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# Synthesis and preliminary biological evaluation of potent and selective 2-(3-alkoxy-1-azetidinyl) quinolines as novel PDE10A inhibitors with improved solubility

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ABSTRACT

We report the discovery of a novel series of 2-(3-alkoxy-1-azetidinyl) quinolines as potent and selective PDE10A inhibitors. Structure–activity studies improved the solubility (pH 7.4) and maintained high PDE10A activity compared to initial lead compound **3**, with select compounds demonstrating good oral bioavailability. X-ray crystallographic studies revealed two distinct binding modes to the catalytic site of the PDE10A enzyme. An ex vivo receptor occupancy assay in rats demonstrated that this series of compounds covered the target within the striatum.



## 1. Introduction

Cyclic nucleotide phosphodiesterases (PDEs) constitute a family of bimetallic hydrolase enzymes that regulate cell signaling mediated by the ubiquitous second messengers, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Specifically, PDEs modulate intracellular levels of cAMP or cGMP by hydrolyzing the 3′—5′ phosphodiester bond producing AMP and GMP, respectively. This 11-membered family of enzymes consists of 21 gene variants that differ in their structure, regulation, localization and substrate specificity.[1] Decreased intracellular cAMP or cGMP levels as a result of upregulation of PDEs have been implicated in various diseases such as cardiovascular disease, neurodegenerative disorders, inflammation and cancer.[2] With the success of PDE5 inhibitors (sildenafil, vardenafil, tadalafil and avanafil) for the treatment of erectile dysfunction and pulmonary hypertension,[3] and the recent approval of the first PDE4 inhibitor (roflumilast) for the treatment of chronic obstructive pulmonary disease, considerable interest has been given to this family of enzymes.

Phosphodiesterase 10A (PDE10A) is predominantly expressed in the medium spiny neurons of the striatum and regulates the intracellular concentrations of both cAMP and cGMP.[4,5] Modulation of neuronal activity through the inhibition of PDE10A effectively increases the striatal levels of both cAMP and cGMP.[6] Due to its localization in the striatum and dual substrate specificity, inhibition of PDE10A activity has recently been the subject of extensive research efforts for the treatment of neurological disorders such as schizophrenia, Parkinson's disease and Huntington's disease.[7] Current antipsychotic agents act as D2 dopamine receptor antagonists that demonstrate effectiveness in treating positive symptoms of schizophrenia (delusions, hallucinations, disorganized behavior and speech) but alone are ineffective in treating negative symptoms (apathy, anhedonia, avolition and social withdrawal)

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0968-0896/

and cognition disorders. In addition, current treatments are associated with common side effects such as diabetes, weight gain, QT prolongation and extrapyramidal syndrome.[8] Preliminary investigations also suggest that activation of the glutamatergic pathway via modulation of NMDA receptor signaling may improve the negative symptoms and cognitive deficits associated with schizophrenia.[9] PDE10A inhibition may treat both positive and negative symptoms and improve cognition in schizophrenic patients by modulating both the dopaminergic and glutamatergic pathways.[10] Notably, selective PDE10A inhibitors have proven effective in several preclinical rodent models of antipsychotic behavior (conditioned avoidance response, phencyclidine- or D-amphetamine-induced hyperactivity), improvement in cognition (prepulse inhibition) and extrapyramidal effects (catalepsy) suggesting PDE10A inhibition as a novel mechanism for the treatment of neurological disorders.[6b]

Recently, we reported our on-going efforts to develop a PDE10A inhibitor for the treatment of schizophrenia.[11,12] Our initial efforts focused on a series of novel cinnoline analogs **1** and **2** (Fig. 1). Although this series showed excellent PDE10A potency and good PDE3 selectivity (>300×) we hypothesized a greater selectivity profile was required to avoid potential cardiovascular side effects.[13] X-ray crystallographic data revealed that compound **1** does not access the Q2 selectivity pocket as defined by residues Met703 and Gly715 and the inability to occupy this pocket may, in fact, be responsible for the modest selectivity profile. We also disclosed the structure activity relationships of a biaryl ether scaffold exemplified by compound **3** as a potent and selective PDE10A inhibitor (>30,000× against PDE3, Fig. 2).[14] Although compound **3** exhibited excellent enzymatic inhibition of PDE10A we hypothesized that its low aqueous solubility would make further development difficult, and could be associated with its high degree of aromaticity. It is well known in the literature that a high degree of aromaticity of a molecule can lead to deleterious effects on aqueous solubility.[15] Given the importance and need to monitor solubility in our SAR efforts, we included solubility assays into our early screening paradigm. Thus, the goal of this investigation was not only to identify a lead molecule with nanomolar PDE10A potency and excellent PDE selectivity but also with improved solubility in comparison to compound **3**. Therefore, our strategy to improve the solubility of our lead molecule **3** was to reduce the degree of aromaticity by replacing an aromatic ring with a saturated heterocycle. In particular, molecular modeling studies suggested an azetidine ring was a viable alternative for the phenyl B-ring by positioning the A- and C-rings in a similar orientation within the PDE10A active site as compound **3**. In this report we describe our synthesis and preliminary biological evaluation of 2-(3-alkoxy-1-azetidinyl) quinolines as novel PDE10A inhibitors for the treatment of schizophrenia (generic structure **4**, Fig. 2).

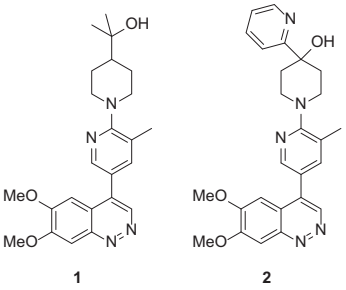



**Figure 1.** Amgen PDE10A inhibitors.

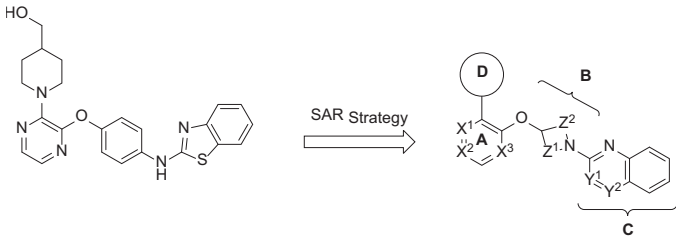



**Figure 2.** PDE10A SAR strategy.

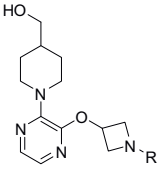
## 2. Results and discussion

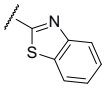
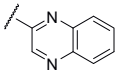
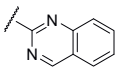
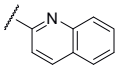
The derivatives prepared in this study were evaluated for their ability to inhibit purified recombinant human PDE10A. In addition, compounds were preliminarily evaluated for aqueous solubility at physiological pH using a phosphate buffered saline (PBS) solubility assay and, for select compounds, in vitro selectivity against other PDE isoforms.

The first compound examined in this study was compound **5** where the aromatic B-ring of compound **3** was replaced with an azetidine moiety. Although compound **5** was 100-fold less potent compared to compound **3**, we were pleased to see it retained significant PDE10A inhibition (Table 1). Our hypothesis of replacing an aromatic ring with an azetidine to improve solubility was realized as compound **5** displayed a 5-fold improvement in solubility. Other analogs containing 6,6-bicyclic aromatic C-rings also proved potent PDE10A inhibitors. Quinoxaline **6** and quinazoline **7** displayed equipotency as PDE10A inhibitors but showed >5-fold improvement in solubility (**6**, **7** vs **5**). The optimal C-ring proved to be quinoline **8** with a 9-fold improvement in potency and a 6-fold improvement in solubility compared to **5**.

With a satisfactory C-ring identified, we continued our SAR investigations with several B-ring modifications of compound **8**. The profiling data for these compounds are reported in Table 2. Expansion of the B-ring to a pyrrolidine proved detrimental.

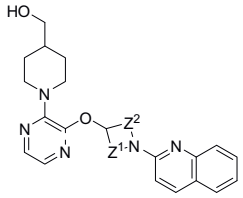
**Table 1**
PDE10A inhibitory activity of C-ring modified analogs




| Compound | R | PDE10A[a] | PBS[b] |
|---|---|---|---|
| **3** | — | 0.2 ± 0.1 | 6 |
| **5** |  | 21 ± 4 | 31 |
| **6** |  | 30 ± 16 | 500 |
| **7** |  | 13 ± 0.9 | 174 |
| **8** |  | 2.4 ± 0.7 | 178 |

[a] $IC_{50}$ values (nM) are the means of at least three independent experiments.
[b] Solubility data reported in μM.

**Table 2**
PDE10A inhibitory activity of B-ring modified analogs



| Compound | $Z^1$ | $Z^2$ | PDE10A[a] | PBS[b] |
|---|---|---|---|---|
| **8** | $CH_2$ | $CH_2$ | 2.4 ± 0.7 | 178 |
| **9** | $CH_2$ | (*R*)-$CH_2CH_2$ | 30 ± 0.4 | 339 |
| **10** | $CH_2$ | (*S*)-$CH_2CH_2$ | 46 ± 3.0 | 315 |
| **11** | $CH_2CH_2$ | $CH_2CH_2$ | 6.5 ± 0.2 | 81 |

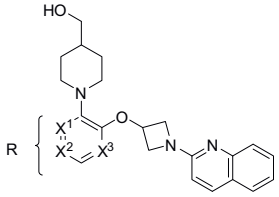
[a] $IC_{50}$ values (nM) are the means of at least three independent experiments.
[b] Solubility data reported in μM.

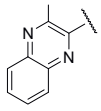
Although compounds **9** and **10** displayed a 2-fold improvement in solubility with respect to compound **8**, the (*R*)- and (*S*)-enantiomers showed a dramatic 13-fold and 19-fold loss in potency (**9**, **10** vs **8**). Further expansion of the B-ring to a six-membered piperidine ring recovered PDE10A potency at the expense of solubility (**11** vs **8**).

As part of our SAR investigation we also studied the effect of the heteroaryl A-ring on PDE10A inhibition and aqueous solubility (Table 3). In our previous study, A-ring modifications had a pronounced effect on PDE10A inhibition.[14] Thus, we investigated the most promising A-rings in this current SAR study. Replacement of a nitrogen atom with a carbon atom gave pyridine **12** with similar PDE10A potency and solubility compared to compound **8**. In contrast, pyridine isomer **13** showed similar PDE10A potency but decreased solubility. Quinoxaline **14** exhibited single digit nanomolar potency but unfortunately, with the larger bicyclic A-ring, exhibited dramatically lower solubility.

A major focus of our SAR investigation was to examine the effect of D-ring analogs and the results for these derivatives are summarized in Tables 4 and 5. We initially examined the effect of saturated, nitrogen-linked D-rings. Extension of the hydroxyl group by a single carbon atom resulted in an 8-fold loss in potency (**15** vs **8**) whereas contracting the hydroxyl group by a single carbon atom decreased potency 23-fold (**16** vs **8**). Contraction of the piperidine ring to the azetidine **17** resulted in a 15-fold loss in potency and 4-fold loss in solubility. A decrease in D-ring size to a five-membered ring resulted in a loss of potency but maintained good solubility (**18** vs **8**). To examine the importance of the hydroxyl group had on potency we replaced the hydroxyl moiety with a methoxy group. Compound **19** exhibited a >60-fold loss in potency and a 3-fold decrease in solubility. Removal of the hydroxyl group entirely resulted in a 13- and 43-fold loss in PDE10A potency and a dramatic loss in solubility (**20**, **21** vs **8**). Interestingly, morpholine **22** displayed equal potency in comparison to compound **20** but the additional oxygen atom markedly improved solubility. Although tertiary amine **23** displayed excellent solubility it was not tolerated in the PDE10A assay exhibiting a >140-fold decrease in potency. In comparison to compound **8**, nitrile **24** and amide **25** showed good in vitro potencies but significantly reduced solubilities.

**Table 3**
PDE10A inhibitory activity of A-ring modified analogs



| Compound | R | PDE10A[a] | PBS[b] |
|---|---|---|---|
| **8** |  | 2.4 ± 0.7 | 178 |
| **12** |  | 1.0 ± 0.2 | 189 |
| **13** |  | 4.7 ± 1.0 | 36 |
| **14** |  | 6.8 ± 0.7 | <1 |

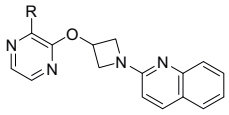
[a] $IC_{50}$ values (nM) are the means of at least three independent experiments.
[b] Solubility data reported in μM.

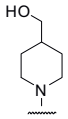
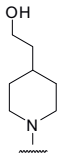
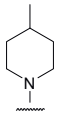
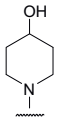
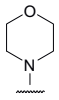
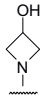
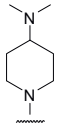
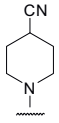
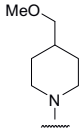
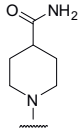
We also examined the SAR of carbocyclic rings in the course of our investigation (Table 5). We were pleased to find by converting the piperidine ring to a phenyl ring resulted in only a modest loss in potency (**26** vs **8**) although the reintroduction of aromaticity did have a deleterious effect on solubility. Placement of the hydroxymethyl group to the *meta* position resulted in a 3-fold loss in potency (**27** vs **26**). Similar to the piperidine SAR, the importance of the hydroxyl group was observed as compounds devoid of the hydrogen bond donor were less potent and significantly less soluble (**28**, **29** vs **26**). Other functional groups such as amides, esters and nitriles were well tolerated but less potent (**30**, **31**, and **32** vs **26**). Although the carbocyclic compounds in general showed modest PDE10A potency they lacked satisfactory solubility. On the other hand, compounds with heteroaromatic D-rings proved to have better overall potency and solubility. In particular, a trend of improved potency was observed in several analogs (3-pyridyl ≈ 4-pyridyl > 5-pyrimidyl > 2-pyridyl). For example, pyrimidine **36** was 3-fold more potent compared to compound **33** whereas pyridine isomers **34** and **35** were 30-fold more potent. Unfortunately, the reverse trend of decreasing solubility was also observed (4-pyridyl < 3-pyridyl < 5-pyrimidyl < 2-pyridyl). Methyl substitution in the *para* and *meta* positions to the A–D ring junction was well tolerated and resulted in excellent PDE10A potency (**38** and **39**). In contrast, methylation in the *ortho* position resulted in a 9-fold loss in potency (**37** vs **34**).[16] Bicyclic heteroaromatic D-rings were also investigated and were well tolerated. Quinolines **40** and **41** displayed modest enzyme potency whereas benzothiazole **42** and amino-quinazoline **43** showed excellent in vitro potency. In general, bicyclic aromatic D-rings showed good to modest in vitro potencies but displayed considerably lower solubility. Given our initial hypothesis that the total aromatic ring count influenced aqueous solubility of a compound, we designed inhibitors containing saturated, carbon-linked D-rings. Gratifyingly, amide **44** exhibited good PDE10A inhibition and excellent solubility. In comparison to compound **44**, carbamate **45** and sulfonamide **46** maintained good aqueous solubility at the detriment of potency. Amide **47**, which contained a quinoxaline A-ring, displayed excellent PDE10A potency (Fig. 3). In general, the carbon-linked piperidine D-rings showed optimal PDE10 potency and solubility.

