Journal of Medicinal Chemistry

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Discovery of 6,7-Dihydro-5*H*-pyrrolo[2,3-*a*]pyrimidines as Orally Available G Protein-Coupled Receptor 119 Agonists

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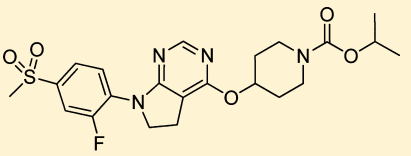
ABSTRACT: GPR119 is a 7-transmembrane receptor that is expressed in the enteroendocrine cells in the intestine and in the islets of Langerhans in the pancreas. Indolines and 6,7-dihydro-5*H*-pyrrolo[2,3-*a*]pyrimidines were discovered as G protein-coupled receptor 119 (GPR119) agonists, and lead optimization efforts led to the identification of 1-methylethyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (GSK1104252A) (**3**), a potent and selective GPR119 agonist. Compound **3** showed excellent pharmacokinetic properties and sufficient selectivity with in vivo studies supporting a role for GPR119 in glucose homeostasis in the rodent. Thus, **3** appeared to modulate the enteroinsular axis, improve glycemic control, and strengthen previous suggestions that GPR119 agonists may have utility in the treatment of type 2 diabetes.



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INTRODUCTION

Type 2 diabetes (T2D) is a chronic disease characterized by insulin resistance, insufficient insulin secretion from pancreatic β-cells, and hyperglycemia. Glycemic control is the key for metabolic homeostasis, and the uncontrolled hyperglycemia leads to long-term complications including organ failure and amputation.[1] Recent estimates suggest that the incidence of diabetes in the U.S. may double over the next 20 years.[2] Presently, less than one-third of T2D patients will achieve the targeted plasma glucose levels with the currently available antidiabetic agents.[3] Furthermore, the currently available treatments either as monotherapies or combination therapies have their own limitations and potential risks.[4] This has prompted the scientific community to search for novel agents for the treatment and prevention of diabetes with novel mechanisms of action.[5]

G Protein-coupled receptor 119 (GPR119) is a class A (rhodopsin-like) 7-transmembrane, G protein-coupled receptor (GPCR) with little homology to other receptors.[6] The human GPR119 receptor consists of 335 amino acids and is highly conserved in mouse and rat.[7] GPR119 is expressed in human insulin-secreting pancreatic islets and incretin (GIP and GLP-1) secreting K- and L-cells of the gastrointestinal (GI) tract.[8] There are some contradictory reports on its cellular subtype localization in islets;[8a,b] however, there seems to be some consensus that the receptor is expressed in the β-cells.[8b,9]

The physiological role of GPR119 remains unknown. Elucidating the role of GPR119 signaling has been hampered by the lack of endogenous ligands that signal solely through GPR119. Lysophosphatidylcholine[6a] (LPC), oleoylethanolamide[10] (OEA), *N*-acylated ethanolamine phospholipids[11] (NAPEs) and *N*-oleoyldopamine[12] (OLDA), and, most recently, 5-hydroxyeicosapentaenoic acid (5-HEPE)[13] have all been suggested as endogenous ligands. However, given that the potency is relatively low or there are selectivity issues, it is difficult to conclusively identify any one of these as the only or true endogenous ligand.

Evidence that activation of GPR119 may play a role in glucose homeostasis mainly comes from selective, small-molecule agonists. Specifically, GPR119 agonists have been shown to elicit nutrient-independent incretin and GI hormone release as well as nutrient-stimulated insulin secretion,[8b,c,14] thereby lowering plasma glucose levels during an oral glucose tolerance test.[14a] Interestingly, there is some evidence to support a role for GPR119 agonists in reducing food intake and promoting weight loss, possibly through the release of GLP-1, which is known to delay gastric emptying.[10] However, Arena Pharmaceuticals have reported that anorectic effects of their GPR119 agonists are still observed in knockout mice.[15] While the details of the mechanism of action of this receptor are not yet fully understood, GPR119 agonists may have the potential to deliver superior glycemic control versus current gold standard oral therapies given that no current antidiabetic medication triggers the incretin and GI hormone release as well as having direct actions on nutrient-stimulated insulin secretion mechanisms for glucose control.[16]

The disclosure by Arena Pharmaceuticals that pyrazolopyrimidines,[17] represented by example **1**, were potent GPR119 agonists[18] led us to surmise that alternative bicyclic structures might be equally active (Figure 1). In this article, we disclose our

Received: September 27, 2012

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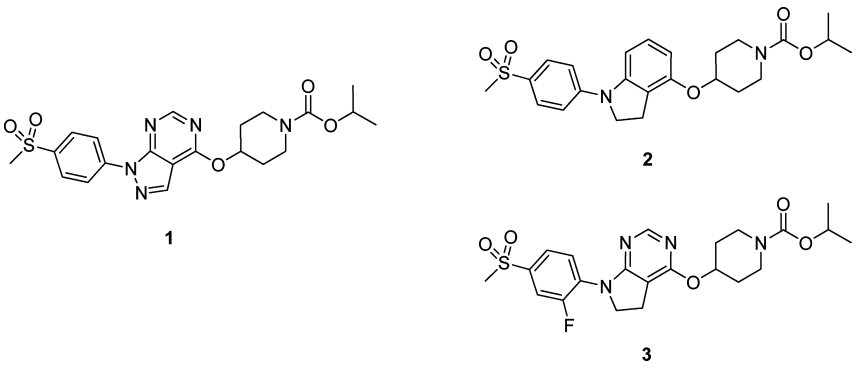
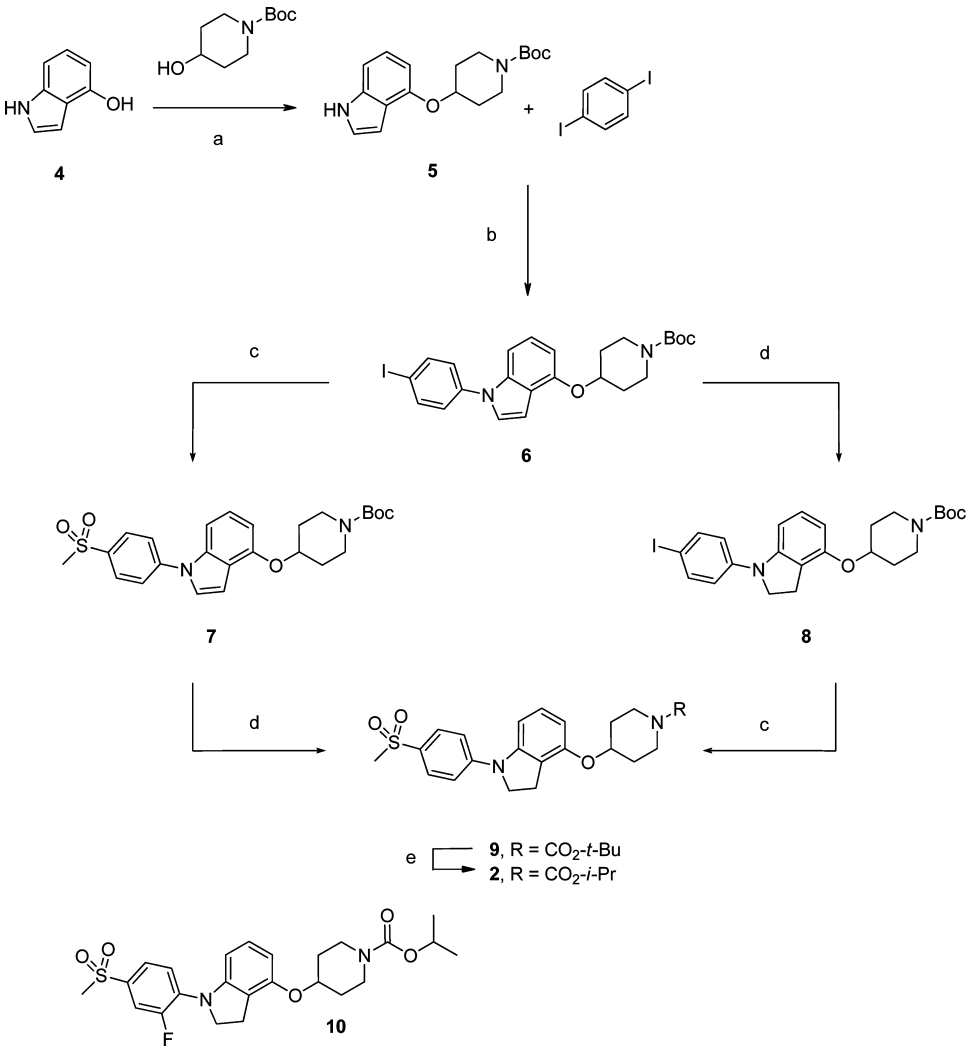


Figure 1. Representative GPR119 agonists.

Scheme 1. Preparation of Indolines 2, 9, and 10[a]



[a]Reagents and conditions: (a) Ph_3P, DIAD, THF, RT, 77%; (b) CuI, K_3PO_4, *trans*-1,2-cyclohexanediamine, toluene, reflux, 8%; (c) CuI, L-proline, NaOH, CH_3SO_2Na, DMSO, 110 °C, 98% for **6**→**7**; (d) $NaCNBH_3$, HOAc, RT, 71% for **7**→**9**; (e) (i) TFA, CH_2Cl_2, RT, (ii) *i*-PrOCOCl, Et_3N, CH_2Cl_2, RT, 54%.

initial discoveries[19] of indolines, such as **2**, and 6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidines (DHPPs), such as **3** (GSK1104252A), as GPR119 agonists.[14a] The structure−activity relationships (SAR) of the DHPP chemotype, in addition to in vitro and in vivo activities of the lead molecule **3**, will be highlighted.

RESULTS

Indoline-based agonists were prepared as shown in Scheme 1. A Mitsunobu reaction between substituted 4-hydroxyindole (**4**) and *N*-Boc-4-hydroxypiperidine afforded the intermediate **5**. Compound **5**, upon *N*-arylation with 1,4-diiodobenzene using Buchwald conditions,[20] yielded indole derivative **6**. A copper-

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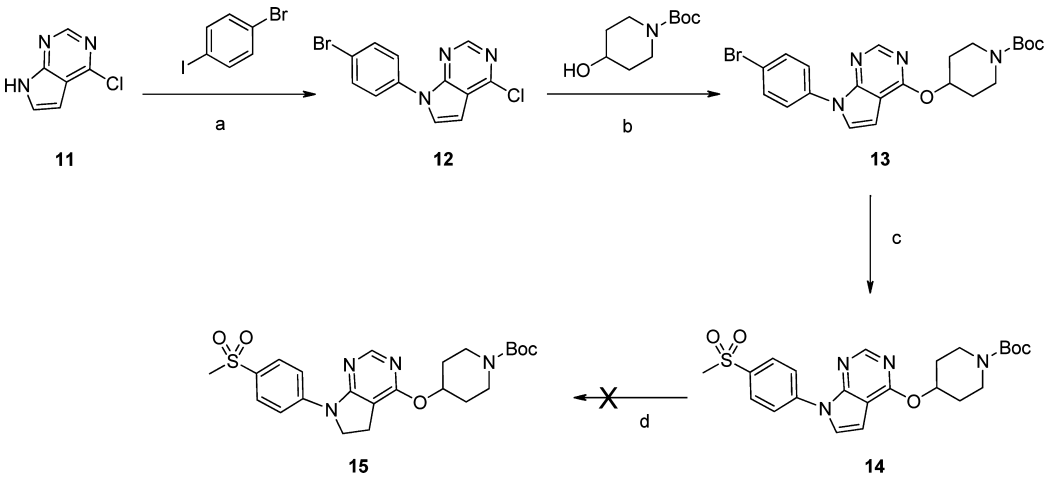
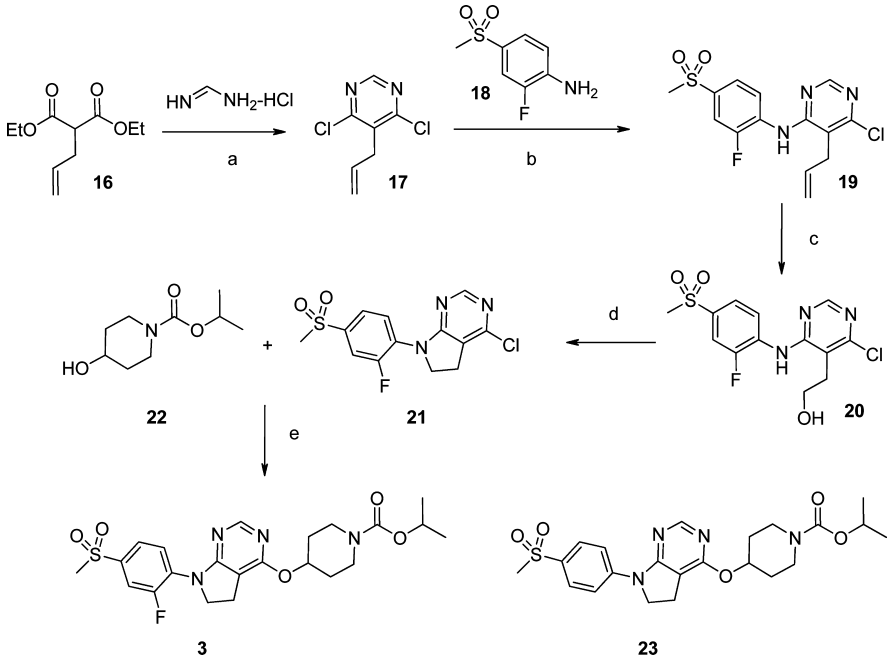
Scheme 2. Attempted Preparation of DHPP Chemotype[a]



[a]Reagents and conditions: (a) CuI, K_3PO_4, toluene, reflux, 30%; (b) NaH, THF, reflux, 70%; (c) CuI, L-proline, NaOH, CH_3SO_2Na, DMSO, 110 °C, 84%; (d) $NaCNBH_3$, HOAc or $NaCNBH_3$, $BF_3{\cdot}OEt_2$, MeOH, reflux or $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH or 10% Pd/C, H_2, MeOH.

Scheme 3. Preparation of the DHPP Chemotype, Exemplifying 3 and 23.[a]



[a]Reagents and conditions: (a (i) 0.5M NaOMe in MeOH, (ii) $POCl_3$, 86% yield from **16**; (b) NaH, THF, reflux; (c) (i) O_3, −78 °C, CH_2Cl_2, (ii) $NaBH_4$, MeOH; (d) Ms_2O, Et_3N, CH_2Cl_2, 0 °C to RT, 46% overall yield from **17**; (e) NaH, THF, reflux, 71%.

mediated sulfonylation[21] was used to install the methyl sulfone group to afford **7**, and then the indole was reduced with $NaCNBH_3$ in acetic acid[22] to afford indoline **9**. Alternatively, indole **6** could first be reduced to afford indoline **8**, then sulfonylated to give compound **9**. Either scheme could be used to provide good yields of the desired indoline. The *tert*-butylcarbamate of compound **9** was removed using 20% trifluoroacetic acid in dichloromethane and then converted to isopropylcarbamate derivative **2** using isopropyl chloroformate in good overall yield. Substituting 4-bromo-2-fluoro-1-iodobenzene in the *N*-arylation step and following the rest of the sequence afforded compound **10**.

Preparation of DHPP-based agonists was attempted as shown in Scheme 2. Transition metal-mediated coupling of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**11**) with 1-bromo-4-iodobenzene afforded *N*-aryl derivative **12**. Introduction of the piperidine moiety was accomplished with treatment of the chloro derivative **12** with the sodium alkoxide in THF at reflux to afford intermediate **13**. Conversion of the bromide to the sulfone using sodium methanesulfinate afforded the pyrrolo[2,3-*d*]pyrimidine intermediate necessary to try the reduction step. Unfortunately, attempts to reduce the pyrrolo[2,3-*d*]pyrimidine of **14** to the desired dihydro derivative **15** using a variety of conditions ($NaCNBH_3$, HOAc; $NaCNBH_3$, $BF_3{\cdot}OEt_2$, MeOH; Pd/C, EtOH; $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH) were unsuccessful.

Our first successful synthesis in the DHPP series is illustrated in Scheme 3.[23] 2-Allyldiethylmalonate (**16**) and formamidine hydrochloride, under basic conditions, gave the 4,6-dihydrox-

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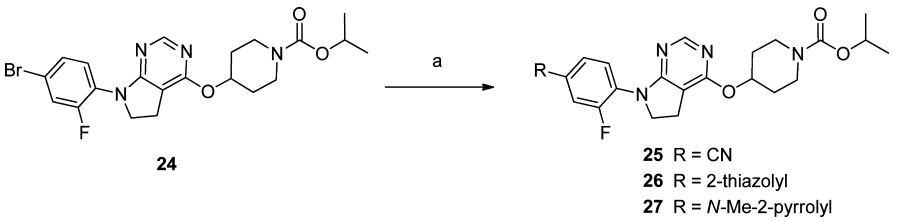
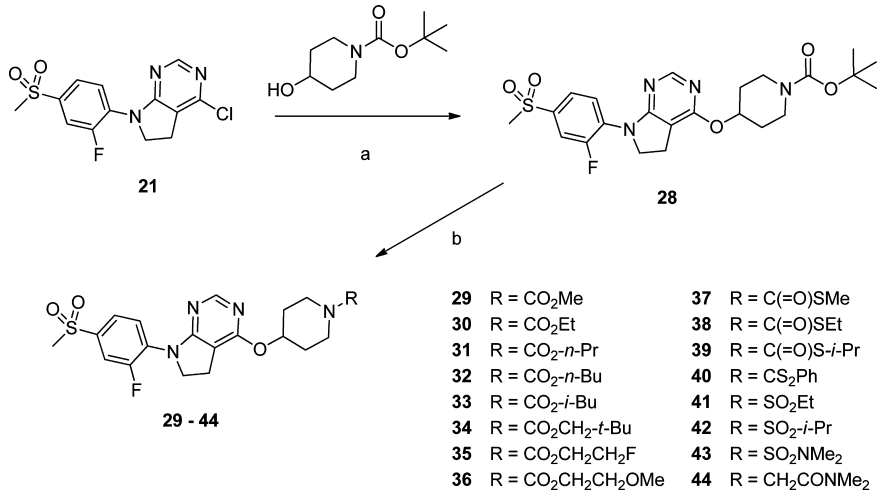
Scheme 4. Synthesis of Phenyl Ring Derivatives 25−27[a]



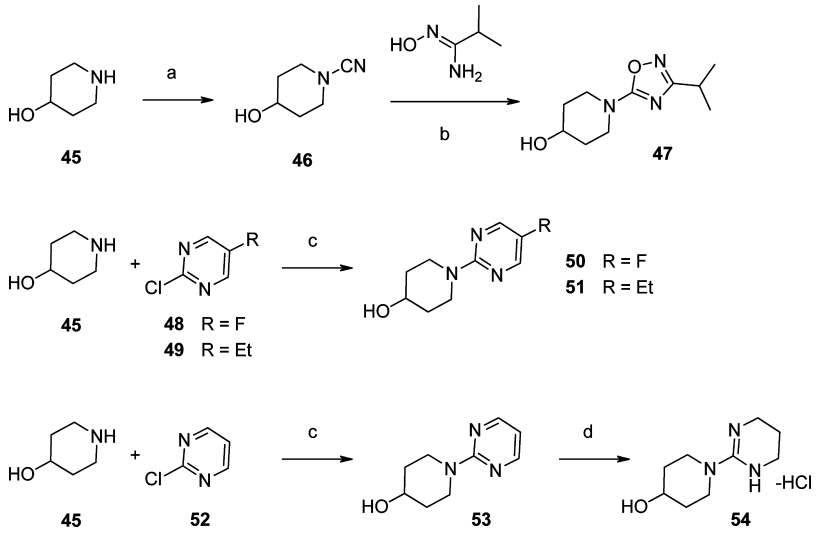
[a]Reagents and conditions: (a) CuCN, NMP, 150 °C, 85% for **25**, or $PdCl_2(Ph_3P)_2$, 2-(tributylstannanyl)-1,3-thiazole, THF, 78 °C, 61% for **26**, or $PdCl_2(Ph_3P)_2$, 1-methyl-2-(tributylstannanyl)-1*H*-pyrrole, THF, 78 °C, 12% for **27**.

Scheme 5. Synthesis of Piperidine Derivatives 29−44[a]



[a]Reagents and conditions: (a) NaH, THF, reflux, 71%; (b) (i) 20% TFA, CH_2Cl_2, RT, (ii) RCO_2Cl, Et_3N (**29−36**); or RC(═O)SCl, Et_3N (**37**, **38**); or 1,1′-carbonyldiimidazole; then MeI in CH_3CN, then *i*-PrSH, Et_3N, CH_2Cl_2 (**39**); RCS_2Ph, Et_3N (**40**); or RSO_2Cl, Et_3N (**41−43**); or $ClCH_2CONEt_2$, Et_3N (**44**).

