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6-Alkoxy-5-aryl-3-pyridinecarboxamides, a New Series of Bioavailable Cannabinoid Receptor Type 1 (CB1) Antagonists Including Peripherally Selective Compounds

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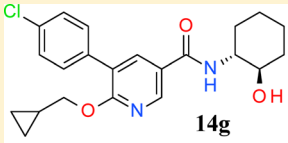
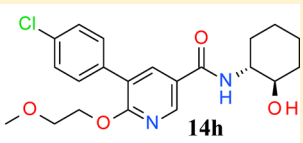
Supporting Information

ABSTRACT: We identified 6-alkoxy-5-aryl-3-pyridinecarboxamides as potent CB1 receptor antagonists with high selectivity over CB2 receptors. The series was optimized to reduce lipophilicity compared to rimonabant to achieve peripherally active molecules with minimal central effects. Several compounds that showed high plasma exposures in rats were evaluated in vivo to probe the contribution of central vs peripheral CB1 agonism to metabolic improvement. Both rimonabant and **14g**, a potent brain penetrant CB1 receptor antagonist, significantly reduced the rate of body weight gain. However, **14h**, a molecule with markedly reduced brain exposure, had no significant effect on body weight. PK studies confirmed similarly high exposure of both **14h** and **14g** in the periphery but 10-fold lower exposure in the brain for **14h**. On the basis of these data, which are consistent with reported effects in tissue-specific CB1 receptor KO mice, we conclude that the metabolic benefits of CB1 receptor antagonists are primarily centrally mediated as originally believed.



14g

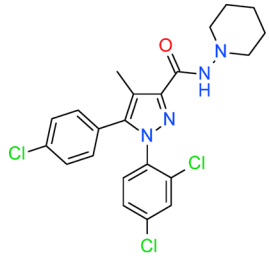


14h

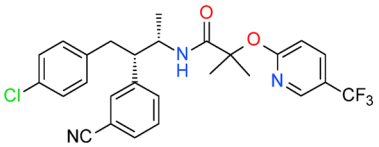
	14g	14h
K_i huCB1-R [nM]	11.4	5.1
EC_{50} GTPγS [nM]	3.9	11.6
rat plasma C_{max}/Dose [ng/mL]	92	179
rat brain/plasma	1.3	0.13
Body weight reduction	yes	no

INTRODUCTION

The CB1 receptor is part of the endocannabinoid system that derives its name from cannabis. While the use of cannabis can be traced back thousands of years,[1] the molecular targets of its pharmacology have been explored in detail only in the last few decades. Starting with the isolation of the main psychoactive constituent of *Cannabis sativa*, Δ9-THC by Mechoulam in 1964,[2] the next decades saw the isolation and characterization of both the CB1[3−5] and CB2 receptors[6] as well as several of their physiological ligands such as anandamide[7] and 2-AG.[8] The field has matured, with over 400 new publications on the cannabinoid system appearing in PubMed each year. Recent reviews have indicated that this breadth of information has uncovered as many questions as it has solved.[9−12] The CB1 receptor is abundantly expressed in both peripheral and the neuronal tissues.[13] Target-based drug discovery has progressed and delivered many different series of CB1-receptor antagonists.[14] These include rimonabant (SR141716A, **1**), which received marketing authorization in the European Union as an antiobesity medication but was later withdrawn due to increased incidence of anxiety, depression, and suicidality, and taranabant (MK-0364, **2**, Figure 1) and otenabant (CP-945,598), which entered late clinical development but were never launched. Although taranabant and otenabant were derived from different structural classes, similar



1 (rimonabant)



2 (taranabant)

Figure 1. CB1 receptor antagonists.

increased incidence of psychiatric side effects led to termination after or during phase III clinical studies.[15−18]

The observed psychiatric side effects appear to preclude the use of CB1 receptor antagonists for non-life-threatening diseases or chronic treatment. However, it has become apparent that the CB1 receptor has peripheral functions, suggesting that peripherally active and selective agents may have therapeutic potential with reduced psychiatric side effects. Indeed, several groups have reported series of peripherally active CB1 receptor

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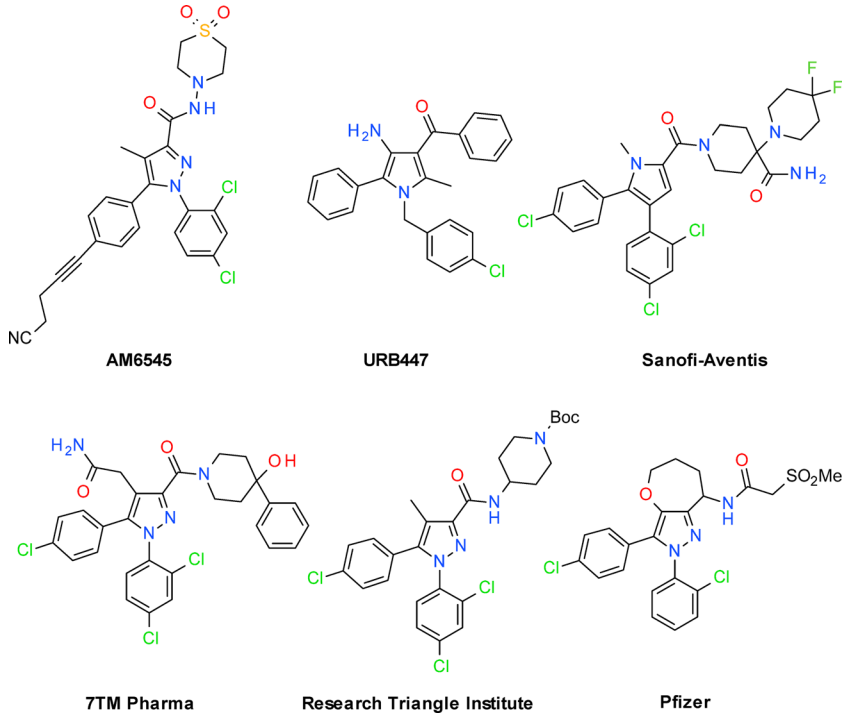
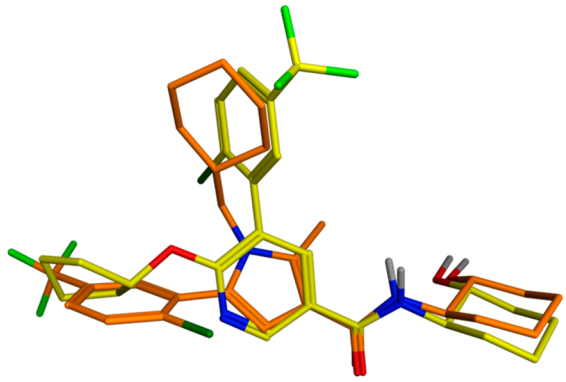


Figure 2. Peripherally selective CB1 receptor antagonists.



Compound	3	4
ClogP	7.3	5.9
hCB1-R IC_{50} [nM]	9.5±3.0	395±116
hCB2-R IC_{50} [nM]	>5000	2390±927
Cl mic rat @ 2 μM [μL min^{-1} kg^{-1}]	1323	367

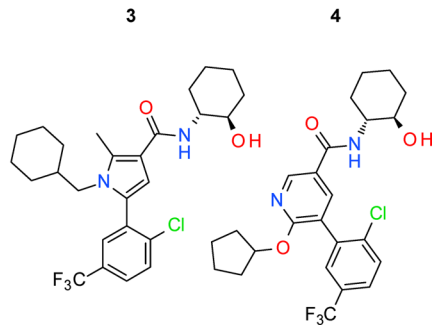


Figure 3. Superposition of low energy conformers of **3** (orange) and **4** (yellow) (upper panel); structures and data for **3** and **4** (lower panel).

antagonists in the past few years,[19,20] with the most common strategy to derive these molecules being the addition of polar groups onto known inhibitor backbones (Figure 2). This either increased polar surface area or conferred effective Pgp-mediated transport leading to reduced CNS exposure.

Our group has pursued a relatively small chemotype that has evolved into more polar and less brain penetrating molecules. We originally explored a series of rimonabant bioisosteres that evolved into compounds such as **3** (Figure 3).[21] Such substituted pyrroles had good CB1 receptor affinity and selectivity but exhibited low metabolic stability especially in rat microsomes. Metabolite profiling revealed multiple oxidative transformations; basically all substituents on the pyrrole were efficiently oxidized in rat microsomes.

Rather than trying to block all metabolically labile sites we employed a scaffold hop, replacing the electron rich pyrrole with

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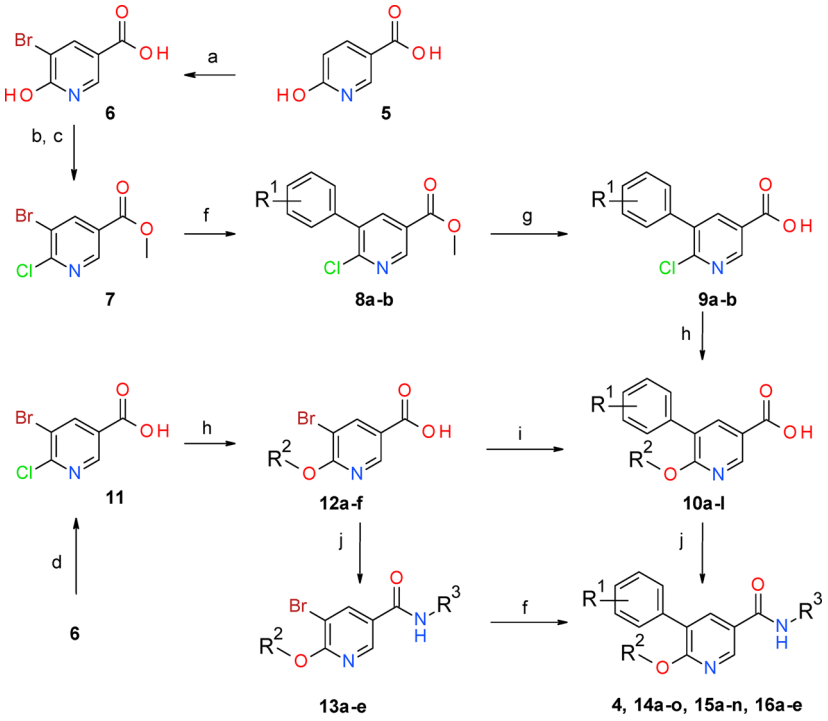
Scheme 1. Synthesis of Compounds[a]



[a]Reagents and conditions: (a) Br_2, AcOH; (b) $POCl_3$, reflux; (c) MeOH, reflux; (d) $POCl_3$, quinoline reflux, then water RT; (f) arylboronic acid, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Na_2CO_3, toluene, water, 90 °C; (g) $LiOH \cdot H_2O$, THF, water, reflux; (h) R^2-OH, KOH, DMSO, MW, 100 °C; (i) arylboronic acid, $(Ph_3P)_4Pd$, Na_2CO_3, DME, water, 85 °C; (j) various amide coupling methods.

a six-membered electron deficient heterocycle. We hypothesized that this strategy would eliminate the need for a methyl substituent on the core and additionally reduce the propensity for oxidation of the phenyl residue by rendering it less electron rich. In addition, the reduction in overall lipophilicity should decrease the susceptibility to oxidative attack by cytochrome P450s. As an initial prototype we chose to make nicotinamide **4** because modeling suggested that a low energy conformer of **4** would superpose sufficiently well onto the energy-minimized structure of **3**.

Compound **4** was still very lipophilic (ClogP of 5.9) with low CB1 receptor affinity (~40-fold less potent compared to **3**), however it was 4 times more stable than **3** in rat liver microsomes. Following these encouraging results, SAR exploration based on compound **4** was initiated by varying the alkoxy and aryl residues. Because subsequent molecules showed both improved affinity and metabolic stability, we also explored variations of the core and amide residue. In the course of this work, we identified several orally active 5-aryl-6-alkoxy-3-pyridinecarboxamides, including peripherally selective compounds.

CHEMISTRY

We explored several variations of the synthesis of 6-alkoxy-5-aryl-3-pyridinecarboxamides and finally selected the route depicted in Scheme 1, which allowed either amide or aryl variations to be performed in the final synthetic step.

All variants of this synthesis started with commercially available 6-hydroxy-nicotinic acid **5**, which was brominated in acetic acid, leading to **6** that was then converted with $POCl_3$ to 6-chloro-5-bromo-nicotinic acid chloride, which was then either hydrolyzed to the acid **11** with water or transformed to the corresponding methyl ester **7** by methanolysis.[22] Suzuki–Miyaura reaction of **7** with arylboronic acids furnished the 5-aryl substituted 3-pyridine carboxylic acid esters **8**, which were saponified to the acids **9**. This was followed by a S_NAr reaction to replace the 6-chloro substituent with alkoxides to give 6-alkoxy-5-aryl-3-pyridine carboxylic acids **10**. This was done on small scale with potassium hydroxide as base in DMSO in a microwave reactor. **During up-scaling tests, we measured the thermal stability of potassium hydroxide/DMSO mixtures in an accelerating rate calorimeter and found exothermic decomposition above 145 °C.** Consequently, for larger batches, we switched to a low temperature process that employed stirring of the above potassium hydroxide/DMSO mixtures for extended times between room temperature and 40 °C.[23] Similar high yields can be obtained by using this low-temperature variant of the reaction. Conventional amide coupling methods converted acids **10a–l** to the corresponding amides **14**, **15**, and **16**. This first synthetic variant allowed installing the alkoxide and amide in the last two steps of the synthesis. Alternatively, the alkoxide addition via the S_NAr reaction was done as first step with the acid **11** to give 6-alkoxy derivatives **12**. These, in turn, could be converted in a second step to the amides **13** and in the last step by Suzuki–Miyaura arylation to compounds **4**, **14**, **15**, and **16**. A final synthetic variant utilized the Suzuki–Miyaura arylation of 6-alkoxy derivatives **12** to afford an alternative route to 6-alkoxy-5-aryl-3-pyridine carboxylic acids **10**.

Some of the 6-alkoxy-5-aryl-3-pyridine carboxylic acids (**10m–q**) were produced by an alternative synthesis that started from 3-bromo-2-chloro-5-methyl-pyridine **22** (Scheme 2) using a series of steps beginning with nucleophilic aromatic substitution of **22** with alkoxides to furnish **23a–e**, followed by Suzuki–Miyaura arylations to give picolines **24a–e**. These were then transformed into the corresponding carboxylic acids **10m–q** by bromination, hydrolysis, and permanganate oxidation.

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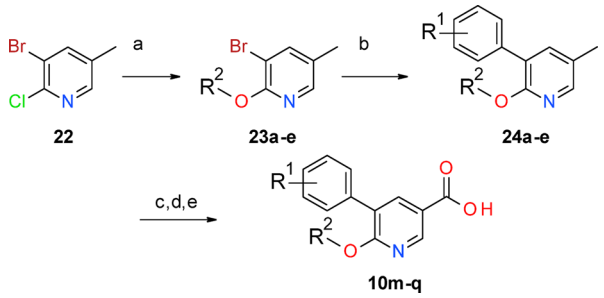
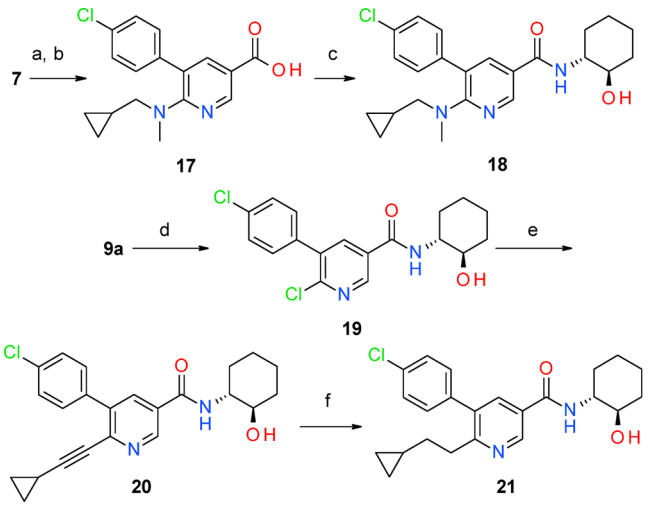
Scheme 2. Synthesis of Compounds 10m−q[a]



[a]Reagents and conditions: (a) R^2-OH, NaH, DMF; (b) arylboronic acid, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Na_2CO_3, toluene, water, 90 °C; (c) NBS, AIBN, CCl_4, hν; (d) NH_4OH, ethanol, reflux; H_2O; (e) Bu_4NMnO_4, pyridine, reflux.

The synthesis of 6-aza and 6-carbon analogues of 6-alkoxy-5-aryl-3-pyridine carboxamides can be accomplished in only 3−4 steps starting from some of the above-described intermediates (Scheme 3). As an example, nucleophilic aromatic substitution of

Scheme 3. Synthesis of Compounds 18, 21[a]



[a]Reagents and conditions: (a) *N*-methyl-cyclopropanemethanamine, DBU, 90 °C then 2N NaOH; (b) *B*-4-chlorophenyl-boronic acid, $(Ph_3P)_4Pd$, Na_2CO_3, DME, water, 85 °C; (c) (1*R*,2*R*)-2-amino-cyclohexanol hydrochloride, DMF, TBTU, DIEA, RT; (d) amine, TBTU, DIEA, DMF, rt; (e) $(Ph_3)_2PdCl_2$, Cu(I)I, TPP-resin, DMF, MW, 120 °C; (f) Pd/C, H_2, EtOAc.

7 with *N*-methyl-cyclopropanemethanamine in the presence of DBU, followed by saponification of the intermediate ester, yielded 5-bromo-6-[(cyclopropylmethyl)methylamino]-3-pyridinecarboxylic acid in 73% yield, which was then converted to **17** by Suzuki−Miyaura arylation followed by amide coupling to furnish **18**. The 6-carba analogue of **14g**, compound **21**, could be prepared from 6-chloro-5-(4-chlorophenyl)-3-pyridinecarboxylic acid (**9a**) by conversion to the amide **19**, followed by Sonogashira coupling with ethynylcyclopropane to afford **20**, and finally palladium-catalyzed hydrogenation to yield **21**.

To explore the effect of varying the nitrogen atom position in the core on CB1 receptor affinity, we pursued the synthesis of isosteric 2-pyridincarboxamides and also prepared the corresponding pyrazine and pyridazine carboxamides (Schemes 4 and 5).

5-Alkoxy-4-aryl-2-pyridine carboxamides (**32a,b**) were prepared from commercially available 2-chloro-3-pyridinol **25** by formylation (to give **26**) followed by iodination to **27** as described by Wishka et al.[24] The corresponding phenolate was selectively alkylated with alkylhalogenides to produce **28a** and **28b** in 86% and 92% yield, respectively. Suzuki−Miyaura coupling with the Pd(dppf) catalyst was regioselective and produced **29a** and **29b** with yields of greater than 97%. Chemoselective reduction with zinc in acetic acid provided the intermediates **30a,b**, which were oxidized to the acids **31a,b** with tetrabutylammoniumpermanganate in pyridine. The final step was an amide coupling that yielded the desired 5-alkoxy-4-aryl-2-pyridine carboxamides **32a,b**.

The synthesis of the isosteric 5-alkoxy-6-aryl-2-pyridinecarboxamides **37a,b** started from commercially available 2-chloro-3-fluoro-pyridine **33**. Suzuki−Miyaura coupling to produce **34** in 65% yield was followed by nucleophilic aromatic substitution with appropriate alkoxides and oxidation with hydrogen peroxide in acetic acid to yield the *N*-oxides **35a,b**. The *N*-oxides could be converted to the nitriles **36a,b** by treatment with dimethylcarbamic chloride and trimethylsilyl cyanide in acetonitrile. Two-step hydrolysis of the nitriles followed by amide coupling afforded the desired 5-alkoxy-6-aryl-2-pyridinecarboxamides **37a,b**.

Synthesis of pyrazines (Scheme 5) was realized from commercially available 3,5-dibromo-2-pyrazinamine **38**, which could be arylated with good regioselectivity (80% yield) to give the 3-arylisomer **39**. Classic diazotization-bromination chemistry furnished the 2,5-dibromo-3-aryl-pyrazine **40**. The nucleophilic aromatic substitution proceeded to **41** as the major isomer and was followed by palladium catalyzed carbonylation to provide the pyrazine carboxylate **42**. 5-Alkoxy-6-aryl-pyrazine-2-carboxamide **44** was obtained from **42** by saponification and coupling with (1*R*,2*R*)-2-amino-cyclohexanol.

Compound **51**, the pyridazine analogue of **14g**, was derived by multistep synthesis from 3,6-dichloro- pyridazine **45**. Nucleophilic aromatic substitution to give the monoalkoxylated product **46** was followed by iodination (to **47**) and Suzuki−Miyaura coupling to provide the 3-chloro-6-alkoxy-5-aryl-pyridazine **48**. Palladium-catalyzed carbonylation, saponification and coupling with (1*R*,2*R*)-2-amino-cyclohexanol provided the 6-alkoxy-5-aryl-pyridazine-3-carboxamide **51**.

RESULTS AND DISCUSSION

All compounds were tested in triplicate in CB1 and CB2 receptor binding assays as previously described.[25] Compounds with K_i values below 100 nM in CB1 receptor binding and lower than 20% inhibition at 3 μM at the CB2 receptor were further tested in a GTPγ[^{35}S] assay in HEK cells overexpressing the human CB1 receptor. All compounds behaved as functional antagonists in these assays. We used ClogP to rank compounds for lipophilicity because the log *D* for the higher lipophilicity compounds could not be easily determined. Rat microsomal clearance was determined as described in the Experimental Section.

Compound **4** with its cyclopentyloxy substituent was a moderately potent CB1 receptor antagonist. Systematic variation of the alkoxy substituent (Table 1) revealed that substituents larger than cyclopentyloxy lead to a 5−10-fold loss of potency, as shown for **14a** and **14b** in comparison with **14c**, while smaller substituents as exemplified by **14d−e** and **14g−i** lead to up to 30−70-fold improved potency compared to **14c**. More detailed examination of the SAR revealed that the size was not the determining factor; rather substitution adjacent to the oxygen atom is detrimental. Consistent with this observation, the 2-

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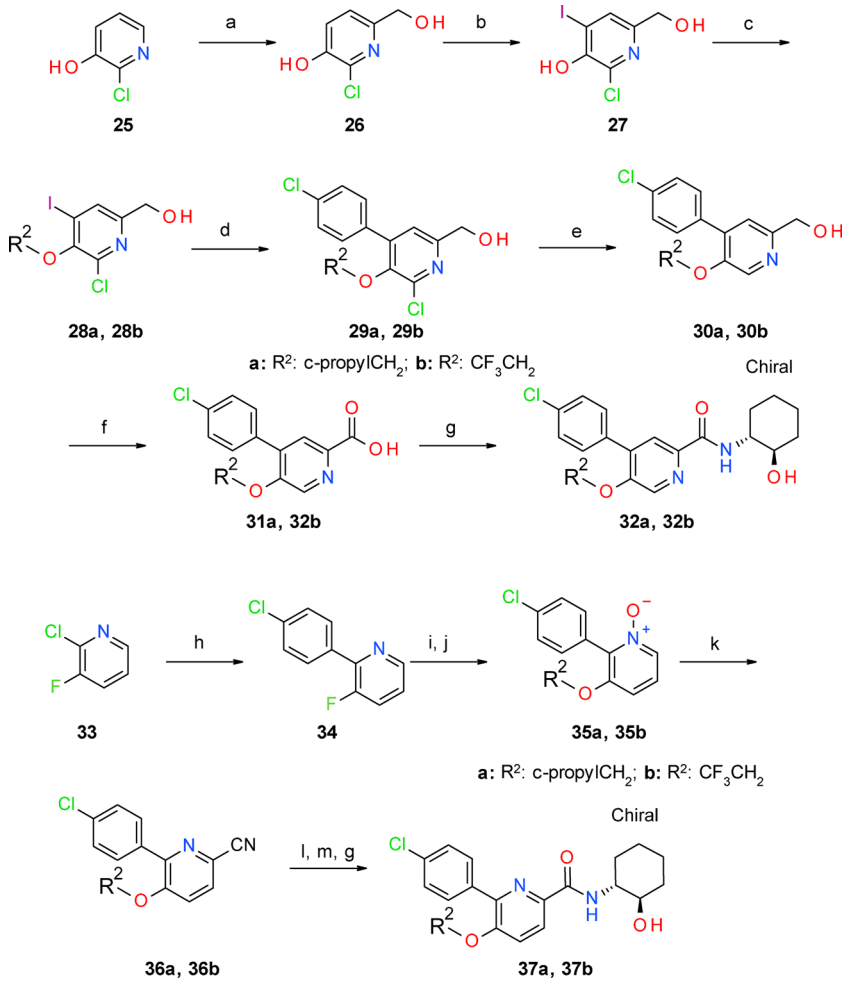
Scheme 4. Synthesis Substituted 2-Pyridine Carboxamides 32a,b and 37a,b[a]



[a]Reagents and conditions: (a) CH_2O, $NaHCO_3$, reflux; (b) I_2, $NaHCO_3$; (c) R^2-X, NaH, DMF, 90 °C; (d) arylboronic acid, Pd(dppf)Cl_2·CH_2Cl_2, Na_2CO_3, toluene, water, 90 °C; (e) Bu_4NBr, Zn, AcOH, 50 °C; (f) Bu_4NMnO_4, pyridine, 80 °C; (g) (1*R*,2*R*)-2-amino-cyclohexanol hydrochloride, DMF, TBTU, DIEA, rt; (h) arylboronic acid, Pd(dppf)Cl_2·CH_2Cl_2, toluene, DMF, Na_2CO_3, water, 90 °C; (i) R^2-OH, base, DMSO, rt; (j) H_2O_2, AcOH, 70 °C; (k) *N*,*N*-dimethyl-carbamic chloride, TMSCN, Et_3N, CH_3CN; (l) AcCl, EtOH, 90 °C; (m) NaOH, THF, water, 80 °C.

propyloxy compound **14f** is 20-fold less potent than the *n*-butyloxy compound **14e**, while compounds with bigger substituents such as benzyloxy- **14j** and the heterocyclylmethyloxy- compounds **14k–n** are all potent CB1 receptor antagonists. The alkoxy oxygen atom itself does not contribute to potency as both the *N*-methyl nitrogen analogue **18** and the carbon analogue **21** have potency similar to **14g**.