To evaluate PDE selectivity, potent PDE10A inhibitors in this series were screened against other PDE isoforms (Table 6). With the exception of compounds **11** and **43**, compounds of this series exhibited >1000-fold selective over the other PDEs.

Determination of the cocrystal structure of compound **8** bound to human PDE10A provided insights into the potency and

**Table 4**
PDE10A inhibitory activity of nitrogen-linked D-ring analogs



| Compound | R | PDE10A[a] | PBS[b] | Compound | R | PDE10A[a] | PBS[b] |
|---|---|---|---|---|---|---|---|
| **8** |  | 2.4 ± 0.7 | 178 | **20** |  | 32 ± 0.9 | <1 |
| **15** |  | 18 ± 0.7 | 84 | **21** |  | 103 ± 2.8 | <1 |
| **16** |  | 54 ± 1.6 | 99 | **22** |  | 29 ± 0.9 | 346 |
| **17** |  | 36 ± 0.1 | 41 | **23** |  | 343 ± 1.4 | 500 |
| **18**[c] |  | 41 ± 0.4 | 167 | **24** |  | 4.1 ± 0.2 | 66 |
| **19** |  | 147 ± 47 | 53 | **25** |  | 11 ± 0.4 | 14 |

[a] $IC_{50}$ values (nM) are the means of at least three independent experiments.
[b] Solubility data reported in μM.
[c] Racemic.

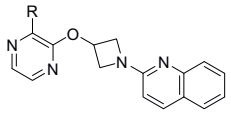
selectivity of this class of molecules (Fig. 4). Several important ligand–protein interactions were observed. First, the hydroxyl moiety of the piperidine D-ring displaces a water molecule in the lipophilic Q1 pocket of the catalytic site forming an H-bond with the backbone carbonyl oxygen of Thr675. As a consequence, the hydroxyl group of Ser667 is oriented away from the ligand. This deep penetration into the catalytic site may explain the high potency for compound **8**. Second, the quinoline moiety occupies the Q2 selectivity pocket adjacent to the sidechain of Met703 and the nitrogen of the quinoline forms a hydrogen bond with Tyr683. The occurrence of the small residue Gly715, present only in PDE10A, allows these compounds to access this pocket, which may explain the high selectivity over other PDEs. Lastly, the azetidine–pyrazine rings form hydrophobic interactions with the hydrophobic clamp as defined by residues Phe719, Phe686 and Ile682.

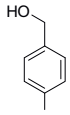
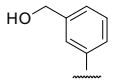
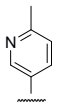
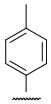
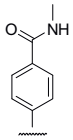
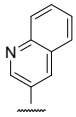
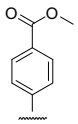
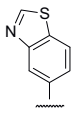
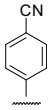
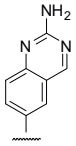
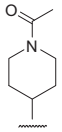
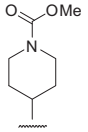
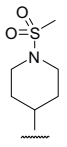
In contrast, the cocrystal structure of compound **47** bound to PDE10A was obtained by X-ray crystallography revealing an alternative binding orientation compounds of this series can adopt within the active site (Fig. 5). The A-ring quinoxaline ring occupies the Q1 pocket forming a π-stacking interaction with Phe719 residue and a π–edge interaction with Phe686 of the hydrophobic clamp. As a consequence, the Ser667 hydroxy sidechain points toward the ligand forming Van der Waals contacts with the quinoxaline ring. The C-ring quinoline occupies the Q2 selectivity pocket engaging in a hydrogen bond with Tyr683. Lastly, the D-ring piperidine is oriented toward the water coordinated metal site.

The in vivo pharmacokinetic profiles for compounds **8**, **44** and **47** are shown in Table 7. In comparison to the high in vivo rat clearance (3.68 L/h/kg) and poor bioavailability (18%) of lead compound **8**, acetyl piperidines **44** and **47** displayed improved in vivo rat plasma pharmacokinetic profiles. Compound **44** afforded lower in vivo clearance (0.96 L/h/kg) and improved oral bioavailability (62%). Compound **47** afforded the best improvement in in vivo clearance (0.57 L/h/kg) while maintaining good oral bioavailability (57%).

Recently, we demonstrated the use of a PDE10 receptor occupancy (RO) assay to correlate in vivo target specificity in rat brain and efficacy in a preclinical rodent model of schizophrenia.[17] With potent and selective PDE10A inhibitors in hand, we profiled our lead molecules to assess whether compound covered the intended target within the striatum as a predictor of in vivo efficacy. To this end, we relied on an ex vivo RO assay using our recently reported PDE10A tracer AMG-7980.[18] The study was conducted in rats, administering a 10 mg/kg oral dose after 60 min. Initial compounds **8** and **14** showed

**Table 5**
PDE10A inhibitory activity of carbon-linked D-ring analogs



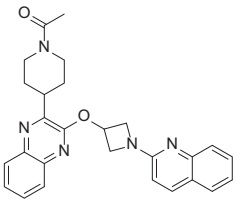
| Compound | R | PDE10A[a] | PBS[b] | Compound | R | PDE10A[a] | PBS[b] |
|---|---|---|---|---|---|---|---|
| **26** |  | 10.3 ± 0.4 | 24 | **37** |  | 98 ± 7.6 | 253 |
| **27** |  | 32 ± 0.8 | 29 | **38** |  | 8.5 ± 1.2 | 21 |
| **28** |  | 39 ± 0.6 | <1 | **39** |  | 5.7 ± 0.4 | 73 |
| **29** |  | 107 ± 2.1 | <1 | **40** |  | 43 ± 0.4 | 47 |
| **30** |  | 45 ± 0.1 | 82 | **41** |  | 38 ± 0.6 | <1 |
| **31** |  | 38 ± 2.0 | <1 | **42** |  | 7.8 ± 0.02 | <1 |
| **32** |  | 45 ± 0.8 | <1 | **43** |  | 6.8 ± 1.4 | <1 |
| **33** |  | 350 ± 2.8 | 349 | **44** |  | 29 ± 8.4 | 491 |
| **34** |  | 11 ± 0.7 | 133 | **45** |  | 64 ± 2.0 | 138 |
| **35** |  | 12 ± 7.0 | 56 | **46** |  | 166 ± 11 | 181 |
| **36** |  | 125 ± 1.4 | 254 | | | | |

[a] $IC_{50}$ values (nM) are the means of at least two independent experiments.
[b] Solubility data reported in μM.

modest 25% and 15% RO, respectively. The low RO result for compound **14** was not surprising due its low solubility. Gratifyingly, piperidine amides **44** and **47** exhibited good RO (46% and 57%, respectively) and demonstrated that this series of compounds crossed the blood–brain barrier reaching the intended target in brain.

## 3. Chemistry

Compounds required for this investigation were synthesized as described in Schemes 1–5. Pyrazine analogs **5**–**11** shown in Tables 1 and 2 were prepared in three steps from commercially available



47

PDE10A $IC_{50}$: 2.6 ± 0.6 nM
PBS (pH 7.4): 41 μM

**Figure 3.** PDE10A enzyme inhibition and solubility data for compound **47**.

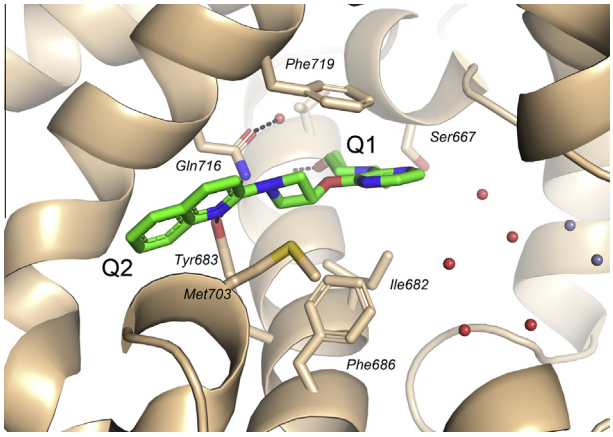



**Figure 4.** 2.77 Å co-crystal of compound **8** (green) within the active site of human PDE10A (PDB ID code 4TPM).

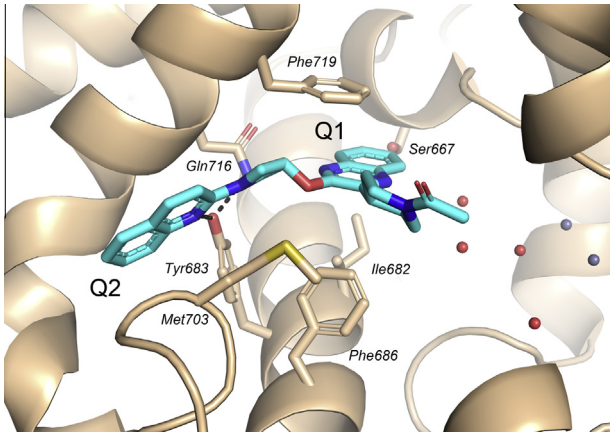



**Figure 5.** 2.65 Å co-crystal of compound **47** (blue) within the active site of human PDE10A (PDB ID code 4TPP).

materials (Scheme 1). Reaction of 2-chloroheterocycles **48**–**51** with the appropriate cyclic amines under thermal conditions gave alcohols **52**–**58**. Deprotonation of the secondary alcohols with sodium hydride followed by treatment with 2,3-dichloropyrazine afforded ethers **59**–**65**. Nucleophilic displacement with 4-piperidinemethanol under microwave conditions provided compounds **5**–**11**. Likewise, analogs **15**–**25** were prepared by treatment of compound **60** with various secondary amines (Scheme 2). Analogs containing an aromatic D-ring **26**–**43**, as shown in Table 5, were prepared under Suzuki coupling conditions between compound **60** and the appropriate boronic acid.

Pyridine analogs **12** and **13** were prepared in two steps from intermediate **53** as shown in Scheme 3. Treatment of intermediate **53** with either sodium hydride and 3-bromo-2-fluoropyridine in DMSO or cesium carbonate and 3-bromo-4-chloropyridine in DMF afforded azetidine ethers **66** and **67**, respectively. Palladium catalyzed coupling of 4-piperidinemethanol with intermediates **66** and **67** provided compounds **12** and **13**, respectively.

Pyrazines containing a carbon-linked piperidine D-ring were synthesized as described in Scheme 4. Suzuki coupling between intermediate **60** and commercially available *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate **68** afforded compound **69**. Hydrogenation of the trisubstituted double bond followed by acid deprotection of the Boc group yielded intermediate 7**0**. Acylation or sulfonylation under basic conditions provided derivatives **44**–**46**.

Analogous to the conditions described previously, quinoxalines **14** and **47** were prepared according to Scheme 5. Reaction between intermediate **53** and 2,3-dichloroquinoxaline in the presence of sodium hydride gave intermediate **71** and nucleophilic displacement using 4-piperidinemethanol afforded quinoxaline **14**. Cross-coupling of quinoxaline **72** and the organozinc derived from benzyl 4-iodopiperidine carboxylate smoothly provided compound **72**. A one step deprotection and acylation procedure provided compound **47**.

## 4. Conclusion

In conclusion, we have discovered a novel series of 3-alkoxy-azetidine inhibitors of PDE10A starting from lead compound **3**. Structure–activity relationship studies resulted in improved aqueous solubility while maintaining high PDE selectivity. X-ray crystallographic data suggested that compounds of this series may adopt one of two different binding modes depending on modifications of the D-ring. The bicyclic C-ring in this series of inhibitors occupied the unique Q2 pocket resulting in high selectivity among other PDEs. Using an ex vivo receptor occupancy assay, it was demonstrated that compounds **44** and **47** reached PDE10A in the striatum of rats. In addition, compounds **44** and **47** exhibited acceptable pharmacokinetic profiles.

**Table 6**
PDE potency for selected analogs[a]

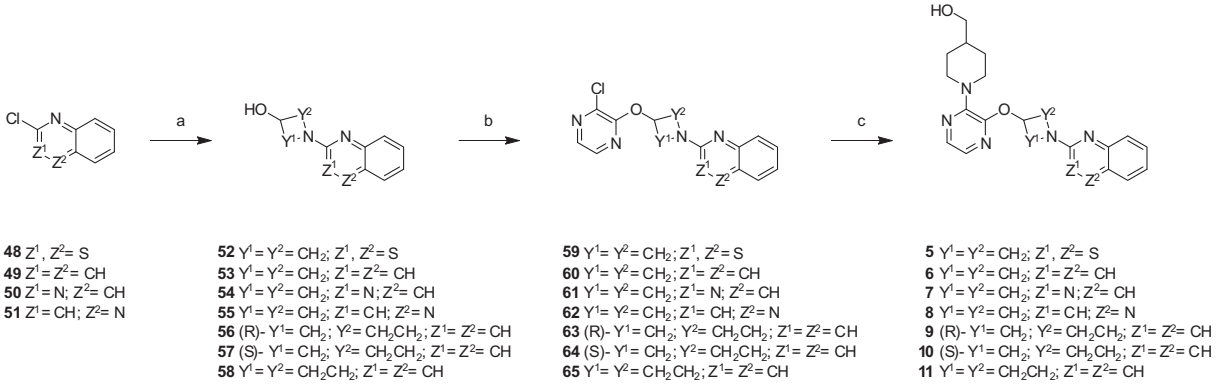
| Compound | PDE1B | PDE2A1 | PDE3A | PDE4D2 | PDE5A | PDE7A1 | PDE8A1 | PDE9A2 | PDE10A2 | PDE11A4 |
|---|---|---|---|---|---|---|---|---|---|---|
| **8** | 8040 | 11,700 | >30,000 | 10,800 | >30,000 | >30,000 | >30,000 | >30,000 | 2.4 | >30,000 |
| **11** | 7920 | 29,700 | >30,000 | 4690 | >30,000 | >30,000 | >30,000 | >30,000 | 6.5 | >30,000 |
| **13** | >30,000 | >30,000 | >30,000 | >30,000 | >30,000 | >30,000 | >30,000 | >30,000 | 4.7 | >30,000 |
| **14** | 7610 | 12,900 | >30,000 | 20,500 | >30,000 | >30,000 | >30,000 | >30,000 | 6.8 | 10,600 |
| **43** | 503 | >30,000 | 208 | 581 | >30,000 | 1170 | >30,000 | >30,000 | 6.8 | >30,000 |
| **44** | >30,000 | >30,000 | >30,000 | >30,000 | >30,000 | >30,000 | >30,000 | >30,000 | 29 | >30,000 |
| **47** | 3680 | 3030 | >30,000 | 5050 | >30,000 | >30,000 | >30,000 | >30,000 | 2.6 | >30,000 |

[a] $IC_{50}$ values (nM) are the means of at least two independent experiments.

