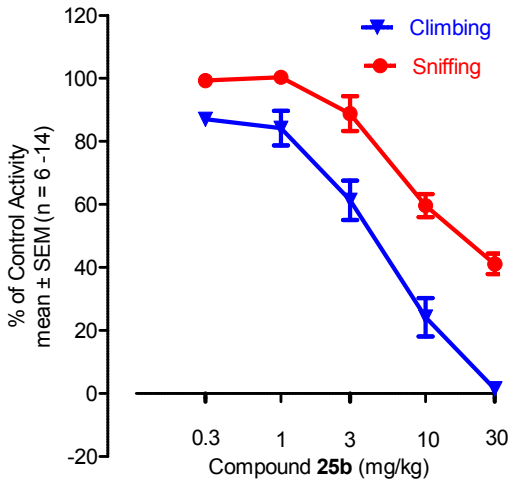


Figure 1. Effect of compound **25b** on apomorphine-induced climbing and sniffing.

Secondly, the compound **25b** was evaluated in MK-801 (dizocilpine)-induced psychosis model in female SD rats, a model constructed on glutamatergic hypothesis of schizophrenia.[23] Dizocilpine, a N-methyl-D-aspartate (NMDA) receptor antagonist, induces both positive and negative symptoms of schizophrenia. In this model, animals were dosed with dizocilpine at 0.2 mg/kg intraperitoneally, and were scored for behavioral signs related to psychosis i.e. hyper-locomotion, stereotypy and ataxia. The compound **25b** was administered orally 1 h prior to dizocilpine injection at 3, 10 and 15 mg/kg dose. The compound **25b** showed reversal of

dizocilpine-induced hyper-locomotion, stereotypy and ataxia in a dose-dependent manner with ED_{50} values of 7.94, 20.29 and 8.75 mg/kg, respectively (Fig. 2). The positive comparator, risperidone, used in this model also produced excellent efficacy. As shown in Figure 3, around 3-fold higher ED_{50} value for stereotypic behavior over hyper-locomotion and ataxia was observed, which is suggestive of an atypical antipsychotic-like profile of compound **25b**. Data from this model clearly demonstrate the ability of PDE10A inhibitor to alleviate the glutamatergic dysfunction of psychosis.

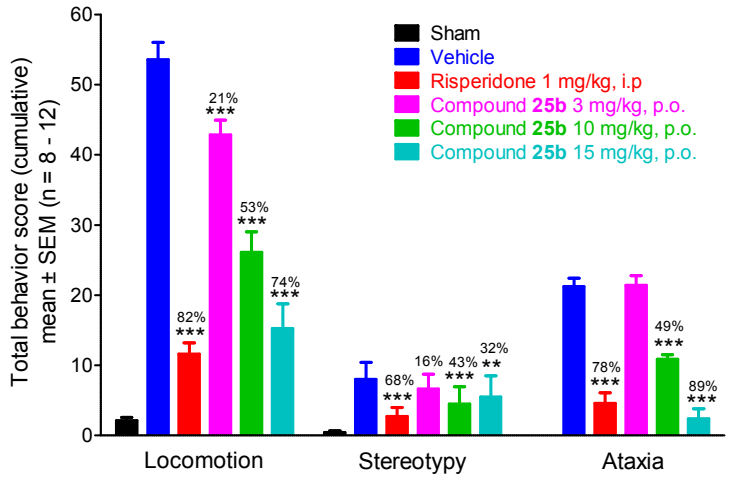


Figure 2. Effect of **25b** on MK-801-induced psychotic behavior in female SD rats. Percentage inhibition depicted over each treatment bar. ** p <0.01; *** p <0.001 vs. vehicle; One-way ANOVA / Tukey's test.

Finally, we tested compound **25b** in quipazine (5-HT_{2A} agonist)-induced head twitch in male SD rats, a model constructed on serotonergic hypothesis of schizophrenia.[24] Compound **25b** was administered orally at 3, 10, 30 and 60 mg/kg, 1.0 h, before the quipazine injection (1 mg/kg, s.c.). In vehicle treated animals, quipazine induced the head twitch behavior, which was dose dependently inhibited by compound **25b** with an ED_{50} of 16.3 mg/kg (Figure 3). Risperidone, a positive comparator used in the experiment also exhibited excellent inhibition of quipazine induced behavior in this model. The data from this experiment suggests that PDE10A inhibitor can also improve the serotonergic dysfunction of psychosis.

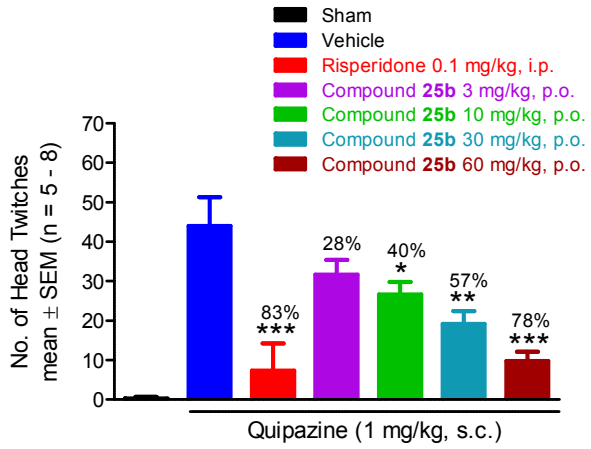


Figure 3. Effect of compound **25b** on quipazine-induced head twitches in male SD rats. Percentage inhibition depicted over each treatment bar. * $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$ vs. vehicle; One-way ANOVA / Tukey's test.

In summary, a series of potent and highly selective novel biaryl pyridone PDE10A inhibitors were discovered through focused library screening and hit to lead optimization through extensive analogue synthesis. Several potent compounds from this class showed very good selectivity over other related PDEs and good *in vitro* microsomal stability across species. This novel class of compounds was screened for PDE10A potency, selectivity, physicochemical properties, CNS penetration and *in vivo* efficacy to yield **18b**. The selected compound **18b** however showed poor pharmacokinetic properties upon oral administration. Careful metabolite profiling revealed that the formation of glucuronide conjugate **26** in both liver and intestine is responsible for relatively low systemic exposure. The issue of poor PKDM profile was addressed by converting the pyridone **18b** to the corresponding enol acetate prodrug **25b**. The prodrug **25b** upon oral dosing quantitatively released the parent compound and showed a 6-fold increase in the exposure. The excellent *in vivo* efficacy results in selected antipsychotic rodent models give scope for further pharmacological and toxicological evaluation of this compound.

EXPERIMENTAL SECTION

General chemistry. Melting points are uncorrected. Infrared spectra were recorded on Perkin Elmer Spectrum One FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz FT NMR spectrometer in either $CDCl_3$ or DMSO-d_6 as specified using tetramethylsilane as internal standard. Chemical shifts are quoted in ppm (δ) relative to TMS (^{1}H) using residual protonated solvent as internal standard. Routine mass spectra (MS) were recorded on a Thermo Finnigan model LCQ Deca XP Max spectrometer using ESI or APCI source at positive or negative polarity mode by direct infusion method. High-resolution mass spectra (HRMS) of test compounds were measured on a Thermo Scientific LTQ Orbitrap Discovery MS system coupled with a LQT Tune Plus software (version 2.5.5 SPI) operating in a positive electron spray ionization (ESI) mode. The chemical purity of the test compounds was determined by reversed phase HPLC on a Shimadzu or Waters system. The analyses were performed on Inertsil ODS-3 (100 x 4.6 mm i.d., 3 μm) column using a binary gradient elution program. The solvents were methanol or acetonitrile as organic phase and 0.1% trifluoroacetic acid (TFA) in water as aqueous phase. A PDA detector was used and the UV detection wavelengths for the compounds were selected according to their characteristic absorption maxima. The injection volume was 20 μL (~ 500 ppm) and the flow rate was 0.8 mL/min. All test compounds used in biological assay were greater than 95% pure by this method.

5-Bromo-6-phenylpyridin-2-amine (2a); **Typical procedure**.[15a] To a stirred solution of 5,6-dibromopyridin-2-amine (10.0 g, 42.21 mmol) in a mixture of methanol (20.0 mL) and toluene (200 mL) was added phenylboronic acid (5.15 g, 42.23 mmol) followed by sodium carbonate (8.95 g, 84.44 mmol) dissolved in water (50 mL). The mixture was purged with nitrogen for 15 min. Tetrakis(triphenylphosphine)palladium(0) (1.46 g, 1.26 mmol) was added to the mixture and heated at 110 °C overnight. The reaction mixture was cooled to room temperature and diluted with water (500 mL). The mixture was extracted with ethyl acetate (3 x 250 mL). The

combined organic layers were washed with water (2 x 250 mL) and dried over anhydrous Na_2SO_4. The solvent was distilled off under reduced pressure and the crude product thus obtained was purified by flash silica gel column chromatography using 15% ethyl acetate in petroleum ether to give 7.21 g (68.6%) of the product as a pale yellow solid.

Intermediates **2b**–**l** were prepared as described in the typical procedure for **2a** by coupling 5,6-dibromopyridin-2-amine and appropriate aryl- or pyridylboronic acid under Suzuki reaction conditions. The characterization data for **2a**–**l** is given in the supporting information.