Both **18** and **21** are, however, inferior to **14g** with respect to ClogP and metabolic stability in rat microsomes due to increased susceptibility to either oxidative *N*-demethylation or benzylic hydroxylation of **18** and **21**, respectively. Of the compounds in Table 1, **14g–j**, **14l**, and **14o** were the most stable in rat microsomes. The increased metabolic stability of these compounds may be, in part, due to the reduced overall lipophilicity compared to **14a**. Alternatively, improved metabolic stability may be due to a reduced rate of hydroxylation of the CH_2-group in α-position to the alkoxy oxygen by interference of neighboring groups (i.e., cyclopropyl for **14g**, CF_3 for **14i**, γ-heteroatoms for **14h**, **14l**, and **14o**). Compound **14g** serves as reference to highlight the SAR of aryl- (Table 2), amide- (Table 3), and core- variations (Table 4) because we have the most complete set of data for analogues of **14g**.

Moving the 4-chloro-atom to the 2-position on the phenyl ring, as in **15b**, led to a 17-fold loss in potency compared to **14g**, which could be partially compensated for by reintroduction of the 4-chloro-atom as in **15a**, which led to only 11-fold loss of potency compared to **14g**. Results with compound **15e** suggest that double substitution in the 2- and 5-position partially restores potency; the 5-position substituent compensating for the negative impact of the 2-position substituent. Polar 4-position substituents were detrimental for CB1-receptor affinity (**15k–n**), with the 4-methoxy group leading to about 6-fold loss of affinity compared to **14g**. However, all halogens and pseudohalogens in the 4-position seem to be equally acceptable, leading to compounds with potent CB1 receptor affinity. Metabolic stability in rat microsomes for **15g** (4-CF_3) and **15h** (4-OCF_3) was excellent, which, for **15h**, was also corroborated by its high and sustained plasma exposure in rat SDPK studies (Supporting Information Figure S2). These data may indicate that modifications that reduce the propensity for arylhydroxylations yield metabolically more stable molecules suitable for in vivo experiments. Alternatively, the two relatively lipophilic compounds, **15g** and **15h**, may be protected from metabolic turnover by high protein binding. In some cases, microsomes actually under predicted the metabolic stability of these

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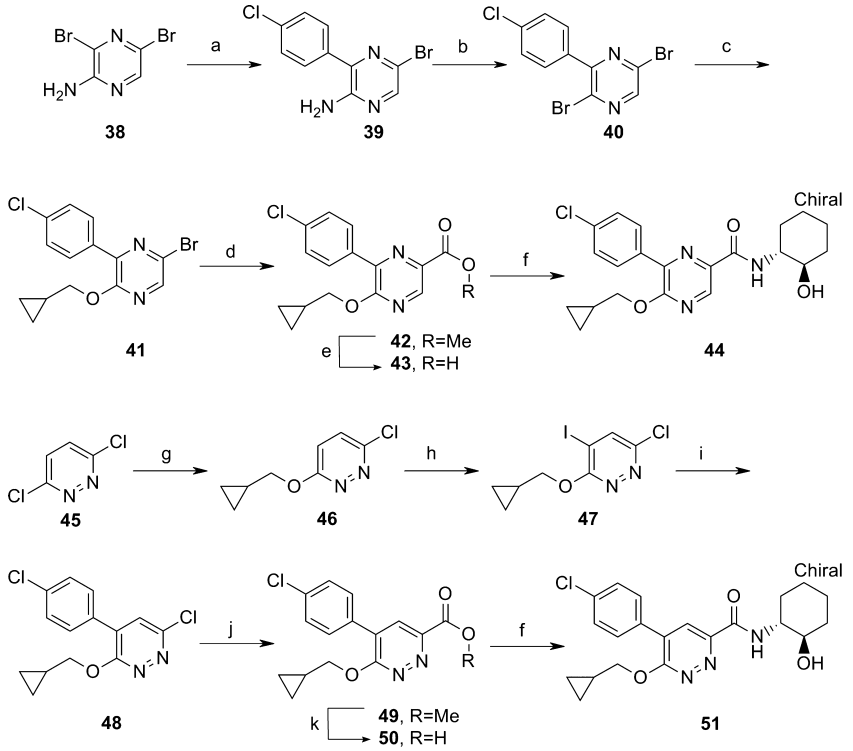
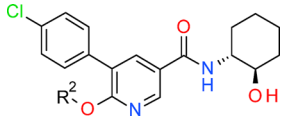
Scheme 5. Synthesis of Compounds 44 and 51 with Pyrazine and Pyridazine Scaffold, Respectively[a]



[a]Reagents and conditions: (a) arylboronic acid, $(Ph_3)_4Pd$, Na_2CO_3, THF/water, 90 °C; (b) isoamylnitrite, TMSBr, CH_2Br_2, rt; (c) cyclopropanemethanol, NaH, DMF, rt; (d) $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, CO, NEt_3, MeOH, 70 bar, 120 °C; (e) LiOH, water, THF, rt; (f) (1*R*,2*R*)-2-amino-cyclohexanol hydrochloride, DMF, TBTU, DIEA, rt; (g) cyclopropanemethanol, NaH, DMSO, rt; (h) *n*-BuLi, TMP, I_2, THF, −75 °C; (i) arylboronic acid, $(Ph_3)_4Pd$, Na_2CO_3, THF/water, 90 °C; (j) $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, CO, NEt_3, MeOH, 70 bar, 120 °C; (k) LiOH, water, THF, rt.

Table 1. In Vitro Pharmacology, ClogP, and Microsomal Stability for Compounds 14a−o



	R^2	hCB1-R K_i [nM]	hCB2-R K_i [nM]	ClogP	Cl mic rat @ 2 μM [μL min^{-1} kg^{-1}]
14a	cyclohexyl	3035 ± 394	>10000	5.8	662
14b	phenyl	1657 ± 625	>10000	5.1	353
14c	cyclopentyl	374 ± 223	>10000	5.3	
14d	cyclobutyl	208 ± 130	>10000	4.7	210
14e	*n*-butyl	43.8 ± 11.0	>10000	5.4	101
14f	2-propyl	1074 ± 127	>10000	4.6	
14g	cyclopropylmethyl	11.4 ± 4.5	>7000	4.8	64
14h	methoxyethyl	5.1 ± 1.6	>10000	3.7	98
14i	2,2,2-trifluoroethyl	12.4 ± 6.7	>7000	4.6	23
14j	benzyl	40.2 ± 14.7	>10000	5.2	20
14k	(3-methyl-isoxazol-5-yl)methyl	10.6 ± 4.8	>10000	3.4	151
14l	pyrimidin-2-ylmethyl	51.6 ± 24.5	>10000	2.7	12
14m	pyridin-4-ylmethyl	58.7 ± 49.2	>10000	3.7	118
14n	pyridin-3-ylmethyl	23.5 ± 8.5	>10000	3.7	374
14o	pyridin-2-ylmethyl	139 ± 93	>10000	3.7	44
18		51.1 ± 20.3	>10000	5.3	1730
21		16.7 ± 3.4	>10000	5.3	1503

compounds, while rat hepatocyte clearance seemed to be more predictive for in vivo behavior. For example, rat hepatocyte clearance for **14g** was 3.3 μL min^{-1} $(10^6$ cells$)^{-1}$ @ 10 μM, and in vivo clearance and V_{ss} in rat at a dose of 1 mg/kg iv was 7.4 mL min^{-1} kg^{-1} and 1.8 L/kg, respectively.

The SAR exploration of the amide side chain revealed that the rimonabant-like side chain (piperidin-1yl) is inferior to the (1*R*,2*R*)-2-hydroxycyclohexyl side chain of **14g**, as shown by the 50-fold loss in potency observed with **16a**. The enantiomer and the diastereoisomers of **14g** (cf. **16c−e**) lose considerable potency for the CB1 receptor. Suitable alternatives leading to

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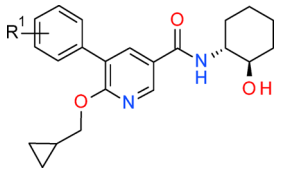
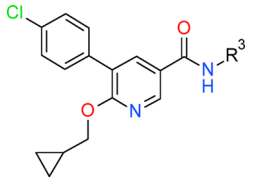
Table 2. In Vitro Pharmacology, ClogP, and Microsomal Stability for Compounds 15a−n



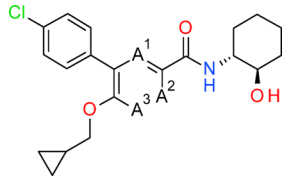
	R^1	hCB1-R K_i [nM]	hCB2-R K_i [nM]	ClogP	Cl mic rat @ 2 μM [μL min^{-1} kg^{-1}]
15a	2,4-dichloro	122 ± 49	>5000	5.2	
15b	2-chloro	190 ± 150	>10000	4.5	
15c	3,4-dichloro	305 ± 201	1260 ± 320	5.4	
15d	3-chloro	129 ± 60	>5000	4.8	
15e	2-chloro-5-CF_3	67.7 ± 21.4	2080 ± 480	5.4	59
15f	4-fluoro	42.8 ± 26.0	>10000	4.2	37
15g	4-CF_3	18.5 ± 1.9	>10000	5.0	9
15h	4-CF_3O	23.6 ± 11.4	>10000	5.2	0−3
15i	4-methoxy	66.4 ± 11.2	>10000	4.1	
15j	4-cyano	23.6 ± 12.7	>10000	3.5	
15k	4-methanesulfonylamino	1900 ± 820	>10000	3.0	
15l	4-sulfamoyl	>10000	>10000	2.4	
15m	4-carboxy	>10000	>10000	3.9	
15n	4-carbamoyl	>8000	>10000	2.7	
14g	4-Cl	11.4 ± 4.5	>7000	4.8	64

Table 3. In Vitro Pharmacology, ClogP, and Microsomal Stability for Compounds 16a−e



	R^3	hCB1-R K_i [nM]	hCB2-R K_i [nM]	ClogP	Cl mic rat @ 2 μM [μL min^{-1} kg^{-1}]
16a	piperidin-1-yl	563 ± 242	>10000	5.2	
16b	(2*R*)-2-cyclopropyl-2-hydroxypropyl	34.3 ± 27.7	>10000	4.5	2.4
16c	(1*S*,2*S*)-2-hydroxycyclohexyl	247 ± 52	2637 ± 342	4.8	
16d	(1*R*,2*S*)-2-hydroxycyclohexyl	186 ± 75	>5000	4.8	163
16e	(1*S*,2*R*)-2-hydroxycyclohexyl	104 ± 48	>7000	4.8	111

Table 4. Pharmacological Data for Core Variants



compd	core (A^1, A^2, A^3)	hCB1-R K_i [nM]	hCB2-R K_i [nM]
32a[a]	C, N, C	>7000	1526 ± 701
37a[a]	N, C, C	1830 ± 1369	863 ± 546
44	N, C, N	25.8 ± 13.5	801 ± 171
51	C, N, N	>5000	>3000
14g	C, C, N	11.4 ± 4.5	>7000

[a]Values measured for **32b** and **37b** confirmed a drastic loss of affinity for the CB1 receptor for these isosters of **14i**.

CB1 affinity similar to the (1*R*,2*R*)-2-hydroxycyclohexyl side chain are many other simple hydroxy-alkyl side chains (data not shown). However, care must be taken to avoid introducing metabolically labile sites. One useful example is compound **16b**, with its tertiary hydroxy group where the cyclopropyl group provides the additional steric bulk in this position that is necessary to obtain high affinity CB1 receptor ligands.

Compound **14g** and some of its core variants (**32a**,**b**, **37a**,**b**, **44**, and **51**) allow us to rationalize the CB1 binding pharmacophore in this compound class. The energy-minimized structure of pyrazine **44** in Figure 4 served as a template to explore the CB1 pharmacophore. In the minimum energy conformer, the orientation of the amide bond is locked via a combination of reduced steric repulsion and the favorable electrostatic interaction between the amide NH H-bond donor with the aromatic nitrogen H-bond acceptor.[26] The amide bond in **14g** has no preference for either of the two possible planar orientations and, therefore, **14g** is readily able to adopt the same conformation as **44**.

The loss in potency observed with the isostere **37a** highlights the relevance of the pyridine nitrogen in both **44** and **14g** to mediate an attractive interaction with the CB1 receptor. The dramatic decrease of binding activity of the isosteric 2-pyridinecarboxamide **32a** and pyridazine **51** compared to **14g** can be rationalized by the different relative orientation of the phenyl and amide substituents. The change in vector arrangement with respect to the aryl group and the amide carbonyl is depicted by the orange arrows overlaid on **44** and **32a** in Figure 4.

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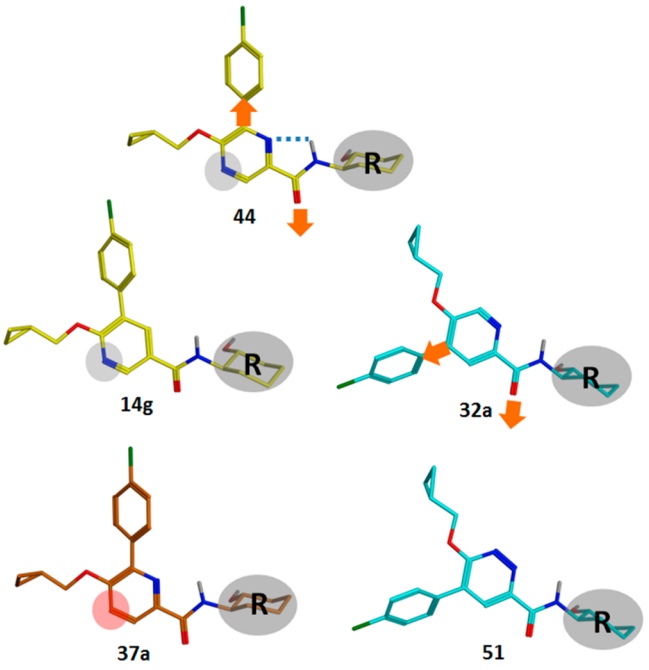

Figure 4. Definition of the pharmacophore for CB1 antagonists based on the pyrazine template **44**. The orientation of the amide group is determined by a combination of reduced steric repulsion and attractive electrostatic interaction between the amide NH and the pyridine nitrogen (marked by the dashed line). CB1 receptor antagonists appear to require optimal positioning of the pyridine nitrogen for efficient receptor interaction (highlighted in **44** and **14g** as opposed to **37a**). In the low energy conformers of **32a** and **51**, the phenyl and amide group adopt a different relative orientation (highlighted by the orange arrows on **44** and **32a**).

The exit vector geometry between the aryl and amide groups appears relevant for CB1 receptor binding. Exit vector geometry in all isosteres except **14g** is constrained by the strong preference of the 2-pyridylamides, 2-pyrazineamides, and 2-pyridazylamides for the depicted planar geometries.[26]

Several compounds were selected based on their in vitro CB1 receptor affinity profiles and stability in rat microsomes and characterized further in functional assays and single dose PK (SDPK) experiments in rats in comparison with rimonabant (Table 5). Compounds **14g** and **14h** were approximately 2-fold less potent with respect to binding and 2- (**14g**) to 6-fold (**14h**) less potent as antagonists in the GTPγ[^{35}S] assay compared to rimonabant. SDPK studies after oral administration showed both **14g** and **14h** to have better bioavailability than rimonabant, leading to substantially higher C_{max} and AUC values (latter are not shown). Dose-normalized plasma exposure of **14g** was 4-fold and of **14h** was 7-fold higher than rimonabant (C_{max}/dose: rimonabant 24.4, **14g** 92.3, **14h** 179 ng/mL). The significantly higher dose-normalized exposure of **14g** and **14h** compensated for their lower in vitro potency compared to rimonabant, allowing us to use them in in vivo experiments at reasonable doses. Plasma exposure of **14g** and **14h** in all in vivo studies was significantly above the K_i for CB1 receptor binding for both total as well as the protein unbound fraction. All three molecules are lipophilic, but rimonabant is by far the most lipophilic of the three, with a ClogP of 6.5 followed by **14g** (ClogP 4.8) and **14h** (ClogP 3.7). This was reflected by significant differences in several parameters such as volume of distribution, which was lowest for **14h**. Bioavailability increased with decreasing

Table 5. Rat PK Data of Selected Compounds Compared with Rimonabant[a]

	rimonabant	14g	14h
K_i hCB1-R [nM]	5.9 ± 4.9	11.4 ± 4.5	5.1 ± 1.6
EC_{50} GTPγ[^{35}S] hCB1-R [nM]	1.5 ± 0.2[c]	3.9 ± 3.3[d]	11.6 ± 8.2[d]
rat Cl [mL min^{-1} kg^{-1}]	54[b]	7.4[e]	18.6[f]
rat Vss [L/kg]	19.5[b]	1.8[e]	0.7[f]
rat plasma C_{max} [ng/mL]	244[g]	729[h]	1615[i]
rat plasma T_{max} [h]	1.5[g]	1.9[h]	0.5[i]
F [%]	nd[b]	23[h]	84[i]
B/P ratio	3−5	∼0.7	∼0.1
rat PPB [%]	99.7	>98.4	96.1
rat plasma $C_{unbound,max}$ [ng/mL]	0.83[g]	<11[h]	63[i]
$C_{unbound,max}$ [nM]	1.8[g]	<28[h]	156[i]

[a]Cl, clearance; Vss, volume of distribution at steady state; F, bioavailability in % at the given dose; B/P ratio, Brain to plasma ratio; PPB, plasma protein binding. [b]Reported values: Cl, ∼17 mL min^{-1} kg^{-1}; Vss, 11.5 L/kg; T_{max}, 1−3 h; F, 12% (male rats).[27] [c]n = 7. [d]n = 3. [e]@ 1 mg/kg iv. [f]@ 3.3 mg/kg iv. [g]@ 10 mg/kg po. [h]@ 7.9 mg/kg po. [i]@ 9 mg/kg po

lipophilicity, most likely due to improved solubility and dissolution rate, while plasma protein binding decreased. As one would expect, lipophilicity, or to be more precise, polar surface area, was directly related to brain/plasma ratio. Both 6-alkoxy-5-aryl-3-pyridinecarboxamides have reduced brain to plasma ratios in comparison to rimonabant. In the case of **14h**, the brain/plasma ratio of 0.1 suggests that doses can be identified that selectively antagonize CB1 receptors outside the CNS.

The set of compounds in Table 5 was selected to explore the relative importance of central and peripheral antagonism of CB1 receptors on food intake and body weight. In the periphery, the high plasma exposure of **14g** and **14h** after oral dosing in rat compensates for their lower affinity compared to rimonabant, while at exposure levels expected to be relevant in the periphery, brain/plasma ratios of these three compounds range from ∼4 for rimonabant to ∼0.1 for **14h**. This 1.5 log unit difference in brain/plasma ratios should be sufficient to probe the relative contributions of peripheral vs central CB1R antagonism to therapeutic response. To exclude the possibility of unexpected non-CB1R-mediated effects, a CEREP binding profile against 80 unrelated receptors and enzymes was performed. Both **14g** and **14h** were confirmed as selective CB1 receptor binders, with **14g** showing no other relevant interactions and **14h** identified only as a weak NK2 receptor antagonist with an IC_{50} of 46 μM.[28]

Compounds were tested in a rat model of diet induced obesity. All compounds were given as food admix. Compounds **14g** and **14h** were administered to deliver 30 mg/kg/day for each, and rimonabant was given at 10 mg/kg/day. Food admix was chosen to ensure the new compounds maintained plasma exposure well above their CB1 receptor K_is throughout the day, as well as to ensure a smooth PK profile by minimizing differences between peak and trough levels. To confirm exposure, the PK profile for **14g** and **14h** was measured after 10 days of food admix in a separate experiment in catheterized rats (Figure 5).

Interindividual variability in exposure was low for **14g**, with plasma C_{max} of 1025 ng/mL and brain levels of 1400 ng/g after 10 days of administration. These were similar to the single dose PK data but showing a slight accumulation in brain, which reached a brain/plasma ratio of 1.3 at steady state. For **14h**, interindividual variability was also low. Plasma C_{max} was 1000 ng/mL and brain levels were 130 ng/g at steady state, giving a calculated brain/

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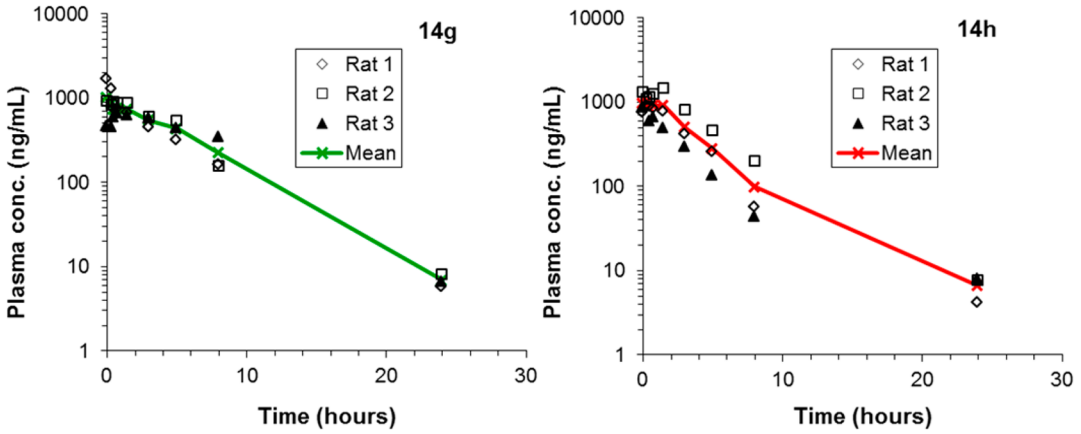

Figure 5. Plasma exposure data for **14g** and **14h** (three individual Sprague–Dawley rats each, 10 days of 30 mg/kg/day as food admix in chow, blood sampling started after removal of food on day 10).

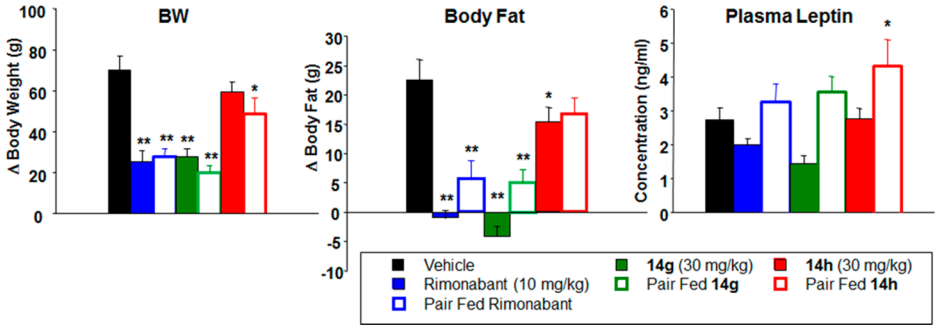

Figure 6. Body weight gain, body fat (determined by MRS) and plasma leptin levels in high fat diet fed Sprague–Dawley ($N = 8–9$) rats after 24 days of dosing with rimonabant (10 mg/kg daily as food admix), **14g** (30 mg/kg daily as food admix), and **14h** (30 mg/kg daily as food admix). Data expressed as mean ± SEM, $*p < 0.05$ or $**p < 0.01$ compared to vehicle (ANOVA followed by Dunnett's posthoc test); nonfilled bars denote paired-feeding groups for rimonabant, **14g**, and **14h**, respectively.

plasma ratio of 0.13. These PK studies confirmed that peripheral exposure levels were well above CB1 receptor K_i for both compounds and that the peripheral/brain selectivity for **14h** was sustained during chronic administration.