Scheme 6. Synthesis of Oxadiazole, Pyrimidine, and Guanidine Intermediates 47, 50, 51, and 54[a]



[a]Reagents and conditions: (a) (i) CNBr, aqueous $NaHCO_3$, CH_2Cl_2; (b) (i) 1N $ZnCl_2$, Et_2O/EtOAc, (ii) 4N HCl, EtOH, ∼30% from **45**; (c) *i*-Pr_2NEt, CH_3CN, reflux, 83% for **50**, 50% for **51**, and 51% for **53**; (d) H_2, 10% Pd/C, HOAc/aqueous HCl, 84%.

ypyrimidine derivative that, upon $POCl_3$ treatment, afforded dichloro compound **17**. Nucleophilic displacement reaction between **17** and 2-fluoro-4-methylsulfonylaniline (**18**) using NaH in THF delivered the pyrimidine derivative **19**. The allyl group of **19** was oxidatively cleaved using ozone, then reduced in situ with $NaBH_4$ to afford alcohol **20**. Selective activation of the alcohol moiety as a mesylate was achieved with Ms_2O and Et_3N in CH_2Cl_2 to afford an intermediate, which spontaneously cyclized to afford the desired key bicyclic core **21**. Introduction of the hydroxypiperidine portion was accomplished as before,

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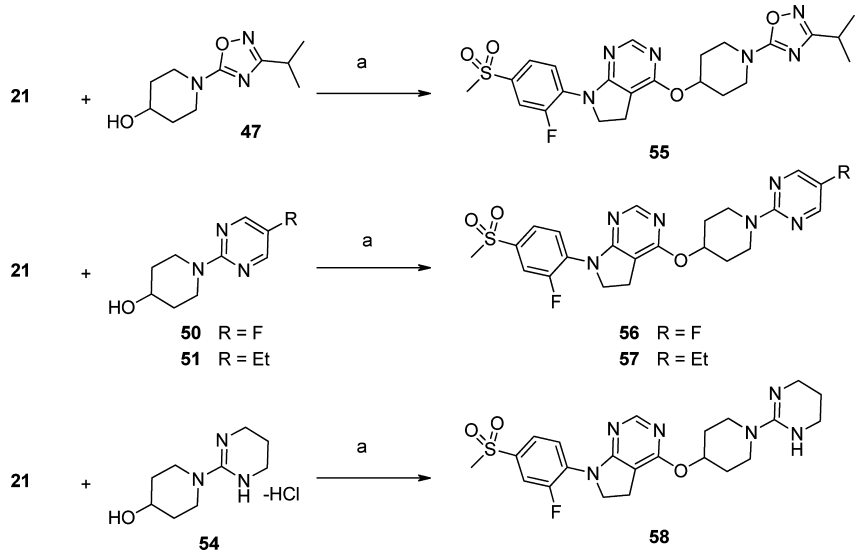
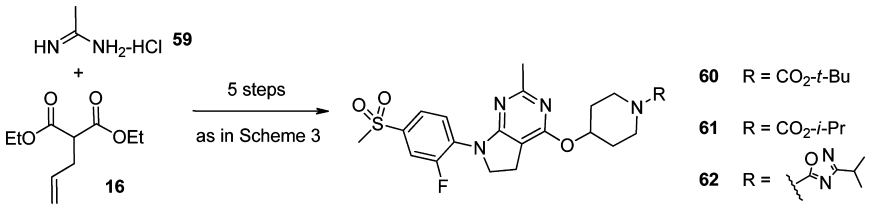
Scheme 7. Synthesis of Oxadiazole, Pyrimidine, and Guanidine Derivatives 55−58[a]



[a]Reagents and conditions: (a) NaH, THF, reflux, 55% for **55**, 39% for **56**, 50% for **57**, and 6% for **58**.

Scheme 8. Preparation of C2-Methyl Analogues 60−62



under basic conditions (NaH, THF, reflux), to provide desired compound **3**.

Compound **23** was prepared by reacting 4-bromoaniline with **17** and then converting the bromide to the methylsulfonyl (CuI, L-proline, NaOH, CH_3SO_2Na, DMSO, 110 °C) in the final step in the synthesis. An improved synthesis of the DHPPs, particularly for key intermediate **21**, employing a reductive amination reaction as the key step, has recently been reported.[24]

Exploration of the SAR of the phenyl region of the DHPPs was most easily accomplished with intermediate **24**, which provided an opportunity to examine the left-hand side of these molecules in a divergent manner (Scheme 4). Compound **24** was prepared from **17** and commercially available 4-bromo-2-fluoroaniline as described for the synthesis of **3** in Scheme 3. The bromide of **24** served as a handle to access a nitrile **25** via Rosenmund−von Braun conditions,[25] or heteroaromatic groups (compounds **26** and **27**) via Suzuki conditions.[26]

On the other end of the molecules, the *N*-Boc protected piperidine **28** served as a convenient spot for analogue synthesis through deprotection, to afford the unprotected piperidine, which could be functionalized. Carbamates **29−36** were prepared from the corresponding chloroformates. The thiocarbamates **37−39** and dithiocarbamate **40** were prepared from *S*-alkyl chloridothiocarbonates[27a] or carbamoylimidazolium salts[27b] and alkyl chlorodithiocarbonates,[27a] respectively (Scheme 5). Sulfonamides **41−43** were prepared from sulfonyl chlorides. 2-Aminoacetamide **44** was prepared from the corresponding 2-chloroacetamide.

While additional substituents on the left- and right-hand side were evaluated, they were prepared by an alternative route: coupling with the appropriate aniline or adding in the appropriately functionalized piperidine, respectively. A prominent feature found on the piperidine ring of many GPR119 agonists[17] is the 1,2,4-oxadiazole. This could be prepared following Scheme 6.[17] 4-Hydroxypiperidine (**45**) was treated with cyanogen bromide in the presence of $NaHCO_3$ to afford the intermediate carbonitrile **46**. Treatment of **46** with *N*-hydroxy-2-methylpropanimidamide in the presence of $ZnCl_2$ afforded the coupled intermediate. Cyclization-dehydration occurred when the intermediate was treated with acid (4N HCl) in EtOH at reflux for 1 h to provide **47**. 1-(5-Fluoropyrimidin-2-yl)piperidin-4-ol (**50**) and 1-(5-ethylpyrimidin-2-yl)piperidin-4-ol (**51**) were prepared from **45** and the corresponding chloropyrimidines **48** and **49**, respectively, in acetonitrile with diisopropylethylamine. 1-(Pyrimidin-2-yl)piperidin-4-ol (**52**) was prepared in a similar manner, and then the pyrimidine ring of **53** was partially reduced with hydrogen and Degussa-type palladium on carbon in a mixture of acetic acid and aqueous hydrochloric acid to afford **54**.

Analogues **55−58** were prepared from the corresponding hydroxypiperidine intermediates with **21** and NaH in refluxing THF as shown in Scheme 7.

Substitution at the C2 position of the pyrimidine ring was explored. Compounds (**60−62**) with a methyl substituent at the C2 position of the DHPPs could be prepared in a similar manner to that described for the unsubstituted analogues shown in Scheme 3 but starting with ethanimidamide hydrochloride (**59**) and **16** (Scheme 8).

Compounds bearing an amino substituent at the C2 position of the pyrimidine ring of the DHPPs were prepared as described in Scheme 9, which shows that the five-membered ring is built

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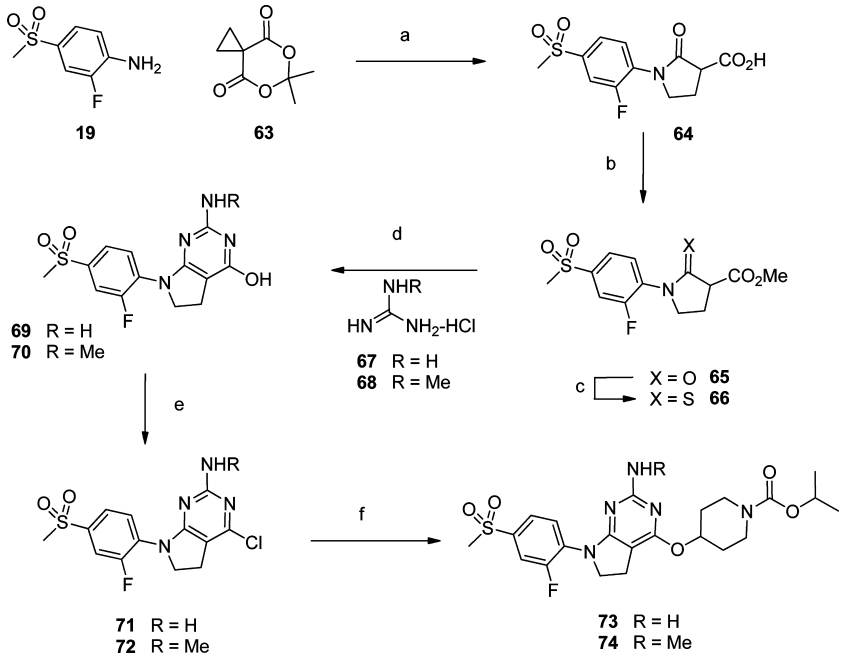
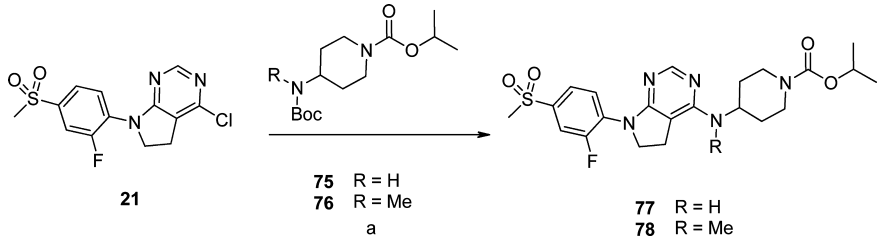
Scheme 9. Preparation of C2-Amino Analogues 73 and 74[a]



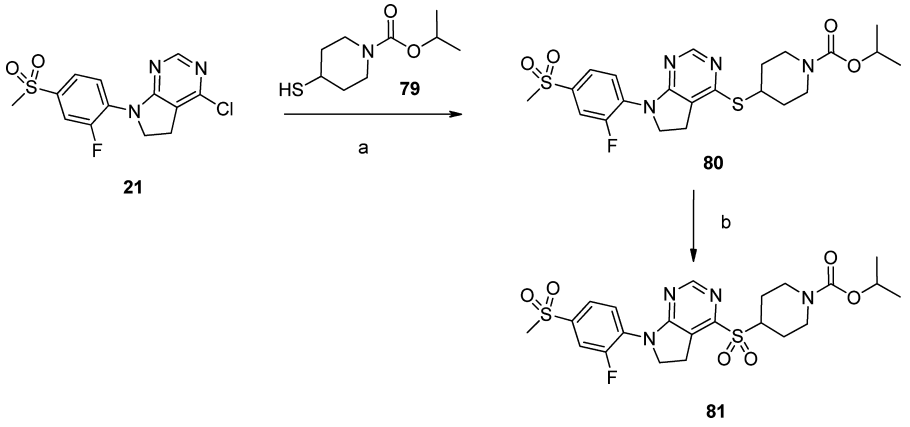
[a]Reagents and conditions: (a) CH_3CN, 60 °C; (b) catalytic amount of concentrated H_2SO_4, MeOH, 43% for 2 steps; (c) P_2S_5, THF, 70 °C, 50%; (d) guanidine hydrochloride or *N*-methyl guanidine hydrochloride, 1M NaOMe, MeOH, 60 → 90 °C; (e) $POCl_3$, Et_3N, 70 °C; (f) NaH, THF, 60 °C, 2% from **61** and 15% from **62**.

Scheme 10. Preparation of Analogues 77 and 78 Bearing a Nitrogen-Atom Linker[a]



[a]Reagents and conditions: (a) K_2CO_3, DMF, μw, 200 → 220 °C, 12% for **77** and 9% for **78**.

Scheme 11. Preparation of Analogues 80 and 81 Bearing a Sulfur-Atom Linker[a]



[a]Reagents and conditions: (a) K_2CO_3, acetone, 60 °C, 71%; (b) *m*-CPBA, CH_2Cl_2, 0 °C, 18%.

first, then construction of the pyrimidine follows. Reaction[28] of 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione (**63**) with aniline **19** afforded the 2-oxo-1-aryl-3-pyrrolidinecarboxylic acid **64**, which could be esterified using Fischer protocol (acid, methanol) to provide **65**. Conversion of the carbonyl moiety to a thiocarbonyl using P_2S_5 or Lawesson's reagent afforded intermediate **66**, which can be reacted with guanidine derivatives (R = H, guanidine hydrochloride, (**67**) or R = Me, *N*-

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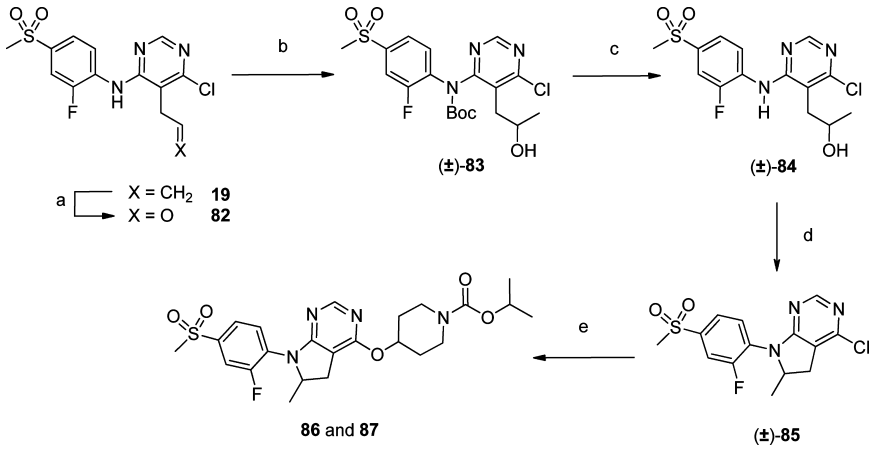
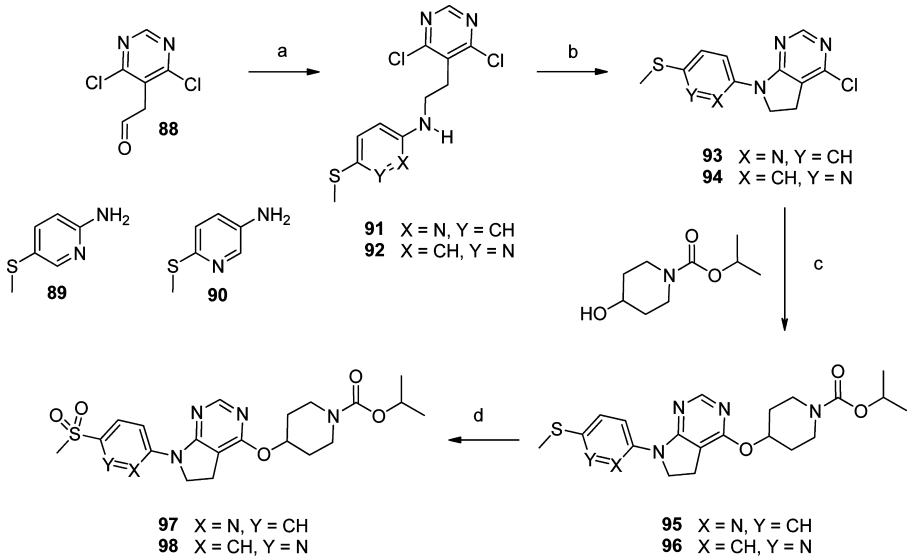
Scheme 12. Preparation of C6-Methyl Analogues 86 and 87[a]



[a]Reagents and conditions: (a) (i) Boc_2O, cat. DMAP, CH_2Cl_2, RT, (ii) $K_2OsO_4{\cdot}2H_2O$, 3:2 acetone/H_2O, $NaIO_4$, RT; (b) 1.4M MeMgBr, THF, 39% from **19**; (c) 20% TFA, CH_2Cl_2, RT; (d) Ms_2O, Et_3N, CH_2Cl_2, RT, 47% from **83**; (e) (i) NaH, THF, reflux; (ii) chiral separation, 82%.

Scheme 13. Preparation of Pyridyl Analogues 97 and 98[a]



[a]Reagents and conditions: (a) $NaCNBH_3$, HOAc, MeOH, −15 °C → RT; (b) KO-*t*-Bu, MeOH, 11% for **93**; (c) NaH, THF, reflux, 88% for **95**; (d) Oxone, MeOH/acetone/H_2O, RT, 81% for **97** and 7% overall yield for **98** from **17**.

methylguanidine hydrochloride (**68**)) in the presence of sodium methoxide to afford bicyclic intermediates **69** (R = H) and **70** (R = Me). Chlorination with $POCl_3$ afforded intermediates **71** and **72**, which was followed by introduction of the hydroxypiperidine portion via the alkoxide to give the desired targets **73** and **74**.

Changes to the linker between the bicyclic core and the piperidine were investigated. The nitrogen-linked analogue **77** was prepared by treating the chloro intermediate **21** with 1-methylethyl 4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1-piperidinecarboxylate (**75**) and heating in a microwave in the presence of potassium carbonate, as shown in Scheme 10. The *N*-methyl derivative **78** was prepared using 1-methylethyl 4-[{[(1,1-dimethylethyl)oxy]carbonyl}(methyl)amino]-1-piperidinecarboxylate (**76**) under conditions described above.

Thio- or sulfonyl-linked analogues were prepared by the following sequence (Scheme 11), which employed 1-methylethyl 4-mercapto-1-piperidinecarboxylate (**79**)[19] as the nucleophile. Treatment of chloro intermediate **21** with mercaptan **79** in acetone in the presence of potassium carbonate at elevated temperature (60 °C) afforded desired compound **80** in good yield (71%). Oxidation of the sulfur to the sulfone oxidation state was accomplished with *m*-CPBA at 0 °C, which afforded compound **81**.

Introduction of a methyl group at the 2-position of the five-membered ring was accomplished by intercepting the *N*-Boc protected aldehyde **82**, prepared from allyl **19**, with methyl Grignard in THF at room temperature in 39% yield to afford racemic alcohol **83** (Scheme 12). After *N*-Boc deprotection to afford intermediate **84**, activation of the secondary alcohol as its mesylate was achieved with methanesulfonyl anhydride in CH_2Cl_2 with triethylamine. The presence of triethylamine likely facilitated cyclization as the isolated product was the pentultimate intermediate **85**. Introduction of the piperidine portion occurred as has been reported for other substrates. The resulting racemate was separated by chiral chromatography to afford individual enantiomers (+)-**86** and (−)-**87**. The assignment of *R*- or *S*-stereochemistry for this enantiomeric pair was not made.

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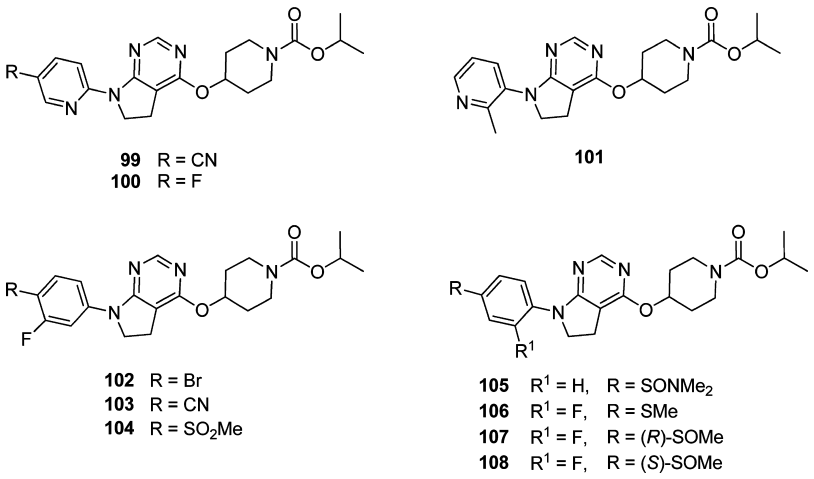
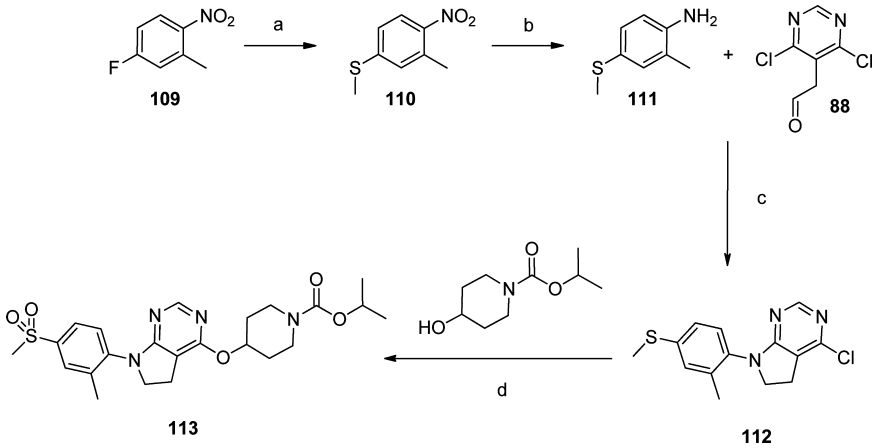


Figure 2. Pyridyl (**99**−**101**) and substituted phenyl (**102**−**108**) analogues.

Scheme 14. Preparation of Sulfone Analogue 113[a]



[a]Reagents and conditions: (a) NaSMe, DMF, 85 °C, 88%; (b) $SnCl_2$, conc HCl, EtOH, 80 °C, 81%; (c) (i) $NaCNBH_3$, HOAc, MeOH, −15 °C → RT, (ii) 4% TFA, 1,2-DCE, MeOH, RT, 31%; (d) (i) NaH, THF, reflux, 72%, (ii) Oxone, MeOH/acetone/H_2O, RT, 29%.

