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Rational design of 6-(2,4-diaminopyrimidinyl)-1,4-benzoxazin-3-ones as small molecule renin inhibitors

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Abstract—We report the design and synthesis of a series of 6-(2,4-diaminopyrimidinyl)-1,4-benzoxazin-3-ones as orally bioavailable small molecule inhibitors of renin. Compounds with a 2-methyl-2-aryl substitution pattern exhibit potent renin inhibition and good permeability, solubility, and metabolic stability. Oral bioavailability was found to be dependent on metabolic clearance and cellular permeability, and was optimized through modulation of the sidechain that binds in the $S3^{sp}$ subsite.

1. Introduction

Hypertension is a leading risk factor for cardiovascular disease, such as congestive heart failure, stroke, and myocardial infarction, and is a major cause of death in the Western world.[1] The renin angiotensin system (RAS) is well established as an endocrine system involved in blood pressure regulation and fluid electrolyte balance (Fig. 1).[2] Activation of the RAS is stimulated by several signals, including a drop in blood pressure, a decrease in the circulating volume, or a reduction in plasma sodium concentration. These signals stimulate the release of renin, which cleaves angiotensinogen at the peptide bond between Leu10 and Val11 to form angiotensin I (AngI). Angiotensin converting enzyme (ACE) then converts AngI into the vasopressor octapeptide angiotensin II (AngII). The binding of AngII to the AT_1 receptor initiates a number of physiological effects, such as sodium and water retention and vasoconstriction, ultimately leading to an increase in blood pressure. Since renin is the rate-limiting step in the RAS cascade and angiotensinogen is the only known renin substrate,

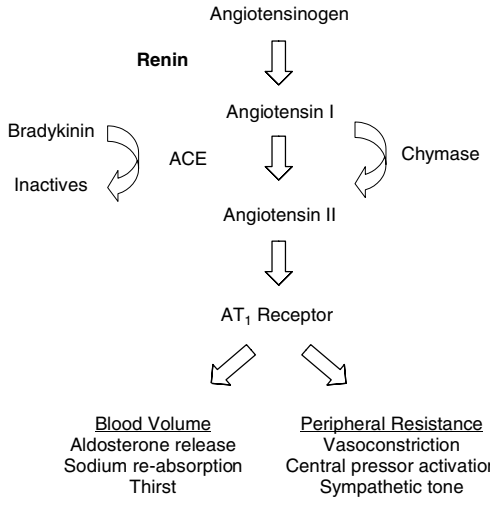

Figure 1. The renin angiotensin system (RAS).

Keywords: Hypertension; Renin; Structure-based drug design; Oral bioavailability.
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renin inhibition is considered to be an attractive antihypertensive strategy. Furthermore, inhibition of renin prevents the formation of AngI and AngII, unlike the angiotensin receptor blockers (ARBs) and ACE inhibitors, which increase AngI levels but do not block ACE-independent AngII production through the hydrolysis of AngI by chymase in human heart tissue. In addition, ACE has been shown to degrade the pharmacologically active peptide bradykinin which has been implicated in a chronic cough side effect that affects 5–35% of patients treated with ACE inhibitors.[3] Therefore, renin inhibitors have been predicted to provide better kidney and heart protection than ACE inhibitors and ARBs while offering superior blood pressure lowering.[4]

Many pharmaceutical companies have advanced renin inhibitors to the clinic during the past few decades. Most programs were based on peptidic or peptidomimetic scaffolds that were designed to mimic the N-terminal sequence of angiotensinogen (Fig. 2). Although potent in vitro renin inhibitory activity was obtained, these scaffolds, exemplified by CI-992 and others, frequently exhibited poor pharmacokinetic properties and low oral bioavailability likely due to high molecular weights (MW > 600), conformational flexibility (>15 rotatable bonds), dissolution limited absorption, and high metabolic clearance.[5,6] Research on these scaffolds reached an apex with the discovery and development of aliskerin by scientists at Novartis and Speedel.[4c,7] Aliskerin was recently approved by the FDA for the treatment of hypertension under the trade name Tekturna® in March, 2007. Like CI-992, aliskerin is a transition-state mimic with high MW = 552 and large number of rotatable bonds (21), but it takes advantage of a subpocket accessible from the S3 region ($S3^{sp}$) that is unique for renin to provide additional potency and specificity against other aspartic proteases. In spite of the low human oral bioavailability (3%), aliskerin exhibits comparable blood pressure reduction to the AT1-receptor antagonist losartan (300 mg daily vs 100 mg daily) due to very potent inhibition of human renin (IC_{50} = 0.6 nM), low plasma protein binding, and an extended in vivo half-life (24 h).[8] Aliskerin has also demonstrated superior protection from AngII-induced end organ damage in a double transgenic rat model, illustrating the potential of renin inhibitors to combat cardiovascular disease.[9] Since the initial disclosure of aliskerin, work around similar templates has been reported.[10] In 1999, the first non-peptidomimetic renin inhibitors, exemplified by Ro-X1, were disclosed by researchers at Roche.[11] The *trans*,*trans*-3,5-dialkoxy-4-aryl-piperidine scaffold of Ro-X1 binds in the renin active site in an induced-fit flap-open conformation with the 3-(2-methoxybenzyloxy)-propanoxy sidechain binding in a large lipophilic pocket that is revealed upon the conformational change in the flap region of the protein. Ro-X1 lowered BP in marmoset monkeys, and prevented cardiac hypertrophy and albuminuria in double transgenic rats that express both human angiotensinogen and renin proteins.[11d] Although a non-peptidomimetic scaffold, Ro-X1 exhibited poor oral bioavailability (6% in dog) due to rapid first pass metabolism of the highly lipophilic compound by CYP3A4.[11e] The *trans*,*trans*-3,5-dialkoxy-4-aryl-piperidine

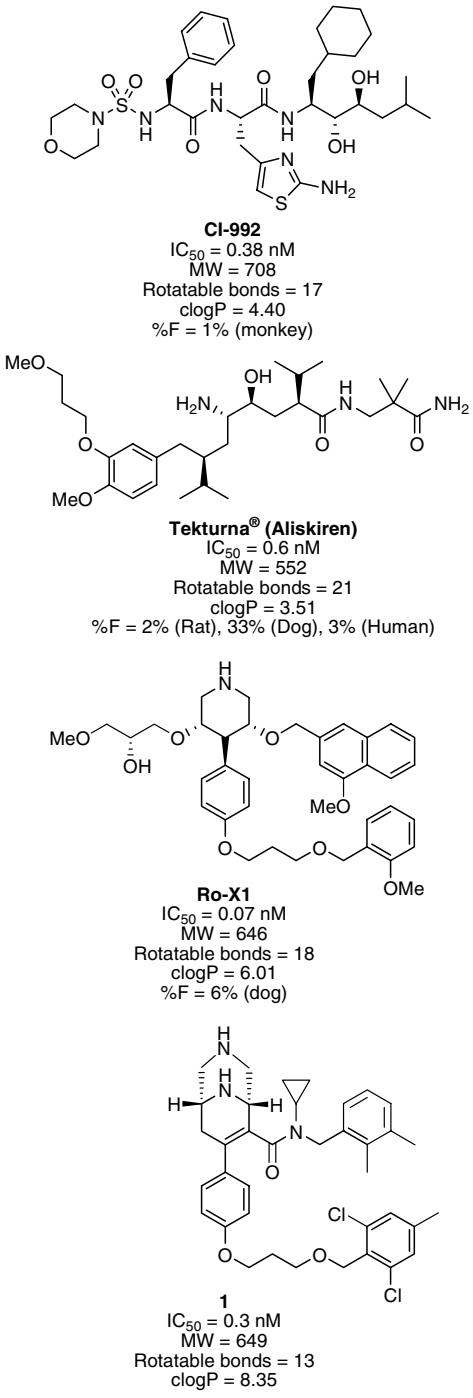


Figure 2. Large molecule renin inhibitors.

scaffold of Ro-X1 has served as the inspiration for the design of similar templates,[12] including compound **1** and previous reports from these laboratories on the design of a 6-alkoxymethyl-1-aryl-2-ketopiperazine scaffold (**2**, Fig. 3).[13] Although compounds based on the 4-aryl-piperidine scaffold have recently entered human clinical trials, these scaffolds frequently possess high molecular weights and *c*log *P* values and large number of rotatable bonds, reducing the likelihood of attaining good drug-like properties. Due to the lipophilic nature of the large renin active site, the design of small molecule renin inhibitors with good drug-like properties has been

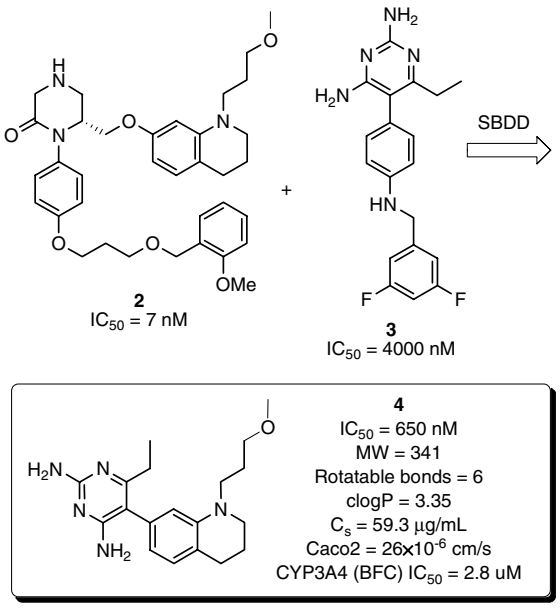


Figure 3. Design of the novel small molecule renin inhibitor **4**.

perceived as difficult to attain, and consequently, there is a clear need for the discovery of novel renin inhibitor templates.

We have recently reported the structure-based design of a novel 7-(2,4-diamino-6-ethyl-pyrimidinyl)-tetrahydroquinoline-based inhibitor of renin, **4** (Fig. 3).[14] This compound was designed based on the overlap observed in the crystal structures of the 6-alkoxymethyl-1-aryl-2-ketopiperazine **2** and 5-aryl-2,4-diamino-6-ethyl-pyrimidine **3** bound within the active site of renin. Compound **4** exhibited submicromolar renin inhibitory activity with a molecular weight of 341 and 6 rotatable bonds, as well as moderate lipophilicity, good solubility, and cellular permeability. In addition, **4** exhibited only modest inhibition of CYP3A4 compared to compounds in our previously reported ketopiperazine series,[13] and was therefore viewed as a promising lead for further structure-activity studies. The 2-aminoheterocycle motif appears to be a new and potentially general template for binding to the catalytic groups of aspartic proteases, as 2-aminopyridines and 2-aminoquinolines have recently been reported to bind in a similar manner to the catalytic aspartate residues in β-secretase.[15] In this paper, we report our structure-activity studies on the 7-(2,4-diamino-6-ethyl-pyrimidinyl)-tetrahydroquinoline template to optimize the renin inhibitory activity and pharmacokinetic properties.

2. Design of 6-(2,4-diaminopyrimidinyl)-1,4-benzoxazin-3-ones

The initial goal of our studies was to improve the potency of **4** to low nanomolar levels. The potency of **4** was driven largely by the extension of the 3-methoxypropyl group into the $S3^{sp}$ subpocket, as analogs that did not access the $S3^{sp}$ subsite were >10-fold less active.[14] While introduction of an ester functionality in the $S3^{sp}$ subsite sidechain led to a >5-fold improvement in potency, the target potency range (<20 nM) could not be achieved solely through manipulation of the $S3^{sp}$ subsite sidechain. In addition, the introduction of an ester group was viewed as a potential metabolic liability, as the corresponding acids were inactive against renin.[14] Consequently, we sought to improve potency through modifications at other sites of the template. Our SAR around the early HTS lead **3** indicated that the renin inhibition activity was driven largely by substituents around the benzylamine ring.[14] Crystal structures of **3** bound in the flap-closed conformation of renin indicated the 3,5-difluorobenzylamine ring occupies the S4 pocket and partly extends into solvent. Overlap of the crystal structures of **3** and **4** indicated that addition of substituents at the tetrahydroquinoline C-3 position might increase potency through additional van der Waals contacts in the S4 pocket (Fig. 4). As 3-substituted tetrahydroquinolines are synthetically challenging targets and less amenable to rapid analoging, we envisioned that replacing the C-4 carbon atom with an oxygen atom would allow for a modular synthesis using readily available α-hydroxyacetate derivatives to introduce the desired substituent (Fig. 5). Our previously reported SAR in the ketopiperazine series (i.e., compound **2**) indicated that 1,4-benzoxazin-3-ones were readily accepted in the S3 pocket.[13d] Accordingly, we targeted a series of 2-substituted-1,4-benzoxazines and 1,4-benzoxazin-3-ones with the goal of optimizing renin inhibitory activity.

3. Chemistry

The unsubstituted 1,4-benzoxazine and 1,4-benzoxazin-3-one analogs **5** and **6** were synthesized as shown in Scheme 1. Alkylation of 4-bromo-2-nitrophenol **48** with ethyl 2-bromoacetate and reduction of the nitro group with Fe/acetic acid followed by in situ cyclization yielded 7-bromo-1,4-benzoxazin-3-one **49**. The 3-methoxypropyl sidechain was introduced by deprotonation of the amide with NaH in DMF, followed by addition

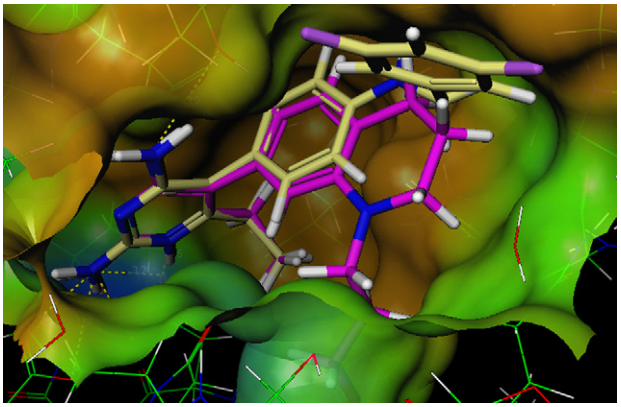


Figure 4. Overlap of the crystal structures of **3** (yellow stick, 1.9 Å resolution, PDB code: 2G24) and **4** (purple stick, 2.2 Å resolution, PDB code: 2G21) in the renin active site (flap-closed conformation). The protein Connolly surface is colored by hydrophobicity. Brown, hydrophobic; blue, hydrophilic.

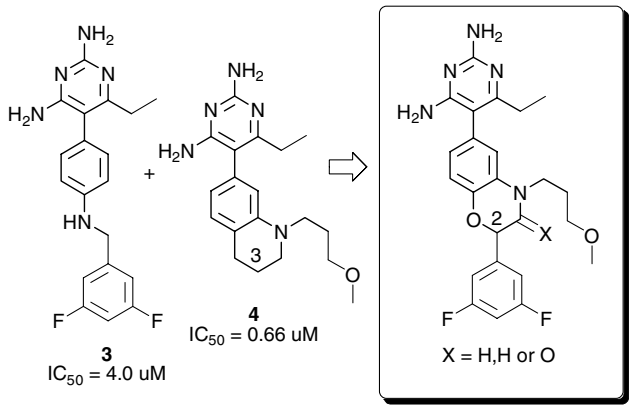
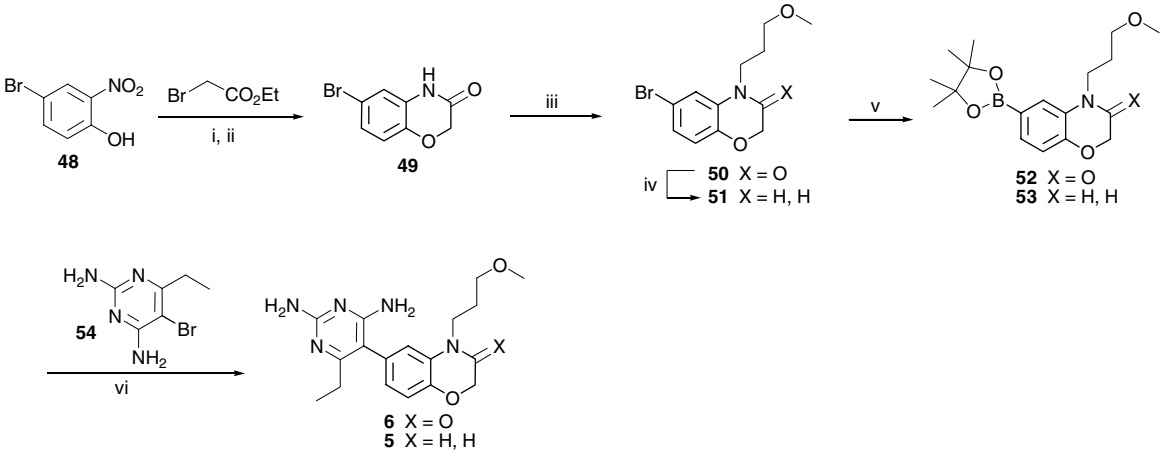


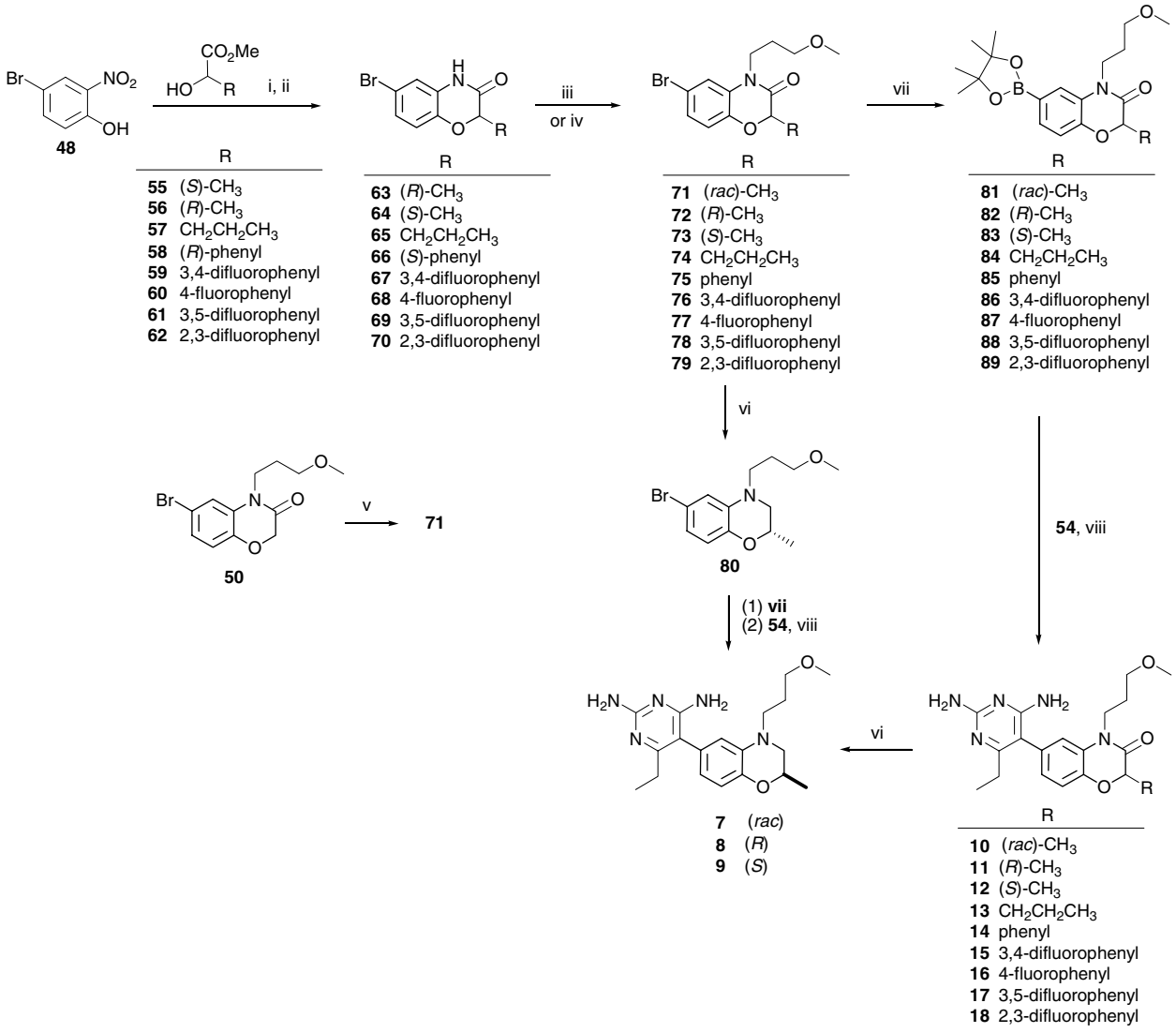
Figure 5. Design of the 1,4-benzoxazine and 1,4-benzoxazin-3-one scaffold.

of 1-bromo-3-methoxypropane to give **50**. Bromide **50** was converted to the boronate **52** by a Pd-catalyzed Miyaura borylation with bis(pinacolato)diboron. Suzuki coupling with 5-bromo-2,4-diamino-6-ethyl-pyrimidine **54**[17] in a 1,4-dioxane/H_2O solvent mixture yielded the desired 1,4-benzoxazin-3-one analog **6**. Best yields in the Suzuki coupling reaction were obtained using CsOH as base in the presence of 300 mol% LiCl. Reduction of the amide bond in intermediate **50** with BH_3–SMe_2 provided the corresponding 1,4-benzoxazine **51**, which was converted to the 1,4-benzoxazine analog **5** in an analogous two-step fashion. Our synthetic approach toward the desired 2-substituted-1,4-benzoxazin-3-ones relied on a Mitsunobu coupling with 2-hydroxy carboxylic ester derivatives and a deprotonation of intermediate **50** and alkylation of the resulting enolate with the appropriate electrophile to introduce the desired substituent (Scheme 2). Mitsunobu coupling of 4-bromo-2-nitrophenol **48** and 2-hydroxy carboxylic esters **55**–**62**, followed by reduction of the nitro group and in-situ cyclization, yielded the corresponding 2-substituted-1,4-benzoxazin-3-ones **63**–**70**. No loss of enantiomeric purity was observed in the Mitsunobu coupling and reduction/cyclization of the chiral 2-hydroxy esters **55**, **56**, and **58**. The racemic 2-methyl-1,4-benzoxazin-3-one **71** was prepared by NaH deprotonation of **50** and alkylation of the resulting enolate with MeI. The 2-methoxypropyl sidechain was introduced by deprotonation of the amide with NaH and treatment with 2-bromo-1-methoxypropane in the presence of 15-crown-5 or alkylation with 2-bromo-1-methoxypropane in the presence of K_2CO_3. While the chirality of **63** and **64** was preserved under the NaH conditions to give the corresponding tertiary amides **72** and **73** with no loss of enantiomeric purity, the more acidic methine proton in **66** was easily deprotonated under these conditions to give **75** as a racemic mixture. Intermediates **81**–**89** were converted to the desired analogs **10**–**18** via the previously described two-step Miyaura borylation and Suzuki coupling method. The racemic 2-methyl-1,4-benzoxazine analog **7** and (2*R*)-**8** were prepared by BH_3–SMe_2 reduction of the 1,4-benzoxazin-3-ones **10** and **11**, respectively. The corresponding (2*S*)-**9** analog was prepared by BH_3–SMe_2 reduction of intermediate **73**, followed by boronate formation and Suzuki coupling.

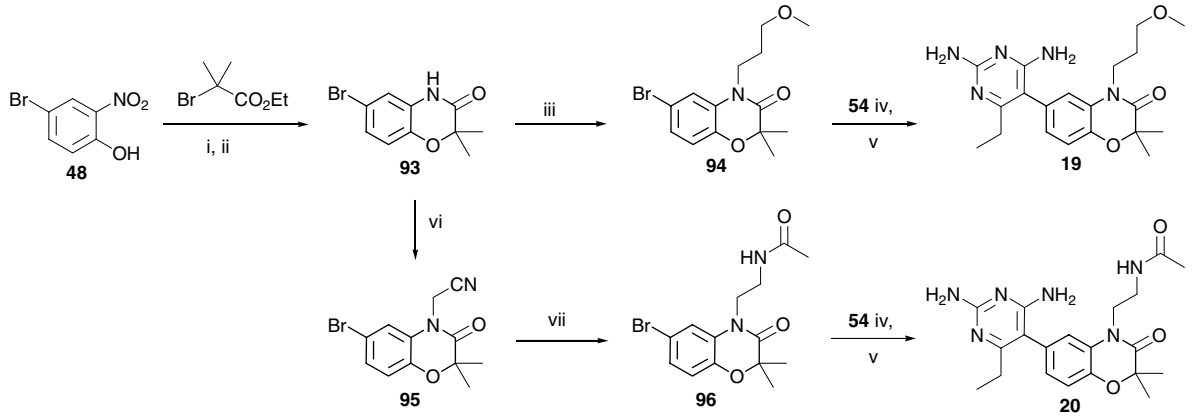
The 2,2-dimethyl analogs **19** and **20** were prepared as shown in Scheme 3. Alkylation of phenol **48** with ethyl 2-bromoisobutyrate under concentrated conditions and nitro reduction/cyclization provided the 2,2-dimethyl-1,4-benzoxazin-3-one **93** in excellent yield. Intermediate **93** was transformed into analog **19** by the standard protocol of alkylation with 1-bromo-3-methoxypropane, boronate formation, and Suzuki coupling. As part of our strategy to improve the metabolic stability, we were also interested in replacing the 3-methoxypropyl sidechain with an *N*-(2-ethyl)acetamide sidechain. This was installed by alkylation of intermediate **93** with bromoacetonitrile to afford nitrile **95**, which was then hydrogenated over Raney nickel in the presence of acetic anhydride to afford the acetamide **96**. Miyaura borylation and Suzuki coupling yielded analog **20**. Other more highly substituted 2,2-disubstituted-1,4-benzoxazin-3-one ring intermediates **95**–**111** were prepared through a convergent nucleophilic aromatic substitution/reduction method using the corresponding α-hydroxyacetate



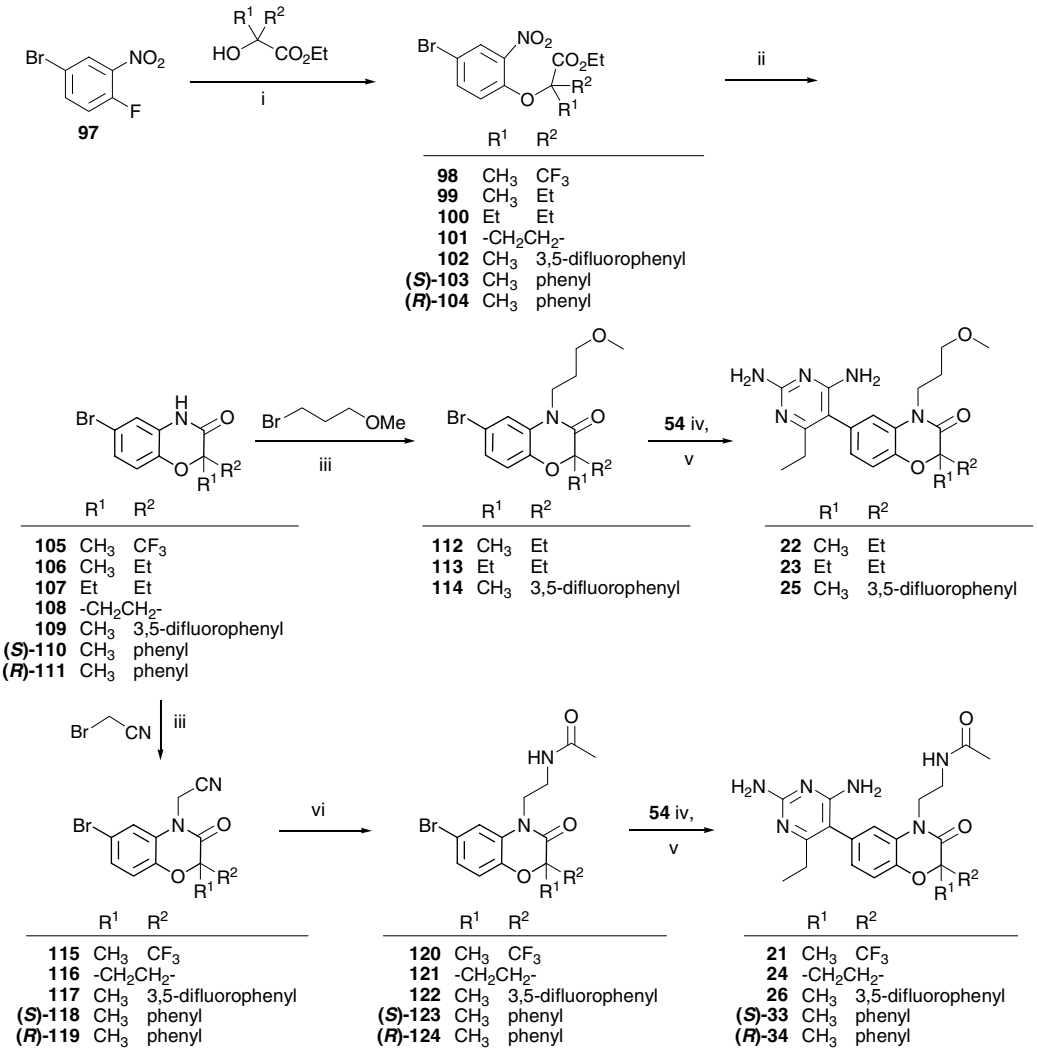
Scheme 1. Reagents and conditions: (i) K_2CO_3, acetone, reflux; (ii) Fe, AcOH, 50 °C; (iii) 1-bromo-3-methoxy propane, NaH, 15-crown-5, DMF, rt; (iv) BH_3–SMe_2, THF, 50 °C; (v) Bis(pinacolato)diboron, $Pd(dppf)_2Cl_2$, KOAc, 1,4-dioxane, 90 °C; (vi) $Pd(PPh_3)_4$, CsOH, LiCl, 1,4-dioxane/H_2O, reflux.