5-(4-Methoxyphenyl)-6-phenylpyridin-2-amine (3a); **Typical procedure.** To a stirred solution of 5-bromo-6-phenylpyridin-2-amine **2a** (7.0 g, 35.58 mmol) in dioxane (80 mL) were added 4-methoxyphenylboronic acid (5.40 g, 35.53 mmol), and cesium carbonate (23.18 g, 71.14 mmol) dissolved in water (40 mL). The mixture was purged with nitrogen for 15 min. Tetrakis(triphenylphosphine)palladium(0) (1.22 g, 1.05 mmol) was added to the mixture and heated overnight at 90 °C under nitrogen atmosphere. The reaction mixture was cooled and diluted with water (300 mL). The mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with water (2 x 250 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to result a brown viscous residue. The residue was purified by flash silica gel column chromatography using 20% ethyl acetate in petroleum ether to afford 5.91 g (76%) of the product as an off-white solid. Mp 110–112 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3H), 6.03 (br s, 2H), 6.49 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 7.21 (s, 5H), 7.38 (d, J = 8.1 Hz, 1H); APCI-MS (*m/z*) 277 $(M+H)^+$.

Intermediates **3b–l** were prepared as described above by coupling **2b–l** with 4-methoxyphenylboronic acid under Suzuki reaction conditions. The spectral data of these intermediates is given in the supporting information.

4-(6-Amino-2-phenylpyridin-3-yl)phenol (4a). Hydrobromic acid in glacial acetic acid (33 % (w/w), 80 mL) was added to 5-(4-methoxyphenyl)-6-phenylpyridin-2-amine **3a** (5.50 g, 19.90 mmol) and the reaction was stirred at 80 °C for 14 h. The mixture was diluted with water (250 mL) and the pH of the solution was adjusted to 8 using solid sodium bicarbonate. The mixture was extracted with ethyl acetate (2 x 300 mL) and the combined organic extracts were washed with water (2 x 300 mL) and brine (300 mL). The organic layer was concentrated under reduced pressure to afford 3.71 g (71%) of the product as an off-white solid. Mp > 250 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 4.54 (br s, 2H), 6.54 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 7.20–7.30 (m, 5H), 7.48 (d, *J* = 8.4 Hz, 1H), 9.36 (br s, 1H); APCI-MS (*m/z*) 263 $(M+H)^+$.

Intermediates **4b–k** were prepared by demethylation of the corresponding **3b–k** as described in the above procedure using hydrobromic acid in glacial acetic acid. Intermediate **4l** was prepared by palladium catalyzed hydrogenolysis of benzyl ether **3l**. The characterization data for **4b–l** is given in the supporting information.

6-Phenyl-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine (6a). To a stirred solution of 4-(6-amino-2-phenylpyridin-3-yl)phenol **4a** (3.5 g, 13.34 mmol) in DMF (30 mL) were added cesium carbonate (13.0 g, 39.89 mmol) and 2-(chloromethyl)quinoline hydrochloride **5a** (2.84 g, 13.26 mmol) and the reaction mixture was heated at 70 °C for 48 h. The mixture was diluted with water (250 mL) and extracted with ethyl acetate (2 x 300 mL). The combined organic

extracts were washed with water (250 mL) and dried over anhydrous Na_2SO_4. The solvent was distilled off under reduced pressure and the residue obtained was purified by flash silica gel column chromatography using 1% methanol in chloroform to yield 4.19 g (78%) of the product as an off-white solid. Mp 175–177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.31 (s, 2H), 6.04 (s, 2H), 6.48 (d, J = 8.4 Hz, 1H), 6.94 (dd, J = 8.7, 21.0 Hz, 4H), 7.20 (br s, 4H), 7.38 (d, J = 8.4 Hz, 1H), 7.59–7.67 (m, 2H), 7.78 (t, J = 7.2 Hz, 1H), 7.98–8.02 (m, 3H), 8.41 (d, J = 8.1 Hz, 1H); HRMS (ESI) calcd for $C_{27}H_{21}N_3O$, $[M+H]^+$, 404.1757; found, 404.1758.

6-(4-Fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine (6b). Compound **6b** was prepared by alkylation of phenol **4b** with 2-(chloromethyl)quinoline hydrochloride **5a** in the presence of excess cesium carbonate as described above to give **6b** (80%) as an off-white solid. Mp 186–188 °C; ^{1}H NMR (DMSO-d_6) δ 5.32 (s, 2H), 6.06 (s, 2H), 6.49 (d, J = 8.4 Hz, 1H), 6.92–7.05 (m, 6H), 7.21–7.26 (m, 2H), 7.38 (d, J = 8.7 Hz, 1H), 7.59–7.67 (m, 2H), 7.78 (t, J = 8.1 Hz, 1H), 7.98–8.02 (m, 2H), 8.41 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 71.2, 107.5, 114.7 (d, J = 21.0 Hz, 2C), 115.0 (2C), 120.0, 123.6, 127.0, 127.6, 128.4, 129.0, 130.3, 130.9 (2C), 132.0 (d, J = 8.0 Hz, 2C), 133.6, 137.4, 137.7, 140.4, 147.4, 153.3, 157.0, 158.0, 158.8, 161.7 (d, J = 242.0 Hz, 1C); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{20}FN_3O$: 422.1663; found: 422.1658.

6-(4-Chlorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine (6c). Compound **6c** was prepared by alkylation of phenol **4c** with 2-(chloromethyl)quinoline hydrochloride **5a** in the presence of excess cesium carbonate as described above to afford **6c** (74%) as an off-white solid. Mp 188–190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.33 (s, 2H), 6.10 (s, 2H), 6.50 (d, J = 8.1 Hz, 1H), 6.93–7.00 (m, 4H), 7.20–7.28 (m, 4H), 7.39 (d, J = 8.1 Hz, 1H), 7.59–7.63 (m, 2H),

7.78 (t, J = 8.1 Hz, 1H), 7.99–8.03 (m, 2H), 8.42 (d, J = 8.1 Hz, 1H); HRMS (ESI) calcd for $C_{27}H_{20}ClN_3O$, $[M+H]^+$, 438.1367; found, 438.1364.

Intermediates **6d–x** were prepared by coupling appropriate phenol selected from **4a**–**l** with appropriate halides or tosylate selected from **5a**–**g**. The characterization data for amines **6d–x** is given in the supporting information.

***N*,*N*-Dimethyl-6-phenyl-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine (7a).** To a stirred solution of **6a** (250 mg, 0.620 mmol) in formic acid (5 mL) was added formaldehyde (5 mL) and the reaction mixture was refluxed for 15 h. The mixture was then diluted with water (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (100 mL) and dried over anhydrous Na_2SO_4. The solvent was distilled off under reduced pressure and the crude material thus obtained was purified by flash silica gel column chromatography using 30% ethyl acetate in petroleum ether to yield 137 mg (51%) of product as an off-white solid. Mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 3.15 (s, 6H), 5.35 (s, 2H), 6.54 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.15–7.21 (m, 3H), 7.35–7.45 (m, 2H), 7.47 (d, J = 8.7 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.65–7.77 (m, 2H), 7.83 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H); IR (neat, cm^{-1}): 2924, 1736, 1595, 1496, 1428, 1240, 1178, 804; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{25}N_3O$: 432.2070; found: 432.2065.

2-({4-[6-Fluoro-2-(4-fluorophenyl)pyridin-3-yl]phenoxy}methyl)quinoline (7b). To a stirred solution of **6b** (300 mg, 0.712 mmol) in chloroform (10 mL) were added tetrafluoroboric acid (0.2 mL, 1.42 mmol) and *tert*-butyl nitrite (0.3 mL, 2.85 mmol). The reaction mixture was stirred overnight at room temperature. The mixture was diluted with water (50 mL) and

neutralized with solid sodium bicarbonate. The mixture was extracted with chloroform (2 x 100 mL) and the combined extracts were washed with water (2 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was distilled off under reduced pressure. The residue thus obtained was purified by flash silica gel column chromatography using 30% ethyl acetate in petroleum ether to yield 146 mg (48%) of the product as off-white solid. Mp 118–120 °C; ^{1}H NMR (DMSO-d_6) δ 5.37 (s, 2H), 7.00–7.15 (s, 6H), 7.19–7.27 (m, 1H), 7.28–7.35 (m, 2H), 7.57–7.70 (m, 2H), 7.79 (t, J = 7.8 Hz, 1H), 7.90–8.03 (m, 3H), 8.43 (d, J = 8.1 Hz, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{18}F_2N_2O$: 425.1460; found: 425.1455.

6-(4-Fluorophenyl)-5-iodopyridine-2-carbonitrile (9). Suzuki coupling reaction of 5-amino-6-bromopyridine-2-carbonitrile **8** (5.0 g, 25.24 mmol) with 4-fluorophenylboronic acid (3.88 g, 27.73 mmol) in the presence of Na_2CO_3 (5.35 g, 50.38 mmol) in a mixture of methanol (30 mL) and toluene (50 mL) using tetrakis(triphenylphosphine)palladium(0) (875 mg, 0.76 mmol) at 110 °C afforded 5.11 g (95%) of 5-amino-6-(4-fluorophenyl)pyridine-2-carbonitrile as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.15 (s, 2H), 7.15 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 8.7 Hz, 2H), 7.59–7.66 (m, 3H); APCI-MS (*m/z*) 212 $(M-H)^-$.