Rimonabant performed as previously reported in high fat diet fed rats,[29] substantially and significantly reducing body weight gain at the dose of 10 mg/kg. Reduced body weight gain was accompanied by a significant reduction in body fat content and decreased plasma leptin levels compared to vehicle-treated animals. These results were similar in animals pair-fed to the rimonabant group which had identical body weight loss, a significant reduction in body fat, but had no reduction in plasma leptin levels. The 6-alkoxy-5-aryl-3-pyridinecarboxamides **14g** and **14h** share similarly high plasma C_{max} values, have similar affinities for the CB1 receptor, but differ by a factor of 10 with respect to brain/plasma ratios. This difference in brain/plasma ratios is very succinctly mirrored in the results of the high fat feeding experiment. Administration of **14g** led to a strong and significant reduction in body weight gain and a significant and even stronger reduction in body fat content than was observed with rimonabant as well as a significant reduction of leptin levels in plasma (Figure 6). Conversely, **14h** had no significant effect on body weight gain, produced a minor reduction in body fat content and had no effect on plasma leptin levels. Pair-fed groups showed the same pattern of effects that were observed in the study with rimonabant. Treatment-related changes in body weight were nicely reproduced in pair-fed animals, with slightly less effect to reduce body fat content but no reduction in plasma leptin. Notably, the pair-fed groups had significantly higher leptin levels vs their corresponding drug group. Moreover, in all cases, leptin levels were even higher than in the vehicle group, albeit the increases were not significant if compared to vehicle.

Leptin is mainly expressed by adipose tissue.[30] Lower plasma leptin levels by reduced adipose mass is expected and has been previously described.[31] The relationship between body fat and leptin levels was fully reproduced in the three drug-treated groups in comparison to vehicle-treated controls. However, this relationship did not appear to hold for the pair-fed groups, which was initially puzzling. It is tempting to ascribe the lower leptin levels in the drug-treated groups compared to the pair-fed groups to an additional metabolic benefit and possibly peripheral effect of CB1 receptor antagonists; however, the plasma leptin levels measured for **14h** did not support this hypothesis. The observation that all pair-fed groups had unexpectedly high plasma leptin levels may have been due to the fact that drug-treated groups were provided ad libitum access to food while pair-fed groups were food restricted. This difference may have influenced stress hormones and leptin levels. Consistent with this notion is that behavioral stressors like restriction stress do increase plasma leptin levels in cafeteria-diet induced obese rats.[32]

To test for effects of CB1 receptor antagonist treatment on glucose tolerance and insulin sensitivity, an oral glucose tolerance test was performed. Both rimonabant and **14g** improved insulin sensitivity in an OGTT assay after 24 days of high fat diet fed Sprague–Dawley rats, as reflected by decreased insulin AUC

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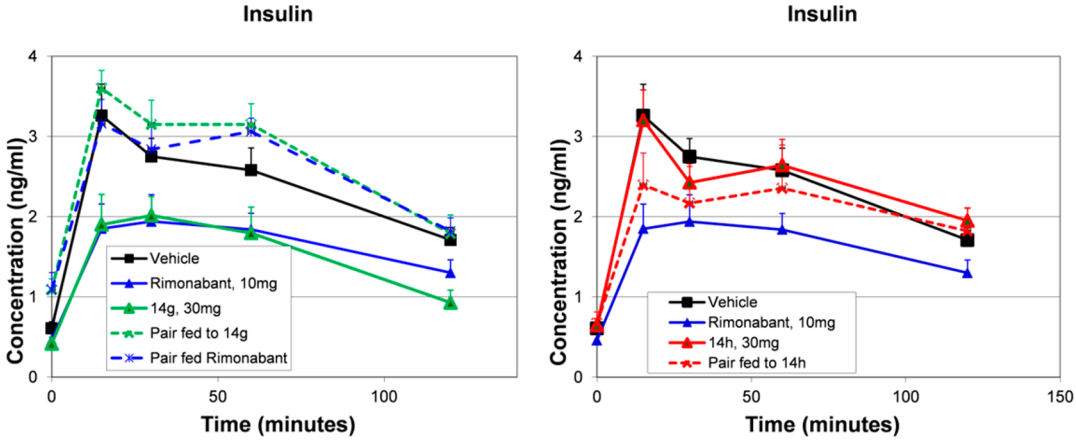

Figure 7. Insulin excursion curves obtained after oral glucose challenge performed after 24 days of CB1 receptor antagonist treatment as detailed in Figure 6 in overnight fasted obese SD (Sprague–Dawley) rats. A glucose load of 2 g/kg body weight was administered as bolus by gavage. Dotted lines denote pair-fed groups. Rimonabant and vehicle curves are shown twice for clarity.

(Figure 7). Glucose excursion curves for all treatment groups were unchanged compared to vehicle (Supporting Information Figure S1). Groups pair-fed to both rimonabant and **14g** showed, despite reduction of body weight gain, no improvement in insulin sensitivity compared to vehicle. Likewise, the peripherally selective CB1 antagonist **14h**, as well as its pair-fed group, showed no improvement in insulin sensitivity compared to the vehicle group. Our data (with **14g**, rimonabant, and their respective pair-fed groups) reinforce the notion that improvement of insulin sensitivity is mainly driven by the central mechanism of action of the compounds; an interpretation that is corroborated by the data for **14h** which did not have an effect on insulin sensitivity in this model.

CONCLUSIONS

6-Alkoxy-5-aryl-3-pyridinecarboxamides are a new, relatively small chemotype that has delivered potent CB1 receptor antagonists with inherent high selectivity over CB2 receptors. The series was optimized to obtain molecules with modest lipophilicity compared to rimonabant, consequently lower brain exposure and, as demonstrated for **14h**, peripherally selective molecules. Selected compounds were shown to be selective vs a panel of unrelated receptors. Several molecules showed high and persistent plasma exposures in rats and were selected as tools for pharmacological investigations. Both rimonabant and **14g** significantly reduced the rate of body weight gain and decreased adiposity in high fat fed rats. However, the poorly brain penetrant molecule **14h** had no significant effect on body weight gain and only a marginal effect on body fat reduction. Both single dose PK and PK after chronic administration as food admix confirmed high plasma exposure for **14h** comparable to the levels reached with **14g**, an equipotent, structurally close analogue. Thus, the lack of pharmacological activity for **14h** could not be explained by lack of peripheral exposure. Indeed, unbound plasma levels of **14h** were achieved that would be expected to provide even greater receptor occupancy than for pharmacologically effective levels of either **14g** or rimonabant. The lack of metabolic effects for **14h** is more likely consistent with its substantially lower exposure in brain tissue, which was similarly low in both single and chronic dosing studies. Although we did not measure unbound fraction in brain, we feel that the low total exposure in brain explains the lack of pharmacological activity for **14h**. This observation suggests that peripheral CB1 antagonism is not sufficient to achieve metabolic benefits, This conflicts with several earlier reports, suggesting that peripherally selective CB1 receptor antagonists retain effects on food intake and body weight. However, two of the earlier compounds, LH-21 and AM6545, were subsequently tested in CB1 receptor knockout mice and were able to reduce body weight even in the absence of CB1 receptors, pointing to off-target pharmacology.[33,34] Results with JD5037 varied depending on the experimental model. In db/db and ob/ob mice, JD5037 improved insulin sensitivity without affecting body weight, while in DIO mice, JD5037 strongly reduced body weight. These data suggested an interaction with leptin signaling that differs between the genetic and diet models.[35] JD5037 has not been evaluated in CB1 receptor knockout mice.

Recently, new evidence from CNS-specific CB1 receptor knockdown experiments in mice has added further support for the relevance of central CB1 receptors for the antiobesity and metabolic benefits of rimonabant.[36,37] These CNS-specific CB1 receptor knock-down animals show the typical body weight and metabolic benefits associated with global CB1 receptor knock out. Moreover, the effects of rimonabant on body weight, glucose, insulin, leptin, and adiponectin were lost in these animals, indicating an essential role for CB1 in the brain to mediate the effects of CB1 receptor antagonists.

On the basis of the preponderance of evidence derived from experience with the molecules detailed above, as well as the emerging literature in tissue-specific CB1 receptor KO animals, we believe that the metabolic benefits of CB1 receptor antagonists are, indeed, and as originally believed, centrally mediated. It is conceivable, however, that peripheral CB1 receptor antagonists may provide other benefits perhaps via anti-inflammatory mechanisms in the periphery and may have relevance in treatment of specific conditions such as hepatic steatosis[11] or ischemia/reperfusion injury.[38]

EXPERIMENTAL SECTION

Compound Synthesis and Characterization. Chemistry. Reactions were conducted under argon atmosphere. Unless otherwise mentioned, all reagents and chemicals were obtained from commercial suppliers and used without further purification. Flash column chromatography was carried out on a Jones Chromatography Flashmaster II system using Telos Flash silica or Isolute FlashSi prepacked columns. Compounds were characterized by a combination of TLC, NMR, and MS analytical techniques as described below. Purity

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of compounds used in bioassays was determined by reverse-phase high performance liquid chromatography (HPLC) analysis to be ≥95% by using an Agilent LC-system consisting of Agilent 1290 high pressure system with DAD detection, a CTC PAL auto sampler, and a Agilent 6520 QTOF. The separation was achieved on a Zorbax Eclipse Plus C18 1.7 μm 2.1 mm × 50 mm column at 55 °C; A = 0.01% formic acid in water; B = 0.01% formic acid in acetonitrile at flow 1 mL/min. Gradient: 0 min 5%B, 0.3 min 5%B, 4.5 min 99%B 5 min 99%B; UV wavelength for purity assessment 265 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400, Bruker AVANCE II 400, or on a Bruker AVANCE III 600 spectrometer and were determined in $CHCl_3$-*d* or DMSO-d_6 with tetramethylsilane (TMS) (0.00 ppm) as the internal reference unless otherwise noted. Chemical shifts are reported in ppm relative to TMS, and coupling constants (*J*) are reported in hertz (Hz). Thin-layer chromatography (TLC) was performed on EMD precoated silica gel 60 F254 plates, and spots were visualized with UV light or chemical detection. Low-resolution mass spectra were obtained using an Applied Biosystem API300, and high resolution LC-MS data were obtained using an Agilent Q-TOF 6520 system.

*5-Bromo-1,6-dihydro-6-oxo-3-pyridinecarboxylic Acid (**6**).* To a suspension of **5** (Acros, 50 g, 0.359 mol) in acetic acid (100 mL) was added bromine (27.7 mL, 0.539 mol) dropwise during 45 min. The temperature rose to 45 °C during the addition, and the resulting mixture was stirred for 18 h at 50 °C. The mixture was concentrated and dried in vacuo (45 °C/20 mbar) to afford an orange solid that was digested with toluene (350 mL). The solid was isolated by filtration, washed with toluene (4 × 50 mL), and dried (40 °C/20 mbar) to produce **6** (78.9 g, quant) as yellow−orange solid.

*5-Bromo-6-chloro-3-pyridinecarboxylic Acid Methyl Ester (**7**).* To **6** (50 g, 0.229 mol) was added phosphorus oxychloride (Aldrich, 170 mL, 1.86 mol), and the resulting mixture was slowly warmed and stirred for 5 h at 70 °C. After cooling volatiles were removed in vacuo, toluene (2 × 100 mL) was added to the residue and the mixture was concentrated twice. The residue was combined with DCM (80 mL) and transferred to a reaction vessel. Methanol (250 mL, 6.18 mol) wad added dropwise during 15 min (caution: very exothermic). The mixture was stirred for 1 h at 70 °C, cooled to room temperature, and concentrated. The residue was dissolved in diethyl ether and neutralized (final pH of 8) by addition of saturated sodium bicarbonate (100 mL) and sodium hydroxide solution (2 N, 390 mL). Phases were separated, the water phase was extracted with additional diethyl ether, and all organic phases were, after a final wash with sodium bicarbonate, combined. The organic phase was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with 35% ethyl acetate in heptane and crystallized from heptane to afford **7** (42.0 g, 73% yield) as white solid; mp 78−79 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 8.53 (d, *J* = 2.0, 1 H), 8.93 (d, *J* = 2.0, 1 H).

*6-Chloro-5-(4-chlorophenyl)-3-pyridinecarboxylic Acid Methyl Ester (**8a**).* To a solution of **7** (70 g, 0.28 mol) in toluene (1200 mL) was added with stirring the [1,1-bis(diphenylphos-phino)ferrocene] dichloropalladium DCM complex (11.4 g, 14 mmol), 4-chlorophenylboronic acid (45.05 g, 0.28 mol), and sodium carbonate solution (280 mL, 2M). The resulting mixture was stirred at 90 °C for 1 h, cooled, and partitioned between water and ethyl acetate. The organic portion was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with DCM/heptane to produce **8a** (52.2 g, 66%) as white solid; mp 105−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 7.40 (d, *J* = 8.8, 2 H), 7.46 (d, *J* = 8.8, 2 H), 8.24 (d, *J* = 2.2, 1 H), 8.89 (d, *J* = 2.2, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{13}H_{10}Cl_2NO_2$ 282.0089; found 282.0083.

*6-Chloro-5-(4-fluorophenyl)-3-pyridinecarboxylic Acid Methyl Ester (**8b**).* Following a procedure similar to the preparation of **8a**, 4-fluorophenylboronic acid (46.1 g, 319 mmol) was used to produce **8b** (49.5 g, 58%) as white solid; mp 95−97 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 7.18 (t, *J* = 8.7, 2 H), 7.45 (dd, *J* = 8.9, 5.3, 2 H), 8.25 (d, *J* = 2.3, 1 H), 8.98 (d, *J* = 2.3, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{13}H_{10}ClFNO_2$ 266.0384; found 266.0382.

*6-Chloro-5-(4-chlorophenyl)-3-pyridinecarboxylic Acid (**9a**).* To a solution of **8a** (52.2 g, 185 mmol) in THF (1300 mL) was added water (400 mL) and lithium hydroxide monohydrate (23.3 g, 555 mmol). The resulting mixture was stirred at reflux temperature for 1 h, cooled, acidified with hydrochloric acid (2 N, 400 mL), and partitioned into diethyl ether. The organic phases were combined, dried over magnesium sulfate, filtered, and concentrated to yield sufficiently pure **9a** (50 g, quant) as off-white solid; mp 189 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s, 4 H), 8.20 (d, *J* = 2.1, 1 H), 8.90 (d, *J* = 2.1, 1 H), 13.70 (br s, 1H). HRMS (*m*/*z*): [M − H$^-$] calcd for $C_{12}H_6Cl_2NO_2$ 265.9776; found 265.9787.

*6-Chloro-5-(4-fluorophenyl)-3-pyridinecarboxylic Acid (**9b**).* Following a procedure similar to the preparation of **9a**, compound **8b** (49.0 g, 184 mmol) was used as starting material to produce **9b** (46.5 g, quant) as off-white solid; mp 182 °C dec. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.36 (t, *J* = 8.9, 2 H), 7.61 (dd, *J* = 8.9, 5.3, 2 H), 8.20 (d, *J* = 2.3, 1 H), 8.90 (d, *J* = 2.3, 1 H), 13.73 (br s, 1H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{12}H_8ClFNO_2$ 252.0228; found 252.0221.

*5-(4-Chlorophenyl)-6-(cyclopropylmethoxy)-3-pyridinecarboxylic Acid (**10a**). General Procedure A.* To a solution of **9a** (30.0 g, 112 mmol) and cyclopropanemethanol (13.5 mL, 168 mmol) in DMSO (225 mL) was added potassium hydroxide powder (25.1 g, 448 mmol). The resulting suspension was divided in 10 portions, heated with stirring for 15 min in the microwave at 100 °C, cooled, poured onto ice/water (500 mL), and citric acid solution (10%, 3.7 L) added. The resulting precipitate was collected by filtration, washed thoroughly with water, and dissolved in ethyl acetate. The ethyl acetate solution was dried over magnesium sulfate, filtered, and concentrated to a final volume of ∼200 mL. The product precipitated from this solution and **10a** (30.0 g, 88%) was obtained by filtration, washing with heptane/ethyl acetate (2:1) and drying in vacuo; mp 191 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.33 (m, 2H), 0.53 (m, 2H), 1.25 (m, 1H), 4.26 (d, *J* = 7, 2H), 7.52 (d, *J* = 8.6, 2 H), 7.66 (d, *J* = 8.6, 2H), 8.12 (d, *J* = 2.1, 1 H), 8.70 (d, *J* = 2.1, 1 H), 13.10 (br s, 1H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{16}H_{15}ClNO_3$ 304.0741; found 304.0734.

*5-(4-Chlorophenyl)-6-(2,2,2-trifluoroethoxy)-3-pyridinecarboxylic Acid (**10b**).* General procedure A, with **9a** (32.0 g, 119 mmol) and trifluoroethanol (10.3 mL, 143 mmol), was used to produce **10b** (37.5 g, 95%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.13 (q, *J* = 9.0, 2H), 7.56 (d, *J* = 8.7, 2 H), 7.64 (d, *J* = 8.7, 2 H), 8.23 (d, *J* = 2.2, 1 H), 8.74 (d, *J* = 2.2, 1 H), 13.37 (br s, 1H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{14}H_8ClF_3NO_3$ 330.0145; found 330.0156.

*6-(Cyclopropylmethoxy)-5-(4-fluorophenyl)-3-pyridinecarboxylic Acid (**10c**).* General procedure A, with **9b** (48.4 g, 192 mmol) and cyclopropanemethanol (23.3 mL, 289 mmol), was used to produce **10c** (41.0 g, 74%) as white solid; mp 182−185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.34 (m, 2H), 0.53 (m, 2H), 1.25 (m, 1H), 4.26 (d, *J* = 7, 2H), 7.30 (t, *J* = 8.9, 2 H), 7.68 (dd, *J* = 8.6, 5.6, 2 H), 8.10 (d, *J* = 1.9, 1 H), 8.68 (d, *J* = 1.9, 1 H), 13.10 (br s, 1H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{16}H_{15}FNO_3$ 288.1036; found 288.1032.

*5-(4-Chlorophenyl)-6-(pyrimidin-2-ylmethoxy)-3-pyridinecarboxylic Acid (**10d**).* General procedure A, with **9a** (6.5 g, 24.2 mmol) and 2-pyrimidinemethanol (2.94 g, 26.7 mmol), was used to produce **10d** (8.3 g, quant) as off-white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.70 (s, 2H), 7.42 (t, *J* = 4.9, 1H), 7.54 (d, *J* = 8.7, 2 H), 7.83 (d, *J* = 8.7, 2 H), 8.18 (d, *J* = 2.3, 1 H), 8.57 (d, *J* = 2.3, 1 H), 8.78 (d, *J* = 4.8, 2 H), 13.16 (br s, 1H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{17}H_{13}ClN_3O_3$ 342.0646; found 342.0644.

*5-(4-Chloro-phenyl)-6-(pyridin-2-ylmethoxy)-3-pyridinecarboxylic Acid (**10e**).* General procedure A, with **9a** (0.4 g, 1.5 mmol) and 2-pyridinemethanol (0.22 mL, 2.2 mmol), was used to produce **10e** (0.39 g, 76%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.57 (s, 2H), 7.32 (t, *J* = 5.4, 1 H), 7.38 (d, *J* = 7.8, 1 H), 7.53 (d, *J* = 8.3, 2 H), 7.73 (d, *J* = 8.3, 2 H), 7.80 (t, *J* = 7.8, 5.6, 1 H), 8.18 (d, *J* = 2.0, 1 H), 8.54 (d, *J* = 4.8, 1 H), 8.71 (d, *J* = 2.0, 1 H), 13.17 (br s, 1H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{18}H_{14}ClN_2O_3$ 341.0693; found 341.0693.

*5-(4-Chloro-phenyl)-6-(pyridin-4-ylmethoxy)-3-pyridinecarboxylic Acid (**10f**).* General procedure A, with **9a** (0.3 g, 1.1 mmol) and 4-pyridinemethanol (0.147 g, 1.3 mmol), was used to produce **10f** (0.27 g, 76%) as off-white solid. MS (ESI) *m*/*z* = 339.1 [M − H$^-$].

*5-(4-Cyanophenyl)-6-(cyclopropyl-methoxy)-3-pyridinecarboxylic Acid (**10g**).* To a solution of **12a** (1.15 g, 4.2 mmol) in toluene (25 mL) and DMF (2.5 mL) was added with stirring the [1,1-

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bis(diphenylphosphino)ferrocene] dichloropalladium DCM complex (0.173 g, 0.21 mmol), *B*-4-cyanophenyl-boronic acid (0.62 g, 4.2 mmol), and sodium carbonate solution (16.9 mL, 2M). The resulting mixture was stirred at 85 °C for 1.5 h, cooled, and partitioned between citric acid solution (10%) and ethyl acetate. The organic portion was dried over Na_2SO_4, filtered, and concentrated. The crude was crystallized from ethyl acetate/heptane (3:1; ~8 mL) to produce **10g** (0.83 g, 67%) as light-brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.34 (m, 2 H), 0.53 (m, 2 H), 1.25 (m, 1 H), 4.28 (d, J = 7.0, 2 H), 7.85 (d, J = 8.5, 2 H), 7.93 (d, J = 8.5, 2 H), 8.18 (d, J = 2.2, 1 H), 8.74 (d, J = 2.2, 1 H), 13.12 (br s, 1 H). HRMS (m/z): [M − H$^-$] calcd for $C_{17}H_{13}N_2O_3$ 293.0932; found 293.0939.

*6-(Cyclopropylmethoxy)-5-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxylic Acid (**10h**).* To a solution of **12a** (2.19 g, 8.05 mmol) in DME (57 mL) was added with stirring tetrakis(triphenylphosphine)-palladium(0) (0.94 g, 0.805 mmol). To this mixture was added *B*-4-(trifluoromethoxy)phenyl-boronic acid (1.99 g, 9.66 mmol) dissolved in ethanol (27 mL) and sodium carbonate solution (7.25 g in 37 mL water). The resulting mixture was stirred at 85 °C for 3.5 h, cooled, filtered through Celite, and concentrated. The residue was partitioned between brine and ethyl acetate. The organic portion was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with a DCM/methanol gradient to produce **10h** (1.79 g, 63%) as off-white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.33 (m, 2 H), 0.53 (m, 2 H), 1.25 (m, 1 H), 4.25 (d, J = 7.2, 2 H), 7.45 (d, J = 8.7, 2 H), 7.77 (d, J = 8.7, 2 H), 8.16 (d, J = 2.1, 1 H), 8.68 (d, J = 2.1, 1 H), 13.45 (br s, 1H). HRMS (m/z): [M − H$^-$] calcd for $C_{17}H_{13}F_3NO_4$ 352.0802; found 352.0807.

*6-(Cyclopropylmethoxy)-5-(4-trifluorophenyl)-3-pyridinecarboxylic Acid (**10i**).* To a solution of **12a** (61 mg, 0.224 mmol) in dioxane (1 mL) was added the [1,1-bis(diphenylphosphino)ferrocene] dichloropalladium DCM complex (8.2 mg, 11 μmol), *B*-4-trifluorophenyl-boronic acid (63.9 mg, 0.336 mmol), and sodium carbonate solution (0.34 mL, 2M). The resulting mixture was shaken at 80 °C for 2 h, cooled, filtered through Celite, and concentrated. The crude was purified by preparative HPLC (Zorbax XDB, acetonitrile/water and 0.05% trifluoroacetic acid) to produce **10i** (15 mg, 20%) as white solid. MS (ESI) m/z = 336.1 [M − H$^-$].

*5-[4-Chlorophenyl]-6-(cyclobutoxy)-3-pyridinecarboxylic Acid (**10j**).* Following a procedure similar to the preparation of **10h**, **12d** (0.22 g, 0.816 mmol) and *B*-4-chlorophenyl-boronic acid (0.145 g, 0.90 mmol) were used to produce **10j** (0.215 g, 89%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.65 (m, 1 H), 1.78 (m, 1 H), 2.06 (m, 2 H), 2.40 (m, 2 H), 5.29 (m, 1 H), 7.53 (d, J = 8.4, 2 H), 7.66 (d, J = 8.4, 2 H), 8.12 (d, J = 2.2, 1 H), 8.68 (d, J = 2.2, 1 H), 13.16 (br s, 1 H). MS (ESI) m/z = 302.2 [M − H$^-$].

*6-(Cyclopropylmethoxy)-5-(2,4-dichlorophenyl)-3-pyridinecarboxylic Acid (**10k**).* Following a procedure similar to the preparation of **10h**, **12a** (0.135 g, 0.496 mmol) and *B*-2,4-dichlorophenyl-boronic acid (0.114 g, 0.597 mmol) were used to produce **10k** (85 mg, 51%) as colorless oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.27 (m, 2 H), 0.47 (m, 2 H), 1.17(m, 1 H), 4.21 (d, J = 7.0, 2 H), 7.48 (d, J = 8.3, 1 H), 7.53 (dd, J = 8.3, 2.1, 1 H), 7.76 (d, J = 2.1, 1 H), 8.01 (d, J = 2.3, 1 H), 8.76 (d, J = 2.3, 1 H), 13.08 (br s, 1 H). HRMS (m/z): [M − H$^-$] calcd for $C_{16}H_{12}Cl_2NO_3$ 336.0194; found 336.0207.

