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Synthesis and Anti-obesity Properties of 6-(4-Chlorophenyl)-3-(4-((3,3-difluoro-1-hydroxycyclobutyl)methoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (BMS-814580): A Highly Efficacious Melanin Concentrating Hormone Receptor-1 (MCHR1) Inhibitor

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J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.6b00676 • Publication Date (Web): 26 Aug 2016

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[#] Metabolic Diseases Chemistry, [+] Metabolic Diseases Biology, °PCO MAP, [β] PCO Discovery Toxicology, [ε]PCO Bioanalytical Research

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Abstract. The potent MCHR1 *in vitro* and *in vivo* antagonist activity of a series of cyclic tertiary alcohols derived from compound **2b** is described. Subsequent pharmacokinetic and pharmacodynamic studies identified BMS-814580 (compound **10**) as a highly efficacious anti-obesity agent with a relatively clean *in vitro* and *in vivo* safety profile.

Introduction.

Melanin concentrating hormone (MCH) is a 19 amino acid cyclic peptide which has been implicated in a variety of physiological conditions including feeding and energy homeostasis in mammals.[1] It is synthesized

primarily in cells within the lateral hypothalamus and *zona incerta* of the central nervous system and is identical in all mammals tested. MCH binds to two class A G protein-coupled receptors (GPCRs), MCHR1 and MCHR2 with a 38% sequence homology between the two isoforms. MCHR1, a 353 amino acid peptide receptor, is found in rodents and higher mammals including humans where it is expressed in the central nervous system including hypothalamus. MCHR2 is expressed in higher mammals such as humans, rhesus monkeys and dogs; it is not expressed in rodents. The overall expression pattern of MCHR2 in the brain is similar to MCHR1. The pharmacological role of MCHR2 has not yet been clearly established.

The prominent role of MCH in feeding and energy homeostasis has been thoroughly reviewed. MCH messenger RNA is up-regulated in the hypothalamus of genetically obese mice.[2] Intracerebroventricular injection of the MCH peptide in mice results in significantly increased food intake.[3] Mice overexpressing MCH are obese and display insulin resistance.[4] MCH knockout mice are lean, hypophagic, resistant to diet induced obesity and exhibit an increased metabolic rate.[5] The observed weight loss in the MCH knockout mice has thus been attributed to a combination of both hypophagia and increased metabolism firmly establishing the potential utility of MCHR1 antagonists as anti-obesity agents.

Pharmacological proof of principle is supported by published studies with several small molecule MCHR1 antagonists demonstrating reduction in feeding and body weight in rats and mice. Several compounds have been advanced into clinical trials.[6] However, to date there are no literature reports of demonstrated weight loss in humans with an inhibitor of MCHR1.[7,8]

A major challenge to the development of many MCHR1 inhibitors is the potential cardiovascular risk often stemming from inhibition of various cardiac ion channels including the human ether-a-go-go related gene (hERG) potassium channel. The ion channel activity is presumably caused by the hydrophobic nature and the amine functionalities present in most compounds described in the literature. Efforts to modulate the basicity or replace the amino groups to avoid off-target cardiovascular effects while maintaining potency against MCHR1 and ensuring acceptable pharmacokinetic properties have met with mixed success.[9]

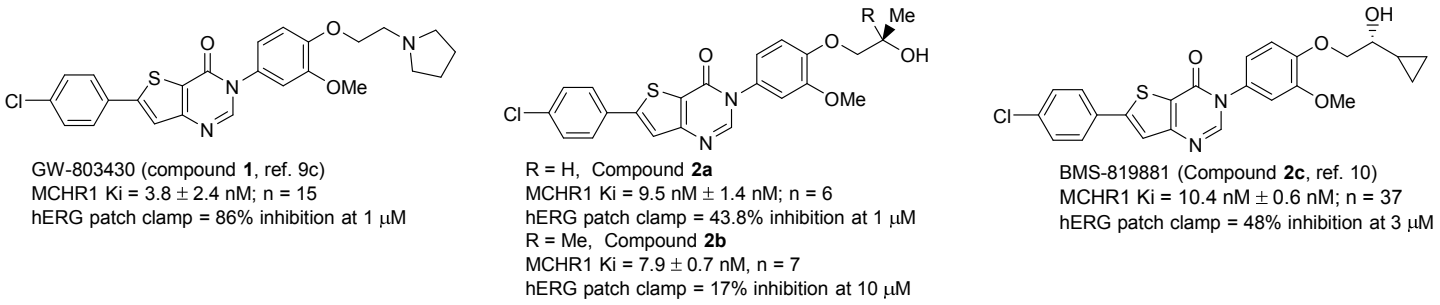


Figure 1. Comparison of MCHR1 binding and hERG activity of selected MCHR1 inhibitors.

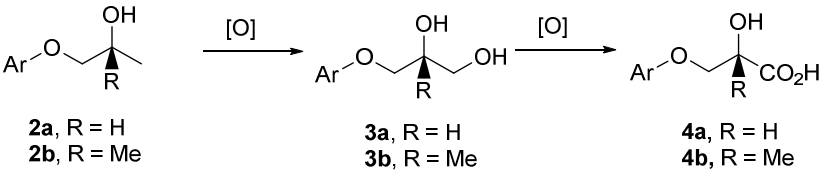


Figure 2. *In vivo* oxidative metabolism of compounds **2a** and **2b** in rats.

We have previously disclosed the discovery of a series of potent non-basic MCHR1 inhibitors with significantly reduced activity against hERG and other cardiac ion channels.[10] The design of the previously disclosed series represented by compounds **2a**, **2b** and **2c** was based on the observation that a screening hit lacking an amino group exhibited MCHR1 activity, suggesting that incorporation of a basic functionality in a MCHR1 inhibitor was not an absolute requirement. This finding, coupled with extensive structure-activity relationship (SAR) studies with numerous series of MCHR1 inhibitors reported in the medicinal chemistry literature, including the well investigated thienopyrimidinones,[11] provided a framework for the execution of our program. A detailed discussion of SAR and *in vitro* and *in vivo* studies have been described leading to the discovery of potent anorectic agents **2a** and **2b**.