Replacement of the *N*-phenyl group with pyridyl rings was accomplished using the sequence shown in Scheme 13. Using the reductive amination strategy with the appropriate aminopyridine derivative (**90** and **91**) and aldehyde **88**, prepared from allyl **17**, the uncyclized intermediates **89** and **90** were prepared, respectively. Unlike the phenyl congeners, which cyclized under acidic conditions (TFA), the pyridyl analogues cyclized more smoothly in the presence of a base such as potassium *t*-butoxide or a trialkylamine (Hunig's base). The resultant chloro intermediates **93** and **94** were then reacted with the alkoxide of the 4-hydroxypiperidine derivative to afford sulfides **95** and **96**. Oxidation of the sulfides to sulfones **97** and **98** was accomplished with Oxone or *m*-CPBA.

Employing a similar strategy as shown in Scheme 13, other pyridyl analogues (compounds **99**, **100**) and substituted phenyl derivatives (**102**−**105**) were prepared (Figure 2). For analogues **99** and **100**, the initial reductive amination step with **88** and commercially available 6-aminonicotinonitrile or 5-fluoropyridin-2-amine, respectively, employed $Na(OAc)_3BH$ and TFA in CH_2Cl_2. In addition, the acidic conditions in the reduction amination step facilitated the ring closure of the five-membered ring, so a separate cyclization step was not needed for each analogue. The synthesis of **99** and **100** were completed by introducing the functionalized hydroxypiperidine **22** as previously shown for other analogues. The synthesis of **101** began with a reduction amination reaction between **88** and commercially available 2-methyl-3-pyridinamine. The subsequent key five-membered ring closing step occurred using a Pd-mediated ($PdCl_2(Ph_3P)_2$, KO-*t*-Bu, toluene, reflux) cyclization reaction. Synthesis of **101** was completed by introducing the functionalized hydroxypiperidine **22** as previously shown for other analogues, in 55% overall yield. Intermediate bromide **102** was prepared from **88** and 4-bromo-3-fluoroaniline in a manner similar to that described for **99**. Bromide **102** was converted to nitrile **103** using CuCN in NMP at 150 °C (7% overall yield from **89**). Sulfone **104** was prepared from **102** using CH_3SO_2Na, CuI, L-proline, and NaOH in DMSO at 110 °C (38% overall yield from **88**). Sulfonamide **105** was prepared from **88** and 4-amino-*N*,*N*-dimethylbenzenesulfonamide in a manner similar to that described for **99** in 17% overall yield. Sulfide **106** was prepared from **88** and 2-fluoro-4-(methylthio)aniline in 34% yield using the same strategy used in the synthesis of **99**. 2-Fluoro-4-(methylthio)aniline was prepared from the commercially available 2-fluoro-4-iodoaniline and $NiBr_2$ (Zn dust, 2,2′-dipyridyl, DMF, 75 °C) in 73% yield. Racemic sulfoxide was prepared from sulfide **106** via oxidation with hydrogen peroxide in hexafluoroisopropanol,[29] to prevent overoxidation. The resultant racemate was separated by chiral chromatography to

dx.doi.org/10.1021/jm301404a | *J. Med. Chem.* XXXX, XXX, XXX−XXX

afford the individual sulfoxide enantiomers **107** (*R* enantiomer) and **108** (*S* enantiomer). The absolute stereochemistry was determined based on VCD spectroscopy.[30]

The synthesis of sulfone **113** began by converting 4-fluoro-2-methyl-1-nitrobenzene (**109**) to the methylthio derivative **110** with sodium thiomethoxide. Reduction of the nitro group led to intermediate **111** that underwent the reduction amination/cyclization sequence with **88** to afford chloride **112**. The hydroxypiperidine portion was appended using NaH in THF, and the sulfide was oxidized with Oxone to complete the synthesis of **113**.

DISCUSSION

In relation to their bicyclic counterparts (represented by **1**), the indolines and DHPPs were initially designed to provide novel compounds with potentially better: (1) potency, (2) systemic exposure after oral administration, due to better solubility from the reduction of aromaticity, and (3) selectivity.

The potency of the indolines and DHPPs were measured using a reporter assay with the human GPR119 receptor stably expressed in CHO-K1 6CRE-luciferase cells.[31] All compounds are referenced to a small molecule GPR119 agonist[32] for evaluation of intrinsic efficacy (% max response) because this reporter assay is not sensitive enough to demonstrate robust activity with the putative endogenous ligands (OEA, LPC, etc.). The results are summarized in Table 1.

It was gratifying to observe that indoline **9** not only showed activity against human GPR119 with a pEC_{50} = 6.8 (92%), it was markedly better than its indole counterpart **7** (pEC_{50} = 6.2 (28%)). In addition, the intrinsic activity of the indoline was much improved over the indole, 92% versus 28%. This served as another impetus to continue to examine compounds with the DHPP scaffold. As anticipated, good activity was also observed with compounds **3** and **23** (pEC_{50} = 7.3 (91%) and pEC_{50} = 6.7 (154%), respectively), bearing the pyrimidine ring nitrogens of the DHPP scaffold.

Substituents on the aryl or heteroaryl ring attached to the dihydropyrrole nitrogen were investigated. Substitution at the 4-position of the *N*-aryl ring was found to be critical for activity. For example, compounds that lacked a functional group that could act as a hydrogen bond acceptor were usually about a log unit less potent than methylsulfone or nitrile. Thiazole **26** and pyrrole **27**, with a heterocycle at the 4-position, were found to retain much of the potency, but not as much as the sulfone. Sulfide **106** also showed intermediate potency with a pEC_{50} = 6.4, typical of a compound that lacked a hydrogen-bond acceptor. The oxidation state of the sulfur turned out to be less important than the stereochemistry. For example, (*R*)-sulfoxide **107** had similar potency to the sulfide and was a log less potent than the (*S*)-isomer **108**, which was equipotent with sulfone **3**.

Substitution at the 2- and 3-positions of the phenyl ring was also examined. A substituent, such as fluoro or methyl, was found to increase potency over their unsubstituted versions, such as **23** (pEC_{50} = 6.9). A very slight preference for a fluoro atom at the 2-position of **3** over the other possible iterations (3-F, **104**, and 2-Me, **113**) was observed.

Similar findings with respect to optimal 4-substitution were observed in the analogues bearing a pyridyl ring in place of the phenyl ring. The methylsulfone in **97** (and **98**) was preferred over the nitrile from **99**, which was better than a fluoro atom found in **100**. The placement of the pyridyl nitrogen at the 2- or 3-position did not affect activity in **97** and **98**, respectively, as each had a $pEC_{50} \geq 6.6$.

Table 1. Potency of Selected Analogues[a]

compd	av pEC_{50}	StDev	av % max	StDev	*n*
2	6.3	0.25	70	6.3	3
3	7.3	0.15	91	15.9	6
7	6.2	0.31	28	5.6	3
9	6.8	0.13	92	12.2	6
10	6.0	0.19	62	15.5	6
23	6.9	0.38	154	26.4	12
25	7.2	0.11	134	6.4	6
26	7.1	0.16	74	10.8	6
27	6.8	0.09	44	5.2	5
28	7.7	0.10	139	18.3	6
29	6.5	0.26	119	34.1	6
30	6.6	0.14	135	12.1	6
31	7.1	0.09	111	13.5	6
32	7.3	0.29	131	22.4	8
33	7.6	0.09	94	5.3	6
34	7.4	0.15	80	5.3	6
35	6.3	0.21	86	10.2	6
36	6.5	0.07	86	13.5	5
37	6.6	0.15	135	25.9	6
38	7.5	0.07	128	13.9	6
39	8.0	0.09	138	9.7	6
40	7.9	0.24	103	19.1	4
41	5.8	0.10	51	10.8	4
42	5.9	0.08	62	7.4	5
43	6.4	0.17	68	4.1	4
44	<5				3
46	6.5	0.22	129	16.8	6
47	7.3	0.14	105	6.0	6
55	7.1	0.15	124	19.3	6
58	5.7	0.02	66	19.0	2
60	6.9	0.33	69	21.1	4
61	7.0	0.12	45	3.1	6
62	6.6	0.18	44	7.0	4
73	6.1	0.07	33	3.4	4
74	<5				6
77	5.7	0.22	64	8.0	6
78	6.2	0.07	88	8.8	6
80	7.1	0.19	69	12.2	5
81	<5				6
86	<5				6
87	<5				6
97	6.9	0.10	111	6.4	6
98	6.6	0.13	97	4.8	6
99	6.1	0.14	105	14.4	6
100	<5				6
101	<5				6
103	6.4	0.38	121	15.3	6
104	6.8	0.11	109	14.7	6
105	6.3	0.07	128	22.6	4
106	6.4	0.24	121	15.3	9
107	6.2	0.31	155	45.1	10
108	7.3	0.22	122	16.2	14
113	7.0	0.24	80	26.8	9

[a]av StDev = average standard deviation; av %max = average percent maximum response; *n* = number of runs.

Structure–activity relationships of the bicyclic scaffold revealed that further substitution on the rings at the 2- and 6-positions did not produce compounds with greater potency. Quite the contrary, these changes produced compounds with

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Table 2. Pharmacokinetic Properties of 3 in Rat and Mouse

species	$t_{1/2}$ (h)	C_{max} (μM)	Cl (mL/min/kg)	DNAUC$_{0-24\ h}$ (μg·h/mL/dose)	V_{ss} (L/kg)	%F	brain:plasma
rat	8.7	9	8.4	2035	1.5	66	0.7
mouse	2.8	20	7.2	1701	0.7	40	nd

diminished activity. Methyl-substituted analogues **60**–**62** were about a log unit less potent, as was amino **73**. The monomethylated analogue, **74**, did not agonize the receptor at measurable levels. The 6-substituted analogues, **86** and **87**, also showed diminished activity. In addition, compared to the oxygen-linked analogues, the nitrogen-linked analogues **77** and **78** were less active. The sulfur-linked analogue **80** was comparable to oxygen analogue **3**; however, the potency of sulfone derivative **81** was not.

A general trend for the requirement of a lipophilic moiety was observed during exploration of the right-hand side. This is most easily seen in the carbamate series. As the size of the alkyl group grew, so did potency. Methyl carbamate **29** was the weakest of the group, while the larger *tert*-butyl carbamate **28**, *iso*-butyl carbamate **33**, and neopentyl carbamate **34** were more potent. When lipophilic portions were substituted with more hydrophilic groups, activity was lost. Replacing a methylene in the *n*-butyl derivative of **32** (pEC$_{50}$ = 7.3) with oxygen (3-methoxypropyl carbamate **36**, pEC$_{50}$ = 6.5) resulted in loss of potency. Similarly, the fluoroethyl derivative **35** was less potent than the corresponding *n*-propyl **31**.

S-Thiocarbamates were also found to be potent. However, these analogues did not seem to offer any advantage over their oxygen congeners. For example, methyl *S*-thiocarbamate **37** had a pEC$_{50}$ = 6, which was about equipotent to methylcarbamate **29** (pEC$_{50}$ = 6.5). Briefly, dithiocarbamates were also investigated. Phenyldithiocarbamate **40** was potent, with a pEC$_{50}$ = 7.9. Unfortunately, these sulfur-containing compounds resulted in low plasma exposure (dose normalized area under the curve, DNAUC$_{0-24h}$ <0.03 μg·h/mL/dose), possibly due to extensive metabolism. In addition, there was the potential for reactive metabolites; thus, this class was deprioritized.

Sulfonamides were also investigated. Alkyl sulfonamides **41** and **42** were active, but a direct comparison between the corresponding carbamate **30** to **41** demonstrates that carbamates are superior (**30**,pEC$_{50}$ = 7.1 versus **41**, pEC$_{50}$ = 5.8). The *N*,*N*-dimethylsulfonamide derivative **43** also showed activity but was still less potent than similar sized carbamates.

Heterocyclic isosteres of the carbamates were examined. The two best replacements that were identified were the oxadiazoles and pyrimidines. For example, oxadiazole **55** and 4-ethylpyrimidine **57** were as potent as carbamate **3**.

While other classes of functional groups (amides, ureas, substituted benzyls, alkyls; data not shown) were explored on the right-hand side, most of them did not show desirable potency (pEC$_{50}$ > 6). One example is acetamide **44**, in which a methylene has been inserted between the carbonyl and the piperidine nitrogen. Although it does preserve the lipophilic substitution with the *N*,*N*-diethyl moiety, this analogue did not agonize the receptor at concentrations lower than 10 μM. The SAR suggests that the more basic piperidine nitrogen is not well tolerated.

In attempts to prepare analogues with increased solubility while preserving the lipophilic alkyl groups, and while not increasing molecular weight[34] significantly, guanidine-containing **58** was prepared. Unfortunately, this analogue was not very potent (pEC$_{50}$ = 5.7).

Having established which arrangement of functional groups on the DHPP scaffold conferred reasonable potency, we turned our attention to identifying compounds possessing the proper combination of potency and plasma exposure. We had ruled out the *S*-thiocarbamates and dithiocarbamates due to putative extensive metabolism. As the size of the alkyl groups on the carbamates grew, potency went up; however, we were mindful to keep MW down in order to identify compounds with desirable developability parameters. Among the carbamates, the best balance of potency, MW, and exposure was the isopropylcarbamate. From a potency perspective, the isopropyloxadiazole and 4-ethylpyrimidine analogues were comparable and attractive. Unfortunately, the AUC$_{0-24h}$ for isopropyloxadiazole **55** in the rat[35] after a 10 mg/kg dose was 0.5 μg·h/mL. 4-Ethylpyrimidine **57** was equally poor in the mouse with a DNAUC$_{0-24h}$ = 0.04 μg·h/mL/dose. Nitrile **25**, however, did show good levels in rat plasma (DNAUC >1 μg·h/mL/dose). Ultimately, methylsulfone **3** emerged as possessing the best balance of potency and solubility. In fasted simulated intestinal fluid, the equilibrium solubility of **3** was 4 μg/mL. Importantly, sulfone **3** was found to have a DNAUC$_{0-24h}$ value of 2 μg·h/mL/dose. In addition, in the rat, it possessed a moderate half-life ($t_{1/2}$ = 8.7 h) and good bioavailability (%F = 66). Additional pharmacokinetic properties of **3**, dosed 30 mg/kg in the rat and mouse, are shown in Table 2.

The selectivity profile of **3** revealed few issues. In a panel against 50 aminergic receptors, **3** showed <20% binding at all receptors at a concentration of 1 μM. In a separate panel of 68 receptors, ion channels, and enzymes, the only activity that registered >50% inhibition or stimulation at 10 μM was monoamine oxidase-B (MAO-B) inhibition (54%). Sulfone **3** did inhibit the cytochrome P450 subtype 2C9 with an IC$_{50}$ = 3 μM. Overall, though, we concluded that the selectivity profile was sufficiently clean to carry forward into target validation studies.

GPR119 agonist **3** was evaluated for its ability to increase incretin and insulin secretion in vitro and ex vivo. Compound **3** caused GLP-1 secretion in GluTag[36] cells with a pEC$_{50}$ = 7.7, which closely approximates its receptor potency (Figure 3). In primary colonic crypt cells harvested from mice, **3** stimulated GLP-1 release in a statistically significant manner over the vehicle treated group (Figure 4) (p < 0.001). The lack of a dose response

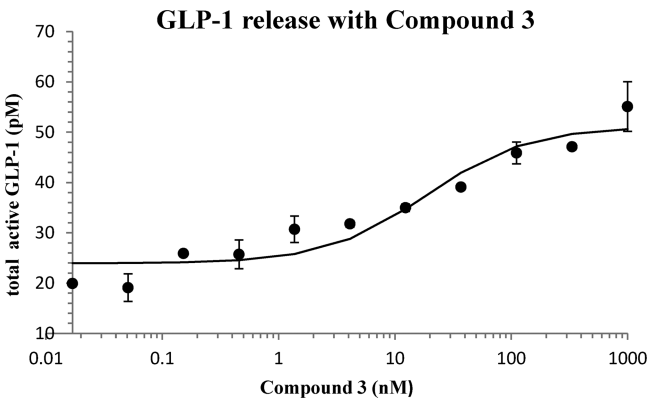

Figure 3. GLP-1 release in GluTag cells with **3**.

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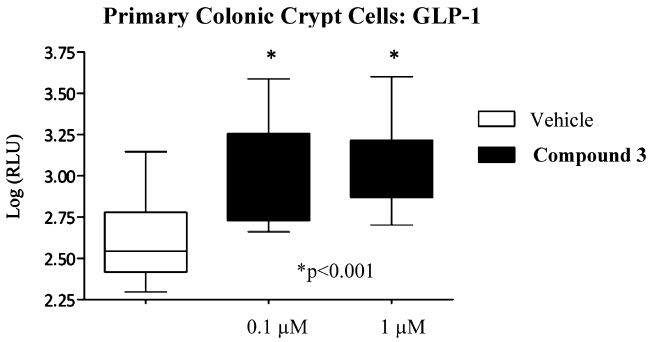

Figure 4. GLP-1 secretion in primary colonic crypt (PCC) cells with **3**.

in this study may be due to the inherent variability in an experiment working with primary cells or possibly that compound **3** had reached the upper plateau on the dose response curve at those doses. In isolated rat islets, **3**, at 0.3 μM, augmented insulin release in the presence of 12 mM glucose ($p < 0.01$). No insulin secretion was observed at 3 mM glucose for either the treated or untreated cells.

To determine if the effects observed in vitro were GPR119-mediated, **3** (30 mg/kg) was administered to wild-type and knockout mice that had been fasted overnight (Figure 5). A near 4-fold increase in GLP-1 and 2-fold increase in GIP, when compared to vehicle ($n = 10$, $p < 0.01$ and $p < 0.01$, respectively), was observed in the WT mice, whereas no increase was observed in GPR119 KO mice. This suggests that the effects on incretin hormone secretion are mediated through GPR119.

Interestingly, there was also a 3-fold increase in PYY levels and a 2-fold increase in glucagon in WT mice, compared to vehicle ($n = 8–10$, $p < 0.01$ and $p < 0.01$, respectively; data not shown). Like the incretins, no effect of **3** on PYY or glucagon secretion was observed in KO mice.

To assess the effects of **3** on islet glucose response in vivo, C-peptide levels were assessed in rats using the hyperglycemic clamp. The plasma glucose levels were elevated and maintained at similar (clamped) levels in both treatment groups throughout the glucose infusion. The glucose infusion rate required to maintain the clamp was significantly increased in the rats treated with **3** (Figure 6), correlating with an increase in both first phase (0–5 min) and second phase (10–90 min) C-peptide profile (Figure 7), a direct reflection of insulin secretion.[37]

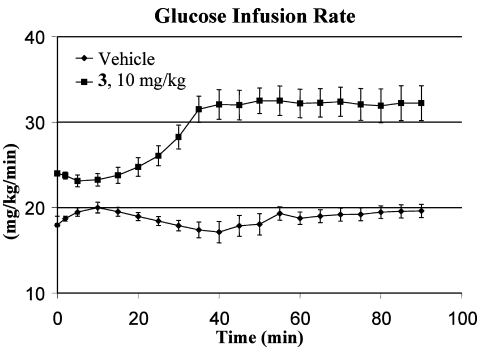

Figure 6. Glucose Infusion Rate with **3**.

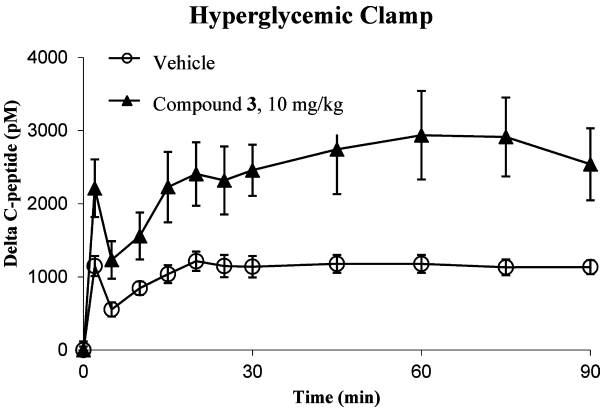

Figure 7. Hyperglycemic clamp with **3**.

With **3** having shown the ability to promote incretin secretion in vitro and in vivo, in addition to demonstrating its effects on insulin secretion in the whole animal, we sought to establish whether or not **3** would impact glucose levels as a reflection of these responses.[19b] In normal rats, **3**, administered orally at 10 mg/kg, decreased the glucose excursion curve by 43% in a glucose tolerance test (data not shown) when glucose was administered intravenously and 38% when glucose was administered orally (Figure 8) ($n = 7$, $p < 0.01$ for each). This

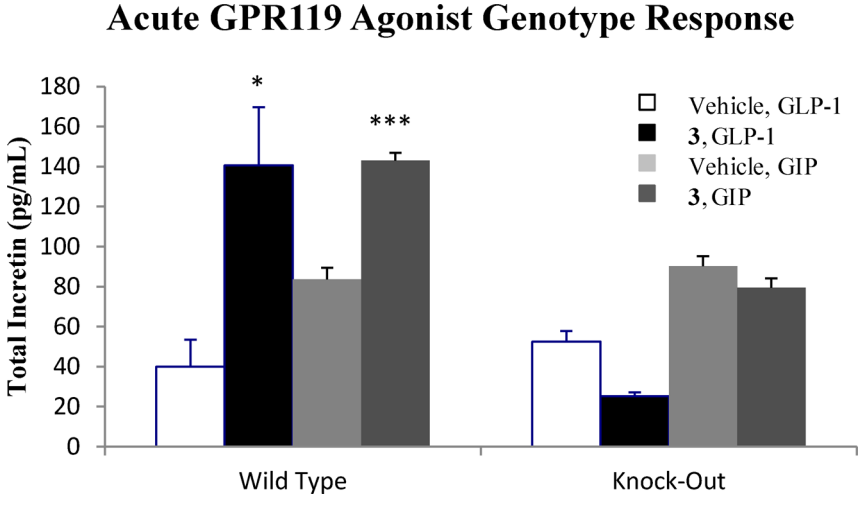

Figure 5. Incretin secretion in WT and KO mice.