To a well stirred solution of 5-amino-6-(4-fluorophenyl)pyridine-2-carbonitrile (5.0 g, 23.45 mmol) and iodine (3.57 g, 28.13 mmol) in chloroform (50 mL) was drop wise added *tert*-butyl nitrite (4.2 mL, 35.31 mmol) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was then diluted with water (100 mL) and extracted with chloroform (2 x 250 mL). The combined organic extracts were washed with water (2 x 200 mL), dried (Na_2SO_4) and filtered. The solvent was distilled off under reduced pressure and the residue obtained was triturated with diethyl ether to yield 4.1 g (54%) of the iodide **9** as white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34 (t, J = 8.7 Hz, 2H), 7.60–7.65 (m, 2H), 7.75 (d, J = 8.1 Hz, 1H), 8.69 (d, J = 8.4 Hz, 1H); APCI-MS (*m/z*) 325 $(M+H)^+$.

Ethyl 6-(4-fluorophenyl)-5-(4-hydroxyphenyl)pyridine-2-carboxylate (10). Suzuki coupling reaction of iodide **9** (3.5 g, 10.79 mmol) with 4-hydroxyphenylboronic acid (1.63 g, 11.82 mmol) using tetrakis(triphenylphosphine)palladium(0) (374 mg, 0.32 mmol) in the presence of cesium carbonate (7.03 g, 21.57 mmol) in dioxane (40 mL) at 80 °C afforded 2.79 g (89%) of 6-(4-fluorophenyl)-5-(4-hydroxyphenyl)pyridine-2-carbonitrile as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.71 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.1 Hz, 2H), 7.15 (t, J = 9.0 Hz, 2H), 7.30–7.38 (m, 2H), 8.00–8.07 (m, 2H), 9.72 (s, 1H); APCI-MS (*m/z*) 291 $(M+H)^+$.

To a stirred solution of 6-(4-fluorophenyl)-5-(4-hydroxyphenyl)pyridine-2-carbonitrile (2.6 g, 8.95 mmol) in ethanol (25 ml) was added 2.0 M sodium hydroxide (5 mL) and the reaction was refluxed overnight. The reaction mixture was diluted with water (100 mL) and the pH was adjusted to 4-5 using 1*N* hydrochloric acid. The mixture was extracted with ethyl acetate (2 x 250 mL). The combined organic extracts were washed with water (250 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford 2.25 g (81%) of 6-(4-fluorophenyl)-5-(4-hydroxyphenyl)pyridine-2-carboxylic acid as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.71 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 8.7 Hz, 2H), 7.37 (t, J = 8.4 Hz, 2H), 7.93 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 7.8 Hz, 1H), 9.65 (s, 1H).

To a stirred solution of 6-(4-fluorophenyl)-5-(4-hydroxyphenyl)pyridine-2-carboxylic acid (2.2 g, 7.11 mmol) in ethanol (20 mL) was drop wise added conc. sulphuric acid (0.2 mL) and the reaction mixture was refluxed overnight. The mixture was cooled to room temperature, diluted with water (150 mL) and neutralized with sodium bicarbonate. The mixture was extracted with ethyl acetate (2 x 250 mL) and the combined organic extracts were washed with water (200 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude residue thus obtained was purified by flash silica gel column chromatography using 10%

ethyl acetate in petroleum ether as eluent to afford 1.88 g (78%) of the titled product **10** as white solid. Mp 210–212 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (t, J = 6.9 Hz, 3H), 4.35 (q, J = 7.2 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.1 Hz, 2H), 7.13 (t, J = 8.70 Hz, 2H), 7.29–7.36 (m, 2H), 7.93 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 9.64 (s, 1H); APCI-MS (*m/z*) 338 $(M+H)^+$.

6-(4-Fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridine-2-carbonitrile (11). Suzuki coupling reaction of iodide **9** (550 mg, 1.69 mmol) with 4-hydroxyphenylboronic acid (257 mg, 1.86 mmol) using tetrakis(triphenylphosphine)palladium(0) (59 mg, 0.051 mmol) in the presence of cesium carbonate (1.1 g, 3.37 mmol) afforded 374 mg (88.7%) of 6-(4-fluorophenyl)-5-(4-hydroxyphenyl)pyridine-2-carbonitrile as a white solid. Mp 248–250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.71 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.1 Hz, 2H), 7.15 (t, J = 9.0 Hz, 2H), 7.30–7.38 (m, 2H), 8.00–8.07 (m, 2H), 9.72 (s, 1H); APCI-MS (*m/z*) 291 $(M+H)^+$.

Alkylation of 6-(4-fluorophenyl)-5-(4-hydroxyphenyl)pyridine-2-carbonitrile (350 mg, 1.21 mmol) with 2-(chloromethyl)quinoline hydrochloride (260 mg, 1.21 mmol) using K_2CO_3 (500 mg, 3.62 mmol) yielded 358 mg (69%) of **11** as an off-white solid. Mp 198–200 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.37 (s, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.11–7.18 (m, 4H), 7.31–7.36 (m, 2H), 7.62–7.68 (m, 2H), 7.79 (t, J = 8.4 Hz, 1H), 7.99–8.05 (m, 2H), 8.07 (br s, 2H), 8.42 (d, J = 8.7 Hz, 1H); IR (KBr, cm^{-1}): 3422, 2853 2233, 1602, 1512, 1247, 1046, 844; HRMS (ESI) calcd for $C_{28}H_{19}FN_3O$, $[M+H]^+$, 432.1506; found, 432.1511.

Ethyl 6-(4-fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridine-2-carboxylate (12a). Alkylation of phenol **10** (2.0 g, 5.92 mmol) with 2-(chloromethyl)quinoline hydrochloride (1.16 g, 6.53 mmol) using K_2CO_3 (2.5 g, 18.08 mmol) at 40 °C yielded 1.03 g (73%) of the product as an off-white solid. Mp 220–222 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, J = 6.6 Hz, 3H), 4.48

(q, J = 7.2 Hz, 2H), 5.42 (s, 2H), 6.90–7.12 (m, 4H), 7.25–7.36 (m, 2H), 7.37–7.41 (m, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.67–7.88 (m, 4H), 8.04–8.16 (m, 2H), 8.25 (d, J = 8.4 Hz, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{23}FN_2O_3$: 479.1765; found: 479.1771.

6-(4-Fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridine-2-carboxylic acid (12b). Hydrolysis of ethyl ester **12a** (100 mg, 0.21 mmol) in ethanol (1.0 mL) using 2.0 M sodium hydroxide (1.0 mL) afforded 84 mg (89%) of **12b** as an off-white solid. Mp 231–233 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.35 (s, 2H), 6.99–7.10 (m, 6H), 7.31 (t, J = 8.4 Hz, 2H), 7.59–7.70 (m, 3H), 7.76–7.85 (m, 2H), 7.97–8.05 (m, 2H), 8.42 (d, J = 8.4 Hz, 1H); IR (KBr, cm^{-1}): 1603, 1565, 1511, 1452, 1245, 1177, 1111, 827; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{19F}N_2O_3$: 451.1452; found: 451.1454.

{6-(4-Fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-yl}methanol (12c). To a stirred and cooled (0 °C) suspension of lithium aluminium hydride (50 mg, 1.31 mmol) in THF (10 mL) was drop wise added a solution of ethyl ester **12a** (200 mg, 0.42 mmol) in THF (5 mL) and the reaction was stirred at the same temperature for 30 min. The mixture was quenched with saturated aqueous solution of Na_2SO_4 (5 mL) and stirred at room temperature for 20 min. The white solid precipitated out was filtered and washed with THF (2 x 5 mL). The filtrate was concentrated under reduced pressure to yield a brown residue. The residue was purified by flash silica gel column chromatography using 20% ethyl acetate in petroleum ether to yield 157 mg (86%) of the product as an off-white solid. Mp 203–205 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.63 (d, J = 5.7 Hz, 2H), 5.35 (s, 2H), 5.44 (br s, 1H), 7.00–7.11 (m, 6H), 7.26–7.34 (m, 2H), 7.50 (d, J = 7.8 Hz, 1H), 7.59–7.68 (m, 2H), 7.74–7.80 (m, 2H), 7.98–8.03 (m, 2H), 8.42 (d, J = 8.7 Hz, 1H); IR (KBr, cm^{-1}): 3231, 2823, 1597, 1509, 1451, 1295, 1249, 1082, 823; HRMS (ESI) calcd for $C_{28}H_{22}FN_2O_2$, $[M+H]^+$, 437.1659; found, 437.1670.

2-Chloro-3-(4-methoxyphenyl)-5-nitropyridine (14). Suzuki coupling reaction of 3-bromo-5-nitropyridin-2-ol **13** (3.5 g, 15.98 mmol) with 4-methoxyphenylboronic acid (2.67 g, 17.57 mmol) using tetrakis(triphenylphosphine)Pd(0) (554 mg, 0.479 mmol) and cesium carbonate (10.41 g, 31.95 mmol) in a mixture of dioxane (40 mL) and water (20 mL) as described in **3a** afforded 3-(4-methoxyphenyl)-5-nitropyridin-2-ol in 2.41 g (61%) yield as pale yellow solid. Mp 96–98 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.79 (s, 3H), 6.99 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.7 Hz, 2H), 8.16 (s, 1H), 8.64 (s, 1H), 12.82 (br s, 1H); APCI-MS (m/z) 247 $(M+H)^+$.

Phosphorous oxychloride (20 mL, 212.61 mmol) was slowly added to 3-(4-methoxyphenyl)-5-nitropyridin-2-ol (2.0 g, 8.12 mmol) and the mixture was heated at 120 °C for 2 h. The excess $POCl_3$ was distilled off and the residue thus obtained was quenched with ice-cold water (500 mL). The mixture was neutralized with solid sodium bicarbonate and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with water (100 mL) and dried (Na_2SO_4). The solution was concentrated under reduced pressure to give 1.6 g (74%) of **14** as an off-white solid. Mp 121−122 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.83 (s, 3H), 7.09 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 8.51 (s, 1H), 9.20 (s, 1H); APCI-MS (m/z) 265, 267 $(M+H)^+$.