Scheme 2. Reagents and conditions: (i) PS–PPh_3, DIAD, CH_2Cl_2, rt; (ii) Fe, AcOH, 50 °C; (iii) NaH, 15-crown-5, DMF, rt, then 1-bromo-3-methoxy propane; (iv) 1-bromo-3-methoxy propane, K_2CO_3, CH_3CN, reflux; (v) NaH, DMF, 0 °C; then MeI; (vi) BH_3-SMe_2, THF, 50 °C; (vii) bis(pinacolato)diboron, $Pd(dppf)_2Cl_2$, KOAc, 1,4-dioxane, 90 °C; (viii) $Pd(PPh_3)_4$, CsOH, LiCl, 1,4-dioxane/H_2O, reflux.



Scheme 3. Reagents and conditions: (i) K_2CO_3, CH_3CN, reflux; (ii) Fe, AcOH, 50 °C; (iii) 1-bromo-3-methoxy propane, NaH, 15-crown-5, DMF, rt; (iv) bis(pinacolato)diboron, $Pd(dppf)_2Cl_2$, KOAc, 1,4-dioxane, 90 °C; (v) $Pd(PPh_3)_4$, CsOH, LiCl, 1,4-dioxane/H_2O, reflux; (vi) K_2CO_3, bromoacetonitrile, CH_3CN, reflux; (vii) H_2, Raney Ni, Ac_2O, THF.

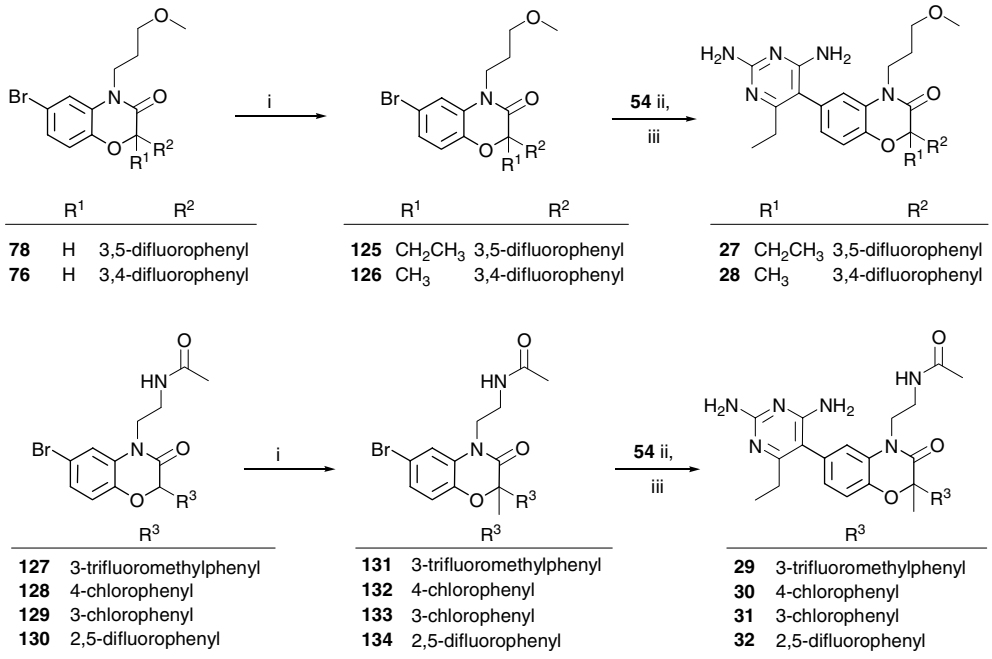


Scheme 4. Reagents and conditions: (i) NaH, 15-crown-5-THF, 0 °C; (ii) Fe, AcOH, 50 °C; (iii) K_2CO_3, CH_3CN, reflux; (iv) bis(pinacolato)diboron, $Pd(dppf)_2Cl_2$, KOAc, 1,4-dioxane, 90 °C; (v) $Pd(PPh_3)_4$, CsOH, LiCl, 1,4-dioxane/H_2O, reflux; (vi) H_2, Raney Ni, Ac_2O, THF.

esters (Scheme 4). Our standard alkylation, boronate formation, and Suzuki coupling route afforded the desired analogs **21**–**26**, **33**, and **34**. Analogs **27** and **28** were prepared by NaH deprotonation of the mono-substituted intermediates **78** and **76**, and alkylation with iodomethane or iodoethane, respectively (Scheme 5). Analogs **29**–**32** with the *N*-ethylacetamide sidechain were synthesized from the corresponding intermediates **127**–**130**, which were prepared as described in Scheme 2, via a similar deprotonation/alkylation sequence utilizing iodomethane.

4. Results and discussion

Surprisingly, the unsubstituted 1,4-benzoxazine ring and 1,4-benzoxazin-3-one ring analogs **5** and **6**, respectively, were 4- to 6-fold less potent than the tetrahydroquinoline ring analog **4** (Table 1). This contrasted with our previously reported SAR work in the 6-alkoxymethyl-1-aryl-2-ketopiperazine scaffold that indicated a 1,4-benzoxazin-3-one ring was readily accepted in the S3 pocket.[13d] However, introduction of a methyl substituent at the C2 position of the 1,4-benzoxazine ring led to a 2-fold improvement in the renin inhibition activity (**7**, $IC_{50} = 0.235$ μM) relative to the lead compound **4**. Both of the 2-methyl-1,4-benzoxazine enantiomers (2*R*)-**8** and (2*S*)-**9** showed equivalent renin inhibitory activity and were within the 2-fold experimental error range of the racemic analog **7**, indicating that the 2-methyl-1,4-benzoxazine template exhibited no strong enantiomeric preference. The corresponding racemic 2-methyl-1,4-benzoxazin-3-one analog **10** showed a modest decrease in renin inhibition activity ($IC_{50} = 0.520$ μM). However, the 2-methyl-1,4-benzoxazin-3-one enantiomers possessed a marked difference in activity. The (*R*)-enantiomer **11** exhibited an $IC_{50} = 0.125$ μM, while the (*S*)-enantiomer **12** was approximately 10-fold less potent ($IC_{50} = 1.04$ μM). We hypothesized that the carbonyl group imposed additional conformational restraints on the 2-methyl-1,4-benzoxazin-3-one ring structure and regidified the 3D conformation of **11**, whereas the corresponding 2-methyl-1,4-benzoxazine analogs **8** and **9** are more conformationally flexible and can adjust to fit the renin active site. The 1,4-benzoxazin-3-ones **11** and **12** also showed a substan-



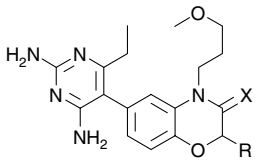
Scheme 5. Reagents and conditions: (i) iodomethane or ethyl iodide, NaH, 15-crown-5, DMF, rt; (ii) bis(pinacolato)diboron, $Pd(dppf)_2Cl_2$, KOAc, 1,4-dioxane, 90 °C; (iii) $Pd(PPh_3)_4$, CsOH, LiCl, 1,4-dioxane/H_2O, reflux.

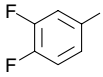
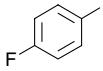
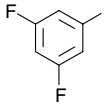
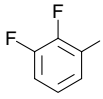
tial increase in metabolic stability, as assessed by the half-life in human liver microsomes (HLM), over the corresponding 1,4-benzoxazines **8** and **9**, presumably due to the ~1 log unit decrease in *c*log*P*. In general, we found that the half-lives of compounds in human liver microsomes (HLM) and rat liver microsomes (RLM) exhibited excellent correlation (Table 3). Therefore, the HLM data were used to guide SAR decisions prior to in vivo PK experiments. Due to the increase in potency and metabolic stability, we decided to focus upon the 1,4-benzoxazin-3-one scaffold in all further analogs. A further increase in the length of the C2-alkyl substituent to a 3-carbon *n*-propyl group resulted in a modest increase in renin inhibitory activity (**13**, IC_{50} = 0.43 μM) compared to the racemic 2-methyl analog **10**. On the other hand, a C2-phenyl substituent resulted in a 2-fold increase in renin inhibition activity (**14**, IC_{50} = 0.220 μM) and substantial decrease in HLM stability. Recognizing that unsubstituted phenyl rings are often metabolic liabilities, we examined the effect of introducing one or more electron-withdrawing fluorine substituents on the C2 phenyl ring on renin inhibition activity and HLM stability. The 3,4-difluoro and 4-fluorophenyl analogs **15** and **16** exhibited similar renin inhibition potencies and HLM stability as the unsubstituted phenyl analog **14**. However, the 3,5-difluorophenyl and 2,3-difluorophenyl analogs **17** and **18** were 2- to 3-fold more potent (IC_{50} = 0.095 and 0.072 μM, respectively), but still exhibited poor HLM stability. Analogs **17** and **18** validated our original hypothesis that an increase in renin inhibition activity could be achieved through manipulation of substituents at the C2 position of a 1,4-benzoxazin-3-one scaffold.

X-ray crystallography of the **17**/renin co-crystal complex revealed that **17** bound in the renin active site with the 3-methoxypropyl sidechain extending into the $S3^{sp}$ subsite, the 3,5-difluorophenyl ring occupying the S4 pocket, and the fluorine atoms extending toward solvent (Fig. 6). The carbonyl of the 1,4-benzoxazin-3-one ring makes no hydrogen bond contacts directly with the protein, but does make a hydrogen bond with a crystallographic water molecule. We believe that the carbonyl group serves to rigidify the 1,4-benzoxazin-3-one ring scaffold to properly orient the 3,5-difluorophenyl substituent. Interestingly, the (*S*)-enantiomer of **17** was observed to bind preferentially in the renin active site as predicted by the initial design envisioned in Fig. 4. This result contrasts with the observed 10-fold difference in activity between the (2*R*)-methyl analog **11** and (2*S*)-methyl analog **12**.

Although a phenyl substituent at the 2-position of the 1,4-benzoxazin-3-one improved renin inhibition activity, analogs **14**–**18** exhibited decreased in vitro metabolic stability, presumably through an increase in lipophilicity as measured by *c*log*P* (Table 1). The addition of electron-withdrawing fluorine substituents around the C2-phenyl ring resulted in no improvement in metabolic stability, indicating that metabolism was occurring elsewhere in the molecule. Accordingly, the site of metabolic liability of **6**, a compound which showed a medium-risk of metabolism in the in vitro HLM screen, was determined using LC/MS/MS methods to identify the metabolites formed in the microsomal incubations. The two main observed metabolites were identified as the oxidative hydroxylation at C2 of the 1,4-benzoxazin-3-one ring to give the C2-hydroxyl metabolite **91** and demethylation of the 3-methoxypropyl sidechain to afford metabolite **92** (Fig. 7). We believe that the 2-methyl substituent in analogs **10**–**12** resulted in improved metabolic stability by steric hindrance of the C2 position. A similar metabolite identification analysis of **10** supported this

Table 1. SAR of 2-monosubstituted-1,4-benzoxazine and 1,4-benzoxazin-3-ones



ID	R[a]	X	RENIN IC_{50} (μM)[b]	HLM $T_{1/2}$ (min)	*c*log *P*
5	H	H,H	2.70	26	2.77
6	H	O	3.90	32	1.70
7	CH_3	H,H	0.235	30	3.29
8	(*R*)-CH_3	H,H	0.325	26	3.29
9	(*S*)-CH_3	H,H	0.310	32	3.29
10	CH_3	O	0.520	>40	2.22
11	(*R*)-CH_3	O	0.125	60	2.22
12	(*S*)-CH_3	O	1.04	>40	2.22
13	$CH_2CH_2CH_3$	O	0.430	31	3.28
14		O	0.220	12	3.5
15		O	0.206	10	3.72
16		O	0.325	16	3.62
17		O	0.095	9	3.79
18		O	0.072	21	3.72

[a] Unless otherwise denoted, all analogs are achiral or racemic mixtures.
[b] IC_{50} values obtained in duplicate using a fluorescent tGFP assay.[13a]

hypothesis as sidechain demethylation was the major metabolite observed with only a minor amount of the C2 hydroxylation metabolite. While the sterically larger 2-phenyl substituent in analogs **14**–**18** provides additional steric bulk around the C2 position, these analogs show reduced metabolic stability presumably because the phenyl ring results in a substantial increase in lipophilicity and increased acidity of the C2 methine hydrogen atom, making this position more susceptible to oxidation through proton abstraction.

Fortunately, the crystal structure of **17** bound in the active site of renin (Fig. 6) provided an important clue to removing the site of oxidative hydroxylation at C2 of the 1,4-benzoxazin-3-one ring. The *S*-enantiomer of **17** was observed to bind preferentially in the renin active site. However, earlier IC_{50} data indicated that the *R*-enantiomer of the 2-methyl analogs **11** and **12** exhibited greater renin inhibition activity (compare **11** and **12**, Table 1). To explain this dichotomy, we hypothesized that the methyl substituent of (*R*)-**11** and the 3,5-difluorophenyl substituent of (*S*)-**17** occupied different space within the renin active site. Closer examination of the crystal structure of **17** indicated a small hydrophobic indentation in the S3 pocket formed by the sidechains of the amino acid residues Phe117, Ala115, and Leu114 that might accept a sterically small hydrophobic substituent. Introduction of a second substituent at C2 of the 1,4-benzoxazin-3-one ring would block the oxidative metabolism, as well as potentially improving renin potency by additional van der Waals contacts with the renin protein.[16] Accordingly, we targeted a series of 2,2-disubstituted-1,4-benzoxazin-3-ones, such as **25** (Fig. 8), for synthesis.

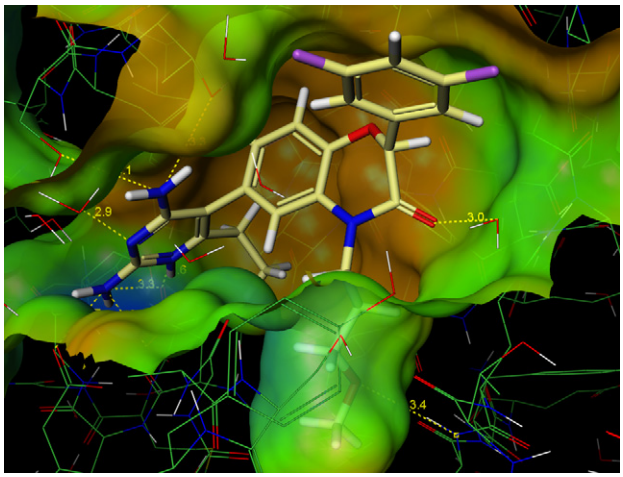


Figure 6. Crystal structure of the **17**/renin complex (2.5 Å resolution, PDB code: 2G1S). The protein Connolly surface is colored by hydrophobicity. Brown, hydrophobic; blue, hydrophilic.

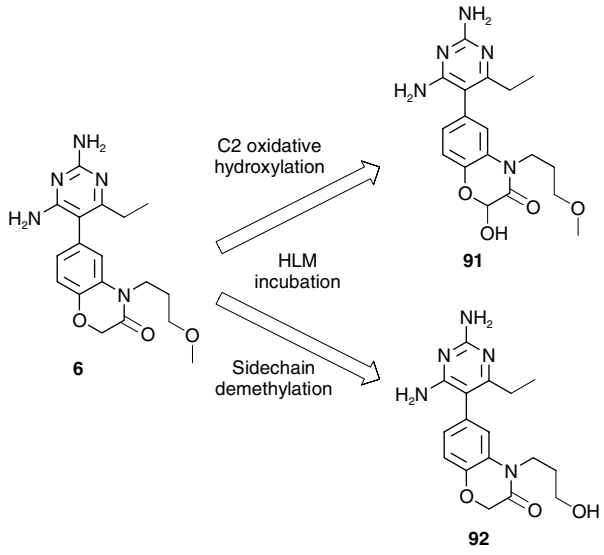


Figure 7. Metabolic analysis of **6**.

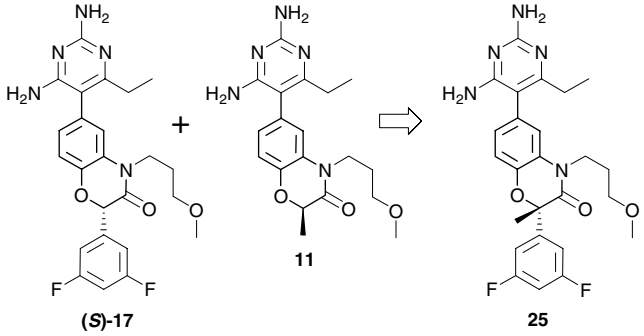
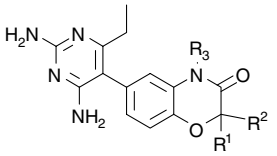


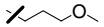
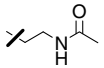
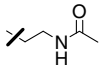
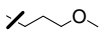
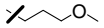
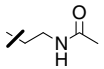
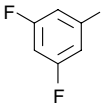
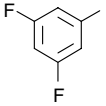
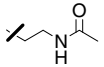
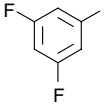
Figure 8. Design of the 2,2-disubstituted 1,4-benzoxazin-3-one scaffold.

We were quite pleased to find that the 2,2-dimethyl-1,4-benzoxazin-3-one **19** (IC_{50} = 0.090 μM, Table 2) resulted in an improvement in renin inhibition activity compared to (*R*)-2-methyl-1,4-benzoxazin-3-one **11** (IC_{50} = 0.125 μM, Table 1), confirming our hypothesis that the pro-(*S*) C2 methyl substituent would improve potency through additional van der Waals contacts with the protein surface. As previously observed, conversion of the 3-methoxypropyl $S3^{sp}$ sidechain to a *N*-(2-ethyl)-acetamide resulted in a further >4-fold improvement in renin inhibition activity (**20**, IC_{50} = 0.020 μM).[11d,13] Analog **20** represented the first compound to meet our potency range criteria. Both **19** and **20** exhibited good HLM stability and solubility, and no appreciable inhibition of cytochrome P450 isozymes, although the *N*-(2-ethyl)-acetamide sidechain of **20** resulted in a substantial reduction in cellular permeability. While the 2,2-dimethyl-1,4-benzoxazin-3-one analogs **19** and **20** exhibited good HLM stability, this may be due to their low lipophilicity as measured by *c*log *P*, as **19** still possessed a site of potential metabolism in the 3-methoxypropyl sidechain. The 2,2-diethyl-1,4-benzoxazin-3-one analog **23** illustrated that HLM stability decreased in more lipophilic analogs with a 3-methoxypropyl sidechain. Adding a methyl at the 2-position of the 2-(3,5-difluorophenyl)-1,4-benzoxazin-3-one template resulted in analog **25**, which possessed single digit nanomolar renin inhibition activity (IC_{50} = 0.007 μM) as a racemic mixture, a >13-fold improvement in potency compared to the corresponding des-methyl analog **17**. Analog **25** exhibited a decreased HLM stability, presumably because the 3-methoxypropyl sidechain still presented a potential site of metabolism within a lipophilic molecule (*c*log *P* = 4.31). Conversion to the *N*-(2-ethyl)-acetamide sidechain resulted in a further improvement in renin inhibition activity (**26**, IC_{50} = 0.001 μM) and excellent HLM stability through a reduction in *c*log *P* (3.41) and by removing a potential site of metabolism. The 2-methyl substituent was optimal, as the 2-ethyl analog **27** exhibited a 25-fold reduction in renin inhibition activity. X-ray crystallography of the **25**/renin complex (Fig. 9) shows the 2-(3,5-difluorophenyl)-2-methyl-1,4-benzoxazin-3-one ring snuggly filling the S3 and S4 pockets, with the methyl substituent making van der Waals contacts with the Phe117, Ala115, and Leu114 residues as designed. In addition, the 3,5-difluorophenyl group is moved slightly to make additional van der Waals contacts with the Pro111 residue. The additional hydrophobic contacts with the protein surface formed upon introduction of the 2-methyl substituent are reflected in the greater enthalpic contributions to the overall energy of binding observed in the previously reported isothermal calorimetry experiments.[18]

Although analogs **25**–**27** demonstrated that addition of a methyl substituent at the C2 position of the 1,4-benzoxazin-3-one resulted in improved renin inhibition activity and blocked a potential site of metabolism, more worrisome was the observation that these analogs also exhibited an increased inhibition of CYP3A4. We hypothesized that variation of the substituents about the C2 aryl ring might result in decreased CYP3A4 inhibition. Accordingly, we prepared analogs **29**–**32** with the *N*-(2-ethyl)-acetamide sidechain to maintain good HLM stability. Analogs with a *c*log *P* < 4 exhibited good HLM stability, while a *c*log *P* > 4 resulted in poor

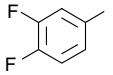
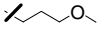
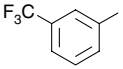
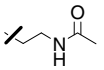
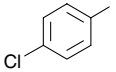
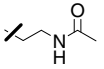
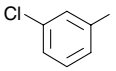
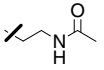
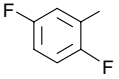
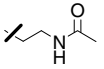
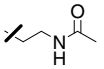
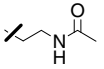
Table 2. SAR of 2,2-disubstituted-1,4-benzoxazin-3-ones



ID	C-2 Config.	R^1	R^2	R^3	In vitro ADME data					Cytochrome P450 inhibition data		
					RENIN IC_{50} (μM)[a]	*c*log *P*	HLM $T_{1/2}$ (min)	Solubility[b] (μg/mL)	Caco-2[c] AB Perm	CYP3A4 IC_{50} (μM)	CYP2D6 IC_{50} (μM)	CYP2C9 IC_{50} (μM)
19	—	CH_3	CH_3		0.090	2.74	>40	34	19	>30	>30	>30
20	—	CH_3	CH_3		0.020	1.86	>40	11	1.7	>30	>30	>30
21	—	CH_3	CF_3		0.017	2.62	>120	200	2.4	>22	>30	>30
22	*rac*	CH_3	CH_2CH_3		0.052	3.27	>40	54	14	>30	8.2	30
23	—	CH_2CH_3	CH_2CH_3		0.245	3.80	16	16	32	3.0	12	15
24	–	–CH_2–	–CH_2–		0.100	1.13	>40	24	5.4	>30	>30	>30
25	*rac*	CH_3			0.007	4.31	12	87	27	1.14	6.3	10.5
26	*rac*	CH_3			0.001	3.41	>60	133	1.4	0.86	>30	>30
27	*rac*	CH_2CH_3			0.175	4.84	18	2.6	17	0.46	3.3	4.9

(*continued on next page*)

Table 2 (*continued*)

ID	C-2 Config.	R^1	R^2	R^3	In vitro ADME data					Cytochrome P450 inhibition data		
					RENIN IC_{50} (μM)[a]	*c*log *P*	HLM $T_{1/2}$ (min)	Solubility[b] (μg/mL)	Caco-2[c] AB Perm	CYP3A4 IC_{50} (μM)	CYP2D6 IC_{50} (μM)	CYP2C9 IC_{50} (μM)
28	*rac*	CH_3			0.066	4.24	10	13	17	0.92	5.7	8.3
29	*rac*	CH_3			0.060	4.00	3	12	8.8	0.12	>30	>22
30	*rac*	CH_3			>0.040	3.84	>60	12	34	0.59	19	12
31	*rac*	CH_3			0.007	3.84	>60	133	0.0	86% at 3 μM	7% at 3 μM	11% at 3 μM
32	*rac*	CH_3			0.007	3.41	>40	2.3	—	1.90	>30	>30
33	*S*	CH_3			0.0008	3.12	>60	119	2.1	>30	>30	>30
34	*R*	CH_3			0.86	3.12	>60	40	1.9	0.53	>30	>30

Fluorometric CYP substrates: BFC (CYP3A4), AMMC (CYP2D6), MFC (CYP2C9).

[a] IC_{50} values determined in duplicate using a fluoresence tGFP assay.[13a]

[b] Aqueous solubility at pH 6.5.

[c] Permeability expressed as $\times 10^{-6}$ cm/s.

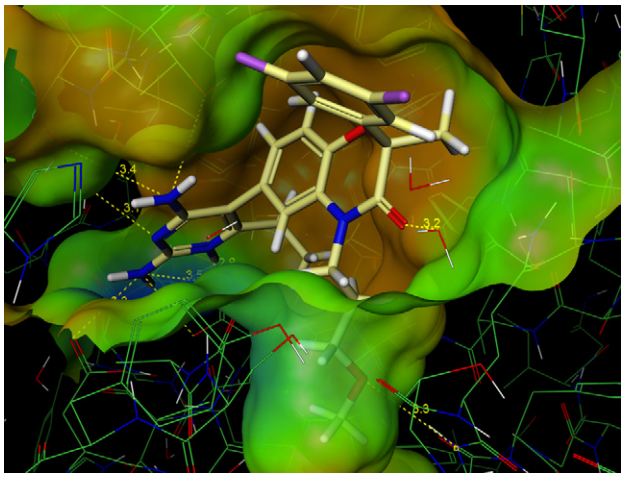


Figure 9. X-ray structure of the **25**/renin complex (2.3 Å resolution, PDB core: 2I4Q), Protein surface of active site is colored by hydrophobicity (Brown, hydrophobic; blue, hydrophilic).

metabolic stability (**29**, HLM $T_{1/2}$ = 3 min). The 3-chlorophenyl analog **31** and 2,5-difluorophenyl analog **32** exhibited the best renin inhibition activity and good metabolic stability, however these analogs still inhibited CYP3A4. All of the analogs **25**–**32** were prepared as racemic mixtures due to ease and speed of preparation. We were able to prepare the discrete enantiomers of the unsubstituted 2-phenyl ring, analogs **33** and **34**. The (*S*)-enantiomer **33** exhibited the most potent renin inhibition activity in this series (IC_{50} = 0.0008 μM), while the (*R*)-enantiomer **34** was approximately 1000-fold less potent. The renin inhibition activity of (*S*)-**33** is comparable to the activity of aliskerin, with a MW = 461 compared to MW = 551. Surprisingly, the chiral (*S*)-2-methyl-2-phenyl analog (*S*)-**33** exhibited a clean CYP inhibition profile in the fluorometric assays, with no appreciable inhibition of CYP3A4, 2D6, or 2C9. On the other hand, the (*R*)-**34** enantiomer exhibited significant inhibition of CYP3A4, indicating that the CYP3A4 inhibition liabilities noted in the racemic compounds may reside solely in the less active and undesired *R*-enantiomer.