While substantial reduction in body weight was seen with select analogs, chronic oral administration of **2a** and **2b** to rats caused biliary lesions in several animals. *In vivo* exposure data of parent compounds and various metabolites established a strong correlation between incidents of the occurrence of lesions and plasma concentrations of the corresponding α-hydroxyacid metabolites (**4a**, **4b**).[10] The apparent involvement of these metabolites in the induction of biliary lesions necessitated designing inhibitors of MCHR1 with more metabolically robust groups adjacent to the alcohol functionality. To that end, a series of alcohols with reduced propensity to produce a carboxyl group in close proximity to the hydroxy functionality were synthesized and evaluated for activity against MCHR1. The previously published efforts were focused on blocking metabolic oxidation of the terminal methyl groups of compounds **2a** and **2b** *via* direct substitution at these sites. Herein we summarize the synthesis and biological evaluation of a series of cyclic tertiary carbinols with particular emphasis on the excellent potency, oral efficacy, and good *in vivo* safety profile of compound **10**.

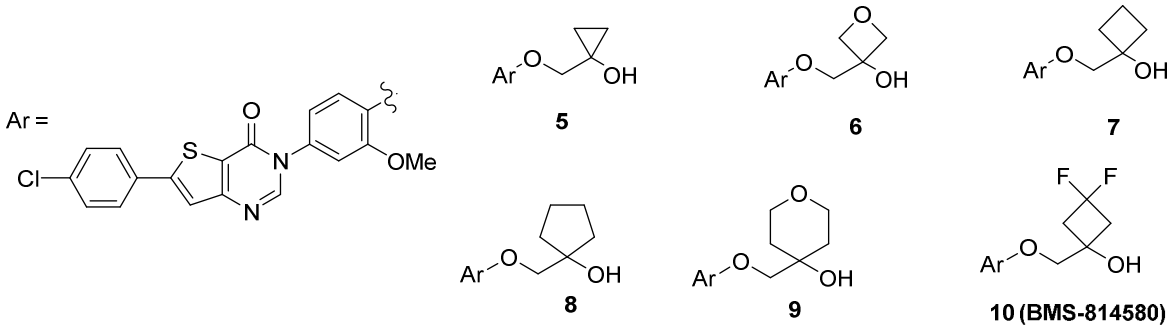
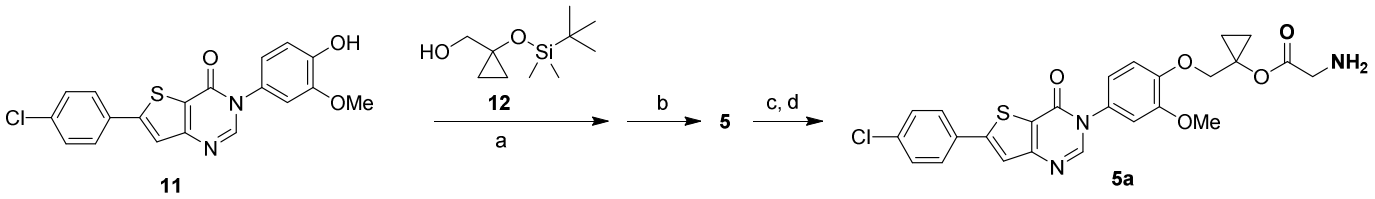


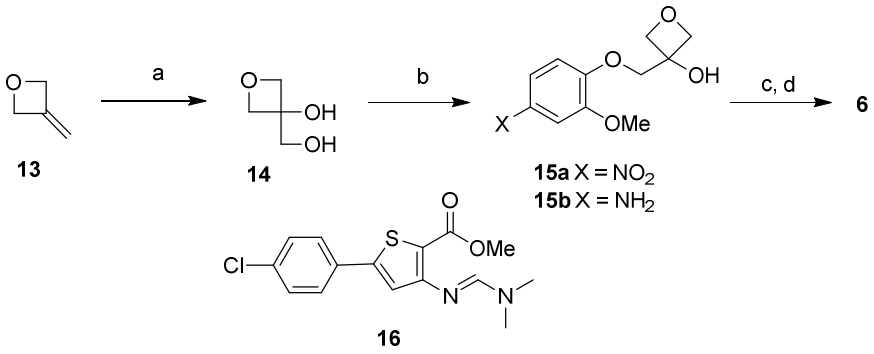
Figure 3. Tertiary alcohols designed to block *in vivo* formation of an α-hydroxy acid metabolite.

Scheme 1.[a]



[a]Reagents and conditions: a) DEAD/triphenylphosphine/DCM, 28%; b) TBAF/THF/89%; c) EDCI/boc-GlyOH/DMAP/CH_2Cl_2/reflux; d) TFA/CH_2Cl_2/RT

Scheme 2.[a]



[a]Reagents and conditions: a) osmium tetroxide/H_2O_2, 49% crude yield; b) NaH/1-chloro-2-methoxy-4-nitrobenzene/DMSO, 28%; c) 10% palladium on C/H_2/50 psi, 93%; d) compound **16**/phenol/130 ^oC