*5-[4-Chlorophenyl]-6-[(3-methyl-5-isoxazolyl)methoxy]-3-pyridinecarboxylic Acid (**10l**).* Following a procedure similar to the preparation of **10h**, **12c** (0.41 g, 1.32 mmol) and *B*-4-chlorophenyl-boronic acid (0.213 g, 1.36 mmol) were used to produce **10l** (0.248 g, 54%) as light-brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3 H), 5.59 (s, 2 H), 6.41 (s, 1 H), 7.53 (d, J = 8.6, 2 H), 7.64 (d, J = 8.6, 2 H), 8.17 (d, J = 2.2, 1 H), 8.73 (d, J = 2.2, 1 H), 13.12 (br s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{17}H_{14}ClN_2O_4$ 345.0637; found 345.0641.

*5-[2-Chloro-5-(trifluoromethyl)phenyl]-6-(cyclopropylmethoxy)-3-pyridinecarboxylic Acid (**10m**).* To a solution of **24a** (1.15 g, 3.4 mmol) in CCl_4 (40 mL) was added with stirring 1-bromo-2,5-pyrrolidinedione (1.38 g, 7.7 mmol) and 2,2′-azobis(2-methylpropionitrile) (6 mg). The mixture was irradiated for 1 h with a 500 W UV lamp. After cooling, the reaction mixture was washed sodium hydrogen sulfite solution (38−40%, 30 mL). The water phase was extracted with dichloromethane; organic phases were washed three times with water, combined, dried over $MgSO_4$, filtered, and concentrated. The residue, consisting mostly of 3-[2-chloro-5-(trifluoromethyl)phenyl]-2-cyclopropylmethoxy-5-dibromomethyl-pyridine, was dissolved in ethanol (28 mL), a concentrated ammonia solution (7 mL) was added, and the mixture was stirred for 1 h at reflux temperature and poured after cooling into a cold hydrochloric acid solution (1 N, 150 mL). Workup proceeded by extraction with diethyl ether and washing the organic phases with ice water and brine. Organic phases were combined, dried over Na_2SO_4, filtered, and concentrated. The residue, consisting mostly of 5-[2-chloro-5-(trifluoromethyl)phenyl]-6-cyclopropylmethoxy-pyridine-3-carbaldehyde, was dissolved in pyridine (17 mL), a solution of tetrabutylammonium permanganate (3.87 g, 10.7 mmol) in pyridine (17 mL) was added, and the resulting mixture was stirred at 80 °C for 5 h. After cooling, the reaction mixture was added to sodium hydrogen sulfite solution (38−40%, 50 mL), hydrochloric acid (2 N; 300 mL) was added, and the mixture was extracted with diethyl ether. Organic phases were combined, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an ethyl acetate/heptane gradient to produce **10m** (0.37 g, 30%) as light-brown solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.27 (m, 2 H), 0.46 (m, 2 H), 1.16 (m, 1 H), 4.23 (d, J = 7.1, 1 H), 7.85 (m, 3 H), 8.11 (d, J = 2.3, 1 H), 8.79 (d, J = 2.3, 1 H), 13.19 (br s, 1 H). HRMS (m/z): [M − H$^-$] calcd for $C_{17}H_{12}ClF_3NO_3$ 370.0463; found 370.0466.

*5-(4-Chloro-phenyl)-6-phenoxy-3-pyridinecarboxylic Acid (**10n**).* Following a procedure similar to the preparation of **10m**, **24b** (0.64 g, 2.2 mmol) was used to produce **10n** (0.33 g, 47%) as yellow foam. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.21 (m, 2 H), 7.25 (t, J = 7.5, 1 H), 7.43 (t, J = 8.0, 2 H), 7.57 (d, J = 8.6, 2 H), 7.78 (d, J = 8.6, 2 H), 8.27 (d, J = 2.2, 1 H), 8.62 (d, J = 2.2, 1 H), 13.29 (br s, 1 H). HRMS (m/z): [M − H$^-$] calcd for $C_{18}H_{11}ClNO_3$ 324.0433; found 324.0439.

*5-(4-Chlorophenyl)-6-cyclopentyloxy-3-pyridinecarboxylic Acid (**10o**).* Following a procedure similar to the preparation of **10m**, **24c** (0.75 g, 2.6 mmol) was used to produce **10o** (0.43 g, 55%) as yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.60 (m, 2 H), 1.65 (m, 2 H), 1.72 (m, 2 H), 1.93 (m, 2 H), 5.56 (m 1 H), 7.52 (d, J = 8.7, 2 H), 7.61 (d, J = 8.7, 2 H), 8.11 (d, J = 2.3, 1 H), 8.71 (d, J = 2.3, 1 H), 13.11 (br s, 1H). HRMS (m/z): [M − H$^-$] calcd for $C_{17}H_{15}ClNO_3$ 316.0746; found 316.0751.

*6-Butoxy-5-(4-chlorophenyl)-3-pyridinecarboxylic Acid (**10p**).* Following a procedure similar to the preparation of **10m**, **24d** (0.86 g, 3.1 mmol) was used to produce **10p** (0.57 g, 65%) as yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.90 (t, J = 7.4, 3 H), 1.39 (m, 2 H), 1.69 (m, 2 H), 4.39 (t, J = 6.6, 2 H), 7.52 (d, J = 8.7, 2 H), 7.63 (d, J = 8.7, 2 H), 8.12 (d, J = 2.2, 1 H), 8.71 (d, J = 2.2, 1 H), 13.13 (br s, 1 H). HRMS (m/z): [M − H$^-$] calcd for $C_{16}H_{15}ClNO_3$ 304.0746; found 304.0753.

*5-(4-Chlorophenyl)-6-(cyclohexyloxy)-3-pyridinecarboxylic Acid (**10q**).* Following a procedure similar to the preparation of **10m**, **24e** (0.92 g, 3.0 mmol) was used to produce **10q** (0.67 g, 64%) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 4 H), 1.69 (m, 2 H), 1.94 (m, 2 H), 5.30 (m, 1 H), 7.46 (d, J = 8.6, 2 H), 7.53 (d, J = 8.6, 2H), 8.21 (d, J = 2.2, 1 H), 8.86 (d, J = 2.2, 1 H), 10.67 (br s, 1 H). MS (ESI) m/z = 330.2 [M − H$^-$].

*5-[2-Chloro-5-(trifluoromethyl)phenyl]-6-cyclopentyloxypyridine-3-carboxylic Acid (**10r**).* Following a procedure similar to the preparation of **10h**, **12g** (0.21 g, 0.734 mmol) and *B*-2-chloro-5-(trifluoromethyl)-phenyl-boronic acid (0.181 g, 0.807 mmol) were used to produce **10r** (67 mg, 24%) as off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50−1.77 (m, 6 H), 1.91 (m, 2 H), 5.58 (m, 1 H), 7.57 (m, 3 H), 8.15 (d, J = 2.2, 1 H), 8.96 (d, J = 2.2, 1 H), 13.0 (br s, 1 H). MS (ESI) m/z = 384.3 [M − H$^-$].

*5-Bromo-6-chloro-3-pyridinecarboxylic Acid (**11**).* Quinoline (15.3 mL) was added dropwise to phosphorus oxychloride (28.8 mL, 0.308 mol) and to this solution was added **6** (56 g, 0.257 mol). The mixture was stirred for 2 h at 120 °C, cooled to below 100 °C, and water (231 mL, 12.8 mol) was added to give a suspension. The solid was collected by filtration and partitioned between diethyl ether and sodium hydroxide solution (1 N, final pH 12.2). The water phase was collected and acidified with hydrochloric acid (1 N, final pH 1). The product precipitated, was collected by filtration, dissolved in ethyl acetate, dried

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over magnesium sulfate, filtered, and concentrated to yield **11** (49.1 g, 81% yield) as beige solid; mp 156−158 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.55 (d, J = 2.1, 1 H), 8.86 (d, J = 2.1, 1 H), 13.9 (br s, 1 H). HRMS (m/z): [M − H$^-$] calcd for $C_6H_2BrClNO_2$ 235.8937; found 235.8946.

*5-Bromo-6-(cyclopropylmethoxy)-3-pyridinecarboxylic Acid (**12a**). General Procedure B.* To a solution of **11** (2.4 g, 10.1 mmol) and cyclopropanemethanol (1.23 mL, 15.2 mmol) in DMSO (8 mL) was added potassium hydroxide powder (2.28 g, 40.6 mmol). The resulting suspension was heated with stirring for 8 min in the microwave at 100 °C, cooled, and poured onto ice/water (30 mL), and citric acid solution (10%, 40 mL) was added. The resulting precipitate was collected by filtration, washed thoroughly with water, and dissolved in ethyl acetate. The ethyl acetate solution was dried over magnesium sulfate, filtered, and concentrated to afford **12a** (2.4 g, 87%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.37 (m, 2H), 0.58 (m, 2H), 1.29 (m, 1H), 4.27 (d, J = 7, 2H),8.35 (d, J = 2.1, 1 H), 8.65 (d, J = 2.1, 1 H), 13.28 (br s, 1H). HRMS (m/z): [MH$^+$] calcd for $C_{10}H_{11}BrNO_3$ 273.9902; found 273.9905.

*5-Bromo-6-(pyridin-3-yl-methoxy)-3-pyridinecarboxylic Acid (**12b**).* General procedure B, with **11** (1.0 g, 4.2 mmol) and 3-pyridinemethanol (0.62 mL, 6.3 mmol), was used to produce **12b** (1.05 g, 80%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.55 (s, 2 H), 7.44 (m, 1 H), 7.90 (m, 1 H), 8.40 (d, J = 2.1, 1 H), 8.56 (m, 1 H), 8.71 (d, J = 2.1, 1 H), 8.72 (m, 1 H), 13.33 (br s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{12}H_{10}BrN_2O_3$ 310.9855; found 310.9853.

*5-Bromo-6-[(3-methyl-5-isoxazolyl)methoxy]-3-pyridinecarboxylic Acid (**12c**).* General procedure B, with **11** (0.50 g, 2.1 mmol) and 3-methyl-5-isoxazolemethanol (0.36 g, 3.2 mmol), was used to produce **12c** (0.43 g, 65%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3 H), 5.61 (s, 2 H), 6.48 (s, 1 H), 8.40 (d, J = 1.9, 1 H), 8.70 (d, J = 1.9, 1 H), 13.18 (br s, 1 H). HRMS (m/z): [M − H$^-$] calcd for $C_{11}H_8BrN_2O_4$ 310.9668; found 310.9679.

*5-Bromo-6-cyclobutoxy-3-pyridinecarboxylic Acid (**12d**).* General procedure B, with **11** (0.25 g, 1.06 mmol) and cyclobutanol (0.115 g, 1.59 mmol), was used to produce **12d** (0.23 g, 81%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.67 (m, 1 H), 1.82 (m, 1 H), 2.11 (m, 2 H), 2.44 (m, 2 H), 5.25 (m, 1 H), 8.34 (d, J = 2.0, 1 H), 8.64 (d, J = 2.0, 1 H), 13.31 (br s, 1 H). HRMS (m/z): [M − H$^-$] calcd for $C_{10}H_9BrNO_3$ 269.9766; found 269.9778.

*6-Benzyloxy-5-bromo-3-pyridinecarboxylic Acid (**12e**).* General procedure B, with **11** (1.00 g, 4.23 mmol) and benzenemethanol (0.65 mL, 6.34 mmol), was used to produce **12e** (0.31 g, 24%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.54 (s, 3 H), 5.51 (s, 2 H), 7.3−7.5 (m, 5 H), 8.40 (d, J = 2.1, 1 H), 8.70 (d, J = 2.1, 1 H), 13.32 (br s, 1 H). MS (ESI) m/z = 308.3, 310.3 [M − H$^-$].

*5-Bromo-6-(2-methoxyethoxy)-3-pyridinecarboxylic Acid (**12f**).* General procedure B, with **11** (4.00 g, 17 mmol) and 2-methoxyethanol (2.0 mL, 25 mmol), was used to produce **12f** (2.90 g, 62%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.32 (s, 3 H), 3.71 (t, J = 4.6, 2 H), 4.54 (t, J = 4.6, 2 H), 8.36 (d, J = 2.0, 1 H), 8.67 (d, J = 2.0, 1 H), 13.34 (br s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_9H_{11}BrNO_4$ 275.9872, 277.9851; found 275.9871, 277.9849.

*5-Bromo-6-cyclopentyloxypyridine-3-carboxylic Acid (**12g**).* General procedure B, with **11** (0.5 g, 2.11 mmol) and cyclopentanol (250 μL, 2.75 mmol), was used to produce **12g** (321 mg, 53%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.55−1.80 (m, 6 H), 1.96 (m, 2 H), 5.50 (m, 1 H), 8.33 (d, J = 2.2, 1 H), 8.67 (d, J = 2.2, 1 H), 13.2 (br s, 1 H). MS (ESI) m/z = 284.2, 286.2 [M − H$^-$].

*5-Bromo-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(2-methoxyethoxy)-3-pyridinecarboxamide (**13a**). General Procedure C.* To a solution of **12f** (5.0 g, 18.1 mmol) in THF (65 mL) was added TBTU (6.4 g, 19.9 mmol), DIEA (15.5 mL, 90.6 mmol), and finally (1*R*,2*R*)-2-amino-cyclohexanol hydrochloride (3.0 g, 19.9 mmol). The reaction was stirred for 4 h at RT and afterward concentrated in vacuo. Purification of the resulting residue was by flash chromatography, eluting with ethyl acetate, afforded **13a** (6.5 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (m, 5H), 1.76 (m, 2H), 2.10 (m, 2H), 3.46 (m, 1H), 3.46 (s, 3 H), 3.79 (t, J = 4.8, 2 H), 4.56 (t, J = 4.8, 2H), 5.14 (br s, OH), 6.20 (bd, J = 7, NH), 8.20 (d, J = 2.3, 1 H), 8.45 (d, J = 2.3, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{15}H_{22}BrN_2O_4$ 375.0743; found 375.0744.

*5-Bromo-6-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**13b**).* General procedure C, with **12a** (3.89 g, 14.3 mmol) was used to produce **13b** (5.02 g, 95%) as off-white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.41 (m, 2 H), 0.51 (m, 2 H), 1.21 (m, 4 H), 1.27 (m, 1 H), 1.64 (m, 2 H), 1.80 (m, 1 H), 1.91 (m 1 H), 3.36 (m, 1 H), 3.58 (m, 1 H), 3.89 (m, 2H), 4.66 (d, J = 4.8, OH), 7.98 (bd, J = 8.2, NH), 8.41 (d, J = 2.4, 1 H), 8.44 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{16}H_{22}BrN_2O_3$ 369.0814; found 369.0802.

*5-Bromo-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(3-pyridinylmethoxy)-3-pyridinecarboxamide (**13c**).* General procedure C, with **12b** (0.25 g, 0.81 mmol) in DMF, was used to produce **13c** (0.21 g, 64%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (m, 4 H), 1.64 (m, 2 H), 1.81 (m, 1 H), 1.89 (m 1 H), 3.39 (m, 1 H), 3.61 (m, 1 H), 4.64 (d, J = 4.8, OH), 5.54 (s, 2 H), 7.43 (dd, J = 7.8, 4.8, 1 H), 7.89 (dt, J = 8.0, 1.9, 1 H), 8.22 (bd, J = 8.3, NH), 8.50 (d, J = 2.0, 1 H), 8.55 (dd, J = 4.8, 1.6, 1 H), 8.64 (d, J = 2.0, 1 H), 8.71 (bd, J = 1.9, 1 H). MS (ESI) m/z = 406.2 [MH$^+$].

*5-Bromo-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(1-methylethoxy)-3-pyridinecarboxamide (**13d**).* General procedure C, with 5-bromo-6-(1-methylethoxy)-3-pyridinecarboxylic acid[39] (21 mg, 0.081 mmol) in DMF, was used to produce **13d** (21 mg, 73%) as white solid. MS (ESI) m/z = 357.0, 359.0 [MH$^+$].

*5-Bromo-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(phenylmethoxy)-3-pyridinecarboxamide (**13e**).* General procedure C, with **12e** (145 mg, 0.47 mmol) in DMA was used to produce **13e** (93 mg, 49%) as orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (m, 4 H), 1.63 (m, 2 H), 1.85 (m, 1 H), 3.40 (m, 1 H), 3.61 (m, 1 H), 4.66 (d, J = 4.7, OH), 5.50 (s, 2 H), 7.3−7.5 (m, 5 H), 8.23 (bd, J = 8.3, NH), 8.49 (d, J = 2.2, 1 H), 8.63 (d, J = 2.2, 1 H). MS (ESI) m/z = 405.3, 407.3 [MH$^+$].

*5-(4-Chlorophenyl)-6-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**14g**), General Procedure D.* To a solution of **10a** (21.5 g, 70.8 mmol) in DMF (650 mL) was added TBTU (25.0 g, 77.9 mmol), DIEA (60.6 mL, 354 mmol), and finally (1*R*,2*R*)-2-amino-cyclohexanol hydrochloride (11.8 g, 77.9 mmol). The reaction was stirred for 16 h at RT and afterward concentrated in vacuo at 45 °C. The resulting residue was purified by flash chromatography, eluting with ethyl acetate/heptane (2:1), and product fractions were concentrated to a final volume of ∼200 mL. The product precipitated from this solution, and **14g** (21.7 g, 76%) was obtained by filtration, washing with heptane/ethyl acetate (1:1) and drying in vacuo; mp 193−194 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.33 (m, 2H), 0.58 (m, 2H), 1.32 (m, 5H), 1.77 (m, 2H), 2.11 (m, 2H), 3.28 (d, J = 5.1, OH), 3.44 (m, 1H), 3.85 (m, 1H), 4.26 (d, J = 7, 2H), 6.06 (bd, J = 7, NH), 7.40 (d, J = 8.6, 2 H), 7.55 (d, J = 8.6, 2H), 8.01 (d, J = 2.4, 1 H), 8.51 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1632; found 401.1629. $[\alpha]_D^{20}$ = −27.3 (c = 1.03, MeOH).

*5-[2-Chloro-5-(trifluoromethyl)phenyl]-6-(cyclopentyloxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**4**).* General procedure D, with **10r** (0.135 g, 0.3 mmol), was used to produce **4** (108 mg, 64%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (m, 4 H), 1.67 (m, 8 H), 1.89 (m, 2 H), 2.11 (m, 2 H), 3.21 (d, J = 5.1, OH), 3.44 (m, 1 H), 3.85 (m, 1H), 5.52 (m, 1 H), 6.02 (d, J = 7, NH), 7.57 (m, 3H), 7.92 (d, J = 2.7, 1 H), 8.64 (d, J = 2.7, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{24}H_{27}ClF_3N_2O_3$ 483.1657; found 483.1674.

*5-(4-Chlorophenyl)-6-(cyclohexyloxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**14a**).* General procedure D, with **10q** (0.1 g, 0.3 mmol), was used to produce **14a** (79 mg, 61%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (m, 8 H), 1.56 (m, 2 H), 1.73 (m, 4 H), 1.94 (m, 2 H), 2.11 (m, 2 H), 3.31 (br s, OH), 3.44 (m, 1 H), 3.84 (m, 1H), 5.23 (1, 1 H), 6.03 (m, NH), 7.39 (d, J = 8.0, 2 H), 7.52 (d, J = 8.0, 2H), 7.99 (s, 1 H), 8.52 (s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{24}H_{30}ClN_2O_3$ 429.1945; found 429.1953.

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(phenoxy)-3-pyridinecarboxamide (**14b**).* General procedure D, with **10n** (80 mg, 0.25 mmol), was used to produce **14b** (77 mg, 74%) as white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (m, 4 H), 1.76 (m, 2 H), 2.10 (m, 2 H), 3.07 (br s, OH), 3.43 (m, 1 H), 3.84 (m, 1 H), 6.03 (m, NH), 7.11 (d, J = 7.8, 2 H), 7.23 (t, J = 7.4, 1 H), 7.41 (t, J = 8.3, 2 H), 7.44 (d, J

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= 8.3, 2 H), 7.62 (d, *J* = 8.3, 2H), 8.17 (d, *J* = 2.4, 1 H), 8.47(d, *J* = 2.4, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{24}H_{24}ClN_2O_3$ 423.1476; found 423.1475.

*5-(4-Chlorophenyl)-6-(cyclopentyloxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**14c**).* General procedure D, with **10o** (100 mg, 0.31 mmol), was used to produce **14c** (82 mg, 63%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (m, 4 H), 1.58−1.84 (m, 8 H), 1.95 (m, 2 H), 2.11 (m, 2 H), 3.28 (d, *J* = 4.8, OH), 3.44 (m, 1 H), 3.85 (m, 1 H), 5.56 (m, 1 H), 6.02 (m, NH), 7.38 (d, *J* = 8.6, 2 H), 7.49 (d, *J* = 8.6, 2 H), 7.99 (d, *J* = 2.4, 1 H), 8.53(d, *J* = 2.4, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{23}H_{28}ClN_2O_3$ 415.1789; found 415.1790.

*5-(4-Chlorophenyl)-6-cyclobutoxy-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**14d**).* General procedure D, with **10j** (210 mg, 0.69 mmol), was used to produce **14d** (160 mg, 58%) as off-white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.22 (m, 4 H), 1.65 (m, 3 H), 1.77 (m, 1 H), 1.87 (m, 2 H), 2.05 (m, 2 H), 2.41 (m, 2 H), 3.41 (m, 1 H), 3.62 (m, 1 H), 4.69 (d, *J* = 4.9, OH), 5.27 (m, 1H), 7.55 (d, *J* = 8.7, 2 H), 7.69 (d, *J* = 8.7, 2 H), 8.21 (d, *J* = 2.3, 1 H), 8.23 (bd, *J* = 8, NH), 8.62(d, *J* = 2.3, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1632; found 401.1629.

*6-Butoxy-5-(4-chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**14e**).* General procedure D, with **10p** (100 mg, 0.33 mmol), was used to produce **14e** (95 mg, 72%) as light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.4, 3 H), 1.25−1.45 (m, 6 H), 1.75 (m, 4 H), 2.11 (m, 2 H), 3.26 (d, *J* = 5.1, OH), 3.44 (m, 1 H), 3.85 (m, 1 H), 4.41 (t, J = 6.5, 1 H), 6.03 (m, NH), 7.40 (d, *J* = 8.6, 2 H), 7.51 (d, *J* = 8.6, 2 H), 8.00 (d, *J* = 2.4, 1 H), 8.52 (d, *J* = 2.4, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{22}H_{28}ClN_2O_3$ 403.1789; found 403.1789.

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(1-methylethoxy)-3-pyridinecarboxamide (**14f**).* General procedure A, with **19** (95.0 mg, 0.260 mmol) and 2-propanol (30 μL, 0.389 mmol), was used to produce **14f** (14 mg, 14%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34(d, *J* = 6.0, 6 H), 1.35 (m, 5 H), 1.77 (m, 2 H), 2.11 (m, 2 H), 3.33 (d, *J* = 4.5, OH), 3.45 (m, 1 H), 3.85 (m, 1 H), 5.45 (spt, *J* = 6.0, 1 H), 6.03 (br. d, *J* = 6.2, NH), 7.39 (d, *J* = 8.6, 2 H), 7.51 (d, *J* = 8.6, 2 H), 7.99 (d, *J* = 2.4, 1 H), 8.53 (d, *J* = 2.5, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{21}H_{26}ClN_2O_3$ 389.1626; found 389.1635.

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(2-methoxyethoxy)-3-pyridinecarboxamide (**14h**). General Procedure E.* To a suspension of **13a** (3.0 g, 8.06 mmol) in toluene (60 mL) was added with stirring the [1,1-bis(diphenylphosphino)ferrocene] dichloropalladium DCM complex (0.33 g, 0.403 mmol), 4-chlorophenylboronic acid (1.33 g, 8.06 mmol), and sodium carbonate solution (8.1 mL, 2M). The resulting mixture was stirred at 90 °C for 16 h, cooled, and partitioned between water and ethyl acetate. The organic portion was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with ethyl acetate/heptane (2:1) to produce **14h** (1.79 g, 55%) as off-white solid; mp 176−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (m, 4 H), 1.77 (m, 2 H), 2.11 (m, 2 H), 3.22 (d, *J* = 5.1, OH), 3.38 (s, 3 H), 3.44 (m, 1 H), 3.73 (t, *J* = 4.8, 2 H), 3.85 (m, 1 H), 4.57 (t, *J* = 4.8, 2 H), 6.05 (bd, *J* = 7, NH), 7.39 (d, *J* = 8.6, 2 H), 7.55 (d, *J* = 8.6, 2 H), 8.02 (d, *J* = 2.4, 1 H), 8.52 (d, *J* = 2.4, 1 H). HRMS (*m*/*z*): [M − H$^-$] calcd for $C_{21}H_{24}ClN_2O_4$ 403.1425; found 403.1430. $[\alpha]_D^{20}$ = −26.2 (*c* = 1.00, MeOH).