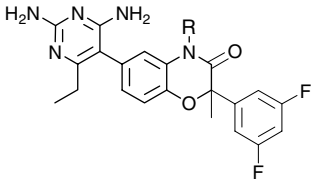
Since 2,4-diaminopyrimidines are common templates for kinase inhibitors, we screened representative compounds for kinase inhibition activity against 19 kinases selected from the Dundee kinase panel to give an initial overview of kinase activity. Compounds **9**, **14**, and **20** showed no significant inhibition of 18/19 kinases, with only moderate kinase activity at 10 μM concentration observed for Met kinase (**9**, 50%; **14**, 40%; and **20**, 61% kinase activity).[19] Additional profiling in the CEREP panel of receptors, enzymes, and kinases revealed no significant off-target activity (data not shown).

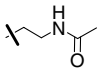
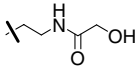
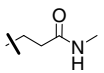
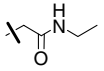
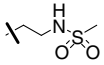
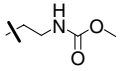
While we had been successful in designing small molecule renin inhibitors with MW < 500 that met our potency range goal with good ADME and CYP inhibition properties, our lead compounds **25** and **26** exhibited poor oral bioavailability in the rat (Table 3). Analog **25** exhibited short HLM and RLM half-lives and <1% oral bioavailability presumably due to rapid first-pass metabolism and high in vivo clearance (48 mL/min/kg). Analog **26** was metabolically stable against HLM and RLM, but showed only slightly improved oral bioavailability (F = 8%) due to poor absorption across the gut wall that was reflected in the low Caco-2 cellular permeability caused by the polarity of the *N*-(2-ethyl)-acetamide sidechain. Analog (*S*)-**33**, which also contained the polar *N*-(2-ethyl)-acetamide sidechain, also exhibited a similar profile of low rat oral bioavailability (F = 10%) likely due to poor cellular permeability. In contrast, the metabolite of the 3-methoxypropyl sidechain in **25**, the 3-hydroxypropyl **35**, exhibited an excellent profile of metabolic stability and cellular permeability, and possessed excellent rat oral bioavailability (F = 44%). Although **35** showed reduced renin inhibition activity, we were encouraged that good rat oral bioavailability could be obtained in the 6-(2,4-diaminopyrimidinyl)-2-aryl-2-methyl-1,4-benzoxazin-3-one template with a metabolically stable and permeable $S3^{sp}$ sidechain. Consequently, we conducted further SAR to identify an $S3^{sp}$ sidechain that possessed the best profile of renin inhibition activity, metabolic stability, cellular permeability, and rat oral bioavailability.

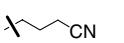
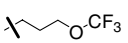
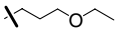
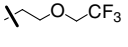
We first attempted to improve the potency of alcohol **35** by varying the length of the $S3^{sp}$ sidechain. Analog **36** with a 2-hydroxyethyl sidechain resulted in poor renin inhibition activity, presumably because the 2-hydroxyethyl chain does not penetrate far enough into the $S3^{sp}$. A longer 4-hydroxybutyl sidechain extended further in the $S3^{sp}$ and resulted in a >20-fold increase in renin inhibition activity (**37**, IC_{50} = 0.043 μM), but decreased HLM and RLM stability and exhibited poor rat oral bioavailability. Introduction of an amide into the alcohol sidechain resulted in single digit renin inhibition activity (**38**, IC_{50} = 0.003 μM), but reduced HLM and RLM stability and increased clearance. We then turned to improving the cellular permeability of the metabolically stable amide sidechain. The reverse amide sidechain analog **39** showed single digit nanomolar renin inhibition, as well as good HLM stability, moderate RLM stability, and improved cellular permeability, but showed no decrease in the in vivo clearance (not dosed orally), and potent inhibition of CYP3A4. An ethyl acetamide reverse amide sidechain resulted in reduced renin inhibition (**40**, IC_{50} = 0.20 μM), as did replacing the *N*-acetamide with a *N*-sulfonamide (**41**, IC_{50} = 0.63 μM). Within the amide sidechain group of compounds, the methyl *N*-(2-ethyl)-carbamate **42** exhibited the best profile of renin inhibition (IC_{50} = 0.002 μM), HLM stability, and rat oral bioavailability (F = 34%). Disappointingly, **42** was again a potent inhibitor of CYP3A4 (IC_{50} = 0.67 μM).

We also investigated improving the metabolic stability of the 3-methoxypropyl sidechain. Replacement of the methoxy ether with a nitrile group resulted in a 10-fold reduction in renin inhibition activity, but good HLM and RLM stability and an improved CYP inhibition profile, in vivo clearance, and oral bioavailability in the rat (**43**, IC_{50} = 0.062 μM, F = 12%). Attempting to block the demethylation of the methoxy ether, we installed a 3-trifluoromethoxypropyl sidechain, but analog

Table 3. Optimization of PK parameters



ID	R	In vitro ADME data					CYP450 inhibition data[a]		Rat in vivo PK parameters				
		Renin IC_{50} (nM)	HLM $T_{1/2}$ (min)	RLM $T_{1/2}$ (min)	Solubility[b] (μg/mL)	Caco-2 AB Perm[c]	CYP3A4 IC50 (μM)	CYP2D6 IC50 (μM)	Cl (ml/min/kg)	Vd_{ss} (L/kg)	$T_{1/2}$ (h)	C_{max} (ng/mL)	F (%)
25[d]		0.007	16	13	87	32	1.14	6.3	48	4.5	1.3	23	0.4
26[d]		0.001	>60	39	95	1.4	0.86	30	37	2.1	2	220	8
35[d]		0.89	>40	>40	28	10	30	30	44	3.1	1.6	180	44
36[e]		1.08	>60	50	89	6.3	8% at 3 μM	8% at 3 μM	32	3.3	1.8	ND	ND
37[e]		0.043	14	7	59	10.6	4.79	6.96	22	2.3	1.6	186	7
38[d]		0.003	19	11	59	1.5	1.67	>30	69	2.9	1.2	ND	ND
39[d]		0.006	37	26	133	5.1	0.16	>30	44	2.1	1.1	ND	ND
40[f]		0.200	>60	>60	89	21	>30	1.89	42	3.1	1.4	60	14
41		0.630	34	25	200	1.8	2.18	15.1	ND	ND	ND	ND	ND
42[e]		0.002	66	—	—	2.1	0.67	>30	45	3.5	1.6	280	34

43[e]		0.062	>60	>60	3.5	—	>30	27.9	28	1.9	1.6	237	12
44[e]		0.182	31	23	7.8	—	0.27	3.22	40	6.3	2.2	200	28
45[f]		0.041	56	16	59	13	1.06	20.6	41	2.0	0.9	<5	0
46[e]		0.188	7	9	27	2.8	46% at 3 μM	37% at 3 μM	40	6	2.3	110	15
rac-**47**[e]		0.141	>60	34	5.2	9	54% at 3 μM	34% at 3 μM	27	5.1	2.5	160	12
(*S*)-**47**[e]		0.048	>60	—	—	—	1.7[g]	0.43[g]	26	5.7	3.0	380	74

ND, not dosed.
[a] Fluorometric CYP substrates: BFC (CYP3A4), AMMC (CYP2D6).
[b] Aqueous solubility at pH 6.5.
[c] Permeability expressed as $\times 10^{-6}$ cm/s.
[d] IV dose = 1 mg/kg, po dose = 5 mg/kg.
[e] IV dose = 1 mg/kg, po dose = 10 mg/kg.
[f] IV dose = 0.33 mg/kg, po dose = 1.67 mg/kg.
[g] Definitive CYP substrates: midazolam (CYP3A4) and dextromethorphan (CYP2D6).

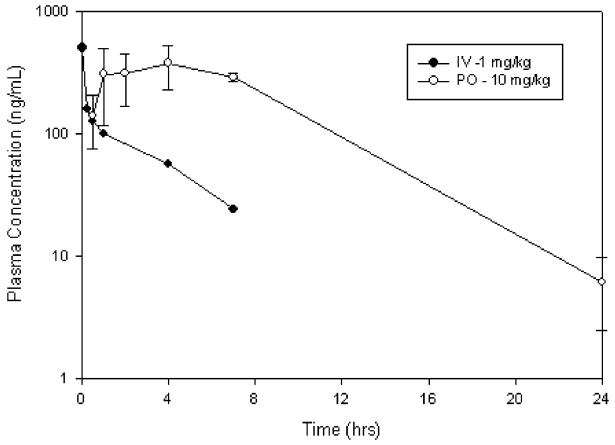


Figure 10. Mean plasma concentrations (±SD) of (*S*)-**47** in the rat.

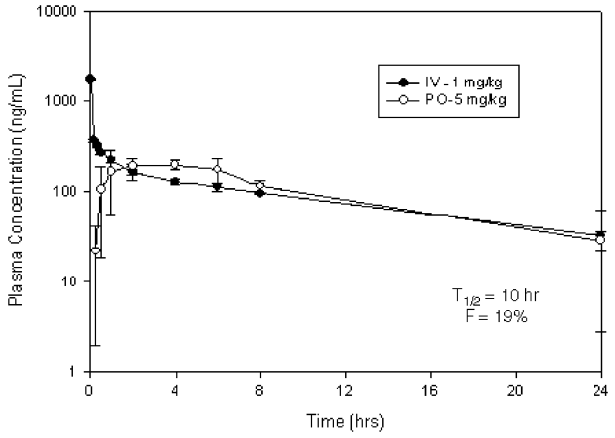


Figure 11. Mean plasma concentrations (±SD) of (*S*)-**47** in the dog.

44 showed only a slight improvement in HLM and RLM stability and no significant change in the in vivo clearance, although the oral bioavailability improved to $F = 28\%$ as a result of the increased volume of distribution. A 3-ethoxypropyl sidechain was installed to sterically block the metabolism of the ether functionality. Although **45** showed improved HLM stability, no improvement in the in vivo clearance or oral bioavailability was observed, presumably as a result of the low RLM stability. A 3-trifluoroethoxypropyl sidechain resulted in a further loss of renin inhibition activity (**46**, $IC_{50} = 0.188\ \mu M$). A 4,4,4-trifluorobutyl sidechain exhibited a similar level of renin inhibition (**47**, $IC_{50} = 0.141\ \mu M$), however this analog exhibited lower in vivo clearance with moderate oral bioavailability ($F = 12\%$). We were encouraged that **47** also exhibited reasonable aqueous solubility, cellular permeability, and only modest inhibition of CYP isozymes in the fluorometric assays as the racemate. On the basis of the decreased in vivo clearance, the two enantiomers were separated to afford (*S*)-**47**, which exhibited a renin $IC_{50} = 0.048\ \mu M$, and excellent oral bioavailability in the rat ($F = 74\%$) with low in vivo clearance and good in vivo half-life (Fig. 10). Analog (*S*)-**47** also exhibited a long in vivo half-life in the dog ($T_{1/2} = 10$ h) with a moderate oral bioavailability ($F = 19\%$, Fig. 11). Surprisingly, definitive CYP inhibition studies indicated (*S*)-**47** exhibited low micromolar inhibition of CYP3A4 ($IC_{50} = 2\ \mu M$), but potent inhibition of CYP2D6 ($IC_{50} = 0.43\ \mu M$). In contrast, the fluorometric assays that were used to routinely screen for CYP inhibition activity had predicted that *rac*-**47** would show little inhibition of CYP2D6 (Table 3).

5. Conclusion

We have designed a novel series of small molecule inhibitors of renin based on a 6-(2,4-diaminopyrimidinyl)-1,4-benzoxazin-3-one template, which represents a significant structural difference from the previously reported peptidomimetic or large-molecule renin inhibitor templates. Improved renin inhibition activity was obtained through the addition of substituents at the 2-position of the 1,4-benzoxazin-3-one ring that provide additional van der Waals contacts with the protein surface in the S3 and S4 pockets. A 2-methyl-2-aryl substitution pattern resulted in compounds with the most potent renin inhibition activity and improved metabolic stability through direct blockade of a site of metabolism. The *S*-enantiomer binds preferentially in the renin active site and exhibits improved CYP inhibition activity relative to the *R*-enantiomer, as measured by fluorometric assays. The 3-methoxypropyl sidechain that binds in the $S3^{sp}$ subsite utilized in early SAR studies resulted in low oral bioavailability due to rapid first pass metabolism. While the *N*-(2-ethyl)-acetamide $S3^{sp}$ subsite sidechain resulted in a ~10-fold improvement in renin inhibition and good microsomal metabolic stability, oral bioavailability was limited by cellular permeability. Improved metabolic stability, cellular permeability, CYP isozyme inhibition, and rat oral bioavailability could be obtained through modulation of the $S3^{sp}$ subsite sidechain. The best oral bioavailability was obtained with sidechains that exhibited good metabolic stability, cellular permeability, and increased volume of distribution. The in vivo clearance of this series does not directly correlate to the metabolic stability and may be reflective of the removal of the compound from the plasma by non-metabolic processes such as tissue distribution or protein binding, as compounds with increased volume of distribution exhibit improved oral bioavailability. While this project was terminated prior to identification of a clinical candidate or assessment of in vivo efficacy, we believe that this work will significantly aid in the design of future renin inhibitors with improved oral bioavailability.

6. Experimental

6.1. Chemistry

6.1.1. General methods. All commercially available chemicals were used without further purification. Anhydrous solvents were purchased from Aldrich Chemical Co. Polymer-supported reagents were swelled by rinsing with anhydrous CH_3CN (3×), THF (3×), and CH_2Cl_2 (3×), and dried under vacuum at room temperature. Melting points were determined on a Mel-temp melting

point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 400 MHz FT NMR spectrometer. Chemical shifts are reported as δ values relative to residual solvent ($CHCl_3$ = 7.26 ppm and DMSO = 2.52 ppm). Purity of final compounds was assessed by analytical HPLC on a Waters photodiode array detector system using the following conditions Column, Symmetry® C-18 4.6 × 150 mm; Solvent A, H_2O/0.1% TFA; Solvent B, CH_3CN/0.1% TFA; flow rate, 2.0 mL/min; run time 25 min; gradient, from 0% to 90% solvent B. IR spectra were recorded an a diamond single-bounce horizontal attenuated total reflectance (ATR) accessory installed in a Avatar 370 FT-IR spectrometer. Optical rotations were recorded on an Autopol IV polarimeter. Combustion analyses (C, H, N, F) were performed by Quantitative Technologies, Inc.

6.1.2. 6-Ethyl-5-[4-(3-methoxypropyl)-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl]-pyrimidine-2,4-diamine (5). *Step 1.* A 500 mL round-bottomed flask was charged with 25.5 g (117 mmol) of 4-bromo-2-nitrophenol **48**, 300 mL of acetone, and 19.4 g (140 mmol) of K_2CO_3. Ethyl bromoacetate (15.6 mL, 140 mmol) was added, and the suspension was heated at reflux for 18 h. After cooling to room temperature, the suspension was filtered through Celite and rinsed with acetone, and the filtrate was concentrated. The solid residue was slurried with hexanes, and the solid was collected on a medium frit funnel and dried under vacuum to provide 31.14 g (88%) 4-bromo-2-nitrophenoxy-acetic acid ethyl ester which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.53 (s, 1H), 4.26 (q, J = 7.1 Hz, 2 H) 4.75 (s, 2H), 6.88 (d, J = 8.8 Hz, 1H,) 7.61 (dd, J = 9.0, 2.4 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H).

Step 2. A solution of (4-bromo-2-nitrophenoxy)-acetic acid ethyl ester (25.01 g, 82.2 mmol) in 400 mL of glacial acetic acid was treated by the slow addition of iron powder (91.9 g, 1.6 mol). The resulting black suspension was heated at an internal temperature of 50 °C for 6 h. After cooling to room temperature, the resulting gray suspension was filtered through a Celite pad, rinsing with EtOAc. The combined filtrates were concentrated under vacuum. The residue was diluted with EtOAc, and washed with deionized H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated until a white precipitate formed. The slurry was diluted with hexanes. The precipitate was collected on a medium frit and dried under reduced pressure to provide 17.24 g (92%) of 6-bromo-4*H*-benzo[1,4]oxazin-3-one **49**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.53 (s, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 7.02 (dd, J = 8.5, 2.4 Hz, 1H), 10.74 (s, 1H). MS(ESI+): m/z 227.9 (M+1) and 229.9 (M+2).

Step 3. A solution of **49** (4.00 g, 17.5 mmol) in 100 mL of anhydrous DMF was cooled in an ice bath under an argon atmosphere. A 60% dispersion of NaH in mineral oil (807 mg, 20.2 mmol) was added in a single portion, and the resulting suspension was stirred in an ice bath for 15 min. 15-Crown-5 (0.10 mL) and 3.22 g (21.0 mmol) of 1-bromo-3-methoxypropane were added, and the reaction mixture was allowed to warm to room temperature and stirred for 18 h. Excess hydride was quenched by the slow dropwise addition of H_2O, and the mixture was poured into 800 mL of H_2O. The aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 20% EtOAc/hexanes) yields 4.33 g (82%) of 6-bromo-4-(3-methoxypropyl)-4*H*-benzo[1,4]oxazin-3-one **50** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.94 (quintet, J = 6.1 Hz, 2H), 3.35 (s, 3H), 3.41 (t, J = 5.9 Hz, 2H), 3.99 (m, 2H), 4.57 (s, 2H), 6.85 (d, J = 8.6 Hz, 1H), 7.09 (dd, J = 8.6, 2.2 Hz, 1H), 7.26 (d, J = 3.0 Hz, 2H). MS(ESI+): m/z 300.0 (M+1) and 302.0 (M+2).

Step 4. A solution of 837 mg (2.79 mmol) of **50** in 30 mL of anhydrous THF was treated with 5.58 mL (11.2 mmol) of 2.0 M $BH_3{\cdot}Me_2S$ in THF and heated in a 50 °C oil bath for 22 h. After the reaction mixture was cooled to room temperature, excess borane was quenched by the slow dropwise addition of methanol. The resulting solution was concentrated and azeotropped from methanol. The crude residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) to afford 773 mg (97%) of 6-bromo-4-(3-methoxypropyl)-3,4-dihydro-2*H*-benzo[1,4]oxazine **51** as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 1.85 (quintet, J = 5.9 Hz, 2H), 3.35 (s, 3H), 3.34 (m, 4H), 3.42 (t, J = 5.7 Hz, 2H), 4.19 (m, 2H), 6.62 (d, J = 8.6 Hz, 1H), 6.68 (dd, J = 8.3, 2.2 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H). MS (ESI+): m/z 286.0 and 288.0 (^{79}Br−M+1 & ^{81}Br−M+2).

Step 5. A suspension of 773 mg (2.70 mmol) of **51**, 823 mg (3.24 mmol) of bis(pinacolato)diboron, and 819 mg (8.34 mmol) of KOAc in 27 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 10 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (441 mg, 0.54 mmol) was added, and the suspension was heated to reflux for 4 h. After cooling to room temperature, the mixture was diluted with EtOAc, filtered through a Celite pad, and concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 25% EtOAc/hexanes) yielded 530 mg (59%) of 4-(3-methoxypropyl)-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4- dihydro-2*H*-benzo[1,4]oxazine **53** as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 12H), 1.90 (quintet, J = 6.8 Hz, 2H), 3.33 (m, 2H), 3.34 (s, 3H), 3.43 (m, 2H), 3.45 (t, J = 5.9 Hz, 2H), 4.25 (m, 2H), 6.77 (d, J = 7.8 Hz, 1H), 7.12 (m, 1H), 7.17 (m, 1H). MS(ESI+): m/z 334.1 (M+1).

Step 6. A round bottomed flask was charged with 529 mg (1.59 mmol) of **53**, 414 mg (1.90 mmol) of 5-bromo-6-ethyl-pyrimidine-2,4-diamine **54**, and 1.55 g (4.76 mmol) of Cs_2CO_3, and 8 mL of anhydrous 1,4-dioxane. The suspension was degassed by Ar sparge for 10 min. $Pd(PPh_3)_4$ (183 mg, 0.16 mmol) was added, and the yellow suspension was degassed again and then heated to reflux for 18 h. After cooling to room

temperature, the black mixture was diluted with EtOAc, filtered through Celite, and concentrated. Purification by flash column chromatography (SiO_2, 100:0 CH_2Cl_2/CH_3OH then gradient to 85:15 CH_2Cl_2/CH_3OH) gave 114 mg (21%) of **5** as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 3H), 1.68 (quintet, J = 6.4 Hz, 2H), 2.09 (q, J = 7.3 Hz, 2H), 3.14 (s, 3H), 3.24 (m, 4H), 3.30 (t, J = 6.1 Hz, 2H), 4.13 (br s, 2H), 5.29 (s, 2H), 5.71 (s, 2H), 6.23 (dd, J = 8.0, 1.6 Hz, 1H), 6.37 (d, J = 1.6 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H). MS(ESI+): m/z 344.1 (M+1). Elem. Anal. Calcd for $C_{18}H_{25}N_5O_2 \cdot 0.05CH_2Cl_2$: C, 62.36; H, 7.28; N, 20.14. Found: C, 62.49; H, 7.04; N, 19.94.

6.1.3. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-4*H*-benzo[1,4]oxazin-3-one (6). *Step 1.* A 50 mL round bottomed flask was flushed with Ar and charged with 640 mg (2.50 mmol) of bis(pinacolato)diboron, 560 mg (0.69 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex, and 680 mg (6.9 mmol) of KOAc. A solution of 690 mg (2.30 mmol) of **49** in 10 mL of anhydrous 1,4-dioxane was added, and the resulting dark red suspension was heated in a 110 °C oil bath for 16 h. The mixture was filtered through Celite and concentrated, and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 50% EtOAc/hexanes) provided 720 mg (90%) of **52** as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 12H) 1.98 (quintet, J = 6.4 Hz, 2H), 3.35 (s, 3H), 3.44 (t, J = 6.1 Hz, 2H), 4.09 (t, J = 7.0 Hz, 2H), 4.60 (s, 2H), 6.97 (d, J = 8.0 Hz, 1H), 7.47 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H). MS(E-SI+): m/z 348.1 (M+1).

Step 2. A mixture of 670 mg (1.93 mmol) of **52**, 420 mg (1.94 mmol) of **54**, and 67 mg (0.058 mmol) of $Pd(PPh_3)_4$ in 15 mL of anhydrous DMF and 7 mL of anhydrous toluene was degassed by Ar sparge for 10 min. K_3PO_4 (620 mg, 2.9 mmol) was added, and the mixture was heated at reflux for 18 h. The mixture was diluted with EtOAc, filtered through Celite, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAC then gradient to 40% MeOH/EtOAc) provided 156 mg (23%) of **5**. ^1H NMR (400 MHz, DMSO-d_6) δ 0.98 (t, J = 7.6 Hz, 3H), 1.76 (quintet, J = 6.5 Hz, 2H), 2.13 (q, J = 7.4 Hz, 2H), 3.17 (s, 3H), 3.34 (t, J = 3.1 Hz, 2H), 3.93 (m, 2H), 4.65 (q, J = 7.3 Hz, 2H), 5.52 (br s, 2H), 5.82 (s, 2H), 6.78 (dd, J = 8.1, 1.7 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H). MS: m/z 358.1 (M+1). Elem. Anal. Calcd for $C_{18}H_{23}N_5O_3 \cdot 0.2$EtOAc: C, 60.25; H, 6.59; N, 18.81. Found: C, 60.27; H, 6.39; N, 18.85.

6.1.4. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-2-methyl-4*H*-benzo[1,4]oxazine (7). A solution of 45 mg (0.12 mmol) of **10** in 10 mL of anhydrous THF was treated with 0.24 mL (0.48 mmol) of 2.0 M $BH_3 \cdot SMe_2$ in THF, and the reaction mixture was heated at 50 °C for 2 h. An additional 0.48 mL of 2.0 M $BH_3 \cdot SMe_2$ in THF was added, and the mixture was heated at 60 °C for 18 h. Excess hydride was quenched by the dropwise addition of MeOH, and the mixture was concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAC then gradient to 20% MeOH/EtOAc) provided 23 mg (52%) of **7**. HRMS Calcd for $C_{19}H_{25}N_5O_3$ (M+1): 358.2243. Found: 358.2248.

6.1.5. (2*R*)-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-2-methyl-4*H*-benzo[1,4]oxazine (8). A solution of 82 mg (0.22 mmol) (2*R*)-6-(2,4-diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxypropyl)-2- methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**11**) in 6 mL of anhydrous THF was treated with 0.44 mL (0.88 mmol) of 2 M BH_3SMe_2 in THF and heated in a 50 °C oil bath for 16 h. After cooling to room temperature, excess borane was quenched by the dropwise addition of MeOH. The mixture was concentrated and azeotropped from MeOH (2×). Purification by flash column chromatography (SiO_2, 100:0 CH_2Cl_2/MeOH then gradient to 90:10 CH_2Cl_2/MeOH) afforded 40 mg of **8** as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 0.98 (t, J = 7.6 Hz, 3 H) 1.29 (d, J = 6.2 Hz, 3H), 1.72 (quintet, J = 7.4 Hz, 2H), 2.15 (q, J = 7.6 Hz, 2H), 2.97–3.07 (m, 2H), 3.19 (s, 3H), 4.14–4.23 (m, 2H), 5.37 (br s, 2H), 5.78 (br s, 2H), 6.29 (dd, J = 8.0, 2.0 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1 H). MS: m/z 358.2 (M+1).

6.1.6. (2*S*)-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-2-methyl-4*H*-benzo[1,4]oxazine (9). *Step 1.* A solution of 750 mg (2.39 mmol) of **73** in 20 mL of THF was treated with 4.77 mL (9.55 mmol) of 2 M $BH_3 \cdot SMe_2$ in THF and heated in a 50 °C oil bath for 7 h. Excess hydride was carefully quenched by the dropwise addition of MeOH. The mixture was concentrated and azeotropped from MeOH. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 20% EtOAc/hexanes) afforded 691 mg (96%) of **80** as a clear viscous oil. $[\alpha]_D^{24.9}$ +2.6° (c 9.7, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 6.4 Hz, 3H), 1.80–1.91 (m, 2H), 3.09 (dd, J = 12.0, 8.3 Hz, 1H), 3.24 (dd, J = 11.7, 2.4 Hz, 1H), 3.30 (dd, J = 14.2, 6.6 Hz, 1H), 3.36 (s, 3H), 3.40 (d, J = 4.0 Hz, 1H), 3.43 (ddd, J = 5.7, 5.7, 1.7 Hz, 1H), 4.13–4.23 (m, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.70 (dd, J = 8.0, 2.0 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H); MS(E-SI+): m/z 300.0, 302.0 ([M+1], 1:1 ratio of Br isotopes).

Step 2. A suspension of 680 mg (2.27 mmol) of **80**, 690 mg (2.72 mmol) of bis(pinacolato)diboron, and 667 mg (6.8 mmol) of KOAc in 12 mL of anhydrous 1,4-dioxane was degassed by an Ar sparge for 10 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (93 mg (0.11 mmol)) was added, and the resulting dark red suspension was heated in a 110 °C oil bath for 4 h. The mixture was filtered through Celite and concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) provided 561 mg (71%) of **90** as a yellow viscous oil. MS(ESI+): m/z 348.2 (M+1).