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effect was similar to LAF237[38] (vildagliptin), a DPP-IV inhibitor used as a positive control.

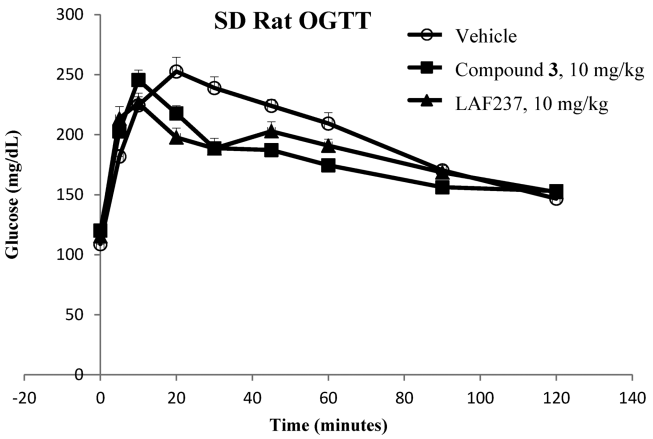

Figure 8. Rat OGTT with **3** and a DPP-IV inhibitor.

While there is a statistically significant increase of GLP-1 upon administration of **3**, we wondered whether the magnitude was sufficient to inhibit gastric emptying, as elevated GLP-1 levels are known to cause a delay. Compound **3**, dosed orally (10 mg/kg) to normal male, SD rats that had been fasted overnight resulted in a 27% reduction of the acetaminophen AUC (0−2 h) when compared to vehicle. It has been shown that acetaminophen is relatively unabsorbed in the stomach while rapidly absorbed and detected in the circulation upon gastric release to the small intestine, making it a suitable marker for determining the rate of gastric emptying.[39]

In a separate species (mouse), we evaluated whether or not compound **3** would affect food intake. Individually housed male, C57BL/6 mice were fasted overnight, then treated with 10 mg/kg of **3**, and food intake was measure at 1, 2, 4, 6, and 24 h post dose (data not shown). There was no effect relative to vehicle-treated animals.

CONCLUSION

A novel series of indolines were found to be potent and selective GPR119 agonists. Optimization of this series led to the 6,7-dihydro-5*H*-pyrrolopyrimidines, best exemplified by compound **3**. SAR analysis of this novel series suggests that a hydrogen-bond acceptor group appended to the *N*-aryl ring significantly boosts potency, while lipophilic groups as extensions from the piperidine ring are preferred. The central region can accommodate a variety of scaffolds, and it has been shown that the bicyclic, 6,7-dihydro-5*H*-pyrrolopyrimidine ring system produces compounds that are potent and selective while possessing favorable pharmacokinetic properties.

Accordingly, compound **3** was used in functional in vitro and in vivo studies. The data suggest that compound **3**-mediated GPR119 activation promotes in vitro (GluTag cells) GLP-1 secretion. It increases GLP-1 and GIP levels in vivo, and this effect is nutrient independent and GPR119 dependent. In vitro, compound **3** augments glucose-stimulated insulin secretion and, in vivo, enhances both first and second phase insulin secretion. Compound **3** also reduces glucose excursions and improves glucose tolerance. When administered orally, **3** has been shown to reduce gastric emptying, with no commensurate effect on food intake.

While the details of the mechanism of action of this receptor are not yet fully understood, small molecule **3** was used to support a role for GPR119 in the control of glucose levels in the rodent. These findings support preclinical reports of others that have identified GPR119 agonists and suggest that GPR119 may be an attractive target for the treatment of type 2 diabetes. Preliminary communications from clinical studies with a few GPR119 agonists, however, show mixed results. As observed in preclinical studies in animals, MBX-2982 showed dose-dependent reductions in glucose and increases in GLP-1 following a mixed meal.[40] Recently, Katz et al. demonstrated that a single-dose of a GPR119 agonist, JNJ-38431055, in healthy subjects increased postprandial GLP-1, GIP, and PYY but did not decreased glucose excursion or increase insulin.[41] Similarly, GSK1292263,[42] a selective GPR119 agonist that comes from a structurally different class than the DHPPs, did not reduce glucose AUC (0−24 h) when administered alone or when codosed with metformin or sitagliptin.[43] Whether GPR119 agonists are able to deliver sustained glucose lowering in type 2 diabetics is at present unclear and awaits longer term studies.

EXPERIMENTAL SECTION

Unless otherwise noted, all nonaqueous reactions were carried out under a nitrogen atmosphere using commercial grade solvents and reagents. ^{1}H NMR spectra were taken on a Varian (Agilent) Inova 400 NMR spectrometer. Chemical shifts are reported in parts per million (ppm, δ) using the residual solvent line as a reference. Splitting patterns are designated using the following abbreviations: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet; br, broad. Coupling constants (J) are reported in hertz (Hz) where relevant. Mass spectrometric analyses were conducted on a Waters Acquity UPLC system and Waters Acquity SQD with alternating positive/negative electrospray ionization scanning from 125 to 1000 amu, with a scan time of 105 ms and an interscan delay of 20 ms. High resolution mass spectrometric analysis was performed on a Waters qTOF Premiere mass spectrometer operating in W mode. Reverse phase HPLC was performed on a Gilson preparative system. The purity of the compounds was established through analytical HPLC analysis on an Agilent HP1100, and all compounds reported in the manuscript have a chemical purity ≥95%.

1-Methylethyl 4-({1-[4-(Methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (2). A solution of 4-hydroxyindole (6.65 g, 50 mmol) in THF (600 mL) at 5 °C under N_2 was treated with 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate (20.1 g, 100 mmol) and triphenylphosphine (26.2 g, 100 mmol). Diisopropyl azodicarboxylate (19.4 mL, 100 mmol) was added dropwise over a 20 min period, and then the mixture was allowed to stir and warm to RT for 8 h. The reaction was concentrated to give an orange oil that was purified by flash chromatography (10→50% EtOAc/hexanes) to afford 1,1-dimethylethyl 4-(1*H*-indol-4-yloxy)-1-piperidinecarboxylate (**5**) (12.3 g, 77%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.03 (br s, 1H), 7.19 (t, J = 2.8 Hz, 1H), 6.99−6.93 (m, 2H), 6.54 (dd, J = 7.2, 1.2 Hz, 1H), 6.41 (app t, J = 2.4 Hz, 1H), 4.63 (m, 1H), 3.67−3.61 (m, 2H), 3.26−3.21 (m, 2H), 1.94−1.87 (m, 2H), 1.64−1.52 (m, 2H), 1.40 (s, 9H). LCMS (ESI): m/z 339 [M + Na]$^+$. A solution of **5** (4.0 g, 12.6 mmol) in 1,4-dioxane (80 mL) at RT under N_2 was treated with CuI (240 mg, 1.3 mmol), K_3PO_4 (4.0 g, 19 mmol), and *trans*-1,2-diaminocyclohexane (0.3 mL, 2.5 mmol), followed by 1,4-diiodobenzene (6.3 g, 19 mmol), and the mixture was heated to reflux for 15 h. The reaction mixture was allowed to cool to RT, diluted with EtOAc (250 mL), and then filtered through a plug of silica (EtOAc wash). The filtrate was concentrated, and the resultant residue was purified by flash chromatography (0→20% EtOAc/hexanes) to afford 524 mg of 1,1-dimethylethyl 4-{[1-(4-iodophenyl)-1*H*-indol-4-yl]oxy}-1-piperidinecarboxylate (**6**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (t, J = 8.8 Hz, 2H), 7.51 (d, J = 3.2 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.12 (t, J = 5.6 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.72 (d, J = 7.2 Hz, 1H), 6.70 (d, J = 3.2

dx.doi.org/10.1021/jm301404a | J. Med. Chem. XXXX, XXX, XXX−XXX

Hz, 1H), 4.70 (m, 1H), 3.66−3.60 (m, 2H), 3.28−3.24 (m, 2H), 1.94−1.89 (m, 2H), 1.66−1.58 (m, 2H), 1.39 (s, 9H). LCMS (ESI): m/z 518 $[M + H]^+$. A solution of **6** (355 mg, 0.69 mmol) in DMSO (4 mL) in a 10 mL glass tube was treated with CuI (13 mg, 0.07 mmol), $MeSO_2Na$ (103 mg, 1.0 mmol), L-proline (16 mg, 0.14 mmol), and NaOH (6 mg, 0.14 mmol). The tube was sealed and then heated at 110 °C for 18 h. The reaction mixture was allowed to cool and then poured onto EtOAc. The mixture was washed with water and brine and was dried over Na_2SO_4 and concentrated. The resultant residue was purified by flash SiO_2 column chromatography to afford 314 mg (98%) of **7** as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 3.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 6.78 (m, 1H), 6.77 (s, 1H), 4.72 (m, 1H), 3.68−3.60 (m, 2H), 3.33−3.22 (m, 2H), 3.28 (s, 3H), 1.97−1.88 (m, 2H), 1.70−1.58 (m, 2H), 1.40 (s, 9H). HRMS (ESI): m/z calcd for $C_{25}H_{30}N_2O_5S$ $[M + Na]^+$ 493.1773, obsd 493.1771. A solution of **7** (310 mg, 0.66 mmol) in acetic acid (4 mL) at RT was treated with $NaCNBH_3$ (0.62 g, 9.9 mmol), and the mixture was stirred at RT for 36 h. The mixture was then diluted with H_2O (40 mL) and stirred for 30 min. The resultant precipitant was filtered (water wash) and recrystallied from methanol to afford 1,1-dimethylethyl 4-({1-[4-(methylsulfonyl)-phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate **9** (218 mg, 71%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (t, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.08 (app t, J = 8.4 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 4.60−4.52 (m, 1H), 4.01 (t, J = 8.8 Hz, 2H), 3.61−3.55 (m, 2H), 3.30−3.21 (m, 2H), 3.13 (s, 3H), 3.01 (t, J = 8.4 Hz, 2H), 1.89−1.84 (m, 2H), 1.39 (s, 9H). LCMS (ESI): m/z 495 $[M + Na]^+$. HRMS (ESI): m/z calcd for $C_{25}H_{32}N_2O_5S$ $[M + Na]^+$ 495.1930, obsd 495.1926. A solution of **9** (140 mg, 0.3 mmol) in CH_2Cl_2 (8 mL) at RT under N_2 was treated with CF_3CO_2H (2 mL), and the reaction mixture was stirred at RT for 2.5 h and then concentrated. The resultant crude material was redissolved in CH_2Cl_2 (4 mL) and treated with DIPEA (0.26 mL, 1.5 mmol), followed by the dropwise addition of a 1M solution of isopropyl chloroformate in toluene (3 mL, 3 mmol). The mixture was stirred at RT for 8 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and then washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and filtered, and the filtrate was concentrated to afford the crude material. The material was purified by flash chromatography (0→20% EtOAc/hexanes) to afford 74 g (54%) of **2** as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (t, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.08 (app t, J = 8.4 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.75 (septuplet, J = 6.0 Hz, 1H), 4.60 (m, 1H), 4.01 (t, J = 8.8 Hz, 2H), 3.60−3.55 (m, 2H), 3.2−3.26 (m, 2H), 3.13 (s, 3H), 3.01 (t, J = 8.4 Hz, 2H), 1.89−1.60 (m, 2H), 1.59−1.52 (m, 2H), 1.17 (d, J = 6.4 Hz, 6H). HRMS (ESI): m/z calcd for $C_{24}H_{30}N_2O_5S$ $[M + H]^+$ 459.1954, obsd 459.1954.

1-Methylethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (3). A solution of sodium methoxide (0.5 M in MeOH, 1.89 L, 0.95 mol) was treated with formamidine hydrochloride (39.0 g, 0.48 mol) under N_2. The mixture was stirred at RT for 1 h. Diethyl allylmalonate (91.5 mL, 0.46 mol) was added to the above mixture, and the resulting reaction mixture was stirred at RT for 36 h. The reaction mixture was filtered and the filtrate was concentrated to afford a crude solid material. The crude material was dissolved in H_2O (1000 mL) and acidified with concentrated HCl. The solid was filtered and dried to afford 62.8 g (90%) of 6-hydroxy-5-(2-propen-1-yl)-4(1*H*)-pyrimidinone as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.65 (br s, 2H), 7.90 (s, 1H), 5.79−5.71 (m, 1H), 4.92 (app dd, J = 17.2, 2.0 Hz, 2H), 2.96 (d, J = 6.0 Hz, 2H). LCMS (ESI): m/z 153 $[M + H]^+$. Under N_2, 6-hydroxy-5-(2-propen-1-yl)-4(1*H*)-pyrimidinone (19.0 g, 125.0 mmol) was treated with phosphorus oxychloride (200 mL). The mixture heated at reflux for 4 h and then allowed to cool to RT. The reaction mixture was poured very slowly onto ice-cold (5 °C) water (2000 mL) with vigorous stirring. The mixture was extracted with CH_2Cl_2. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and the filtrate concentrated to afford 22.7 g (96%) of 4,6-dichloro-5-(2-propen-1-yl)pyrimidine (**17**) as a light-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (s, 1H), 5.90−5.80 (m, 1H), 5.17−5.09 (app m, 2H), 3.65 (app d, J = 6.4 Hz, 2H). LCMS (ESI): m/z 190 $[M + H]^+$. A slurry of NaH (7.94 g, 60% dispersion in mineral oil, washed with anhydrous toluene) in THF (50 mL) under N_2 at RT was treated with 2-fluoro-4-(methylsulfonyl)aniline (12.5 g, 66.1 mmol) in THF (150 mL). The mixture was stirred at RT for 1 h and then treated with a solution of **17** (12.5 g, 66.1 mmol) in THF (50 mL). The resulting reaction mixture was heated at reflux for 3 h, and then the mixture was allowed to cool to room temperature, poured slowly onto H_2O (600 mL), and then extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and the filtrate concentrated. The crude product was crystallized from EtOAc to give 10.3 g of solid material. The mother liquor was concentrated and purified by flash chromatography to give an additional 9.35 g of product. A total yield of 19.7 g (87%) of 6-chloro-*N*-[2-fluoro-4-(methylsulfonyl)phenyl]-5-(2-propen-1-yl)-4-pyrimidinamine (**19**) was obtained as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (s, 1H), 8.29 (s, 1H), 7.83 (dd, J = 9.2, 1.6 Hz, 1H), 7.78−7.72 (m, 2H), 5.96−5.86 (m, 1H), 5.10 (dd, J = 10.4, 1.2 Hz, 1H), 5.05 (dd, J = 16.0, 1.6 Hz, 1H), 3.58 (d, J = 5.6 Hz, 2H), 3.27 (s, 3H). LCMS (ESI): m/z 342 $[M + H]^+$. A stream of ozone was bubbled into a solution of **19** (15 g, 44 mmol) in CH_2Cl_2 (600 mL) and MeOH (150 mL) at −78 °C for 4 h, at which time the solution turned light-blue. A stream of N_2 was bubbled through the solution until the blue disappeared. Solid $NaBH_4$ (6.7 g, 176 mmol) was added portionwise over 10 min, and the reaction was stirred at −78 °C for 4 h and allowed to warm to RT overnight. The reaction mixture was carefully poured onto 1N HCl (1 L) and then was extracted with EtOAc (4 × 500 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford crude 2-(4-chloro-6-((2-fluoro-4-(methylsulfonyl)phenyl)-amino)pyrimidin-5-yl)ethanol (**20**, 15 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.57 (s, 1H), 8.38 (s, 1H), 8.03 (t, J = 8.2 Hz, 1H), 7.82 (dd, J = 10.4, 2.0 Hz, 1H), 7.74 (dd, J = 8.6, 1.8 Hz, 1H), 3.73 (t, J = 5.8 Hz, 2H), 3.25 (s, 3H), 2.97 (t, J = 5.8 Hz, 2H). LCMS (ESI): m/z 346 $[M + H]^+$. A solution of **20** (15 g, 44 mmol) in CH_2Cl_2 (250 mL) was cooled to 5 °C and treated with Et_3N (36.4 mL, 263 mmol) and Ms_2O (15.3 g, 88 mmol), and the mixture was stirred and allowed to warm to RT over a 15 h period. The reaction was diluted with CH_2Cl_2 (500 mL), quenched by the addition of water, and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (0→2% MeOH/$CHCl_3$) afforded 4-chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (**21**, 6.6 g, 46%) as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H), 7.94 (app t, J = 7.6 Hz, 1H), 7.90 (dd, J = 15.6, 1.6 Hz, 1H), 7.79 (dd, J = 8.4, 2.0 Hz, 1H), 4.20 (t, J = 8.4 Hz, 2H), 3.27 (s, 3H), 3.23 (t, J = 8.8 Hz, 2H). LCMS (ESI): m/z 328 $[M + H]^+$. A slurry of NaH (0.73 g, 60% dispersion in mineral oil, washed with anhydrous toluene) in anhydrous THF (15 mL) was treated with a solution of 1-methylethyl 4-hydroxy-1-piperidinecarboxylate (**22**, 1.09 g, 5.80 mmol) in THF (15 mL). The mixture was heated at reflux for 0.5 h and then allowed to cool to RT. A solution of **21** (2.0 g, mmol) in THF (30 mL) was added, and the reaction was heated at reflux for 1.5 h. The reaction mixture was allowed to cool to RT, poured onto H_2O (150 mL), and then extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and then concentrated. The crude product was purified by flash chromatography (0→2% MeOH/$CHCl_3$) to afford **3** (1.96 g, 71%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.96 (app t, J = 8.4 Hz, 1H), 7.84 (dd, J = 11.2, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 5.30 −5.24 (m, 1H), 4.76 (septuplet, J = 6.0 Hz, 1H), 4.14 (t, J = 8.4 Hz, 2H), 3.70−3.64 (m, 2H), 3.25 (s, 3H), 3.40−3.21 (m, 2H), 3.05 (t, J = 8.8 Hz, 2H), 1.95−1.90 (m, 2H), 1.67−1.51 (m, 2H), 1.17 (d, J = 6.0 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_5S$ $[M + H]^+$ 479.1764, obsd 479.1765.

1-Methylethyl 4-({1-[2-Fluoro-4-(methylsulfonyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (10). Compound **10** was prepared as a white solid in 10% overall yield from **5** in a similar manner to that described for **2** using 4-bromo-2-fluoro-1-iodobenzene. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.79 (dd, J = 11.6, 2.0 Hz, 1H), 7.68 (dd, J = 8.4, 2.0 Hz, 1H), 7.59 (app t, J = 8.4 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.56 (d, J = 8.4 Hz, 2H), 6.36 (dd, J = 7.6,

dx.doi.org/10.1021/jm301404a | J. Med. Chem. XXXX, XXX, XXX−XXX

4.4 Hz, 1H), 4.76 (septuplet, J = 6.4 Hz, 1H), 4.58 (m, 1H), 4.0 (t, J = 8.4 Hz, 1H), 3.68−3.57 (m, 2H), 3.30−3.21 (m, 2H), 3.22 (s, 3H), 3.02 (t, J = 8.8 Hz, 2H), 1.92−1.82 (m, 2H), 1.61−1.52 (m, 2H), 1.17 (d, J = 6.4 Hz, 6H). HRMS (ESI): m/z calcd for $C_{24}H_{29}FN_2O_5S$ $[M + H]^+$ 461.1859, obsd 461.1860.

***tert*-Butyl 4-((7-(4-(Methylsulfonyl)phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)oxy)piperidine-1-carboxylate (14).** 7-(4-Bromophenyl)-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**12**) was prepared as an off-white solid in 30% yield from 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine in a similar manner to that described for **6** using 4-bromo-1-iodobenzene. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 8.15 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.80 (m, 2H), 7.68 (d, J = 8.5 Hz, 1H), 6.89 (m, 1H). LRMS (ESI): m/z 310/308 $[M + H]^+$. A solution of **12** (420 mg, 1.36 mmol) in DMF (5 mL) was treated with *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (1.2 g, 3.6 mmol) and Cs_2CO_3 (0.72 g, 3.6 mmol), and the mixture was stirred at heated at 110 °C for 18 h under N_2. The mixture was allowed to cool and then was diluted with EtOAc and water. The organic layer was washed with water and brine dried over Na_2SO_4, and filtered. The filtrate was concentrated and purified by flash chromatography to give *tert*-butyl 4-((7-(4-bromophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)oxy)piperidine-1-carboxylate (**13**, 0.45 g, 70%) as a white foam. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.84 (m, 2H), 7.74 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 6.75 (m, 1H), 5.48 (m, 1H), 3.70 (m, 2H), 3.23 (m, 2H), 1.98 (m, 2H), 1.66 (m, 2H), 1.40 (s, 9H). LRMS (ESI): m/z 475/473 $[M + H]^+$. *tert*-Butyl 4-((7-(4-(methylsulfonyl)phenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)oxy)-piperidine-1-carboxylate (**14**) was prepared as an off-white solid in 84% yield from **13** in a similar manner to that described for **7**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.51 (s, 1H), 8.21 (d, J = 8.8 Hz, 2H), 8.09 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 3.7 Hz, 1H), 6.83 (d, J = 3.7 Hz, 1H), 5.50 (m, 1H), 3.74−3.66 (m, 2H), 3.27 (s, 3H), 2.48 (m, 2H), 2.03−1.99 (m, 2H), 1.70−1.62 (m, 2H), 1.40 (s, 9H). LRMS (ESI): m/z 473 $[M + H]^+$.