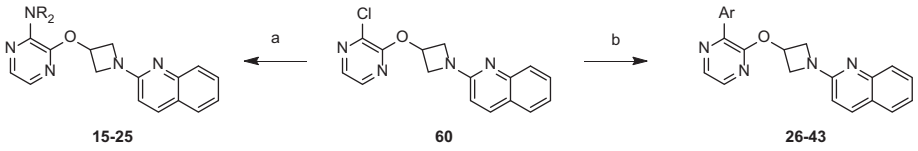
**Table 7**
Pharmacokinetic profiles of selected compounds in male Sprague–Dawley rats

| Compound | CL (L/h/kg) | IV (2 mg/kg)[a] | | PO (10 mg/kg)[b] | |
|---|---|---|---|---|---|
| | | Vdss (L/kg) | $t_{1/2}$ (h) | $AUC_{(0-\infty)}$ (ng*h/mL) | *F* (%) |
| **8** | 3.68 | 4.81 | 6.42 | 1.30 | 18 |
| **44** | 0.96 | 1.55 | 3.64 | 17.4 | 62 |
| **47** | 0.57 | 1.55 | 2.35 | 27.9 | 57 |

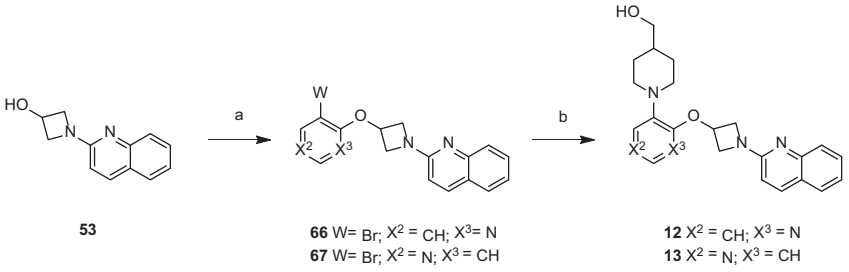
[a] In DMSO.
[b] Vehicles used: 1% Tween, 2% HPMC with methanesulfonic acid, pH 2.2.



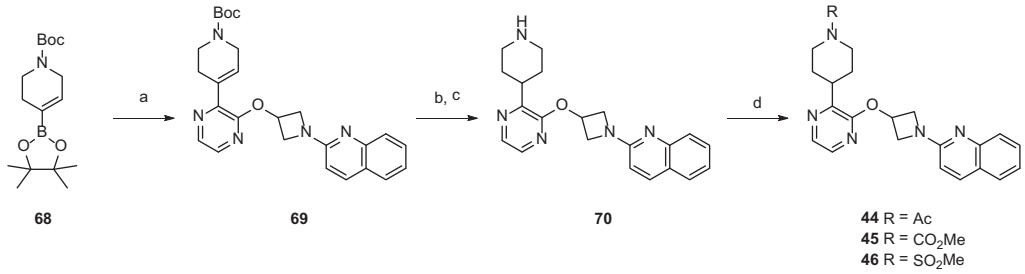

**Scheme 1.** Reagents and conditions: (a) 3-hydroxyazetidine, 3-hydroxypyrrolidine, or 4-hydroxypiperidine, $Et_3N$, DMF, 90 °C; (b) 2,3-dichloropyrazine, NaH, DMF, 90 °C; (c) 4-piperidinemethanol, $K_2CO_3$, *i*PrOH/water, μW, 160 °C, 5 h.



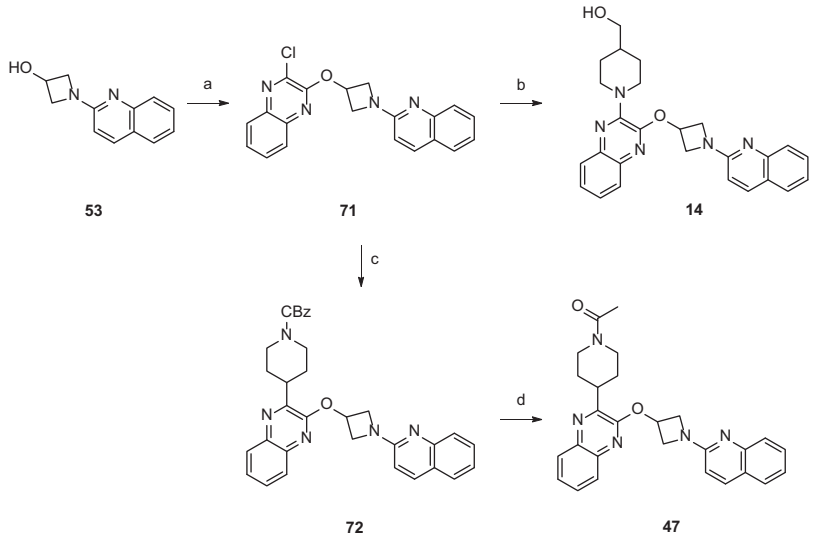

**Scheme 2.** Reagents and conditions: (a) secondary amine, $K_2CO_3$, *i*PrOH/water, μW, 160 °C, 5 h; (b) $ArB(OH)_2$, $Pd(PPh_3)_4$, $Na_2CO_3$, dioxane/water, 110 °C or, for example **33,** $Pd(PPh_3)_4$, 2-tributylstannyl-pyridine, toluene, 110 °C.




**Scheme 3.** Reagents and conditions: (a), NaH, DMSO, then 3-bromo-2-fluoropyridine, 5 °C to rt or $Cs_2CO_3$, 3-bromo-4-chloropyridine, DMF, 90 °C; (b) 4-piperidinemethanol, $Pd_2dba_3$, MePhos, LiHMDS, THF, 65 °C or 4-piperidinemethanol, $Pd_2dba_3$, *t*-ButylXphos, $K_3PO_4$, toluene, 100 °C.




**Scheme 4.** Reagents and conditions: (a) intermediate **60**, $Pd(dppf)Cl_2$, $K_3PO_4$, dioxane/$H_2O$ (b) Pd/carbon, $H_2$, MeOH, rt; (c) HCl, MeOH, rt; (d) RCl, $Et_3N$, DCM, 0 °C.




**Scheme 5.** Reagents and conditions: (a) 2,3-dichloroquinoxaline, NaH, DMF, 90 °C; (b) 4-piperidinemethanol, $K_2CO_3$, *i*PrOH/$H_2O$, μW, 160 °C, 5 h; (c) benzyl 4-iodopiperidine carboxylate, zinc, TMSCl, 1,2-dibromoethane, $PdCl_2$dppf $CH_2Cl_2$, CuI, DMA, 80 °C; (d) $H_2$, $Pd(OH)_2$, $Ac_2O$, toluene, rt.

## 5. Experimental section

### 5.1. Chemistry

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as dichloromethane ($CH_2Cl_2$), dimethylformamide (DMF), dimethylsulfoxide (DMSO), dioxane, ethyl acetate (EtOAc), tetrahydrofuran (THF), ethylene glycol dimethyl ether (DME), dimethylacetamide (DMA) and toluene were obtained from Aldrich Chemical Co. in Sure/Seal bottles. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. Microwave assisted reactions were performed in Biotage Initiator Sixty microwave reactor. Flash chromatography was performed using EM Science silica gel 60 (230–400 mesh ASTM) or prepacked silica gel cartridges (Biotage or RediSep). All yields reported are isolated yields. Reactions were monitored using Agilent 1100 series LC/MSD SL high performance liquid chromatography (HPLC) systems with UV detection at 254 nm and a low resonance electrospray positive ionization mode (ESI). All final compounds were purified to >95% purity, as determined by high performance liquid chromatography (HPLC). HPLC methods used the following: Agilent 1100 spectrometer, Zorbax SB-C18 column (50 mm × 3.0 mm, 3.5 μm) at 40 °C with a 1.5 mL/min flow rate; solvent A of 0.1% TFA in water, solvent B of 0.1% TFA in MeCN; 0.0–3.0 min, 5–95% B; 3.0–3.5 min, 95% B; 3.5–3.51 min, 5% B. Flow from UV detector was split (50:50) to the MS detector, which was configured with APIES as ionizable source. $^1$H NMR spectra were recorded on a Bruker DRX 300 MHz, Bruker DRX 400 MHz, Bruker AV 400 MHz, Varian 300 MHz, or a Varian 400 MHz spectrometer at ambient temperature. Chemical shifts are expressed in parts per million (ppm, $\delta$ units). Significant $^1$H NMR data are reported in the following order: multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants. All high resolution mass spectrometry (HRMS) data were acquired on a Synapt G2HDMS instrument (Waters Corporation, Manchester, UK) operated in positive electrospray ionization mode.

#### 5.1.1. 1-(Benzo[*d*]thiazol-2-yl)azetidin-3-ol (52)

To a room temperature solution of 2-chlorobenzothiazole **48** (2.50 mL, 19.20 mmol) in DMSO (30 mL) was added 3-hydroxyazetidine hydrochloride (4.10 g, 37.4 mmol) followed by cesium carbonate (24.20 g, 74.3 mmol). The reaction was heated at 85 °C under nitrogen overnight. The reaction was cooled to room temperature and partitioned between EtOAc/brine and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were evaporated onto silica gel and purified by flash chromatography eluting with 2 M $NH_3$ in MeOH/$CH_2Cl_2$ (0–5%) to give 3.35 g (85%) of the title compound as a white crystalline solid. $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.68 (dd, $J$ = 7.89, 0.73 Hz, 1H), 7.51 (dd, $J$ = 8.11, 0.51 Hz, 1H), 7.33 (td, $J$ = 7.71, 1.24 Hz, 1H), 7.13 (td, $J$ = 7.60, 1.17 Hz, 1H), 4.81 (tt, $J$ = 6.65, 4.46 Hz, 1H), 4.37–4.51 (m, 2H), 3.97–4.08 (m, 2H). MS (ESI) $m/z$: 207.1 [M+H].

#### 5.1.2. 1-Quinolin-2-yl-azetidin-3-ol (53)

Triethylamine (4.5 g, 41.0 mmol), 2-chloroquinoline **49** (3.35 g, 20.5 mmol) and azetidin-3-ol (1.5 g, 20.5 mmol) were dissolved in DMF (50 mL) and the resulting mixture was heated to 100 °C overnight. The mixture was diluted with water (100 mL) and extracted with EtOAc (2 × 70 mL). The combined organic extracts were combined and washed with water (50 mL) and brine (50 mL), dried over $Na_2SO_4$, and filtered. The filtrate was evaporated in vacuo and the residue was purified by flash column chromatography eluting with 20–70% EtOAc/petroleum ether to give 3.20 g (78%) of the title compound as a white solid. $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.00 (d, $J$ = 8.92 Hz, 1H), 7.63–7.76 (m, 2H), 7.47–7.62 (m, 1H), 7.26 (ddd, $J$ = 8.00, 6.98, 1.10 Hz, 1H), 6.72 (d, $J$ = 8.92 Hz, 1H), 4.76 (tt, $J$ = 6.58, 4.46 Hz, 1H), 4.34–4.53 (m, 2H), 3.91–4.07 (m, 2H). MS (ESI) $m/z$: 201 [M+H] calcd for $C_{12}H_{12}N_2O$ 200.

#### 5.1.3. 1-(Quinazolin-2-yl)azetidin-3-ol (54)

The title compound was prepared in a similar manner as **52** using 3-hydroxyazetidine hydrochloride and 2-chloroquinazoline **50**. (78%) white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.18 (d, $J$ = 0.44 Hz, 1H), 7.84 (dd, $J$ = 8.04, 0.88 Hz, 1H), 7.72 (ddd, $J$ = 8.55, 6.94, 1.46 Hz, 1H), 7.52 (d, $J$ = 8.48 Hz, 1H), 7.27 (td, $J$ = 7.45, 1.02 Hz, 1H), 5.70 (d, $J$ = 6.43 Hz, 1H), 4.60 (qt, $J$ = 6.53, 4.53 Hz, 1H), 4.33 (dd, $J$ = 9.57, 6.94 Hz, 2H), 3.87 (dd, $J$ = 10.23, 4.53 Hz, 2H). MS (ESI) $m/z$: 202 [M+H].

#### 5.1.4. 1-(Quinoxalin-2-yl)azetidin-3-ol (55)

The title compound was prepared in a similar manner as **53** using azetidin-3-ol and 2-chloroquinoxaline **51**. (80%) light-yellow crystalline solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.32 (s, 1H), 7.82 (d, $J$ = 8.04 Hz, 1H), 7.50–7.69 (m, 2H), 7.38 (ddd, $J$ = 8.22, 5.88, 2.41 Hz, 1H), 5.79 (d, $J$ = 6.43 Hz, 1H), 4.66 (qt, $J$ = 6.53, 4.53 Hz, 1H), 4.32–4.50 (m, 2H), 3.80–4.08 (m, 2H). MS (ESI) $m/z$: 202 [M+H].