4-[2-(4-Fluorophenyl)-5-nitropyridin-3-yl]phenol (15). Suzuki coupling reaction of 2-chloro-3-(4-methoxyphenyl)-5-nitropyridine **14** (1.5 g, 5.66 mmol) with 4-fluorophenylboronic acid (872 mg, 6.23 mmol) using tetrakis(triphenylphosphine)palladium(0) (196 mg, 0.17 mmol) and sodium carbonate (1.2 g, 11.32 mmol) in mixture of methanol (2 mL), toluene (20 mL) and water (20 mL) as described in **2a** afforded 1.62 g (88%) of 2-(4-fluorophenyl)-3-(4-methoxyphenyl)-5-nitropyridine as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.76 (s, 3H), 6.94 (d, J = 8.4 Hz, 2H), 7.14–7.22 (m, 4H), 7.39–7.43 (m, 2H), 8.47 (s, 1H), 9.39 (s, 1H); APCI-MS (m/z) 325 $(M+H)^+$.

To a stirred solution of 2-(4-fluorophenyl)-3-(4-methoxyphenyl)-5-nitropyridine (1.5 g, 4.62 mmol) in dry dichloromethane (15 mL) was added boron tribromide (1.0 M in dichloromethane, 12 mL) at 0 °C and the mixture was further stirred at room temperature for 6 h. The reaction mixture was poured into ice cold water (50 mL) and neutralized using solid sodium bicarbonate. The mixture was extracted with chloroform (2 x 50 mL). The combined organic layers were washed with water (50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue obtained was triturated with pentane to afford 910 mg (63%) **15** as an off-white solid. Mp 231–233 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.74 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.18 (t, J = 9.0 Hz, 2H), 7.39–7.44 (m, 2H), 8.44 (s, 1H), 9.37 (s, 1H), 9.73 (br s, 1H); APCI-MS (*m/z*) 311 $(M+H)^+$.

2-({4-[2-(4-Fluorophenyl)-5-nitropyridin-3-yl]phenoxy}methyl)quinoline (16a). Alkylation of phenol **15** (900 mg, 2.90 mmol) with 2-(chloromethyl)quinoline hydrochloride (869 mg, 4.06 mmol) using cesium carbonate (1.89 g, 5.80 mmol) yielded 1.05 g (72%) of **16a** as off-white solid. Mp 188–190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (s, 2H), 6.93–7.02 (m, 4H), 7.12 (d, J = 8.4 Hz, 2H), 7.38–7.42 (m, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.45 (s, 1H), 9.41 (s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{18}FN_3O_3$: 452.1405; found: 452.1407.

6-(4-Fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-3-amine (16b). To a stirred solution of nitropyridine **16a** (600 mg, 1.33 mmol) in ethanol (15 mL) was added a solution of ammonium chloride (720 mg, 13.46 mmol) in water (7 mL) and the mixture was heated to reflux. Iron powder (220 mg, 3.92 mmol) was portion wise added to the mixture at reflux temperature and further stirred at the same temperature for 30 min. The mixture was filtered

through celite and washed with ethanol (10 mL). The filtrate was concentrated under reduced pressure and the residue thus obtained was diluted with water (100 mL) and ethyl acetate (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with water (2 x 100 mL) and dried over anhydrous Na_2SO_4. The solvent was distilled off under reduced pressure and the residue obtained was purified by flash silica gel column chromatography using 30% ethyl acetate in petroleum ether to yield 443 mg (79%) of the product as pale yellow solid. Mp 150–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (br s, 2H), 5.37 (s, 2H), 6.83–7.00 (m, 5H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.21–7.27 (m, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.14 (br s, 1H), 8.21 (d, *J* = 8.7 Hz, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{20}FN_3O$: 422.1663; found: 422.1665.

6-(4-Fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-3-ol (17a). A solution of sodium nitrite (50 mg, 0.72 mmol) in water (1.0 mL) was drop wise added to a stirred and cooled (0 °C) solution of **16b** (200 mg, 0.47 mmol) in 50 % aqueous sulfuric acid (5 mL). The reaction mixture was stirred for 10 min at the same temperature. The mixture was then diluted with ice-cold water (20 mL) and neutralized with solid sodium bicarbonate. The mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The compound was concentrated under reduced pressure and the crude material thus obtained was purified by column chromatography using 30% ethyl acetate in petroleum ether to yield 77 mg (38%) of the product as off-white solid. Mp 175–176 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.35 (s, 2H), 7.00–7.11 (m, 7H), 7.18–7.24 (m, 2H), 7.60–7.69 (m, 2H), 7.79 (t, *J* = 7.2 Hz, 1H), 8.01 (br s, 2H), 8.18 (s, 1H), 8.43 (d, *J* = 8.1 Hz, 1H), 10.13 (br s, 1H); IR (KBr, cm^{-1}): 3444, 2924, 1604, 1513, 1444, 1227, 1179, 831; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{20}FN_2O_2$: 423.1503; found: 423.1517.

2-({4-[5-Fluoro-2-(4-fluorophenyl)pyridin-3-yl]phenoxy}methyl)quinoline (17b). Diazotization of amine **16b** (200 mg, 0.47 mmol) using *tert*-butyl nitrite (0.2 mL, 1.68 mmol) and tetrafluoroboric acid (60 μL, 0.95 mmol) as described in the case of **7b** afforded 59 mg (29%) of **17b** as a white solid. Mp 142–143 °C; ^{1}H NMR (DMSO-d_6) δ 5.37 (s, 2H), 7.02–7.07 (m, 3H), 7.09–7.16 (m, 3H), 7.23–7.32 (m, 2H), 7.60–7.68 (m, 2H), 7.75–7.81 (m, 2H), 7.96–8.03 (m, 2H), 8.43 (d, J = 8.4 Hz, 1H), 8.63 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{19}F_2N_2O$: 425.1460; found: 425.1472.

6-Phenyl-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18a). Compound **18a** was prepared by diazotization of aminopyridine **6a** (400 mg, 0.99 mmol) using sodium nitrite (685 mg, 9.92 mmol) and 50% aq. sulfuric acid (5.0 mL) followed by in-situ hydrolysis of the diazonium salt as described in the case of **17a**. The residue obtained after work up was purified by silica gel column chromatography using 1% methanol in chloroform to afford 325 mg (81%) of the pyridone derivative as an off-white solid. Mp 239–241 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.30 (s, 2H), 6.41 (d, J = 7.8 Hz, 1H), 6.85–6.98 (m, 4H), 7.17–7.35 (m, 5H), 7.50 (d, J = 8.7 Hz, 1H), 7.55–7.69 (m, 2H), 7.70–7.85 (m, 1H), 7.92–8.03 (m, 2H), 8.40 (d, J = 8.4 Hz, 1H), 11.75 (br s, 1H); IR (KBr, cm^{-1}): 3413, 2757, 1658, 1609, 1512, 1242, 1185, 828; HRMS (ESI) calcd for $C_{27}H_{21}N_2O_2$, $[M+H]^+$, 405.1597; found, 405.1600.

6-(4-Fluorophenyl)-5-[4-quinolin-2-ylmethoxy)phenyl]pyridine-2(1*H*)-one (18b). Diazotization of aminopyridine **6b** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18b** (75%) as an off-white solid. Mp 226–228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.31 (s, 2H), 6.43 (d, J = 9.3 Hz, 1H), 6.85–6.98 (m, 4H), 7.12 (t, J = 8.7 Hz, 2H), 7.20–7.30 (m, 2H), 7.50 (d, J = 9.3 Hz, 1H), 7.57–7.67 (m, 2H), 7.78 (t, J = 7.2 Hz,

1H), 7.98–8.01 (m, 2H), 8.41 (d, J = 7.2 Hz, 1H), 11.79 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 70.7, 79.1, 114.6 (2C), 115.0 (d, J = 20.6 Hz, 2C), 117.3, 118.3, 119.6 (2C), 126.5, 127.1, 127.9, 128.5, 129.8, 130.5, 131.1, 131.9 (d, J = 9.15 Hz, 2C), 137.0, 143.4, 144.3, 146.9, 156.8, 157.4, 162.0 (d, J = 245.1 Hz, 1C), 162.2; IR (KBr, cm^{-1}): 3409, 2855, 1651, 1511, 1247, 1184, 1042, 826; HRMS (ESI) calcd for $C_{27}H_{19F}N_2O_2$, $[M+H]^+$, 423.1503; found, 423.1508.

6-(4-Chlorophenyl)-5-[4-quinolin-2-ylmethoxy)phenyl]pyridine-2(1*H*)-one (18c). Diazotization of aminopyridine **6c** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18c** (78%) as an off-white solid. Mp 224–226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.32 (s, 2H), 6.45 (d, J = 9.3 Hz, 1H), 6.93–6.99 (m, 4H), 7.22 (d, J = 8.1 HZ, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.7 Hz, 1H), 7.57–7.68 (m, 2H), 7.78 (t, J = 7.2 Hz, 1H), 7.99–8.01 (m, 2H), 8.42 (d, J = 8.1 Hz, 1H), 11.81 (br s, 1H); IR (KBr, cm^{-1}): 3398, 2852, 1652, 1510, 1457, 1221, 1176, 822; HRMS (ESI) calcd for $C_{27}H_{20}ClN_2O_2$, $[M+H]^+$, 439.1207; found, 439.1214.