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(2,2,2-trifluoroethoxy)-3-pyridinecarboxamide (**14i**).* General procedure D, with **10b** (36.3 g, 109 mmol), was used to produce **14i** (38.0 g, 81%) as white solid; mp 186−187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (m, 4 H), 1.65 (m, 2 H), 1.87 (m, 2 H), 3.40 (m, 1 H), 3.64 (m, 1 H), 4.66 (d, *J* = 4.8, OH), 5.11 (q, *J* = 9.0, 2 H), 7.58 (d, *J* = 8.6, 2 H), 7.66 (d, *J* = 8.6, 2 H), 8.28 (bd, *J* = 8.1, NH), 8.31 (d, *J* = 2.4, 1 H), 8.66 (d, *J* = 2.4, 1 H). $[\alpha]_D^{20}$ = −23.6 (*c* = 1.00, MeOH). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{20}H_{21}ClF_3N_2O_3$ 429.1193; found 429.1193.

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(phenylmethoxy)-3-pyridinecarboxamide (**14j**).* General procedure E, with **13e** (85 mg, 0.210 mmol) and 4-chlorophenylboronic acid (37.2 mg, 0.231 mmol), was used to produce **14j** (51 mg, 55%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.23 (m, 4 H), 1.65 (m, 2 H), 1.87 (m, 2 H), 3.40 (m, 1 H), 3.64 (m, 1 H), 4.65 (d, *J* = 5.0, OH), 5.49 (s, 2 H), 7.30 (t, *J* = 7.4, 1 H), 7.36 (7, *J* = 7.3, 2 H), 7.41 (d, *J* = 7.6, 2 H), 7.53 (d, *J* = 8.7, 2 H), 7.69 (d, *J* = 8.7, 2 H), 8.21 (bd, *J* = 8.2, NH), 8.23 (d, *J* = 2.3, 1 H), 8.66 (d, *J* = 2.3, 1 H). HRMS (*m*/*z*): [M − H$^-$] calcd for $C_{25}H_{24}ClN_2O_3$ 435.1475; found 435.1483.

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-[(3-methyl-5-isoxazolyl)methoxy]-3-pyridinecarboxamide (**14k**).* General procedure D, with **10l** (58 mg, 0.168 mmol), was used to produce **14k** (46 mg, 62%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (m, 4 H), 1.78 (m, 2 H), 2.12 (m, 2 H), 2.28 (s, 3H), 3.44 (m, 1 H), 3.86 (m, 1 H), 5.52 (s, 2 H), 6.08 (s, 1 H), 6.12 (bd, *J* = 7, 1 H), 7.40 (d, *J* = 8.7, 2 H), 7.49 (d, *J* = 8.7, 2 H), 8.04 (d, *J* = 2.4, 1 H), 8.54 (d, *J* = 2.4, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{23}H_{25}ClN_3O_4$ 442.1534; found 442.1531.

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(2-pyrimidinylmethoxy)-3-pyridinecarboxamide (**14l**).* General procedure D, with **10d** (9.25 g, 27.1 mmol), was used to produce **14l** (8.5 g, 72%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (m, 4 H), 1.76 (m, 2 H), 2.10 (m, 2 H), 3.19 (d, *J* = 4.8, OH), 3.42 (m, 1 H), 3.83 (m, 1 H), 5.72 (s, 2 H), 6.04 (bd, *J* = 7.3, NH), 7.19 (t, *J* = 4.9, 1 H), 7.40 (d, *J* = 8.6, 2 H), 7.71 (d, *J* = 8.6, 2 H), 8.06 (d, *J* = 2.4, 1 H), 8.41 (d, *J* = 2.4, 1 H), 8.70 (d, *J* = 4.9, 2 H). $[\alpha]_D^{20}$ = −23.7 (MeOH). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{23}H_{24}ClN_4O_3$ 439.1537; found 439.1533.

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(4-pyridinylmethoxy)-3-pyridinecarboxamide (**14m**).* General procedure D, with **10f** (60 mg, 0.176 mmol), was used to produce **14m** (59 mg, 77%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (m, 4 H), 1.77 (m, 2 H), 2.12 (m, 2 H), 3.99 (br s, OH), 3.44 (m, 1 H), 3.85 (m, 1 H), 5.51 (s, 2 H), 6.05 (bd, *J* = 6.7, NH), 7.24 (d, *J* = 6.0, 2 H), 7.44 (d, *J* = 8.6, 2 H), 7.54 (d, *J* = 8.6, 2 H), 8.06 (d, *J* = 2.4, 1 H), 8.52 (d, *J* = 2.4, 1 H), 8.57 (d, *J* = 6.0, 2 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{24}H_{25}ClN_3O_3$ 438.1585; found 438.1579.

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(3-pyridinylmethoxy)-3-pyridinecarboxamide (**14n**).* General procedure E, with **13c** (99 mg, 0.244 mmol) and 4-chlorophenylboronic acid (43 mg, 0.276 mmol), was used to produce **14n** (89 mg, 83%) as white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (m, 4 H), 1.77 (m, 2 H), 2.11 (m, 2 H), 3.15 (d, *J* = 4.6, OH), 3.44 (m, 1 H), 3.85 (m, 1 H), 5.52 (s, 2 H), 6.07 (bd, *J* = 7, NH), 7.27 (dd, *J* = 8.0, 4.8, 1 H), 7.40 (d, *J* = 8.8, 2 H), 7.49 (d, *J* = 8.8, 2 H), 7.70 (dt, *J* = 8.1, 1.9, 1 H), 8.04 (d, *J* = 2.4, 1 H), 8.55 (dd, J = 4.8, 2.0, 1 H), 8.55 (d, *J* = 2.4, 1 H), 8.67 (bd, *J* = 1.9, 1 H). HRMS (*m*/*z*): [M − H$^-$] calcd for $C_{24}H_{23}ClN_3O_3$ 436.1428; found 436.1432.

*5-(4-Chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-6-(2-pyridinylmethoxy)-3-pyridinecarboxamide (**14o**).* General procedure D, with **10e** (100 mg, 0.293 mmol), was used to produce **14o** (102 mg, 79%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (m, 4 H), 1.77 (m, 2 H), 2.11 (m, 2 H), 3.18 (d, *J* = 5.1, OH), 3.44 (m, 1 H), 3.85 (m, 1 H), 5.61 (s, 2 H), 6.06 (bd, *J* = 7.0, NH), 7.20 (dd, *J* = 5.4, 7.3, 1 H), 7.29 (d, *J* = 7.8, 1 H), 7.41 (d, *J* = 8.6, 2 H), 7.58 (d, *J* = 8.6, 2 H), 7.65 (dt, *J* = 1.8, 7.8, 1 H), 8.08 (d, *J* = 2.4, 1 H), 8.52 (d, *J* = 2.4, 1 H), 8.58 (bd, *J* = 4.8, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{24}H_{25}ClN_3O_3$ 438.1585; found 438.1570.

*6-(Cyclopropylmethoxy)-5-(2,4-dichlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**15a**).* General procedure E, with **13b** (100 mg, 0.270 mmol) and *B*-(2,4-dichlorophenyl)-boronic acid (56.3 mg, 0.295 mmol), was used to produce **15a** (49 mg, 42%) as light-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.29 (m, 2 H), 0.52 (m, 2 H), 1.21 (m, 1H), 1.33 (m, 4 H), 1.77 (m, 2 H), 2.11 (m, 2 H), 3.27 (brd, OH), 3.44 (m, 1 H), 3.85 (m, 1 H), 4.23 (d, *J* = 7.0, 2 H), 6.03 (brd, *J* = 7.0, NH), 7.24 (d, *J* = 8.2, 1 H), 7.26 (d, *J* = 2.1,1 H), 7.32 (dd, *J* = 8.2, 2.1, 1 H) 7.89 (d, *J* = 2.5, 1 H), 8.59 (d, J = 2.4, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{22}H_{25}Cl_2N_2O_3$ 435.1237; found 435.1244.

*5-(2-Chlorophenyl)-6-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**15b**).* General procedure E, with **13b** (100 mg, 0.271 mmol) and *B*-(2-chlorophenyl)-boronic acid (46.6 mg, 0.298 mmol), was used to produce **15b** (82 mg, 76%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.29 (m, 2 H), 0.45 (m, 2 H), 1.21 (m, 1 H), 1.34 (m, 4 H), 1.76 (m, 2 H), 2.1 (m, 2 H), 3.36 (br s, OH), 3.43 (m, 1 H), 3.85 (m, 1 H), 4.24 (d, *J* = 7.0, 2 H), 6.04 (brd, *J* = 6.9, NH), 7.32 (m, 3 H), 7.47 (m, 1H), 7.89 (d, *J* = 2.5, 1 H), 8.61 (d, *J* = 2.5, 1 H). HRMS (*m*/*z*): [MH$^+$] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1627; found 401.1639.

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*6-(Cyclopropylmethoxy)-5-(3,4-dichlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**15c**).* General procedure E, with **13b** (49 mg, 0.134 mmol) and *B*-(3,4-dichlorophenyl)-boronic acid (26 mg, 0.138 mmol), was used to produce **15c** (35 mg, 60%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.36 (m, 2 H), 0.61 (m, 2 H), 1.32 (m, 5 H), 1.78 (m, 2 H), 2.11 (m, 2 H), 3.30 (d, J = 5.0, OH), 3.46 (m, 1 H), 3.86 (m, 1 H), 4.27 (d, J = 7.1, 2 H), 6.08 (bd, J = 7, NH), 7.48 (m, 2 H), 7.75 (d, J = 1.9, 1 H), 8.03 (d, J = 2.6, 1 H), 8.52 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{25}Cl_2N_2O_3$ 435.1237; found 435.1243.

*5-(3-Chlorophenyl)-6-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**15d**).* General procedure E, with **13b** (97 mg, 0.263 mmol) and *B*-(3-chlorophenyl)-boronic acid (41 mg, 0.262 mmol), was used to produce **15d** (53 mg, 50%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.36 (m, 2 H), 0.60 (m, 2 H), 1.32 (m, 5 H), 1.78 (m, 2 H), 2.12 (m, 2 H), 3.32 (d, J = 4.8, OH), 3.43 (m, 1 H), 3.86 (m, 1 H), 4.28 (d, J = 7.1, 2 H), 6.04 (bd, J = 6.9, NH), 7.36 (m, 2 H), 7.49 (m, 1 H), 7.64 (m, 1 H), 8.02 (d, J = 2.4, 1 H), 8.54 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1626; found 401.1632.

*5-[2-Chloro-5-(trifluoromethyl)phenyl]-6-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**15e**).* General procedure D, with **10m** (90 mg, 0.242 mmol), was used to produce **15e** (83.0 g, 73%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.29 (m, 2 H), 0.52 (m, 2 H), 1.32 (m, 5 H), 1.77 (m, 2 H), 2.12 (m, 2 H), 3.18 (d, J = 5.1, OH), 3.45 (m, 1 H), 3.85 (m, 1 H), 4.24 (d, J = 7.0, 2 H), 6.03 (bd, J = 6.7, NH), 7.60 (m, 3 H), 7.94 (d, J = 2.4, 1 H), 8.62 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{25}ClF_3N_2O_3$ 469.1506; found 469.1504.

*6-(Cyclopropylmethoxy)-5-(4-fluorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**15f**).* General procedure D, with **10c** (25.0 g, 87 mmol), was used to produce **15f** (29.3 g, 88%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34 (m, 2 H), 0.58 (m, 2 H), 1.33 (m, 5 H), 1.76 (m, 2 H), 2.10 (m, 2 H), 3.44 (br s, OH), 3.44 (m, 1 H), 3.85 (m, 1 H), 4.26 (d, J = 7.0, 2 H), 6.11 (bd, J = 7.0, NH), 7.12 (t, J = 8.7, 2 H), 7.58 (dd, J = 5.5, 8.9, 2 H), 8.00 (d, J = 2.4, 1 H), 8.50 (d, J = 2.4, 1 H). $[\alpha]_D^{20}$ = −16.4 (MeOH). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{26}FN_2O_3$ 385.1928; found 385.1925.

*6-(Cyclopropylmethoxy)-5-(4-trifluoromethylphenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**15g**).* General procedure E, with **13b** (100 mg, 0.271 mmol) and *B*-(4-trifluorophenyl)-boronic acid (56.6 mg, 0.298 mmol), was used to produce **15g** (85 mg, 72%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.34 (m, 2 H), 0.59 (m, 2 H), 1.32 (m, 5 H), 1.78 (m, 2 H), 2.12 (m, 2 H), 3.25 (br d, J = 3.8, OH), 3.45 (m, 1 H), 3.86 (m, 1 H), 4.28 (d, J = 7.2, 2 H), 6.06 (br d, J = 7.2, NH), 7.69 (d, J = 7.9, 2 H), 7.73 (d, J = 7.9, 2 H), 8.06 (d, J = 2.4, 1 H), 8.55 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{26}F_3N_2O_3$ 435.1906; found 435.1906.

*6-(Cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-5-[4-(trifluoromethoxy)phenyl]-3-pyridinecarboxamide (**15h**).* General procedure D, with **10h** (428 mg, 1.211 mmol), was used to produce **15h** (498 mg, 91%) as colorless foam. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.34 (m, 2 H), 0.59 (m, 2 H), 1.32 (m, 5 H), 1.77 (m, 2 H), 2.12 (m, 2 H), 3.30 (bd, J = 5.0, OH), 3.44 (m, 1 H), 3.86 (m, 1 H), 4.27 (d, J = 7.1, 2 H), 6.06 (bd, J = 7.1, NH), 7.28 (d, J = 8.8, 2 H), 7.65 (d, J = 8.8, 2 H), 8.03 (d, J = 2.4, 1 H), 8.52 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{26}F_3N_2O_4$ 451.1839; found 451.1857.

*6-(Cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-5-(4-methoxyphenyl)-3-pyridinecarboxamide (**15i**).* General procedure E, with **13b** (100 mg, 0.271 mmol) and *B*-(4-methoxyphenyl)-boronic acid (45.3 mg, 0.298 mmol), was used to produce **15i** (88 mg, 7482%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.35 (m, 2 H), 0.58 (m, 2 H), 1.33 (m, 5 H), 1.77 (m, 2 H), 2.10 (m, 2 H), 3.43 (br s, OH), 3.44 (m, 1 H), 3.85 (m, 1 H), 3.86 (s, 3H), 4.26 (d, J = 7.1, 2 H), 6.04 (br d, J = 7.1, NH), 6.97 (d, J = 8.3, 2 H), 7.57 (d, J = 8.3, 2 H), 7.99 (d, J = 2.5, 1 H), 8.48 (d, J = 2.5, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{29}N_2O_4$ 397.2122; found 397.2133.

*5-(4-Cyanophenyl)-6-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**15j**).* General procedure D, with **10g** (200 mg, 0.679 mmol), was used to produce **15j** (192 mg, 72%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.33 (m, 2 H), 0.59 (m, 2 H), 1.33 (m, 5 H), 1.77 (m, 2 H), 2.11 (m, 2 H), 3.15 (d, J = 5.1, OH), 3.45 (m, 1 H), 3.85 (m, 1 H), 4.28 (d, J = 7.3, 2 H), 6.09 (bd, J = 7.3, NH), 7.72 (s, 4 H), 8.06 (d, J = 2.4, 1 H), 8.55 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{26}N_3O_3$ 392.1974; found 392.1974.

*6-(Cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-5-(4-methanesulfonylamino-phenyl)-3-pyridinecarboxamide (**15k**).* General procedure E, with **13b** (99.1 mg, 0.268 mmol) and *B*-[4-[(methylsulfonyl)amino]phenyl]-boronic acid (87.8 mg, 0.408 mmol) in DME with Cs_2CO_3 as base and tetrakis(triphenylphosphine)-palladium(0), was used to produce **15k** (86.2 mg, 70%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.34 (m, 2 H), 0.53 (m, 2 H), 1.25 (m, 5 H), 1.64 (m, 2 H), 1.87 (m, 2 H), 3.05 (s, 3 H), 3.39 (m, 1 H), 3.63 (m, 1 H), 4.24 (d, J = 7.1, 2 H), 4.63 (d, J = 5.1, OH), 7.30 (d, J = 8.0, 2 H), 7.64 (d, J = 8.0, 2 H), 8.16 (d, J = 8.1, NH), 8.18 (d, J = 2.3, 1 H), 8.58 (d, J = 2.3, 1 H), 9.90 (s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{30}N_3O_5S$ 460.1898; found 460.1909.

*6-(Cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-5-(4-sulfamoyl-phenyl)-3-pyridinecarboxamide (**15l**).* General procedure E, with **13b** (99.5 mg, 0.269 mmol) and *B*-(4-sulfamoylphenyl)-boronic acid (81.9 mg, 0.407 mmol) in DME with Cs_2CO_3 as base and tetrakis(triphenylphosphine)palladium(0), was used to produce **15k** (99.6 mg, 83%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.34 (m, 2 H), 0.53 (m, 2 H), 1.25 (m, 5 H), 1.65 (m, 2 H), 1.87 (m, 2 H), 3.40 (m, 1 H), 3.64 (m, 1 H), 4.25 (d, J = 7.1, 2 H), 4.64 (d, J = 5.0, OH), 7.43 (s, 2 H), 7.85 (d, J = 9.0, 2 H), 7.91 (d, J = 9.0, 2 H), 8.19 (d, J = 8.2, NH), 8.25 (d, J = 2.3, 1 H), 8.65 (d, J = 2.3, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{28}N_3O_5S$ 446.1744; found 446.1755.

*4-[2-Cyclopropylmethoxy-5-((1R,2R)-2-hydroxy-cyclohexylcarbamoyl)-pyridin-3-yl]-benzoic Acid (**15m**).* General procedure E, with **13b** (99.4 mg, 0.269 mmol) and 4-boronobenzoic acid (67.6 mg, 0.407 mmol) in DME with Cs_2CO_3 as base, was used to produce **15k** (95.1 mg, 86%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.34 (m, 2 H), 0.53 (m, 2 H), 1.25 (m, 5 H), 1.64 (m, 2 H), 1.87 (m, 2 H), 3.39 (m, 1 H), 3.64 (m, 1 H), 4.25 (d, J = 7.1, 2 H), 4.65 (d, J = 4.9, OH), 7.80 (d, J = 8.5, 2 H), 8.03 (d, J = 8.5, 2 H), 8.20 (d, J = 8.2, NH), 8.27 (d, J = 2.4, 1 H), 8.65 (d, J = 2.3, 1 H), 13.0 (br s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{27}N_2O_5$ 411.1914; found 411.1921.

*5-(4-Carbamoyl-phenyl)-6-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**15n**).* General procedure E, with **13b** (101.4 mg, 0.274 mmol) and *B*-(4-carbamoylphenyl)-boronic acid (67.8 mg, 0.411 mmol) in DME with Cs_2CO_3 as base and tetrakis(triphenylphosphine)palladium(0), was used to produce **15k** (89.8 mg, 80%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.34 (m, 2 H), 0.53 (m, 2 H), 1.25 (m, 5 H), 1.65 (m, 2 H), 1.87 (m, 2 H), 3.40 (m, 1 H), 3.64 (m, 1 H), 4.25 (d, J = 7.1, 2 H), 4.65 (d, J = 5.0, OH), 7.42 (br s, 1H), 7.75 (d, J = 8.5, 2 H), 7.97 (d, J = 8.5, 2 H), 8.04 (br s, 1 H), 8.20 (d, J = 8.2, NH), 8.25 (d, J = 2.3, 1 H), 8.63(d, J = 2.3, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{28}N_3O_4$ 410.2074; found 410.2082.

*5-(4-Chloro-phenyl)-6-cyclopropylmethoxy-N-piperidin-1-yl-3-pyridinecarboxamide (**16a**).* General procedure D, with **10a** (70 mg, 0.230 mmol) and 1-amino-piperidine (28 μL, 0.261 mmol), was used to produce **16a** (66 mg, 74%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34 (m, 2 H), 0.55 (m, 2 H), 1.27 (m, 1 H), 1.46 (br s, 2 H), 1.77 (br s, 4 H), 2.88 (br s, 4 H), 4.26 (d, J = 7, 1 H), 6.69 (br s, NH), 7.40 (d, J = 8.6, 2 H), 7.56 (d, J = 8.6, 2 H), 7.99 (br s, 1 H), 8.45 (br s, 1 H) major rotamer. HRMS (m/z): [MH$^+$] calcd for $C_{21}H_{25}ClN_3O_2$ 386.1635; found 386.1634.

*5-(4-Chlorophenyl)-N-[(2R)-2-cyclopropyl-2-hydroxypropyl]-6-(cyclopropylmethoxy)-3-pyridinecarboxamide (**16b**).* General procedure D, with **10a** (100 mg, 0.329 mmol) and (αR)-α-(aminomethyl)-α-methyl-cyclopropanemethanol (42 mg, 0.365 mmol), was used to produce **16b** (124 mg, 94%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34 (m, 3 H), 0.42 (m, 2 H), 0.50 (m, 1 H), 0.58 (m, 2 H), 0.93 (m, 1 H), 1.18 (s, 3 H), 1.28 (m, 1 H), 2.05 (s, OH), 3.50 (dd, J = 13.7, 5.4, 1 H), 3.64 (dd, J = 13.7, 6.4 1 H), 4.27 (d, J = 7, 2 H), 6.50 (br s, NH), 7.41 (d, J = 8.6, 2 H), 7.56 (d, J = 8.6, 2 H), 8.04 (d, J = 2.4, 1 H), 8.53 (d, J = 2.4, 1 H). $[\alpha]_D^{20}$ = 1.1 (c = 0.558, MeOH). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1632; found 401.1631.

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*5-(4-Chlorophenyl)-6-(cyclopropylmethoxy)-N-[(1S,2S)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**16c**).* General procedure D, with **10a** (50 mg, 0.166 mmol) and (1S,2S)-2-amino-cyclohexanol hydrochloride (27.6 mg, 0.182 mmol), was used to produce **16c** (50 mg, 75%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.33 (m, 2 H), 0.53 (m, 2 H), 1.23 (m, 5 H), 1.63 (m, 2 H), 1.84 (m, 2 H), 3.39 (m, 1 H), 3.64 (m, 1H), 4.24 (d, J = 7.1, 2 H), 4.64 (d, J = 5, OH), 7.55 (d, J = 8.9, 2 H), 7.69 (d, J = 8.9, 2 H), 8.18 (bd, J = 8.3, NH), 8.21 (d, J = 2.4, 1 H), 8.62 (d, J = 2.4, 1 H). $[\alpha]_D^{20}$ = 26.3 (c = 1.0, MeOH). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1627; found 401.1631.

*5-(4-Chlorophenyl)-6-(cyclopropylmethoxy)-N-[(1R,2S)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**16d**).* To a suspension of **10a** (1.5 g, 4.94 mmol) in DCM (1.5 mL) was added 1-chloro-*N*,*N*,2-trimethyl-1-propen-1-amine (0.75 mL, 5.68 mmol) dropwise. The mixture was stirred for 30 min at room temperature and added to a solution of (1S,2R)-2-amino-cyclohexanol hydrochloride (0.94 g, 6.17 mmol) and DIEA (2.05 mL, 12.4 mmol) in DMF (2.0 mL). The reaction was stirred for 1 h at room temperature and afterward partitioned between ethyl acetate and citric acid solution (1 M). Organic phases were combined, dried with magnesium sulfate, filtered, and concentrated. The resulting residue was purified by flash chromatography, eluting with ethyl acetate/heptane (1:20 to 1:1) to afford **16d** (1.88 g, 95%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.33 (m, 2H), 0.53 (m, 2H), 1.24 (m, 1 H), 1.31 (m, 2 H), 1.47 (m, 2 H), 1.54 (m, 1 H), 1.66 (m, 1 H), 1.74 (m, 2 H), 3.86 (m, 2 H), 4.24 (d, J = 7, 2H), 4.64 (d, J = 3.9, OH), 7.54 (d, J = 8.7, 2 H), 7.70 (d, J = 8.7, 2H), 8.04 (bd, J = 7.7, NH), 8.23 (d, J = 2.4, 1 H), 8.62 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1632; found 401.1628. $[\alpha]_D^{20}$ = +34.0 (c = 0.992, MeOH).