#### 5.1.5. (*R*)-1-(Quinolin-2-yl)pyrrolidin-3-ol (56)

The title compound was prepared in a similar manner as **53** using (*R*)-3-hydroxypyrrolidine and 2-chloroquinoline **49**. (66%) light-yellow crystalline solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.98 (d, $J$ = 9.06 Hz, 1H), 7.60–7.72 (m, 1H), 7.51–7.57 (m, 1H), 7.43–7.51 (m, 1H), 7.15 (ddd, $J$ = 7.93, 6.54, 1.61 Hz, 1H), 6.86 (d, $J$ = 9.06 Hz, 1H), 4.97 (d, $J$ = 3.65 Hz, 1H), 4.35–4.53 (m, 1H), 3.40–3.73 (m, 4H), 1.98–2.14 (m, 1H), 1.85–1.98 (m, 1H). MS (ESI) $m/z$: 215 [M+H].

#### 5.1.6. (*S*)-1-(Quinolin-2-yl)pyrrolidin-3-ol (57)

The title compound was prepared in a similar manner as **53** using (*S*)-3-hydroxypyrrolidine and 2-chloroquinoline **49**. (65%) light-yellow crystalline solid. $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.94 (d, $J$ = 9.06 Hz, 1H), 7.68 (d, $J$ = 8.48 Hz, 1H), 7.62 (dd, $J$ = 7.89, 1.32 Hz, 1H), 7.50 (ddd, $J$ = 8.48, 6.94, 1.53 Hz, 1H), 7.17 (ddd, $J$ = 7.97, 6.94, 1.17 Hz, 1H), 6.86 (d, $J$ = 9.06 Hz, 1H), 4.56 (tt, $J$ = 4.59, 2.43 Hz, 1H), 3.66–3.81 (m, 3H), 3.54–3.66 (m, 1H), 1.97–2.30 (m, 2H). MS (ESI) $m/z$: 215 [M+H].

#### 5.1.7. 1-(Quinolin-2-yl)piperidin-4-ol (58)

The title compound was prepared in a similar manner as **53** using 4-hydroxypiperidine and 2-chloroquinoline **49**. (60%) white amorphous solid. $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.95 (d, $J$ = 9.21 Hz, 1H), 7.62 (d, $J$ = 8.33 Hz, 2H), 7.43–7.55 (m, 1H), 7.21 (m, $J$ = 7.45, 7.45, 1.02 Hz, 1H), 7.16 (d, $J$ = 9.35 Hz, 1H), 4.20–4.37 (m, 2H), 3.88 (tt, $J$ = 8.90, 4.26 Hz, 1H), 3.18–3.35 (m, 2H), 1.97 (dq, $J$ = 12.81, 3.67 Hz, 2H), 1.56 (dtd, $J$ = 13.03, 9.56, 9.56, 3.80 Hz, 2H). MS (ESI) [M+H]: 229.1 calcd for $C_{14}H_{16}N_2O$ 228.

#### 5.1.8. 2-(3-((3-Chloropyrazin-2-yl)oxy)azetidin-1-yl)benzo[*d*]thiazole (59)

To a 100 mL 3-neck round bottom flask was charged 1-(benzo[*d*]thiazol-2-yl)azetidin-3-ol **52** (1.96 g, 9.50 mmol) and 2,3-dichloropyrazine (1.55 g, 10.40 mmol). DMSO (24 mL) was added and the mixture was cooled in an ice bath. Sodium hydride, 57% dispersion in mineral oil (0.460 g, 10.93 mmol) was added in portions over 15 min. Upon complete addition, the reaction was stirred at room temperature for 1 h. The reaction was recooled to 0 °C and quenched with water. The reaction mixture was extracted with EtOAc (3×) and the combined organic layers were washed with brine. The organic solution was evaporated onto silica gel and purified by flash chromatography eluting with 0–50% EtOAc/hexanes to give 2.45 g (81%) of an off-white crystalline solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.26 (d, $J$ = 2.63 Hz, 1H), 8.16 (d, $J$ = 2.78 Hz, 1H), 7.80 (dd, $J$ = 7.89, 0.88 Hz, 1H), 7.52 (d, $J$ = 7.45 Hz, 1H), 7.31 (td, $J$ = 7.67, 1.17 Hz, 1H), 7.04–7.18 (m, 1H), 5.55–5.73 (m, 1H), 4.61 (ddd, $J$ = 9.61, 6.47, 1.02 Hz, 2H), 4.25 (ddd, $J$ = 9.65, 3.80, 1.02 Hz, 2H). MS (ESI) $m/z$: 319.0, 320.9 [M+H].

#### 5.1.9. 2-[3-(3-Chloro-pyrazin-2-yloxy)-azetidin-1-yl]-quinoline (60)

To a solution of 1-(quinolin-2-yl)azetidin-3-ol **53** (3.20 g, 16.0 mmol) in DMF (30 mL) at 0 °C was added sodium hydride (60% wt in mineral oil) (1.28 g, 32 mmol). The mixture was stirred at room temperature for 60 min and then 2,3-dichloropyrazine (2.37 g, 16.0 mmol) was added. The reaction mixture was heated to 90 °C overnight and then diluted with water (60 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (60 mL) and brine (60 mL), dried over $Na_2SO_4$, and filtered. The filtrate was evaporated in vacuo and the residue was purified by flash column chromatography eluting with 5–30% EtOAc/petroleum ether to give 3.0 g (60%) of the title compound as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.27 (d, $J$ = 2.78 Hz, 1H), 8.15 (d, $J$ = 2.78 Hz, 1H), 8.06 (d, $J$ = 8.92 Hz, 1H), 7.73 (d, $J$ = 7.31 Hz, 1H), 7.46–7.64 (m, 2H), 7.24 (ddd, $J$ = 7.97, 6.58, 1.39 Hz, 1H), 6.81 (d, $J$ = 8.77 Hz, 1H), 5.49–5.69 (m, 1H), 4.45–4.69 (m, 2H), 4.17 (ddd, $J$ = 9.90, 3.84, 0.88 Hz, 2H). MS (ESI) $m/z$: MS (ESI) [M+H]: 313.0, 314.9. Calcd for $C_{16}H_{13}ClN_4O$ 312.

#### 5.1.10. 2-(3-((3-Chloropyrazin-2-yl)oxy)azetidin-1-yl)quinazoline (61)

The title compound was prepared in a similar manner as **60** using 2,3-dichloropyrazine and compound **54**. (63%) white crystalline solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.24 (d, $J$ = 0.44 Hz, 1H), 8.26 (d, $J$ = 2.78 Hz, 1H), 8.15 (d, $J$ = 2.78 Hz, 1H), 7.88 (dd, $J$ = 8.04, 1.02 Hz, 1H), 7.76 (ddd, $J$ = 8.55, 6.94, 1.46 Hz, 1H), 7.56 (d, $J$ = 8.33 Hz, 1H), 7.32 (ddd, $J$ = 7.97, 6.94, 1.02 Hz, 1H), 5.59 (tt, $J$ = 6.47, 3.84 Hz, 1H), 4.62 (ddd, $J$ = 10.30, 6.50, 1.02 Hz, 2H), 4.21 (ddd, $J$ = 10.27, 3.84, 1.10 Hz, 2H). MS (ESI) $m/z$: 314.0, 316.0 [M+H].

#### 5.1.11. 2-(3-((3-Chloropyrazin-2-yl)oxy)azetidin-1-yl)quinoxaline (62)

The title compound was prepared in a similar manner as **60** using 2,3-dichloropyrazine and compound **55**. (62%) off-white crystalline solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.39 (s, 1H), 8.27 (d, $J$ = 2.78 Hz, 1H), 8.16 (d, $J$ = 2.63 Hz, 1H), 7.85 (d, $J$ = 7.89 Hz, 1H), 7.54–7.70 (m, 2H), 7.42 (ddd, $J$ = 8.22, 6.18, 2.12 Hz, 1H), 5.54–5.71 (m, 1H), 4.71 (ddd, $J$ = 10.16, 6.50, 0.88 Hz, 2H), 4.31 (ddd, $J$ = 10.16, 3.80, 1.10 Hz, 2H). MS (ESI) $m/z$: 327.0, 329.0 [M+H].

#### 5.1.12. (*R*)-2-(3-((3-Chloropyrazin-2-yl)oxy)pyrrolidin-1-yl)quinoline (63)

The title compound was prepared in a similar manner as **60** using 2,3-dichloropyrazine and compound **56**. (69%) light-yellow glass. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.29 (d, $J$ = 2.78 Hz, 1H), 8.10 (d, $J$ = 2.78 Hz, 1H), 8.02 (d, $J$ = 9.06 Hz, 1H), 7.63–7.75 (m, 1H), 7.53–7.59 (m, 1H), 7.44–7.53 (m, 1H), 7.18 (ddd, $J$ = 7.97, 6.58, 1.53 Hz, 1H), 6.93 (d, $J$ = 9.06 Hz, 1H), 5.75 (m, 1H), 3.90–4.02 (m, 1H), 3.75–3.90 (m, 2H), 3.67 (td, $J$ = 9.87, 7.16 Hz, 1H), 2.21–2.48 (m, 2H). MS (ESI) $m/z$: 327 [M+H].

#### 5.1.13. (*S*)-2-(3-((3-Chloropyrazin-2-yl)oxy)pyrrolidin-1-yl)quinoline (64)

The title compound was prepared in a similar manner as **60** using 2,3-dichloropyrazine and compound **57**. (79%) light-yellow glass. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.29 (d, $J$ = 2.63 Hz, 1H), 8.10 (d, $J$ = 2.78 Hz, 1H), 8.02 (d, $J$ = 9.06 Hz, 1H), 7.63–7.75 (m, 1H), 7.53–7.60 (m, 1H), 7.45–7.53 (m, 1H), 7.18 (ddd, $J$ = 7.93, 6.61, 1.53 Hz, 1H), 6.93 (d, $J$ = 8.92 Hz, 1H), 5.75 (m, 1H), 3.90–4.03 (m, 1H), 3.74–3.90 (m, 2H), 3.67 (td, $J$ = 9.87, 7.16 Hz, 1H), 2.24–2.48 (m, 2H). MS (ESI) $m/z$: 327 [M+H].

#### 5.1.14. 2-(4-((3-Chloropyrazin-2-yl)oxy)piperidin-1-yl)quinoline (65)

The title compound was prepared in a similar manner as **60** using 2,3-dichloropyrazine and compound **58**. (70%) white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J$ = 2.74 Hz, 1H), 7.94 (d, $J$ = 2.74 Hz, 1H), 7.91 (d, $J$ = 9.19 Hz, 1H), 7.72 (d, $J$ = 8.41 Hz, 1H), 7.61 (d, $J$ = 7.82 Hz, 1H), 7.49–7.58 (m, 1H), 7.18–7.26 (m, 1H), 7.06 (d, $J$ = 9.10 Hz, 1H), 5.31–5.50 (m, 1H), 4.03–4.23

(m, 2H), 3.64–3.85 (m, 2H), 2.10–2.24 (m, 2H), 1.92–2.05 (m, 2H). MS (ESI) [M+H]: 341 calcd for $C_{18}H_{17}ClN_4O$ 340.

#### 5.1.15. 2-(3-((3-Bromopyridin-2-yl)oxy)azetidin-1-yl)quinoline (66)

The title compound was prepared in a similar manner as **59** using 3-bromo-2-fluoropyridine and compound **53**. (91%) light-tan glass. $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.12 (dd, $J$ = 4.90, 1.68 Hz, 1H), 7.90–8.04 (m, 2H), 7.61–7.77 (m, 2H), 7.47–7.60 (m, 1H), 7.24 (ddd, $J$ = 7.97, 6.87, 1.10 Hz, 1H), 6.93 (dd, $J$ = 7.67, 4.90 Hz, 1H), 6.73 (d, $J$ = 9.06 Hz, 1H), 5.59 (tt, $J$ = 6.50, 4.17 Hz, 1H), 4.56–4.72 (m, 2H), 4.11–4.30 (m, 2H). MS (ESI) $m/z$: 356.0, 358.0 [M+H].

#### 5.1.16. 2-Chloro-3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)quinoxaline (71)

The title compound was prepared in a similar manner as **60** using 2,3-dichloroquinoxaline and compound **53**. (60%) white crystalline solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.07 (d, $J$ = 8.92 Hz, 1H), 8.00 (dd, $J$ = 8.33, 1.02 Hz, 1H), 7.88–7.95 (m, 1H), 7.83 (td, $J$ = 7.60, 1.46 Hz, 1H), 7.68–7.78 (m, 2H), 7.58–7.65 (m, 1H), 7.49–7.58 (m, 1H), 7.20–7.32 (m, 1H), 6.84 (d, $J$ = 8.77 Hz, 1H), 5.59–5.83 (m, 1H), 4.67 (dd, $J$ = 9.65, 6.58 Hz, 2H), 4.26 (dd, $J$ = 10.16, 3.73 Hz, 2H). MS (ESI) $m/z$: 363.0, 365.0 [M+H].

#### 5.1.17. 2-(3-((3-Bromopyridin-4-yl)oxy)azetidin-1-yl)quinoline (67)

To a solution of 1-(quinolin-2-yl)azetidin-3-ol **53** (320 mg, 1.60 mmol) in DMF (10 mL) was added cesium carbonate (1.04 g, 3.2 mmol) and 3-bromo-4-chloropyridine (307 mg, 1.60 mmol). The mixture was stirred at 90 °C overnight and then diluted with water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over $Na_2SO_4$, and filtered. The filtrate was evaporated in vacuo and the residue was purified by flash column chromatography eluting with 5–30% EtOAc/petroleum ether to give 350 mg (61%) of the title product as white solid. MS (ESI) [M+H]: 356 calcd for $C_{17}H_{14}BrN_3O$ 355. MS (ESI) $m/z$: 355 [M+H].