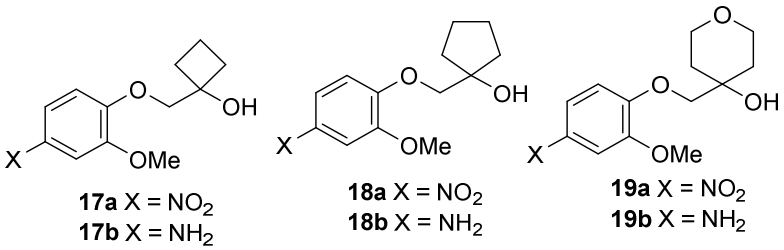
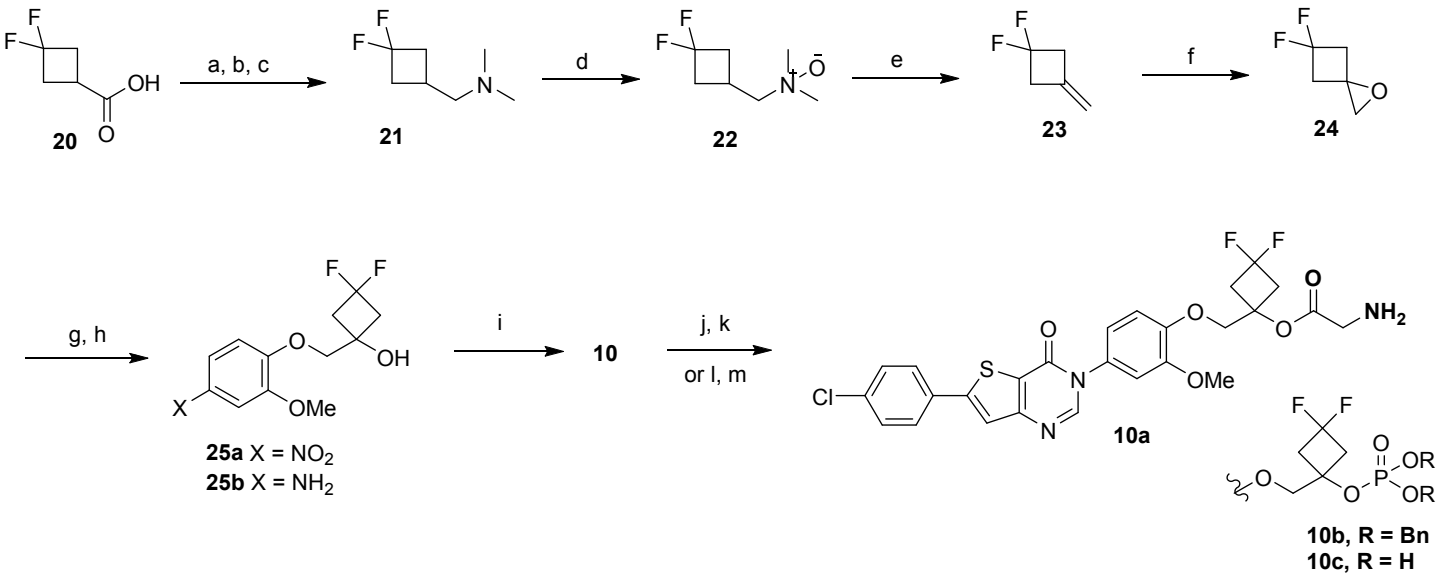


Figure 4.

Scheme 3.[a]



[a]Reagents and conditions: a) oxalyl chloride/CH_2Cl_2; b) dimethylamine/THF, 77% from **20**; c) LAH/THF, 55%; d) H_2O_2/ MeOH; e) 165 ^oC neat, 66% from amine **22**; f) m-CPBA/CH_2Cl_2, quantitative yield; g) potassium 2-methoxy-4-nitrophenolate/NaH_2PO_4/CH_3CN/water/CH_2Cl_2/135 ^oC, steel bomb, 64%; h) 10% Pd-C/MeOH/H_2, 100%; i) compound **16**/phenol/130 ^oC, 75%; j) EDCI/boc-GlyOH/DMAP/CH_2Cl_2/reflux; k) TFA/CH_2Cl_2/RT, 86% 2 steps; l) dibenzyl diisopropylphosphoramidite/triazole then H_2O_2; m) TFA (neat, 3h at RT), 84%.

Chemistry:

The cyclopropyl alcohol **5** was synthesized *via* Mitsunobu coupling of the readily available alcohol **12** with the known intermediate **11** (Scheme 1).[12] Synthesis of the oxetane analog **6** originated with methylene oxetane **13**[13] and involved osmium tetroxide mediated dihydroxylation prior to coupling with 1-chloro-2-methoxy-4-nitrobenzene (Scheme 2). Preparation of the tertiary alcohols **7**, **8** and **9** involved synthesis of the corresponding readily accessible nitrobenzene derivatives outlined in Figure 4.

Synthesis of compound **10** required preparation of the previously unknown spirocyclic epoxide **24** which originated from the readily available difluorocyclobutane carboxylic acid **20**.[14] Conversion of **20** to the corresponding amide followed by lithium aluminum hydride mediated reduction afforded the tertiary amine **21**. Oxidation of **21** using hydrogen peroxide in methanol afforded the N-oxide **22**. Pyrolysis of crude **22** (neat) *via* the Cope elimination reaction at 165 ^oC afforded the methylene cyclobutane derivative **23** under slightly

reduced pressure.[15] Finally, oxidation of **23** using m-CPBA in dichloromethane gave the desired spirocyclic epoxide **24** as a low boiling colorless liquid in quantitative yield.[16] The epoxide **24** was treated with potassium 2-methoxy-4-nitrophenolate followed by reduction and condensation with **16** as described previously to afford **10**.[10] It is noteworthy that efforts to prepare compound **10** from the corresponding vicinal diol, similar to the ones described for compound **6**, failed presumably due to lack of stability of the relatively strained and electron deficient difluorocyclobutane ring under strongly basic conditions.

Results and Discussion.

Our interest in compound **2b** was based on the excellent potency and robust reduction in body weight seen in rats (Tables 1, 2) as well as its relatively clean *in vitro* profile.[10] A multi-pronged investigation was initiated to design analogs of **2b** that would preclude formation of the putative hepatotoxic metabolites. In a previously reported approach, replacement of these labile methyls with groups not prone to oxidation led to the discovery of **2c**. The discussion here is limited to the design, synthesis and *in vitro* and *in vivo* evaluation of a series of cyclic tertiary alcohols directly derived from cyclization of the methyls of compound **2b**. Our finding that a 3,3-diflurocyclobutanol can be employed as metabolically more robust isosteric counterpart of the gem dimethylcarbinol moiety of **2b** culminated the discovery of compound **10** as a highly efficacious anorectic agent with an excellent safety profile.

Table 1. *In vitro* data and physical properties.