1-Methylethyl 4-({7-[4-(Methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (23). Compound **23** was prepared as an off-white solid in 34% overall yield from **17** in a similar manner to that described for **3** using 4-bromoaniline. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.98−7.90 (m, 4H), 5.38 (m, 1H), 4.93 (septuplet, J = 6.4 Hz, 1H), 4.15 (t, J = 8.8 Hz, 2H), 3.83 (br m, 2H), 3.37−3.30 (m, 2H), 3.12 (t, J = 8.8 Hz, 2H), 3.04 (s, 3H), 2.12−1.96 (m, 2H), 1.80−1.69 (m, 2H), 1.25 (d, J = 6.4 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{28}N_4O_5S$ $[M + H]^+$ 477.1859, obsd 477.1857.

1-Methylethyl 4-{[7-(4-Cyano-2-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate (25). 1-Methylethyl 4-{[7-(4-bromo-2-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate (**24**) was prepared as an off-white solid in 19% overall yield from **17** in a similar manner to that described for **3** using 4-bromo-2-fluoroaniline. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (s, 1H), 7.63 (dd, J = 10.8, 2.0 Hz, 1H), 7.56 (app t, J = 8.4 Hz, 1H), 7.42 (dd, J = 8.8, 2.0 Hz, 1H), 5.25 (m, 1H), 4.75 (septuplet, J = 6.4 Hz, 1H), 4.00 (t, J = 9.2 Hz, 2H), 3.72−3.68 (m, 2H), 3.22 (m, 2H), 3.02 (t, J = 8.8 Hz, 2H), 1.94−1.89 (m, 2H), 1.60−1.55 (m, 2H), 1.17 (d, J = 6.4 Hz, 6H). LCMS (ESI): m/z 481 $(M + H)^+$. A solution of **24** (100 mg, 0.209 mmol) in NMP (2 mL) was treated with CuCN (42 mg, 0.47 mmol) under N_2. The resulting mixture was heated to 150 °C for 15 h. The mixture was cooled to RT, poured onto H_2O (25 mL), and the mixture extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash SiO_2 column chromatography to afford **25** (76 mg, 85%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.23 (s, 2H), 7.95−7.89 (m, 2H), 7.68 (dd, J = 8.0, 2.0 Hz, 1H), 5.27 (m, J = 4.0 Hz, 1H), 4.76 (septuplet, J = 6.4 Hz, 1H), 4.14 (t, J = 8.0 Hz, 2H), 3.70−3.64 (m, 2H), 3.25−3.21 (m, 2H), 3.04 (t, J = 8.4 Hz, 2H), 1.95−1.90 (m, 2H), 1.61−1.53 (m, 2H), 1.17 (d, J = 6.0 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{24}FN_5O_3$ $[M + H]^+$ 426.1942, obsd 426.1942.

1-Methylethyl 4-({7-[2-Fluoro-4-(1,3-thiazol-2-yl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (26). A solution of **24** (108 mg, 0.23 mmol) in THF (4 mL) under N_2 was treated with $PdCl_2(Ph_3P)_2$ (16 mg, 0.023 mmol) and 2-(tributylstannanyl)-1,3-thiazole (85 mg, 0.23 mmol), and the reaction mixture was refluxed for 12 h. The mixture was quenched by the addition of water and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography afforded **26** (66 mg, 61%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (s, 1H), 7.92 (d, J = 3.2 Hz, 1H), 7.84−7.79 (m, 2H), 7.78−7.74 (m, 2H), 5.26 (m, 1H), 4.76 (septuplet, J = 6.0 Hz, 1H), 4.10 (t, J = 8.8 Hz, 1H), 3.71−3.65 (m, 2H), 3.25−3.21 (m, 2H), 3.05 (t, J = 8.8 Hz, 2H), 1.95−1.91 (m, 2H), 1.61−1.53 (m, 2H), 1.17 (d, J = 6.4 Hz, 6H). HRMS (ESI): m/z calcd for $C_{24}H_{26}FN_5O_3S$ $[M + H]^+$ 484.1819, obsd 484.1817.

1-Methylethyl 4-({7-[2-Fluoro-4-(1-methyl-1*H*-pyrrol-2-yl)-phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (27). Compound **27** was prepared as a white solid in 12% yield from **24** in a similar manner to that described for **26** using 1-methyl-2-(tributylstannanyl)-1*H*-pyrrole. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.36 (dd, J = 12.4, 2.0 Hz, 1H), 7.27 (dd, J = 8.4, 1.6 Hz, 1H), 6.84 (t, J = 2.0 Hz, 1H), 6.23 (dd, J = 3.6, 2.0 Hz, 1H), 6.04 (t, J = 3.2 Hz, 1H), 5.28−5.22 (m, 1H), 4.76 (septuplet, J = 6.0 Hz, 1H), 4.04 (t, J = 9.2 Hz, 2H), 3.67 (s, 3H), 3.71−3.65 (m, 2H), 3.23 (app t, J = 10.0 Hz, 2H), 3.04 (t, J = 9.2 Hz, 2H), 1.95−1.90 (m, 2H), 1.61−1.52 (m, 2H), 1.17 (d, J = 6.0 Hz, 6H). HRMS (ESI): m/z calcd for $C_{26}H_{30}FN_5O_3$ $[M + H]^+$ 480.2411, obsd 480.2411.

1,1-Dimethylethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)-phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (28). Compound **28** was prepared as a light-yellow solid in 73% yield from **21** in a similar manner to that described for **3** using 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.96 (app t, J = 7.6 Hz, 1H), 7.84 (dd, J = 11.2, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 5.26 (m, 1H), 4.14 (t, J = 8.0 Hz, 2H), 3.68−3.62 (m, 2H), 3.25 (s, 3H), 3.18−3.16 (m, 2H), 3.05 (t, J = 9.2 Hz, 2H), 1.94−1.89 (m, 2H), 1.59−1.53 (m, 2H), 1.39 (s, 9H). HRMS (ESI): m/z calcd for $C_{23}H_{29}FN_4O_5S$ $[M + H]^+$ 493.1921, obsd 493.1921.

Methyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (29). A solution of **28** (1.0 g, 2.0 mmol) in CH_2Cl_2 (40 mL) was treated with CF_3CO_2H (10 mL) at RT and stirred for 2 h. The reaction mixture was concentrated and then redissolved in CH_2Cl_2 (20 mL) and treated with Et_3N (1.7 mL, ∼6 equiv). A portion of the material (2.2 mL, ∼0.20 mmol) was treated with methyl chloroformate (200 μL) at RT for 18 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and then washed with water and brine, dried over Na_2SO_4, and then concentrated to afford the crude product, which was purified by flash chromatography to afford **29** (76 mg, 85%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.84 (dd, J = 11.2, 2.0 Hz, 1H), 7.73 (dd, J = 8.4, 2.4 Hz, 1H), 5.30−5.22 (m, 1H), 4.14 (t, J = 8.4 Hz, 2H), 3.58 (s, 3H), 3.70−3.64 (m, 2H), 3.28−3.24 (app br m, 2H), 3.25 (s, 3H), 3.05 (t, J = 8.8 Hz, 2H), 1.96−1.91 (m, 2H), 1.64−1.54 (m, 2H). HRMS (ESI): m/z calcd for $C_{20}H_{23}FN_4O_5S$ $[M + H]^+$ 451.1451, obsd 451.1452.

Ethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (30). Compound **30** was prepared as a white solid in 91% yield from **28** in a similar manner to that described for **29** using ethyl chloroformate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.96 (t, J = 7.6 Hz, 1H), 7.83 (dd, J = 11.2, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 5.28−5.24 (m, 1H), 4.14 (t, J = 8.4 Hz, 2H), 4.02 (q, J = 7.2 Hz, 2H), 3.71−3.65 (m, 2H), 3.26−3.24 (br s, 2H), 3.25 (s, 3H), 3.05 (t, J = 8.8 Hz, 2H), 1.96−1.90 (br m, 2H), 1.62−1.54 (m, 2H), 1.17 (t, J = 6.8 Hz, 3H). HRMS (ESI): m/z calcd for $C_{21}H_{25}FN_4O_5S$ $[M + H]^+$ 465.1605, obsd 465.1605.

***n*-Propyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (31).** Compound **31** was prepared as a white solid in 75% yield from **28** in a similar manner to that described for **29** using *n*-propyl chloroformate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.84 (dd, J = 10.8, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.4 Hz, 1H), 5.30−5.24 (m, 1H), 4.14 (t, J = 8.4 Hz, 2H), 3.94 (t, J = 6.8 Hz,

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2H), 3.72−3.66 (m, 2H), 3.30−3.24 (br m, 2H), 3.05 (t, J = 8.4 Hz, 2H), 1.98−1.88 (m, 2H), 1.62−1.52 (m, 4H), 0.87 (t, J = 7.2 Hz, 2H). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_5S$ $[M + H]^+$ 479.1764, obsd 479.1764.

***n*-Butyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (32).** Compound **32** was prepared as a white solid in 77% yield from **28** in a similar manner to that described for **29** using *n*-butyl chloroformate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.84 (dd, J = 10.8, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.4 Hz, 1H), 5.30−5.24 (m, 1H), 4.14 (t, J = 8.0 Hz, 2H), 3.98 (t, J = 6.4 Hz, 2H), 3.71−3.66 (m, 2H), 3.26−3.24 (br s, 2H), 3.25 (s, 3H), 3.05 (t, J = 8.8 Hz, 2H), 1.96−1.90 (m, 2H), 1.62−1.49 (m, 4H), 1.36−1.26 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H). HRMS (ESI): m/z calcd for $C_{23}H_{29}FN_4O_5S$ $[M + H]^+$ 493.1921, obsd 493.1920.

2-Methylpropyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (33). Compound **33** was prepared as a white solid in 83% yield from **21** in a similar manner to that described for **3** using 2-methylpropyl 4-hydroxy-1-piperidinecarboxylate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.96 (app t, J = 8.0 Hz, 1H), 7.84 (dd, J = 10.8, 1.6 Hz, 1H), 7.74 (dd, J = 8.8, 2.0 Hz, 1H), 5.28 (m, 1H), 4.14 (t, J = 8.0 Hz, 2H), 3.78 (d, J = 6.8 Hz, 2H), 3.71−3.68 (m, 2H), 3.25 (s, 3H), 3.30−3.27 (m, 2H), 3.05 (t, J = 8.8 Hz, 2H), 1.97−1.91 (m, 2H), 1.88−1.80 (m, 1H), 1.63−1.54 (m, 2H), 0.87 (d, J = 6.8 Hz, 6H). HRMS (ESI): m/z calcd for $C_{23}H_{29}FN_4O_5S$ $[M + H]^+$ 493.1921, obsd 493.1920.

2,2-Dimethylpropyl 4-({7-[2-Fluoro-4-(methylsulfonyl)-phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (34). Compound **34** was prepared as a white solid in 72% yield from **21** in a similar manner to that described for **3** using 2,2-dimethylpropyl 4-hydroxy-1-piperidinecarboxylate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H), 7.96 (app t, J = 8.0 Hz, 1H), 7.84 (dd, J = 10.8, 1.6 Hz, 1H), 7.74 (dd, J = 8.8, 2.0 Hz, 1H), 5.29 (m, 1H), 4.14 (t, J = 8.4 Hz, 2H), 3.70 (s, 2H), 3.73−3.64 (m, 2H), 3.25 (s, 3H), 3.30−3.27 (m, 2H), 3.06 (t, J = 8.8 Hz, 2H), 1.97−1.90 (m, 2H), 1.62−1.52 (m, 2H), 0.89 (s, 9H). HRMS (ESI): m/z calcd for $C_{24}H_{31}FN_4O_5S$ $[M + H]^+$ 507.2077, obsd 507.2078.

2-Fluoroethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (35). Compound **35** was prepared as a white solid in 58% yield from **28** in a similar manner to that described for **29** using 2-fluoroethyl chloridocarbonate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.84 (dd, J = 10.8, 2.4 Hz, 1H), 7.74 (dd, J = 8.8, 2.0 Hz, 1H), 5.31−5.25 (m, 1H), 4.65 (app t, J = 4.0 Hz, 1H), 4.53 (app t, J = 3.6 Hz, 1H), 4.27 (app t, J = 4.0 Hz, 1H), 4.19 (app t, J = 4.0 Hz, 1H), 4.14 (t, J = 8.0 Hz, 2H), 3.70 (m, 2H), 3.28−3.25 (br s, 2H), 3,25 (s, 3H), 3.06 (t, J = 8.8 Hz, 2H), 1.98−1.90 (m, 2H), 1.65−1.56 (m, 2H). HRMS (ESI): m/z calcd for $C_{21}H_{24}F_2N_4O_5S$ $[M + H]^+$ 483.1514, obsd 483.1514.

2-(Methyloxy)ethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)-phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (36). Compound **36** was prepared as a white solid in 65% yield from **28** in a similar manner to that described for **29** using 2-(methyloxy)ethyl chloroformate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.96 (t, J = 7.6 Hz, 1H), 7.84 (dd, J = 11.2, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 5.30−5.26 (m, 1H), 4.16−4.09 (m, 2H), 3.72−3.66 (m, 2H), 3.50 (t, J = 4.4 Hz, 2H), 3.24 (s, 3H), 3.28−3.24 (br s, 2H), 3.05 (t, J = 8.8 Hz, 2H), 5.30−5.26 (m, 1H), 4.16−4.09 (m, 2H), 3.72−3.66 (m, 2H), 3.50 (t, J = 4.4 Hz, 2H), 3.28−3.24 (br s, 2H), 3.24 (s, 6H), 3.05 (t, J = 8.8 Hz, 2H), 1.98−1.90 (m, 2H), 1.63−1.54 (m, 2H). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_6S$ $[M + H]^+$ 495.1714, obsd 495.1715.

***S*-Methyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (37).** Compound **37** was prepared as a white solid in 85% yield from **28** in a similar manner to that described for **29** using *S*-methyl chloroformate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.96 (app t, J = 8.4 Hz, 1H), 7.84 (dd, J = 10.8, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 5.36−5.28 (m, 2H), 4.14 (t, J = 8.0 Hz, 2H), 3.74 (br s, 2H), 3.42−3.34 (m, 2H), 3.25 (s, 3H), 3.06 (t, J = 8.8 Hz, 2H), 2.24 (s, 3H), 1.96 (br s, 2H), 1.62 (m, 2H). HRMS (ESI): m/z calcd for $C_{20}H_{23}FN_4O_4S_2$ $[M + H]^+$ 467.1222, obsd 467.1222.

***S*-Ethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (38).** Compound **38** was prepared as a white solid in 87% yield from **28** in a similar manner to that described for **29** using *S*-ethyl chloroformate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.84 (dd, J = 11.2, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 5.36−5.29 (m, 1H), 4.14 (t, J = 8.4 Hz, 2H), 3.76 (app br s, 2H), 3.41−3.36 (m, 2H), 3.25 (s, 3H), 3.06 (t, J = 8.8 Hz, 2H), 2.81 (q, J = 7.2 Hz, 2H), 1.96 (br s, 2H), 1.62 (br s, 2H), 1.18 (t, J = 7.6 Hz, 2H). HRMS (ESI): m/z calcd for $C_{21}H_{25}FN_4O_4S_2$ $[M + H]^+$ 481.1380, obsd 481.1380.

***S*-(1-Methylethyl) 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbothioate (39).** A solution of **28** (2.0 g, 4.1 mmol) was treated with a 20% solution of CF_3CO_2H in CH_2Cl_2 (50 mL) at RT, and the mixture was stirred for 3 h. The reaction mixture was concentrated and then redissolved in CH_2Cl_2 (150 mL) and treated with 1,1′-(oxomethanediyl)bis-1*H*-imidazole (725 mg, 4.47 mmol) at 5 °C. The reaction mixture was allowed to warm to ambient temperature and allowed to stir for 24 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with water, and the organic layer was dried over Na_2SO_4 and then concentrated to afford crude product, which was recrystallized from CH_2Cl_2 to give (1.9 g, 97%) of 7-[2-fluoro-4-(methylsulfonyl)phenyl]-4-{[1-(1*H*-imidazol-1-ylcarbonyl)-4-piperidinyl]oxy}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (s, 1H), 8.02 (s, 1H), 7.96 (app t, J = 8.0 Hz, 1H), 7.84 (dd, J = 11.2, 2.4 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 7.47 (s, 1H), 7.02 (s, 1H), 5.40−5.28 (m, 1H), 4.15 (t, J = 8.4 Hz, 2H), 3.71 (m, 2H), 3.48−3.42 (m, 2H), 3.25 (s, 3H), 3.07 (t, J = 9.2 Hz, 2H), 2.10−2.02 (m, 2H), 1.83−1.75 (m, 2H); LRMS (ESI): m/z 487 $(M + H)^+$. A solution of 7-[2-fluoro-4-(methylsulfonyl)phenyl]-4-{[1-(1*H*-imidazol-1-ylcarbonyl)-4-piperidinyl]oxy}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (1.9 g, 3.90 mmol) in CH_3CN (30 mL) and CH_2Cl_2 (30 mL) was treated with methyl iodide (1.46 mL, 23.5 mmol) at RT under N_2. The reaction mixture was stirred at RT for 24 h and then concentrated to afford 1-{[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]-carbonyl}-3-methyl-1*H*-imidazol-3-ium iodide (2.46 g, 100%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.55 (s, 1H), 8.24 (s, 1H), 8.03 (app t, J = 3.6 Hz, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.86−7.82 (m, 2H), 7.75 (dd, J = 8.4, 2.0 Hz, 1H), (app t, J = 8.0 Hz, 1H), 5.42 (m, 1H), 4.16 (t, J = 8.4 Hz, 2H), 3.90 (s, 3H), 3.71 (br s, 2H), 3.50 (br s, 2H), 3.25 (s, 3H), 3.07 (t, J = 9.2 Hz, 2H), 2.12−2.04 (br m, 2H), 1.88−1.80 (m, 2H). A suspension of the above salt (315 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) was treated with Et_3N (70 μL, 0.5 mmol) and isopropylthiol (38 mg, 0.5 mmol) at RT under N_2. The reaction mixture was stirred at RT for 18 h and then quenched by the addition of water. The aqueous was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and concentrated. Purification by flash chromatography afforded **39** (156 mg, 63%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H), 7.96 (app t, J = 8.0 Hz, 1H), 7.84 (app br d, J = 10.8 Hz, 1H), 7.74 (app br d, J = 6.8 Hz, 1H), 5.30−5.28 (m, 1H), 4.14 (t, J = 8.4 Hz, 2H), 3.46 (m, 1H), 3.37−3.30 (br m, 2H), 3.25 (s, 3H), 3.06 (t, J = 8.4 Hz, 2H), 1.94 (app br s, 2H), 1.61 (app br s, 2H), 1.26 (d, J = 6.4 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_4S_2$ $[M + H]^+$ 495.1536, obsd 495.1536.

Phenyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarbodithioate (40). Compound **40** was prepared as a white solid in 55% yield from **28** in a similar manner to that described for **29** using phenyl chloridodithiocarbonate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (s, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.85 (dd, J = 11.2, 2.0 Hz, 1H), 7.75 (dd, J = 8.4, 1.6 Hz, 1H), 7.48−7.40 (m, 5H), 5.48−5.42 (m, 1H), 4.46 (app br s, 1H), 4.22 (br s, 2H), 4.16 (t, J = 8.4 Hz, 2H), 4.06 (br s, 2H), 3.26 (s, 3H), 3.09 (t, J = 8.8 Hz, 2H), 2.20−2.06 (br s, 2H), 1.92−1.72 (br s, 2H). HRMS (ESI): m/z calcd for $C_{25}H_{25}FN_4O_3S_3$ $[M + H]^+$ 545.1152, obsd 545.1152.

dx.doi.org/10.1021/jm301404a | *J. Med. Chem.* XXXX, XXX, XXX−XXX

4-{[1-(Ethylsulfonyl)-4-piperidinyl]oxy}-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]-pyrimidine (41). Compound **41** was prepared as a tan solid in 70% yield from **28** in a similar manner to that described for **29** using ethanesulfonyl chloride. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.86 (app t, J = 8.5 Hz, 1H), 7.78−7.68 (m, 2H), 5.42−5.25 (m, 1H), 4.26 (t, J = 8.5 Hz, 2H), 3.69−3.52 (m, 2H), 3.35−3.23 (m, 2H), 3.19 (t, J = 8.5 Hz, 2H), 3.06 (s, 3H), 2.99 (q, J = 7.8 Hz, 2H), 2.20−2.05 (m, 2H), 1.98−1.81 (m, 2H), 1.38 (t, J = 8.5 Hz 3H). HRMS (ESI): m/z calcd for $C_{20}H_{25}FN_4O_5S_2$ $[M + H]^+$ 485.1329, obsd 485.1328.