#### 5.1.18. (1-(3-((1-(Benzo[*d*]thiazol-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidin-4-yl)methanol (5)

A glass microwave reaction vessel was charged with 2-(3-((3-chloropyrazin-2-yl)oxy)azetidin-1-yl)benzo[*d*]thiazole **59** (0.153 g, 0.480 mmol) and 4-piperidinemethanol (0.171 g, 1.485 mmol). DMSO (1 mL) was added and the reaction mixture was sealed under argon and heated at 120 °C overnight. The reaction was cooled to room temperature and diluted with water. The slurry was extracted with EtOAc (3×) and the combined organic layers were evaporated onto silica gel and purified by flash chromatography eluting with 0–100% EtOAc/hexanes to give 116 mg (61%) of a white crystalline solid. $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.77 (d, $J$ = 2.92 Hz, 1H), 7.71 (d, $J$ = 7.60 Hz, 1H), 7.47–7.60 (m, 2H), 7.28–7.41 (m, 1H), 7.07–7.23 (m, 1H), 5.66 (tt, $J$ = 6.50, 4.09 Hz, 1H), 4.68 (dd, $J$ = 9.50, 7.31 Hz, 2H), 4.28 (dd, $J$ = 10.01, 3.58 Hz, 4H), 3.47 (d, $J$ = 6.28 Hz, 2H), 2.89 (td, $J$ = 12.53, 2.12 Hz, 2H), 1.85 (dd, $J$ = 13.01, 1.75 Hz, 2H), 1.64–1.80 (m, 1H), 1.39 (qd, $J$ = 12.20, 3.87 Hz, 1H). HRMS (ESI): calcd for $C_{20}H_{24}N_5O_2S$ [M+H] 398.1650. Found: 398.1650.

#### 5.1.19. 1-[3-(1-Quinolin-2-yl-azetidin-3-yloxy)-pyrazin-2-yl]-piperidin-4-ol (16)

To a mixture of 2-[3-(3-chloro-pyrazin-2-yloxy)-azetidin-1-yl]-quinoline (312 mg, 1.0 mmol) and piperidin-4-ol (0.101 g, 1.0 mmol) and potassium carbonate (0.276 g, 2.0 mmol) was added *i*PrOH (3 mL) and water (1.0 ml). The solution was heated to 160 °C in the microwave for 5 h. The mixture was concentrated and extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and filtered. The filtrate was evaporated in vacuo and the residue was purified by flash column chromatography eluting with 20–60% EtOAc/petroleum ether to give 67 mg (18%) of the title product as a white solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.86–7.72 (m, 3H), 7.58–7.47 (m, 3H), 7.30–7.20 (m, 1H), 6.56 (d, $J$ = 8.8 Hz, 1H), 5.51 (s, 1H), 4.63–4.59 (m, 2H), 4.23–4.19 (m, 1H), 3.97–3.94 (m, 2H), 3.86–3.84 (m, 1H), 3.12–3.09 (m, 2H), 2.20–1.93 (m, 3H), 1.66–1.60 (m, 2H). HRMS (ESI): calcd for $C_{21}H_{23}N_5O_2$ [M+H] 378.1925. Found: 378.1931.

#### 5.1.20. (1-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidin-4-yl)methanol (6)

The title compound was prepared in a similar manner as **16** using 4-piperidinemethanol and compound **60**. (50%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.96 (d, $J$ = 9.2 Hz, 1H), 7.70–7.31 (m, 3H), 7.54–7.49 (m, 2H), 7.25–7.23 (m, 1H), 6.66 (d, $J$ = 9.2 Hz, 1H), 5.52 (s, 2H), 4.62–4.58 (s, 2H), 4.22–4.17(m, 4H), 3.41–3.39 (m, 2H), 2.79–2.78 (m, 2H), 1.79–1.75 (m, 3H); 1.34–1.30 (m, 2H). HRMS (ESI): calcd for [M+H] 392.2081. Found: 392.2087.

#### 5.1.21. (1-(3-((1-(Quinazolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidin-4-yl)methanol (7)

The title compound was prepared in a similar manner as **16** using 4-piperidinemethanol and compound **61**. (59%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 9.02 (s, 1H), 7.74–7.67 (m, 3H), 7.53 (d, $J$ = 8.4 Hz, 1H), 7.47 (d, $J$ = 2.8 Hz, 1H), 7.27–7.23 (m, 1H), 5.51–5.54 (m, 1H), 4.64–4.59 (m, 2H), 4.22–4.18 (m, 4H), 3.49–3.40 (m, 2H), 2.81–2.75 (m, 2H), 1.78–1.75 (m, 2H), 1.66–1.64 (m, 2H), 1.37–1.27 (m, 2H). HRMS (ESI): calcd for $C_{21}H_{25}N_6O_2$ [M+H] 393.2034. Found: 393.2040.

#### 5.1.22. (1-(3-((1-(Quinoxalin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidin-4-yl)methanol (8)

The title compound was prepared in a similar manner as **16** using 4-piperidinemethanol and compound **62**. (50%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.23 (s, 1H), 7.82–7.79 (m, 1H), 7.69 (d, $J$ = 2.8 Hz, 1H), 7.64–7.62 (m, 2H), 7.59 (d, $J$ = 1.2 Hz, 1H), 7.40–7.36 (m, 1H), 5.56–5.55 (m, 1H), 4.72–4.68 (m, 2H), 4.31–4.20 (m, 4H), 3.40–3.39 (m, 2H), 2.84–2.77 (m, 2H), 1.79–1.76 (m, 3H), 1.34–1.30 (m, 2H). HRMS (ESI): calcd for $C_{21}H_{25}N_6O_2$ [M+H] 393.2034. Found: 393.2037.

#### 5.1.23. (*R*)-(1-(3-((1-(Quinolin-2-yl)pyrrolidin-3-yl)oxy)pyrazin-2-yl)piperidin-4-yl)methanol (9)

The title compound was prepared in a similar manner as **16** using 4-piperidinemethanol and compound **63**. (17%) amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.16 (s, 1H), 8.03–7.98 (m, 1H), 7.72–7.67 (m, 2H), 7.54–7.52 (m, 1H), 7.46–7.41 (m, 2H), 6.88–6.86 (m, 1H), 5.83 (s, 1H), 4.27–3.98 (m, 7H), 3.59–3.40 (m, 1H), 2.99–2.83 (m, 2H), 2.54–2.53 (m, 2H), 2.01–1.72 (m, 3H), 1.41–1.32 (m, 2H). HRMS (ESI): calcd for $C_{23}H_{28}N_5O_2$ [M+H] 406.2237. Found: 406.2237.

#### 5.1.24. (*S*)-(1-(3-((1-(Quinolin-2-yl)pyrrolidin-3-yl)oxy)pyrazin-2-yl)piperidin-4-yl)methanol (10)

The title compound was prepared in a similar manner as **16** using 4-piperidinemethanol and compound **64**. (23%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.37 (s, 1H), 7.91–7.88 (m, 2H), 7.68–7.67 (m, 1H), 7.60–7.59 (m, 1H), 7.54–7.50 (m, 1H), 7.30–7.20 (m, 2H), 5.90–5.89 (m, 1H), 4.23–4.09 (m, 7H), 4.01–3.99 (m, 1H), 2.93–2.86 (m, 2H), 2.61–2.59 (m, 2H), 1.78–1.75

(m, 3H), 1.33–1.27 (m, 2H). HRMS (ESI): calcd for $C_{23}H_{28}N_5O_2$ [M+H] 406.2237. Found: 406.2243.

#### 5.1.25. (1-(3-((1-(Quinolin-2-yl)piperidin-4-yl)oxy)pyrazin-2-yl)piperidin-4-yl)methanol (11)

The title compound was prepared in a similar manner as **16** using 4-piperidinemethanol and compound **65**. (48%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.40 (d, $J$ = 9.6 Hz, 1H), 7.91 (s, 2H), 7.67–7.66 (m, 1H), 7.57–7.53 (m, 4H), 5.56–5.54 (m, 1H), 4.23–4.20 (m, 2H), 4.09–4.06 (m, 5H), 3.47–3.40 (m, 2H), 2.94–2.87 (m, 2H), 2.35–2.69 (m, 2H), 2.17–2.12 (m, 2H), 2.00 (s, 2H), 1.85–1.81 (m, 1H), 1.37–1.35 (m, 2H). HRMS (ESI): calcd for $C_{24}H_{30}N_5O_2$ [M+H] 420.2393. Found: 420.2400.

#### 5.1.26. (1-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)quinoxalin-2-yl)piperidin-4-yl)methanol (14)

The title compound was prepared in a similar manner as **16** using 4-piperidinemethanol and compound **71**. (60%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.35 (d, $J$ = 9.2 Hz, 1H), 7.90 (d, $J$ = 8.0 Hz, 1H), 7.82–7.78 (m, 2H), 7.71–7.66 (m, 2H), 7.54–7.40 (m, 3H), 7.00 (d, $J$ = 9.2 Hz, 1H), 5.79–5.83 (m, 1H), 5.07–5.03 (m, 2H), 4.68–4.65 (m, 2H), 4.52–4.49 (m, 2H), 3.47–3.45 (m, 2H), 3.07–3.01 (m, 2H), 1.92–1.76 (m, 3H), 1.49–1.39 (m, 2H). HRMS (ESI): calcd for $C_{26}H_{28}N_5O_2$ [M+H] 442.2237. Found: 442.2240.

#### 5.1.27. 2-(1-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidin-4-yl)ethanol (15)

The title compound was prepared in a similar manner as **16** using 4-piperidineethanol and compound **60**. (100%) light-yellow oil. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.12 (d, $J$ = 9.68 Hz, 1H), 7.71–7.84 (m, 2H), 7.50–7.68 (m, 3H), 7.29 (t, $J$ = 8.36 Hz, 1H), 6.85 (d, $J$ = 9.24 Hz, 1H), 5.43–5.57 (m, 1H), 4.62 (dd, $J$ = 10.56, 7.04 Hz, 2H), 4.05–4.25 (m, 6H), 2.76 (t, $J$ = 13.86 Hz, 2H), 1.71 (d, $J$ = 14.96 Hz, 3H), 1.09–1.44 (m, 4H). HRMS (ESI): calcd for $C_{23}H_{28}N_5O_2$ [M+H] 406.2237. Found: 406.2241.

#### 5.1.28. 1-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)azetidin-3-ol (17)

The title compound was prepared in a similar manner as **16** using 3-hydroxyazetidine and compound **60**. (43%) off-white amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.04 (d, $J$ = 9.24 Hz, 1H), 7.49–7.75 (m, 4H), 7.38 (d, $J$ = 3.08 Hz, 1H), 7.19–7.28 (m, 1H), 6.79 (d, $J$ = 9.24 Hz, 1H), 5.66 (d, $J$ = 6.16 Hz, 1H), 5.44–5.53 (m, 1H), 4.52 (dd, $J$ = 10.56, 6.60 Hz, 3H), 4.27–4.38 (m, 2H), 4.02–4.14 (m, 2H), 3.84–3.88 (m, 1H). MS (ESI) [M+H]: 350.1617. Calcd for $C_{19}H_{20}N_5O_2$ [M+H] 350.1617.

#### 5.1.29. *rac*-{1-[3-(1-Quinolin-2-yl-azetidin-3-yloxy)-pyrazin-2-yl]-pyrrolidin-3-yl}-methanol (18)

The title compound was prepared in a similar manner as **16** using pyrrolidin-3-yl-methanol and compound **60**. (43%) off-white amorphous solid. (61%), tan amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.37 (d, $J$ = 9.35 Hz, 1H), 7.92 (d, $J$ = 7.45 Hz, 1H), 7.73–7.86 (m, 2H), 7.62 (d, $J$ = 3.22 Hz, 1H), 7.53 (ddd, $J$ = 8.00, 6.61, 1.61 Hz, 1H), 7.30 (d, $J$ = 3.07 Hz, 1H), 7.00 (d, $J$ = 9.35 Hz, 1H), 5.62 (tt, $J$ = 6.72, 4.09 Hz, 1H), 4.90–5.04 (m, 2H), 4.53–4.66 (m, 2H), 3.80–3.98 (m, 2H), 3.68–3.80 (m, 1H), 3.48–3.68 (m, 3H), 2.49 (m, 1H), 2.00–2.20 (m, 1H), 1.77 (dq, $J$ = 12.42, 7.94 Hz, 1H). HRMS (ESI): calcd for $C_{21}H_{24}N_5O_2$ [M+H] 378.1930. Found: 378.1929.

#### 5.1.30. 2-(3-((3-(4-(Methoxymethyl)piperidin-1-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (19)

The title compound was prepared in a similar manner as **16** using 4-(methoxymethyl)piperidine and compound **60**. (78%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.87–7.73 (m, 3H), 7.59–7.47 (m, 3H), 7.22–7.21 (m, 1H), 6.58–6.56 (m, 1H), 5.51 (s, 1H), 4.62–4.61 (m, 2H), 4.20–4.16 (m, 4H), 3.31–3.22 (m, 5H), 2.81–2.75 (m, 2H), 1.80–1.77 (m, 3H), 1.36–1.27 (m, 2H). HRMS (ESI): calcd for [M+H] 406.2243. Found: 406.2250.

#### 5.1.31. 2-(3-((3-(Piperidin-1-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (20)

The title compound was prepared in a similar manner as **16** using piperidine and compound **60**. (60%) amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J$ = 8.8 Hz, 1H), 7.76–7.75 (m, 2H), 7.61 (d, $J$ = 8.4 Hz, 1H), 7.60–7.55 (m, 1H), 7.48 (d, $J$ = 2.8 Hz, 1H), 7.25–7.21 (m, 1H), 6.61 (d, $J$ = 8.8 Hz, 1H), 5.56–5.52 (m, 1H), 4.66–4.62 (m, 2H), 4.26–4.23 (m, 2H), 3.48–3.45 (m, 4H), 1.68–1.66 (m, 6H). HRMS (ESI): calcd for $C_{21}H_{24}N_5O$ [M+H] 362.1976. Found: 362.1980.

#### 5.1.32. 2-(3-((3-(4-Methylpiperidin-1-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (21)

The title compound was prepared in a similar manner as **16** using 4-methylpiperidine and compound **60**. (60%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.32 (d, $J$ = 9.6 Hz, 1H), 7.87 (d, $J$ = 8.0 Hz, 1H), 7.78–7.76 (m, 3H), 7.52–7.50 (m, 2H), 6.96 (d, $J$ = 9.6 Hz, 1H), 5.66–5.61 (m, 1H), 4.97 (s, 2H), 4.55–4.59 (m, 2H), 4.22–4.19 (m, 2H), 2.94–2.87 (m, 2H), 1.98–1.72 (m, 2H), 1.65–1.60 (m, 1H), 1.35–1.26 (m, 2H), 1.27–1.26 (s, 3H). HRMS (ESI): calcd for $C_{22}H_{26}N_5O$ [M+H] 376.2132. Found: 376.2128.