Compd	*Ki* (nM)[a]	Compound stability in liver microsomes (% remaining)[b]			Solubility (μg/mL)[c]			LogP[d]	% Free[e]
		Human	Rat	Mouse	Parent compd	Glycinate	Phosphate		
2b	7.9 ± 0.7; (n = 7)	100	98	90	<1	<1	<1	4.5	0.8
5	17.5 ± 7.0; (n = 3)	94	61	99	<1	ND	NA	4.1	ND
6	8.7 ± 0.8; (n = 3)	100	47	100	<1	<1	NA	3.8	ND
7	9.8 ± 1.8; (n = 3)	ND	24	ND	<1	<1	NA	4.7	ND
8	11.9 ± 0.8; (n = 3)	73	14	ND	<1	NA	NA	4.7	ND
9	11.2 ± 2.8; (n = 3)	87	27	98	<1	NA	NA	4.2	ND
10	16.9 ±	90	95	100	<1	<1	4	4.8	0.2

							5.9; (n = 12)

[a] Human MCHR1 binding affinities were measured as described in reference 10. [b] Compounds were incubated with liver microsomes at 3.0 μM for 10 minutes. [c] Solubility of parent compounds and prodrugs at pH 6.4 in 50 mM phosphate buffer. [d] HPLC logP at pH 7.0. [e] Plasma protein binding in rat. ND = not determined. NA = not available (prodrug not prepared).

SAR studies had revealed that the binding site tolerated a wide range of polar and non-polar functionalities adjacent to the hydroxyl group. Thus, all tertiary alcohols described in this report displayed potent antagonism at the human MCHR1 receptor with *K*i values ranging between 8 and 18 nM (Table 1). Binding affinities approximated that of **2b** but were 3 to 6 times lower than the 2.9 nM value measured for the tertiary amine derivative **1** (GW-803430). Affinity towards rat MCHR1 (data not shown) was comparable to the human receptor presumably due to the high homology between the two. Evaluation of select analogs, including the lead compound **10**, against MCHR2 showed no inhibitory activity at concentrations up to 10 μM.

Although the discovery that a hydroxy group could replace the tertiary amine functionality was critical in addressing ion channel related issues with MCHR1 inhibitors, this modification induced such a severe reduction in aqueous solubility that *in vivo* evaluation required administration of these alcohols as their corresponding pro-drug. Extensive screening of a variety of acidic, basic and sugar based derivatives led to the identification of glycine and phosphate esters as suitable prodrugs for the various tertiary alcohols.[10] Plasma samples from animals in all *in vivo* studies were analyzed to determine exposures of parent compounds as well as the corresponding prodrugs. The amounts of the unconverted prodrugs found in the plasma were generally very low and often did not reach detection limits even at the earliest measurement time points.

Table 2. Pharmacokinetics (PK) and pharmacodynamics (PD) data: Plasma and brain concentrations of cyclic tertiary alcohols and the effect on body weights in Sprague-Dawley rats.

Compd	Dosed as[a]	8 h Rat PK study[b]			4 Days PD study[c]	Day 4 parent compd concentrations at 20 h	
		AUC (μM • h)	Brain (nM)	Plasma (nM)	% Weight loss	Brain (nM)	Plasma (nM)
2b	glycinate	45	7800	3530	6.1%[d]	1116	682
5	glycinate (**5a**)	5.9	<3	113	NT	-	-
6	glycinate (**6a**)	34.9	1130	1164	0%[e]	<3	37
7	parent (**7**)	0.2	<3	6	NT	-	-
	glycinate (**7a**)	1.3	<3	15	NT		
9	parent (**9**)	0.4	<3	29	NT	-	-
10	glycinate (**10a**)	38.1	11330	4500	6.4%[d]	7955	12801

[a] Rats were dosed orally with parent compound or a prodrug; prodrugs doses were adjusted to parent compounds. Vehicle = 0.5% Methocel/0.1% Tween 80/99.4% distilled water. [b] Dose = 10 mg/kg, plasma and brain concentrations are reported 8 h post dose, n = 2. [c] Compounds were dosed at 3, 10 and 30 mg/kg orally once a day for 4 days; weight loss data is reported only for the 10 mg/kg dose, n = 8; reduction in body weight is reported as % change from baseline body weight compared to vehicle treated animals. [d] No biliary lesions were seen with compounds **2b** or **10** in this model; lesions were seen with **2b** only after 28 days in an efficacy study in DIO rats, see reference 10 for details. [e] Biliary lesions were seen in 40% of the animals at 30 mg/kg dose; no reduction in body weight seen at any of the doses used. NT = not tested.

Brain and plasma exposures of alcohols **5-10** in Sprague-Dawley (SD) rats were determined following 10 mg/kg oral dosing as the glycine pro-drug prior to *in vivo* efficacy evaluation in a 4 days sub chronic rat weight

loss model (Table 2). It is noteworthy that over the course of the program we had realized that prolonged plasma and brain exposures to the drug were required in order to achieve significant (>5%) reduction in body weight in our primary 4 day *in vivo* efficacy model. Achieving *in vivo* efficacy was further complicated by the fact that most compounds in this series displayed very high plasma protein binding (>98%) necessitating exposures exceeding the nanomolar range and reaching micromolar concentrations *in vivo*.

The cyclopropyl alcohol **5**, designed to block metabolic oxidation of methyl groups of **2b** that would produce a carboxyl group, was a potent inhibitor of MCHR1 (K_i 17.5 ± 7.0 nM). While modest overall plasma exposures were achieved with **5** after a 10 mg/kg oral dose (0-8 h AUC = 5.9 μM • h, dosed as the glycine prodrug **5a**), the plasma concentration of **5** at the 8 hour time point was rather low (113 nM). In addition, there was no detectable amount of compound **5** present in the rat brain after 8 hours. Compound **5** was thus deemed unsuitable for further *in vivo* studies. The cyclobutyl and tetrahydropyranyl alcohols (**7** and **9** respectively) also designed to block formation of α-hydroxy acid metabolites, failed to exhibit sufficient plasma and brain exposures as well, when evaluated both as parent compounds and/or glycine prodrugs (Table 2).