6-(2-Fluorophenyl)-5-[(4-quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18d). Diazotization of 6-(2-fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine **(6d)** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18d** (75%) as an off-white solid. Mp 227–229 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.28 (s, 2H), 6.48 (br s, 1H), 6.87–6.95 (m, 4H), 7.10–7.20 (m, 2H), 7.26 (br s, 1H), 7.38 (br s, 1H), 7.53–7.64 (m, 3H), 7.76–7.81 (m, 1H), 7.99 (d, J = 7.5 Hz, 2H), 8.40 (d, J = 7.8 Hz, 1H), 11.89 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{20}FN_2O_2$: 423.1503; found: 423.1502.

6-(3-Fluorophenyl)-5-[(4-quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18e). Diazotization of 6-(3-fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine **(6e)**

followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18e** (77%) as an off-white solid. Mp 231–233 °C; ^{1}H NMR (DMSO-d_6) δ 5.31 (s, 2H), 6.46 (d, J = 8.1 Hz, 1H), 6.95–7.01 (m, 5H), 7.08–7.17 (m, 2H), 7.25–7.30 (m, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.60–7.66 (m, 2H), 7.78 (t, J = 7.8 Hz, 1H), 8.00 (d, J = 7.2 Hz, 2H), 8.40 (d, J = 8.4 Hz, 1H), 11.80 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{20}FN_2O_2$: 423.1503; found: 423.1503.

6-(2,4-Difluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18f). Diazotization of 6-(2,4-difluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine **(6f)** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18f** (80%) as an off-white solid. Mp 244–246 °C; ^{1}H NMR (DMSO-d_6) δ 5.28 (s, 2H), 6.52 (d, J = 7.5 Hz, 1H), 6.91–7.00 (m, 4H), 7.04 (t, J = 7.8 Hz, 1H), 7.20 (t, J = 8.7 Hz, 1H), 7.29–7.37 (m, 1H), 7.50–7.64 (m, 3H), 7.76 (t, J = 7.8 Hz, 1H), 7.96 (d, J = 7.5 Hz, 2H), 8.38 (d, J = 8.7 Hz, 1H), 11.90 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{19}F_2N_2O_2$: 441.1409; found: 441.1418.

6-(2-Methylphenyl)-5-[(4-quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18g). Diazotization of 5-[4-(quinolin-2-ylmethoxy)phenyl]-6-(o-tolyl)pyridin-2-amine **6g** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18g** (76%) as an off-white solid. Mp 241–242 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.00 (s, 3H), 5.26 (s, 2H), 6.40 (d, J = 9.3 Hz, 1H), 6.87 (dd, J = 8.7, 16.2 Hz, 4H), 7.11–7.22 (m, 3H), 7.23 (br s, 1H), 7.53 (d, J = 9.6 Hz, 1H), 7.58–7.63 (m, 2H), 7.77 (t, J = 7.2 Hz, 1H), 7.99 (d, J = 8.1 Hz, 2H), 8.39 (d, J = 8.7 Hz, 1H), 11.70 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{23}N_2O_2$: 419.1754; found: 419.1764.

6-(4-Methylphenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18h). Diazotization of 5-[4-(quinolin-2-ylmethoxy)phenyl]-6-(p-tolyl)pyridin-2-amine **6h** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18h** (81%) as an off-white solid. Mp 200–202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 5.34 (s, 2H), 6.56 (d, *J* = 9.3 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.09 (s, 4H), 7.47–7.58 (m, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 8.20 (d, *J* = 8.7 Hz, 1H), 9.61 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{23}N_2O_2$: 419.1754; found: 419.1752.

5-[4-(Quinolin-2-ylmethoxy)phenyl]-6-[4-(trifluoromethyl)phenyl]pyridin-2(1*H*)-one (18i). Diazotization of 5-[4-(quinolin-2-ylmethoxy)phenyl]-6-[4-(trifluoromethyl)phenyl]pyridin-2-amine **6i** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18i** (77%) as an off-white solid. Mp 224–226 °C; ^{1}H NMR (DMSO-d_6) δ 5.31 (s, 2H), 6.51 (d, *J* = 8.7 Hz, 1H), 6.92–7.00 (m, 4H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.54–7.66 (m, 5H), 7.78 (t, *J* = 8.7 Hz, 1H), 7.97–8.01 (m, 2H), 8.40 (d, *J* = 9.0 Hz, 1H), 11.80 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{20}FN_2O_2$: 473.1471; found: 473.1483.

6-(4-Methoxyphenyl)-5-[(4-quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18j). Diazotization of 6-(4-methoxyphenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine **6j** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18j** (84%) as an off-white solid. Mp 244–246 °C; ^{1}H NMR (DMSO-d_6) δ 3.72 (s, 3H), 5.30 (s, 2H), 6.36 (d, *J* = 9.3 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 2H), 6.94 (br s, 4H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 9.3 Hz, 1H), 7.58–7.66 (m, 2H), 7.78 (t, *J* = 8.1 Hz, 1H), 8.01 (br s, 2H), 8.40 (d, *J* = 8.4 Hz, 1H), 11.65 (br s, 1H); IR (KBr, cm^{-1}): 3432, 2839, 1651, 1608, 1509, 1256, 1181, 824; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{23}N_2O_3$: 435.1703; found: 435.1706.

3-[4-(Quinolin-2-ylmethoxy)phenyl]-2,3'-bipyridin-6(1*H*)-one (18k). Diazotization of 3-[4-(quinolin-2-ylmethoxy)phenyl]-[2,3'-bipyridin]-6-amine **6k** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18k** (77%) as an off-white solid. Mp 186–188 °C; ^{1}H NMR (DMSO-d_6) δ 5.31 (s, 2H), 6.49 (d, J = 8.7 Hz, 1H), 6.91–7.00 (m, 4H), 7.27–7.35 (m, 1H), 7.53–7.66 (m, 4H), 7.78 (t, J = 7.8 Hz, 1H), 7.99 (d, J = 7.5 Hz, 2H), 8.36–8.48 (m, 3H), 11.90 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{19}N_3O_2$: 406.1550; found: 406.1554.

3-[4-(Quinolin-2-ylmethoxy)phenyl]-2,4'-bipyridin-6(1*H*)-one (18l). Diazotization of 3-[4-(quinolin-2-ylmethoxy)phenyl]-[2,4'-bipyridin]-6-amine **6l** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18l** (82%) as an off-white solid. Mp 236–238 °C; ^{1}H NMR (DMSO-d_6) δ 5.33 (s, 2H), 6.95–7.03 (m, 4H), 7.29 (br s, 2H), 7.60–7.67 (m, 4H), 7.79 (t, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 8.42 (d, J = 8.4 Hz, 1H), 8.54 (br s, 2H), 11.73 (br s, 1H); IR (KBr, cm^{-1}): 3422, 2758, 1651, 1591, 1510, 1458, 1245, 1177, 828; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{20}N_3O_2$: 406.1550; found: 406.1547.

5-[4-(Naphthalen-2-ylmethoxy)phenyl]-6-phenylpyridin-2(1*H*)-one (18m). Diazotization of 5-[4-(naphthalen-2-ylmethoxy)phenyl]-6-phenylpyridin-2-amine **6m** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18m** (84%) as an off-white solid. Mp 280–282 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (s, 2H), 6.59 (d, J = 9.3 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 7.18–7.27 (m, 3H), 7.23–7.33 (m, 3H), 7.47–7.56 (m, 4H), 7.79–7.90 (m, 3H), 9.47 (br s, 1H); IR (KBr, cm^{-1}): 3421, 2852, 1659, 1609, 1512, 1458, 1235, 1188, 828; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{22}NO_2$: 404.1645; found: 404.1643.

5-[4-(1,5-Naphthyridin-2-ylmethoxy)phenyl]-6-phenylpyridin-2(1*H*)-one (18n). Diazotization of 5-{4-[(1,5-naphthyridin-2-yl)methoxy]phenyl}-6-phenylpyridin-2-amine **6n** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18n** (85%) as an off-white solid. Mp 236–238 °C; ^{1}H NMR (DMSO-d_6) δ 5.35 (s, 2H), 6.41 (d, J = 9.3 Hz, 1H), 6.85–6.99 (m, 4H), 7.17–7.25 (m, 2H), 7.24–7.32 (m, 3H), 7.50 (d, J = 9.3 Hz, 1H), 7.79–7.83 (m, 1H), 7.89 (d, J = 9.0 Hz, 1H), 8.40–8.50 (m, 2H), 9.00 (br s, 1H), 11.76 (br s, 1H); IR (KBr, cm^{-1}): 3422, 2923, 1657, 1614, 1510, 1242, 823; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{20}N_3O_2$: 406.1550; found: 406.1555.

6-(4-Fluorophenyl)-5-[4-(1,5-naphthyridin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18o). Diazotization of 5-{4-[(1,5-naphthyridin-2-yl)methoxy]phenyl}-6-(4-fluorophenyl)pyridin-2-amine **6o** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18o** (84%) as an off-white solid. Mp 234–236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.36 (s, 2H), 6.43 (d, J = 9.0 Hz, 1H), 6.92–6.98 (m, 4H), 7.09–7.15 (m, 2H), 7.22–7.27 (m, 2H), 7.51 (d, J = 9.3 Hz, 1H), 7.79–7.84 (m, 1H), 7.89 (d, J = 8.7 Hz, 1H), 8.41–8.49 (m, 2H), 9.00 (br s, 1H), 11.76 (br s, 1H); IR (KBr, cm^{-1}): 3421, 2865, 1651, 1607, 1511, 1245, 1183, 829; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{19}FN_3O_2$: 424.1455; found: 424.1469.