*5-(4-Chloro-phenyl)-6-cyclopropylmethoxy-N-((1S,2R)-2-hydroxy-cyclohexyl)-3-pyridinecarboxamide (**16e**).* Following a procedure similar to the preparation of **16d**, **10a** (1.50 g, 4.94 mmol) and (1R,2S)-2-amino-cyclohexanol hydrochloride (0.94 g, 6.17 mmol) were used to produce **16e** (1.88 g, 95%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.33 (m, 2H), 0.53 (m, 2H), 1.24 (m, 1 H), 1.31 (m, 2 H), 1.47 (m, 2 H), 1.55 (m, 1 H), 1.66 (m, 1 H), 1.75 (m, 2 H), 3.86 (m, 2 H), 4.24 (d, J = 7, 2H), 4.64 (d, J = 3.9, OH), 7.54 (d, J = 8.7, 2 H), 7.70 (d, J = 8.7, 2H), 8.04 (bd, J = 7.7, NH), 8.23 (d, J = 2.4, 1 H), 8.62 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1632; found 401.1624. $[\alpha]_D^{20}$ = −32.3 (c = 0.988, MeOH).

5-Bromo-6-[(cyclopropylmethyl)methylamino]-3-pyridinecarboxylic Acid. A mixture of **7** (1.00 g, 4.0 mmol), *N*-methyl-cyclopropanemethanamine hydrochloride (1:1) (1.21 g, 10 mmol), and DBU (3.07 g, 20 mmol) was stirred for 3 h at 90 °C. Sodium hydroxide solution (2 N, 4 mL) was added, and heating continued for 15 min. The mixture was cooled, brought to a pH of ∼4 with hydrochloric acid (2 N, 4 mL) and citric acid (10%), and partitioned into ethyl acetate. The organic portion was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with a DCM/methanol gradient to produce the title compound (0.83 g, 73%) as colorless solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.20 (m, 2 H), 0.48 (m, 2 H), 1.08 (m, 1 H), 3.10 (s, 3H), 3.40 (d, J = 6.8, 2 H), 8.18 (d, J = 2.0, 1 H), 8.63 (d, J = 2.0, 1 H), 12.80 (br s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{11}H_{14}BrN_2O_2$ 285.0233, 287.0214; found 285.0239, 287.0220.

*5-(4-Chlorophenyl)-6-[(cyclopropylmethyl)methylamino]-3-pyridinecarboxylic A (**17**).* Following a procedure similar to the preparation of **10h**, 5-bromo-6-[(cyclopropylmethyl)methylamino]-3-pyridinecarboxylic acid (0.40 g, 1.40 mmol) and *B*-4-chlorophenyl-boronic acid (0.249 g, 1.54 mmol) were used to produce **17** (0.323 g, 73%) as brownish foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.05 (m, 2 H), 0.38 (m, 2 H), 0.92 (m, 1 H), 2.74 (s, 3 H), 3.11 (m, 2 H), 7.48 (m, 4 H), 7.81 (d, J = 2.2, 1 H), 8.63 (d, J = 2.2, 1 H), 12.79 (br s, 1 H). MS (ESI) m/z = 315.3 [M − H$^-$].

*5-(4-Chlorophenyl)-6-[(cyclopropylmethyl)methylamino]-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**18**).* General procedure D, with **17** (120 mg, 0.379 mmol), was used to produce **18** (133 mg, 85%) as colorless foam. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.03 (m, 2 H), 0.37 (m, 2 H), 0.89 (m, 1 H), 1.21 (m, 4 H), 1.64 (m, 2 H), 1.86 (m, 2 H), 2.76 (s, 3 H), 3.05 (d, J = 6.8, 2 H), 3.38 (m, 1 H), 3.62 (m, 1 H), 4.60 (d, J = 5.1, OH), 7.50 (d, J = 8.7, 2 H), 7.54 (d, J = 8.7, 2 H), 7.91 (d, J = 2.4, 1 H), 8.00 (bd, J = 8.1, NH), 8.61(d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{29}ClN_3O_2$ 414.1948; found 414.1947.

*6-Chloro-5-(4-chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**19**).* Following a procedure similar to the preparation of **14g**, **9a** (1.4 g, 5.2 mmol) was used to produce **19** (1.4 g, 73%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) 1.34 (m, 4 H), 1.78 (m, 2 H), 2.13 (m, 2 H), 2.71 (d, J = 5.7, OH), 3.46 (m, 1 H), 3.86 (m, 1 H), 6.31 (bd, J = 7.0, NH), 7.39 (d, J = 8.7, 2 H), 7.46 (d, J = 8.7, 2 H), 8.07 (d, J = 2.4, 1 H), 8.73 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{18}H_{19}Cl_2N_2O_2$ 365.0818; found 365.0825.

*5-(4-Chlorophenyl)-6-(2-cyclopropylethynyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-3-pyridinecarboxamide (**20**).* To a solution of **19** (0.47 g, 1.28 mmol) in DMF (8 mL) was added with stirring bis(triphenylphosphine)palladium(II)dichloride (54 mg, 0.077 mmol), copper(I)iodide (15 mg, 0.077 mmol), triphenylphosphine resin (174 mg, 1.48 mmol/g), ethynylcyclopropane (0.13 mL, 1.54 mmol), and *N*,*N*-diethylamine (2 mL). The resulting mixture was microwaved twice for 25 min at 120 °C, cooled, filtered, and partitioned between water and ethyl acetate. The organic portion was washed with water and sodium bicarbonate solution, dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with ethyl acetate/heptane gradient to produce **20** (0.31 g, 61%) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.75 (m, 2H), 0.87 (m, 2 H), 1.35 (m, 5 H), 1.77 (m, 2 H), 2.12 (m, 2 H), 3.10 (d, J = 5.3, OH), 3.46 (m, 1 H), 3.87 (m, 1 H), 6.30 (bd, J = 7.3, NH), 7.42 (d, J = 8.7, 2 H), 7.51 (d, J = 8.7, 2 H), 8.05 (d, J = 2.1, 1 H), 8.84 (d, J = 2.1, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{24}ClN_2O_2$ 395.1521; found 395.1528.

*5-(4-Chlorophenyl)-6-(2-cyclopropylethyl)-N-[(1R,2R)-2-hydroxy-cyclohexyl]-3-pyridinecarboxamide (**21**).* To a solution of **20** (0.247 g, 0.63 mmol) in ethyl acetate (35 mL) was added palladium on carbon (45 mg, 10%). The resulting mixture was hydrogenated at 0.4 bar and room temperature, palladium was removed by filtration over diatomaceous earth, and the solution was concentrated to give **21** (0.19 g, 76%) as yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.10 (m, 2 H), 0.31 (m, 2H), 1.20 (m, 1H), 1.32 (m, 4 H), 1.53 (m, 2H), 1.76 (m, 2 H), 2.11 (m, 2 H), 2.88 (t, J = 7.6, 2H), 3.17 (d, J = 5.1, OH), 3.45 (m, 1 H), 3.85 (m, 1 H), 6.20 (bd, J = 7, NH), 7.25 (d, J = 8.3, 2 H), 7.43 (d, J = 8.3, 2 H), 7.88 (d, J = 2.4, 1 H), 8.90 (d, J = 2.4, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{23}H_{28}ClN_2O_2$ 399.1834; found 399.1837.

*3-Bromo-2-(cyclopropylmethoxy)-5-methyl-pyridine (**23a**).* To a solution of cyclopropane−methanol (2.15 mL, 26.6 mmol) in DMF (50 mL) was added sodium hydride dispersion (1.16 g, ∼55% in oil, 26.6 mmol). The resulting suspension was stirred for 1 h at room temperature, 3-bromo-2-chloro-5-methyl-pyridine (**22**, Combi-Blocks, 5.0 g, 24.2 mmol) was added, and the mixture was stirred for 6 h at 70 °C. After cooling, the reaction mixture was poured onto saturated sodium bicarbonate solution (1200 mL) and partitioned into diethyl ether and all organic phases were, after a final wash with sodium bicarbonate, combined, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography, eluting with heptane/ethyl acetate (8:1) to afford **23a** (3.1 g, 53%) as reddish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (m, 2H), 0.59 (m, 2H), 1.31 (m, 1H), 2.23 (s, 3 H), 4.18 (d, J = 7, 2H), 7.64 (d, J = 1.9, 1 H), 7.85 (d, J = 1.9, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{10}H_{13}BrNO$ 242.0175, 244.0155; found 242.0181, 244.0160.

*3-Bromo-5-methyl-2-phenoxy-pyridine (**23b**).* Following a procedure similar to the preparation of **23a**, phenol (1.33 g, 14.1 mmol) and 3-bromo-2-chloro-5-methyl-pyridine (3.77 g, 18.2 mmol) were used to produce **23b** (1.42 g, 42%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3 H), 7.12 (d, J = 7.5, 2 H), 7.20 (t, J = 7.4, 1 H), 7.40 (t, J = 7.7, 2 H), 7.76 (s, 1 H), 7.88 (s, 1 H).

*3-Bromo-2-cyclopentyloxy-5-methyl-pyridine (**23c**).* Following a procedure similar to the preparation of **23a**, cyclopentanol (1.45 mL, 16.0 mmol) and 3-bromo-2-chloro-5-methyl-pyridine (3.0 g, 14.5 mmol) were used to produce **23c** (1.75 g, 47%) as reddish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (m, 2 H), 1.83 (m, 4 H), 1.94 (m, 2 H), 2.22 (s, 3 H), 5.40 (m, 1 H), 7.61 (d, J = 2.2, 1 H), 7.87 (d, J = 2.2, 1 H).

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HRMS (m/z): [MH^+] calcd for $C_{11}H_{15}BrNO$ 256.0332, 258.0312; found 256.0338, 258.0317.

*3-Bromo-2-butoxy-5-methyl-pyridine (**23d**).* Following a procedure similar to the preparation of **23a**, 1-butanol (2.44 mL, 26.6 mmol) and 3-bromo-2-chloro-5-methyl-pyridine (5.0 g, 24.2 mmol) were used to produce **23d** (4.20 g, 71%) as reddish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.5, 3 H), 1.50 (m, 2 H), 1.78 (m, 2 H), 2.23 (s, 3 H), 4.32 (t, J = 6.5, 2 H), 7.63 (d, J = 2.2, 1 H), 7.87 (d, J = 2.2, 1 H). HRMS (m/z): [MH^+] calcd for $C_{10}H_{15}BrNO$ 244.0332, 246.0312; found 244.0340, 246.0320.

*3-Bromo-2-cyclohexyloxy-5-methyl-pyridine (**23e**).* Following a procedure similar to the preparation of **23a**, cyclohexanol (2.84 mL, 26.6 mmol) and 3-bromo-2-chloro-5-methyl-pyridine (5.0 g, 24.2 mmol) were used to produce **23e** (3.1 g, 47%) as reddish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (m, 1 H), 1.45 (m, 2 H), 1.55 (m, 1 H), 1.62 (m, 2 H), 1.80 (m, 2 H), 1.93 (m, 2 H), 2.22 (s, 3 H), 5.06 (m, 1 H), 7.62 (d, J = 2.2, 1 H), 7.85 (d, J = 2.2, 1 H). HRMS (m/z): [MH^+] calcd for $C_{12}H_{17}BrNO$ 270.0488, 272.0468; found 270.0491, 272.0471.

*3-(2-Chloro-5-(trifluoromethyl)phenyl)-2-cyclopropylmethoxy-5-methyl-pyridine (**24a**).* To a solution of **23a** (1.0 g, 4.1 mmol) in toluene (7 mL) was added with stirring the [1,1-bis-(diphenylphosphino)ferrocene] dichloropalladium DCM complex (0.169 g, 0.02 mmol), *B*-[2-chloro-5-(trifluoromethyl)phenyl]-boronic acid (1.39 g, 6.2 mmol), and sodium carbonate solution (6.2 mL, 2M). The resulting mixture was stirred at 90 °C overnight, cooled, and eluted over Chem Elut (Varian) with ethyl acetate. The solution was concentrated and purified by flash chromatography, eluting with an ethyl acetate/heptane gradient to produce **24a** (1.21 g, 86%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (m, 2 H), 0.49 (m, 2 H), 1.18 (m, 1 H), 2.30 (s, 3 H), 4.15 (d, J = 7.0, 1 H), 7.36 (d, J = 2.4, 1 H), 7.57 (m, 3 H), 8.01 (d, J = 2.4, 1 H). HRMS (m/z): [MH^+] calcd for $C_{17}H_{16}ClF_3NO$ 342.0867; found 342.0870.

*3-(4-Chloro-phenyl)-5-methyl-2-phenoxy-pyridine (**24b**).* Following a procedure similar to the preparation of **24a**, **23b** (0.79 g, 2.99 mmol) and *B*-[4-chloro-phenyl]-boronic acid (0.70 g, 4.49 mmol) were used to produce **24b** (0.61 g, 68%) as yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 7.07 (d, J = 8.0, 2 H), 7.15 (t, J = 8.0, 1 H), 7.35 (t, J = 8.0, 2 H), 7.40 (d, J = 8.6, 2 H), 7.55 (s, 1 H), 7.57 (d, J = 8.6, 2 H), 7.98 (s, 1 H). MS (ESI) m/z = 296.3 [MH^+].

*3-(4-Chloro-phenyl)-2-cyclopentyloxy-5-methyl-pyridine (**24c**).* Following a procedure similar to the preparation of **24a**, **23c** (0.85 g, 3.3 mmol) and *B*-[4-chloro-phenyl]-boronic acid (0.82 g, 5.0 mmol) were used to produce **24c** (0.74 g, 78%) as yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6−1.8 (m, 6 H), 1.78 (m, 2 H), 2.28 (s, 1 H), 5.46 (m, 1 H), 7.36 (d, J = 8.4, 2 H), 7.39 (d, J = 2.2, 1 H), 7.47(d, J = 8.4, 2 H), 7.95 (d, J = 2.2, 1 H). MS (ESI) m/z = 288.1 [MH^+].

*2-Butoxy-3-(4-chloro-phenyl)-5-methyl-pyridine (**24d**).* Following a procedure similar to the preparation of **24a**, **23d** (1.0 g, 4.1 mmol) and *B*-[4-chloro-phenyl]-boronic acid (0.96 g, 6.1 mmol) were used to produce **24d** (0.86 g, 76%) as yellowish oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.89 (t, J = 7.4, 3 H), 1.37 (m, 2 H), 1.65 (m, 2 H), 2.79 (s, 3 H), 4.27 (t, J = 6.6, 2 H), 7.49 (d, J = 8.8, 2 H), 7.59 (d, J = 8.8, 2 H), 7.60 (d, J = 2.3, 1 H), 7.98 (d, J = 2.3, 1 H). HRMS (m/z): [MH^+] calcd for $C_{16}H_{19}ClNO$ 276.1150; found 276.1155.

*3-(4-Chloro-phenyl)-2-cyclohexyloxy-5-methyl-pyridine (**24e**).* Following a procedure similar to the preparation of **24a**, **23e** (1.00 g, 3.7 mmol) and *B*-[4-chloro-phenyl]-boronic acid (0.91 g, 5.6 mmol) were used to produce **24e** (0.91 g, 82%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (m, 4 H), 1.69 (m, 2 H), 1.91 (m, 2 H), 2.28 (s, 3 H), 5.12 (m, 1 H), 7.36 (d, J = 8.6, 2 H), 7.39 (s, 1 H), 7.52 (d, J = 8.6, 2H), 7.92 (s, 1 H). MS (ESI) m/z = 302.1 [MH^+].

*6-Chloro-5-hydroxy-2-pyridinemethanol (**26**).* To a suspension of 2-chloro-3-hydroxy-pyridine (**25**, 15.0 g, 116 mmol) in water (110 mL) was added sodium bicarbonate (14.6 g, 174 mmol). The resulting suspension was stirred for 15 min (foam formation) warmed to 90 °C, and a formaldehyde solution (37% in water, 30.2 mL, 405 mmol) was added in portions over 18 h. After cooling the reaction mixture, ice (75 g) was added to the mixture and the pH was adjusted to 1 with hydrochloric acid (6 N, 30 mL, CO_2 evolution). The product was partitioned into ethyl acetate; all organic phases were combined, dried with Na_2SO_4, filtered, and concentrated. The solid residue was digested with dichloromethane to afford **26** (12.0 g, 65%) as off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.40 (d, J = 5.7, 2H), 5.31 (t, J = 5.8, OH), 7.27 (d, J = 8.2, 1 H), 7.33 (d, J = 8.2, 1 H), 10.45 (br s, 1 H). HRMS (m/z): [MH^+] calcd for $C_6H_7ClNO_2$ 160.0160; found 160.0161.

*6-Chloro-5-hydroxy-4-iodo-2-pyridinemethanol (**27**).* To a solution of **26** (11.6 g, 72.7 mmol) in water (200 mL) was added sodium bicarbonate (18.3 g, 218 mmol). The resulting suspension was stirred for 15 min (foam formation) cooled to 0 °C, and iodide (19.4 g, 76.3 mmol) was added. The mixture was stirred at 0 °C for 18 h and afterward allowed to reach room temperature. Sodium hydrogen sulfite solution (2 N, 20 mL) was added slowly with cooling, and the pH was adjusted carefully to 3 with hydrochloric acid (2 N). The product was partitioned into ethyl acetate; all organic phases were combined, dried with $MgSO_4$, filtered, and concentrated. **27** (11.4 g; mp 142−144 °C) crystallized from the concentrated solution and additional material (3.1 g, 70% total) could be obtained by chromatography (heptane/ethyl acetate 2:1) of the residue obtained from the mother liquor as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.40 (s, 2H), 5.42 (br s, OH), 7.75 (s, 1 H), 10.34 (br s, 1 H). HRMS (m/z): [MH^+] calcd for $C_6H_6ClINO_2$ 285.9126; found 285.9133.

*6-Chloro-5-(cyclopropylmethoxy)-4-iodo-2-pyridinemethanol (**28a**).* To a solution of **27** (45.0 g, 158 mmol) in DMF (450 mL) was added sodium hydride dispersion (6.3 g, ∼60% in oil, 158 mmol) in portions. The resulting suspension was stirred for 30 min at room temperature, (bromomethyl)cyclopropane (19.3 mL, 189 mmol, dropwise) was added, and the mixture was stirred at 90 °C for 4 h. Solvent was removed in high vacuum, ice−water (800 mL) was added, and the mixture was extracted with ethyl acetate. Organic layers were washed with water and brine, combined, dried over Na_2SO_4, filtered, and concentrated to a volume of ∼200 mL. *n*-Heptane (150 mL) was added with stirring. The product precipitated, was filtered, washed (ethyl acetate/*n*-heptane 1:1), and dried to give **28a** (46.1 g, 86%) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.41 (m, 2H), 0.67 (m, 2 H), 1.41 (m, 1 H), 2.66 (br s, OH), 3.90 (d, J = 7.3, 2 H), 4.67 (br s, 2H), 7.71 (s, 1 H). HRMS (m/z): [MH^+] calcd for $C_{10}H_{12}ClINO_2$ 339.9601; found 339.9592.

*6-Chloro-4-iodo-5-(2,2,2-trifluoroethoxy)-2-pyridinemethanol (**28b**).* To a solution of **27** (40.0 g, 140 mmol) in hexamethylphosphoramide (400 mL) was added sodium hydride dispersion (5.6 g, ∼60% in oil, 140 mmol) in portions. The resulting suspension was stirred for 45 min at room temperature, 1,1,1-trifluoro-methanesulfonic acid 2,2,2-trifluoroethyl ester (23.4 mL, 168 mmol, dropwise) was added, and the mixture was stirred at 120 °C for 24 h. After cooling, the mixture was poured into water (1500 mL), acidified with hydrochloric acid (2 N, 100 mL), and extracted with ethyl acetate. Organic layers were washed with water, combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography, eluting with ethyl acetate/heptane (1:1) to produce **28b** (47.4 g, 92%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.47 (d, J = 5.9, 2 H), 4.69 (q, J = 8.9, 2 H), 5.64 (t, J = 5.9, OH), 7.89 (s, 1 H). HRMS (m/z): [MH^+] calcd for $C_8H_7ClF_3INO_2$ 367.9157; found 367.9159.

*6-Chloro-4-(4-chlorophenyl)-5-(cyclopropylmethoxy)-2-pyridinemethanol (**29a**).* To a solution of **28a** (23.0 g, 67.7 mmol) in toluene (250 mL) was added with stirring the [1,1-bis(diphenylphosphino)-ferrocene] dichloropalladium DCM complex (2.75 g, 3.4 mmol), *B*-(4-chlorophenyl)boronic acid (10.6 g, 67.7 mmol), and sodium carbonate solution (67.7 mL, 2M). The resulting mixture was stirred at 90 °C for 1.5 h, cooled, and partitioned between water and ethyl acetate. The organic portion was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with an ethyl acetate/heptane gradient to produce **29a** (21.2 g, 97%) as light-brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.05 (m, 2H), 0.45 (m, 2 H), 1.00 (m, 1 H), 2.81 (t, J = 5.6, OH), 3.49 (d, J = 7.3, 2 H), 4.74 (d, J = 5.6, 2 H), 7.24 (s, 1 H), 7.45 (d, J = 8.7, 2 H), 7.60 (d, J = 8.7, 2 H). HRMS (m/z): [MH^+] calcd for $C_{16}H_{16}Cl_2NO_2$ 324.0558; found 324.0554.

*6-Chloro-4-(4-chlorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinemethanol (**29b**).* Following a procedure similar to the preparation of **29a**, **28b** (23.0 g, 62.6 mmol) was used to produce **29b** (22.0 g, quant) as brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.77 (t, J = 5.6, OH), 4.03 (q, J

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= 8.2, 2 H), 4.77 (d, J = 5.6, 2 H), 7.30 (s, 1 H), 7.47 (d, J = 8.7, 2 H), 7.55 (d, J = 8.7, 2 H). HRMS (m/z): [MH$^+$] calcd for $C_{14}H_{11}Cl_2F_3NO_2$ 352.0119; found 352.0116.

*4-(4-Chlorophenyl)-5-(cyclopropylmethoxy)-2-pyridinemethanol (**30a**).* To a solution of **29a** (22.9 g, 70.6 mmol) in acetic acid (95%, 70 mL) was added at 40 °C with stirring tetramethylammonium bromide (0.111 g, 0.71 mmol) and in several portions zinc powder (13.85 g, 212 mmol). The resulting mixture was stirred for 18 h at 50 °C, more zinc powder (12.0 g, 183 mmol) was added, and stirring was continued for another 6 h. After cooling, the mixture was poured into water (1000 mL), conc NaOH solution (130 mL) was added, and the zinc hydroxide precipitate was removed by filtration over diatomaceous earth. The precipitate was washed with ethyl acetate (10 × 200 mL), and the water phase was extracted with ethyl acetate; all organic phases were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography, eluting with an ethyl acetate/methanol gradient to produce **30a** (16.4 g, 80%) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.29 (m, 2H), 0.59 (m, 2 H), 1.20 (m, 1 H), 3.46 (bt, J = 5.1, OH), 3.90 (d, J = 6.8, 2 H), 4.79 (d, J = 5.0, 2 H), 7.20 (s, 1 H), 7.42 (d, J = 8.6, 2 H), 7.57 (d, J = 8.6, 2 H), 8.27 (s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{16}H_{17}ClNO_2$ 290.0948; found 290.0938.

*4-(4-Chlorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinemethanol (**30b**).* Following a procedure similar to the preparation of **30a**, **29b** (22.0 g, 62.5 mmol) was used to produce **30b** (16.5 g, 83%) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.33 (bt, J = 5.2, OH), 4.34 (q, J = 8.0, 2 H), 4.78 (d, J = 5.2, 2 H), 7.28 (s, 1 H), 7.45 (d, J = 8.7, 2 H), 7.52 (d, J = 8.7, 2 H) 8.31 (s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{14}H_{12}ClF_3NO_2$ 318.0509; found 318.0502.

*4-(4-Chlorophenyl)-5-(cyclopropylmethoxy)-2-pyridinecarboxylic Acid (**31a**).* To a solution of **30a** (16.3 g, 56.3 mmol) in pyridine (250 mL) was added a solution of tetrabutylammonium permanganate (40.66 g, 113 mmol) in pyridine (120 mL). The combined solution was stirred for 1 h at 80 °C. After cooling, the mixture was poured into water (1500 mL), saturated sodium hydrogensulfite solution (110 mL) was added, and after acidification with concentrated hydrochloric acid (400 mL) the resulting suspension was stirred for 15 min at room temperature. Solids were removed by filtration, washed well with water, and the filtrate was concentrated in vacuo to produce **31a** (16.4 g, 96%) as off-white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.34 (m, 2H), 0.56 (m, 2 H), 1.22 (m, 1 H), 4.12 (d, J = 4.0, 2 H), 7.20 (s, 1 H), 7.56 (d, J = 8.7, 2 H), 7.71 (d, J = 8.7, 2 H), 7.98 (s, 1 H), 8.53 (s, 1 H), 12.98 (br s, 1H). HRMS (m/z): [MH$^+$] calcd for $C_{16}H_{15}ClNO_3$ 304.0741; found 304.0742.