7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-({1-[(1-methylethyl)sulfonyl]-4-piperidinyl}oxy)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (42). Compound **42** was prepared as a tan solid in 54% yield from **28** in a similar manner to that described for **29** using 2-propanesulfonyl chloride. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.91 (app t, J = 8.5 Hz, 1H), 7.87−7.60 (m, 2H), 5.49−5.20 (m, 1H), 4.31 (t, J = 8.5 Hz, 2H), 3.80−3.52 (m, 2H), 3.42−3.26 (m, 2H), 3.24−3.12 (m, 4 H), 2.23−1.99 (m, 2H), 1.98−1.81 (m, 2H), 1.97−1.75 (m, 2H), 1.32 (d, J = 6.8 Hz, 6H). HRMS (ESI): m/z calcd for $C_{21}H_{27}FN_4O_5S_2$ $[M + H]^+$ 499.1485, obsd 499.1484.

4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-*N*,*N*-dimethyl-1-piperidinesulfonamide (43). Compound **43** was prepared as a tan solid in 54% yield from **28** in a similar manner to that described for **29** using *N*,*N*-dimethylsulfamoyl chloride. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.00 (app t, J = 8.5 Hz, 1H), 7.76−7.67 (m, 2H), 5.38−5.29 (m, 1H), 4.19 (t, J = 8.5 Hz, 2H), 3.57−3.48 (m, 2H), 3.29−3.20 (m, 2H), 3.13 (t, J = 8.5 Hz, 2H), 3.04 (s, 3H), 2.84 (s, 6H), 2.13−2.02 (m, 2H), 1.96−1.85 (m, 2H). HRMS (ESI): m/z calcd for $C_{20}H_{26}FN_5O_5S_2$ $[M + H]^+$ 500.1438, obsd 500.1438.

***N*,*N*-Diethyl-2-[4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinyl]acetamide trifluoroacetate (44).** Compound **44** was prepared as a white solid in 37% yield from **28** in a similar manner to that described for **29** using 2-chloro-*N*,*N*-dimethylacetamide, diisopropylethylamine and a catalytic amount of sodium iodide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.96 (app t, J = 8.5 Hz, 1H), 7.76−7.73 (m, 2H), 5.58−5.39 (m, 1H), 4.22 (t, J = 8.5 Hz, 2H), 4.08 (s, 2H), 3.74−3.58 (m, 2H), 3.56−3.43 (m, 2H), 3.41−3.16 (m, 6H), 3.06 (s, 3H), 2.43−2.30 (m, 2H), 2.29−2.17 (m, 2H), 1.18−1.12 (m, 6H). HRMS (ESI): m/z calcd for $C_{24}H_{32}FN_5O_4S$ $[M + H]^+$ 506.2237, obsd 506.2236.

7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-({1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinyl}oxy)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (55). Sodium bicarbonate (41 g, 0.494 mol) was dissolved in water (20 mL) and cooled to 0 °C. A solution of 4-hydroxypiperidine (**45**, 25 g, 0.25 mol) in CH_2Cl_2 (75 mL) was added to the above solution with vigorous stirring. A solution of cyanogen bromide (28 g, 0.27 mol) in CH_2Cl_2 (25 mL) was then added and the ice bath was removed, and the mixture was stirred at ambient temperature for 18 h. Solid sodium carbonate (75 g) was then added until the pH was adjusted to ∼7, and then $MgSO_4$ (25 g) was added to remove water. The solids were removed via filtration and were washed several times with CH_2Cl_2. The filtrate was concentrated, and the resultant 4-hydroxy-1-piperidinecarbonitrile **46** (24.8 g) was used without purification. A solution of **46** (12.9 g, 0.1 mol) and *N*-hydroxy-2-methylpropanimidamide (12.8 g, 0.13 mol) in a mixture of EtOAc (500 mL) and ether (100 mL) was treated with a 1N solution of $ZnCl_2$ (120 mL, 0.12 mol) in ether. The mixture was stirred for 15 min, and the supernatant was decanted off. The residue was washed 2 times with 250 mL of ether, which was decanted off after each wash. The residue was then dissolved in a mixture of 4N HCl (50 mL) and EtOH (100 mL). The resulting solution was refluxed for 1 h, the solvent was reduced to about 25 mL, and 25 g of Na_2CO_3 was added along with 100 mL of CH_2Cl_2. The solids were removed via filtration. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give 1-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-4-piperidinol **47** (16 g) as a tan oil that was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04−3.74 (m, 3H), 3.44−3.20 (m, 2H), 2.78 (m, 1H), 2.05−1.80 (m, 2H), 1.74−1.49 (m, 2H), 1.38−1.13 (m, 6H). Compound **55** was prepared as a white solid in 55% yield from **21** in a similar manner to that described for **3** using **47**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (s, 1H), 7.99 (app t, J = 7.6 Hz, 1H), 7.87 (app br d, J = 10.8 Hz,1H), 7.78 (app br t, J = 8.4 Hz, 1H), 5.36 (br m, 1H), 4.18 (t, J = 8.8 Hz, 2H), 3.82−3.78 (m, 2H), 3.56−3.50 (m, 2H), 3.28 (s, 3H), 3.10 (t, J = 8.4 Hz, 2H), 2.83 (septuplet, J = 6.8 Hz, 1H), 2.09 (m, 2H), 1.78 (m, 2H), 1.20 (d, J = 6.8 Hz, 6H). HRMS (ESI): m/z calcd for $C_{23}H_{27}FN_6O_4S$ $[M + H]^+$ 503.1877, obsd 503.1879.

7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{[1-(5-fluoro-2-pyrimidinyl)-4-piperidinyl]oxy}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]-pyrimidine (56). A solution of 4-hydroxypiperidine (**45**, 1.53 g, 15.1 mmol) in acetonitrile (50 mL) was treated with diisopropylethylamine (7.9 mL, 45.3 mmol) and 5-fluoro-2-chloropyrimidine (**48**, 2.0 g, 15.1 mmol) under N_2, and the reaction mixture was refluxed for 10 h. The reaction was concentrated and then purified by flash chromatography to afford 1-(5-fluoro-2-pyrimidinyl)-4-piperidinol (**50**, 2.46 g, 83%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (s, 2H), 4.37−4.31 (m, 2H), 3.97−3.91 (m, 1H), 3.32−3.25 (m, 2H), 1.98−1.92 (m, 2H), 1.77 (br s, 1H), 1.57−1.48 (m, 2H). LCMS (ESI): m/z 198 $[M + H]^+$. Compound **56** was prepared as a white solid in 39% yield from **21** in a similar manner to that described for **3** using 1-(5-fluoro-2-pyrimidinyl)-4-piperidinol (**50**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 2H), 8.24 (s, 1H), 7.96 (app t, J = 7.6 Hz, 1H), 7.84 (dd, J = 10.8, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 1.6 Hz, 1H), 5.36 (m, 1H), 4.16−4.10 (m, 2H), 4.14 (t, J = 8.4 Hz, 2H), 3.55−3.44 (m, 2H), 3.25 (s, 3H), 3.05 (t, J = 8.8 Hz, 2H), 2.03−1.98 (m, 2H), 1.66−1.60 (m, 2H). HRMS (ESI): m/z calcd for $C_{22}H_{22}F_2N_6O_3S$ $[M + H]^+$ 461.1859, obsd 461.1859

4-{[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]oxy}-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]-pyrimidine (57). 1-(5-Ethyl-2-pyrimidinyl)-4-piperidinol (**51**) was prepared in a similar manner to that described for 1-(5-fluoro-2-pyrimidinyl)-4-piperidinol (**50**) using 5-ethyl-2-chloropyrimidine (**49**). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (s, 1H), 4.67 (br s, 1H), 4.24−4.18 (m, 2H), 3.68 (m, 2H), 3.19−3.12 (m, 2H), 2.38 (q, J = 7.6 Hz, 2H), 1.75−1.69 (m, 2H), 1.31−1.22 (m, 2H), 1.09 (t, J = 7.2 Hz, 3H). LRMS (ESI): m/z 207 $(M + H)^+$. Compound **57** was prepared as a white solid in 50% yield from **21** in a similar manner to that described for **3** using 1-(5-ethyl-2-pyrimidinyl)-4-piperidinol (**51**). ^{1}H NMR (400 MHz, DMSO-d_6): δ8.24 (s, 3H), 7.96 (app t, J = 8.4 Hz, 1H), 7.84 (dd, J = 10.8, 2.0 Hz, 1H), 7.74 (dd, J = 8.4, 2.0 Hz, 1H), 5.36 (m, 1H), 4.20−4.18 (m, 2H), 4.14 (t, J = 8.4 Hz, 2H), 3.51−3.45 (m, 2H), 3.25 (s, 3H), 3.05 (t, J = 8.8 Hz, 2H), 2.41 (q, J = 7.6 Hz, 2H), 2.01−1.97 (m, 2H), 1.65−1.48 (m, 2H), 1.11 (t, J = 7.6 Hz, 3H). HRMS (ESI): m/z calcd for $C_{24}H_{27}FN_6O_3S$ $[M + H]^+$ 499.1928, obsd 499.1932.

7-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{[1-(1,4,5,6-tetrahydro-2-pyrimidinyl)-4-piperidinyl]oxy}-6,7-dihydro-5*H*-pyrrolo-[2,3-*d*]pyrimidine (58). 1-(2-Pyrimidinyl)-4-piperidinol (**53**) was prepared in 81% yield as a white solid in a similar manner to that described for **50** using 2-chloropyrimidine. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 4.6 Hz, 2H), 6.49 (t, J = 4.8 Hz, 1H), 4.49−4.33 (m, 2H), 4.01−3.88 (m, 1H), 3.37−3.21 (m, 2H), 2.02−1.90 (m, 2H), 1.60−1.45 (m, 2H). LRMS (ESI): m/z 180 $(M + H)^+$. A solution of 1-(2-pyrimidinyl)-4-piperidinol (**53**, 300 mg, 1.67 mmol) in acetic acid (10 mL) was treated with 10% palladium on carbon (Degussa type, 100 mg) and concentrated hydrochloric acid (0.5 mL), and the mixture was placed under an atmosphere of hydrogen (40 psi) for 18 h at room temperature. The reaction mixture was then filtered and the solvent was removed to give 1-(1,4,5,6-tetrahydro-2-pyrimidinyl)-4-piperidinol **54** (304 mg, 84%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (m, 2H), 4.03−3.41 (m, 3H), 2.95−2.86 (m, 4H), 2.09−1.55 (m, 6H), 1.55−1.18 (m, 2H). Compound **58** was prepared as a white solid in 6% yield from **21** in a similar manner to that described for **3** using **54** and DMF as solvent. ^{1}H NMR (400 MHz, CD_3OD): δ 8.46 (s, 1H), 8.17 (s, 1H), 7.95 (app t, J = 8.5 Hz, 1H), 7.88−7.66 (m, 2H), 5.54−5.37 (m, 1H), 4.20 (t, J = 8.5 Hz, 2H), 3.75−3.57 (m, 2H), 3.49−3.33 (m, 6H), 3.19−3.07 (m, 5H), 2.21−2.06 (m, 2H), 2.01−1.76 (m, 4H). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_6O_3S$ $[M + H]^+$ 475.1928, obsd 475.1927.

1,1-Dimethylethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)-phenyl]-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (60). Compound **60** was prepared as a white solid in 15% overall yield from ethanimidamide hydrochloride and **16** in addition to 2-fluoro-4-(methylsulfonyl)aniline and 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate in a similar manner to that described for **3**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (m, 1H), 7.69

dx.doi.org/10.1021/jm301404a | *J. Med. Chem.* XXXX, XXX, XXX−XXX

(m, 2H), 5.38 (m, 1H), 4.25 (t, J = 7.3 Hz, 2H), 3.87 (m, 2H), 3.32 (m, 2H), 3.04 (m, 5H), 1.97 (m, 2H), 1.73 (m, 2H), 1.46 (s, 9H). HRMS (ESI): m/z calcd for $C_{24}H_{31}FN_4O_5S$ $[M + H]^+$ 507.2077, obsd 507.2078.

1-Methylethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-2-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (61). Compound **61** was prepared as a white solid in 98% overall yield from **56** in a similar manner to that described for the Boc deprotection and isopropylcarbamate formation of **2**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (m, 2H), 7.69 (m, 2H), 5.38 (m, 1H), 4.93 (m, 1H), 4.19 (t, J = 7.3 Hz, 2H), 3.75 (m, 2H), 3.35 (m, 2H) 3.05 (m, 5H), 2.47 (s, 3H), 1.95 (m, 2H), 1.71 (m, 2H), 1.17 (d, J = 6.8 Hz, 6H). HRMS (ESI): m/z calcd for $C_{23}H_{29}FN_4O_5S$ $[M + H]^+$ 493.1921, obsd 493.1920.

1-Methylethyl 4-({2-Amino-7-[2-fluoro-4-(methylsulfonyl)-phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (73). A solution of 2-fluoro-4-(methylsulfonyl)aniline (**19**, 3.3 g, 17.3 mmol) in acetonitrile (10 mL) under N_2 was treated with 6,6-dimethyl-5,6-dioxaspiro[2.5]octane (**63**, 9.7 g, 57 mmol) and stirred and heated at 60 °C for 3 h. The reaction mixture was allowed to cool to RT and was concentrated. The residue was heated at 70 °C for 5 h to afford **64**. Methanol (15 mL) and concentrated H_2SO_4 (0.2 mL) were added, and the mixture was heated to reflux for 2 h. The mixture was concentrated, and the residue was purified by flash chromatography to give methyl 1-[2-fluoro-4-(methylsulfonyl)phenyl]-2-oxo-3-pyrrolidinecarboxylate **65** (2.3 g, 43%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (br d, J = 10.0 Hz, 1H), 7.81−7.73 (m, 2H), 3.85 (br t, J = 7.2 Hz, 2H), 3.75 (t, J = 8.7 Hz, 1H), 3.68 (s, 3H), 3.30−3.25 (br s, 3H), 2.45−2.35 (m, 2H). LRMS (ESI): m/z 316 $(M + H)^+$. A solution of **65** (2.3 g, 7.2 mmol) in THF (100 mL) under N_2 was treated with P_2S_5 (3.9 g, 8.7 mmol) and was heated at 70 °C for 12 h. The mixture was filtered and the solid washed twice with EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography to afford methyl 1-[2-fluoro-4-(methylsulfonyl)phenyl]-2-thioxo-3-pyrrolidinecarboxylate **66** (1.2 g, 50%) as a pale-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (br d, J = 9.3 Hz, 1H), 7.89 (br d, J = 8.3 Hz, 1H), 7.81 (app t, J = 7.5 Hz, 1H), 4.12−4.08 (m, 3H), 3.70 (s, 3H), 3.30 (s, 3H), 2.60−2.50 (m, 2H). LRMS (ESI): m/z 332 $[M + H]^+$. A solution of guanidine hydrochloride (**67**, 0.3 g, 3.2 mmol) in anhydrous MeOH (3 mL) was treated with freshly prepared 1M NaOMe/MeOH (3.2 mL, 3.2 mmol), and the mixture was stirred for 30 min at ambient temperature under N_2. The mixture was filtered and the filtrate added to **62** (0.22 g, 0.64 mmol). The yellow mixture was stirred for 5 min then concentrated and heated stepwise from 60 to 90 °C with a slight vacuum for 1 h. The mixture was allowed to cool to ambient temperature, and H_2O was added. The pH was adjusted to 6 with 1 M HCl/H_2O, and the mixture was stirred at ambient temperature for 18 h. The solid was filtered and dried in vacuum for 2 h to provide 2-amino-7-[2-fluoro-4-(methylsulfonyl)phenyl]-1,5,6,7-tetrahydro-4*H*-pyrrolo[2,3-*d*]-pyrimidin-4-one **69** (0.12 g) as an yellow solid. LRMS (ESI): m/z 325 $[M + H]^+$. A suspension of the crude **69** (0.12 g, 0.36 mmol) in $POCl_3$ (1.2 mL) was carefully treated with $(i\text{-Pr})_2$NEt (0.13 mL, 0.1 g, 0.72 mmol), and the mixture was slowly heated to 70 °C. After 1 h, the mixture was concentrated and the residue was partitioned between EtOAc/CH_2Cl_2 and saturated $NaHCO_3$/H_2O. The organic phase was filtered, dried over Na_2SO_4, and concentrated to afford 4-chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]-pyrimidin-2-amine **71** (51 mg) as a dark-green solid. LRMS (ESI): m/z 343 $[M + H]^+$. Compound **73** was prepared as an off-white solid in 7% yield from **71** in a similar manner to that described for **3** using 1-methylethyl 4-hydroxy-1-piperidinecarboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10−8.00 (br s, 1H), 7.70−7.65 (m, 2H), 5.30 (br s, 1H), 4.90 (septuplet, J = 6.0 Hz, 1H), 4.85−4.60 (m, 2H), 4.15 (br t, J = 7.7 Hz, 2H), 3.85−3.70 (m, 2H), 3.40−3.30 (m, 2H), 3.05 (s, 3H), 2.95 (t, J = 8.5 Hz, 2H), 2.00−1.95 (m, 2H), 1.85−1.80 (m, 2H), 1.24 (d, J = 6.0 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{28}FN_5O_5S$ $[M + H]^+$ 494.1873, obsd 494.1872.

1-Methylethyl 4-{[7-[2-Fluoro-4-(methylsulfonyl)phenyl]-2-(methylamino)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-oxy}-1- piperidinecarboxylate (74). Compound **74** was prepared as an off-white foam in 15% overall yield from *N*-methylguanidine hydrochloride (**68**) and **66** in a similar manner to that described for **73**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15−8.05 (br s, 1H), 7.70−7.65 (m, 2H), 5.30 (br s, 1H), 4.90 (septuplet, J = 6.0 Hz, 1H), 4.85−4.60 (m, 1H), 4.15 (br t, J = 7.3 Hz, 2H), 3.85−3.70 (m, 2H), 3.40−3.30 (m, 2H), 3.05 (s, 3H), 2.95 (t, J = 8.5 Hz, 2H), 2.92 (d, J = 4.9 Hz, 3H), 2.00−1.95 (m, 2H), 1.85−1.80 (m, 2H), 1.24 (d, J = 6.0 Hz, 6H). HRMS (ESI): m/z calcd for $C_{23}H_{30}FN_5O_5S$ $[M + H]^+$ 508.2030, obsd 508.2030.

1-Methylethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}amino)-1-piperidinecarboxylate trifluoroacetate (77). A solution of 1,1-dimethylethyl 4-piperidinylcarbamate (512 mg, 2.6 mmol) in CH_2Cl_2 (25 mL) was treated with Et_3N (0.71 mL, 5.1 mmol) followed by the dropwise addition of isopropylchloroformate (1.0M in toluene, 2.8 mL, 2.8 mmol) via addition funnel at RT. The reaction mixture was stirred at RT for 17 h, then washed with water, dried over $MgSO_4$, filtered, and concentrated to afford 1-methylethyl 4-({[(1,1-dimethylethyl)oxy]-carbonyl}amino)-1-piperidinecarboxylate **75** (585 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.85 (septuplet, J = 6.4 Hz, 1H), 4.63−4.48 (m, 1H), 4.13−3.89 (m, 2H), 3.55 (br s, 1H), 2.82 (t, J = 11.7 Hz, 2H), 1.88−1.85 (m, 2H), 1.39 (s, 9H), 1.29−1.22 (m, 2H), 1.19 (d, J = 6.1 Hz, 6H). A solution of **21** (50 mg, 0.15 mmol) in DMF (1.5 mL) was treated with **75** (87 mg, 0.31 mmol) and K_2CO_3 (42 mg, 0.31 mmol), and the reaction mixture was sealed and heated in a microwave for 20 min at 200 °C. The reaction mixture was then heated in a microwave an additional 60 min at 220 °C. The reaction mixture was then diluted with water and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by reverse phase HPLC to give **77** (11 mg, 12%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.81−7.77 (m, 2H), 7.72−7.69 (m, 1H), 4.91 (septuplet, J = 6.4 Hz, 1H), 4.29 (t, J = 9.0 Hz, 2H), 4.23−4.12 (m, 2H), 3.79−3.68 (m, 1H), 3.43−3.38 (m, 2H), 3.09 (s, 3H), 2.96−2.86 (m, 2H), 1.97−1.93 (m, 2H), 1.77−1.67 (m, 2H), 1.25 (d, J = 6.4 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{28}FN_5O_4S$ $[M + H]^+$ 478.1924, obsd 478.1924.

1-Methylethyl 4-[{7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}(methyl)amino]-1-piperidinecarboxylate trifluoroacetate (78). Compound **76** was prepared as a colorless oil in 87% yield from from 1,1-dimethylethyl methyl(4-piperidinyl)carbamate in a similar manner to that described for **75**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.88 (septuplet, J = 6.4 Hz, 1H), 4.28−4.16 (m, 3H), 2.77−2.71 (m, 2H), 2.68 (s, 3H), 1.62−1.57 (m, 2H), 1.55−1.50 (m, 2H), 1.44 (s, 9H), 1.21 (d, J = 6.4 Hz, 6H). Compound **78** was prepared as a yellow solid in 9% yield from **21** and **75** in a similar manner to that described for **77**. HRMS (ESI): m/z calcd for $C_{23}H_{30}FN_5O_4S$ $[M + H]^+$ 492.2081, obsd 492.2083.