The potential use of an oxetane ring to block *in vivo* metabolism has been described previously.[17] Incorporation of this functionality afforded potent MCHR1 inhibitor **6** (K_i 8.7 ± 0.8 nM). Compound **6** displayed high plasma exposures in the rat PK study (0-8 hours AUC = 34.9 μM • h) and over 1 μM plasma and brain concentrations after 8 hours when dosed as the glycine prodrug **6a**. However, **6** failed to produce a significant reduction in body weight in the 4 days efficacy study in rat. Analysis of the brain and plasma samples from this study revealed exceedingly low plasma concentrations (37 nM) with no detectable amount of **6** in the brain at the 20 hour time point. The plasma concentrations of **6** had dropped by >95% during the 8 to 20 h time course. The lower plasma and brain concentrations seen with **6** at a later time point can be rationalized by the relatively faster *in vitro* clearance of the parent compounds in a rat liver microsomes based assay (only 47% remaining after incubation for 10 minutes *vs.* 98% remaining for **2b**, Table 1). The failure to produce a reduction in body weight in rats by compounds with fast clearance perhaps underscores the significance of the requirement for a prolonged and sustained inhibition of MCHR1 in this model.

Efforts to design and prepare analogs with more metabolically robust alcohols continued resulting in the generation of a wide range of potent inhibitors of MCHR1. The list of analogs ranged from highly non-polar polyfluorinated compounds to analogs incorporating more polar functionalities such as hydroxyl and sulfone groups (analogs not shown). However, most of these compounds proved inadequate in reducing body weight *in vivo* in the rat model presumably due to higher molecular weight, poor aqueous solubility or high polar surface area. The focus on designing CNS penetrant analogs with low molecular weight prompted a reexamination of the failure of the oxetane (compound **6)** and the cyclobutane (compound **7**) derivatives. Although oxidative metabolites had not been identified, we hypothesized that fluorination of compound **7** would diminish the susceptibility of the four membered ring towards metabolic oxidation.

Synthesis of a fluorocyclobutanol analog proved initially cumbersome as the requisite precursors were not readily available. Nonetheless, the efforts succeeded resulting in the generation of the potent difluorocyclobutane derived MCHR1 inhibitor **10** (K_i 16.9 ± 5.9 nM). *In vitro* evaluation of compound **10** in rat liver microsomes (Table 1) revealed adequate metabolic stability with 95% remaining after incubation for 10 minutes. Upon oral dosing of the corresponding glycine prodrug **10a** at 10 mg/kg, high *in vivo* exposure of the parent compound (0-8 h AUC = 38 μM•h) as well as high 8 h brain (11.3 μM) and plasma (4.5 μM) concentrations were attained. The distribution of **10** in to the brain was high with a brain-to-plasma concentration ratio of 2.5 at 8 h time point (Table 2). Further assessment of compound **10** at 10 mg/kg in the sub chronic 4 day *in vivo* efficacy model demonstrated a significant 6.4% reduction in body weight in rats. The degree of reduction in body weight with compound **10** was comparable to the lead tertiary alcohol **2b** in this model (Table 2).

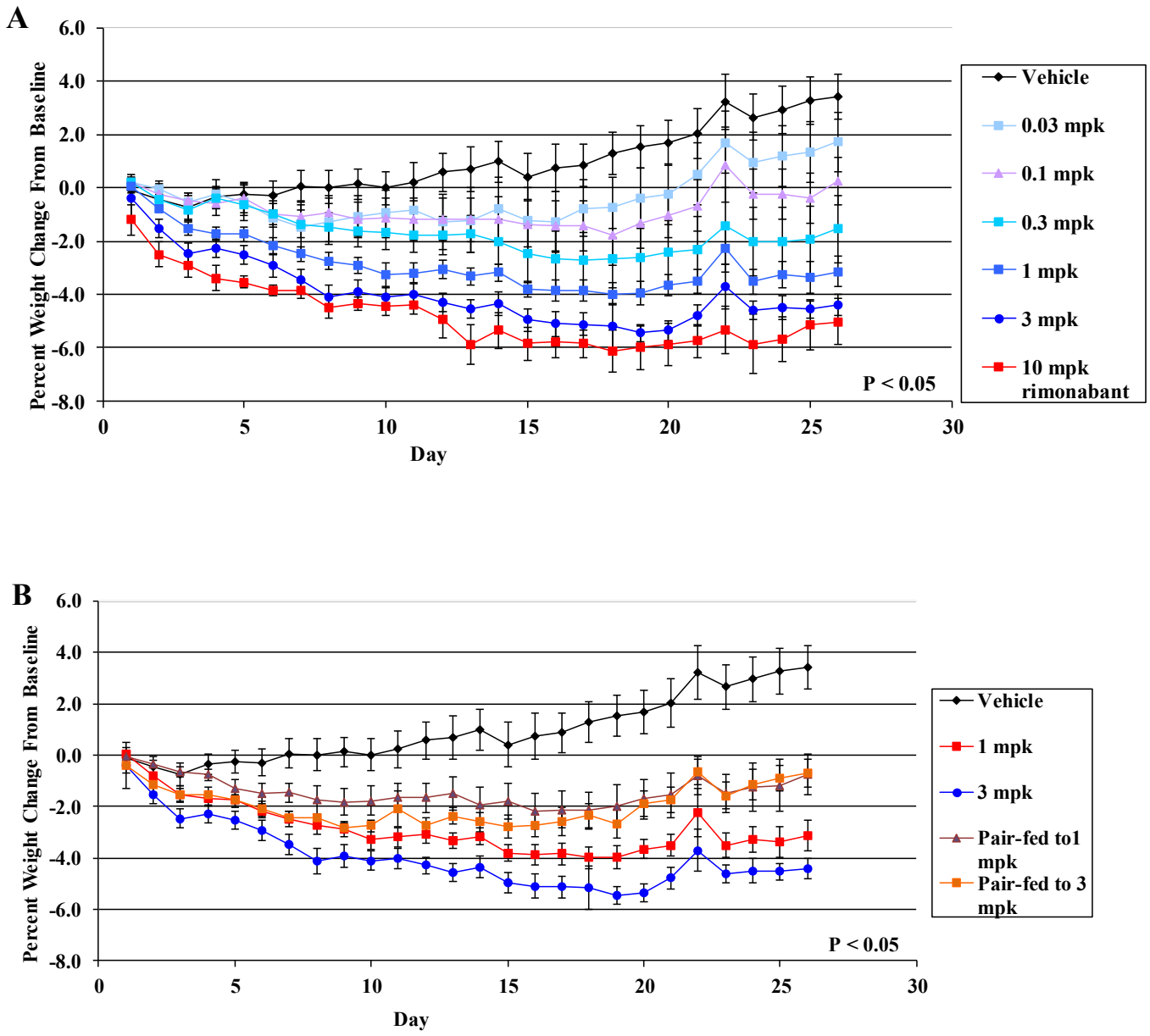


Figure 5. **A.** Effect of compound **10** (dosed as **10c**) on body weights after once daily oral dosing in DIO rats for 28 days (data plotted for 26 days); n = 8; vehicle: 14% propylene glycol, 1% tween, 85% water, v/v/v. Body weight and consumption of food and water were measured daily, see reference 18 for details. **B.** Comparison of weight reduction seen in pair-fed animals to the corresponding animals dosed with compound **10** at 1 and 3 mg/kg.