Step 3. A mixture of 561 mg (1.62 mmol) of **90**, 421 mg (1.94 mmol) of **54**, and 1.58 g (4.85 mmol) of Cs_2CO_3 in

8 mL of anhydrous 1,4-dioxane was degassed by freeze–pump–thaw techniques (2×). $Pd(PPh_3)_4$ (187 mg, 0.16 mmol) was added, and the yellow suspension was heated at 100 °C for 18 h. The mixture was diluted with EtOAc, filtered through Celite, and concentrated. Purification by flash column chromatography (SiO_2, 100:0 CH_2Cl_2/MeOH then gradient to 85:15 CH_2Cl_2/MeOH) gave 191 mg (33%) of **9** as a white solid. $[\alpha]_D^{24}$ −9.4 (*c* 4.6, MeOH); ^1H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 3H), 1.24 (d, J = 6.2 Hz, 3H), 1.67 (quintet, J = 6.6 Hz, 2H), 2.09 (q, J = 7.4 Hz, 2H), 2.97 (m, 1H), 3.14 (s, 3H), 3.25 (m, 4H), 3.29 (t, J = 6.0 Hz, 2H), 4.13 (br s, 1H), 5.30 (br s, 1H), 5.71 (s, 2H), 6.24 (dd, J = 7.9, 1.7 Hz, 1H), 6.38 (d, J = 1.4 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H); MS(ESI+): *m*/*z* 358.1 (M+1). Elem. Anal. Calcd for $C_{19}H_{27}N_5O_2$: C, 63.84; H, 7.61; N, 19.59. Found: C, 63.61; H, 7.37; N, 19.07.

6.1.7. (*rac*)-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-2-methyl-4*H*-benzo[1,4]oxazin-3-one (10). *Step 1.* A solution of 2.8 g (9.3 mmol) of **50** in 100 mL of THF was cooled in a dry ice/acetone bath. LiHMDS (10 mL, 10 mmol, 1.0 M in THF) was added in a dropwise fashion, and the reaction mixture was stirred at −78 °C for 15 min. Iodomethane (0.70 mL, 11.2 mmol) was added slowly, and the mixture was stirred at −78 °C for 2 h. The cold bath was removed, and the mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was partially concentrated, diluted with H_2O, and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 30% EtOAc/hexanes) yielded 1.12 (38%) of **71** as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, J = 6.8 Hz, 3H), 1.92 (ddd, J = 13.4, 6.2, 6.0 Hz, 2H), 3.34 (s, 3H), 3.40 (t, J = 5.9 Hz, 2H), 3.97 (t, J = 7.0 Hz, 2H), 4.58 (q, J = 6.8 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 7.08 (dd, J = 8.6, 2.2 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H); MS(ESI+): *m*/*z* 314.0, 316.0 ([M+1], 1:1 ratio of Br isotopes).

Step 2. A suspension of 785 mg (2.50 mmol) of **71**, 700 mg (2.8 mmol) of bis(pinacolato)diboron, and 700 mg (8.0 mmol) of KOAc in 20 mL of anhydrous 1,4-dioxane was degassed by an Ar sparge for 10 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (200 mg (0.25 mmol)) was added, and the resulting dark red suspension was heated in a 110 °C oil bath for 16 h. The mixture was filtered through Celite, concentrated, and partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 50% EtOAc/hexanes) yielded 600 mg (66%) of **81** as an oil. MS(ESI+): *m*/*z* 362.1 (M+1).

Step 3. A mixture of 0.58 g (1.61 mmol) of **81**, 349 mg (1.61 mmol) of **54**, and 56 mg (0.05 mmol) of $Pd(PPh_3)_4$ in 15 mL of anhydrous DMF and 7 mL of anhydrous toluene was degassed by Ar sparge for 10 min. K_3PO_4 (0.51 g, 2.4 mmol) was added, and the yellow suspension was heated at 100 °C for 18 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 40% MeOH/EtOAc) gave 130 mg (22%) of **10**. ^1H NMR (400 MHz, DMSO-d_6) δ 0.98 (t, J = 7.6 Hz, 3H), 1.44 (d, J = 6.8 Hz, 3H), 1.74 (dd, J = 13.1, 6.5 Hz, 2H), 2.13 (q, J = 7.5 Hz, 2H), 3.16 (s, 3H), 3.32 (t, J = 6.0 Hz, 2H), 3.92 (m, 2H), 4.71 (m, 1H), 5.57 (br s, 2H), 5.83 (s, 2H), 6.78 (d, J = 7.6 Hz, 1H), 6.94 (s, 1H), 7.04 (d, J = 7.8 Hz, 1H). MS: *m*/*z* 372.1 (M+1). Elem. Anal. Calcd for $C_{19}H_{25}N_5O_3 \cdot 0.5\ H_2O$: C, 61.29; H, 6.79; N, 18.81. Found: C, 61.38; H, 6.59; N, 18.41.

6.1.8. (2*R*)-6-(2,4-diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxypropyl)-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (11). *Step 1.* A solution of 1.73 g (7.93 mmol) of 4-bromo-2-nitrophenol (**48**) and 0.75 (6.61 mmol) of ethyl (*S*)-lactate in 100 mL of anhydrous CH_2Cl_2 was treated with 6.82 g (10.6 mmol, 1.55 mmol/g) of polymer supported-triphenylphosphine. The resulting suspension was stirred at room temperature for 10 min and then cooled in an ice bath. Diisopropyl azodicarboxylate (1.56 mL, 7.93 mmol) was added to the suspension in a dropwise fashion. The dark yellow suspension was allowed to warm to room temperature while stirring over 19 hours. The resin was collected on a medium frit and rinsed with CH_2Cl_2 (3×). The filtrate was concentrated and the crude residue was purified by flash chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) to yield 1.033 g (49%) of (*R*)-ethyl 2-(4-bromo-2-nitrophenoxy)propanoate as a viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.68 (d, J = 6.8 Hz, 3H), 4.21 (dq, J = 7.3, 1.7 Hz, 2H), 4.80 (q, J = 6.9 Hz, 1H), 6.86 (d, J = 9.1 Hz, 1H), 7.57 (dd, J = 8.8, 2.5 Hz, 1H), 7.95 (d, J = 2.4 Hz, 1H).

Step 2. A solution of 1.03 g (3.25 mmol) of ethyl (*R*)-2-(4-bromo-2-nitrophenoxy)propanoate in 20 mL of glacial acetic acid was treated with 3.63 g (64.9 mmol) of iron dust and heated in a 50 °C oil bath for 4 h. The resulting gray suspension was cooled to room temperature, diluted with EtOAc, and filtered through a Celite plug. The filtrate was washed with deionized H_2O and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to afford 1.38 g of (*R*)-6-bromo-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**63**) as a solid which was used without further purification. $[\alpha]_D$ −21.2° (*c* 4.9, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, J = 6.8 Hz, 3H), 4.66 (q, J = 6.8 Hz, 1H), 6.87 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 7.09 (dd, J = 8.6, 2.2 Hz, 1H), 8.46 (s, 1H). MS(ESI+): *m*/*z* 241.9, 243.9 (1:1 ratio, Br isotopes).

Step 3. A solution of 600 mg (2.48 mmol) of (*R*)-6-bromo-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**63**) in 20 mL of anhydrous DMF under an Ar atmosphere was cooled in an ice bath and treated with 455 mg (2.97 mmol, 60% dispersion in mineral oil) of NaH in a single portion. The resulting gray suspension was stirred in an ice bath for 10 min and treated with 2–3 drops of 15-crown-5, followed by 455 mg (2.97 mmol) of 1-bromo-3-methoxypropane. The reaction mixture was

stirred while warming to room temperature over 1 h. Excess hydride was quenched by the careful addition of H_2O, and the reaction mixture was poured into 300 mL of H_2O. The aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude residue by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 20% EtOAc/hexanes) provided 528 mg (68%) of (*R*)-6-bromo-4-(3-methoxypropyl)-2-methyl-2*H*-benzo[*b*][1,4]oxazin- 3(4H)-one (**72**) as a clear viscous oil. $[\alpha]_D$ −31.6° (*c* 8.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (d, J = 6.6 Hz, 3H), 1.94 (quintet, J = 6.2 Hz, 2H), 3.36 (s, 3H), 3.42 (t, J = 6.0 Hz, 2H), 3.96–4.01 (t, J = 6.8 Hz, 2H), 4.60 (q, J = 6.8 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.10 (dd, J = 8.6, 2.2 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H). MS (ESI+): *m*/*z* 314.0, 316.0 (1:1 ratio, Br isotopes).

Step 4. An oven-dried 50 mL round bottom flask was flushed with Ar and charged with 525 mg (1.67 mmol) of (*R*)-6-bromo-4-(3-methoxypropyl)-2-methyl-2*H*-benzo[*b*] [1,4]oxazin- 3(4H)-one (**72**), 509 mg (2.01 mmol) of bis(pinnocolato)diborane, 492 mg (5.01 mmol) of potassium acetate, and 9 mL on anhydrous 1,4-dioxane. The reaction mixture was degassed by bubbling Ar gas through the white suspension for 15 min. $PdCl_2$(dppf)–dichloromethane complex (68 mg, 80 mmol) was added in a single portion, and the resulting orange suspension was heated to reflux for 8 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through Celite, and concentrated. The residue was purified by flash chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 20% EtOAc/hexanes) to yield 441 mg (73%) of (*R*)-4-(3-methoxypropyl)-2-methyl-6-(4,4,5,5-tetramethyl-1, 3,2-dioxaborolan-2-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**82**) as a viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 12H), 1.54 (d, J = 6.8 Hz, 3H), 1.97 (quintet, J = 6.4 Hz, 2H), 3.35 (s, 3H), 3.43 (t, J = 6.1 Hz, 2H), 4.08 (t, J = 7.0 Hz, 2H), 4.63 (q, J = 6.8 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 7.47 (dd, J = 7.8, 1.2 Hz, 1H), 7.52 (d, J = 1.2 Hz, 1H). MS(ESI+): *m*/*z* 362.2 [M+1].

Step 5. An oven-dried flask was flushed with N_2 and charged with 440 mg (1.22 mmol) of (*R*)-4-(3-methoxypropyl)-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (**82**), 397 mg (1.83 mmol) of 5-bromo-6-ethyl-pyrimidine-2,4-diamine **54**,[17] 155 mg (3.65 mmol) of LiCl, 1.19 g (3.65 mmol) of Cs_2CO_3, 8 mL of 1,4-dioxane, and 1 mL of deionized H_2O. The reaction mixture was degassed by bubbling N_2 through the white suspension for 15 min. $Pd(PPh_3)_4$ (141 mg, 0.122 mmol) was added, and the light yellow suspension was heated to reflux for 20 h. The reaction mixture was cooled, diluted with EtOAc, and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% CH_2Cl_2 then gradient to 85:15 CH_2Cl_2/CH_3OH) to provide 207 mg (46%) of (2*R*)-6-(2,4-diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxypropyl)-2-methyl-2*H*-benzo [*b*][1,4]oxazin-3(4*H*)-one (**11**) as a solid. $[\alpha]_D$ −25.3° (*c* 5.5, CH_3OH); IR(ATR) 3450, 3309, 3149, 2975, 2876, 1665, 1628, 1558, 1448, 1384, 1269, 1112 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 3H), 1.40 (d, J = 6.6 Hz, 3H), 1.72 (m, 2H), 2.09 (q, J = 7.6 Hz, 2H), 3.12 (s, 3H), 3.28 (t, J = 6.1 Hz, 2H), 3.88 (m, 2H), 4.62–4.71 (m, 1H), 5.51 (m, 2H), 5.78 (br s, 2H), 6.74 (d, J = 7.8 Hz, 1H), 6.90 (d, J = 5.8 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 16.9, 28.2, 27.1, 38.9, 58.5, 69.4, 73.4, 106.69, 117.9, 126.3, 129.6, 131.1, 143.8, 162.7, 166.6, 167.1. HRMS (ESI) *m*/*z* Calcd for $C_{19}H_{26}N_5O_3$ $(M+H)^+$ 372.2035. Found: 372.2039. Elem. Anal. Calcd for $C_{19}H_{25}N_5O_3$: C, 61.44; H, 6.78; N, 18.69. Found: C, 61.23; H, 6.78; N, 18.69.

6.1.9. (2*S*)-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxypropyl)-2-methyl-4*H*-benzo[1,4]oxazin-3-one (12). The title compound was prepared via the identical route as described above for analog **11**, utilizing methyl (*R*)-lactate to afford a white solid foam. $[\alpha]_D^{24.7}$ +23.8 (*c* 3.7, CH_3OH), IR(ATR) 3448, 3429, 3405, 3314, 3174, 2973, 2927, 1669, 1623, 1554, 1440, 1373, 1260, 1106, 872, 665 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6)δ 0.93 (t, J = 7.6 Hz, 3H), 1.40 (d, J = 6.6 Hz, 3H), 1.70 (quintet, J = 6.7 Hz, 2H), 2.09 (q, J = 7.5 Hz, 2H), 3.12 (s, 3H), 3.28 (t, J = 7.5 Hz, 2H), 3.87 (m, 2H), 4.67 (m, 1H), 5.50 (br s, 2H), 5.77 (s, 2H), 6.74 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 5.9 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9, 16.9, 27.6, 28.2, 38.9, 58.5, 69.9, 73.4, 106.7, 117.9, 126.3, 129.6, 131.1, 162.7, 162.9. HRMS (ESI) *m*/*z* Calcd for $C_{19}H_{26}N_5O_3$ $(M+H)^+$: 372.2035. Found: 372.2025. Elem. Anal. Calcd for $C_{19}H_{25}N_5O_3 \cdot 0.3H_2O$: C, 60.67; H, 6.65; N, 18.62. Found: C, 60.67; H, 6.84; N, 18.40.

6.1.10. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-2-propyl-4*H*-benzo[1,4]oxazin-3-one (13). *Step 1.* A solution of 2.5 g (11 mmol) of 4-bromo-2-nitrophenol (**48**) and 1.4 g (9.08 mmol) of 2-hydroxyvaleric acid ethyl ester **57** in 50 mL of anhydrous CH_2Cl_2 was treated with 5.1 g (15 mmol, 3 mmol/g) of polymer-supported PPh_3, and the resulting suspension was stirred at room temperature for 10 min. The mixture was cooled in an ice bath, and 2.23 mL (11.5 mmol) of DIAD was added in a dropwise fashion. The resulting yellow suspension was stirred for 18 h while slowly warming to room temperature. The resin was collected on a coarse frit and rinsed with CH_2Cl_2 (3×). The combined filtrates were concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) gave 3.2 g (97%) of ethyl 2-(4-bromo-2-nitro-phenoxy)-butyrate (**57**). MS(ESI+): *m*/*z* 348.0, 350.0 ([M+1], 1:1 ratio of Br isotopes).

Step 2. A solution of 3.1 g (9.0 mmol) of **57** in 125 mL of glacial acetic acid was treated with 5.0 g (90 mmol) of Fe dust, and the resulting black suspension was heated in a 60 °C oil bath for 18 h. After cooling to room temperature, the gray suspension was filtered through a Celite pad, rinsing with EtOAc (200 mL). The filtrate was concentrated, and the residue was dissolved in EtOAc and

washed with H_2O (2×). The organic layer was dried over $MgSO_4$, filtered, and concentrated to 2.36 g (98%) of **65** as an opaque oil that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.5 Hz, 3H), 1.52–1.63 (m, 2H), 1.84–1.92 (m, 2H), 4.59 (dd, J = 8.1, 5.1 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 7.09 (dd, J = 8.6, 2.2 Hz, 1H), 8.90 (br s, 1H); MS(ESI+): *m*/*z* 270.0, 272.0 ([M+1], 1:1 ratio of Br isotopes).

Step 3. The residue from Step 2 was dissolved in 60 mL of anhydrous DMF and cooled in an ice bath. A 60% dispersion of NaH in mineral oil (426 mg, 10.6 mmol) was added in portions, and the resulting suspension was stirred for 30 min. 1-Bromo-3-methoxypropane (1.63 g, 10.6 mmol) was added, the ice bath was removed, and the mixture was stirred at ambient temperature for 18 h. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to give 2.53 g (87%) of **74** that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$)δ 0.93 (t, J = 7.3 Hz, 3 H), 1.44–1.56 (m, 2H), 1.71–1.81 (m, 2H), 1.87–1.94 (m, 2H), 3.33 (s, 3H), 3.38 (t, J = 5.9 Hz, 2H), 3.90–3.99 (m, 2H), 4.51 (dd, J = 8.0, 4.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.06 (dd, J = 8.0, 2.0 Hz, 1H), 7.22 (d, J = 2.20 Hz, 1H); MS(ESI+): *m*/*z* 344.1, 346.1 ([M+1], 1:1 ratio of Br isotopes).

Step 4. A suspension of 2.2 g (6.4 mmol) of **74**, 1.8 mg (7.1 mmol) of bis(pinacolato)diboron, and 2.0 g (19 mmol) of KOAc in 40 mL of anhydrous 1,4-dioxane was degassed by an Ar sparge for 10 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (520 mg (0.64 mmol)) was added, and the resulting dark red suspension was heated in a 110 °C oil bath for 16 h. The mixture was filtered through Celite, concentrated, and partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 50% EtOAc/hexanes) yielded 1.8 g (72%) of **84** as an oil MS(ESI+): *m*/*z* 391.0 (M+1).

Step 5. A mixture of 1.68 g (4.32 mmol) of **84**, 1.1 g (5.2 mmol) of **54**, 500 mg (13 mmol) of LiCl, and 500 mg (0.43 mmol) of $Pd(PPh_3)_4$ in 40 mL of anhydrous 1,4-dioxane and 10 mL of H_2O was degassed by Ar sparge for 10 min. Cs_2CO_3 (4.0 g, 13 mmol) was added, and the mixture was heated at reflux for 18 h. The black mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 40% MeOH/EtOAc) gave 356 mg (21%) of **13**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H), 1.48 (m, 2H), 1.76 (m, 4H), 2.12 (m, 2H), 3.17 (s, 3H), 3.33 (t, J = 6.1 Hz, 2H), 3.92 (m, 2H), 4.61 (m, 1H), 5.57 (br s, 2 H), 5.83 (s, 2H), 6.78 (m, 1H), 6.94 (m, 1H), 7.04 (m, 1H). MS: *m*/*z* 400.2 [M+1]. Elem. Anal. Calcd for $C_{21}H_{29}N_5O_3$: C, 63.14; H, 7.32; N, 17.53. Found: C, 63.08; H, 7.38; N, 17.27.

6.1.11. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-2-phenyl-4*H*-benzo[1,4]oxazin-3-one (14). *Step 1.* A solution of 1.09 g (4.99 mmol) of 4-bromo-2-nitrophenol **48** and 0.75 g (4.16 mmol) of ethyl *R*-(−)-mandelate **58** in 50 mL of anhydrous CH_2Cl_2 was treated with 1.84 g (6.66 mmol) of polymer-supported PPh_3, and the resulting suspension was stirred at room temperature for 10 min. The mixture was cooled in an ice bath, and 0.98 mL (4.99 mmol) of diisopropyl azadicarboxylate was added in a dropwise fashion. The resulting yellow suspension was stirred for 18 h while slowly warming to room temperature. The resin was collected on a coarse frit and rinsed with CH_2Cl_2 (3×). The combined filtrates were concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) gave 1.41 g (89%) of ethyl (2*S*)-2-(4-bromo-2-nitro-phenoxy)-mandelate as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 1.20 (t, J = 7.2 Hz, 3H), 4.12–4.23 (m, Hz, 2H), 5.72 (s, 1H), 6.91 (d, J = 9.0 Hz, 1H), 7.38–7.46 (m, 3H), 7.57–7.64 (m, 3H), 8.04 (d, J = 2.4 Hz, 1H).

Step 2. Ethyl (2*S*)-2-(4-bromo-2-nitro-phenoxy)-mandelate (1.41 g, 3.71 mmol) was dissolved in 205 mL of glacial acetic acid. Fe dust (4.15 g, 74 mmol) was added, and the resulting black suspension was heated in a 60 °C oil bath for 18 h. After cooling to room temperature, the gray suspension was diluted with EtOAc and filtered through a Celite pad. The filtrate was washed with H_2O (2×) and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated to 1.071 g (95%) of **66** as a white solid that was used without further purification. $[\alpha]_D^{24}$ −79.8° (*c* 5.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 2.2 Hz, 1H), 7.10 (dd, J = 8.6, 2.2 Hz, 1H), 7.35–7.40 (m, 3H), 7.41–7.45 (m, 2H), 8.60 (br s, 1H); MS(ESI+): *m*/*z* 303.9, 305.9 ([M+1], 1:1 ratio of Br isotopes).

Step 3. A solution of 750 mg (2.47 mmol) of **66** in 20 mL of anhydrous DMF was cooled in an ice bath. A 60% dispersion of NaH in mineral oil (108 mg, 2.71 mmol) was added, and the resulting suspension was stirred for 15 min. 1-Bromo-3-methoxypropane (453 mg, 2.96 mmol) and 0.1 mL of 15-crown-5 was added, the ice bath was removed, and the mixture was stirred at ambient temperature for 4 h. The reaction mixture was diluted with H_2O and extracted with EtOAc (3×). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) gave 524 mg (56%) of **75** as a white solid that was racemic by chiral HPLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92–2.04 (m, 2H), 3.35 (s, 3H), 3.37–3.47 (m, 2H), 4.01 (quintet, J = 7.1 Hz, 1H), 4.09 (quintet, J = 6.8 Hz, 1H), 5.71 (s, 2H), 6.92 (d, J = 8.6 Hz, 1H), 7.09 (dd, J = 8.6, 2.2 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.30–7.39 (m, 5 H); MS(ESI+): *m*/*z* 376.0, 378.0 ([M+1], 1:1 ratio of Br isotopes).

Step 4. A suspension of 524 mg (1.39 mmol) of **75**, 424 mg (1.67 mmol) of bis(pinacolato)diboron, and

410 mg (4.18 mmol) of KOAc in 14 mL of anhydrous 1,4-dioxane was degassed by an Ar sparge for 10 min. Pd–Cl_2(dppf)–CH_2Cl_2 complex (57 mg (0.07 mmol)) was added, and the resulting dark red suspension was heated in a 110 °C oil bath for 16 h. The mixture was filtered through Celite, concentrated, and partitioned between EtOAc:H_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 30% EtOAc/hexanes) yielded 412 mg (70%) of **85** as a white solid. MS(ESI+): *m*/*z* 424.0 (M+1).

Step 5. A mixture of 412 mg (0.97 mmol) of **85**, 254 mg (1.17 mmol) of **54**, 124 mg (2.92 mmol) of LiCl, and 952 mg (2.92 mmol) of Cs_2CO_3 in 8 mL of anhydrous 1,4-dioxane was degassed by freeze–pump–thaw techniques (2×). $Pd(PPh_3)_4$ (113 mg, 0.097 mmol) was added, and the mixture was heated at 100 °C for 18 h. The black mixture was diluted with EtOAc and filtered through Celite. Purification by flash column chromatography (SiO_2, 100% CH_2Cl_2 then gradient to 85:15 CH_2Cl_2:MeOH) gave 117 mg (28%) of **14** as a brown-white solid that exists as a 1:1 mixture of restricted rotational isomers. ^{1}H NMR (400 MHz, DMSO-d_6)δ 0.88–1.06 (m, 3H), 1.80 (quintet, J = 7.0 Hz, 2H), 2.12 (m, 2H), 3.18 (s, 3H), 3.36 (t, J = 6.2 Hz, 2H), 3.89–4.12 (m, 2H), 5.52 (br s, 2H), 5.77–5.90 (m, 3H), 6.81 (d, J = 8.0 Hz, 1H), 6.99 (s, 1H), 7.09 (d, J = 9.0 Hz, 1H), 7.32–7.47 (m, 5H); MS(ESI+): *m*/*z* 434.2 [M+1]. Elem. Anal. Calcd for $C_{24}H_{27}N_5O_3 \cdot 0.3CH_2Cl_2$: C, 63.71; H, 6.00; N, 15.08. Found: C, 63.74; H, 6.25; N, 14.85.

6.1.12. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-2-(3,4-difluoro-phenyl)-4*H*-benzo[1,4]oxazin-3-one (15). Step 1. A solution of 4.10 g (21.1 mmol) of (3,4-difluorophenyl)-hydroxyacetic acid **131** and 0.90 mL of 37% aqueous HCl in 90 mL of MeOH was heated to reflux for 18 h, cooled to room temperature, and concentrated. The residue was partitioned between saturated $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 3.87 g (91%) of methyl (3,4-difluorophenyl)hydroxyacetate (**59**), which was used without further purification. MS(ESI+): *m*/*z* 201.0 (M−1).

Step 2. A suspension of 3.79 g (18.7 mmol) of **59**, 4.16 g (18.7 mmol) of 4-bromo-2-nitrophenol **48**, and (18.1 g, 28.1 mmol) of polymer-supported PPh_3 in 200 mL of anhydrous CH_2Cl_2 at 0 °C was treated with 4.26 mL (20.6 mmol) of DIAD in a dropwise fashion. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and stirred for 48 h. The mixture was filtered through a medium frit, and the filtrate was washed with 1 N NaOH, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 10.41 g (100%) of (4-bromo-2-nitrophenoxy)-(3,4-difluorophenyl)acetic acid methyl ester, which was used directly without further purification.

Step 3. Glacial AcOH (100 mL) and 10.47 g (187.5 mmol) of iron dust were added to 10.41 g (18.7 mmol) of (4-bromo-2-nitrophenoxy)-(3,4-difluorophenyl)acetic acid methyl ester and the mixture was heated at 60 °C for 3 h. The reaction mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to a light yellow solid. Trituration with CH_2Cl_2 and hexanes afforded 4.77 g (75%) of 6-bromo-2-(3,4-difluorophenyl)-4*H*-benzo[1,4]oxazin-3-one **67** as a light yellow-orange solid. MS(ESI+): *m*/*z* 340.0, 341.9 ([M+1], 1:1 ratio of Br isotopes).

Step 4. A mixture of 4.76 g (14.0 mmol) of **67**, 2.03 g (14.7 mmol) of K_2CO_3, and 2.25 g (14.7 mmol) of 1-bromo-3-methoxypropane in 100 mL of anhydrous CH_3CN was heated to reflux for 16 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was concentrated to afford 5.84 g (100%) of **76** as a viscous orange oil that solidified upon standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91–1.99 (m, 2H), 3.34 (s, 3H), 3.35–3.44 (m, 2H), 3.97–4.09 (m, 2H), 6.92 (d, J = 8.6 Hz, 1H), 7.11 (dd, J = 6.6, 2.0 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1 H); MS(ESI+): *m*/*z* 412.0, 414.0 ([M+1], 1:1 ratio of Br isotopes).

Step 5. A solution of 500 mg (1.21 mmol) of **76** in 15 mL of anhydrous 1,4-dioxane was treated with 461 mg (1.82 mmol) of bis(pinacolato)diboron and 356 mg (3.63 mmol) of KOAc, and degassed by N_2 sparge for 15 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (49 mg (0.06 mmol)) was added, and the resulting dark red suspension was heated in a 110 °C oil bath for 16 h. The mixture was cooled to room temperature and treated with 591 mg (2.72 mmol) of **54**, 154 mg (3.63 mmol) of LiCl, 1.18 g (3.62 mmol) of Cs_2CO_3, and 4 mL of H_2O. The resulting biphasic mixture was degassed by N_2 sparge for 15 min. $Pd(PPh_3)_4$ (386 mg, 0.33 mmol) was added, and the mixture was heated at reflux for 20 h. The black mixture was diluted with CH_2Cl_2 and filtered through a SiO_2 pad, rinsing with MeOH. Purification by flash column chromatography (SiO_2, 100% CH_2Cl_2 then gradient to 90:10 CH_2Cl_2/MeOH) then (SiO_2, 100% EtOAc then gradient to 90:10 EtOAc/MeOH) gave 266 mg (39%) of **15** as a light yellow solid that exists as a 1:1 mixture of restricted rotational isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, J = 7.6 Hz, 3H), 1.91 (quintet, J = 6.1 Hz, 2H), 2.25 (q, J = 8.0 Hz, 2H), 3.26 (s, 3H), 3.36–3.44 (m, 2H), 3.99–4.09 (m, 2H), 4.51 (br s, 1H), 4.57 (br s, 1H), 4.85 (br s, 2H), 5.63 (s, 1H), 6.89 (dd, J = 8.0, 2.0 Hz, 1H), 6.93 (m, 1H), 7.12 (dd, J = 8.1, 2.2 Hz, 1H) 7.14–7.19 (m, 1H), 7.29 (m, 2 H). MS(ESI+): *m*/*z* 470.2 [M+1].