#### 5.1.33. 4-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)morpholine (22)

The title compound was prepared in a similar manner as **16** using morpholine and compound **60**. (60%) amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.35 (d, $J$ = 9.2 Hz, 1H), 7.90 (d, $J$ = 8.0 Hz, 1H), 7.81–7.78 (m, 3H), 7.59 (d, $J$ = 3.2 Hz, 1H), 7.54–7.52 (m, 1H), 6.98 (d, $J$ = 9.2 Hz, 1H), 5.67–5.64 (m, 1H), 4.98–4.93 (m, 2H), 4.61–4.55 (m, 2H), 3.81–3.79 (m, 4H), 3.56–3.53 (m, 4H). HRMS (ESI): calcd for $C_{20}H_{22}N_5O_2$ [M+H] 364.1769. Found: 364.1766.

#### 5.1.34. *N,N*-Dimethyl-1-(3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidin-4-amine (23)

The title compound was prepared in a similar manner as **16** using 4-dimethylaminopiperidine and compound **60**. (77%) light-yellow oil. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.04 (d, $J$ = 9.68 Hz, 1H), 7.67–7.83 (m, 2H), 7.48–7.62 (m, 3H), 7.18–7.29 (m, 1H), 6.79 (d, $J$ = 8.80 Hz, 1H), 5.45–5.57 (m, 1H), 4.55 (dd, $J$ = 10.12, 7.04 Hz, 2H), 4.04–4.24 (m, 5 H), 2.78 (t, $J$ = 14.08 Hz, 2H), 2.15 (s, 6H), 1.74–1.88 (m, 2H), 1.33–1.51 (m, 2H). HRMS (ESI): calcd for $C_{23}H_{29}N_6O$ [M+H] 405.2397. Found: 405.2399.

#### 5.1.35. 1-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidine-4-carbonitrile (24)

The title compound was prepared in a similar manner as **16** using 4-cyanopiperidine and compound **60**. (15%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.94–7.92 (m, 1H), 7.73 (d, $J$ = 2.8 Hz, 1H), 7.65–7.64 (m, 2H), 7.55–7.51 (m, 2H), 7.20–7.18 (m, 1H), 6.65 (d, $J$ = 9.2 Hz, 1H), 5.51 (s, 1H), 4.60–4.55 (m, 2H), 4.18–4.14 (s, 2H), 3.79–3.73 (m, 2H), 3.35–3.29 (m, 2H), 2.95–2.93 (m, 1H), 2.01–1.96 (m, 2H), 1.94–1.89 (m, 2H). HRMS (ESI): calcd for $C_{22}H_{23}N_6O$ [M+H] 387.1929. Found: 387.1928.

#### 5.1.36. 1-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidine-4-carboxamide (25)

The title compound was prepared in a similar manner as **16** using isonipecotamide and compound **60**. (50%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.97–7.96 (m, 1H), 7.89 (d, $J$ = 9.2 Hz, 1H), 7.70–7.69 (m, 2H), 7.57–7.52 (m, 1H),

7.44–7.43 (m, 1H), 6.53 (d, $J$ = 9.2 Hz, 1H), 5.54–5.47 (m, 2H), 5.39 (s, 1H), 4.73 (s, 1H), 4.32 (s, 1H), 4.19–4.18 (m, 2H), 2.84–2.77 (m, 2H), 2.54–2.51 (m, 1H), 2.37–2.29 (m, 1H); 1.96–1.73 (m, 4H). HRMS (ESI): calcd for $C_{22}H_{25}N_6O_2$ [M+H] 405.2034. Found: 405.2035.

#### 5.1.37. (1-(2-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyridin-3-yl)piperidin-4-yl)methanol (12)

A glass microwave reaction vessel was charged with 2-(3-((3-bromopyridin-2-yl)oxy)azetidin-1-yl)quinoline **66** (0.176 g, 0.494 mmol), 4-piperidinemethanol (0.076 g, 0.660 mmol), 2-(dicyclohexylphosphino)-2′-methylbiphenyl (0.015 g, 0.041 mmol) and $Pd_2(dba)_3$ (0.020 g, 0.022 mmol). The vessel was capped and evacuated/purged with argon (3×). A 1.0 M solution of lithium bis(trimethylsilyl)amide in THF (1.1 ml, 1.10 mmol) was added and the reaction mixture was heated at 65 °C overnight. The reaction was cooled to room temperature, diluted with EtOAc, evaporated onto silica gel and purified by flash chromatography eluting with 2 M $NH_3$ in MeOH/$CH_2Cl_2$ (0–5%) to give 81 mg (42%) of a tan crystalline solid. $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.00 (d, $J$ = 8.92 Hz, 1H), 7.75 (dd, $J$ = 4.97, 1.61 Hz, 1H), 7.61–7.71 (m, 2H), 7.54 (ddd, $J$ = 8.44, 6.98, 1.39 Hz, 1H), 7.29 (dd, $J$ = 7.75, 1.61 Hz, 1H), 7.19–7.27 (m, 1H), 6.94 (dd, $J$ = 7.60, 4.97 Hz, 1H), 6.74 (d, $J$ = 8.92 Hz, 1H), 5.59 (tt, $J$ = 6.45, 4.15 Hz, 1H), 4.59–4.71 (m, 2H), 4.20 (dd, $J$ = 10.38, 4.09 Hz, 2H), 3.55 (d, $J$ = 11.84 Hz, 2H), 3.45 (d, $J$ = 6.14 Hz, 2H), 2.51–2.71 (m, 2H), 1.74–1.93 (m, 2H), 1.52–1.70 (m, 1H), 1.34–1.52 (m, 2H). HRMS (ESI): calcd for $C_{23}H_{27}N_4O_2$ [M+H] 391.2128. Found: 391.2134.

#### 5.1.38. (1-(4-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyridin-3-yl)piperidin-4-yl)methanol (13)

A mixture of (3-((3-Bromopyridin-4-yl)oxy)azetidin-1-yl) quinoline **67** (0.30 mmol), 4-piperidinemethanol (0.30 mmol), $Pd_2(dba)_3$ (0.03 mmol), *t*-ButylXphos (0.03 mmol) and $K_3PO_4$ (0.6 mmol) in toluene (10 mL) was stirred at 100 °C for 10 h. The mixture was left to reach room temperature and filtered through a pad of Celite™ and the filter cake was washed with $CH_2Cl_2$ (20 mL). The combine filtrate was evaporated in vacuo and the residue was purified by flash column chromatography eluting with 30–50% EtOAc/petroleum ether. Further purification by reverse phase HPLC eluting with 10–80% water/MeCN afforded 40 mg (40%) of the title compound as an amorphous solid. $^1$H NMR ($CD_3OD$, 400 MHz): $\delta$ 8.16–8.14 (m, 2H), 7.89 (d, $J$ = 8.8 Hz, 1H), 7.73 (d, $J$ = 8.2 Hz, 1H), 7.61–7.59 (m, 2H), 7.25–7.23 (m, 1H), 6.59 (d, $J$ = 9.2 Hz, 1H), 6.46 (d, $J$ = 4.2 Hz, 1H), 5.14–5.12 (m, 1H), 4.62–4.58 (m, 2H), 4.26–4.23 (m, 2H) 3.52–3.50 (m, 4H), 2.83–2.62 (m, 3H), 1.83–1.80 (m, 2H), 1.63–1.62 (m, 1H), 1.48–1.41 (m, 2H). MS (ESI) [M+H]: 391.2132. Calcd for $C_{23}H_{26}N_4O_2$ [M+H] 391.2128.

#### 5.1.39. (4-(3-(1-(Quinolin-2-yl)azetidin-3-yloxy)pyrazin-2-yl)phenyl)methanol (26)

A glass microwave vessel was charged with compound **60** (40 mg, 0.128 mmol), 4-(hydroxymethyl)phenylboronic acid (29 mg, 0.192 mmol), sodium carbonate (41 mg, 0.384 mmol), and dioxane/water (1.0 mL:0.18 mL). The solution was purged with nitrogen for 5 min, then $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) was added. The reaction mixture was stirred and heated at 120 °C for 64 h. The reaction mixture was filtered and washed with EtOAc/MeOH. The was concentrated and purified by reverse phase HPLC to give 21 mg (43%) of the title compound as an amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.16 (d, $J$ = 2.64 Hz, 1H), 7.99 (d, $J$ = 2.64 Hz, 1H), 7.82 (d, $J$ = 8.36 Hz, 3H), 7.51 (d, $J$ = 8.80 Hz, 1H), 7.28–7.43 (m, 2H), 7.22 (d, $J$ = 8.36 Hz, 2H), 7.03 (t, $J$ = 7.70 Hz, 1H), 6.59 (d, $J$ = 9.24 Hz, 1H), 5.36–5.46 (m, 1H), 4.29–4.43 (m, 4H), 3.92–4.01 (m, 2H). HRMS (ESI): calcd for $C_{23}H_{21}N_4O_2$ [M+H] 385.1660. Found: 385.1658.

#### 5.1.40. (3-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)phenyl)methanol (27)

The title compound was prepared in a similar manner as **26** using 3-(hydroxymethyl)phenylboronic acid and compound **60**. (79%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.39 (d, $J$ = 2.64 Hz, 1H), 8.22 (d, $J$ = 2.64 Hz, 1H), 7.91–8.08 (m, 3H), 7.71 (d, $J$ = 8.80 Hz, 1H), 7.35–7.63 (m, 4H), 7.23 (t, $J$ = 8.14 Hz, 1H), 6.79 (d, $J$ = 9.24 Hz, 1H), 5.58–5.68 (m, 1H), 5.34 (d, $J$ = 5.72 Hz, 1H) 4.51–4.63 (m, 4H), 4.16 (dd, $J$ = 10.56, 4.40 Hz, 2H). HRMS (ESI): calcd for $C_{23}H_{21}N_4O_2$ [M+H] 385.1660. Found: 385.1651.

#### 5.1.41. 2-(3-((3-Phenylpyrazin-2-yl)oxy)azetidin-1-yl)quinoline (28)

The title compound was prepared in a similar manner as **26** using phenylboronic acid and compound **60**. (64%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.28–8.25 (m, 1H), 8.10–8.08 (m, 1H), 7.98–7.95 (m, 2H), 7.84 (d, $J$ = 8.8 Hz, 1H), 7.61–7.55 (m, 2H), 7.47–7.30 (m, 4H), 7.19–7.16 (m, 1H), 6.55 (d, $J$ = 8.8 Hz, 1H), 5.52–5.49 (m, 1H), 4.54–4.49 (m, 2H), 4.13–4.09 (m, 2H). HRMS (ESI): calcd for $C_{22}H_{19}N_4O$ [M+H] 355.1555. Found: 355.1561.

#### 5.1.42. 2-(3-((3-(*p*-Tolyl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (29)

The title compound was prepared in a similar manner as **26** using *p*-tolyl boronic acid and compound **60**. (53%), amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 2.8 Hz, 1H), 8.00–7.97 (m, 3H), 7.86 (d, $J$ = 9.2 Hz, 1H), 7.74 (d, $J$ = 8.4 Hz, 1H), 7.60–7.51 (m, 2H), 7.26–7.20 (m, 3H), 6.58 (d, $J$ = 9.2 Hz, 1H), 5.63–5.59 (m, 1H), 4.06–4.62 (m, 2H), 4.29–4.25 (m, 2H); 2.38 (s, 3H). HRMS (ESI): calcd for $C_{23}H_{21}N_4O$ [M+H] 369.1711. Found: 369.1718.

#### 5.1.43. *N*-Methyl-4-(3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)benzamide (30)

The title compound was prepared in a similar manner as **26** using 4-(*N*-methylaminocarbonyl)phenylboronic acid and compound **60**. (72%) amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.31–8.25 (m, 2H), 8.09–8.08 (m, 2H), 8.07–7.79 (m, 3H), 7.70–7.69 (m, 2H), 7.43–7.39 (m, 1H), 6.90–6.87 (m, 1H), 5.69–5.65 (m, 1H), 4.92–4.88 (m, 4H), 4.55–4.51 (m, 2H), 2.84 (s, 3H). HRMS (ESI): calcd for $C_{24}H_{22}N_5O_2$ [M+H] 412.1769. Found: 412.1773.

#### 5.1.44. Methyl 4-(3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)benzoate (31)

The title compound was prepared in a similar manner as **26** using 4-methoxycarbonylphenylboronic acid and compound **60**. (43%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.44 (d, $J$ = 2.64 Hz, 1H), 8.17–8.31 (m, 3H), 8.00–8.11 (m, 3H), 7.72 (d, $J$ = 9.24 Hz, 1H), 7.49–7.64 (m, 2H), 7.18–7.29 (m, 1H), 6.80 (d, $J$ = 9.24 Hz, 1H), 5.59–5.70 (m, 1H), 4.59 (dd, $J$ = 10.34, 6.82 Hz, 2H), 4.20 (dd, $J$ = 10.34, 4.18 Hz, 2H), 3.87 (s, 3H). HRMS (ESI): calcd for $C_{24}H_{21}N_4O_3$ [M+H] 413.1609. Found: 413.1612.

#### 5.1.45. 4-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)benzonitrile (32)

The title compound was prepared in a similar manner as **26** using 4-cyanophenylboronic acid and compound **60**. (53%) amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J$ = 1.6 Hz, 1H), 8.21 (d, $J$ = 2.8 Hz, 1H), 7.87–7.82 (m, 3H), 7.80–7.55 (m, 5H),

7.50–7.46 (m, 1H), 6.95 (d, $J$ = 9.6 Hz, 1H), 5.77–5.73 (m, 1H), 5.00–4.91 (m, 2H), 4.64–4.60 (m, 2H). HRMS (ESI): calcd for $C_{23}H_{18}N_5O$ [M+H] 380.1508. Found: 380.1505.