Encouraged by the efficacy data from the sub chronic study, compound **10** was further evaluated in a chronic diet-induced obese (DIO) rat model for 28 days (Figure 5) using obese male SD rats (8 rats/group).[18] Animal

were dosed once daily at doses ranging from 0.03 to 3 mg/kg with compound **10** administered as the phosphate prodrug **10c**.[19] Body weight and food consumption were measured daily. In addition to the vehicle and positive control (10 mg/kg rimonabant)[20] animal groups, two pair-fed groups matching the food intake of animals administered 1 and 3 mg/kg doses of the drug were also included in this study in order to assess contribution of reduction in food intake to overall weight loss. Compound **10** was well tolerated; moreover, histopathology revealed no signs of biliary toxicity at the end of the study. Compound **10** dose dependently reduced body weight in DIO rats compared to the vehicle treated animals giving a linear dose response (R = 0.998). The benchmark requirement for efficacy in obesity (5% reduction in bodyweight) was achieved at a 0.3 mg/kg dose of **10** dosed as the phosphate prodrug **10c** on day 25. The reduction in body weight at the 3 mg/kg dose (7.8%) was roughly comparable to the positive control rimonabant (8.5% at 10 mg/kg) group.

Figures 5B shows comparisons of changes in body weight for the 1 and 3 mg/kg pair-fed groups *vs.* the corresponding drug treated animals. While the untreated rats on limited diet lost slightly over 4% of body weight (*vs.* vehicle) during the course of this study, matched rats treated with 1 and 3 mg/kg doses lost significantly more body weight (6.6 and 7.8% respectively). Table 3 outlines food calories consumed by the various cohorts including the pair-fed animals in addition to the body weight changes. The data shows that animals treated with **10** dose dependently consumed fewer calories compared to the vehicle control group. The plasma concentrations at 2 and 24 h time points (Table 3) for 0.3 and 3 mg/kg doses suggests that the prolonged exposure to **10** and the resulting sustained inhibition of MCHR1 may be contributing to the robust weight loss seen in this model. The pair-fed data suggests that the reduction in consumed calories only partially accounts for the observed weight loss seen in DIO rats, perhaps suggesting a role for MCHR1 in modulating metabolic rate.[5]

Compound **10** exhibits potent binding affinity (K_i 17 nM) for human MCHR1. It is a potent and selective functional antagonist (K_b 117 nM) of human MCHR1 in a FLIPR-based assay[10] exhibiting no activity against MCHR2 at 10 μM. Compound **10** also exhibits potent binding affinities for cynomolgus monkey and rat MCHR1 (K_i 4.9 and 11.5 nM respectively). The phosphate prodrug **10c** displays weak binding affinity for

MCHR1 (K_i = 2.92 μM). Compound **10** displayed high plasma protein binding in all species tested with 0.2, 0.1, 0.3, 0.4, 0.2 and 0.3 % free drug respectively in rat, DIO rat, dog, cynomolgus monkey, rabbit and human. The potential for compound **10** to cause drug-drug interactions appears low since **10** is neither a substrate nor an inhibitor (>40 μM) of cytochrome P450 enzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, and 3A4), nor an inducer of CYP3A4. There was no evidence of significant receptor binding or enzyme inhibition at 10 μM in a broad panel of Panlab assays.[21] Results of Ames and *in vitro* micronucleus assays were negative, suggesting a low potential for mutagenicity.

Compound **10** displayed modest *in vitro* ion channel inhibition of 43%, 21% and 15% respectively for hERG, Na (4 Hz) and L-type Ca channels at 10 μM. However, subsequent evaluation in an anesthetized rabbit model revealed no compound related effects on QT or QRS duration up to plasma concentrations of 38 μM suggesting no hERG or sodium channel related effects. In addition, there was no compound related effect on mean arterial blood pressure or heart rate in this model.

Full PK studies were carried out with **10** in three distinct animal species (rat, dog and cynomolgus monkey) using the phosphate prodrug **10c** at a 10 mg/kg oral dose while using the parent compound **10** at an intravenous dose of 1 mg/kg (Table 4). Compound **10** displayed modest absolute oral bioavailability in all three species; 54% (rat), 33% (dog) and 46% (monkey). The volume of distribution of **10** was 4.1, 7.2, and 5.4 L/kg in rats, dogs, and monkeys, respectively. Extended toxicity studies with compound **10** (dosed as **10c**) in rat demonstrated adequate safety, producing no hepatobiliary lesions at up to 100 mg/kg daily dose for 30 days.

Table 3. Caloric intake *vs.* reduction in body weights in DIO rats after once daily oral dosing of compound **10** (dosed as **10c**).

Treatment	% Weight change	% Reduction in consumed calories	Plasma conc. of **10** (μM)[a]	
			2 h	24 h
Vehicle	0	0	-	-
10 (0.03 mg/kg)	-1.7	-6.5	ND	ND
10 (0.1 mg/kg)	-3.2	-10.5	ND	ND
10 (0.3 mg/kg)	-5.0	-12.8	2.0 ± 0.6	1.2 ± 0.1
10 (1 mg/kg)	-6.6	-14.5	ND	ND
10 (3 mg/kg)	-7.8	-14.7	13.5 ± 0.5	14.4 ± 0.4
pair-fed to 1 mg/kg of **10**	-4.2	-14.3	-	-
pair-fed to 3 mg/kg of **10**	-4.1	-14.7	-	-
rimonabant (10 mg/kg)	-8.5	-27	-	-

[a] Plasma concentrations of the phosphate prodrug **10c** were undetectable (<2 nM). ND = not determined.