Diagnostic peaks for the restricted rotational isomer: 1.08 (t, J = 7.6 Hz, 3H), 2.29 (q, J = 8.0 Hz, 2H), 5.68 (s, 1H).

6.1.13. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-2-(4-fluoro-phenyl)-4H-benzo[1,4]oxazin-3-one (16). *Step 1.* A solution of 2.00 g (11.8 mmol) of (4-fluorophenyl)-hydroxyacetic acid and 0.5 mL of 37% aqueous HCl in 50 mL of MeOH was heated to reflux for 6 h, cooled to room temperature, and concentrated.

The residue was partitioned between saturated $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 2.04 g (94%) of methyl (4-fluorophenyl)-hydroxyacetate (**60**), which was used without further purification. MS(ESI+): *m/z* 201.0 (M−1).

Step 2. A suspension of 2.01 g (10.93 mmol) of **60**, 2.43 g (10.9 mmol) of 4-bromo-2-nitrophenol **48**, and (10.6 g, 16.38 mmol) of polymer-supported PPh_3 in 100 mL of anhydrous CH_2Cl_2 was cooled in an ice bath and treated with 2.5 mL (12.06 mmol) of DIAD in a dropwise fashion. The reaction mixture was stirred at 0 °C to 16 h, allowed to warm to room temperature, and stirred for 35 h. The mixture was filtered through a medium frit, and the filtrate was washed with 1 N NaOH, 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 6.03 g of a sticky, light-yellow solid, which was used directly without further purification.

Step 3. The residue from Step 2 was dissolved in 100 mL of glacial AcOH and treated with 11.05 g (198 mmol) of iron dust. The mixture was heated at 60 °C for 45 min. The reaction mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to a light-yellow solid. Trituration with CH_2Cl_2 afforded 4.96 g (78%) of 6-bromo-2-(3,4-difluorophenyl)-4*H*-benzo[1,4]oxazin-3-one **68** as a light-yellow-tan solid that was used without further purification.

Step 4. A mixture of 2.47 g (7.66 mmol) of **68**, 1.06 g (7.67 mmol) of K_2CO_3, and 1.17 g (7.65 mmol) of 1-bromo-3-methoxypropane in 100 mL of anhydrous CH_3CN was heated to reflux for 14 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was concentrated to give 3.08 g (100%) of **77** as a light-yellow oil that solidified upon standing. ^{1}H NMR (400 MHz, $CDCl_3$)δ 1.94–2.01 (m, 2H), 3.35 (s, 3H), 3.38–3.46 (m, 2H), 4.05 (dq, J = 19.3, 7.2 Hz, 2H), 5.66 (s, 1H), 6.91 (d, J = 8.6 Hz, 1H), 6.99–7.06 (m, 2H), 7.10 (dd, J = 8.6, 2.2 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.32–7.37 (m, 2H); MS(ESI+): *m/z* 394.0, 396.0 ([M+1], 1:1 ratio of Br isotopes).

Step 5. A solution of 1.29 g (3.27 mmol) of **77** in 15 mL of anhydrous 1,4-dioxane was treated with 1.22 g (4.80 mmol) of bis(pinacolato)diboron and 1.18 g (3.68 mmol) of KOAc, and degassed by N_2 sparge for 15 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (163 mg (0.20 mmol)) was added, and the resulting dark red suspension was heated in a 110 °C oil bath for 15 h. The mixture was cooled to room temperature and filtered through a SiO_2 pad, rinsing with EtOAc. The filtrate was concentrated and purified by flash column chromatography (SiO_2, 100% CH_2Cl_2 then gradient to 10% EtOAc/CH_2Cl_2) to yield 1.14 g (79%) of **87** as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 12 H) 2.00 (quintet, J = 6.4 Hz, 2H), 3.34 (s, 3H), 3.43 (ddd, J = 6.0, 2.3 Hz, 3H), 4.13 (t, J = 7.8 Hz, 3H), 5.69 (s, 1H), 6.95–7.07 (m, 3H), 7.36 (dd, J = 8.8, 5.1 Hz, 2H), 7.47 (dd, J = 7.9, 1.1 Hz, 1H), 7.51 (s, 1H). MS(E-SI+): *m/z* 360.2 [M+1].

Step 6. A solution of 313 mg (0.709 mmol) of **87** in 3 mL of anhydrous 1,4-dioxane and 1 mL of H_2O was treated with 346 mg (1.59 mmol) of **54**, 90 mg (2.12 mmol) of LiCl, and 0.69 g (2.12 mmol) of Cs_2CO_3. The resulting mixture was degassed by Ar sparge for 25 min. $Pd(PPh_3)_4$ (410 mg, 0.36 mmol) was added, and the mixture was heated at 150 °C by microwave heating for 2 h. The black mixture was diluted with MeOH and filtered through a Celite pad, rinsing with MeOH. The resulting solution was concentrated, dissolved in CH_2Cl_2, and washed with 1 N HCl. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% CH_2Cl_2 then gradient to 90:10 CH_2Cl_2/MeOH), then (SiO_2, 100% EtOAc then gradient to 90:10 EtOAc/MeOH) gave 134 mg (42%) of **16** as a light-yellow solid that exists as a 1:1 mixture of restricted rotational isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.6 Hz, 3H), 1.95 (quintet, J = 7.1 Hz, 2H), 2.28 (q, J = 7.7 Hz, 2H), 3.28 (s, 3H), 3.43 (m, 2H), 4.06 (ddd, J = 7.3, 7.3, 3.3 Hz, 2H), 4.48 (br s, 1H), 4.55 (br s, 1H), 4.84 (br s, 2H), 5.73 (s, 1H), 6.89 (dd, J = 8.1, 1.7 Hz, 1H), 6.94 (dd, J = 4.8, 1.6 Hz, 1H), 7.06 (ddd, J = 8.7, 8.7, 3.2 Hz, 2H), 7.10 (dd, J = 8.1, 2.0 Hz, 1H), 7.42 (dd, J = 7.32, 5.37 Hz, 2 H); MS(ESI+): *m/z* 452.2 [M+1].

Diagnostic peaks for the restricted rotational isomer: 1.13 (t, J = 7.6 Hz, 3H), 2.33 (q, J = 7.57 Hz, 2H), 5.67 (s, 1H).

6.1.14. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-4-(3-methoxy-propyl)-4*H*-benzo[1,4]oxazin-3-one (17). *Step 1.* A solution of 2.00 g (10.6 mmol) of 3,5-difluoromandelic acid in 50 mL of MeOH was treated with 0.5 mL concd HCl and heated to reflux for 6 h. After cooling to room temperature, the solution was concentrated under rotary evaporation. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 1.84 g (85%) of methyl 3,5-difluoromandelate as a white solid that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (d, J = 5.4 Hz, 1H), 3.82 (s, 3H), 5.17 (d, J = 5.4 Hz, 1H), 6.78 (tt, J = 8.8, 2.3 Hz, 1H), 6.97–7.05 (m, 2 H).

Step 2. To a solution of 2.4 g (11 mmol) of 4-bromo-2-nitrophenol (**48**) and 1.84 g (9.08 mmol) of methyl 3,5-difluoromandelate in 50 mL of anhydrous CH_2Cl_2 under an Ar atmosphere, polymer-supported PPh_3 (4.8 g, 3 mmol/g) was added and the resulting suspension was stirred at room temperature for 10 min. The mixture was cooled in an ice bath, and 2.10 ml (10.86 mmol) of diisopropyl azadicarboxylate was added in a dropwise fashion. The resulting yellow suspension was stirred for 18 h while slowly warming to room temperature. The resin was collected on a coarse frit and rinsed with CH_2Cl_2 (3×). The combined filtrates

were concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) gave 3.3 g of ethyl (4-bromo-2-nitro-phenoxy)-(3,5-difluoro-phenyl)-acetate. ^{1}H NMR (400 MHz, $CDCl_3$)δ 3.77 (s, 3H), 5.70 (s, 1H), 6.86 (tt, J = 8.8, 2.4 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 7.14–7.22 (m, 2H), 7.63 (dd, J = 8.8, 2.4 Hz, 1H), 8.08 (d, J = 2.4 Hz, 1H).

Step 3. Ethyl (4-bromo-2-nitro-phenoxy)-(3,5-difluoro-phenyl)-acetate (3.3 g, 7.74 mmol) was dissolved in 125 mL of glacial acetic acid. Fe dust (4.3 g, 77 mmol) was added, and the resulting black suspension was heated in a 60 °C oil bath for 18 h. After cooling to room temperature, the gray suspension was filtered through a Celite pad, rinsing with EtOAc (200 mL). The filtrate was concentrated, and the residue was dissolved in EtOAc and washed with H_2O (2×). The organic layer was dried over $MgSO_4$, filtered, and concentrated to a pale yellow solid that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 6.80 (tt, J = 8.8, 2.3 Hz, 1H), 6.96–6.99 (m, 2H), 7.00–7.03 (m, 2H), 7.14 (dd, J = 8.6, 2.2 Hz, 1H), 8.76 (br s, 1H). MS(ESI+): m/z 339.9, 340.9 [M+1, 1:1 ratio of Br isotopes].

Step 4. The solid residue was dissolved in 60 mL of anhydrous DMF, and the solution was cooled in a ice bath. NaH (263 mg, 6.59 mmol, 60% dispersion in mineral oil) was added in portions, and the reaction mixture was stirred at 0 °C for 30 min. 1-Bromo-3-methoxypropane (1.1 g, 7.1 mmol) was added, and the mixture was stirred at room temperature for 18 h. Excess hydride was quenched by the slow addition of H_2O. The resulting mixture was diluted with H_2O and extracted with EtOAc (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) afforded 0.96 g (50%) of **78** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91–1.99 (m, 2H), 3.33 (s, 3H), 3.35–3.44 (m, 2H), 3.95–4.10 (m, 2H), 5.65 (s, 1H), 6.74 (tt, J = 8.8, 2.1 Hz, 1H), 6.94 (m, 2H), 6.95 (d, J = 8.6 Hz, 1H), 7.12 (dd, J = 8.4, 2.1 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H); MS(ESI+): m/z 414.0 [M+1].

Step 5. A 250 mL round bottom flask was flushed with Ar and charged with 610 mg (2.40 mmol) of bis(pinacolato)diboron, 643 mg (6.55 mmol) KOAc, and 357 mg (0.437 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex. A solution of 900 mg (2.18 mmol) of **78** in 50 mL of anhydrous 1,4-dioxane was added, and the resulting dark orange suspension was heated at 110 °C for 16 h. The resulting black mixture was filtered through a Celite plug and concentrated. The residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 50% EtOAc/hexanes) gave 337 mg (34%) of **88** as a solid foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 12H), 1.99 (quintet, J = 6.84 Hz, 2H), 3.33 (s, 3H), 3.36–3.46 (m, 2H), 4.12 (m, 2H), 6.71 (tt, J = 8.0, 4.0 Hz, 1H), 6.90–7.00 (m, 21H), 7.08 (d, J = 4.0 Hz, 1H), 7.49 (dd, J = 8.0, 2.0 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H); MS(ESI+): m/z 414.0 [M+1].

Step 6. A mixture of 181 mg (0.836 mmol) of 5-bromo-6-ethyl-2,4-diamine **54**,[17] 320 mg (0.697 mmol) **88**, 89 mg (0.089 mmol) LiCl, and 81 mg (0.07 mmol) $Pd(PPh_3)_4$ in 30 mL of 1,4-dioxane and 4 mL H_2O was degassed by sparging with Ar for 10 min. Cs_2CO_3 (681 mg, 2.09 mmol) was added, and the mixture was heated to reflux for 18 h. The black suspension was diluted with EtOAc and filtered through a Celite plug. The filtrate was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 40% MeOH/EtOAc) provided 327 mg (22%) of 6-(2,4-diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-4-(3-methoxy-propyl)-4*H*-benzo[1,4]oxazin-3-one **17** as a glassy solid. IR(ATR) 3322, 3172, 2974, 1678, 1597, 1555, 1442, 1262, 1119 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94 (m, 3 H), 1.76 (m, 2H), 2.09 (m, 2H), 3.12 (s, 3H), 3.32 (t, J = 6.1 Hz, 2H), 3.95 (m, 2H), 5.53 (br s, 2H), 5.83 (m, 2H), 5.92 (s, 1H), 6.81 (dd, J = 8.1, 1.7 Hz, 1H), 6.99 (s, 1H), 7.10 (d, J = 6.6 Hz, 2H), 7.14 (d, J = 8.3 Hz, 1H), 7.27 (tt, J = 9.3, 2.2 Hz, 2 H). HRMS (ESI) m/z Calcd for $C_{24}H_{26}F_2N_5O_3$ $(M+H)^+$ 470.2003. Found: 470.2018. Elem. Anal. Calcd for $C_{24}H_{25}F_2N_5O_3$·0.3EtOAc: C, 62.22; H, 5.92; N, 13.95. Found: C, 62.20; H, 5.88; N, 14.20.

6.1.15. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxy-propyl)-2-(2,3-difluoro-phenyl)-4*H*-benzo[1,4]oxazin-3-one (18). *Step 1.* A solution of 4.48 g (22.2 mmol) of methyl (2,3-difluorophenyl)-hydroxyacetate **62** and 4.94 g (22.2 mmol) of 4-bromo-2-nitrophenol **48** in 225 mL of anhydrous CH_2Cl_2 was treated with 21.5 g (33.3 mmol, 1.55 mmol/g) of polymer-supported PPh_3 and cooled in an ice bath. DIAD (5.06 mL, 24.4 mmol) was added dropwise, and the resulting bright-orange suspension was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for an additional 45 h. The resin was removed by filtration through a coarse frit, rinsing with CH_2Cl_2. The filtrate was washed with 1 N NaOH, H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated to give 12.74 g of a moist yellow solid that was used without purification in the following step.

Step 2. The residue from the preceding step was dissolved in 100 mL of glacial acetic acid and treated with 12.25 g (219 mmol) of iron dust. The resulting black suspension was heated at 60 °C for 1 h. After cooling to room temperature, the gray suspension was filtered through Celite, rinsing with EtOAc. The filtrate was washed with H_2O (3×), saturated aqueous $NaHCO_3$ (2×), and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in 50 mL of CH_2Cl_2 and precipitated by addition of 50 mL of hexanes and cooling in an ice bath. The solid was collected on a medium frit to give 2.347 g (32%) of 6-bromo-2-(3,4-difluorophenyl)-4*H*-benzo[1,4]oxazin-3-one **70** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.01 (s, 1H), 6.92–6.98 (m, 1H), 7.10 (s, 1H), 7.11 (dd, J = 7.6,

2.4 Hz, 2H), 7.23–7.32 (m, 2H), 7.52 (dddd, J = 10.2, 7.8, 7.1, 3.12 Hz, 1H), 11.16 (s, 1H); MS(ESI+): *m/z* 339.9, 341.9 ([M^+], 1:1 ratio of Br isotopes).

Step 3. A solution of 585 mg (1.72 mmol) of **70** in 9 mL of anhydrous CH_3CN was treated with 316 mg (3.06 mmol) of 1-bromo-3-methoxypropane and 285 mg (2.06 mmol) of K_2CO_3 and heated to reflux for 18 h. The mixture was cooled to room temperature, diluted with EtOAc, filtered through a Celite plug, and concentrated. Purification by flash column chromatography (SiO_2. 5% EtOAc/hexanes then gradient to 20% EtOAc/hexanes) afforded 289 mg (38%) of **79** as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01 (quintent, J = 6.50 Hz, 2H), 3.37 (s, 3H), 3.46 (t, J = 5.8 Hz, 2H), 4.08 (ddd, J = 7.0, 7.0, 3.3 Hz, 2H), 5.80 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.07–7.11 (m, 2H), 7.12 (dd, J = 8.6, 2.1 Hz, 1H), 7.17–7.25 (m, 1H), 7.34 (d, J = 2.1 Hz, 1 H); MS(ESI+): *m/z* 411.9, 413.9 ([M^+], 1:1 ratio of Br isotopes).

Step 4. A solution of 289 mg (0.70 mmol) of **79** in 20 mL of anhydrous 1,4-dioxane was treated with 267 mg (1.05 mmol) of bis(pinacolato)diboron and 206 mg (2.10 mmol) of KOAc, and degassed by N_2 sparge for 15 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (29 mg (0.036 mmol)) was added, and the resulting dark red suspension was heated at reflux for 14 h. The mixture was cooled to room temperature and treated with 342 mg (1.58 mmol) of **54**, 89 mg (2.10 mmol) of LiCl, 685 mg (2.10 mmol) of Cs_2CO_3, and 5 mL of H_2O. The resulting mixture was degassed by N_2 sparge for 15 min. $Pd(PPh_3)_4$ (203 mg, 0.18 mmol) was added, and the mixture was heated at reflux for 4 h. The black mixture was diluted with CH_2Cl_2 and washed with H_2O, 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and filtered. The solution was partially concentrated and loaded onto a 20 g pad of SiO_2. The column was washed with CH_2Cl_2 until the filtrates were colorless. The product was then eluted from the column by washing with MeOH. The filtrate was concentrated, and purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 10% MeOH/EtOAc), gave 86 mg (26%) of **18** as an amber solid that exists as a 1:1 mixture of restricted rotational isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, J = 7.6 Hz, 3H), 1.88–2.05 (m, 2H), 2.33 (q, J = 7.6 Hz, 2H), 3.29 (s, 3H), 3.45 (t, J = 6.0 Hz, 2H), 4.00–4.17 (m, 2H), 4.54 (bs, 2H), 4.82 (br s, 2H), 5.31 (s, 1H), 6.90 (ddd, J = 8.0, 2.0, 2.0 Hz, 1H), 02 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 8.0, 2.0 Hz, 1H), 7.12–7.17 (m, 2H), 7.19–7.26 (ddd, J = 9.9, 7.8, 7.8, 2.0 Hz, 1H); MS(ESI+): *m/z* 470.1 [M+1].

Diagnostic peaks for the restricted rotational isomer: 1.12 (t, J = 7.6 Hz, 3H), 2.34 (q, J = 7.6 Hz, 2H), 5.82 (br s, 2H), 5.85 (br s, 2 H).

6.1.16. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-4-(3-methoxypropyl)-2,2-dimethyl-4*H*-benzo[1,4]oxazin-3-one (19). *Step 1.* A solution of 22.7 g (104 mmol) of 4-bromo-2-nitrophenol **48** in 200 mL of anhydrous CH_3CN was treated with 17.2 g (125 mmol) of K_2CO_3 and 18.3 mL (125 mmol) of ethyl 2-bromoisobutyrate, and heated to reflux for 6 h. An additional 18.5 mL of ethyl 2-bromoisobutyrate was added and the suspension was heated at reflux for an additional 18 h. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through Celite. The filtrate was concentrated to an orange oil that was used without further purification.

Step 2. The oil was dissolved in 500 mL of glacial acetic acid and treated with 58.1 g (1040 mmol) of Fe powder. The black suspension was heated at 60 °C for 3 h. After cooling to room temperature, the gray suspension was filtered through Celite, which was rinsed with 200 mL of EtOAc (4×). The combined filtrates were concentrated to dryness. The solid residue was triturated with EtOAc and filtered through Celite to remove inorganic salts. The filtrate was washed with H_2O (3×) and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The solid residue was recrystallized from hexanes to yield 14.72 g of 6-bromo-2,2-dimethyl-4*H*-benzo[1,4]oxazin-3-one **93** as a tan-white solid. The mother liquor was concentrated and the residue recrystallized from hexanes to yield an additional 4.46 g of **93** (72% total yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 6H), 6.83 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 7.08 (dd, J = 8.3, 2.2 Hz, 1H), 9.48 (br s, 1H); MS(ESI+): *m/z* 255.9, 257.9 [M+1, 1:1 ratio of Br isotopes].

Step 3. A solution of 14.9 g (58.2 mmol) of 6-bromo-2,2-dimethyl-4*H*-benzo[1,4]oxazin-3-one **93** in 150 mL of anhydrous DMF was cooled in an ice bath and treated with 2.8 g (70.0 mmol) of a 60% dispersion of NaH in mineral oil in a single portion. The resulting mixture was stirred at 0 °C for 15 min. 1-Bromo-3-methoxypropane (11.0 g, 70.0 mmol) was then added in a dropwise fashion over 5 min. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for 16 h. The mixture was diluted with 600 mL of H_2O and extracted with EtOAc (3× 200 mL). The combined organics were washed with H_2O (2× 50 mL) and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 40% EtOAc/hexanes) afforded 15.8 g (80%) of **94** as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39 (s, 6H), 1.76 (quintet, J = 7.1 Hz, 2H), 3.22 (s, 3H), 3.33 (t, J = 6.0 Hz, 2H), 3.92 (t, J = 7.1 Hz, 2H), 6.94 (d, J = 8.6 Hz, 1H), 7.17 (dd, J = 8.4, 2.1 Hz, 1H), 7.36 (d, J = 2.2 Hz, 1H); MS(ESI+): *m/z* 328.0 330.0 [M+1, 1:1 ratio of Br isotopes].

Step 4. A mixture of 573 mg (1.75 mmol) of **94**, 532 mg (2.10 mmol) of bis(pinacolato)diboron, and 514 mg (5.24 mmol) of KOAc in 9 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 20 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (71 mg, 0.087 mmol) was added, and the resulting deep orange suspension was heated in a 100 °C oil bath for 2.5 h. After cooling to room temperature, 568 mg (2.62 mmol) of **54**, 1.71 g (5.24 mmol) of Cs_2CO_3, 222 mg (5.24 mmol) of LiCl, and 1.1 mL of H_2O were added. The mixture was degassed by Ar sparge for 10 min, and 202 mg

(0.175 mmol) $Pd(PPh_3)_4$ was added. The mixture was heated in a 100 °C oil bath for 18 h. After cooling to room temperature, the mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% CH_2Cl_2 then gradient to 85:15 CH_2Cl_2/MeOH) gave 115 mg (17%) of **19** as a gray solid. IR (ATR) 3427, 3153, 2976, 1666, 1631, 1555, 1449, 1385, 1361, 1263, 1122, 811 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6)δ 0.98 (t, J = 7.6 Hz, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 1.75 (quintet, J = 6.6 Hz, 2H), 2.14 (qd, J = 7.5, 1.3 Hz, 2H), 3.17 (s, 3H), 3.32 (m, 2H), 3.91 (m, 2H), 5.59 (bs, 2H), 5.83 (s, 2H), 6.79 (dd, J = 8.0, 4.0 Hz, 1H), 6.92 (d, J = 4.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.2, 27.5, 39.6, 39.8, 57.9, 69.3, 77.2, 128.8, 130.2, 141.8, 162.0, 162.3, 166.5, 167.6. HRMS (ESI) m/z Calcd for $C_{20}H_{28}N_5O_3$ $(M+H)^+$ 386.2191. Found 386.2174. Elem. Anal. Calcd for $C_{20}H_{27}N_5O_3$: C, 62.32; H, 7.06; N, 18.17. Found: C, 62.04; H, 7.10; N, 17.88.

6.1.17. *N*-(2-(6-(2,4-diamino-6-ethyl-pyrimidin-5-yl)-2,2-dimethyl-3-oxo-2,3-dihydrobenzo[*b*][1,4]-oxazin-4-yl)-ethyl)-acetamide (20). *Step 1.* A solution of 2.50 g (9.76 mmol) of 6-bromo-2,2-dimethyl-4*H*-benzo[1,4] oxazin-3-one **93** in 50 mL of anhydrous DMF was cooled in an ice bath under an Ar atmosphere and treated with 429 mg (10.7 mmol) of 60% NaH in mineral oil. The resulting gray suspension was stirred at 0 °C for 15 min. 15-Crown-5 (0.1 mL) and 1.41 g (11.71 mmol) of bromoacetonitrile were added. The ice bath was removed, and the reaction mixture was stirred at room temperature for 18 h. Excess hydride was quenched by the slow addition of H_2O, and the resulting slurry was poured into 1 L of H_2O. The aqueous layer was extracted with EtOAc (3×). The combined organics were washed with H_2O (2×) and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 20% EtOAc/hexanes) afforded 3.00 g (98%) of 2-(6-bromo-2,2-dimethyl-3-oxo-2,3-dihydrobenzo-[*b*][1,4]-oxazin-4-yl)- acetonitrile **95** as a clear viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 6H), 4.79 (s, 2H), 6.89 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 2.2 Hz, 1H), 7.20 (dd, J = 8.6, 2.2 Hz, 1H). MS(ESI+): m/z 296.9, 298.9 ([M+1], Br isotopes, 1:1 ratio).

Step 2. A solution of 1.03 g (3.49 mmol) of **95**, 0.49 mL (5.24 mmol) of Ac_2O, and 50 mL of THF was treated with 1.0 g of Raney nickel. The reaction mixture was shaken under 50 psi of H_2 pressure for 12 h. The catalyst was removed by filtration through a Celite plug, and the filtrate was concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 100% EtOAc) yielded 886 mg (74%) of *N*-(2-(6-bromo-2,2-dimethyl-3-oxo-2,3-dihydrobenzo[*b*][1,4] oxazin-4-yl)- ethyl)-acetamide **96** as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 6H), 1.97 (s, 3H), 3.54 (q, J = 5.6 Hz, 2H), 4.05 (t, J = 6.4 Hz, 2H), 5.97 (br s, 1H), 6.84 (d, J = 8.6 Hz, 1H), 7.12 (dd, J = 8.6, 2.2 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H). MS(ESI+): m/z 341.0, 343.0 ([M+1], Br isotopes, 1:1 ratio).

Step 3. A solution of 885 mg (2.59 mmol) of **96**, 790 mg (3.11 mmol) bis(pinacolato)diboron, and 764 mg (7.78 mmol) of KOAc in 15 mL of anhydrous 1,4-dioxane was degassed by N_2 sparge for 20 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (106 mg, 0.13 mmol) was added, and the mixture was heated in an 85 °C oil bath for 18 h. After cooling to room temperature, the mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated. Purification by flash column chromatography (SiO_2,75% EtOAc/hexanes then gradient to 100% EtOAc) gave 1.04 g (100%) of *N*-{2-[2,2-dimethyl-3-oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-ethyl}-acetamide as a dark solid foam. MS(ESI+): m/z 389.2 [M+1].

Step 4. A mixture of 397 mg (1.02 mmol) of *N*-{2-[2,2-dimethyl-3-oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-ethyl}-acetamide, 266 mg (1.23 mmol) of **54**, 515 mg (3.07 mmol) of $CsOH{\cdot}H_2O$, and 130 mg (3.07 mmol) of LiCl was suspended in 6 mL of anhydrous 1,4-dioxane and 0.75 mL of H_2O. After degassing by N_2 sparge for 20 min, 118 mg (0.10 mmol) of $Pd(PPh_3)_4$ was added, and the resulting yellow suspension was heated in a 100 °C oil bath for 18 h. The reaction mixture was diluted with EtOAc, dried over $MgSO_4$, and filtered through a Celite plug. The filtrate was concentrated, and the residue purified by flash column chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH then gradient to 80:20 CH_2Cl_2/MeOH) to afford 149 mg (37%) of **20** as a solid white foam. IR(ATR) 3441, 3339, 1664, 1618, 1549, 1441, 1384, 1358, 1263 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 3H), 1.38 (s, 6H), 1.66 (s, 3H), 2.10 (q, J = 7.6 Hz, 3H), 3.12 (m, 2H), 3.83 (dd, J = 6.9, 6.9 Hz, 2H), 5.52 (br s, 2H), 5.78 (br s, 2H), 6.73 (dd, J = 8.0, 1.7 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 1.8 Hz, 1H), 7.95 (t, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 23.1, 24.2, 28.1, 36.3, 77.8, 106.8, 117,6, 118.3, 126.4, 129.7, 130.7, 142.4, 162.5, 163.0, 168.5, 170.2. HRMS (ESI+) Calcd for $C_{20}H_{27}N_6O_3$ $(M+H)^+$: 399.2144. Found: 399.2138.