#### 5.1.46. 2-(3-((3-(Pyridin-3-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (34)

The title compound was prepared in a similar manner as **26** using pyridine-3-boronic acid and compound **60**. (95%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.22 (s, 1H), 8.63 (d, $J$ = 5.28 Hz, 1H), 8.39–8.49 (m, 2H), 8.29 (d, $J$ = 2.64 Hz, 1H), 8.05 (d, $J$ = 9.24 Hz, 1H), 7.72 (d, $J$ = 9.24 Hz, 1H), 7.48–7.64 (m, 3H), 7.19–7.30 (m, 1H), 6.80 (d, $J$ = 9.24 Hz, 1H), 5.57–5.73 (m, 1H), 4.59 (dd, $J$ = 10.56, 7.04 Hz, 2H), 4.19 (dd, $J$ = 10.56, 3.96 Hz, 2H). HRMS (ESI): calcd for $C_{21}H_{18}N_5O$ [M+H] 356.1508. Found: 356.1507.

#### 5.1.47. 2-(3-((3-(Pyridin-4-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (35)

The title compound was prepared in a similar manner as **26** using pyridine-4-boronic acid and compound **60**. (53%) amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.71–8.60 (m, 2H), 8.30–8.29 (s, 1H), 8.07 (d, $J$ = 2.8 Hz, 1H), 7.95–7.97 (m, 2H), 7.81 (d, $J$ = 8.4 Hz, 1H), 7.54–7.52 (m, 1H), 7.49–7.45 (m, 2H), 7.18–7.15 (m, 1H), 6.53 (d, $J$ = 8.8 Hz, 1H), 5.60–5.57 (m, 1H), 4.62–4.58 (m, 2H), 4.23–4.20 (m, 2H). HRMS (ESI): calcd for $C_{21}H_{18}N_5O$ [M+H] 356.1508. Found: 356.1512.

#### 5.1.48. 2-(3-((3-(Pyrimidin-5-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (36)

The title compound was prepared in a similar manner as **26** using 5-pyrimidylboronic acid and compound **60**. (34%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.35 (d, $J$ = 2.64 Hz, 1H), 8.05 (d, $J$ = 9.68 Hz, 1H), 7.49–7.76 (m, 5 H), 7.18–7.29 (m, 1H), 6.81 (d, $J$ = 9.24 Hz, 1H), 5.62–5.71 (m, 1H), 4.59 (dd, $J$ = 10.34, 7.26 Hz, 2H), 4.22 (dd, $J$ = 10.34, 4.18 Hz, 2H). HRMS (ESI): calcd for $C_{20}H_{71}N_6O$ [M+H] 357.1461. Found: 357.1461.

#### 5.1.49. 2-(3-((3-(2-Methylpyridin-3-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (37)

The title compound was prepared in a similar manner as **26** using 2-methylpyridine-3-boronic acid, pinacol ester and compound **60**. (60%) amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.78 (s, 1H), 8.51–8.38 (m, 2H), 8.27 (s, 1H), 8.13–8.10 (m, 1H), 7.86–7.84 (m, 2H), 7.69–7.62 (m, 2H), 7.42–7.38 (m, 1H), 6.68 (d, $J$ = 8.4 Hz, 1H), 5.68 (s, 1H), 5.01–4.90 (m, 2H), 4.57–4.52 (m, 2H); 2.75 (s, 3H). HRMS (ESI): calcd for $C_{22}H_{20}N_5O$ [M+H] 370.1664. Found: 370.1668.

#### 5.1.50. 2-(3-((3-(6-Methylpyridin-3-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (38)

The title compound was prepared in a similar manner as **26** using 2-methylpyridine-5-boronic acid and compound **60**. (45%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.10 (s, 1H), 8.22–8.46 (m, 3H), 8.06 (d, $J$ = 9.24 Hz, 1H), 7.72 (d, $J$ = 8.36 Hz, 1H), 7.49–7.64 (m, 2H), 7.39 (d, $J$ = 9.24 Hz, 1H), 7.19–7.30 (m, 1H), 6.80 (d, $J$ = 9.24 Hz, 1H), 5.65 (d, $J$ = 6.60 Hz, 1H), 4.60 (dd, $J$ = 10.34, 7.26 Hz, 2H), 4.19 (dd, $J$ = 10.12, 3.96 Hz, 2H), 2.52 (s, 3H). HRMS (ESI): calcd for $C_{22}H_{20}N_5O$ [M+H] 370.1664. Found: 370.1661.

#### 5.1.51. 2-(3-((3-(2-Methylpyridin-4-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (39)

The title compound was prepared in a similar manner as **26** using 2-picoline-4-boronic acid and compound **60**. (46%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.56 (d, $J$ = 5.28 Hz, 1H), 8.45 (d, $J$ = 2.64 Hz, 1H), 8.33 (d, $J$ = 2.64 Hz, 1H), 8.05 (d, $J$ = 9.24 Hz, 1H), 7.83–7.92 (m, 2H), 7.72 (d, $J$ = 9.24 Hz, 1H), 7.49–7.63 (m, 2H), 7.19–7.29 (m, 1H), 6.80 (d, $J$ = 9.24 Hz, 1H), 5.60–5.69 (m, 1H), 4.60 (dd, $J$ = 10.34, 7.26 Hz, 2H), 4.21 (dd, $J$ = 10.56, 4.40 Hz, 2H), 2.54 (s, 3H). HRMS (ESI): calcd for $C_{22}H_{20}N_5O$ [M+H] 370.1664. Found: 370.1667.

#### 5.1.52. 5-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)quinoline (40)

The title compound was prepared in a similar manner as **26** using quinolin-5-boronic acid and compound **60**. (87%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.88 (dd, $J$ = 4.18, 1.54 Hz, 1H), 8.49 (d, $J$ = 3.08 Hz, 1H), 8.38 (d, $J$ = 2.64 Hz, 1H), 8.13 (d, $J$ = 8.80 Hz, 2H), 8.01 (d, $J$ = 9.68 Hz, 1H), 7.77–7.92 (m, 2H), 7.36–7.75 (m, 4H), 7.17–7.27 (m, 1H), 6.71 (d, $J$ = 9.24 Hz, 1H), 5.51–5.65 (m, 1H), 4.49 (dd, $J$ = 9.90, 7.26 Hz, 2H), 3.92 (dd, $J$ = 10.56, 4.40 Hz, 2H). HRMS (ESI): calcd for $C_{25}H_{20}N_5O$ [M+H] 406.1664. Found: 406.1671.

#### 5.1.53. 3-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)quinoline (41)

The title compound was prepared in a similar manner as **26** using quinoline-3-boronic acid and compound **60**. (39%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.55 (d, $J$ = 2.20 Hz, 1H), 9.07 (s, 1H), 8.51 (d, $J$ = 2.64 Hz, 1H), 8.33 (d, $J$ = 2.64 Hz, 1H), 8.03–8.20 (m, 3H), 7.50–7.90 (m, 5 H), 7.27 (d, $J$ = 7.92 Hz, 1H), 6.84 (d, $J$ = 9.24 Hz, 1H), 5.64–5.75 (m, 1H), 4.60–4.70 (m, 2H), 4.23–4.36 (m, 2H). HRMS (ESI): calcd for $C_{25}H_{20}N_5O$ [M+H] 406.1664. Found: 406.1671.

#### 5.1.54. 5-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)benzo[d]thiazole (42)

The title compound was prepared in a similar manner as **26** using 1,3-benzthiazol-6-ylboronic acid and compound **60**. (38%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.80 (s, 1H), 8.45 (d, $J$ = 2.64 Hz, 1H), 8.17–8.32 (m, 3H), 8.08 (d, $J$ = 9.68 Hz, 1H), 7.73 (d, $J$ = 8.36 Hz, 1H), 7.51–7.66 (m, 3H), 7.21–7.31 (m, 1H), 6.83 (d, $J$ = 9.24 Hz, 1H), 5.68 (s, 1H), 4.59–4.68 (m, 2H), 4.24 (d, $J$ = 14.96 Hz, 2H). HRMS (ESI): calcd for $C_{23}H_{18}N_5OS$ [M+H] 412.1229. Found: 412.1239.

#### 5.1.55. 6-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)quinazolin-2-amine (43)

The title compound was prepared in a similar manner as **26** using 2-aminoquinazolin-6-ylboronic acid and compound **60**. (27%) amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.11 (s, 1H), 8.49–8.60 (m, 2H), 8.35 (d, $J$ = 2.54 Hz, 1H), 8.09 (d, $J$ = 2.54 Hz, 1H), 7.92 (d, $J$ = 9.00 Hz, 1H), 7.77 (d, $J$ = 7.63 Hz, 1H), 7.52–7.70 (m, 4H), 6.64 (d, $J$ = 8.80 Hz, 1H), 5.64–5.75 (m, 1H), 5.35 (br s, 2H), 4.73 (t, $J$ = 7.82 Hz, 2H), 4.35 (d, $J$ = 5.67 Hz, 2H). MS (ESI) [M+H]: 422.1726. Calcd for $C_{24}H_{20}N_7O$ [M+H] 422.1729.

#### 5.1.56. 2-(3-((3-(Pyridin-2-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (33)

A solution of compound **60** (312 mg, 1.0 mmol), 2-tributylstannyl-pyridine (369 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.04 mmol) in toluene (10 mL) was stirred at 110 °C under $N_2$ atmosphere overnight. The reaction mixture was filtered through Celite™ and washed with $CH_2Cl_2$ (30 mL). The filtrate was concentrated and the crude product was purified by flash column chromatography eluting with 30–50% EtOAc/petroleum ether to give 80 mg (23%) as an amorphous solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 9.09–8.97 (m, 2H), 8.74–8.70 (m, 2H), 8.70–8.60 (m, 1H), 8.51 (d, $J$ = 2.4 Hz, 1H), 8.33 (d, $J$ = 9.6 Hz, 1H), 8.12–8.09 (m, 1H), 7.86 (d, $J$ = 8.4 Hz, 1H), 7.78–7.76 (m, 2H), 7.47–7.50 (m, 1H), 6.98 (d, $J$ = 9.2 Hz, 1H), 5.91–5.88 (m, 1H), 5.15–5.03 (m,

4H). HRMS (ESI): calcd for $C_{21}H_{18}N_5O$ [M+H] 356.1508. Found: 356.1514.

### 5.1.57. *tert*-Butyl 4-(3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (69)

To a solution of compound **60** (624 mg, 2.0 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate **68** (618 mg, 2.0 mmol) and $K_3PO_4$ (848 mg, 4.0 mmol) in 1,4-dioxane (20 mL) and $H_2O$ (4 mL) was added Pd(dppf)$Cl_2$ (146 mg, 0.2 mmol) then the reaction mixture was stirred at 110 °C under $N_2$ atmosphere overnight. The reaction mixture was filtered through Celite™ and washed with $CH_2Cl_2$ (50 mL). The filtrate was concentrated and the crude product was purified by silica gel column to give 600 mg (65%) of the title compound as an off-white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.18 (d, $J$ = 2.35 Hz, 1H), 7.94 (d, $J$ = 2.35 Hz, 1H), 7.91 (d, $J$ = 8.80 Hz, 1H), 7.77 (br s, 1H), 7.62 (d, $J$ = 8.02 Hz, 1H), 7.57 (t, $J$ = 7.53 Hz, 1H), 7.19–7.32 (m, 2H), 6.88 (br s, 1H), 6.62 (d, $J$ = 8.80 Hz, 1H), 5.53–5.67 (m, 1H), 4.67 (br s, 2H), 4.27 (br s, 2H), 4.14 (br s, 2H), 3.61 (t, $J$ = 5.38 Hz, 2H), 2.70 (br s, 2H), 1.48 (s, 9H). MS (ESI) [M+H]: 460 calcd for $C_{26}H_{29}N_5O_3$ 459.

### 5.1.58. 2-(3-((3-(Piperidin-4-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline hydrochloride (70)

A mixture of compound **69** (459 mg, 1.0 mmol) and 10% Pd–C (50% wet, 300 mg) in MeOH (20 mL) was stirred under $H_2$ (30 psi) at room temperature overnight then the reaction mixture was filtered through Celite™ and washed with MeOH. The filtrate was concentrated in vacuo to give 400 mg (86%) of *tert*-butyl 4-(3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidine-1-carboxylate. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.20 (d, $J$ = 2.78 Hz, 1H), 8.08 (d, $J$ = 2.78 Hz, 1H), 8.05 (d, $J$ = 8.77 Hz, 1H), 7.72 (d, $J$ = 7.45 Hz, 1H), 7.48–7.63 (m, 2H), 7.23 (ddd, $J$ = 7.97, 6.50, 1.46 Hz, 1H), 6.80 (d, $J$ = 8.77 Hz, 1H), 5.57 (tt, $J$ = 6.36, 4.02 Hz, 1H), 4.56 (dd, $J$ = 9.65, 6.58 Hz, 2H), 4.12 (dd, $J$ = 9.87, 4.17 Hz, 2H), 4.03 (d, $J$ = 12.72 Hz, 2H), 3.23 (tt, $J$ = 11.60, 3.45 Hz, 1H), 2.86 (br s, 2H), 1.80 (d, $J$ = 10.82 Hz, 2H), 1.49–1.69 (m, 2H), 1.31–1.48 (m, 9 H). MS (ESI) [M+H]: 463 calcd for $C_{26}H_{31}N_5O_3$ 462.

To *tert*-butyl 4-(3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidine-1-carboxylate (400 mg, 0.86 mmol) was added 4 M HCl in MeOH (20 mL). The reaction mixture was stirred at room temperature for 30 min and concentrated. The residue was dried under high vacuum to give 310 mg (100%) of the title compound as a white solid. MS (ESI) [M+H]: 362 calcd for $C_{21}H_{23}N_5O$ 361.

### 5.1.59. Methyl 4-(3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidine-1-carboxylate (45)

To a solution of compound **70** (100 mg, 0.29 mmol) in dry $CH_2Cl_2$ (10 mL) was added $Et_3N$ (1 mL). The reaction mixture was cooled to 0 °C with an ice bath, and methyl chloroformate (54 mg, 0.58 mmol) was added dropped to the reaction mixture. After 1 h, the reaction mixture was warmed to room temperature, and stirred overnight. Then the reaction mixture was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under vacuum to give the crude product. The crude product was purified via flash chromatography eluting with 20–45% EtOAc/petroleum ether to give 93 mg (79%) of the title compound as a white solid. $^1$H NMR ($CD_3OD$, 400 MHz) $\delta$ 8.38–8.35 (m, 1H), 8.18–8.17 (m, 1H), 8.17–8.02 (m, 1H), 7.92–7.90 (m, 1H), 7.83–7.76 (m, 2H), 7.55–7.51 (m, 1H), 7.01–6.99 (m, 1H), 5.70–5.67 (m, 1H), 5.00–4.95 (m, 1H), 4.63–4.59 (m, 2H), 4.58–4.24 (m, 2H), 4.21–3.69 (m, 2H), 3.35 (s, 3H), 3.35–3.34 (m, 2H), 3.02–3.01 (m, 2H), 1.81–1.75 (m, 2H). HRMS (ESI): calcd for $C_{23}H_{26}N_5O_3$ [M+H] 420.2030. Found: 420.2039.