*4-(4-Chlorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxylic Acid (**31b**).* Following a procedure similar to the preparation of **31a**, **30b** (0.50 g, 1.57 mmol) was used to produce **31b** (0.53 g, quant) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.09 (q, J = 8.8, 2 H), 7.58 (d, J = 8.8, 2 H), 7.66 (d, J = 8.8, 2 H), 8.02 (s, 1 H), 8.66 (s, 1 H), 13.16 (br s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{14}H_{10}ClF_3NO_3$ 332.0296; found 332.0299.

*4-(4-Chlorophenyl)-5-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-2-pyridinecarboxamide (**32a**).* General procedure D, with **31a** (100 mg, 0.329 mmol), was used to produce **32a** (105 mg, 80%) as colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.33 (m, 2 H), 0.63 (m, 2 H), 1.25 (m, 1 H), 1.40 (m, 4 H), 1.78 (m, 2 H), 2.10 (m, 2 H), 3.49 (m, 1 H), 3.57 (d, J = 4.0, OH), 3.81 (m, 1 H), 3.99 (d, J = 6.7, 2 H), 7.42 (d, J = 8.6, 2 H), 7.61 (d, J = 8.6, 2 H), 7.89 (bd, J = 7.3, NH), 8.18 (s, 1 H), 8.22 (s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1362; found 401.1633.

*4-(4-Chlorophenyl)-5-(2,2,2-trifluoroethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-2-pyridinecarboxamide (**32b**).* General procedure D, with **31b** (200 mg, 0.603 mmol), was used to produce **32b** (226 mg, 87%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.21−1.34 (m, 4 H), 1.64 (m, 2 H), 1.91 (m, 2 H), 3.47 (m, 1 H), 3.59 (m, 1 H), 4.69 (d, J = 5.5, OH), 5.07 (q, J = 8.7, 2 H), 7.58 (d, J = 8.7, 2 H), 7.65 (d, J = 8.7, 2 H), 7.99 (s, 1 H), 8.31 (bd, J = 8.1, NH), 8.57 (s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{20}H_{20}ClF_3N_2O_3$ 429.1193; found 429.1192.

*2-(4-Chlorophenyl)-3-fluoro-pyridine (**34**).* To a solution of 2-chloro-3-fluoro-pyridine (**33**, 36.2 g, 0.275 mol) in toluene (380 mL) and DMF (40 mL) was added with stirring the [1,1-bis(diphenylphosphino)ferrocene] dichloropalladium DCM complex (4.5 g, 5.5 mmol), *B*-4-chlorophenylboronic acid (43.5 g, 0.278 mol), sodium carbonate (43.8 g, 413 mmol), and water (80 mL). The resulting mixture was stirred at 90 °C for 5 h, cooled, and partitioned between water and ethyl acetate. The organic portion was washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography, eluting with a heptane/ethyl acetate gradient to produce **34** (37.2 g, 65%) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (m, 1 H), 7.46 (d, J = 8.8, 2 H), 7.50 (m, 1 H), 7.95 (d, J = 8.8, 2 H), 8.52 (d, J = 4.6, 1 H). MS (ESI) m/z = 208.03 [MH$^+$].

2-(4-Chlorophenyl)-3-(cyclopropylmethoxy)-pyridine. To a solution of **34** (28.5 g, 137 mmol) in DMSO (160 mL) was added sodium hydride dispersion (7.8 g, ∼55% in oil, 179 mmol) in portions. The resulting suspension was stirred for 30 min at room temperature, cyclopropanemethanol (14.0 mL, 172 mmol, dropwise) was added, and the mixture was stirred at room temperature for 3 h. Afterward, water (1000 mL) was added carefully and the mixture was extracted with DCM. Organic layers were washed with brine, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an ethyl acetate/heptane gradient to produce the title compound (30.1 g, 84%) as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.33 (m, 2 H), 0.63 (m, 2H), 1.25 (m, 1 H), 3.87 (d, J = 6.8, 2 H), 7.20 (m, 1 H), 7.25 (d, J = 6.8, 1 H,) 7.41 (d, J = 8.4, 2 H), 7.98 (d, J = 8.4, 2 H), 8.30 (d, J = 5.7, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{15}H_{15}ClNO$ 260.0842; found 260.0840.

2-(4-Chlorophenyl)-3-(2,2,2-trifluoroethoxy)-pyridine. To a solution of **34** (0.425 g, 2.04 mmol) in DMSO (5 mL) was added cesium carbonate and (1.33 g, 4.08 mmol) and 2,2,2-trifluoroethanol (1.5 mL, 20 mmol), and the mixture was stirred at room temperature for 40 min. The resulting mixture was partitioned between water and ethyl acetate. Organic layers were washed with brine, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an ethyl acetate/heptane gradient to produce the title compound (0.38 g, 65%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.34 (q, J = 8.0, 2 H), 7.28 (m, 2 H), 7.43 (d, J = 8.7, 2 H), 7.89 (d, J = 8.7, 2 H), 8.43 (m, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{13}H_{10}ClF_3NO$ 288.0403; found 288.0397.

*2-(4-Chlorophenyl)-3-cyclopropylmethoxy-pyridine 1-oxide (**35a**).* To a solution of 2-(4-chlorophenyl)-3-(cyclopropylmethoxy)-pyridine (30.0 g, 116 mmol) in acetic acid (300 mL) was added hydrogen peroxide solution (606 mL 30% in water). The resulting solution was stirred for 5 h at 70 °C. After cooling, the mixture was poured into saturated bicarbonate solution and the mixture was extracted with DCM. Organic layers were washed with water and brine, combined, dried over $MgSO_4$ and charcoal, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an ethyl acetate/methanol gradient to produce **35a** (25.4 g, 80%) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.23 (m, 2 H), 0.56 (m, 2H), 1.11 (m, 1 H), 3.82 (d, J = 6.8, 2 H), 6.89 (m, 1 H), 7.14 (m, 1 H), 7.44 (d, J = 8.8, 2 H), 7.52 (d, J = 8.8, 2 H), 8.03 (m, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{15}H_{15}ClNO_2$ 276.0791; found 276.0788.

*2-(4-Chlorophenyl)-3-(2,2,2-trifluoroethoxy)-pyridine 1-oxide (**35b**).* Following a procedure similar to the preparation of **35a**, 2-(4-chlorophenyl)-3-(2,2,2-trifluoroethoxy)-pyridine (1.0 g, 3.48 mmol) was used to produce **35b** (0.71 g, 67%) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.28 (q, J = 7.9, 2 H), 6.92 (d, J = 8.7, 1 H), 7.21 (m, 1 H), 7.46 (d, J = 8.7, 2 H), 7.50 (d, J = 8.7, 2 H), 8.14 (d, J = 6.6, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{13}H_{10}ClF_3NO_2$ 304.0352; found 304.0337.

*6-(4-Chlorophenyl)-5-(cyclopropylmethoxy)-2-pyridinecarbonitrile (**36a**).* To a solution of **35a** (25.2 g, 91 mmol) in acetonitrile (500 mL) was added triethylamine (26.7 mL, 192 mmol) and *N*,*N*-dimethylcarbamic chloride (9.2 mL, 101 mmol) with stirring. Five minutes later, trimethylsilylcyanide (34.4 mL, 274 mmol) was added and the resulting solution was stirred for 15 h at 90 °C. After cooling, the mixture was partitioned between water and ethyl acetate; organic layers were washed with brine, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an heptane/ethyl acetate gradient to produce **36a** (14.2 g, 55%) as light−yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.38 (m, 2 H), 0.70

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(m, 2H), 1.30 (m, 1 H), 3.96 (d, J = 7.0, 2 H), 7.26 (d, J = 8.5, 1 H), 7.43 (d, J = 8.7, 2 H), 7.61 (d, J = 8.5, 1 H), 8.00 (d, J = 8.7, 2 H). HRMS (m/z): [MH^+] calcd for $C_{16}H_{14}ClN_2O$ 285.0795; found 285.0793.

*6-(4-Chlorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarbonitrile (**36b**).* Following a procedure similar to the preparation of **36a**, **35b** (89 mg, 0.29 mmol) was used to produce **36b** (56 mg, 61%) as light-yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.46 (q, J = 7.8, 2 H), 7.33 (d, J = 8.5, 1 H), 7.46 (d, J = 8.7, 2 H), 7.68 (d, J = 8.5, 1 H), 7.91 (d, J = 8.7, 2 H). HRMS (m/z): [$MHCO_2^-$] calcd for $C_{15}H_9ClF_3N_2O_3$ 357.0254; found 357.0270.

6-(4-Chlorophenyl)-5-(cyclopropylmethoxy)-2-pyridinecarboxylic Acid. Acetyl chloride (2.6 mL, 35 mmol) was added to ethanol (40 mL) at 0 °C. After stirring for 5 min at 0 °C, **36a** (104 mg, 7.0 mmol) was added and the mixture was stirred for 20 h at 90 °C. After cooling, the mixture was concentrated, partitioned between water and ethyl acetate; organic layers were washed with brine, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was redissolved in THF (15 mL) and water (7 mL), lithium hydroxide monohydrate (0.59 g, 14 mmol) was added, and the mixture was stirred for 5 h at 80 °C. After cooling, the mixture was brought to pH 6 with acetic acid and extracted with DCM. Organic layers were washed with water and brine, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an heptane/ethyl acetate gradient to produce the title compound (1.01 g, 47%) as light-yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.39 (m, 2 H), 0.70 (m, 2 H), 1.30 (m, 1 H), 3.99 (d, J = 7.0, 2 H), 7.41 (d, J = 8.6, 1 H), 7.46 (d, J = 8.7, 2 H), 7.94 (d, J = 8.7, 2 H), 8.16 (d, J = 8.6, 1 H), COOH not visible (br s at 1.60). HRMS (m/z): [MH^+] calcd for $C_{16}H_{15}ClNO_3$ 304.0735; found 304.0736.

6-(4-Chlorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxylic Acid. Acetyl chloride (0.12 mL, 1.66 mmol) was added to ethanol (2 mL) at 0 °C. After stirring for 5 min at 0 °C, **36b** (104 mg, 0.33 mmol) was added and the mixture was stirred for 20 h at 80 °C. After cooling, the mixture was concentrated, partitioned between water and ethyl acetate; organic layers were washed with brine, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was redissolved in THF (2 mL), sodium hydroxide solution (2 N, 1 mL) was added, and the mixture was stirred for 30 h at 80 °C. After cooling the mixture was brought to pH 6 with acetic acid and extracted with DCM. Organic layers were washed with water and brine, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an heptane/ethyl acetate gradient to produce the title compound (54 mg, 49%) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.49 (q, J = 7.7, 2 H), 7.47 (d, J = 8.5, 1 H), 7.49 (d, J = 8.7, 2 H), 7.85 (d, J = 8.7, 2 H), 8.23 (d, J = 8.5, 1 H), 10.69 (br s, 1 H). HRMS (m/z): [MH^+] calcd for $C_{14}H_{10}ClF_3NO_3$ 332.0301; found 332.0298.

*6-(4-Chlorophenyl)-5-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-2-pyridinecarboxamide (**37a**).* General procedure D, with 6-(4-chlorophenyl)-5-(cyclopropylmethoxy)-2-pyridinecarboxylic acid (180 mg, 0.593 mmol), was used to produce **37a** (174 mg, 73%) as off-white foam. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.36 (m, 2 H), 0.59 (m, 2 H), 1.25 (m, 4 H), 1.31 (m, 1 H), 1.64 (m, 2 H), 1.91 (m, 2 H), 3.47 (m, 1 H), 3.59 (m, 1 H), 4.03 (d, J = 7.0, 2 H), 4.71 (d, J = 5.5, OH), 7.55 (d, J = 8.8, 2 H), 7.68 (d, J = 8.7, 1 H), 7.98 (d, J = 8.7, 1 H), 8.11 (d, J = 8.8, 2 H), 8.12 (bd, J = 7.0, NH). HRMS (m/z): [MH^+] calcd for $C_{22}H_{26}ClN_2O_3$ 401.1632; found 401.1630.

*6-(4-Chlorophenyl)-5-(2,2,2-trifluoroethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-2-pyridinecarboxamide (**37b**).* General procedure D, with 6-(4-chlorophenyl)-5-(2,2,2-trifluoroethoxy)-2-pyridinecarboxylic acid (150 mg, 0.452 mmol), was used to produce **37b** (117 mg, 60%) as off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.49 (q, J = 7.7, 2 H), 7.47 (d, J = 8.6, 1 H), 7.49 (2, J = 8.7, 2 H), 7.85 (d, J = 8.7, 2 H), 8.23 (d, J = 8.6, 1 H), 10.69 (br s, 1 H). HRMS (m/z): [MH^+] calcd for $C_{14}H_{10}ClF_3NO_3$ 332.0301; found 332.0298.

*5-Bromo-3-(4-chlorophenyl)-2-pyrazinamine (**39**).* To a solution of 3,5-dibromo-2-pyrazinamine (**38**, 14.4 g, 57 mmol) in THF (360 mL) and water (360 mL) was added with stirring tetrakis-(triphenylphosphine)palladium(0) (3.29 g, 29.9 mmol). To this mixture was added *B*-4-chlorophenyl-boronic acid (9.36 g, 9.66 mmol) and potassium carbonate (15.8 g, 114 mmol). The resulting mixture was stirred at reflux temperature for 4 h, cooled, and partitioned between water and ethyl acetate. The organic portion was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with ethyl acetate in heptane (1:3) to produce **39** (12.99 g, 80%) as yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.76 (br s, NH_2), 7.48 (d, J = 8.6, 2 H), 7.69 (d, J = 8.6, 2 H), 8.09 (s, 1 H). HRMS (m/z): [MH^+] calcd for $C_{10}H_8BrClN_3$ 283.9585, 285.9562; found 283.9587, 285.9564.

*2,5-Dibromo-3-(4-chlorophenyl)-pyrazine (**40**).* To a solution of **39** (2.36 g, 8.3 mmol) in dibromomethane (15 mL) was added with stirring isoamylnitrite (1.3 mL g, 9.4 mmol). To this mixture was added a solution of trimethylbromosilane (1.5 g, 9.8 mmol) in dibromomethane (5 mL). The resulting mixture was stirred at room temperature for 1 h and poured into sodium bicarbonate solution (30 mL, 10%). The organic portion was purified by flash chromatography, eluting with ethyl acetate in heptane (1:9) to produce **40** (2.13 g, 74%) as light-yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 8.8, 2 H), 7.75 (d, J = 8.8, 2 H), 8.43 (s, 1 H). MS (ESI) m/z = 346.0, 348.0, 350.0 [M].

*5-Bromo-3-(4-chlorophenyl)-2-(cyclopropylmethoxy)-pyrazine (**41**).* To a solution of cyclopropanemethanol (79.3 mg, 1.1 mmol) in DMSO (2 mL) was added sodium hydride dispersion (96 mg, ~55% in oil, 2.2 mmol). The resulting suspension was stirred for 45 min at room temperature, **40** (348 mg, 1.0 mmol) was added, and the mixture was stirred at room temperature for 3 h. The mixture was portioned between ethyl acetate and water; organic layers were washed with water and brine, combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an heptane/DCM gradient to produce **41** (190 mg, 59%) as colorless crystals; mp 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.36 (m, 2 H), 0.64 (m, 2 H), 1.29 (m, 1 H), 4.17 (d, J = 7.3, 2 H), 7.45 (d, J = 8.7, 2 H), 7.73 (d, J = 8.7, 1H), 8.01 (s, 1 H). MS (ESI) m/z = 339.2, 341.2 [MH^+].

*6-(4-Chlorophenyl)-5-(cyclopropylmethoxy)-2-pyrazinecarboxylic Acid Methyl Ester (**42**).* To a solution of **41** (195 mg, 0.574 mmol) in methanol (3.5 mL) and ethyl acetate (1.5 mL) was added the [1,1-bis(diphenylphos-phino)ferrocene] dichloropalladium DCM complex (21.2 mg, 0.0259 mmol) and triethylamine (0.161 mL, 1.15 mmol). The resulting solution was stirred in a CO atmosphere (70 bar) at 110 °C for 18 h. The mixture was concentrated and purified by flash chromatography, eluting with an heptane/DCM gradient to produce **42** (168 mg, 92%) as light-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.41 (m, 2 H), 0.66 (m, 2 H), 1.33 (m, 1 H), 4.00 (s, 3 H), 4.35 (d, J = 7.3, 2 H), 7.45 (d, J = 8.7, 2 H), 8.13 (d, J = 8.7, 2 H), 8.79 (s, 1 H). MS (ESI) m/z = 319.1 [MH^+].

*6-(4-Chlorophenyl)-5-(cyclopropylmethoxy)-2-pyrazinecarboxylic Acid (**43**).* To a solution of **42** (0.16 g, 0.50 mmol) in THF (2 mL), methanol (0.5 mL) and water (0.5 mL) was added lithium hydroxide solution (2 mL, 1 M in water), and the mixture was stirred for 2 h at room temperature. Afterward, citric acid solution (10 mL, 10%) was added, and the organic phase was separated, dried over $MgSO_4$, filtered, and concentrated to produce **43** (0.152 g, 94%) as off-white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.40 (m, 2 H), 0.59 (m, 2 H), 1.33 (m, 1 H), 4.34 (d, J = 7.3, 2 H), 7.61 (d, J = 8.8, 2 H), 8.15 (d, J = 8.8, 1 H), 8.77 (s, 1 H), 13.33 (br s, 1 H). HRMS (m/z): [MH^+] calcd for $C_{15}H_{14}ClN_2O_3$ 305.0687; found 305.0691.

*6-(4-Chlorophenyl)-5-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxy-cyclohexyl]-pyrazine-2-carboxamide (**44**).* General procedure D, with **43** (50 mg, 0.164 mmol), was used to produce **44** (36 mg, 55%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (m, 2 H), 0.65 (m, 2 H), 1.2–1.5 (m, 5 H), 1.78 (m, 2 H), 2.11 (m, 2 H), 3.36 (d, J = 4.4, OH), 3.50 (m, 1 H), 3.85 (m, 1 H), 4.35 (d, J = 7.3, 2 H), 7.48 (d, J = 8.9, 2 H), 7.64 (bd, J = 7.7, NH), 8.05 (d, J = 8.9, 2 H), 8.87 (s, 1 H). [MH^+] calcd for $C_{21}H_{25}ClN_3O_3$ 402.1579; found 402.1595.

*3-Chloro-6-(cyclopropylmethoxy)-pyridazine (**46**).* To a solution of cyclopropanemethanol (17.95 mL, 222 mmol) in DMSO (150 mL) was added sodium hydride dispersion (8.86 g, ~60% in oil, 222 mmol, in portions). The resulting suspension was stirred for 30 min at room temperature, and the resulting solution was added dropwise at room temperature to a solution of 3,6-dichloro-pyridazine (**45**, 30.0 g, 201 mmol) in DMSO (300 mL). Stirring at room temperature was

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continued for another hour; afterward, the mixture was partitioned between ethyl acetate and water, and organic layers were washed with water and brine, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an heptane/ethyl acetate gradient to produce **46** (27.2 g, 73%) as white solid. ^{1}H NMR (000 MHz, $CDCl_3$) δ 0.38 (m, 2 H), 0.64 (m, 2 H), 1.32 (m, 1 H), 4.30 (d, 2 H), 6.96 (d, 1 H), 7.33 (d, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_8H_{10}ClN_2O$ 185.0476; found 185.0481.

*3-Chloro-6-(cyclopropylmethoxy)-5-iodo-pyridazine (**47**).* To a solution of 2,2,6,6-tetramethylpiperidine (79.67 mL, 459 mmol) in THF (800 mL) was added dropwise at room temperature 1.6 N *n*-butyllithium in hexane (285 mL, 456 mmol). Stirring was continued for 20 min, and afterward the solution was cooled to −78 °C. A precooled solution of **46** (24.2 g, 131 mmol) in THF (500 mL) was added rapidly (−69 °C maximum), and the mixture was stirred for 5 min at −75 °C before a precooled solution of iodine (39.9 g, 157 mmol) in THF (500 mL) was added rapidly (−54 °C maximum). Stirring continued at −75 °C for 15 min, the mixture was quenched by addition of saturated ammonium chloride solution, and afterward the mixture was partitioned between ethyl acetate and water; organic layers were washed with water, combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography, eluting with an heptane/DCM gradient to produce **47** (10.3 g, 25%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.42 (m, 2 H), 0.65 (m, 2H), 1.37 (m, 1H), 4.37 (d, J = 7.1, 2 H), 7.90 (s, 1 H). MS (ESI) m/z = 310.9 [MH$^+$].

*3-Chloro-6-(cyclopropylmethoxy)-5-(4-chlorophenyl)-pyridazine (**48**).* To a solution of **47** (14.7 g, 47.2 mmol) in THF (380 mL) and water (380 mL) was added with stirring tetrakis(triphenylphosphine)-palladium(0) (2.7 g, 2.36 mmol). To this mixture was added *B*-4-chlorophenyl-boronic acid (7.38 g, 47.2 mmol) and potassium carbonate (13.1 g, 94.4 mmol). The resulting mixture was stirred at reflux temperature for 25 h, cooled, and partitioned between water and ethyl acetate. The organic portion was dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography, eluting with an heptane/ethyl acetate gradient to produce **48** (4.40 g, 32%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.37 (m, 2 H), 0.62 (m, 2 H), 1.34 (m, 1 H), 4.41 (d, J = 7.1, 2 H), 7.39 (s, 1 H), 7.47 (d, J = 8.6, 2 H), 7.62 (d, J = 8.6, 2 H). MS (ESI) m/z = 295.1, 297.1 [MH$^+$].

*5-(4-Chlorophenyl)-6-(cyclopropylmethoxy)-3-pyridazinecarboxylic Acid Methyl Ester (**49**).* To a solution of **48** (4.4 g, 14.9 mmol) in methanol (53 mL) was added the [1,1-bis(diphenylphos-phino)-ferrocene] dichloropalladium−DCM complex (531 mg, 0.65 mmol) and triethylamine (4.16 mL, 29.8 mmol). The resulting solution was stirred in a CO atmosphere (70 bar) at 120 °C for 20 h. The mixture was filtered, concentrated, and purified by flash chromatography, eluting with an heptane/ethyl acetate gradient to produce **49** (2.93 g, 62%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.41 (m, 2H), 0.63 (m, 2 H), 1.39 (m, 1 H), 4.05 (s, 3 H), 4.54 (d, J = 7.1, 2 H), 7.48 (d, J = 8.6, 2 H), 7.68 (d, J = 8.6, 2 H), 8.11 (s, 1 H). MS (ESI) m/z = 319.2 [MH$^+$].

*5-(4-Chlorophenyl)-6-(cyclopropylmethoxy)-3-pyridazinecarboxylic Acid (**50**).* To a solution of **49** (2.85 g, 8.94 mmol) in THF (30 mL) was added lithium hydroxide solution (11.6 mL, 1 M in water), and the mixture was stirred for 30 min at room temperature. Afterward, the mixture was acidified with hydrochloric acid (1 N), and the precipitate was filtered and dried to give **50** (2.56 g, 94%) as white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.40 (m, 2 H), 0.58 (m, 2 H), 1.33 (m, 1 H), 4.47 (d, J = 7.3, 2 H), 7.60 (d, J = 8.7, 1 H), 7.82(d, J = 8.7, 2 H), 8.09 (s, 1 H), 13.67 (br s, 1 H). HRMS (m/z): [MH$^+$] calcd for $C_{15}H_{14}ClN_2O_3$ 305.0687; found 305.0688.

*5-(4-Chlorophenyl)-6-(cyclopropylmethoxy)-N-[(1R,2R)-2-hydroxycyclohexyl]-pyridazine-3-carboxamide (**51**).* Following a procedure similar to the preparation of **16c**, **50** (100 mg, 0.33 mmol) and (1*R*,2*R*)-2-amino-cyclohexanol hydrochloride (47 mg, 0.41 mmol) were used to produce **51** (90 mg, 68%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (m, 2 H), 0.65 (m, 2 H), 1.2−1.45 (m, 5 H), 1.77 (m, 2 H), 2.10 (m, 2 H), 3.18 (d, J = 4.2, OH), 3.49 (m, 1 H), 3.88 (m, 1 H), 4.49 (d, J = 7.2, 2 H), 7.47 (d, J = 8.7, 2 H), 7.69 (d, J = 8.7, 2 H), 8.00 (bd, NH), 8.23 (s, 1 H). [MH$^+$] calcd for $C_{21}H_{25}ClN_3O_3$ 402.1580; found 402.1579.

Cell Culture. CHO-K1 β-arrestin cells (DiscoveRx Inc., Fremont, CA) expressing human CB1 and human CB2 were cultured in F-12 Nutrient Mixture (HAM) supplemented with 10% FBS, 300 μg/mL hygromycin, and 800 μg/mL Geneticin (G418). Cells were incubated in a humidified atmosphere at 37 °C with 5% CO_2.