6.1.18. *N*-{2-[6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-methyl-3-oxo-2-trifluoromethyl-2,3-dihydro-benzo[1,4]-oxazin-4-yl]-ethyl}-acetamide (21). *Step 1.* A solution of 1.16 g (6.74 mmol) of methyl 3,3,3-trifluoro-2-methyl-propionate in 20 mL of anhydrous THF was treated with 308 mg (7.70 mmol) of a 60% NaH dispersion in mineral oil. The resulting orange solution was stirred at room temperature for 10 min. Then, 5 drops of 15-crown-5 were added via syringe, followed by 1.41 g (6.42 mmol) of 4-bromo-2-nitrofluorobenzene 97. The resulting orange solution was stirred at room temperature for 17 h and then heated in a 45 °C oil bath for 8 h. Excess hydride was quenched by the careful addition of MeOH. The solution was diluted with EtOAc, and then washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 10% EtOAc/hexanes) yielded 1.60 g of **98**.

Step 2. A solution of 1.60 g (4.14 mmol) of **98** in 20 mL of glacial acetic acid was treated with 2.31 g (41.4 mmol)

of iron dust and heated in a 60 °C oil bath for 4 h. The resulting gray suspension was cooled to room temperature, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated to dryness. The solid residue was dissolved in EtOAc and washed with H_2O (3×) and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 10% EtOAc/hexanes) gave 1.105 g (86%) of **105** as a clear oil. MS(ESI+): *m/z* 307.9, 309.9 [M+1], Br isotopes, 1:1 ratio.

Step 3. A solution of 1.11 g (3.56 mmol) of **105** and 0.30 mL (4.28 mmol) of bromoacetonitrile in 20 mL of anhydrous CH_3CN was treated with 0.59 g (4.28 mmol) of K_2CO_3, and heated to reflux for 18 h. The mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) yielded 0.96 g (77%) of **115** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$)δ 1.79 (s, 3H), 4.78 (d,J = 17.6 Hz, 1H), 4.94 (d, J = 17.6 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 2.1 Hz, 1H), 7.27 (dd, J = 8.8, 2.2 Hz, 1H); MS(ESI+): *m/z* 347.9, 349.9 ([M−1], 1:1 ratio of Br isotopes).

Step 4. A solution of 0.96 g (2.74 mmol) of **115** and 1 mL of Ac_2O in 50 mL of THF was treated with 1.0 g Raney nickel. The resulting suspension was shaken under a 22 psi H_2 atmosphere for 1 h. The mixture was filtered through Celite and concentrated. Purification by flash column chromatography (SiO_2, 15% EtOAc/hexanes then gradient to 70% EtOAc/hexanes) yielded 300 mg (28%) of **120** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3H); 1.95 (s, 3H), 3.52 (q, J = 6.5 Hz, 2H), 3.99 (ddd, J = 20.5, 12.7, 6.5 Hz, 1H); 4.18 (ddd, J = 21.1, 14.1, 6.8 Hz, 1H), 5.79 (br s, 1H), 6.89 (d, J = 8.6 Hz, 1H), 7.15 (dd, J = 8.6, 2.2 Hz, 1H), 7.41 (d, J = 2.15 Hz, 1H); MS(ESI+): *m/z* 394.9, 396.9 ([M−1], 1:1 ratio of Br isotopes).

Step 5. A solution of 295 mg (0.747 mmol) of **120**, 227 mg (0.89 mmol) of bis(pinacolato)diboron, and 220 mg (2.24 mmol) of KOAc in 10 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 15 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (31 mg, 0.037 mmol) was added, and the resulting red-orange mixture was heated at 90 °C for 18 h. After cooling to room temperature, the black mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated. The crude residue was dissolved in 12 mL of anhydrous 1,4-dioxane and 1.5 mL of H_2O. LiCl (95 mg, 2.24 mmol), 194 mg (0.90 mmol) of **54**, and 376 mg (2.24 mmol) of CsOH·H_2O was added, and the resulting suspension was degassed by Ar sparge for 20 min. $Pd(PPh_3)_4$ (86 mg, 0.075 mmol) were added, and the mixture was heated in a 100 °C oil bath for 23 h. The mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated. Purification by flash column chromatography (SiO_2, 100:0 CH_2Cl_2/MeOH then gradient to 80:20 CH_2Cl_2/MeOH) followed by preparatory reverse phase HPLC (10% CH_3CN/H_2O/0.1% TFA then gradient to 60% CH_3CN/H_2O/0.1% TFA) yielded 145 mg of the TFA salt of **21** as a white solid. IR(ATR) 3398, 3124, 1675, 1638, 1532, 1452, 1389, 1373, 1194, 1157, 1140 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99 (t, J = 7.6 Hz, 3H), 1.63 (s, 3H), 1.65 (s, 3H), 2.22 (q, J = 7.42 Hz, 2H), 3.19 (m, 2H), 3.91 (m, 2 H) 6.82 (d, J = 8.6 Hz, 1H), 6.91 (dt, J = 8.2, 2.1 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.26 (dd, J = 8.4, 1.4 Hz, 1H), 7.56 (bs, 2 H) 7.98 (t, J = 5.9 Hz, 1H), 8.15 (d, J = 10.6 Hz, 1H) 12.36 (s, 1H). HRMS Calcd for [$C_{20}H_{23}F_3N_6O_3$+H]: 453.1862. Found: 453.1858.

Diagnostic peaks for the minor rotational isomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99 (t, J = 7.6 Hz, 3H), 1.67 (s, 2H), 3.14 (m, 1H), 3.32 (m, 1H), 3.83 (m, 1H), 3.98 (m, 1H).

6.1.19. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-ethyl-4-(3-methoxy-propyl)-2-methyl-4*H*-benzo[1,4]oxazin-3-one (22). *Step 1.* A solution of 2.52 g (19.1 mmol) of methyl 2-methyl-2-hydroxy-butanate in 80 mL of anhydrous THF was treated with 873 mg (21.8 mmol) of a 60% NaH dispersion in mineral oil. The resulting gray suspension was stirred at room temperature for 10 min. Then, 5 drops of 15-crown-5 were added via syringe, followed by 2.24 mL (18.2 mmol) of 4-bromo-2-nitrofluorobenzene 97. The resulting yellow suspension was stirred at room temperature for 17 h. Excess hydride was quenched by the careful addition of MeOH. The solution was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 20% EtOAc/hexanes) afforded 3.89 g (64%) of **99** as a yellow oil.

Step 2. A solution of 3.55 g (10.7 mmol) of **99** in 150 mL of glacial acetic acid was treated with 5.97 g (107 mmol) of iron dust and heated in a 60 °C oil bath for 18 h. The resulting gray suspension was cooled to room temperature, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated to dryness. The solid residue was dissolved in EtOAc and washed with H_2O (3×) and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 2.83 g (98%) of **106** as an opaque oil that was used without further purification. MS(ESI+): *m/z* 272.0, 274.0 [M+1], Br isotopes, 1:1 ratio.

Step 3. A solution of 1.50 g (5.6 mmol) of **106** in 25 mL of anhydrous DMF was cooled in an ice bath and treated with 290 mg (7.2 mmol) of a 60% dispersion of NaH in mineral oil in portions. The resulting mixture was stirred at 0 °C for 30 min and then treated with 1.0 g (6.7 mmol) of 1-bromo-3-methoxypropane. The ice bath was removed, and the reaction mixture was stirred at room temperature for 16 h. Excess NaH was carefully quenched by the dropwise addition of H_2O. The mixture was diluted with H_2O and extracted with EtOAc (3×). The combined organics were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2. 5% EtOAc/hexanes then gradient to 20% EtOAc/hexanes) afforded 1.65 mg (87%) of **112**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.5 Hz,

3H), 1.44 (s, 3H), 1.69 (q, J = 14.34, 7.4 Hz, 2H), 1.83–1.97 (m, 4H), 3.34 (s, 3H), 3.39 (t, J = 6.0 Hz, 2H), 3.87–4.05 (m, 2H), 6.81 (d, J = 8.6 Hz, 1 H), 7.06 (dd, J = 8.6, 2.2 Hz, 1H), 7.19 (d, J = 2.2 Hz, 1H); MS(ESI+): m/z 342.1, 344.1 ([M^+], 1:1 ratio of Br isotopes).

Step 4. A solution of 1.2 g (5.6 mmol) of **112** in 40 mL of anhydrous 1,4-dioxane was treated with 1.2 g (4.6 mmol) of bis(pinacolato)diboron, 1.0 g (11.0 mmol) of KOAc, and 290 mg (0.35 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex. The resulting dark red suspension was heated in a 110 °C oil bath for 16 h. The mixture was cooled to room temperature and filtered through Celite, rinsing with EtOAc. The filtrate was concentrated to an oil, which was used without purification in the following reaction. MS(ESI+): m/z 390.3 [M^+].

Step 5. The residue was dissolved in 40 mL of anhydrous 1,4-dioxane and 8 mL of H_2O, and treated with 0.91 g (4.2 mmol) of **54**, 400 mg (11 mmol) of LiCl, 2.0 g (11 mmol) of $CsOH{\cdot}H_2O$, and 410 mg (0.35 mmol) of $Pd(PPh_3)_4$. The resulting mixture was degassed by Ar sparge for 15 min and then heated at reflux for 16 h. The resulting black mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with H_2O, dried over Na^2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 40% MeOH/EtOAc) and precipitation from EtOAc yielded 334 mg (24%) of **22** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (m, 3H), 0.93 (t, J = 7.8 Hz, 3H), 1.39 (s, 3H), 1.63 (m, 1H), 1.70 (m, 2H), 1.84 (m, 1H), 2.09 (q, J = 6.6 Hz, 2H), 3.12 (s, 3H), 3.28 (m, 2H), 3.87 (m, 2H), 5.51 (br s, 2H), 5.74 (br s, 2H), 6.72 (d, J = 7.3 Hz, 1H), 6.85 (s, 1H), 6.95 (d, J = 7.3 Hz, 1H); MS(ESI+): m/z 400.6 (M+1). Elem. Anal. Calcd for $C_{21}H_{29}N_5O_3{\cdot}0.2H_2O$: C, 62.66; H, 7.35; N, 17.40. Found: C, 62.65; H, 7.17; N, 17.07.

6.1.20. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2,2-diethyl-4-(3-methoxy-propyl)-4*H*-benzo[1,4]oxazin-3-one (23). *Step 1.* A solution of 1.05 g (7.16 mmol) of methyl 2-ethyl-2-hydroxy-butanate in 35 mL of anhydrous THF was treated with 327 mg (8.18 mmol) of a 60% NaH dispersion in mineral oil. The resulting gray suspension was stirred at room temperature for 10 min. Then, 5 drops of 15-crown-5 were added via syringe, followed by 0.84 mL (6.82 mmol) of 4-bromo-2-nitrofluorobenzene 97. The resulting yellow suspension was stirred at room temperature for 17 h. Excess hydride was quenched by the careful addition of MeOH. The solution was diluted with EtOAc, and then washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 10% EtOAc/hexanes) afforded 821 mg (35%) of **100** as a yellow oil.

Step 2. A solution of 820 mg (2.28 mmol) of **100** in 10 mL of glacial acetic acid was treated with 1.27 g (22.8 mmol) of iron dust and heated in a 60 °C oil bath for 3 h. The resulting gray suspension was cooled to room temperature, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated to dryness. The solid residue was dissolved in EtOAc and washed with H_2O (3×) and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 20% EtOAc/hexanes) afforded 821 mg (35%) of **107** as a yellow oil to yield 531 mg (82%) of 107 as a tan-white solid. MS(ESI+): m/z 284.0, 286.0 [M+1], Br isotopes, 1:1 ratio.

Step 3. A solution of 530 mg (1.87 mmol) of **107** in 10 mL of anhydrous DMF was cooled in an ice bath and treated with 82 mg (2.06 mmol) of a 60% dispersion of NaH in mineral oil. The resulting gray suspension was stirred at 0 °C for 15 min, and then treated with 0.1 mL of 15-crown-5 and 343 mg (2.24 mmol) of 1-bromo-4-methoxypropane. The reaction mixture was stirred at room temperature for 16 h, and then poured into 250 mL of H_2O and extracted with EtOAc (3×). The combined organic layers were washed with H_2O (2×) and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes, then gradient to 20% EtOAc/hexanes) gives 527 mg of **113** as a clear viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.9 Hz, 6H), 2.06 (q, J = 7.6 Hz, 4H), 3.75 (s, 3H), 6.75 (d, J = 8.8 Hz, 1H), 7.48 (dd, J = 9.0, 2.7 Hz, 1H). MS(ESI−): m/z 356.0, 358.0 (M^+, 1:1 ratio of Br isotopes).

Step 4. A 50 mL oven-dried Schlenk flask was charged with 525 mg (1.47 mmol) of **113**, 449 mg (1.77 mmol) of bis(pinacolato)diboron, 434 mg (4.42 mmol) of KOAc, and 8 mL of anhydrous 1,4-dioxane under an Ar atmosphere. The clear suspension was degassed by Ar sparge through the suspension for 15 min. $PdCl_2$(dppf)–CH_2Cl_2 1:1 complex (60 mg, 0.07 mmol) was added in a single portion, and the resulting brick-red suspension was heated in a 90 °C oil bath for 3 h. After cooling to r.t., the reaction mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated. The residue was used without further purification in the following reaction. MS(ESI+): m/z 404.3 (M+1).

Step 5. The residue was dissolved in 8 mL of 1,4-dioxane and 1 mL of H_2O under an Ar atmosphere. Cs_2CO_3 (1.44 g, 4.42 mmol), 187 mg (4.42 mmol) of LiCl, and 480 mg (2.21 mmol) of **54** were added, and the resulting dark suspension was degassed by Ar sparge for 20 min. $Pd(PPh_3)_4$ (170 mg, 0.154 mmol) was added, and the mixture was heated in a 100 °C oil bath for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated. Purification by flash column chromatography (SiO_2, 100:0 CH_2Cl_2/MeOH, then gradient to 90:10 CH_2Cl_2/MeOH) yielded 56 mg (12%) of **23** as a green-white solid foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, J = 6.8 Hz, 6H), 0.93 (t, J = 7.3 Hz, 3H), 1.62–1.73 (m, 4H), 1.83 (quintet, J = 7.3 Hz, 2H), 2.09 (q, J = 7.2 Hz, 2H), 3.12 (s, 3H), 3.28 (q, J = 4.0 Hz, 2H), 3.828 (m, 2H), 5.52 (br s, 2 H) 5.77 (bs, 2H), 6.72 (dd, J = 8.0, 2.0 Hz, 1 H), 6.83 (d, J = 4.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H); MS(ESI) 414.2 (M+H).

6.1.21. *N*-{2-[6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2,2-[cyclopropyl]-3-oxo-benzo[1,4]oxazin-4-yl]-ethyl}-acetamide (24). *Step 1.* A solution of 932 mg (7.16 mmol) of ethyl 2-hydroxy-cyclopropylacetate in 20 mL of anhydrous THF was treated with 327 mg (8.18 mmol) of a 60% NaH dispersion in mineral oil. The resulting gray suspension was stirred at room temperature for 10 min. Then, 5 drops of 15-crown-5 were added via syringe, followed by 0.84 mL (6.82 mmol) of 4-bromo-2-nitrofluorobenzene 97. The resulting yellow suspension was stirred at room temperature for 17 h. Excess hydride was quenched by the careful addition of MeOH. The solution was diluted with EtOAc, and then washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 10% EtOAc/hexanes) afforded 1.60 g (71%) of **101** as a yellow oil.

Step 2. A solution of 1.60 g (4.84 mmol) of **101** in 20 mL of glacial acetic acid was treated with 2.70 g (48.4 mmol) of iron dust and heated in a 60 °C oil bath for 3 h. The resulting gray suspension was cooled to room temperature, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated to dryness. The solid residue was dissolved in EtOAc and washed with H_2O (3×) and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 1.24 g (100%) of **108** as a white solid that was used without further purification. MS(ESI+): *m*/*z* 253.9, 256.0 [M+1], Br isotopes, 1:1 ratio.

Step 3. A solution of 1.24 g (4.87 mmol) of 108 and 0.41 ml (5.85 mmol) of bromoacetonitrile in 25 mL of anhydrous CH_3CN was treated with 0.74 g (5.36 mmol) of K_2CO_3 and heated to reflux for 18 h. The mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 15% EtOAc/hexanes) yielded 1.07 g (75%) of **116** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 1.31 (dd, J = 8.4, 5.7 Hz, 2H), 1.48 (dd, J = 8.7, 5.4 Hz, 2H), 4.81 (s, 2H), 6.83 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 8.6, 2.0 Hz, 1H); MS(E-SI+): *m*/*z* 293.0, 294.0 ([M−1], 1:1 ratio of Br isotopes).

Step 4. A solution of 1.07 g (3.64 mmol) of **116** and 0.51 mL (5.47 mmol) of Ac_2O in 50 mL of THF was treated with 1.0 g Raney nickel. The resulting suspension was shaken under a 51 psi H_2 atmosphere for 17 h. The mixture was filtered through Celite and concentrated. Purification by flash column chromatography (SiO_2, 10% EtOAc/hexanes then gradient to 70% EtOAc/hexanes) yielded 0.802 g (65%) of **121** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (dd, J = 8.0, 4.9 Hz, 2H), 1.40 (dd, J = 8.2, 5.5 Hz, 2H), 1.98 (s, 3H), 3.55 (q, J = 6.1 Hz, 2H), 4.06 (t, J = 6.5 Hz, 2H), 6.05 (bs, 1H), 6.75 (d, J = 8.4 Hz, 1H), 7.11 (dd, J = 8.4, 2.1 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H); MS(E-SI+): *m*/*z* 339.0, 341.0 ([M−1], 1:1 ratio of Br isotopes).

Step 5. A solution of 750 mg (2.21 mmol) of **121**, 674 mg (2.65 mmol) of bis(pinacolato)diboron, and 651 mg (6.63 mmol) of KOAc in 11 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 15 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (90 mg, 0.111 mmol) was added, and the resulting red-orange mixture was heated at 90 °C for 18 h. After cooling to room temperature, the black mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated. The crude residue was dissolved in 7 mL of anhydrous 1,4-dioxane and 0.9 mL of H_2O. LiCl (281 mg, 6.63 mmol), 576 mg (2.65 mmol) of **54**, and 1.11 g (6.63 mmol) of $CsOH{\cdot}H_2O$ were added, and the resulting suspension was degassed by Ar sparge for 20 min. $Pd(PPh_3)_4$ (255 mg, 0.22 mmol) was added, and the mixture was heated in a 100 °C oil bath for 18 h. The mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated. Purification by flash column chromatography (SiO_2, 95:5 CH_2Cl_2/MeOH then gradient to 70:30 CH_2Cl_2/MeOH) followed by preparatory reverse phase HPLC (10% CH_3CN/H_2O/0.1% TFA then gradient to 60% CH_3CN/H_2O/0.1% TFA) yielded 280 mg of the TFA salt of **24** as a white solid. IR(ATR) 3365, 3103, 1674, 1629, 1399, 1193, 1169, 1143 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02 (t, J = 7.6 Hz, 3H), 1.19 (ddd, J = 10.0, 5.5, 3.6 Hz, 2H), 1.26 (ddd, J = 10.4, 7.3, 2.2 Hz, 2H), 1.70 (s, 3H), 2.24 (q, J = 7.5 Hz, 2H), 3.11–3.29 (m, 2H), 3.81–3.91 (m, 2H), 6.84 (dd, J = 8.1, 1.9 Hz, 1H), 6.91 (br s, 1H), 6.98 (d, J = 8.2 Hz, 1H), 7.45 (br s, 2H), 8.01 (t, J = 5.9 Hz, 1H), 8.13 (bs, 1H), 12.08 (bs, 1H); HRMS Calcd for [$C_{20}H_{24}N_6O_3$+H]: 397.1988. Found: 397.2006. Elem. Anal. Calcd for $C_{20}H_{24}N_6O_3{\cdot}1.8TFA\cdot 0.5H_2O$: C, 46.35; H, 4.41; N, 13.72; F, 16.93. Found: C, 46.65; H, 4.41; N, 13.72.

6.1.22. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-4-(3-methoxy-propyl)-2-methyl-4*H*-benzo[1,4]oxazin-3-one (25). *Step 1.* A solution of 1.50 g (6.50 mmol) of 2-(3,5-difluorophenyl)-2-hydroxy-propionic acid ethyl ester in 40 mL of anhydrous THF was treated with 312 mg (7.80 mmol) of a 60% NaH dispersion in mineral oil. The resulting gray suspension was stirred at room temperature for 10 min. Then, 30 μL of 15-crown-5 was added via syringe, followed by 1.50 g (6.83 mmol) of 4-bromo-2-nitrofluorobenzene **97**. The resulting orange solution was stirred at room temperature for 17 h. Excess hydride was quenched by the careful addition of MeOH. The solution was diluted with EtOAc, and then washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness.

Step 2. The orange residue was dissolved in 20 mL of glacial acetic acid, treated with 3.63 g (65.0 mmol) of iron dust, and heated in a 60 °C oil bath for 4 h. The resulting gray suspension was cooled to room temperature, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated to dryness. The solid residue was dissolved in EtOAc and washed with H_2O (3×) and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 15% EtOAc/hexanes) gave 1.87 g (5.28 mmol) **109** as a white semisolid (81%, 2 steps). ^{1}H NMR (400 MHz, CDCl3) δ 1.89 (s, 3H), 6.71 (tt, J = 8.6, 2.4 Hz, 1H), 6.89 (d, J = 2.2 Hz, 1H), 6.96–7.01 (m, 3H), 7.11 (dd, J = 8.6, 2.2 Hz, 1H), 8.28

(br s, 1H); MS(ESI+): *m/z* 353.8, 355.8 [M+1], Br isotopes, 1:1 ratio.

Step 3. A solution of 850 mg (2.4 mmol) of *rac*-6-bromo-2-(3,5-difluoro-phenyl)-2-methyl-4*H*-benzo[1,4]oxazin-3-one **109** in 10 mL of anhydrous CH_3CN was treated with 460 mg (3.0 mmol) of 1-bromo-3-methoxypropane and 365 mg (2.64 mmol) of K_2CO_3, and heated at reflux for 18 h. The resulting suspension was cooled to room temperature, diluted with EtOAc, and filtered through a Celite plug. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 10% EtOAc/hexanes) gave 752 mg (73%) of **114** as a light-yellow low-melting solid. ^{1}H NMR (400 MHz, $CDCl_3$)δ 1.82 (s, 3H), 1.87–1.97 (m, 2H), 3.29 (s, 3H), 3.33–3.28 (m, 1H), 3.35-3.40 (m, 1H), 3.91 (ddd, J = 14.3, 7.3, 7.2 Hz, 1H), 4.05 (ddd, J = 14.3, 7.3, 7.2 Hz, 1H), 6.61 (tt, J = 8.7, 2.4 Hz, 1H), 6.85–6.90 (m, 2H), 6.91 (d, J = 8.56 Hz, 1H), 7.04 (dd, J = 8.6, 2.2 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H); MS(ESI+): *m/z* 426.0, 427.9 ([M+1], 1:1 ratio of Br isotopes).

Step 4. A 100 mL round bottom flask was flushed with Ar and charged with 560 mg (1.31 mmol) of **114**, 430 mg (1.70 mmol) of bis(pinacolato)diboron, 400 mg (4.0 mmol) of KOAc, 110 mg (0.13 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex, and 20 mL of anhydrous 1,4-dioxane. The resulting dark orange suspension was heated at 110 °C for 16 h. After cooling to room temperature, the resulting black mixture was filtered through a Celite plug and concentrated to a viscous oil that was used without further purification. MS(ESI+): *m/z* 474.1 [M+1].

Step 5. The residue from Step 4 was dissolved in 20 mL of 1,4-dioxane and 5 mL of H_2O. 5-bromo-6-ethyl-2,4-diaminopyrimidine **54** (340 mg, 1.60 mmol), 200 mg (4.0 mmol) LiCl, and 700 mg (4.0 mmol) $CsOH{\cdot}H_2O$ were added, and the resulting suspension was degassed with Ar sparge for 10 min. $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) was added and the reaction mixture was heated at reflux for 18 h. The black suspension was diluted with EtOAc and filtered through a Celite plug. The filtrate was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 40% MeOH/EtOAc) provided 327 mg (22%) of **25** as a glassy solid. Purification by preparative reverse-phase HPLC (CH_3CN/H_2O with 0.1% TFA) followed by lyophilization afforded the TFA salt of **25** as a white amorphous powder that exists as a mixture of restricted rotational isomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J = 7.6 Hz, 3H), 1.74 (m, 2H), 1.77 (s, 3H), 2.06 (q, (J = 8.0 Hz, 2H)), 3.13 (s, 3H), 3.28 (t, J = 5.9 Hz, 2H), 3.92 (m, 2H), 6.75 (br s, 1H), 6.88 (ddd, J = 8.0, 4.0, 4.0 Hz, 1H), 6.99–7.06 (m, 3H), 7.15 (m, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.72 (br s, 2H), 8.05 (br s, 1H), 12.67 (br s, 1H). HRMS (ESI+) Calcd for $C_{25}H_{27}F_2N_5O_3$ $(M+H)^+$: 483.2082. Found: 484.2148 (M+1). Elem. Anal. Calcd for $C_{25}H_{27}F_2N_5O_3{\cdot}1.5$TFA: C, 51.49; H, 4.40; N, 10.74. Found: C, 51.46; H, 4.56; N, 10.95.

Diagnostic peaks for the minor rotational isomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99 (t, J = 8.0 Hz, 3H), 1.36 (s, 3H), 2.17 (q, J = 4 Hz, 2H), 8.03, (br s, 1H), 12.75 (br s, 1H).

6.1.23. *N*-{2-[6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-2-methyl-3-oxo-2,3-dihydro-benzo-[1,4]oxazin-4-yl]-ethyl}-acetamide (26). *Step 1.* A solution of 5.00 g (14.1 mmol) of **109** in 50 mL of anhydrous CH_3CN was treated with 1.97 mL (28.24 mmol) of bromoacetonitrile and 2.34 g (16.9 mmol) of K_2CO_3, and heated at reflux for 18 h. The resulting suspension was cooled to room temperature, diluted with EtOAc, and filtered through a Celite plug. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 5% EtOAc/hexanes then gradient to 20% EtOAc/hexanes) gave 3.17 g (57%) of **117** as a white solid. MS(ESI+): *m/z* 391.9, 393.9 ([M+1], 1:1 ratio of Br isotopes).

Step 2. A solution of 3.17 g (8.07 mmol) of **117** and 1.00 g (12.2 mmol) of NaOAc in 10 mL of Ac_2O and 90 mL of AcOH was treated with 1.5 g of Raney nickel and hydrogenated under a 50 psi H_2 atmosphere at 50 °C for 24 h. The mixture was filtered through Celite and concentrated to dryness. Purification by flash column chromatography (SiO_2, 60% EtOAc/hexanes then gradient to 100% EtOAc) afforded 2.48 g (70%) of **122** as a white solid foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 3H), 1.99 (s, 3H), 3.51 (m, 2H), 3.98 (dt, J = 14.2, 6.2, 6.2 Hz, 1H), 4.20 (ddd, J = 14.1, 67.0, 6.8 Hz, 1H), 5.94 (br s, 1H), 6.69 (tt, J = 8.67, 2.3 Hz, 1H), 6.86–6.93 (m, 2H), 6.97 (d, J = 8.6 Hz, 1H), 7.14 (dd, J = 8.6, 2.1 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H); MS(ESI+): *m/z* 439.0, 441.0 ([M+1], 1:1 ratio of Br isotopes).