### 5.1.60. 1-(4-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)pyrazin-2-yl)piperidin-1-yl)ethanone (44)

The title compound was prepared in a similar manner as **45** using acetyl chloride and compound **70**. 33% colorless solid. $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.13 (d, $J$ = 2.78 Hz, 1H), 7.98–8.07 (m, 2H), 7.68 (d, $J$ = 8.33 Hz, 2H), 7.55 (ddd, $J$ = 8.40, 6.94, 1.46 Hz, 1H), 7.18–7.32 (m, 1H), 6.76 (d, $J$ = 8.92 Hz, 1H), 5.63 (tt, $J$ = 6.43, 4.09 Hz, 1H), 4.54–4.72 (m, 3H), 4.23 (ddd, $J$ = 6.83, 5.88, 3.07 Hz, 2H), 4.02 (m, $J$ = 13.74 Hz, 1H), 3.41 (tt, $J$ = 11.47, 3.87 Hz, 1H), 3.26 (dd, $J$ = 13.45, 3.22 Hz, 1H), 2.80 (td, $J$ = 12.83, 2.70 Hz, 1H), 2.11 (s, 3H), 1.62–2.03 (m, 4H). HRMS (ESI): calcd for $C_{23}H_{26}N_5O_2$ [M+H] 404.2081. Found: 404.2087.

### 5.1.61. 2-(3-((3-(1-(Methylsulfonyl)piperidin-4-yl)pyrazin-2-yl)oxy)azetidin-1-yl)quinoline (46)

The title compound was prepared in a similar manner as **45** using methanesulfonyl chloride and compound **70**. (77%) amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.19 (d, $J$ = 2.8 Hz, 1H), 8.13 (d, $J$ 9.2 Hz, 1H), 7.99–7.93 (m, 2H), 7.76–7.70 (m, 2H), 7.48–7.44 (m, 1H), 6.62 (d, J = 9.2 Hz, 1H), 5.58 (s, 1H), 5.14–4.39 (m, 4H), 3.23–3.10 (m, 1H), 3.92–3.93 (m, 2H), 2.90–2.81 (m, 2H), 2.81 (s, 3H), 1.97–1.96 (m, 4H). HRMS (ESI): Calcd for $C_{22}H_{26}N_5O_3S$ [M+H] 440.1751. Found: 440.1758.

### 5.1.62. Benzyl 4-(3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)quinoxalin-2-yl)piperidine-1-carboxylate (72)

A premixed mixture of TMSCl and 1,2-dibromoethane (7:5, v/v, 0.80 mL total volume added) was added dropwise over 5 min to a suspension of zinc (1.622 g, 24.8 mmol) in DMA (12 mL) under argon atmosphere. The mixture was stirred for 15 min before benzyl 4-iodopiperidine-1-carboxylate[19] (7.13 g, 20.7 mmol) was added dropwise over 15 min as a solution in DMA (6 mL). This mixture was stirred for an additional 15 min before adding to quinoxaline **71** below.

The above (1-((benzyloxy)carbonyl)piperidin-4-yl)zinc(II) iodide (8.49 g, 20.7 mmol) solution was added slowly to a suspension of 2-chloro-3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)quinoxaline **71** (5.0 g, 13.8 mmol), copper(I) iodide (0.262 g, 1.378 mmol), and Pd(dppf)$Cl_2$ dichloromethane adduct (0.56 g, 0.69 mmol) in DMA (15 mL) under argon. This mixture was stirred at 80 °C for 2 h, then cooled to room temperature. EtOAc was added and the suspension was filtered through Celite™ to remove insoluble material. The filtrate was then diluted with more EtOAc and then washed with water (3×), brine (1×), dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. This oil was purified by silica gel chromatography eluting with 0–100% EtOAc/hexane to give 6.93 g (92%) of the title compound an off-white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.72 (qd, $J$ = 12.32, 3.91 Hz, 2H), 1.91–2.02 (m, 2H), 3.03 (br s, 2H), 3.45 (tt, $J$ = 11.47, 3.40 Hz, 1H), 4.15 (d, $J$ = 13.11 Hz, 2H), 4.22 (dd, $J$ = 9.88, 4.01 Hz, 2H), 4.65 (dd, $J$ = 9.68, 6.55 Hz, 2H), 5.10 (s, 2H), 5.72 (tt, $J$ = 6.41, 4.16 Hz, 1H), 6.82 (d, $J$ = 8.80 Hz, 1H), 7.23 (td, $J$ = 7.34, 1.37 Hz, 1H), 7.28–7.34 (m, 1H), 7.35–7.40 (m, 4H), 7.51–7.56 (m, 1H), 7.57–7.61 (m, 1H), 7.61–7.67 (m, 1H), 7.69–7.75 (m, 2H), 7.83 (dd, $J$ = 8.22, 1.17 Hz, 1H), 7.96 (dd, $J$ = 8.22, 1.17 Hz, 1H), 8.06 (d, $J$ = 8.80 Hz, 1H). MS (ESI) $m/z$: 546.2 [M+H]. Calcd for $C_{33}H_{31}N_5O_3$: 545.2.

### 5.1.63. 1-(4-(3-((1-(Quinolin-2-yl)azetidin-3-yl)oxy)quinoxalin-2-yl)piperidin-1-yl)ethanone (47)

Palladium hydroxide, 20 wt % Pd (dry basis) on carbon, wet, Degussa type e101 ne/w (1.15 g, 1.63 mmol) was added to a mixture of benzyl 4-(3-((1-(quinolin-2-yl)azetidin-3-yl)oxy)quinoxalin-2-yl)piperidine-1-carboxylate **72** (5.93 g, 10.9 mmol)

and acetic anhydride (3.08 mL, 32.6 mmol) in THF (50 mL) under argon atmosphere. The mixture was placed under 1 atm hydrogen and the mixture was heated to 50 °C for 6 h. The filtrate was diluted with EtOAc, transferred to a separatory funnel, and washed with satd $NaHCO_3$ (2×), dried over $MgSO_4$, filtered, and concentrated in vacuo to give an oil. This oil was purified by silica gel chromatography eluting with 0–100% acetone/hexane to give 3.34 g (68%) of the title compound as a white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.71 (qd, $J$ = 12.39, 4.30 Hz, 1H), 1.90 (qd, $J$ = 12.42, 4.01 Hz, 1H), 2.03–2.12 (m, 2H), 2.13 (s, 3H), 2.83 (td, $J$ = 12.76, 2.25 Hz, 1H), 3.28–3.38 (m, 1H), 3.59 (tt, $J$ = 11.49, 3.47 Hz, 1H), 4.05 (d, $J$ = 13.69 Hz, 1H), 4.30–4.37 (m, 2H), 4.61 (d, $J$ = 13.30 Hz, 1H), 4.77 (dd, $J$ = 9.29, 6.75 Hz, 2H), 5.84 (ddd, $J$ = 6.41, 4.06, 2.25 Hz, 1H), 6.94 (d, $J$ = 9.00 Hz, 1H), 7.34 (td, $J$ = 7.34, 1.17 Hz, 1H), 7.61–7.67 (m, 1H), 7.68–7.72 (m, 1H), 7.72–7.77 (m, 1H), 7.80–7.86 (m, 2H), 7.94 (dd, $J$ = 8.22, 1.17 Hz, 1H), 8.07 (dd, $J$ = 8.12, 1.08 Hz, 1H), 8.17 (d, $J$ = 8.80 Hz, 1H). HRMS (ESI): calcd for $C_{27}H_{28}N_5O_3$ [M+H] 454.2243. Found: 454.2247.

### 5.2. Solubility assay

Compounds as 10 mM DMSO stock solutions were dispensed into 96 deep well plates at a volume of 10 μL per well. Four copies of identical plates were created. The DMSO was removed in a Genevac Evaporator for 2.5 h, 40 °C, under full vacuum. After dry down was complete, a Tecan Evo Liquid Handler was used to transfer 200 μL of the buffer to the corresponding plate copy. The buffer used was phosphate-buffered saline (PBS, pH 7.4) and the solvent DMSO was used to create the standard plate for comparison. The plates were sealed and centrifuged at 1000 rpm for 1 min to push all liquid from walls to the bottom of the wells. The plates were shaken at 1500 rpm on a 3 mm radius orbital shaker for 1 h. The samples were equilibrated at room temperature for 72 h. The plates were centrifuged at 4000 rpm for 30 min. The supernatant was analyzed by LC/MS, at 215 nm, 2 μL injection volume. Peak area in PBS was compared to DMSO standard to determine solubility, accurate within the range of 5–500 μM.

### 5.3. Biology

#### 5.3.1. Enzyme assay

The purified human PDE enzymes were obtained from BPS Bioscience (San Diego, CA). IMAP™ TR-FRET progressive binding system, FAM-cAMP or FAM-cGMP substrates were obtained from Molecular Devices (Sunnyvale, CA). The PDE IMAP assay was conducted in a 384-well black Greiner polypropylene plate (Sigma, St. Louis, MO). PDE inhibitors were serial diluted in 100% DMSO and dispensed into assay plate at 200 nL per well (65 nL per well in case of PDE 10) using Echo® Liquid Handling System from LABCYTE. Ten μL of PDE enzyme in IMAP reaction buffer (10 mM Tris–HCl, pH 7.2, 10 mM $MgCl_2$, 0.05% $NaN_3$, and 0.01% Tween-20) was added into the assay wells. The PDE enzyme concentration used was based on each lot of enzyme activity, to ensure enzyme reaction falls in a linear range under assay condition. Enzyme was pre-incubated with inhibitors for 60 min at room temperature before addition of 10 μL of substrate, which results in 100 nM of FAM-cAMP or FAM-cGMP in the reaction. In the PDE assays, FAM-cAMP was used as substrate for PDE isoforms 1B, 2A1, 3A, 4D2, 7A1, 8A1, 10A2, 11A4 and FAM-cGMP was used as substrate for isoforms 5A, 9A2. Enzyme reaction was allowed to proceed at room temperature for 90 min, and the reaction is stopped by 55 μL addition of binding reagent according to manufacturer's recommendation. The mixture is further incubated at room temperature for additional 4 h, and signal was read on an Envision multimode reader (PerkinElmer). Fluorescence signals were measured at 520 nm and 485 nm. The signal ratio at 520/485 nm corresponded to the generation of reaction product of AMP/GMP, and it was used in all data analysis. Values from DMSO-treated wells were normalized to POC = 100, and no-enzyme wells were normalized to POC = 0. $IC_{50}$ values were determined by using the Genedata Screener V9.0.1. The curve fitting algorithm used for dose response data analysis in Genedata Screener is a custom implementation of a robust curve-fitting algorithm called ROUT (Robust regression with outlier detection) and uses a four-parameter logistical (4PL) Hill model.

#### 5.3.2. Ex vivo RO

Adult male Sprague Dawley rats® weighing 180–225 g (Harlan, San Diego) were cared for in accordance to the Guide for the Care and Use of Laboratory Animals, 8th Edition. Animals were group-housed at an Association for Assessment and Accreditation of Laboratory Animal Committee, internationally-accredited facility in nonsterile ventilated micro-isolator housing on corn cob bedding. All research protocols were approved by the Amgen, Thousand Oaks Institutional Animal Care and Use Committee. Animals had ad libitum access to pelleted feed (Harlan Teklad 2020X, Indianapolis, IN) and water (on-site generated reverse osmosis) via automatic watering system. Animals were maintained on a 12:12 h light/ark cycle in rooms at (70 ± 5 °F, 50 ± 20% RH) and had access to enrichment opportunities (nesting materials and plastic domes). All animals were sourced from approved vendors who meet or exceed animal health specifications for the exclusion of specific pathogens (i.e., mouse parvovirus, Helicobacter). Rats were allowed at least 3 days of acclimation prior to any procedures.

PDE10 inhibitors were dissolved in 2% hydroxypropylmethylcellulose (HPMC), 1% Tween-80, pH 2.2 with methanesulfonic acid. 4 rats per group were dosed orally with either vehicle or 3 mg/kg PDE10 inhibitors and then returned to their home cage to allow for absorption of the compounds. After 4 h rats were sacrificed by $CO_2$ inhalation. Blood was obtained by heart puncture and plasma was frozen and stored at −80 °C for exposure analysis. Brains were removed and immediately frozen in chilled methylbutane, and stored at −80 °C until cutting. Three coronal brain slices per brain containing the striatum were cut at 20 μm using a cryostat and placed onto microscope slides, air-dried and stored at −20 °C. For radioligand binding experiments, slides were thawed at room temperature and then incubated with 1 nM $^3$H-5-(6,7-bis(methyloxy)-4-cinnolinyl)-3-methyl-*N*-(1-methylethyl)-2-pyridinamine[18] in binding buffer (150 mM Phosphate-buffered saline containing 2 mM $MgCl_2$ and 100 mM DTT, pH 7.4) for 1 min at 4 °C. To assess nonspecific binding, slides containing adjacent brain sections were incubated in the same solution with addition of 10 mM 2-(((4-(4-(4-pyridinyl)-1*H*-pyrazol-5-yl)phenyl)oxy)methyl)quinoline[20], an unlabelled, structurally unrelated PDE10 antagonist. Afterwards slides were washed 3 times in ice-cold binding buffer, dipped into distilled water to remove buffer salts, and dried under a stream of cold air. Emission of beta particles from the sections was counted for 8 h in a Beta Imager 2000 (Biospace, Paris, France) and digitized and analyzed using M3 Vision software (Biospace, Paris, France). Total binding radioactivity in the striatum was measured as cpm/mm$^2$ in hand-drawn regions of interest and averaged across the three sections per brain. Nonspecific binding was subtracted to obtain specific binding values and percent occupancy was calculated by setting vehicle specific binding as 0% occupancy.

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