Table 4. Pharmacokinetics data for compound 10 in rat, dog and cynomolgus monkey.[a]

Species	Compd (mg/kg)	Route of admin	C_{max} (μM)	T_{max} (h)	$AUC_{0-\infty}$ μM•h	$T_{1/2}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)	F (%)
rat	**10** (1)	i.v.	-	-	11.5	>24	0.9	4.1	-
	10c (10)	p.o.	4.0	6.7	107	-	-	-	54
dog	**10** (1)	i.v.	-	-	5.2	16.0	6.9	7.2	-
	10c (10)	p.o.	1.2	9.3[b]	15.3	-	-	-	33
monkey	**10** (1)	i.v.	-	-	22.1	37.0	1.7	5.4	-
	10c (10)	p.o.	1.2	10.7[c]	87.0	-	-	-	46

[a] Vehicles: IV, PEG400:DMAC:water (70:5:25); PO, Methocel:Tween80:water (0.5:0.1:99.4). [b] n = 3; individual animal data, 2 h, 2 h, 24 h; one dog had T_{max} at 2 hours followed by a second peak at 24 hours; T_{max} for all 3 dogs before the 24 h time point was 2 h.[22] [c] n = 3, individual animal data, 4 h, 4 h, 24 h; one monkey displayed delayed oral absorption.[22]

In summary, the improved metabolic stability conferred upon replacement of the dimethylcarbinol of **2b** with a 3,3-difluorocyclobutanol moiety without incurring any loss of favorable properties illustrates the advantages conferred by this novel structural modification. The data presented here as well as data from additional *in vivo* studies in rats and higher species support further consideration of **10** as an anti-obesity agent. The worldwide prevalence of obesity and the scarcity of safe and effective anti-obesity drugs clearly emphasizes a vital need for new anti-obesity treatments with improved therapeutic margins.[23] Although the potential involvement of MCHR2 in weight management in humans is a possible explanation for the current inability of MCHR1 selective molecules to exhibit weight loss in humans, the challenge to demonstrating efficacy in humans with

MCHR1 inhibitors, as has been suggested by Souers at al.[9], may be discovering a molecule such as **10** (BMS-814580) with prolonged and sustained *in vivo* exposure and a safe therapeutic index.

Experimental Section

General. All reagents and solvents used were of commercial quality and were primarily obtained from Aldrich Chemical Co., Sigma Chemical Co., Lancaster Chemical Co., Acros Chemical Co. or EM Science Chemical Co. ^{1}H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) spectra were recorded on JEOL GSX400 and JEOL JNM-ECP500 spectrometers using tetramethylsilane as an internal standard. Chemical shifts are given in parts per million (ppm) in δ units. All flash chromatographic separations were performed using E. Merck silica gel (particle size, 0.040−0.063 mm). Reactions were monitored by TLC using 0.25 mm E. Merck silica gel plates (60 F254). LC-MS data were recorded on a Shimadzu LC-10AT equipped with a SIL-10A injector and a SPD-10AV detector, normally operating at 220 nm and interfaced with a Micromass ZMD mass spectrometer.

Analytical HPLC and LC-MS analyses were carried out using the following methods: Method A; Phenomenex Luna S5 C18 4.6x30 mm column/water-MeOH-TFA 90:10:0.1 to 10:90:0.1 gradient over 2 min at 4 mL/min with 1 min hold at the end of the gradient. Method B; SunFire C18 3.5 micron 4.6x150 mm column/water-CH_3CN-TFA 95:5:0.05 to 5:95:0.05 gradient over 15 min, 1 mL/min, 3 min hold. Method C; XBridge Phenyl 3.5 micron 4.6x150 mm column/water-CH_3CN-TFA 95:5:0.05 to 5:95:0.05 gradient over 15 min, 1 mL/min, 3 min hold. Method D; YMC S5 C18 4.6x50 mm column/water-MeOH-H_3PO_4 90:10:0.2 to 10:90:0.2 gradient over 4 min, 4 mL/min, 1 min hold. Method E; Phenomenex Synergi 4μ ODS 4.6x50 mm column/water-MeOH-H_3PO_4 90:10:0.2 to 10:90:0.2 gradient over 4 min, 4 mL/min, 1 min hold. Method F (used with LC/MS); YMC S5 C18 4.6x50 mm column/water-MeOH-TFA 90:10:0.1 to 10:90:0.1 gradient over 4 min, 4 mL/min, 1 min hold. Method G; Zorbax SB C18, 4.6x75 mm column/water-MeOH-H_3PO_4 90:10:0.2 to 10:90:0.2 gradient over 30 min, 1 mL/min. Method H; Phenomenex Luna S5 C18 4.6x30 mm column/10 mM NH_4OAc in water-CH_3CN 95:5 to 5:95 gradient over 2 min, 4 mL/min, 1 min hold. Method I; Phenomenex Luna S5 C18 4.6x30 mm column/water-CH_3CN-TFA 95:5:0.05 to 5:95:0.05 gradient over 4 min, 4 mL/min, 1 min hold. Method J; Zorbax SB C18, 4.6x75 mm column/water-MeOH-H_3PO_4 90:10:0.2 to 10:90:0.2 gradient over 8 min, 1

mL/min. Method K (used with LC/MS); Phenomenex Luna C18 4.6x50 mm column/water-MeOH-TFA 90:10:0.1 to 10:90:0.1 gradient over 4 min, 4 mL/min.

All final compounds were of ≥ 95% purity by the LC/MS and analytical HPLC systems and were characterized by NMR analysis. Samples prepared for *in vivo* studies were of ≥ 98% purity.

6-(4-Chlorophenyl)-3-(4-((1-hydroxycyclopropyl)methoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (5): A solution of methyl 1-hydroxycyclopropanecarboxylate (465.2 mg, 3.61 mmol), *t*-butyldimethylsilyl chloride (752 mg, 4.89 mmol) and imidazole (644 mg, 9.37 mmol) in DMF (4.5 mL) was stirred at 35 °C for 15 h. After cooling to RT, the solution was diluted with ether, washed with brine, dried (Na_2SO_4), concentrated and the residue was subjected to flash chromatograph (silica gel/hexane-ethyl acetate 95:5) to give methyl 1-((tert-butyldimethylsilyl)oxy)cyclopropanecarboxylate (658 mg, 79 % yield) as a colorless oil.