Step 3. A suspension of 3.07 g (6.99 mmol) of **122**, 1.7 g (2.1 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex, 2.3 g (9.1 mmol) of bis(pinacolato)diboron, and 2.1 g (21 mmol) of KOAc in 35 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 20 min and then heated at 110 °C for 2.5 h. After cooling to room temperature, the black mixture was diluted with EtOAc and washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 25% MeOH/EtOAc) gave 3.9 g of an impure black solid that was used without further purification. MS(ESI+): *m/z* 487.2 [M+1].

Step 4. A suspension of 2.9 g (6 mmol) of the residue from Step 3, 1.29 g (5.96 mmol) of **54**, 0.76 g (18 mmol) of LiCl, and 3.0 g (18 mmol) of $CsOH{\cdot}H_2O$ in 40 mL of 1,4-dioxane and 4 mL of H_2O was degassed by Ar sparge for 20 min. $Pd(PPh_3)_4$ (0.69 g, 0.6 mmol) was added, and the mixture was heated to reflux for 2 h. After cooling to room temperature, the mixture was diluted with EtOAc and washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 18%

MeOH/EtOAc isocratic) yielded 0.67 g (23%) of **26** as an off-white powder. An additional 0.36 mg (35% total yield) of **26** could be obtained by preparatory reverse-phase HPLC (10% CH_3CN/H_2O/0.1% TFA then gradient to 70% CH_3CN/H_2O/0.1% TFA) of the impure fractions and neutralization of the resulting TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 7.4 Hz, 3H), 1.71 (s, 3H), 1.81 (s, 3H), 2.02 (q, J = 7.3 Hz, 2H), 3.12–3.25 (m, 1H), 3.27–3.37 (m, 1H), 3.85–4.08 (m, 2H), 5.58 (br s, 1H), 5.76 (br s, 1H), 5.97 (br s, 2H), 6.83 (t, J = 7.2 Hz, 1H), 7.06 (s, 1H), 7.10 (d, J = 6.3 Hz, 2H), 7.16–7.27 (q, J = 8.6 Hz, 1H), 8.02 (t, J = 6.0 Hz, 1H). MS(ESI+): *m/z* 497.1 (M+1). Elem. Anal. Calcd for $C_{25}H_{26}F_2N_6O_3{\cdot}1.1H_2O$: C, 57.93; H, 5.53; N, 16.21; H_2O, 4.21. Found: C, 58.15; H, 5.52; N, 16.14; H_2O, 4.38.

Diagnostic peaks for the minor rotational isomer: ^{1}H NMR (400 MHz, DMSO-d_6)δ 0.98 (t, J = 7.4 Hz, 3H), 2.16 (q, J = 4 Hz, 2H).

6.1.24. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-2-ethyl-4-(3-methoxy-propyl)-4*H*-benzo-[1,4]oxazin-3-one (27). *Step 1.* A solution of 900 mg (2.18 mmol) of **78** in 25 mL of anhydrous DMF was cooled in an ice bath and treated with 120 mg (3.1 mmol) of a 60% dispersion of NaH in mineral oil in portions. The resulting orange solution was stirred at 0 °C for 30 min. Iodoethane (0.23 mL, 2.8 mmol) was added, the ice bath was removed, and the mixture was stirred at room temperature for 16 h. Excess hydride was quenched by the dropwise addition of H_2O, and the mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 20% EtOAc/hexanes) yielded 790 mg (82%) of **125** as an opaque oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 1.01 (t, J = 7.3 Hz, 3H), 1.84–1.98 (m, 2H), 2.05 (dq, J = 14.7, 7.3 Hz, 1H), 2.37 (dq, J = 14.5, 7.3 Hz, 1H) 3.32 (ddd, J = 9.5, 6.8, 4.9 Hz, 1H), 3.33 (s, 3H), 3.39 (ddd, J = 9.5, 6.4, 4.9 Hz, 2H), 3.95 (ddd, J = 14.4, 7.2, 7.2 Hz, 1H,) 4.05 (ddd, J = 14.0, 7.6, 6.0 Hz, 1H), 6.66 (tt, J = 8.7, 2.4, 2.3 Hz, 1H), 6.87–6.95 (m, 2H), 6.98 (d, J = 8.6 Hz, 1 H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H), 7.14 (d, J = 2.2 Hz, 1H); MS(ESI+): *m/z* 439.0, 441.0 ([M−1], 1:1 ratio of Br isotopes).

Step 2. A suspension of 680 mg (1.54 mmol) of **125**, 510 mg (2.00 mmol) of bis(pinacolato)diboron, 500 mg (5.0 mmol) of KOAc, and 130 mg (0.15 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex in 40 mL of anhydrous 1,4-dioxane was heated at 110 °C for 16 h. After cooling to room temperature, the black mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated to a black oil that was used without further purification. MS(ESI+): *m/z* 488.3 [M+1].

Step 3. The residue was dissolved in 30 mL of anhydrous 1,4-dioxane and 6 mL of H_2O and treated with 200 mg (5 mmol) of LiCl, 400 mg (1.8 mmol) of **54**, and 255 mg (0.15 mmol) of $Pd(PPh_3)_4$. The mixture was degassed by Ar sparge for 10 min, and then treated with 800 mg (5.0 mmol) of $CsOH{\cdot}H_2O$ and heated at reflux for 18 h. The mixture was diluted with EtOAc and filtered through a Celite plug. The filtrate was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 0:100 MeOH/EtOAc then gradient to 20:80 MeOH/EtOAc) and precipitation from CH_3CN afforded 146 mg (19%) of **27** as a white powder that exists as a 1:1 mixture of restricted rotational isomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.85 (t, J = 7.6 Hz, 3H), 0.93 (m, 3H), 1.70 (m, 2H), 1.95 (m, 2H), 2.07 (m, 1H), 2.28 (m, 1H), 3.12 (s, 3H), 3.26 (m, 2H), 3.93 (m, 2H), 5.36 (br s, 1H), 5.57 (br s, 1H), 5.79 (s, 2H), 6.85 (m, 2H), 7.04 (s, 2H), 7.15 (m, 1H), 7.26 (d, J = 8.1 Hz, 1H). MS(ESI+): *m/z* 498.2 (M+1). Elem. Anal. Calcd for $C_{26}H_{29}F_2N_5O_3 0.25H_2O$: C, 66.22; H, 5.92; N, 13.95. Found: C, 62.20; H, 5.88; N, 14.20.

Diagnostic peaks for the rotational isomer: 0.86 (t, J = 7.6 Hz, 3H).

6.1.25. 6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-(3,4-difluoro-phenyl)-4-(3-methoxy-propyl)-2-methyl-4*H*-benzo[1,4]oxazin-3-one (28). *Step 1.* A solution of 500 mg (1.21 mmol) of **76** in 15 mL of anhydrous THF was cooled in an ice bath and treated with 73 mg (3.04 mmol) of a 60% dispersion of NaH in mineral oil. The reaction mixture was stirred at 0 °C for 30 min and then 94 μL (1.5 mmol) of MeI was added. The reaction mixture was allowed to warm to room temperature while stirring for 17 h. Excess hydride was quenched by the dropwise addition of H_2O, and the mixture was concentrated and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the combined organic extracts are washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 530 mg (quantitative) of **126**, which was used directly in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13 (m, 2H), 7.05 (m, 3H), 6.91 (d, J = 8.4 Hz, 1H), 4.05 (m, 1H), 3.93 (m, 1H), 3.34 (m, 2H), 3.32 (s, 3H), 1.92 (m, 2H), 1.82 (s, 3H).

Step 2. A mixture of 0.53 g (1.21 mmol) of **126**, 357 mg (3.64 mmol) of KOAc, and 462 mg (1.82 mmol) of bis(pinacolato)diboron in 20 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 20 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (50 mg, 0.061 mmol) was added, and the reaction mixture was heated to reflux for 13 h and then cooled to room temperature. LiCl (154 mg, 3.63 mmol), 592 mg (2.73 mmol) of **54**, 1.18 g (3.62 mmol) of Cs_2CO_3, and 5 mL of H_2O were added. The resulting suspension was degassed by N_2 sparge for 20 min. $Pd(PPh_3)_4$ (350 mg, 0.303 mmol) was added, and the mixture was heated to reflux for 4.5 h, cooled to room temperature, and stirred for 93 h. The solvent was evaporated, and the resulting residue was partitioned between CH_2Cl_2 and H_2O. The biphasic mixture was filtered through a pad of Celite. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$ for 14 h. Polymer-supported PPh_3 was added and the suspension was stirred at room temperature for 1 h. The mixture

was filtered, concentrated to one-third the original volume, and filtered through a SiO_2 pad. The pad was sequentially washed with CH_2Cl_2, EtOAc, and MeOH. The MeOH wash was concentrated to provide the crude product. Purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 30% MeOH/EtOAc) gave 123 mg (21%) of **28** as an off-white solid that exists as a 2:1 mixture of restricted rotational isomers. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (m, 1H), 7.12 (m, 2H), 7.06 (m, 1H), 6.80 (m, 2H), 4.82 (br s, 2H), 4.51 (br s, 1H), 4.38 (br s, 1H), 4.03 (m, 1H), 3.96 (m, 1H), 3.37 (m, 2H), 3.25 (s, 3H), 2.28 (q, J = 7.6 Hz, 1H), 2.15 (q, J = 7.6 Hz, 1H), 1.88 (m, 2H), 1.86 (s, 3H), 0.97 (t, J = 7.6 Hz, 3H). MS(ESI+): m/z 484.1 (M+1).

Diagnostic peaks for the minor rotational isomer: 1.08 (t, J = 7.6 Hz, 2H).

6.1.26. *N*-{2-[6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-methyl-3-oxo-2-(3-trifluoromethyl-phenyl)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-ethyl}-acetamide (29). *Step 1.* 4-Bromo-2-nitrophenol **48** (1.2 g, 5.6 mmol) and 1.1 g (4.7 mmol) of hydroxy-(3-trifluoromethyl-phenyl)-acetic acid methyl ester were dissolved in 40 mL of anhydrous CH_2Cl_2 under an Ar atmosphere. Polymer-supported PPh_3 (1.6 mmol/g, 5.8 g, 7.5 mmol) was added, and the resulting suspension was cooled in an ice bath and treated dropwise with 1.1 mL (5.6 mmol) of DIAD. The bright yellow suspension was stirred at ambient temperature for 16 h. The resin was collected on a medium frit, rinsing with CH_2Cl_2. The filtrates were concentrated in vacuo and then purified by flash column chromatography (SiO_2, 100% hexanes then gradient to 40% EtOAc/hexanes) to yield 1.52 g (75%) of (4-bromo-2-nitro-phenoxy)-(3-trifluoromethyl-phenyl)-acetic acid methyl ester. MS(ESI+): m/z 431.9, 433.9 ([M−1], 1:1 ratio of Br isotopes).

Step 2. A solution of 1.5 g (3.5 mmol) of (4-bromo-2-nitro-phenoxy)-(3-trifluoromethyl-phenyl)-acetic acid methyl ester in 20 mL of glacial acetic acid was treated with 1.9 g (35 mmol) of iron dust and heated at 60 °C for 4 h. The gray suspension was cooled to room temperature and filtered through a pad of celite, rinsing with EtOAc and THF. The combined organic filtrates were concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to yield 1.13 g (88%) of 6-bromo-2-(3-trifluoromethyl-phenyl)-4*H*-benzo[1,4]oxazin-3-one **138** as a solid. MS(ESI+): m/z 371.9, 374.0 ([M+1], 1:1 ratio of Br isotopes).

Step 3. A suspension of 1.1 g, 3.0 mmol of **138** in 15 mL of dry CH_3CN was treated with 0.45 g (3.3 mmol) of K_2CO_3, and 0.25 mL (3.5 mmol) of bromoacetonitrile, and heated to 90 °C for 20 h. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite, rinsing with EtOAc. The filtrates are concentrated in vacuo and purified by flash column chromatography (SiO_2, 100% hexanes then gradient to 40% EtOAc/hexanes) to give 0.86 g (71%) of [6-bromo-2-(3-trifluoromethyl-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]-oxazin- 4-yl]-acetonitrile **139**. MS(ESI+): m/z 410.0, 412.0 ([M−1], 1:1 ratio of Br isotopes).

Step 4. A solution of 0.8 g (1.9 mmol) of 139 in 1 mL Ac_2O and 15 mL of anhydrous THF was treated with 0.5 g of Raney Nickel and shaken under a 20 psi H_2 atmosphere for 15 h. The suspension was filtered, and the filtrate was concentrated. Purification by flash column chromatography (SiO_2, 50% EtOAc/hexanes then gradient to 100% EtOAc) afforded 0.53 g (60%) of **127**. MS(ESI+): m/z 457.0, 459 ([M+1], 1:1 ratio of Br isotopes).

Step 5. A solution of 0.49 g (1.1 mmol) of **127** in 8 mL of anhydrous DMF was cooled in an ice bath and treated with 51 mg (1.3 mmol) of a 60% dispersion of NaH in mineral oil in one portion. The mixture was stirred at 0 °C for 30 min, and then 70 μL (1.1 mmol) of iodomethane was added, and the mixture was stirred at ambient temperature for 18 h. The suspension was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield 0.49 g (82%) of **131** that was used without further purification. MS(ESI+): m/z 471,473.0 ([M+1], 1:1 ratio of Br isotopes).

Step 6. A suspension of 0.25 g (0.31 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex, 0.34 g (1.4 mmol) of bis(pinacolato)diboron, and 0.31 g (3.1 mmol) of KOAc in 15 mL of anhydrous 1,4-dioxane was degassed Ar sparge. A solution of 0.49 g (1.04 mmol) of **131** in 6 mL of anhydrous 1,4-dioxane was added, and the mixture was heated at 110 °C for 4 h. The mixture was diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was dissolved in 10 mL of anhydrous 1,4-dioxane and 0.5 mL of H_2O, and treated with 0.33 g (1.5 mmol) of **54**, 0.13 g (3.0 mmol) of LiCl, 0.5 g (3.0 mmol) of $CsOH{\cdot}H_2O$, and 120 mg (0.1 mmol) of $Pd(PPh_3)_4$. The resulting black mixture was heated to reflux for 18 h. The mixture was cooled, diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO, 10% EtOAc then gradient to 25% MeOH/EtOAc) followed by preparatory reverse-phase HPLC (10–60% acetonitrile in water (with 0.1% TFA)) gave 42 mg (8%) of **29** as the TFA salt. ^{1} H NMR (DMSO-d_6, 400 MHz) δ: 8.10 (m, 1H,), 8.01 (m, 1H), 7.7–7.46 (m, 6H), 7.22 (m, 1H), 7.14 (m, 1H), 6.85 (m, 2H), 3.90 (m, 2H), 3.20 (m, 2H), 2.15 (m, 2H), 1.80 (s, 3H), 1.69 (s, 3H), 0.9 (m, 3H); MS(ESI+): m/z 529.1 (M+1).

6.1.27. *N*-{2-[6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-methyl-3-oxo-2-(4-chloro-phenyl)-2,3-dihydro-benzo[1,4]-oxazin-4-yl]-ethyl}-acetamide (30). *Step 1.* A solution of 1.3 g (6 mmol) of 4-bromo-2-nitrophenol 48 and 1.0 g (5 mmol) of (4-chloro-phenyl)-hydroxy-acetic acid methyl ester in 35 mL of anhydrous CH_2Cl_2 was treated with 5.0 g (8.0 mmol, 1.6 mmol/g) of polymer-supported PPh_3 and cooled in an ice bath. DIAD (1.1 mL, 6.0 mmol) was added dropwise, and the resulting yellow suspension was stirred at ambient temperature for 18 h.

The resin was collected on a medium frit and washed with CH_2Cl_2. The filtrates were concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 40% EtOAc/hexanes) yielded 1.86 g (93%) of (4-bromo-2-nitro-phenoxy)-(4-chloro-phenyl)-acetic acid methyl ester. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.60 (s, 3H), 6.37 (s, 1H), 7.80 (dd, J = 9.0,2.4 Hz, 1H), 7.28 (d, J = 9.3 Hz, 1H), 7.49 (m, 4H), 8.11 (d, J = 2.7 Hz, 1H).

Step 2. A solution of 1.37 g (3.4 mmol) of (4-bromo-2-nitro-phenoxy)-(4-chloro-phenyl)-acetic acid methyl ester in 20 mL of glacial AcOH was treated with 1.90 g (34 mmol) of iron dust and then heated at 60 °C for 4 h. The resulting gray suspension was cooled to room temperature and filtered through Celite, rinsing with EtOAc and THF. The filtrate volume was concentrated under reduced pressure, diluted with EtOAc, and washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to yield 1.14 g (98%) of 6-bromo-2-(4-chloro-phenyl)-4*H*-benzo[1,4]oxazin-3-one **140**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 5.78 (s, 1H), 6.95 (m, 1H), 7.00 (m, 1H), 7.03 (m, 1H), 7.41 (m, 2H), 7.35 (m, 2H), MS(ESI+): *m*/*z* 337.9, 339.9 ([M+1], 1:1 ratio of Br isotopes).

Step 3. A suspension of 1.10 g (3.2 mmol) of **140** in 15 mL of dry CH_3CN was treated with 0.49 g (3.6 mmol) of K_2CO_3 and 0.27 mL (3.9 mmol) of bromoacetonitrile, and then heated at reflux for 20 h. The mixture was diluted with EtOAc, filtered through Celite, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 40% EtOAc/hexanes) gave 0.74 g (60%) of [6-bromo-2-(4-chloro-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-acetonitrile **141**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.55 (s, 1H), 7.43 (m, 2H), 7.35 (m, 2H), 7.24 (m, 1H), 7.06 (d, 1H, J = 8.6 Hz), 6.00 (s, 1H), 5.13 (m, 2H). MS(ESI+): *m*/*z* 376.0, 378.0 ([M−1], 1:1 ratio of Br isotopes).

Step 4. A solution of 1.8 g (4.8 mmol) of **141** in 50 mL of THF was treated with 1 mL of Ac_2O and 1.5 g of Raney Nickel. The mixture was shaken under a 30 psi H_2 atmosphere for 19 h. The suspension was filtered through Celite, and the filtrate was concentrated. The residue was dissolved in ~50 mL of boiling EtOAc, then allowed to cool to room temperature. The precipitate was collected on a medium frit and dried to yield 0.90 g (45%) of **128** as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.71 (s, 3H), 3.20 (m, 2H), 3.90 (m, 2H), 5.83 (s, 1H), 6.96 (d, J = 8.6 Hz, 1H), 7.12 (dd, J = 8.6 Hz, 2.1 Hz, 1H), 7.33 (m, 2H), 7.41 (m, 2H), 7.52 (d, J = 2.1 Hz, 1H), 8.05 (t, J = 5.8 Hz, 1H), MS(ESI+): *m*/*z* 422.9, 424.9 ([M+1], 1:1 ratio of Br isotopes).

Step 5. A solution of 0.85 g (2 mmol) of **128** in 8 mL anhydrous DMF under an Ar atmosphere was cooled in an ice bath and treated with 96 mg (2.4 mmol) of a 60% dispersion of NaH in mineral oil in one portion. The mixture was stirred at 0 °C for 30 min and then treated with 0.12 mL (2 mmol) of MeI. The ice bath was removed, and the mixture was stirred at ambient temperature for 16 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2 100% EtOAc then gradient to 20% MeOH/EtOAc) yielded 0.64 g (73%) of **132**. MS(ESI+): *m*/*z* 436.9, 438.9 ([M+1], 1:1 mixture of Br isotopes).

Step 6. A suspension of 0.36 g (0.44 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex, 0.48 g (1.9 mmol) of bis(pinacolato)diboron, and 0.43 g (4.4 mmol) of KOAc in 4 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 10 min and then treated with a solution of 0.64 g (1.5 mmol) of 132 in 6 mL of anhydrous 1,4-dioxane. The mixture was heated to 110 °C for 4 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in 10 mL of anhydrous 1,4-dioxane and 1 mL of H_2O, and treated with 0.32 g (1.5 mmol) of **54**, 89 mg (2.1 mmol) of LiCl, 0.35 g (2.1 mmol) of $CsOH{\cdot}H_2O$, and 81 mg (0.07 mmol) of $Pd(PPh_3)_4$. The resulting suspension was heated to reflux for 16 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 100% EtOAc then gradient to 40% MeOH/EtOAc), followed by purification by preparatory reverse-phase HPLC (10–60% CH_3CN in H_2O with 0.1% TFA), provided 87 mg (12%) of the TFA salt of **30** as a white powder. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.10 (m, 1H,), 8.01 (m, 1H), 7.4 (m, 4H), 7.16 (m, 2H), 6.8 (m, 2H), 3.90 (m, 2H), 3.20 (m, 2H), 2.15 (m, 2H), 1.75 (s, 3H), 1.70 (s, 3H), 0.9 (m, 3 H). MS: *m*/*z* 495.0, 497.1 ([M+1], 2:1 ratio of Cl isotopes).

6.1.28. *N*-{2-[6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-methyl-3-oxo-2-(3-chloro-phenyl)-2,3-dihydro-benzo[1,4]-oxazin-4-yl]-ethyl}-acetamide (31). *Step 1.* A solution of 1.3 g (6 mmol) of 4-bromo-2-nitrophenol **48** and 1.0 g (5 mmol) of (3-chloro-phenyl)-hydroxy-acetic acid methyl ester in 40 mL of anhydrous CH_2Cl_2 was treated with 5.0 g (8.0 mmol, 1.6 mmol/g) of polymer-supported PPh_3 and cooled in an ice bath. DIAD (1.2 mL, 6.0 mmol) was added dropwise, and the resulting yellow suspension was stirred at ambient temperature for 18 h. The resin was collected on a medium frit and washed with CH_2Cl_2. The filtrates were concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 40% EtOAc/hexanes) yielded 1.45 g (73%) of (4-bromo-2-nitro-phenoxy)-(3-chloro-phenyl)-acetic acid methyl ester. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.67 (s, 3H), 6.44 (s, 1H), 7.34 (d, J = 9.3 Hz, 1H), 7.45–7.52 (m, 3H), 7.56–7.60 (m, 1H), 7.86 (dd, J = 9.0, 2.4 Hz, 1H), 8.18 (d, J = 2.4 Hz, 1H).

Step 2. A solution of 1.45 g (3.62 mmol) of (4-bromo-2-nitro-phenoxy)-(3-chloro-phenyl)-acetic acid methyl ester in 20 mL of glacial AcOH was treated with 2.0 g (36 mmol) of iron dust and then heated at 60 °C for

2 h. The resulting gray suspension was cooled to room temperature and filtered through Celite, rinsing with THF. The filtrate volume was concentrated under reduced pressure, diluted with EtOAc, and washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated to yield 1.21 g (99%) of 6-bromo-2-(3-chloro-phenyl)-4*H*-benzo[1,4]oxazin-3-one **142**. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 5.85 (s, 1H), 7.03 (d, J = 8.6 Hz, 1H). 7.06 (d, J = 2.3 Hz, 1H). 7.12 (dd, J = 8.6, 2.3 Hz, 1H), 7.31–7.34 (dddd, J = 6.6, 1.9, 1.9, 0.6 Hz, 1H), 7.40–7.47 (m, 3H), 11.11 (s, 1H); MS(ESI+): *m/z* 336.9, 338.9, 340.9 ([M+1]$^+$, 3:4:1 isotopic ratio).

Step 3. A suspension of 1.2 g (3.5 mmol) of 142 in 15 mL of dry CH_3CN was treated with 0.54 g (3.9 mmol) of K_2CO_3 and 0.30 mL (4.3 mmol) of bromoacetonitrile, and then heated at reflux for 20 h. The mixture was diluted with EtOAc, filtered through Celite, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 40% EtOAc/hexanes) gave 1.0 g (75%) of [6-bromo-2-(3-chloro-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]- acetonitrile **143** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.19 (d, J = 4.5 Hz, 2H), 6.06 (s, 1H), 7.14 (d, J = 8.6 Hz, 1H), 7.30 (dd, J = 8.6, 2.1 Hz, 1H), 7.34 (dddd, J = 7.2, 1.6, 1.6, 0.6 Hz, 1H), 7.41–7.50 (m, 3H), 7.61 (d, J = 2.1 Hz, 1H). MS(ESI+): *m/z* 376.0, 378.0, 380.0 ([M−1]$^-$, 3:4:1 isotopic ratio).

Step 4. A solution of 1.0 g (2.6 mmol) of **143** in 100 mL of MeOH was treated with 1 mL of Ac_2O and 1.0 g of Raney Nickel. The mixture was shaken under a 50 psi H_2 atmosphere for 88 h. The suspension was filtered through Celite, and the filtrate was concentrated. Purification by flash column chromatography (SiO_2, 50% EtOAc/hexanes then gradient to 100% EtOAc) yielded 0.49 g (44%) of **129** as a white solid foam. MS(ESI+): *m/z* 422.6, 424.6, 428.6 ([M+1]$^+$, 3:4:1 isotopic ratio).

Step 5. A solution of 0.41 g (0.97 mmol) of **129** in 8 mL anhydrous DMF under an Ar atmosphere was cooled in an ice bath and treated with 46 mg (1.2 mmol) of a 60% dispersion of NaH in mineral oil in one portion. The mixture was stirred at 0 °C for 30 min and then treated with 60 μL (0.97 mmol) of MeI. The ice bath was removed, and the mixture was stirred at ambient temperature for 16 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was washed with 10% aqueous citric acid, H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.41 g of **133** that was used without further purification. MS(ESI+): *m/z* 437.0, 438.9, 440.9 ([M+1]$^+$, 3:4:1 isotopic ratio).

Step 6. A suspension of 0.41 g (0.94 mmol) of **133**, 0.23 g (0.28 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex, 0.31 g (1.2 mmol) of bis(pinacolato)diboron, and 0.28 g (2.8 mmol) of KOAc in 15 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 10 min and then heated to 110 °C for 4 h. After cooling to ambient temperature, the mixture was diluted with EtOAc and filtered through a Celite pad. The filtrate was concentrated to a black oil that was used without further purification.

Step 7. The residue from the previous reaction was dissolved in 10 mL of anhydrous 1,4-dioxane and 0.5 mL of H_2O, and treated with 0.31 g (1.4 mmol) of **54**, 120 mg (2.8 mmol) of LiCl, 0.47 g (2.8 mmol) of CsOH·H_2O, and 110 mg (0.09 mmol) of $Pd(PPh_3)_4$. The resulting suspension was heated to reflux for 16 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 100% EtOAc then gradient to 25% MeOH/EtOAc), followed by purification by preparatory reverse-phase HPLC (10–60% CH_3CN in H_2O with 0.1% TFA), provided 68 mg of the TFA salt of **31** as a white powder that exists as a 2:1 mixture of restricted rotational isomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.6 Hz, 3H), 1.74 (s, 3H), 1.82 (s, 3H), 2.12 (q, J = 7.3 Hz, 2H), 3.14–3.25 (m, 1H), 3.25–3.33 (m, 1H), 3.88–4.04 (m, 2H), 6.92 (ddd, J = 8.3, 8.3, 1.8 Hz, 1H), 7.20 (dd, J = 7.0, 1.8 Hz, 1H), 7.26 (dd, J = 8.2, 4.1 Hz, 1H), 7.34–7.44 (m, 3H), 7.46 (m, 1H), 8.06 (m 2H), 8.17 (d, J = 21.1 Hz, 1H), 12.17 (d, J = 19.3 Hz, 1H); MS(ESI+): *m/z* 495.1, 497.1 ([M+1]$^+$, 3:1 isotopic ratio).

Diagnostic peaks for the minor restricted rotational isomer: 1.04 (t, J = 7.51 Hz, 3H), 1.81 (s, 3H), 2.27 (q, J = 7.60 Hz, 2 H).