6-(4-Chlorophenyl)-5-[4-(pyridin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18p). Diazotization of 6-(4-chlorophenyl)-5-[4-(pyridin-2-ylmethoxy)phenyl]pyridin-2-amine **6p** followed by hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18p** (77%) as off-white solid. Mp 237–239 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.12 (s, 2H), 6.46 (d, J = 9.3 Hz, 1H), 6.93 (dd, J = 8.4, 13.5 Hz, 4H), 7.22 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 6.0 Hz, 3H),

7.50 (t, *J* = 9.3 Hz, 2H), 7.82 (t, *J* = 7.2 Hz, 1H), 8.51–8.57 (m, 1H), 11.75 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}ClN_2O_2$: 389.1051; found: 389.1049.

5-[4-(1,3-Benzothiazol-2-ylmethoxy)phenyl]-6-(4-fluorophenyl)pyridin-2(1*H*)-one (18q). Diazotization of 5-[4-(1,3-benzothiazol-2-ylmethoxy)phenyl]-6-(4-fluorophenyl)pyridin-2-amine **6q** followed by *in-situ* hydrolysis of the diazonium salt as described for **18a** gave the pyridone **18q** (82%) as an off-white solid. Mp 238–240 °C; ^{1}H NMR (DMSO-d_6) δ 5.55 (s, 2H), 6.44 (d, *J* = 9.3 Hz, 1H), 6.93–7.01 (m, 4H), 7.11 (d, *J* = 8.7 Hz, 2H), 7.20–7.30 (m, 2H), 7.42–7.58 (m, 3H), 8.00 (d, *J* = 9.0 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 11.80 (s, 1H); IR (KBr, cm^{-1}): 3422, 2850, 1651, 1607, 1508, 1452, 1240, 1176, 838; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{17}FN_2O_2S$: 429.1067; found: 429.1072

6-Phenyl-5-[4-(1*H*-pyrrolo[3,2-*b*]pyridin-5-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18r). Coupling reaction of phenol **4a** (600 mg, 1.314 mmol) with (1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl)methyl 4-methylbenzenesulfonate **5f** (307 mg, 0.91 mmol) in the presence of cesium carbonate (641 mg, 1.97 mmol) in DMF (20 mL) at room temperature overnight gave 280 mg of 6-phenyl-5-{4-[(1-tosyl-1*H*-pyrrolo[3,2-b]pyridin-5-yl)methoxy]phenyl}pyridin-2-amine **6r**. Intermediate **6r** on diazotization and *in-situ* hydrolysis of the diazonium salt as described in the case of **18a** gave the corresponding pyridone intermediate as an off-white solid (80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.54 (br s, 2H), 5.19 (s, 2H), 6.54 (d, *J* = 8.4 Hz, 1H), 6.85 (br s, 3H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.21–7.29 (m, 5H), 7.47 (d, *J* = 8.4 Hz, 3H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.81 (br s, 2H), 8.27 (d, *J* = 8.1 Hz, 1H).

To a stirred solution of the above *N*-tosyl intermediate (145 mg, 0.264 mmol) in methanol (10 mL) was added 2.0 M sodium hydroxide (2.0 mL) and the reaction mixture was stirred at room temperature for 30 min. Methanol was evaporated under reduced pressure and the residue thus

obtained was diluted with water (20 mL). The mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were washed with water (50 mL) and dried over anhydrous Na_2SO_4. The residue obtained after evaporation of solvent was purified by flash silica gel column chromatography using 3% methanol in chloroform to yield 86 mg (82%) of **18r** as an off-white solid. Mp > 250 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (s, 2H), 6.59 (d, *J* = 9.3 Hz, 1H), 6.73–6.80 (m, 1H), 6.88 (dd, *J* = 8.4, 15.0 Hz, 4H), 7.18–7.23 (m, 3H), 7.30–7.36 (m, 3H), 7.50 (br s, 2H), 7.71 (d, *J* = 8.1 Hz, 1H), 11.36 (br s, 1H) 11.75 (br s, 1H); IR (KBr, cm^{-1}): 3421, 2853, 1655, 1609, 1509, 1235, 1179, 829; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{19}N_3O_2$: 394.1550; found: 394.1544.

6-(4-Fluorophenyl)-5-[4-(1*H*-pyrrolo[3,2-*b*]pyridin-5-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18s). The coupling reaction of phenol **4b** with di-tosylate **5f** afforded aminopyridine **6s** which on subsequent diazotization and deprotection as described in the case of **18r** afforded the pyridone **18s** (79%) as an off-white solid. Mp 264–266 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.14 (s, 2H), 6.43 (d, *J* = 9.3 Hz, 1H), 6.53 (s, 1H), 6.87–6.95 (m, 4H), 7.13 (t, *J* = 8.7 Hz, 2H), 7.21–7.27 (m, 3H), 7.50 (d, *J* = 9.3 Hz, 1H), 7.65 (br s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 11.35 (s, 1H), 11.79 (br s, 1H); IR (KBr, cm^{-1}): 3414, 2866, 1654, 1607, 1508, 1222, 1180, 825; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{19}FN_3O_2$: 412.1455; found: 412.1451.

6-(4-Chlorophenyl)-5-[4-(1*H*-pyrrolo[3,2-*b*]pyridin-5-ylmethoxy)phenyl]pyridin-2(1*H*)-one (18t). The coupling reaction of phenol **4c** with di-tosylate **5f** afforded aminopyridine **6t** which on subsequent diazotization and deprotection as described in the case of **18r** afforded pyridone **18t** (76%) as an off-white solid. Mp 257–258 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.15 (s, 2H), 6.40–6.55 (m, 1H), 6.59 (s, 1H), 6.90–6.96 (m, 4H), 7.23 (d, *J* = 8.4 Hz, 3H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.66 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 11.36 (s, 1H), 11.81 (br s,

1H); IR (KBr, cm^{-1}): 3420, 2924, 1655, 1609, 1510, 1221, 1177, 825; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{19}ClN_3O_2$: 428.1160; found: 428.1162.

3-[4-(1*H*-Pyrrolo[3,2-*b*]pyridin-5-ylmethoxy)phenyl]-2,4'-bipyridin-6(1*H*)-one (18u). The coupling reaction of phenol **4k** with di-tosylate **5f** afforded aminopyridine **6u** which on subsequent diazotization and deprotection as described in the case of **18r** afforded the pyridone **18u** (76%) as an off-white solid. Mp 176–178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.15 (s, 2H), 6.53 (br s, 2H), 6.94 (dd, *J* = 8.4, 18.9 Hz, 4H), 7.20–7.24 (m, 3H), 7.56 (d, *J* = 9.3 Hz, 1H), 7.65 (br s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 8.45–8.50 (m, 2H), 11.34 (br s, 1H), 11.75 (br s, 1H); IR (KBr, cm^{-1}): 3420, 2924, 1651, 1613, 1510, 1412, 1237, 1177, 829; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}N_4O_2$: 395.1502; found: 395.1498.

6-(4-Fluorophenyl)-5-[4-(1-methyl-1*H*-pyrrolo[3,2-b]pyridin-5-ylmethoxy)phenyl] pyridin-2(1*H*)-one (18v). Coupling reaction of phenol **4b** (623 mg, 2.14 mmol) with (1-methyl-1*H*-pyrrolo[3,2-b]pyridin-5-yl)methyl 4-methylbenzenesulfonate **5g** (880 mg, 2.78 mmol) in the presence of cesium carbonate (1.8 g, 5.52 mmol) in DMF (20 mL) overnight at room temperature gave 296 mg (31.3%) of 6-(4-fluorophenyl)-5-{4-[(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl)methoxy]phenyl}pyridin-2-amine **6v**. Diazotization of **6v** followed by *in-situ* hydrolysis of the diazonium salt as described in the case of **18a** gave the pyridone **18v** (85%) as an off-white solid. Mp 260–262 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 5.15 (s, 2H), 6.43 (d, *J* = 9.3 Hz, 1H), 6.52 (br s, 1H), 6.87–6.95 (m, 4H), 7.12 (t, *J* = 8.7 Hz, 2H), 7.25 (t, *J* = 8.4 Hz, 3H), 7.50 (d, *J* = 9.3 Hz, 1H), 7.63 (br s, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 11.79 (br s, 1H); IR (KBr, cm^{-1}): 3399, 2919, 1651, 1610, 1508, 1236, 1176, 844; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}FN_3O_2$: 426.1612; found: 426.1609.

6-(4-Chlorophenyl)-5-[4-(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-5-ylmethoxy)phenyl] pyridin-2(1*H*)-one (18w). The coupling reaction of phenol **4c** with tosylate **5g** afforded aminopyridine **6w** which on subsequent diazotization followed by *in-situ* hydrolysis of the diazonium salt afforded the pyridone **18w** (77%) as an off-white solid. Mp 206–208 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.80 (s, 3H), 5.15 (s, 2H), 6.43 (d, J = 9.3 Hz, 1H), 6.52 (br s, 1H), 6.86–6.94 (m, 4H), 7.20 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.7 Hz, 1H), 7.63 (br s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 11.78 (br s, 1H); IR (KBr, cm^{-1}): 3429, 2863, 1645, 1598, 1511, 1236, 1093, 830; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}ClN_3O_2$: 442.1316; found: 442.1313.