1-Methylethyl 4-({7-[4-(Methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}thio)-1-piperidinecarboxylate (80). A solution of 4-bromopiperidine hydrochloride (5.0 g, 20.4 mmol) in dichloromethane (100 mL) under N_2 at 0 °C was treated with diisopropylethylamine (7.8 mL, 44.9 mmol) followed by the dropwise addition of a 1.0 M solution of isopropyl chloroformate in toluene (20.4 mL, 20.4 mmol). The mixture was stirred and allowed to warm to 25 °C over a 3 h period. The reaction was quenched by the addition of 1N HCl and diluted with EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give 1-methylethyl 4-bromo-1-piperidinecarboxylate as a colorless oil that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ4.91 (septuplet, J = 6.2 Hz, 1H), 4.35 (m, J = 3.8 Hz, 1H), 3.71 (m, 2H), 3.36 (m, 2H), 2.09 (m, 2H), 1.93 (m, 2H), 1.24 (d, J = 6.2 Hz, 6H). A solution of 1-methylethyl 4-bromo-1-piperidinecarboxylate (4.0 g, 16 mmol) in DMF (40 mL) under N_2 at 25 °C was treated with potassium thioacetate (3.4 g, 29.8 mmol), and the mixture was stirred and heated at 100 °C for 3.5 h. The reaction mixture was allowed to cool to 25 °C and was quenched by the addition of water and diluted with EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with water, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated to dark-brown oil. Purification by

dx.doi.org/10.1021/jm301404a | *J. Med. Chem.* XXXX, XXX, XXX−XXX

flash chromatography (80 g silica column, 10→20% EtOAc/hexane) afforded 1-methylethyl 4-(acetylthio)-1-piperidinecarboxylate (2.3 g, 59%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.91 (septuplet, J = 6.2 Hz, 1H), 4.35 (m, J = 3.8 Hz, 1H), 3.71 (m, 2H), 3.36 (m, 2H), 2.09 (m, 2H), 1.93 (m, 2H), 1.24 (d, J = 6.2 Hz, 6H). A solution of 1-methylethyl 4-(acetylthio)-1-piperidinecarboxylate (2.3 g, 9.4 mmol) in THF:water (1:1, 50 mL) under N_2 at 0 °C was treated with 1N NaOH (11.2 mL, 11.2 mmol), and the mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of aqueous citric acid, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine and were dried ($MgSO_4$) and concentrated to give a brown oil. Purification by flash chromatography (40 g silica column, 10→25% EtOAc/hexane) afforded 1-methylethyl 4-mercapto-1-piperidinecarboxylate **79** (1.6 g, 89%) as an amber oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.72 (septuplet, J = 6.4 Hz, 1H), 3.80 (overlapping br s, 2H), 2.96−2.79 (br m, 3H), 2.64 (d, J = 7.1 Hz, 1H), 1.90−1.82 (m, 2H), 1.38−1.27 (m, 2H), 1.15 (d, J = 6.4 Hz, 6H). A solution of **79** (82 mg, 0.43 mmol) in acetone (2 mL) was treated with **21** under N_2 at 25 °C followed by K_2CO_3 (89 mg, 0.64 mmol), and the mixture was stirred and heated in a sealed vial at 60 °C for 62 h. The reaction mixture was allowed to cool to 25 °C and was concentrated to ∼$^1/_3$ volume and purified by flash chromatography (12 g silica column, 10→60% EtOAc/hexane, 35 min gradient) to afford **80** (150 mg, 71%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H), 7.96 (t, J = 8.1 Hz, 1H), 7.85 (d, J = 11.2 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 4.74 (septuplet, J = 6.2 Hz, 1H), 4.15 (app t, J = 8.5 Hz, 2H), 4.11 (obscured m, 1H), 3.82 (br d, J = 12.7 Hz, 2H), 3.25 (s, 3H), 3.07 (br m, 2H), 2.99 (app t, J = 8.5 Hz, 2H), 2.01 (br d, J = 12.7 Hz, 2H), 1.52 (m, 2H), 1.16 (d, J = 6.2 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_4S_2$ $[M + H]^+$ 495.1536, obsd 495.1537.

1-Methylethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}sulfonyl)-1-piperidinecarboxylate (81). A solution of **80** (145 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) was treated with *m*-CPBA (77% maximum by weight, 105 mg, 0.47 mmol) under N_2 at 0 °C, and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture was quenched by the addition of methanol, concentrated to ∼$^1/_3$ volume, and purified by reverse phase HPLC (C18 column, 10→100% CH_3CN/H_2O + 0.5% trifluoroacetic acid, 10 min gradient) to give **81** (28 mg, 18%) as a white solid after lyophilization. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.02−7.97 (overlapping m, 2H), 7.88 (d, J = 8.2 Hz, 1H), 4.79 (septuplet, J = 6.0 Hz, 1H), 4.26 (app t, J = 8.0 Hz, 2H), 4.08 (br m, 2H), 3.84 (br m, 2H), 3.55 (app t, J = 8.0 Hz, 2H), 3.34 (s, 3H), 2.89 (br m, 2H), 1.95 (br d, J = 11.4 Hz, 2H), 1.54 (m, 2H), 1.20 (d, J = 6.0 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_6S_2$ $[M + H]^+$ 527.1432, obsd 527.1435.

(±)-1-Methylethyl 4-({7-[2-Fluoro-4-(methylsulfonyl)-phenyl]-6-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (86 and 87). A solution of allyl **19** (3.42 g, 10 mmol) in 3:2 acetone/H_2O (250 mL) was treated with $K_2OsO_4{\cdot}2H_2O$ (147 mg, 0.4 mmol). Solid $NaIO_4$ (8.56 g, 40 mmol) was added portionwise, and the reaction was stirred for 4 h. The workup gave 1,1-dimethylethyl [6-chloro-5-(2-oxoethyl)-4-pyrimidinyl][2-fluoro-4-(methylsulfonyl)phenyl]carbamate (**82**, 5.0 g, 100%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.63 (s, 1H), 8.82 (s, 1H), 7.95 (dd, J = 9.6, 2.0 Hz, 1H), 7.77 (dd, J = 8.4, 1.6 Hz, 1H), 7.59 (app t, J = 7.6 Hz, 1H), 3.93 (s, 2H), 3.30 (s, 3H), 1.38 (s, 9H). A solution of **82** (2.0 g, 4.51 mmol) in anhydrous THF (50 mL) was treated with a 1.4 M solution of methylmagnesium bromide in THF (6.5 mL, 9.1 mmol) at RT under N_2. The resultant mixture was stirred at RT for 3 h. The reaction mixture was poured onto 10% aqueous HCl (200 mL), and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and then concentrated to afford the crude product, which was purified by flash chromatography to afford (±)-1,1-dimethylethyl [6-chloro-5-(2-hydroxypropyl)-4-pyrimidinyl]-[2-fluoro-4-(methylsulfonyl)phenyl]carbamate (**83**, 0.82 g, 39%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.28 (s, 1H), 7.84 (dd, J = 9.6, 2.0 Hz, 1H), 7.80−7.68 (m, 2H), 5.06−4.99 (m, 1H), 3.28 (s, 3H), 3.14−3.10 (m, 1H), 3.05−3.02 (m, 1H), 1.33 (d, J = 6.2 Hz, 3H), 1.25 (s, 9H). LRMS (ESI): m/z 460 $(M + H)^+$. A solution of **83** (0.8 g, 1.7 mmol) in CH_2Cl_2 (20 mL) was treated with CF_3CO_2H (5 mL) at RT under N_2. The reaction mixture was stirred at RT for 3 h and then concentrated to afford (±)-1-(4-chloro-6-{[2-fluoro-4-(methylsulfonyl)phenyl]amino}-5-pyrimidinyl)-2-propanol **84**, which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.84 (s, 1H), 8.42 (s, 1H), 8.16 (app, t, J = 8.0 Hz, 1H), 7.82 (dd, J = 10.4, 2.0 Hz, 1H), 7.73 (dd, J = 8.8, 1.6 Hz, 1H), 5.87 (d, J = 2.8 Hz, 1H), 4.07 (app br s, 1H), 3.24 (s, 3H), 2.94−2.83 (m, 2H), 1.20 (d, J = 6.4 Hz, 3H). LRMS (ESI): m/z 360 $(M + H)^+$. A solution of **84** (1.7 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (0.72 mL, 5.2 mmol) followed by methanesulfonic anhydride (0.61 g, 3.5 mmol) at RT for 24 h. The reaction was diluted with CH_2Cl_2 and quenched by the addition of water. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography afforded (±)-4-chloro-7-[2-fluoro-4-(methylsulfonyl)phenyl]-6-methyl-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine **85** (0.27 g, 47% overall for two steps) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H), 7.93 (app dd, J = 10.8, 1.2 Hz, 1H), 7.87−7.81 (m, 2H), 4.80−4.72 (m, 1H), 3.45 (dd, J = 17.2, 9.6 Hz, 1H), 3.30 (s, 3H), 2.87 (dd, J = 17.2, 7.2 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H). LRMS (ESI): m/z 342 $(M + H)^+$. A racemic mixture of **86** and **87** was prepared as a white solid in 82% yield from **85** and 1-methylethyl 4-hydroxy-1-piperidinecarboxylate in a similar manner to that described for **3**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (s, 1H), 7.87 (app br d, J = 10.4 Hz, 1H), 7.82 (app br d, J = 7.6 Hz, 1H), 7.77 (dd, J = 8.4, 1.6 Hz, 1H), 5.30−5.22 (m, 1H), 4.78−4.66 (m, 2H), 3.68−3.64 (m, 2H), 3.32−3.28 (m, 1H), 3.28 (s, 3H), 3.28−3.22 (m, 2H), 2.68 (app dd, J = 16.0, 7.2 Hz, 1H), 1.96−186 (m, 2H), 1.62−1.50 (m, 2H), 1.19 (app d, J = 5.6 Hz, 3H), 1.17 (d, J = 6.0 Hz, 6H). LRMS (ESI): m/z 493 $(M + H)^+$. The racemic mixture (200 mg) was subjected to Chiral HPLC [column: Chiralpak OJ (analytical), Chiralpak OJ (prep); mobile phase, 95% CO_2, 5% MeOH:$CHCl_3$ (90:1); 2 mL/min; pressure 140 bar, temperature 30 °C, 215 nm, and 280 nm)] analysis and then separated into two (+ and −) enantiomers. Enantiomer 1, (+)-**86**: Retention time = 19.96 min, 46 mg (%ee >98%). HRMS (ESI): m/z calcd for $C_{23}H_{29}FN_4O_5S$ $[M + H]^+$ 493.1921, obsd 493.1920. Specific rotation in 50:50 DCM:methanol vol/vol, 25 °C, 589 nm = +119.17°. Enantiomer 2, (−)-**87**: Retention time = 21.0 min, 66 mg (%ee >98%). HRMS (ESI): m/z calcd for $C_{23}H_{29}FN_4O_5S$ $[M + H]^+$ 493.1921, obsd 493.1921. Specific rotation in 50:50 DCM:methanol vol/vol, 25 °C, 589 nm = −97.06°.

1-Methylethyl 4-({7-[5-(Methylsulfonyl)-2-pyridinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate Hydrochloride (97). A solution of 2-amino-5-iodopyridine (11.6 g, 52.6 mmol) in MeOH (250 mL) was treated with sodium thiomethoxide (5.16 g, 73.6 mmol) and copper powder (1.07 g, 16.8 mmol) at RT. The reaction mixture was heated in a sealed tube at 120 °C for 68 h. The reaction mixture was then cooled to RT and filtered through a pad of Celite. The pad was rinsed with MeOH, and the combined organics were concentrated and redissolved in EtOAc. The organic layer was washed with water, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 5-(methylthio)-2-pyridinamine **89** (6.23 g, 84%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.51−7.48 (m, 1H), 6.48−6.45 (m, 1H), 4.35 (br s, 2H), 2.38 (s, 3H). A solution of **17** (18.9 g, 0.1 mol) in acetone/water (1:1, 1 L) was treated with $K_2OsO_4{\cdot}2H_2O$ (1.47 g, 4 mmol) followed by the portiowise addition of $NaIO_4$ (64.2 g, 0.4 mol). The reaction mixture was stirred at RT for 4 h and then filtered through a plug of silica (CH_2Cl_2 wash). The filtrate was extracted with CH_2Cl_2, and the extracts were concentrated. Purification by flash chromatography afforded (4,6-dichloro-5-pyrimidinyl)acetaldehyde **88** (10 g, 45%). A solution of **88** (3.4 g, 17.8 mmol) in MeOH (180 mL) was treated with **89** (3.0 g, 21.4 mmol) at RT. The reaction mixture was cooled to −15 °C with an ice/methanol bath and glacial acetic acid (3.1 mL, 53.4 mmol) and $NaBH_3CN$ (3.4 g, 53.4 mmol) were added. The reaction mixture was stirred at −15 °C for 15 min and then allowed to warm to RT and stir for 19 h. The reaction mixture was then diluted with water (50 mL) and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to afford *N*-[2-(4,6-

dx.doi.org/10.1021/jm301404a | J. Med. Chem. XXXX, XXX, XXX−XXX

dichloro-5-pyrimidinyl)ethyl]-5-(methylthio)-2-pyridinamine **91** as a yellow oil. The crude oil was dissolved in THF (500 mL) and then treated with *t*-BuOK (5.99 g, 53.4 mmol) at RT. The reaction mixture immediately changed to a brown color and was stirred at RT for 22 h. The reaction mixture was quenched with water (50 mL), concentrated, and then redissolved in EtOAc (200 mL). The organic layer was washed with water, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to a brown oil. The crude oil was purified by flash chromatography (20→40% EtOAc/hexanes; monitoring at 319 nm) to afford 4-chloro-7-[5-(methylthio)-2-pyridinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine **93** (550 mg, 11%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, J = 9.0 Hz, 1H), 8.43 (s, 1H), 8.29 (d, J = 2.4 Hz, 1H), 7.67 (dd, J = 8.8, 2.4 Hz, 1H), 4.37−4.33 (m, 2H), 3.16 (t, J = 8.8 Hz, 2H), 2.47 (s, 3H). 1-Methylethyl 4-({7-[5-(methylthio)-2-pyridinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (**95**) was prepared as a off-white solid in 88% yield from **93** and 1-methylethyl 4-hydroxypiperidinecarboxylate in a similar manner to that described for **3**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73−8.66 (m, 1H), 8.42−8.39 (m, 1H), 8.30 (d, J = 2.4 Hz, 1H), 8.77−8.70 (m, 1H), 5.39−5.32 (m, 1H), 4.92 (septuplet, J = 6.1 Hz, 1H), 4.46−4.36 (m, 2H), 3.85−3.76 (m, 2H), 3.36−3.30 (m, 2H), 3.12−3.05 (m, 2H), 2.48 (s, 3H), 2.03−1.95 (m, 2H), 1.79−1.70 (m, 2H), 1.25 (d, J = 6.4 Hz, 6H). LRMS (ESI): m/z 430 (M + H)$^+$. A solution of **95** (186 mg, 0.43 mmol) in MeOH (4 mL) and acetone (3 mL) was treated with a solution of Oxone (798 mg, 1.3 mmol) in water (4 mL) via pipet at RT. A white solid precipitated immediately, and the reaction mixture was stirred at RT for 1 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 and extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting solid was dissolved in a mixture of Et_2O (8 mL) and acetone (3 mL) warmed with a heat gun and was treated with HCl (1.0M in Et_2O, 0.88 mL), during which time a white solid precipitated. The solid was filtered, washed with Et_2O, and dried under high vacuum to afford **97** (190 mg, 81%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, J = 2.4 Hz, 1H), 8.83 (s, 1H), 8.18 (dd, J = 8.8, 2.2 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 5.56 (septuplet, J = 4.2 Hz, 1H), 4.93 (app quintuplet, J = 6.4 Hz, 1H), 4.57 (t, J = 8.8 Hz, 2H), 3.89−3.83 (m, 2H), 3.38−3.29 (m, 4H), 3.05 (s, 3H), 2.10−2.04 (m, 2H), 1.84−1.76 (m, 2H), 1.26 (d, J = 6.4 Hz, 6H). HRMS (ESI): m/z calcd for $C_{21}H_{27}FN_5O_3S$ [M + H]$^+$ 462.1811, obsd 462.1810.

1-Methylethyl 4-({7-[6-(Methylsulfonyl)-3-pyridinyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate Hydrochloride (98). 6-(Methylthio)-3-pyridinamine **90** was prepared as a brown solid in 26% yield from 5-amino-2-bromopyridine in a similar manner to that described for **89**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 2.9 Hz, 1H), 7.06−7.00 (m, 1H), 6.92−6.89 (m, 1H), 3.50 (br s, 2H), 2.51 (s, 3H). Compound **98** was prepared as a white solid in 7% overall yield from **88** and **90** in a similar manner to that described for **97**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (d, J = 2.4 Hz, 1H), 8.57 (dd, J = 8.8, 2.7 Hz, 1H), 8.37 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 5.36 (septuplet, J = 3.9 Hz, 1H), 4.91 (app quintuplet, J = 6.4 Hz, 1H), 4.14 (t, J = 8.8 Hz, 2H), 3.84−3.76 (m, 2H), 3.35−3.28 (m, 2H), 3.18 (s, 3H), 3.15 (t, J = 8.8 Hz, 2H), 2.02−1.95 (m, 2H), 1.77−1.68 (m, 2H), 1.24 (d, J = 6.4 Hz, 6H). HRMS (ESI): m/z calcd for $C_{21}H_{27}FN_5O_5S$ [M + H]$^+$ 462.1811, obsd 462.1811.

1-Methylethyl 4-{[7-(5-Cyano-2-pyridinyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate (99). Compound **99** was prepared as a white solid in 5% overall yield from **88** and 2-amino-5-cyanopyridine in a similar manner to that described for **97**, except that $Na(OAc)_3BH$ and CF_3CO_2H was used in the reduction amination step in place of $NaCNBH_3$ and acetic acid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90−8.85 (m, 1H), 8.61−8.57 (m, 1H), 8.42 (s, 1H), 7.87−7.82 (m, 1H), 5.42−5.33 (m, 1H), 4.99−4.90 (m, 1H), 4.35 (t, J = 8.61 Hz, 2H), 3.89−3.74 (m, 2H), 3.42−3.29 (m, 2H), 3.07 (t, J = 8.1 Hz, 2H), 2.08−1.94 (m, 2H), 1.83−1.70 (m, 2H), 1.27 (d, J = 6.2 Hz, 6H). HRMS (ESI): m/z calcd for $C_{21}H_{24}FN_6O_3$ [M + H]$^+$ 409.1988, obsd 409.1989.

1-Methylethyl 4-{[7-(5-Fluoro-2-pyridinyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate (100). Compound **100** was prepared as a white solid in 15% overall yield from **88** and 2-amino-5-fluoropyridine in a similar manner to that described for **99**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (dd, J = 9.3, 4.0 Hz, 1H), 8.35 (s, 1H), 8.17 (d, J = 3.11 Hz, 1H), 7.47−7.40 (m, 1H), 5.41−5.30 (m, 1H), 5.00−4.89 (m, 1H), 4.30 (t, J = 8.6 Hz, 2H), 3.89−3.73 (m, 2H), 3.42−3.30 (m, 2H), 3.04 (t, J = 8.6 Hz, 2H), 2.07−1.93 (m, 2H), 1.84−1.67 (m, 2H), 1.26 (d, J = 6.2 Hz, 6H). HRMS (ESI): m/z calcd for $C_{20}H_{24}FN_5O_3$ [M + H]$^+$ 402.1942, obsd 402.1942.

1-Methylethyl 4-{[7-(2-Methyl-3-pyridinyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate (101). *N*-[2-(4,6-Dichloro-5-pyrimidinyl)ethyl]-2-methyl-3-pyridinamine was prepared from **88** and 2-methyl-3-pyridinamine in a similar manner to that described for **91**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 7.95−7.94 (m, 1H), 7.71−7.66 (m, 2H), 6.63 (app t, J = 5.6 Hz, 1H), 3.59 (app q, J = 6.0 Hz, 2H), 3.08 (t, J = 6.4 Hz, 2H), 2.40 (s, 3H), LRMS (ESI): m/z 285 (M + H)$^+$. A solution of *N*-[2-(4,6-dichloro-5-pyrimidinyl)ethyl]-2-methyl-3-pyridinamine (∼11.0 g) in toluene (200 mL) was treated with $PdCl_2(Ph_3P)_2$ (1.36 g, 2 mmol), potassium *tert*-butoxide (8.7 g, 77.7 mmol), and K_2CO_3 (10.7 g, 77.7 mmol) at RT under N_2. The reaction mixture was stirred and refluxed for 18 h. The reaction mixture was allowed to cool to RT and then filtered through a pad of Celite. The filtrate was concentrated and purified by flash chromatography to afford 4-chloro-7-(2-methyl-3-pyridinyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (0.85 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (dd, J = 4.8, 1.2 Hz, 1H), 8.11 (s, 1H), 7.75 (dd, J = 8.0, 1.6 Hz, 1H), 7.31 (dd, J = 8.0, 4.8 Hz, 1H), 4.03 (t, J = 8.8 Hz, 2H), 3.20 (t, J = 8.4 Hz, 2H), 2.34 (s, 3H), LRMS (ESI): m/z 247 (M + H)$^+$. Compound **101** was prepared as a white solid in 55% overall yield from 4-chloro-7-(2-methyl-3-pyridinyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine and 1-methylethyl 4-hydroxypiperidinecarboxylate in a similar manner to that described for **3**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.36 (dd, J = 4.8, 1.2 Hz, 1H), 8.05 (s, 1H), 7.69 (dd, J = 8.0, 1.6 Hz, 1H), 7.26 (dd, J = 8.0, 4.8 Hz, 1H), 5.27−5.20 (m, 1H), 4.27 (septuplet, J = 6.4 Hz, 1H), 3.94 (t, J = 8.8 Hz, 2H), 3.71−3.66 (m, 2H), 3.21 (app br t, J = 10.0 Hz, 2H), 3.04 (t, J = 9.2 Hz, 2H), 2.35 (s, 3H), 1.95−1.89 (m, 2H), 1.60−1.50 (m, 2H), 1.17 (d, J = 6.0 Hz, 6H). HRMS (ESI): m/z calcd for $C_{21}H_{27}N_5O_3$ [M + H]$^+$ 398.2191, obsd 398.2191.