6.1.29. *N*-{2-[6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-methyl-3-oxo-2-(2,5-difluoro-phenyl)-2,3-dihydro-benzo[1,4]-oxazin-4-yl]-ethyl}-acetamide (32). *Step 1.* A solution of 4.67 g (21.0 mmol) of 4-bromo-2-nitrophenol **48** and 4.04 g (20.0 mmol) of (2,5-difluoro-phenyl)-hydroxy-acetic acid methyl ester in 200 mL of anhydrous CH_2Cl_2 was treated with 19.35 g (30.0 mmol, 1.55 mmol/g) of polymer-supported PPh_3 and cooled in an ice bath. DIAD (4.3 mL, 21.8 mmol) was added dropwise, and the resulting yellow suspension was stirred at ambient temperature for 2 h. The resin was collected on a medium frit and washed with CH_2Cl_2. The filtrates were washed with 1 N NaOH, H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 10.17 g of a light-yellow solid that was used without further purification.

Step 2. The residue was slurried in 80 mL of glacial AcOH and treated with 7.39 g (132 mmol) of iron dust. The black suspension was heated at 60 °C for 5 h. The resulting gray suspension was cooled to room temperature, diluted with toluene, and filtered through Celite, rinsing with additional toluene. The filtrate was washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting light-yellow solid was triturated with CH_2Cl_2. The solid was collected on a medium frit and dried under vacuum to yield 4.86 g (71%) of 6-bromo-2-(2,5-difluoro-phenyl)-4*H*-benzo[1,4]oxazin-3-one **144**. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 5.92 (s, 1H), 6.95 (dd, J = 9.3, 1.5 Hz, 1H), 7.09 (s, 1H), 7.10 (dd, J = 9.5, 2.2 Hz, 2H), 7.31–7.39 (m, 3H), 11.11 (s, 1H); MS(ESI+): *m/z* 339.9, 341.9 ([M+1]$^+$, 1:1 ratio of Br isotopes).

Step 3. A suspension of 1.00 g (2.94 mmol) of **144** in 25 mL of dry CH_3CN was treated with 406 mg (2.94 mmol) of K_2CO_3 and 0.21 mL (2.94 mmol) of bromoacetonitrile, and then heated at reflux for 3 h. The mixture was filtered through Celite and concentrated to give 1.17 g (100%) of [6-bromo-2-(2,5-difluoro-phenyl)-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl]-acetonitrile **145** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (d, J = 17.6 Hz, 1H), 4.96 (d, J = 17.6 Hz, 1H), 5.78 (s, 1H), 6.97–7.00 (m, 1H), 7.08–7.14 (m, 3H), 7.25 (s, 1H), 7.26 (dd, J = 8.1, 1.5 Hz, 1H).

Step 4. A solution of 1.17 g (2.94 mmol) of **145** in 45 mL of THF was treated with 5 mL of Ac_2O and 1.5 g of Raney Nickel. The mixture was shaken under a 50 psi H_2 atmosphere for 15 h. The suspension was filtered through Celite, and the filtrate was concentrated. Purification by flash column chromatography (SiO_2, 100% CH_2Cl_2 then gradient to 35% EtOAc/CH_2Cl_2) yielded 0.85 g (68%) of **130** as a white solid foam. ^{1}H NMR (400 MHz, DMSO-d_6)δ 1.76 (s, 3H), 3.21–3.30 (m, 2H), 3.91–4.02 (m, 2H), 5.94 (s, 1H), 7.00 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 8.3, 2.2 Hz, 1H), 7.31–7.40 (m, 3H), 7.61 (d, J = 2.2 Hz, 1H), 8.10 (t, J = 6.0 Hz, 1H); MS(ESI+): m/z 425.0, 427.0 ($[M+1]^+$, 1:1 ratio of Br isotopes).

Step 5. A solution of 0.42 mL (3.0 mmol) of diisopropylamine in 10 mL of anhydrous THF was cooled in an ice bath under a N_2 atmosphere and treated with 1.8 mL (2.9 mmol) of 1.6 M *n*-BuLi in hexanes. The mixture was stirred at 0 °C for 35 min and then treated with a solution of 0.51 g (1.20 mmol) of 130 in 15 mL anhydrous THF. The ice bath was removed and the mixture was stirred at room temperature for 45 min. The mixture was then chilled in a dry ice/acetone bath and treated with 75 μL (1.21 mmol) of MeI. The dry ice bath was allowed to warm to room temperature while the reaction mixture was stirred for 14 h. An additional 15 μL of MeI was added, and the mixture was stirred at room temperature for 3 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% CH_2Cl_2 then gradient to 50% EtOAc/CH_2Cl_2) afforded 155 mg (27%) of **134**. ^{1}H NMR (400 MHz, $CDCl_3$)δ 1.92 (s, 3 H), 1.96–2.00 (m, 3H), 3.52–3.64 (m, 2H), 4.02 (ddd, J = 14.3, 6.3, 6.3 Hz, 1H), 4.25 (ddd, J = 14.23, 6.6, 6.6 Hz, 1H), 5.94 (s, 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.96–7.05 (m, 3H), 7.10 (dd, J = 8.6, 2.1 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H); MS(ESI+): m/z 439.9, 441.9 ($[M+1]^+$, 1:1 ratio of Br isotopes).

Step 6. A suspension of 155 mg (0.35 mmol) of **134**, 15 mg (0.03 mmol) of $PdCl_2$(dppf)–CH_2Cl_2 complex, 134 mg (0.53 mmol) of bis(pinacolato)diboron, and 104 mg (1.06 mmol) of KOAc in 20 mL of anhydrous 1,4-dioxane was degassed by N_2 sparge for 50 min and then heated to 110 °C for 18 h. After cooling to ambient temperature, the mixture was treated with 4 mL of H_2O, 0.31 g (1.4 mmol) of **54**, 45 mg (1.06 mmol) of LiCl, 345 mg (1.06 mmol) of Cs_2CO_3, and 102 mg (0.09 mmol) of $Pd(PPh_3)_4$. The resulting suspension was heated to reflux for 21 h. After cooling to ambient temperature, the mixture was diluted with CH_2Cl_2, washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and filtered through 20 g of SiO_2. The SiO_2 pad was washed sequentially with CH_2Cl_2, EtOAc, and MeOH. The MeOH filtrate was concentrated. Purification by flash column chromatography (SiO_2 100% EtOAc then gradient to 30% MeOH/EtOAc) provided 33 mg (18%) of **32** as a gray powder that exists as a 1.5:1 mixture of restricted rotational isomers. ^{1}H NMR (400 MHz, DMSO-d_6)δ 0.90 (t, J = 7.4 Hz, 3H), 1.74 (s, 3H), 1.84 (s, 3H), 2.07 (q, J = 7.5 Hz, 1H), 2.14–2.26 (m, 1H), 3.96 (m, 2H), 5.82 (bs, 2H), 6.78 (t, J = 8.3 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.0 Hz, 1H), 7.20 (q, J = 6.5 Hz, 1H), 7.42 (t, J = 7.3 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.54–7.61 (m, 1H), 7.98 (bs, 1H); MS(ESI+): m/z 497.2 $[M+1]^+$.

Diagnostic peaks for the minor isomer: 1.00 (t, J = 7.3 Hz, 3H), 1.81 (s, 3H).

6.1.30. *N*-{2-[(2*S*)-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-methyl-3-oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl]-ethyl}-acetamide ((*S*)-33). *Step 1.* A solution of 1.22 g (7.12 mmol) of (*S*)-2-phenyl-2-hydroxy-propionic acid methyl ester in 20 mL of anhydrous THF was treated with 325 mg (8.13 mmol) of a 60% NaH dispersion in mineral oil. The resulting gray suspension was stirred at room temperature for 10 min. Then, 5 drops of 15-crown-5 were added via syringe, followed by 1.49 g (6.78 mmol) of 4-bromo-2-nitrofluorobenzene **97**. The resulting orange solution was stirred at room temperature for 17 h. Excess hydride was quenched by the careful addition of MeOH. The solution was diluted with EtOAc, and then washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness.

Step 2. The residue was dissolved in 20 mL of glacial acetic acid, treated with 3.79 g (67.8 mmol) of iron dust, and heated in a 60 °C oil bath for 4 h. The resulting gray suspension was cooled to room temperature, diluted with EtOAc, and filtered through a Celite pad. The filtrate was concentrated to dryness. The solid residue was dissolved in EtOAc and washed with H_2O (3×) and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 5% EtOAc/hexanes) gave 1.72 g of (*S*)-**103** as a clear oil (80%, 2 steps). MS(ESI+): m/z 318.0, 319.9 [M+1], Br isotopes, 1:1 ratio.

Step 3. A solution of 1.72 g (5.41 mmol) of (*S*)-**103** and 0.45 ml (6.49 mmol) of bromoacetonitrile in 60 mL of anhydrous CH_3CN was treated with 0.82 g (5.95 mmol) of K_2CO_3 and heated to reflux for 18 h. The mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, 100% hexanes then gradient to 15% EtOAc/hexanes) yielded 1.65 g (85%) of

(*S*)-**118** as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H), 4.65 (d, J = 17.5 Hz, 1H), 5.04 (d, J = 17.5 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H), 7.00 (d, J = 2.7 Hz, 1H), 7.15 (dd, J = 8.5, 2.1 Hz, 1H), 7.27–7.32 (m, 5 H); MS(ESI+): *m*/*z* 356.0, 358.0 ([M−1], AP^-, 1:1 ratio of Br isotopes).

Step 4. A solution of 1.64 g (4.59 mmol) of (*S*)-**118** and 0.65 mL (6.89 mmol) of Ac_2O in 50 mL of THF was treated with 1.5 g Raney nickel. The resulting suspension was shaken under a 52 psi H_2 atmosphere for 20 h. The mixture was filtered through celite and concentrated. Purification by flash column chromatography (SiO_2, 15% EtOAc/hexanes then gradient to 70% EtOAc/hexanes) yielded 1.08 g (58%) of (*S*)-**123** as a white solid. $[\alpha]_D^{25}$ −138.1 ° (*c* 7.3, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 1.97 (s, 3H), 3.52 (quintet, J = 6.1 Hz, 2H), 3.98 (ddd, J = 14.2, 6.3, 6.3 Hz, 1H), 4.21 (ddd, J = 14.3, 6.6, 6.4 Hz, 1H), 5.89 (br s, 1H), 6.96 (d, J = 8.0 Hz, 1H), 7.09 (dd, J = 8.0, 2.0 Hz, 1H), 7.22 (d, J = 2 Hz, 1H), 7.24–7.30 (m, 3H), 7.32–7.35 (m, 2 H); MS(ESI+): *m*/*z* 403.0, 405.0 ([M−1], 1:1 ratio of Br isotopes).

Step 5. A solution of 1.08 g (2.67 mmol) of (*S*)-**123**, 812 mg (3.20 mmol) of bis(pinacolato)diboron, and 785 mg (8.00 mmol) of KOAc in 15 mL of anhydrous 1,4-dioxane was degassed by N_2 sparge for 15 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (109 mg, 0.133 mmol) were added, and the resulting red-orange mixture was heated at 90 °C for 18 h. After cooling to room temperature, the black mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated. The crude residue was dissolved in 12 mL of anhydrous 1,4-dioxane and 1.5 mL of H_2O. LiCl (339 mg, 8.00 mmol), 0.69 g (3.20 mmol) of **54**, and 1.34 g (8.00 mmol) of CsOH·H_2O was added, and the resulting suspension was degassed by N_2 sparge for 20 min. $Pd(PPh_3)_4$ (308 mg, 0.27 mmol) was added, and the mixture was heated in a 100 °C oil bath for 18 h. The mixture was diluted with EtOAc, filtered through a Celite plug, and concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 10% MeOH/EtOAc) followed by preparatory reverse phase HPLC (10% CH_3CN/H_2O/0.1% TFA then gradient to 60% CH_3CN/H_2O/0.1% TFA) yielded 437 mg of the TFA salt of (*S*)-**33** as a white solid that exists as a 2:1 mixture of restricted rotational isomers. Chiral HPLC Rt = 19.2 min, enantiomeric purity = 100% (Chiralpak AD, 250 × 4.6 mm, isocratic eluant = 80:20 v/v hexane/isopropyl alcohol, 0.8 mL/min); IR(ATR) 3322, 3176, 1665, 1659, 1441, 1372, 1269, 1200, 1178, 1132 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6)δ 0.82 (t, J = 7.6 Hz, 3H), 1.68 (s, 3H), 1.75 (s, 3H), 2.01 (q, J = 7.5 Hz, 2H), 3.13 (m, 1H), 3.25 (m, 1H), 3.88 (m, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.81 (bs, 1H), 7.09–7.32 (m, 5H), 7.38 (d, J = 7.2 Hz, 1H), 7.51 (br s, 2H), 8.00 (q, J = 6.1 Hz, 1H), 8.10 (br s, 1H), 12.29 (br s, 1 H); HRMS Calcd for [$C_{25}H_{28}N_6O_3$+H]: 461.2301. Found: 461.2306. Elem. Anal. Calcd for $C_{25}H_{28}N_6O_3$1.0TFA1.1H_2O: C, 54.68; H, 5.29; N, 14.18; F, 9.52; H_2O, 3.25. Found: C, 54.29; H, 5.13; N, 13.94; F, 9.13; H_2O, 2.94.

Diagnostic peaks for the minor restricted rotational isomer: ^{1}H NMR (400 MHz, DMSO-d_6)δ 0.98 (t, J = 7.5 Hz, 2H), 2.20 (q, J = 7.6 Hz, 1H), 6.64 (bs, 1H), 6.84 (d, J = 8.0 Hz, 1H), 8.05 (br s, 1 H).

6.1.31. *N*-{2-[(2*R*)-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-methyl-3-oxo-2-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl]-ethyl}-acetamide ((*R*)-34). The title compound (*S*)-**34** was prepared as described above, utilizing (*R*)-2-phenyl-2-hydroxy-propionic acid methyl ester. Purification by preparative reverse-phase HPLC (CH_3CN/H_2O with 0.1% TFA) followed by lyophilization provided 698 mg of the TFA salt of (*S*)-**34** as a white amorphous powder that exists as a 2:1 mixture of rotational isomers and exhibits identical spectral characteristics as (*S*)-**33** in all respects except for chiral HPLC retention time. Chiral HPLC Rt = 23.7 min, enantiomeric purity = 100% (Chiralpak AD, 250 × 4.6 mm, isocratic eluant = 80:20 v/v hexane/isopropyl alcohol, 0.8 mL/min).

6.1.32. *rac*-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-4-(3-hydroxy-propyl)-2-methyl-4H-benzo-[1,4]oxazin-3-one (35). *Step 1.* A solution of 981 mg (2.79 mmol) of *rac*-6-bromo-2-(3,5-difluoro-phenyl)-2-methyl-4*H*-benzo[1,4]oxazin-3-one **109** in 15 mL of anhydrous CH_3CN was treated with 424 mg (3.07 mmol) of K_2CO_3 and 0.81 mL (3.49 mmol) of (3-bromopropanoxy)-*t*-butyldimethylsilane, and was heated at reflux for 23 h. After cooling to room temperature, the suspension was diluted with CH_3CN, filtered through a celite pad, and concentrated. Purification by flash chromatography (SiO_2, 100% hexanes, then gradient to 15% EtOAc/hexanes) gave 1.31 g (89%) of *rac*-6-bromo-4-[3-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-2-(3,5-difluoro-phenyl)-2-methyl-4H-benzo[1,4]oxazin-3-one **135** as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$)δ 0.08 (s, 6H), 0.92 (s, 9H), 1.84 (s, 3H), 1.84 (m, 2H), 3.69 (t, J = 5.9 Hz, 2 H), 3.93 (ddd, J = 14.0, 9.6, 6.04 Hz, 1H), 4.07 (ddd, J = 15.0, 9.6, 5.7 Hz, 1H), 6.65 (tt, J = 8.8, 2.3 Hz, 1H), 6.88 (m, 2 H) 6.93 (d, J = 8.6 Hz, 1H), 7.08 (dd, J = 8.6, 2.1 Hz, 1H), 7.14 (d, J = 2.1 Hz, 1 H). MS(ESI+): *m*/*z* 526.0, 528.0 (M+1, 1:1 ratio of Br isotopes).

Step 2. A solution of 1.31 g (2.49 mmol) of **135**, 0.75 g (2.99 mmol) of bis(pinacolato)diboron, and 0.73 g (7.48 mmol) of KOAc in 12 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 15 min. $PdCl_2$(dppf)–CH_2Cl_2 complex (102 mg, 0.125 mmol) was added, and the resulting orange red suspension was heated in a 95 °C oil bath for 8 h. After cooling to room temperature, the black mixture was diluted with EtOAc, filtered through celite, and concentrated. The residue was dissolved in 8 mL of anhydrous 1,4-dioxane and 1 mL of H_2O, and treated with 1.26 g (7.48 mmol) of CsOH · H_2O, 317 mg (7.48 mmol) of LiCl, and 649 mg (2.99 mmol) of **54**. The resulting suspension was degassed by Ar sparge for 20 min. $Pd(PPh_3)_4$ (288 mg, 0.25 mmol) was added, and the mixture was heated in a 100 °C oil bath for 18 h. The mixture was diluted with EtOAc, dried over $MgSO_4$, filtered through a celite plug, and concentrated. Purification by flash column chromatography (SiO_2, 100% EtOAc then gradient to 10%

MeOH/EtOAc) gave 585 mg (40%) of *rac*-4-[3-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-6-(2,4-diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-2-methyl-4*H*-benzo[1, 4]oxazin-3-one **136** as a brown viscous oil. MS(ESI+): *m*/*z* 584.2 (M+1).

Step 3. A solution of 584 mg (1.00 mmol) of **136** in 10 mL of CH_3OH was treated with 0.1 mL of conc. HCl and stirred at room temperature for 1 h. The reaction mixture was made basic by the addition of saturated aqueous $NaHCO_3$, diluted with H_2O, and partitioned with EtOAc (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 100:0 CH_2Cl_2/CH_3OH, then gradient to 90:10 CH_2Cl_2/CH_3OH) afforded 209 mg (45%) of **35** as a white solid that exists as a 2:1 mixture of rotational isomers: mp 183–188 °C; IR(ATR) 3477, 3323, 3181, 2937, 1672, 1594, 1551, 1436, 1269, 1119, 987 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6)δ 0.79 (t, J = 6.8 Hz, 2H), 1.65 (m, 2H), 1.75 (s, 3H), 1.93 (q, J = 6.8 Hz, 2H), 3.38 (q, J = 6.0 Hz, 2H), 3.92 (m, 2H), 4.50 (t, J = 5.2 Hz, 1H), 5.31 (bs, 1H), 5.51 (bs, 1H), 5.78 (bs, 2H), 6.78 (m, 1H), 6.89 (m, 1H), 7.00 (m, 2H), 7.16 (m, 2 H). HRMS Calcd for $C_{24}H_{26}F_2N_5O_3$ $(M+H)^+$: 470.2003. Found: 470.1982. Elem. Anal. Calcd for $C_{24}H_{25}F_2N_5O_3$: C, 61.40; H, 5.37; N, 14.92. Found: C, 60.99; H, 5.55; N, 14.22.

Diagnostic peaks for the minor rotational isomer: ^1H NMR (400 MHz, DMSO-d_6) δ 0.91 (t, J = 7.0 Hz, 3H), 2.06 (q, J = 6.9 Hz, 2H).

6.1.33. *rac*-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-2-methyl-4-(4,4,4-trifluoro-butyl)-4*H*-benzo[1,4]oxazin-3-one (47). *Step 1.* A solution of 1.20 g (3.39 mmol) of *rac*-6-bromo-2-(3,5-difluoro-phenyl)-2-methyl-4*H*-benzo[1,4]oxazin-3-one **109** in 15 mL of anhydrous CH_3CN was treated with 562 mg (4.07 mmol) of K_2CO_3 and 0.78 g (4.07 mmol) of 1-bromo-4,4,4-trifluorobutane, and was heated at reflux for 18 h. After cooling to room temperature, the suspension was diluted with CH_3CN, filtered through a Celite pad, and concentrated. Purification by flash chromatography (SiO_2, 100% hexanes, then gradient to 15% EtOAc/hexanes) gave 1.45 g (92%) of *rac*-6-bromo-4-[4,4,4-trifluoro-butyl]-2-(3,5-difluoro-phenyl)-2-methyl-4*H*-benzo [1,4]oxazin-3-one **137** as a clear viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 3H), 1.94 (dq, J = 7.0, 7.0 Hz, 2H), 2.15–2.26 (m, 2H), 4.01 (t, J = 7.5 Hz, 2H), 6.69 (tt, J = 8.7, 2.3 Hz, 1H), 6.86–6.92 (m, 2H), 6.94 (d, J = 2.0 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 7.14 (dd, J = 8.4, 2.2 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) -66.52, -108.33. MS(ESI+): *m*/*z* 412.0, 414.0 (M+1, 1:1 ratio of Br isotopes).

Step 2. A solution of 1.45 g (3.12 mmol) of **137**, 0.95 g (3.75 mmol) of bis(pinacolato)diboron, and 0.92 g (9.37 mmol) of KOAc in 20 mL of anhydrous 1,4-dioxane was degassed by Ar sparge for 15 min. $PdCl_2$(dppf)-CH_2Cl_2 complex (128 mg, 0.156 mmol) were added, and the resulting orange red suspension was heated in a 95 °C oil bath for 22 h. After cooling to room temperature, the black mixture was diluted with EtOAc, filtered through Celite, and concentrated. MS(ESI+): *m*/*z* 512.2.

The residue was dissolved in 16 mL of anhydrous 1,4-dioxane and 2 mL of H_2O. $CsOH \cdot H_2O$ (1.57 g, 9.37 mmol), 397 mg (9.37 mmol) of LiCl, and 813 mg (3.75 mmol) of **54** was added, and the resulting suspension was degassed by Ar sparge for 20 min. $Pd(PPh_3)_4$ (361 mg, 0.31 mmol) was added, and the mixture was heated in a 100 °C oil bath for 18 h. The mixture was diluted with EtOAc, dried over $MgSO_4$, filtered through a Celite plug, and concentrated. Purification by flash column chromatography (SiO_2, 100% CH_2Cl_2 then gradient to 10% CH_2Cl_2/MeOH/) and recrystallization from EtOAc/hexanes gave 464 mg (28%) of *rac*-**47** as a gray solid that exists as a 1:1 mixture of rotational isomers. IR(ATR) 3499, 3350, 3155, 2970, 1672, 1598, 1571, 1555, 1440, 1248, 1139, 986 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6)δ 0.82 (t, J = 7.3 Hz, 3H), 1.73 (m, 2H), 1.81 (s, 3H), 1.96 (q, J = 7.6 Hz, 2H), 2.33 (s, 2H), 3.97 (m, 2 H) 5.36 (br s, 1H), 5.56 (br s, 1H), 5.80 (bs, 2H), 6.83 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 11.7 Hz, 1H), 7.06 (d, J = 6.6 Hz, 2H), 7.22 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.4, 20.1, 26.5, 28.1, 30.4, 36.9, 81.2, 104.5, 106.6, 109.4, 117.9, 118.8, 127.0, 128.3, 129.5, 131.7, 142.4, 161.7, 162.7, 164.2, 165.8, 167.1. HRMS(ESI) Calcd for $C_{25}H_{25}F_5N_5O_2$ $(M+H)^+$: 522.1928. Found: 522.1921. Elem. Anal. Calcd for $C_{25}H_{24}F_5N_5O_2$: C, 57.58; H, 4.64; N, 13.43; F, 18.22. Found: C, 57.20; H, 4.45; N, 13.02; F, 17.49.

Diagnostic peaks for the second rotational isomer: ^1H NMR (400 MHz, DMSO-d_6) δ 0.94 (t, J = 7.2 Hz, 3H), 2.10 (m, 2 H), 4.05 (m, 2H).

6.1.34. (*R*)-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-2-methyl-4-(4,4,4-trifluorobutyl)-4*H*-benzo[1,4]oxazin-3-one (*R*-47). Purification of a 400 mg sample of *rac*-6-(2,4-diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-2-methyl-4-(4,4,4-trifluorobutyl)-4*H*-benzo[1,4]oxazin-3-one **47** by chiral preparatory HPLC (Chiralpak AD, 250 × 21 mm, isocratic 90:10 hexane:isopropanol, 17 mL/min) yields 123 mg of a white solid as the first eluting peak. Spectral data were identical to those of racemic **47** except for optical rotation and chiral HPLC retention time: $[\alpha]_D$ +97.9° (*c* 2.9, methanol). Chiral analytical HPLC Rt = 16.50 min, enantiomeric purity = 100% (Chiralpak AD, 250 × 4.6 mm, 90/10 hexanes/ isopropanol, 0.8 mL/min).

6.1.35. (*S*)-6-(2,4-Diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-2-methyl-4-(4,4,4-trifluorobutyl)-4H-benzo[1,4]oxazin-3-one (*S*-47). Purification of a 400 mg sample of *rac*-6-(2,4-diamino-6-ethyl-pyrimidin-5-yl)-2-(3,5-difluoro-phenyl)-2-methyl-4-(4,4,4-trifluorobutyl)-4H-benzo[1,4]oxazin-3-one by chiral preparatory HPLC (Chiralpak AD, 250 × 21 mm, 90/10 hexanes/isopropanol, 17 mL/min) yields 162 mg of a white solid as the second eluting peak with an analytical HPLC purity = 100% (copy of the HPLC trace is available in the Supporting Information). Spectral data were identical

in all respects to those of the racemic **47** except for optical rotation and chiral HPLC retention time: $[\alpha]_D$ −109.0° (c = 3.5, methanol). Chiral analytical HPLC Rt = 22.75 min, enantiomeric purity = 100% (Chiralpak AD, 250 × 4.6 mm, 90/10 hexanes/ isopropanol, 0.8 mL/min).

6.2. In vitro assays

The renin assay utilized a tandem Green Flourescent Protein (tGFP) substrate (175 nM) that was hydrolyzed by renin (50.4 IU/well), which recognized the leucine–valine site of the linker on the substrate. Once cleaved, the emission ratio changes. The change was monitored by the ratio of 530 nM (topaz) over 475 nM (W1B) with the excitation set at 432 nM and the cutoff at 515 nM. The assay used a 384-well plate format that was read using a Gemini XS fluorometric plate reader (Molecular Devices). Compounds were screened at a starting concentration of 10 μM and used a 4-fold 11-point dilution regiment.

6.3. In vivo pharmacokinetic studies

The pharmacokinetic profiles were assessed in male Sprague–Dawley rats and male beagle dogs. Rats were administered a 5 or 10 mg/kg dose orally as a suspension, or a 1 mg/kg intravenous bolus. To aid screening throughput, rats were also dosed with multiple compounds in a single formulation at 1.67 mg/kg orally or 0.33 mg/kg intravenously. Dogs were administered a 5-mg/kg dose orally as a suspension, or a 1 mg/kg intravenous bolus over 5 minutes. Serial blood samples (for plasma) were collected from each animal over a 24-hour period following dosing. The plasma samples were analyzed for drug concentrations using LC/MS/MS methods. The pharmacokinetic parameters were determined from the plasma concentration time data using non-compartmental analysis (Watson, V6.4.0.04).

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Supplementary data

Experimental details and characterization data for compounds **36-46** are available on-line. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.05.069.

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19. Compounds **9**, **14**, and **20** exhibited >70% kinase activity at 10 μM concentration against the following 18 kinases in the Dundee kinase panel: Abl, Arg(m), Aurora-A, Axl, Bmx, c-Raf, cSRC, FGFR3, Flt3, JNK3, MST2, p70S6K, PDGFRα, Rse, Rsk1, Syk, Tie2, and ZAP-70. Moderate activity at 10 μM concentration was observed for Met (**9**, 50%; **14**, 40%; and **20**, 61% kinase activity). Unless otherwise indicated, all kinase proteins were of human form.