Radioligand Binding Assay. For membrane preparation, stably transfected cells were treated for 24 h with 5 mM butyrate in growth medium before harvesting, followed by homogenization in 15 mM Hepes, 0.3 mM EDTA, 1 mM EGTA, 2 mM $MgCl_2$, and complete EDTA-free protease inhibitor (Roche Applied Science, Rotkreuz, Switzerland), pH 7.4, using a glass potter and centrifugation at 47800*g* at 4 °C for 30 min. The pellet was then rehomogenized twice in the same buffer and centrifuged (47800*g*, 4 °C, 30 min). The final pellet was then resuspended in 75 mM Tris, 0.3 mM EDTA, 1 mM EGTA, 12.5 mM $MgCl_2$, and 250 mM sucrose, pH 7.4, at a protein concentration of 1−3 mg per mL, aliquoted, frozen on dry ice, and stored at −80 °C. Saturation binding was performed with 0.05−2.6 nM [^{3}H]CP55940 (Perkin-Elmer) and 1.0 μg of membrane protein. CP55940 (10 μM) was used to define nonspecific binding. More than 95% of the total binding signal was specific. Assay buffer consisted of 50 mM Tris-HCl, 5 mM $MgCl_2$, 2.5 mM EGTA, and 0.1% fatty acid-free BSA, pH 7.4. Assays were initiated by addition of membranes in a final volume of 250 μL per well. Assays were incubated for 3 h at room temperature and then vacuum filtered and rinsed with wash buffer (50 mM Tris-HCl, 5 mM $MgCl_2$, 2.5 mM EGTA, and 0.5% fatty acid-free BSA, pH 7.4) on a Filtermate cell harvester through Packard GF/B filters presoaked in 0.3% polyethylenimine.

For competition binding, membrane preparations were incubated with 0.3 nM [^{3}H]CP55940 in the presence or absence of increasing concentrations of ligands for 60 min at 30 °C in a final volume of 0.2 mL of 50 mM Tris-HCl, 5 mM $MgCl_2$, 2.5 mM EGTA, 0.1% fatty acid-free BSA, and 1% DMSO, pH 7.4, buffer, gently shaking. Nonspecific binding was defined with 10 μM CP55940. All binding reactions were terminated by vacuum filtration onto 0.5% polyethylenimine presoaked GF/B filter plates (Packard) followed by seven brief washes with 2 mL of ice-cold binding buffer containing 0.5% fatty acid-free BSA. Plates were dried at 50 °C for 1 h, and liquid scintillation counting was used to determine bound radiolabel. IC_{50} values and Hill slopes were determined by a four-parameter logistic model using ActivityBase (ID Business Solution, Ltd.). K_i values were determined by the generalized Cheng−Prusoff equation.[40]

GTPγ[^{35}S] Binding Assay. Membranes were generated as described.[25] Fractions were washed and diluted in assay buffer (10 mM HEPES, 32 mM $MgCl_2$, 100 mM NaCl, 20 μM GDP, pH 7.4), homogenized briefly using a Polytron and incubated for 10 min at 30 °C. Following preincubation, assay-mixtures were prepared in 96-well microtiter plates. The composition of the assay mixtures in a final volume of 200 μL of assay buffer per well was as follows: 25 μg of membrane protein (pretreated as described above), 0.25 nM GTPγ-[^{35}S], and the test compounds at the appropriate concentrations. Nonspecific binding was measured in the presence of unlabeled GTPγ[S] in excess (10 μM). All binding reactions were terminated by vacuum filtration onto GF/B filter plates (Packard) presoaked with wash buffer followed by three brief washes with 2 mL of ice-cold wash buffer (Tris 50 mM, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.5% fatty acid free BSA). Plates were dried at 50 °C for 1 h, and liquid scintillation counting was used to determine bound radiolabel in a Packard TopCount (Canberra Packard SA, Zürich, Switzerland).

Microsomal Stability Testing. Incubations were performed in 96-well deep-well plates with a final incubation volume of 600 μL. Incubations contained (finally) 2 μM test compound, 0.5 mg/mL rat liver microsomes, and NADPH regenerating system. Then 50 μL aliquots were removed after 1, 3, 6, 9, 15, 25, 35, and 45 min and quenched in 150 μL of acetonitrile containing internal standard. Samples were then cooled and centrifuged before analysis by LC-MS/MS.

Log peak area ratio (test compound peak area/internal standard peak area) was plotted against incubation time and a linear fit made to the data with emphasis upon the initial rate of compound disappearance. The slope of the fit is then used to calculate the intrinsic clearance:

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$$\text{Clmic}(\mu\text{L/min /mg}) = -\text{slope}(\text{min}^{-1}) \times 1000/[\text{protein concentration}(\text{mg/mL})]$$

Results were not corrected for protein binding in the microsomal incubation.

Hepatocytes Stability Testing: Short Overview. Freshly isolated rat hepatocytes were incubated in suspension in a Williams E medium supplemented with 10% FCS. The hepatocyte suspension cultures were freshly prepared by liver perfusion (as described by Seglen[41]). Incubations of a test compound at 2 μM test concentration in suspension cultures of 1 Mio cells/mL (~1 mg/mL protein concentration) were performed in 96-well plates and shaken at 900 rpm for up to 3 h in a 5% CO_2 atm and 37 °C. After 2, 10, 20, 40, 60, 120, and 180 min, 100 μL of cell suspension in each well was quenched with 200 μL of methanol containing an internal standard. Samples were then cooled and centrifuged before analysis by LC-MS/MS.

Log peak area ratio (test compound peak area/internal standard peak area) was plotted against incubation time and a linear fit made to the data with emphasis upon the initial rate of compound disappearance. The slope of the fit was then used to calculate the intrinsic clearance:

$$\text{Clint}(\mu\text{L/min /1} \times 10^6\text{cells}) = -\text{slope}(\text{min}^{-1}) \times 1000/[\text{protein concentration}(\text{mg/mL})]$$

PK Study after 10 Days Food Admix Administration. **14g** and **14h** were administered by feed admix to male Sprague–Dawley rats (n = 3/test compound) at 30 mg/kg/d each over 10 days. The feed admix chow was replaced by drug-free high fat diet (HFD) chow at the time of first blood sampling. The rats were implanted with a jugular vein catheter 4 days before start of sample collection. After change to the drug-free HFD chow, serial blood samples were collected from the indwelling catheter (K_3EDTA as anticoagulant) over a period of 24 h. Drug levels in plasma were analyzed by LC-MS.

High Fat Diet Rat Study. A group of 80 male Sprague–Dawley rats (Iffa Credo/Charles River France; 10 weeks-old) was fed a high fat diet (from SSNIFF 43% of energy, 19% fat, and equivalent to KLIBA 2157) during 3 weeks (min average BW~450 g). Ambient temperature was approximately 21 °C, and relative humidity 55–65%. A 12 h light–dark cycle was maintained in the room with test being performed during the light phase. Access to tap water was ad libitum. At the end of the feeding period, obese rats (high responders) were selected using the following criteria: the difference in average BW of high responders compared with that of rats fed standard chow diet was at least 2 times the standard deviation (SD) of the average BW of the standard chow diet group:

$$[\text{BW(obese)} - \text{BW(chow)} \geq 2 \times \text{SD(chow)}]$$

The rest of the diet-resistant rats (low responders) were kept for separate investigation, such as pharmacokinetic characterization in age-matched rats. Seven homogeneous groups of obese animals (n = 9) according to BW, the body fat content (measured by MRS at the end of the growing period) were constituted and rats were transferred to single cages.

Treatment was given as food admix. Doses were 10 mg/kg/day for rimonabant and 30 mg/kg/day for **14g** and **14h** administered as food admix. During the treatment, body weight (BW) and food intake (FI) are daily measured. Total body fat and lean mass were measured noninvasively (by MRS). Liver triglyceride content was measured by MRS from isolated liver harvested and kept frozen in dry ice. Satellite groups of three rats each treated with either **14g** or **14h** were reserved for PK determination after 10 days of treatment.

After 24 days of treatment, body fat content (fast mass) was measured noninvasively by MRS method; blood was collected for plasma parameters measurement and leptin plasma levels were measured by ELISA assay (BioVendor, Heidelberg, Germany). OGTT was performed after overnight fasting. Glucose challenge (2 g/kg BW) was given as bolus per gavage and blood collected at several time-points post glucose load (+15/+30 + 60′ and +120′) to measure blood glucose (by GlucoTrend) and plasma insulin (by ELISA). Afterward, organs were harvested (epididymal fat pads, liver, and brain) for further analysis.

■ ASSOCIATED CONTENT

Supporting Information

CEREP data for **14g** and **14h**, as well as glucose excursion data from the high fat diet rat study and PK data for **15h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare the following competing financial interest(s): The authors are or have been employees of F. Hoffmann-La Roche AG.

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■ ABBREVIATIONS USED

AIBN, 2,2′-azobis(2-methylpropannitrile); 2-AG, 2-arachidonoylglycerol; ANOVA, analysis of variance; AUC, area under the curve; CB2, cannabinoid receptor type 2; DIO, diet-induced obesity; DBU, 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]-azepine; DCM, dichloromethane; DEAD, 1,2-diazenedicarboxylic acid 1,2-diethyl ester; DIEA, N,N-diisopropylethylamine; DME, dimethoxyethane; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; GTP, guanosine triphosphate; HEK, human embryonic kidney (cells); KO, knock out; LC-MS, liquid chromatography–mass spectrometry; MS, mass spectrometry; MW, microwave; NBS, 1-bromo-2,5-pyrrolidinedione; NMR, nuclear magnetic resonance; OGTT, oral glucose tolerance test; Pgp, P-glycoprotein; PK, pharmacokinetic; RT, room temperature; SAR, structure–activity relationship; SD, standard deviation; SDPK, single dose PK; SEM, standard error of the mean; TBTU, O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate; THF, tetrahydrofuran; TMP, 2,2,6,6-tetramethylpiperidine; TMSBr, bromotrimethylsilane; TMSCN, trimethylsilanecarbonitrile; TPP, triphenylphosphine

■ REFERENCES

(1) Touwn, M. The religious and medicinal uses of Cannabis in China, India and Tibet. *J. Psychoactive Drugs* **1981**, *13*, 23–34.

(2) Gaoni, Y.; Mechoulam, R. Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish. *J. Am. Chem. Soc.* **1964**, *86*, 1646−1647.
(3) Devane, W. A.; Dysarz, F. A., III; Johnson, M. R.; Melvin, L. S.; Howlett, A. C. Determination and characterization of a cannabinoid receptor in rat brain. *Mol. Pharmacol.* **1988**, *34*, 605−613.
(4) Matsuda, L. A.; Lolait, S. J.; Brownstein, M. J.; Young, A. C.; Bonner, T. I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* **1990**, *346*, 561−564.
(5) Gerard, C.; Mollereau, C.; Vassart, G.; Parmentier, M. Nucleotide sequence of a human cannabinoid receptor cDNA. *Nucleic Acids Res.* **1990**, *18*, 7142.
(6) Munro, S.; Thomas, K. L.; Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61−65.
(7) Devane, W. A.; Hanus, L.; Breuer, A.; Pertwee, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* **1992**, *258*, 1946−1949.
(8) Sugiura, T.; Kondo, S.; Sukagawa, A.; Nakane, S.; Shinoda, A.; Itoh, K.; Yamashita, A.; Waku, K. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem. Biophys. Res. Commun.* **1995**, *215*, 89−97.
(9) Pacher, P.; Bátkai, S.; Kunos, G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol. Rev.* **2006**, *58*, 389−462.
(10) Guindon, J.; Hohmann, A. G. The endocannabinoid system and cancer: therapeutic implication. *Br. J. Pharmacol.* **2011**, *163*, 1447−1463.
(11) Mallat, A.; Teixeira-Clerc, F.; Deveaux, V.; Manin, S.; Lotersztajn, S. The endocannabinoid system as a key mediator during liver diseases: new insights and therapeutic openings. *Br. J. Pharmacol.* **2011**, *163*, 1432−1440.
(12) Montecucco, F.; Di Marzo, V. At the heart of the matter: the endocannabinoid system in cardiovascular function and dysfunction. *Trends Pharmacol. Sci.* **2012**, *33*, 331−340.
(13) Abood, M.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Cravatt, B. F.; Devane, W. A.; Elphick, M. R.; Felder, C. C.; Herkenham, M.; Howlett, A. C.; Kunos, G.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. Cannabinoid receptors: CB1 receptor. *IUPHAR database (IUPHAR-DB)*; International Union of Basic and Clinical Pharmacology: Kansas City, Kansas, 2013; http://www.iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=56 and references cited therein.
(14) Janero, D. R.; Makriyannis, A. Cannabinoid receptor antagonists: pharmacological opportunities, clinical experience, and translational prognosis. *Expert Opin. Emerging Drugs* **2009**, *14*, 43−65.
(15) Sam, A. H.; Salem, V.; Ghatei, M. A. Rimonabant: From RIO to Ban. *J. Obes.* **2011**, Article ID 432607.
(16) *FDA Briefing Document NDA 21-888, Zimulti (rimonabant) Tablets, 20 mg, Sanofi Aventis, Advisory Committee*; U.S. Food and Drug Administration: Silver Spring, MD, June 13, 2007; http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf
(17) Proietto, J.; Rissanen, A.; Harp, J. B.; Erondu, N.; Yu, Q.; Suryawanshi, S.; Jones, M. E.; Johnson-Levonas, A. O.; Heymsfield, S. B.; Kaufman, K. D.; Amatruda, J. M. A clinical trial assessing the safety and efficacy of the CB1R inverse agonist taranabant in obese and overweight patients: low-dose study. *Int. J. Obes.* **2010**, *34*, 1243−1254.
(18) Aronne, L. J.; Finer, N.; Hollander, P. A.; England, R. D.; Klioze, S. S.; Chew, R. D.; Fountaine, R. J.; Powell, C. M.; Obourn, J. D. Efficacy and safety of CP-945,598, a selective cannabinoid CB1 receptor antagonist, on weight loss and maintenance. *Obesity* **2011**, *19*, 1404−1414.
(19) (a) Fulp, A.; Bortoff, K.; Seltzman, H.; Zhang, Y.; Mathews, J.; Snyder, R.; Fenell, T.; Maitra, R. Design and synthesis of cannabinoid receptor 1 antagonists for peripheral selectivity. *J. Med. Chem.* **2012**, *55*, 2820−2834. (b) Tam, J.; Vemuri, V. K.; Liu, J.; Batkai, S.; Mukhopadhyay, B.; Godlewski, G.; Osei-Hyiaman, D.; Ohnuma, S.; Ambudkar, S. V.; Pickel, J.; Makriyannis, A.; Kunos, G. Peripheral CB1 cannabinoid receptor blockade improves cardiometabolic risk in mouse models of obesity. *J. Clin. Invest.* **2010**, *120*, 3735−3735. (c) Tarzia, G.; LoVerme, J.; Duranti, A.; Tontini, A.; Spadoni, G.; Mor, M.; Rivara, S.; Stella, N.; Xu, C.; Piomelli, D. Synthesis and characterization of a peripherally restricted CB(1) cannabinoid antagonist, URB447, that reduces feeding and body-weight gain in mice. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 639−643. (d) Barth, F.; Hortala, L.; Rinaldi-Carmona, M.; Congy, C.; Boulu, L.; Sadoun, F.; Fabre, G.; Finance, O. Rational design of a novel peripherally restricted, orally active CB(1) cannabinoid antagonist containing a 2,3-diarylpyrrole motif. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4573−4577. (e) Hogberg, T.; Receveur, J. M.; Murray, A.; Linget, J. M.; Norregaard, P. K.; Cooper, M.; Bjurling, E.; Nielsen, P. A. Conversion of 4-cyanomethyl-pyrazole-3-carboxamides into CB1 antagonists with lowered propensity to pass the blood−brain barrier. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 453−457. (f) Hogberg, T.; Cooper, M.; Receveur, J. M.; Bjurling, E.; Norregaard, P. K.; Nielsen, P. A.; Skold, N. Exploring SAR features in diverse library of 4-cyanomethylpyrazole-3-carboxamides suitable for further elaborations as CB1 antagonists. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 26−30. (g) Sasmal, P. K.; Reddy, D. S.; Talwar, R.; Venkatesham, B.; Balasubrahmanyam, D.; Kannan, M.; Srinivas, P.; Kumar, K. S.; Devi, B. N.; Jadhav, V. P.; Khan, S. K.; Mohan, P.; Chaudhury, H.; Bhuniya, D.; Iqbal, J.; Chakrabarti, R. Novel pyrazole-3-carboxamide derivatives as cannabinoid-1 (CB1) antagonists: journey from non-polar to polar amides. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 562−568.
(20) Dow, L. D.; Carpino, P. A.; Gautreau, D.; Hadcock, J. R.; Iredale, P. A.; Kelly-Sullivan, D.; Lizano, J. S.; O'Connor, R. E.; Schneider, S. R.; Scott, D. A.; Ward, K. A. Design of a potent CB1 receptor antagonist series: potential scaffold for peripherally-targeted agents. *ACS Med. Chem. Lett.* **2012**, *3*, 397−401.
(21) Mayweg, A.; Marty, H. P.; Mueller, W.; Narquizian, R.; Neidhart, W.; Pflieger, P.; Roever, S. Novel CB1 receptor inverse agonists. WO 2004060870 A1, 2004.
(22) (a) Kuo, G.-H.; Prouty, C.; Wang, A.; Emanuel, S.; DeAngelis, A.; Zhang, Y.; Song, F.; Beall, L.; Connolly, P. J.; Karnachi, P.; Chen, X.; Gruninger, R. H.; Sechler, J.; Fuentes-Pesquera, A.; Middleton, S. A.; Jolliffe, L.; Murray, W. V. Synthesis and structure−activity relationships of pyrazine−pyridine biheteroaryls as novel, potent, and selective vascular endothelial growth factor receptor-2 inhibitors. *J. Med. Chem.* **2005**, *48*, 4892−4909. (b) Andjelkovic, M.; Benardeau, A.; Chaput, E.; Hebeisen, P.; Nettekoven, M.; Obst Sander, U.; Panousis, C. G.; Roever, S. 3-Pyridinecarboxamide and 2-pyrazinecarboxamide derivatives as HDL-cholesterol raising agents. WO 2008040651 A1, 2008.
(23) The stability of a mixture of 0.3 g potassium hydroxide powder in 3 mL of DMSO was tested in an accelerating rate calorimeter under pseudoadiabatic conditions. Decomposition occurred above 145 °C and led to a fast rise in temperature (64.6 °C/min) and pressure. From the obtained data, we extrapolate time to maximum rate of 8 h at 136 °C and 24 h at 119 °C. Reaction temperatures of 100 °C may be acceptable if proper safety procedures are followed.
(24) Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. Stereoselective Synthesis of Furo[2,3-*c*]pyridine Pyrimidine Thioethers, A New Class of Potent HIV-1 Non-nucleoside Reverse Transcriptase Inhibitors. *J. Org. Chem.* **1998**, *63*, 7851−7859.
(25) Alig, L.; Alsenz, J.; Andjelkovic, M.; Bendels, S.; Bénardeau, A.; Bleicher, K.; Bourson, A.; David-Pierson, P.; Guba, W.; Hildbrand, S.; Kube, D.; Lübbers, T.; Mayweg, A. V.; Narquizian, R.; Neidhart, W.; Nettekoven, M.; Plancher, J.-M.; Rocha, R.; Rogers-Evans, M.; Röver, S.; Schneider, G.; Taylor, S.; Waldmeier, P. Benzodioxoles: Novel Cannabinoid-1 Receptor Inverse Agonists for the Treatment of Obesity. *J. Med. Chem.* **2008**, *51*, 2115−2127.
(26) Kuhn, B.; Mohr, P.; Stahl, M. Intramolecular Hydrogen Bonding in Medicinal Chemistry. *J. Med. Chem.* **2010**, *53*, 2601−2611.
(27) Data for rimonabant can be found in the registration dossiers, e.g.: *Scientific Discussion*; European Medicines Agency: London, 2006; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000666/WC500021284.pdf
(28) A summary of the CEREP data can be found in the Supporting Information.

(29) Flamment, M.; Gueguen, N.; Wetterwald, C.; Simard, G.; Malthièry, Y.; Ducluzeau, P. H. Effects of the cannabinoid CB1 antagonist rimonabant on hepatic mitochondrial function in rats fed a high-fat diet. *Am. J. Physiol. Endocrinol. Metab.* **2009**, *297*, E1162−E1170.
(30) Ahima, R. S.; Flier, J. S. Adipose Tissue as an Endocrine Organ. *Trends Endocrinol. Metab.* **2000**, *11*, 327−332.
(31) Poirier, B.; Bidouard, J.-P.; Cadrouvele, C.; Marniquet, X.; Staels, B.; O'Connor, S. E.; Janiak, P.; Herbert, J.-M. The anti-obesity effect of rimonabant is associated with an improved serum lipid profile. *Diabetes, Obes. Metab.* **2005**, *7*, 65−72.
(32) Macedo, I. C.; Medeiros, L. F.; Oliveira, C.; Oliveira, C. M.; Rozisky, J. R.; Scarabelot, V. L.; Souza, A.; Silva, F. R.; Santos, V. S.; Cioato, S. G.; Caumo, W.; Torres, I. L. Cafeteria diet-induced obesity plus chronic stress alter serum leptin levels. *Peptides* **2012**, *38*, 189−196.
(33) Chen, R. Z.; Frassetto, A.; Lao, J. Z.; Huang, R. R.; Xiao, J. C.; Clements, M. J.; Walsh, T. F.; Hale, J. J.; Wang, J.; Tong, X.; Fong, T. M. Pharmacological evaluation of LH-21, a newly discovered molecule that binds to cannabinoid CB1 receptor. *Eur. J. Pharmacol.* **2008**, *584*, 338−342.
(34) Cluny, N. L.; Vemuri, V. K.; Chambers, A. P.; Limebeer, C. L.; Bedard, H.; Wood, J. T.; Lutz, B.; Zimmer, A.; Parker, L. A.; Makriyannis, A.; Sharkey, K. A. A novel peripherally restricted cannabinoid receptor antagonist, AM6545, reduces food intake and body weight, but does not cause malaise, in rodents. *Br. J. Pharmacol.* **2010**, *161*, 629−642.
(35) Tam, J.; Cinar, R.; Liu, J.; Godlewski, G.; Wesley, D.; Jourdan, T.; Szanda, G.; Mukhopadhyay, B.; Chedester, L.; Liow, J. S.; Innis, R. B.; Cheng, K.; Rice, K. C.; Deschamps, J. R.; Chorvat, R. J.; McElroy, J. F.; Kunos, G. Peripheral cannabinoid-1 receptor inverse agonism reduces obesity by reversing leptin resistance. *Cell Metab.* **2012**, *16*, 167−179.
(36) Pang, Z.; Wu, N. N.; Zhao, W.; Chain, D. C.; Schaffer, E.; Zhang, X.; Yamdagni, P.; Palejwala, V. A.; Fan, C.; Favara, S. G.; Dressler, H. M.; Economides, K. D.; Weinstock, D.; Cavallo, J. S.; Naimi, S.; Galzin, A. M.; Guillot, E.; Pruniaux, M. P.; Tocci, M. J.; Polites, H. G. The central cannabinoid CB1 receptor is required for diet-induced obesity and rimonabant's antiobesity effects in mice. *Obesity* **2011**, *19*, 1923−1934.
(37) Quarta, C.; Bellocchio, L.; Mancini, G.; Mazza, R.; Cervino, C.; Braulke, L. J.; Fekete, C.; Latorre, R.; Nanni, C.; Bucci, M.; Clemens, L. E.; Heldmaier, G.; Watanabe, W.; Leste-Lassere, T.; Maitre, M.; Tedesco, L.; Fanelli, F.; Reuss, S.; Klaus, S.; Srivastava, R. K.; Monory, K.; Valerio, A.; Grandis, A.; De Giorgio, R.; Pasquali, R.; Nisoli, E.; Cota, D.; Lutz, B.; Marsicano, G.; Pagotto, U. CB1 Signaling in Forebrain and Sympathetic Neurons Is a Key Determinant of Endocannabinoid Actions on Energy Balance. *Cell Metab.* **2010**, *11*, 273−285.
(38) Mukhopadhyay, P.; Rajesh, M.; Bátkai, S.; Patel, V.; Kashiwaya, Y.; Liaudet, L.; Evgenov, O. V.; Mackie, K.; Haskó, G.; Pacher, P. CB1 cannabinoid receptors promote oxidative stress and cell death in murine models of doxorubicin-induced cardiomyopathy and in human cardiomyocytes. *Cardiovasc. Res.* **2010**, *85*, 773−784.
(39) Cusack, K. P.; Breinlinger, E. C.; Fix-Stenzel, S.-R.; Stoffel, R. H.; Woller, K. R. Novel oxadiazole compounds. WO 2011071570 A1, 2011.
(40) Cheng, Y.; Prusoff, W. H. Relationship between the inhibition constant (K1) and the concentration of inhibitor which causes 50% inhibition (I50) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.
(41) Seglen, P. O. Preparation of isolated rat liver cells. *Methods Cell Biol.* **1976**, *13*, 29−83.