3-{4-[(1-Methyl-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl)methoxy]phenyl}-2,4'-bipyridin-6(1*H*)-one (18x). The coupling reaction of phenol **4k** with tosylate **5g** afforded aminopyridine **6x** which on subsequent diazotization followed by *in-situ* hydrolysis of the diazonium salt afforded the pyridone **18x** (79%) as an off-white solid. Mp 250–252 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.81 (s, 3H), 5.16 (s, 2H), 6.53 (br s, 2H), 6.90–6.98 (m, 4H), 7.21 (br s, 2H), 7.27 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.64 (br s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 8.49 (br s, 2H), 11.38 (br s, 1H); IR (KBr, cm^{-1}): 3424, 2852, 1651, 1588, 1509, 1236, 1024, 828; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{20}N_4O_2$: 409.1659; found: 409.1662.

2-({4-[2-(4-Fluorophenyl)-6-methoxypyridin-3-yl]phenoxy}methyl)quinoline (19) and **6-(4-fluorophenyl)-1-methyl-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (20).** To a stirred solution of pyridone **18b** (200 mg, 0.47 mmol) in DMF (3 mL) was added potassium carbonate (100 mg, 0.72 mmol) followed by methyl iodide (0.04 mL, 0.64 mmol) and the reaction mixture was stirred overnight at room temperature. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were

washed with water (50 mL) and dried over anhydrous Na_2SO_4. The solvent was distilled off under reduced pressure and the residue thus obtained was purified by flash silica gel column chromatography using 30% ethyl acetate in petroleum ether to yield 91 mg (44%) of ether **19** as an off-white solid. Mp 158–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (s, 3H), 5.37 (s, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.87–6.92 (m, 4H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.37 (t, *J* = 6.0 Hz, 2H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.66–7.74 (m, 2H), 7.84 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H); IR (KBr, cm^{-1}): 2850, 1602, 1587, 1475, 1286, 1248, 1016, 820; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{22}FN_2O_2$: 437.1659; found: 437.1670. Further elution using the same solvent mixture afforded 105 mg (51%) of pyridone **20** as an off-white solid. Mp 180–181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31 (s, 3H), 5.30 (s, 2H), 6.68 (d, *J* = 9.0 Hz, 1H), 6.78–6.84 (m, 4H), 6.98–7.04 (m, 2H), 7.07–7.12 (m, 2H), 7.40 (d, *J* = 9.3 Hz, 1H), 7.53–7.62 (m, 2H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 8.18 (d, *J* = 9.0 Hz, 1H); IR (KBr, cm^{-1}): 2922, 1665, 1608, 1501, 1426, 1243, 1159, 839; HRMS (ESI) calcd for $C_{28}H_{22}FN_2O_2$, $[M+H]^+$, 437.1659; found, 437.1670.

6-(4-Methoxyphenyl)-5-phenylpyridin-2-amine (21a). Suzuki coupling reaction of 5,6-dibromopyridin-2-amine **1** (5.0 g, 19.84 mmol) with 4-methoxyphenylboronic acid (3.0 g, 19.84 mmol) using tetrakis(triphenylphosphine) palladium(0) (0.681 g, 0.589 mmol) in the presence of sodium carbonate (4.20 g, 39.62 mmol) in a mixture of toluene (60 mL) and methanol (10 mL) as described in the procedure for **2a** gave 4.89 g (83%) of 5-bromo-6-(4-methoxyphenyl)pyridin-2-amine as pale yellow solid. Mp 145–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.51 (br s, 2H), 6.34 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.59–7.69 (m, 3H); APCI-MS (*m/z*) 279, 281 $(M+H)^+$.

5-Bromo-6-(4-methoxyphenyl)pyridin-2-amine (2.0 g, 7.16 mmol) on second Suzuki coupling reaction with phenyl boronic acid (873 mg, 7.15 mmol) using tetrakis(triphenylphosphine)

palladium(0) (248 mg, 0.21 mmol) in the presence of cesium carbonate (4.66 g, 14.30 mmol) in dioxane (25 mL) gave 1.88 g (95%) of **21a** as white solid. Mp 174–175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.70 (s, 3H), 6.05 (br s, 2H), 6.47 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 6.9 Hz, 2H), 7.14–7.23 (m, 5H), 7.38 (d, J = 8.4 Hz, 1H); APCI-MS (*m/z*) 277 $(M+H)^+$.

Intermediates **21b–d** were prepared from 5,6-dibromopyridin-2-amine and appropriate boronic acids by two consecutive Suzuki coupling reaction as described above and the analytical data is given in supporting information.

4-(6-Amino-3-phenylpyridin-2-yl)phenol (22a). Demethylation of **21a** (1.8 g, 6.51 mmol) using BBr_3 (1.6 ml, 16.86 mmol) as described in the case of **15** afforded 1.39 g (81%) of **22a** as an off-white solid. Mp 202–204 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.73 (d, J = 7.5 Hz, 2H), 6.83–6.98 (m, 1H), 6.99–7.14 (m, 4H), 7.25–7.32 (m, 3H), 7.85–7.93 (m, 1H), 9.95 (br s, 2H), 13.34 (br s, 1H); APCI-MS (*m/z*) 263 $(M+H)^+$.

Intermediates **22b–d** were prepared by demethylation of intermediate **21b-d** as described above. The spectral data of these compounds is given in the supporting information.

5-Phenyl-6-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine (23a). Alkylation of 4-(6-amino-3-phenylpyridin-2-yl)phenol **20a** (400 mg, 1.52 mmol) with 2-(chloromethyl)quinoline hydrochloride **5a** (370 mg, 1.72 mmol) using potassium carbonate (630 mg, 4.56 mmol) in DMF (15 mL) as described above in procedure for synthesis of **6a** afforded 406 mg (66%) of the title compound as an off-white solid. Mp 168–170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.32 (s, 2H), 6.05 (br s, 2H), 6.47 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 9.0 Hz, 2H), 7.06 (d, J = 7.5 Hz, 2H),

7.14–7.21 (m, 5H), 7.38 (d, J = 9.0 Hz, 1H), 7.61–7.66 (m, 2H), 7.78 (t, J = 8.1 Hz, 1H), 8.00 (br s, 2H), 8.40 (d, J = 8.7 Hz, 1H); APCI-MS (*m/z*) 404 $(M+H)^+$.

Intermediates **23b–d** were prepared as described above by alkylation of the coresponding phenols **22b–d** with 2-(chloromethyl)quinoline **5a** and the analytical data of these compounds is given in supporting information.

5-Phenyl-6-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (24a). Diazotization of 5-phenyl-6-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-amine **23a** (120 mg, 0.297 mmol) followed by *in-situ* hydrolysis of the diazonium salt as described in the typical procedure for **18a** gave 88 mg (73%) of pyridone **24a** as an off-white solid. Mp 226–228 °C; ^{1}H NMR (DMSO-d_6) δ 5.34 (s, 2H), 6.39 (d, J = 9.3 Hz, 1H), 6.96–7.03 (m, 4H), 7.12–7.20 (m, 5H), 7.50 (d, J = 9.3 Hz, 1H), 7.60–7.65 (m, 2H), 7.79 (t, J = 7.2 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 8.42 (d, J = 8.1 Hz, 1H), 11.70 (br s, 1H); IR (KBr, cm^{-1}): 2922, 1665, 1608, 1501, 1426, 1243, 1159, 839; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{21}N_2O_2$: 405.1597; found: 405.1593.

Pyridones **24b–d** were prepared by diazotization and *in situ* hydrolysis of apprpriate amine intermediate as described above.

5-(4-Fluorophenyl)-6-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2(1*H*)-one (24b).

Yield: 75%; off-white solid. Mp 202–204 °C; ^{1}H NMR (DMSO-d_6) δ 5.35 (s, 2H), 6.39 (d, J = 8.7 Hz, 1H), 6.98–7.05 (m, 6H), 7.14 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 9.3 Hz, 1H), 7.60–7.67 (m, 2H), 7.79 (t, J = 8.1 Hz, 1H), 8.00 (d, J = 7.5 Hz, 2H), 8.42 (d, J = 8.1 Hz, 1H), 11.73 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{20}FN_2O_2$: 423.1503; found: 423.1498.

6-[4-(Quinolin-2-ylmethoxy)phenyl]-5-[4-(trifluoromethyl)phenyl]pyridin-2(1*H*)-one (24c). Yield: 70%; off-white solid. Mp 267–269 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.36 (s, 2H), 6.43 (d, J = 9.3 Hz, 1H), 7.01 (d, J = 8.7 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 7.54–7.67 (m, 5H), 7.78 (t, J = 7.8 Hz, 1H), 7.97–8.02 (m, 2H), 8.41 (d, J = 8.7 Hz, 1H), 11.82 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{20}F_3N_2O_2$: 473.1471; found, 473.1473.

2-[4-(Quinolin-2-ylmethoxy)phenyl]-3,4'-bipyridin-6(1*H*)-one (24d).

Yield: 67%; off-white solid; mp 235–236 °C; ^{1}H NMR (DMSO-d_6) δ 5.38 (s, 2H), 6.47 (d, J = 9.3 Hz, 1H), 7.05 (d, J = 9.0 Hz, 2H), 7.17–7.22 (m, 4H), 7.60–7.68 (m, 3H), 7.79 (t, J = 7.5 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 8.32–8.46 (m, 3H), 12.01 (br s, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{20}N_3O_2$: 406.1550; found: 406.1549.