1-Methylethyl 4-{[7-(4-Cyano-3-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate (103). 1-Methylethyl 4-{[7-(4-bromo-3-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate (**102**) was prepared as a white solid in 38% overall yield from **88** and 4-bromo-3-fluoroaniline in a similar manner to that described for **97**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.84 (dd, J = 12.0, 2.4 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.34 (dd, J = 8.8, 2.8 Hz, 1H), 5.37−5.32 (m, 1H), 4.93 (septuplet, J = 6.0 Hz, 1H), 4.04 (t, J = 8.8 Hz, 2H), 3.82−3.76 (br m, 2H), 3.36−3.30 (m, 2H), 3.07 (t, J = 8.8 Hz, 2H), 2.02−1.95 (m, 2H), 1.77−1.69 (m, 2H), 1.25 (d, J = 6.4 Hz, 6H). LRMS (ESI): m/z 481 [M + H]$^+$. Compound **103** was prepared as a white solid in 19% yield from 1-methylethyl 4-{[7-(4-bromo-3-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate in a similar manner to that described for **25**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (s, 1H), 8.11 (dd, J = 13.6, 1.6 Hz, 1H), 7.84 (app t, J = 8.0 Hz, 1H), 7.74 (dd, J = 8.8, 2.0 Hz, 1H), 5.32−5.25 (m, 1H), 4.75 (septuplet, J = 6.4 Hz, 1H), 4.10 (t, J = 8.8 Hz, 2H), 3.70−3.64 (m, 2H), 3.24 (app J = 9.6 Hz, 2H), 3.03 (t, J = 8.8 Hz, 2H), 1.96−1.89 (m, 2H), 1.61−1.53 (m, 2H), 1.16 (d, J = 6.0 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{24}FN_5O_3$ [M + H]$^+$ 426.1941, obsd 426.1943.

1-Methylethyl 4-({7-[3-Fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (104). 1-Methylethyl 4-{[7-(4-bromo-3-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate was prepared as a white solid in 38% overall yield from 4-bromo-3-fluoroaniline and **88** in a similar manner to that described for **97**, except the cyclization occurred spontaneously. Compound **104** was prepared from 1-methylethyl 4-{[7-(4-bromo-3-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy}-1-piperidinecarboxylate and sodium methanesulfinate using the sulfonylation reaction conditions described for **2**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s,

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1H), 8.15 (d, J = 13.5 Hz, 1H), 7.88 (dt, J = 8.7, 2.2 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 5.35 (m, 1H), 4.93 (septuplet, J = 6.2 Hz, 1H), 4.11 (t, J = 8.0 Hz, 2H), 3.80 (m, 2H), 3.37−3.31 (m, 2H), 3.20 (s, 3H), 3.12 (t, J = 8.4 Hz, 2H), 2.94 (m, 2H), 2.02−1.90 (m, 2H), 1.80−1.70 (m, 2H), 1.25 (d, J = 6.3 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_5S$ $[M + H]^+$ 479.1764, obsd 479.1764.

1-Methylethyl 4-[(7-{4-[(Dimethylamino)sulfonyl]phenyl}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)oxy]-1-piperidinecarboxylate (105). Compound **105** was prepared as a white solid in 17% overall yield from 4-amino-*N*,*N*-dimethylbenzenesulfonamide and **88** in a similar manner to that described for **99**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 5.42−5.30 (m, 1H), 4.99−4.86 (m, 1H), 4.14 (t, J = 8.8 Hz, 2H), 3.91−3.75 (m, 2H), 3.41−3.27 (m, 2H), 3.12 (t, J = 8.8 Hz, 2H), 2.70 (s, 6H), 2.09−1.92 (m, 2H), 1.83−1.66 (m, 2H), 1.26 (d, J = 6.2 Hz, 6H). HRMS (ESI): m/z calcd for $C_{23}H_{31}N_5O_5S$ $[M + H]^+$ 490.2124, obsd 490.2124.

1-Methylethyl 4-({7-[2-Fluoro-4-(methylthio)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (106). A slurry of nickel(II) bromide (9.12 g, 42 mmol), 2,2′-dipyridyl (6.56 g, 42 mmol), and zinc dust (55 g, 844 mmol) in anhydrous DMF (300 mL) were treated with 2-fluoro-4-iodoaniline (100 g, 0.42 mol) and dimethyldisulfide (96 mL, 1.06 mol) under N_2. The resultant mixture was stirred at 75 °C for 1.5 h. The reaction mixture was concentrated. The crude residue was dissolved in Et_2O (500 mL), filtered through a pad of Celite, and washed with Et_2O. The filtrate was concentrated and purified by flash chromatography to afford [2-fluoro-4-(methylthio)phenyl]amine (48.7 g, 73%) as a brown liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (s, 1H), 8.86 (s, 1H), 7.00 (dd, J = 11.2, 2.0 Hz, 1H), 6.93 (dd, J = 8.4, 4.0 Hz, 1H), 6.70 (t, J = 8.8 Hz, 1H), 4.21 (s, 2H), 3.69 (br s, 2H), 2.40 (s, 3H). LRMS (ESI): m/z 158 $(M + H)^+$. Compound **106** was prepared as an off-white solid in 34% overall yield from [2-fluoro-4-(methylthio)phenyl]amine in a similar manner to that described for **99**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (s, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.21 (dd, J = 12.0, 2.0 Hz, 1H), 7.09 (dd, J = 8.0, 2.0 Hz, 1H), 5.26−5.20 (m, 1H), 4.75 (septuplet, J = 6.4 Hz, 1H), 3.96 (t, J = 8.8 Hz, 2H), 3.70−3.64 (m, 2H), 3.22 (app t, J = 9.6 Hz, 2H), 3.01 (t, J = 8.8 Hz, 2H), 1.94−1.88 (m, 2H), 1.59−1.50 (m, 2H), 1.17 (d, J = 6.4 Hz, 6H). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_3S$ $[M + H]^+$ 447.1866, obsd 447.1865.

(±)-1,1-Dimethylethyl 4-({1-[4-(Methylsulfinyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (107 and 108). A solution of **106** (200 mg, 0.454 mmol) and hexafluoroisopropanol (2.5 mL) was treated with 30% aqueous H_2O_2 (100 μL). The mixture was stirred at RT for 0.5 h. A saturated sodium sulfide solution (8 mL) was introduced to the above mixture and stirred for 5 min. Layers were separated, and the organic layer was concentrated and purified by flash chromatography (0→20% EtOAc/hexanes) to afford a racemic mixture of **107** and **108** (178 mg, 86%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61 (t, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.04 (app t, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 4.56 (septuplet, J = 3.2 Hz, 1H), 3.98 (t, J = 8.8 Hz, 2H), 3.60−3.55 (m, 2H), 3.25−3.22 (m, 2H), 2.99 (t, J = 8.4 Hz, 2H), 2.69 (s, 3H), 1.88−1.83 (m, 2H), 1.58−1.49 (m, 2H), 1.39 (s, 9H). LRMS (ESI): m/z 457 $(M + H)^+$.

(*R*)-1,1-Dimethylethyl 4-({1-[4-(Methylsulfinyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (107). The racemic sulfoxide (150 mg) was subjected to Chiral HPLC (column: Chiralpak AS (analytical), Chiralpak (prep); mobile phase, 78% CO_2, 22% MeOH (14 mL/min), pressure 140 bar, temperature 40 °C, 240 nm)) analysis and then was separated into its (*R* and *S*) enantiomers. Retention time was 11.57 min for the first eluting enantiomer, which provided 33 mg (%ee >98%). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_4S$ $[M + H]^+$ 463.1815, obsd 463.1816.

(*S*)-1,1-Dimethylethyl 4-({1-[4-(Methylsulfinyl)phenyl]-2,3-dihydro-1*H*-indol-4-yl}oxy)-1-piperidinecarboxylate (108). Retention time was 14.04 min for the second eluting isomer, 38 mg (%ee >97%). HRMS (ESI): m/z calcd for $C_{22}H_{27}FN_4O_4S$ $[M + H]^+$ 463.1815, obsd 463.1815.

1-Methylethyl 4-({7-[2-Methyl-4-(methylsulfonyl)phenyl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate (113). A solution of 4-fluoro-2-methyl-1-nitrobenzene (**109**, 2.4 g, 19.3 mmol) in DMF was treated with sodium methoxide (1.5 g, 21.3 mmol) and stirred and heated at 85 °C for 1 h. The mixture was allowed to cool to RT and was treated with water and extracted with EtOAc (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford 2-methyl-4-(methylthio)-1-nitrobenzene (**110**, 3.1 g, 88%) as an orange residue. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.27 (dd, J = 8.6, 2.0 Hz, 1H), 2.54 (s, 3H). LRMS (ESI): m/z 184 $(M + H)^+$. Tin(II) chloride (10.7 g, 56.4 mmol) was added portionwise to concentrated HCl (20 mL) at RT. The mixture was treated with a solution of 2-methyl-4-(methylthio)-1-nitrobenzene (3.1 g, 17.1 mmol) in ethanol (10 mL). The mixture was stirred and heated at 80 °C for 1 h. The mixture was allowed to cool to RT, the pH was adjusted to ∼10 with 10N NaOH, and extracted with EtOAc (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford 2-methyl-4-(methylthio)aniline (**111**, 2.1 g, 81%) as a dark oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.00 (s, 1H), 6.96 (dd, J = 8.3, 2.0 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 2.34 (s, 3H), 2.07 (s, 3H). LRMS (ESI): m/z 154 $(M + H)^+$. Compound **104** was prepared as a white solid in 5% overall yield from **111** and **88** in a similar manner to that described for **97**, with the exception that CF_3CO_2H was used for the cyclization step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.86 (s, 1H), 7.79 (dd, J = 8.4, 1.7 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 5.37−5.29 (m, 1H), 5.00−4.83 (m, 1H), 3.99 (t, J = 8.8 Hz, 2H), 3.80 (d, J = 11.4 Hz, 2H), 3.40−3.23 (m, 2H), 3.13 (t, J = 8.8 Hz, 2H), 3.03 (s, 3H), 2.34 (s, 3H), 1.92 (dt, J = 6.3, 3.0 Hz, 2H), 1.23 (d, J = 6.2 Hz, 6H). LRMS (ESI): m/z 475 $(M + H)^+$. HRMS (ESI): m/z calcd for $C_{23}H_{30}N_4O_5S$ $[M + H]^+$ 475.2015, obsd 475.2014.

GLP-1 Release from GluTag Cells with 3. GLUTag cells were cultured in Dulbecco's Modified Eagles Medium (Sigma-Aldrich) containing 5.5 mM glucose, 10% fetal bovine serum, and 2 mM L-glutamine.

GLUTag cells were plated in 384-well cell culture plates coated with Matrigel (BD Biosciences) and grown to 80% confluence in Dulbecco's Modified Eagle'S Medium (Sigma-Aldrich) containing 1000 mg/L glucose, pyroxidine HCl, and sodium bicarbonate and supplemented with 2 mM L-glutamine and 10% fetal bovine serum. On the day of the experiment, cell media was removed and cells were preincubated for 30 min in Kreb's Ringers assay buffer (120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 22 mM $NaHCO_3$, 10 mM Hepes, 0.1% BSA, 10 mM D-glucose, and DPP-IV inhibitor (Millipore DPP4−010). Following preincubation, media was again removed and replaced with KRB assay buffer containing GSK252 at varying concentrations. Cells were incubated for 2 h in a 37 °C, 5% CO_2 incubator. After the incubation period, media was collected and centrifuged to remove any floating cells and assayed for GLP-1.

Capture antibody (Abcam ab23468) was biotinylated using the QuickPlex Biotin NHS Ester kit (MSD R91DS-1) according to the manufacturer's protocol. Detection antibody (Abcam ab26278) was sulfo-tagged using a MSD SULFO-TAG NHS Ester kit according to the manufacturer's protocol (MSD R91AN-1). Active GLP-1 was measured using a chemiluminescent detection assay specific for amidated forms of GLP-1 (1−36 amide, 7−36 amide, and 9−36 amide). Briefly, 15 μL of cell supernatant plus 5 μL of assay buffer containing 2 μg/mL biotinylated anti-GLP-1 capture antibody, 2 μg/mL sulfo-tagged anti-GLP-1 detection antibody, 8% BSA Fraction V (Sigma-Aldrich), 4× DPP-IV inhibitor (Millipore) in PBS pH = 7.4 were added to each well of a 384 Standard avidin-coated plate (MSD L21AA-1). Plates were sealed, shaken briefly, and incubated overnight at 40 °C. The following day, samples were aspirated from wells and washed 3 times with 1× Tris wash buffer (MSD R61TX-1). Wash buffer was aspirated, and 35 μL 1× Read T buffer (MSD R92TC-2) was added. Plates were read on an MSD Sector 6000 instrument.

Primary Colonic Crypt Secretion of GLP-1 with 3. Primary colonic crypts were prepared from 6−8 week old C57BL/6 male mice. Intestine was removed, cecum to rectum, filled and flushed three times with cold PBS, and then slit open longitudinally and cut into 2−3 mm lengths. Tissue sections from five animals were pooled and washed with Hank's Balanced Salt Solution (Gibco) five times, allowing sections to

dx.doi.org/10.1021/jm301404a | J. Med. Chem. XXXX, XXX, XXX−XXX

sediment under gravity each time, and then transferred to a Petri dish and diced to a very fine mince. The tissue slurry was incubated in 0.1% Collagenase II−S (Sigma), 0.2% Dispase I (Becton Dickenson), 2000 Kunitz DNase-I (Sigma), and 0.1% Hyaluronidase I−S (Sigma) in culture media (Dulbecco's Modified Eagles Medium Hi Glucose (Gibco), 10% heat inactivated FBS (Gibco), 1× Pen/Strep (Gibco)) for 15 min at 37 °C while gently rocking. First digest was triturated 50 times with a 10 mL pipet, and the contents allowed to sediment under gravity for 1 min. Then 20 mL of the supernatant was carefully removed . Two additional digests were performed on the remaining tissue fragments with fresh enzyme solution as described above, saving the supernatant each time. All digest fractions were pooled for gentle spins (3 min, 300 rpm in swinging bucket centrifuge) and washed in Hank's Balanced Salt Solution containing 5 mM β-mercaptoethanol until the supernatant was clear. The pellet of crypts was resuspended in culture media and seeded on 384-well cell culture plates coated with Matrigel (BD Biosciences) and allowed to attach for 24 h. GLP-1 levels were measured as described above.

Incretin Secretion in WT and KO Mice with 3. First, 17-week-old transgenic male (WT) and GPR119 knockout (KO) mice (Charles River Laboratories, USA) were fasted overnight and then randomly distributed into treatment groups (n = 8 and 10 per group, repsectively). Animals received wither vehicle (0.5% HPMC/0.1% Tween80) or compound **3** (30 mg/kg) by oral gavage at a dose volume of 10 mL/kg. Then 60 min after the oral gavage, mice were anesthetized using isofluorane and a blood sample was collected by cardiac puncture. All mice were euthanized by cervical dislocation immediately following cardiac puncture. Blood samples were placed in chilled K_2-EDTA coated capiject tubes (cat. no. T-MQK, Terumo Medical Corp., Elkton, MD) supplemented with a DPP-4 inhibitor and Aprotenin (Trasylol; Bayer Pharmaceuticals, West Haven, CT), yielding a final concentration of 30 μL and 250 KIU/mL, respectively. The tubes were immediately centrifuged at 4 °C and the plasma collected and stored at −80 °C for subsequent hormone measurements. Total GLP-1 levels were determined using a Multi-Array electrochemoluminescence assay from Meso Scale Discovery (cat. no. K110-FAC-2; Gaithersburg, MD). Total GIP levels were determined using an ELISA assay (cat. no. EZRMGIP-55K, Linco Diagnostic Services, St. Charles, MO). Data are represented as box plots summarizing the distribution of data for each treatment group. Horizontal lines represent the mean data.

Hyperglycemic Clamp in Rats with 3. Male Wistar rats (Taconic Farms, USA), weighing 300−350 g, had catheters surgically implanted into the jugular and femoral veins and allowed to recover for one week following the surgery. Animals were fasted overnight. Animals were then randomly assigned to treatment groups, vehicle (n = 19), compound **3** (1 mg/kg, n = 8), or compound **3** (10 mg/kg, n = 8), and baseline blood samples were collected from the jugular vein. Animals were administered vehicle or compound **3** by oral gavage. A second blood sample was collected approximately 90 min after the oral gavage and immediately prior to starting the hyperglycemic clamp. The clamp was initiated by infusing an empirically determined glucose bolus over 15−30 s into the femoral vein, followed by a variable rate glucose infusion adjusted to achieve a stable plasma glucose level of 190−210 mg/dL. After infusion of the glucose bolus, blood samples were collected every 5 min for glucose measurements. Samples for C-peptide levels were collected at 2, 5, 10, 15, 20, 25, 30, 45, 60, 90, and 120 min during the hyperglycemic clamp. All blood samples were placed in individual tubes containing a gel clot activator (cat. no. T-MG, Terumo Medical Corporation, Elkton, MD) and allowed to clot at room temperature for 20 min before centrifugation and collection of serum. Glucose levels were measured using an Olympus AU640 analyzer (Olympus America Inc., Melville, NY) and C-peptide levels by an RIA (Linco Diagnostic Services, St. Charles, MO).

Mouse Food Intake with 3. Individually housed, male C57BL/6 mice were fasted overnight. Body weights were recorded, and compound **3** (10 mg/kg in dose volume of 10 mL/kg, 10% DMSO:30% solutol:60% HP-β-CD) was delivered by oral gavage at time = −60 min. Control (Exendin-4, 100 μg/kg in dose volume of 10 mL/kg, Polypeptide) was delivered IP at time = −30 min. At time = 0 min, food hoppers containing normal chow (Purina) were weighed and reintroduced. Hopper wights were recorded after 1, 2, 4, 6, and 24 h

Rat Gastric Emptying with 3. Male Sprague−Dawley rats (Charles River Laboratories, USA) were fasted overnight and administered vehicle (dose volume of 10 mL/kg, 0.5% HPMC/0.1% Tween80) or compound **3** (10 mg/kg in dose volume of 10 mL/kg) orally at time = −120 min. At time = −15 min, the positive control rat cohort was administered Pramlintide (15 μg in dose volume of 10 mL/kg, Polypeptide). At time = 0, baseline plasma samples were collected, followed by gavage of acetominophen (65 mg in vehicle at a dose volume of 10 mL/kg). The concentration time profile of acetominophen was measured over the next 3 h.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Analytical Chemistry group of Matt Lochansky and Iris Scherer for performing HRMS analysis for the compounds reported and Manon Villeneuve, Yang Zhao, Eric Pullen, Eric Wentz, and Bill Hall for performing chiral separations. We also thank Brad Henke for preparing compound **114** to be used as the standard in the in vitro assay.

ABBREVIATIONS USED

T2D, type 2 diabetes; GPR119, G protein-coupled receptor 119; GIP, glucose-dependent insulinotropic peptide; DPP-4, dipeptidyl peptidase-4; LPC, lysophosphatidylcholine; OEA, oleoylethanolamide; NAPE, *N*-acylethanolamide; OLDA, *N*-oleoyldopamine; DHPP, 6,7-dihydro-5*H*-pyrrolopyrimidine; DIAD, diisopropyl azodicarboxylate; 1,2-DCE, 1,2-dichloroethane; pEC_{50}, negative logarithm of the EC_{50}; EC_{50}, effective concentration at half-maximal response; av, average; StDev, standard deviation; AUC_{0-24h}, area under the curve from 0 to 24 h; $DNAUC_{0-24h}$, dose normalized area under the curve from 0 to 24 h; C_{max}, maximum concentration; Cl_b, blood clearance; V_{ss}, volume of distribution; KO, knockout; PYY, peptide YY; SD, Sprague−Dawley; nd, not determined; HPMC, hydroxypropylmethylcellulose; HP-β-CD, hydroxypropyl-β-cyclodextrin; FBS, fetal bovine serum

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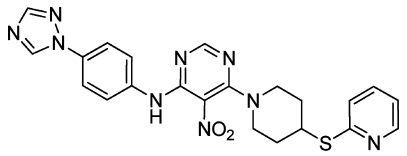
(32) All compounds are referenced to a small molecule GPR119 agonist for evaluation of intrinsic efficacy (%max response) because this reporter assay is not sensitive enough to demonstrate robust activity of putative endogenous ligands (OEA, LPC, etc.). Our experience with the ∼3000 compounds made for the program is that compounds with ∼80−200% max response are likely full agonists. Compounds with consistent levels of receptor activation below 80% may be partial agonists. The degree of variability in the assay accounts for the large range considered as full agonists. The structure of our standard compound **114**, with an EC_{50} = 0.2 μM (max response = 100%), is shown below. This compound is reported[33] to have an EC_{50} = 0.13 μM in a cAMP assay.



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dx.doi.org/10.1021/jm301404a | *J. Med. Chem.* XXXX, XXX, XXX−XXX