6-Phenyl-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-yl acetate (25a); **Typical procedure.** To a stirred solution of pyridone **18a** (100 mg, 0.25 mmol) in dry tetrahydrofuran (10 mL) was added triethylamine (140 µL, 1.0 mmol) followed by acetic anhydride (70 µL, 0.74 mmol) and the reaction mixture was stirred overnight at room temperature. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with water (20 mL) and dried over anhydrous Na_2SO_4. The residue obtained after evaporation of solvent was purified by flash silica gel column chromatography using 30% ethyl acetate in petroleum ether to yield 98 mg (88%) of acetate **25a** as an off-white solid. Mp 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 5.36 (s, 2H), 6.93 (d, J = 8.4 Hz, 2H), 7.06–7.11 (m, 3H), 7.27–7.32 (m, 5H), 7.56 (t, J = 7.8 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.72–7.79 (m, 2H), 7.84 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 8.20 (d, J = 8.7 Hz, 1H); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{22}N_2O_3$: 447.1703; found: 447.1705.

6-(4-Fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-yl acetate (25b). Acetylation of pyridone **18b** (1.0 g, 2.37 mmol) with acetic anhydride (0.7 mL, 7.41 mmol) in the presence of triethylamine (1.3 mL, 9.32 mmol) in dry tetrahydrofuran (10 mL) as described above yielded 934 mg (85%) of acetate **25b** as an off-white solid. Mp 146–148 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.31 (s, 3H), 5.35 (s, 2H), 7.02 (d, J = 8.4 Hz, 2H), 7.11 (t, J = 8.7 Hz, 4H), 7.21–7.29 (m, 3H), 7.58–7.67 (m, 2H), 7.77 (t, J = 7.2 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.80 (br s, 2H), 8.41 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.3, 71.3, 115.3 (d, J = 21.0 Hz, 2C), 115.7 (2C), 120.1, 127.1, 127.6, 128.4, 129.0, 130.3, 131.1 (2C), 131.4, 132.1 (d, J = 8.0 Hz, 2C), 134.0, 135.7 (2C), 137.5, 143.0, 147.4, 154.2, 156.4, 157.8, 158.0, 162.2 (d, J = 244.0 Hz, 1C), 169.6; IR (KBr, cm^{-1}): 1767, 1608, 1598, 1511, 1449, 1216, 1191, 827; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{22}FN_2O_3$: 465.1609; found: 465.1622.

6-(2,4-Difluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-yl acetate (25c). Acetylation of pyridone **18f** (90 mg, 0.20 mmol) with acetic anhydride (60 µL, 0.63 mmol) in the presence of triethylamine (110 µL, 0.79) in dry tetrahydrofuran (2 mL) as described in the case of **25a** yielded 80 mg (81%) of **25c** as an off white solid. Mp 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 5.36 (s, 2H), 6.62 (t, J = 9.3 Hz, 1H), 6.84–6.93 (m, 3H), 7.05 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.1 Hz, 1H), 7.35–7.43 (m, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.83 (t, J = 7.8 Hz, 2H), 8.07 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H); HRMS (ESI) calcd for $C_{29}H_{20}F_2N_2O_3$, $[M+H]^+$, 483.1514; found, 483.1517.

6-(4-Fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-yl dimethylcarbamate (25d). To a stirred solution of pyridone **18b** (100 mg, 0.24 mmol) in dry THF (5 mL) was added anhydrous potassium carbonate (70 mg, 0.50 mmol) followed by dimethylcarbamoyl chloride (0.03 mL, 0.33 mmol) and the reaction mixture was heated overnight at 70 °C. The mixture was cooled to room temperature and quenched with ice-cold water (30 mL). The mixture was

extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with water (50 mL) and dried over anhydrous Na_2SO_4. The solvent was distilled off under reduced pressure and the residue thus obtained was purified by flash silica gel column chromatography using 22% acetone in petroleum ether to afford 83 mg (71%) of **25d** as an off-white solid. Mp 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (s, 3H), 3.15 (s, 3H), 5.37 (s, 2H), 6.86–6.95 (m, 4H), 7.04–7.11 (m, 3H), 7.29–7.34 (m, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.72–7.77 (m, 2H), 7.84 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H); IR (KBr, cm^{-1}): 3443, 2926, 1715, 1606, 1514, 1390, 1244, 1167, 818; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{25}FN_3O_3$: 494.1874; found: 494.1868.

6-(4-Fluorophenyl)-5-[4-(quinolin-2-ylmethoxy)phenyl]pyridin-2-yl β-D-glucopyranoside (26). To a stirred solution of pyridone **18b** (350 mg, 0.83 mmol) in dichloromethane (10 mL) was added acetobromo-α-D-glucose (682 mg, 1.66 mmol) followed by silver carbonate (343 mg, 1.24 mmol) and the reaction mixture was stirred at room temperature for 3 days in the dark. The mixture was filtered to remove inorganic salts and the filtrate was evapourated under reduced pressure to result a dark residue. The residue was purified by flash silica gel column chromatography using 20% acetone in petroleum ether to yield 380 mg (62%) of tetraacetyl β-D-glucopyranoside derivative as an off-white solid.

To a solution of the above acetate (350 mg, 0.48 mmol) in acetone (10 mL) was added 1*N* sodium hydroxide (7 mL) and the mixture was stirred for 3 h at room temperature. The mixture was diluted with water (20 mL) and the white solid separated out was collected by filtration. Analytically pure material was obtained by further purification by flash silica gel column chromatography using 5% methanol in chloroform to afford 217 mg (78%) of glucuronide **26** as an off-white solid. Mp 156–158 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.16 (d, *J* = 4.8 Hz, 4H), 3.68 (br s, 2H), 4.63 (br s, 1H), 5.02 (d, *J* = 4.8 Hz, 1H), 5.13 (br s, 1H), 5.31 (br s, 1H), 5.36 (s,

2H), 5.75 (br s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 7.01–7.10 (m, 6H), 7.32 (t, J = 6.9 Hz, 2H), 7.60–7.66 (m, 2H), 7.69–7.81 (m, 2H), 8.01 (br s, 2H), 8.43 (d, J = 8.7 Hz, 1H); IR (KBr, cm^{-1}): 3375, 2923, 1599, 1584, 1509, 1457, 1244, 1059, 826; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{30}FN_2O_7$: 585.2031; found: 585.2049.

ASSOCIATED CONTENT

Supporting Information

Characterization data for intermediates **2a**–**l**, **3b**–**l**, **4b**–**l**, **5f**–**g**, **6d**–**x**, **21b–d**, **22b**–**d** and **23b**–**d**, detailed *in vitro* and *in vivo* assay procedures and scanned ^{1}H NMR spectra of selected compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org."

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ABBREVIATIONS USED

SD rats, Sprague Dawley rats, D2 receptor, dopamine 2 receptor; 5-HT2A, 5-hydroxytryptamine (serotonin) receptor 2A; cAMP, 3′,5′-cyclic adenosine monophosphate; cGMP, 3′,5′-cyclic guanosine monophosphate; CNS, central nervous system; BBr_3, boron tribromide ; THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; $POCl_3$, phosphorus

oxychloride; Na_2CO_3, sodium carbonate; SAR, structure–activity relationship; Tyr, tyrosine; NADPH, nicotinamide adenine dinucleotide phosphate; PAMPA, parallel artificial membrane permeability assay; hERG, human ether-a-go-go-related gene; HEK cells, human embryonic kidney cells; tPSA, topological polar surface area; PKDM, Pharmacokinetics and drug metabolism; UDPGA, uridine 5'-diphosphoglucuronic acid; NMP, *N*-methyl-2-pyrrolidone; PEG 200, polyethylene glycol 200; NMDA receptor, N-methyl-D-aspartate receptor; LTD4 receptor, leukotriene D4 receptor; Na_2SO_4, sodium sulphate; h, hours; min, minutes; mp, melting point; NMR, nuclear magnetic resonance; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MW, molecular weight; HPLC, high-performance liquid chromatography; HRMS, high resolution mass spectroscopy; ESI, electrospray ionization; APCI, atmospheric pressure chemical ionization; $[M + H]^+$, protonated mass of the free base of the compound; $CDCl_3$, deuterated chloroform; DMSO-*d*6, deuterated dimethyl sulfoxide.

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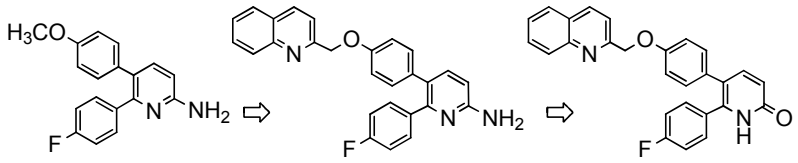

3a inactive **6b** IC_{50}: 2740 nM **8b** IC_{50}: 1.6 nM

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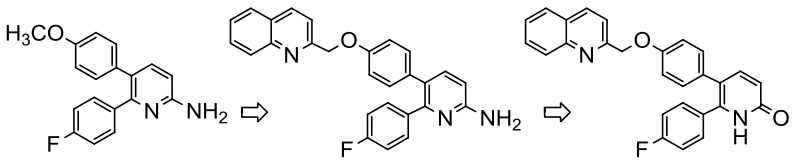

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