To a solution of the above ester in toluene (6.8 mL) was added 1*M* DIBALH in toluene (6.3 mL, 6.30 mmol) dropwise at -78 °C. The mixture was stirred at -78 to -70 °C for 2 h followed by the addition of methanol (2.5 mL). The mixture was allowed to come to RT. Stirring was continued at RT for 15 h and then the resulting gelatinous mixture was filtered through a sintered glass funnel. The funnel contents were rinsed with DCM and the combined filtrates were concentrated to provide crude alcohol **12** (501 mg, 87% crude yield).

To a stirred suspension of 6-(4-chlorophenyl)-3-(4-hydroxy-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (**11**) (72 mg, 0.187 mmol),[12] crude alcohol **12** from above (38 mg, 0.16 mmol) and triphenylphosphine (55 mg, 0.21 mmol) in DCM (1.0 mL) at RT was added diethyl azodicarboxylate (34 µL, 0.209 mmol) dropwise. Stirring was continued at RT for 13 h and the reaction mixture was passed through a silica gel column eluting with DCM-Ether (95:5) to obtain 3-(4-((1-((*t*-Butyldimethylsilyl)oxy)cyclopropyl)methoxy)-3-methoxyphenyl)-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one (24 mg, 26 % yield) as a white solid. This material was dissolved in THF (0.9 mL) followed by the addition of tetrabutylammonium fluoride in THF (1*M*, 50 µL, 0.05 mmol). The mixture was stirred at RT for 2 h, diluted with water (2.0 mL) and extracted with DCM. The

organic phase was dried (Na_2SO_4) and concentrated. The residue was subjected to flash chromatography (silica gel/DCM-EtOAc 30:70 to 20:80 gradient) to afford compound **5** (17 mg, 0.037 mmol) as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.15 (1H, s), 7.71 (2H, d, J=8.3 Hz), 7.57 (1H, s), 7.47 (2H, d, J=8.3 Hz), 7.07 – 7.00 (1H, m), 6.99 – 6.92 (2H, m), 4.09 (2H, s), 3.89 (3H, s), 0.96 – 0.87 (2H, m), 0.69 (2H, dd, J=6.6, 5.3 Hz); LC/MS (ESI) *m/z* 455 $[M+H]^+$; analytical HPLC t_R 3.55 min (method K), 6.54 min (method J); HRMS (ESI) *m/z* 455.08262 $[M+H]^+$, calcd for $C_{23}H_{19}O_4N_2SClH^+$ 455.08268.

1-**((4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)methyl)cyclopropyl glycinate (5a).** To a stirred suspension of 6-(4-Chlorophenyl)-3-(4-((1-hydroxycyclopropyl)methoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (**5**) (25.5 mg, 0.056 mmol), 4-pyrrolidinopyridine (13.0 mg, 0.088 mmol) and boc-GlyOH (34.0 mg, 0.194 mmol) at 42 °C was added *N*,*N*′-diisopropylcarbodiimide (26 µL, 0.168 mmol) over a 15 min period. After the addition was complete, the mixture was stirred at 42 °C for 1.3 h and then at RT for 3h. The final mixture was diluted with EtOAc (30 mL) and washed with cold phosphate buffer solution (0.5M KH_2PO_4 + H_3PO_4 added to pH 3, 2x15 mL) and cold 2% $NaHCO_3$ (3x15 mL). The organic layer was dried (Na_2SO_4) and evaporated. The residue was subjected to flash chromatography (two consecutive columns: silica gel/hexane-EtOAc 30:70 followed by silica gel/DCM-Ether 60:40) to afford 1-((4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)methyl)cyclopropyl (tert-butoxycarbonyl)glycinate (31.2 mg, 91 % yield) as a white solid. The last material was treated with 1:2 TFA-DCM (0.9 mL) for 30 min. The volatiles were evaporated and the residue was taken up in DCM (20 mL) and washed with cold 2% $NaHCO_3$. The organic solution was dried (Na_2SO_4) and evaporated to afford the tittle compound (24.6 mg, 94 % yield) as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1H, s), 7.66 (2H, br d, J=8.3 Hz), 7.54 (1H, s), 7.45 (2H, br d, J=8.3 Hz), 7.03 (1H, br d, J=8.3 Hz), 6.96 (1H, br s), 6.92 (1H, d, J=8.3 Hz), 4.36 (2H, s), 3.89 (3H, s), 3.43 (2H, br s), 1.06 (4H, br d, J=13.2 Hz); LC/MS (ESI) *m/z* 512 $[M+H]^+$; analytical HPLC t_R 3.14 min (method K), 5.55 min (method J).

6-(4-Chlorophenyl)-3-(4-((3-hydroxyoxetan-3-yl)methoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (6). A mixture of **15b** (280 mg, 1.243 mmol), **16** (401 mg, 1.243 mmol)[12] and phenol (3.0 g) was

heated at 135 ºC for 20 min, diluted with methanol, cooled to 0 ºC and filtered to obtain the crude product. Trituration of the solid with methanol yielded **6** (190 mg, 0.4 mmol, 33 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-D6) δ 8.40 (1 H, s), 7.98 (1 H, s), 7.93 (2 H, d, J=8.6 Hz), 7.58 (2 H, d, J=8.6 Hz), 7.22 (1 H, d, J=2.3 Hz), 7.18 (1 H, d, J=8.8 Hz), 7.06 (1 H, dd, J=8.6, 2.3 Hz), 6.04 (1 H, s), 4.53 (2 H, d, J=6.5 Hz), 4.49 (2 H, d, J=6.5 Hz), 4.16 (2 H, s), 3.79 (3 H, s); LC/MS (ESI) *m/z* 471 $[M+H]^+$; analytical HPLC t_R 2.34 min (method A), 3.92 min (method D), 4.3 min (method E).

3-((4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)methyl)oxetan-3-yl glycinate (6a). *N,N'*-Diisopropylcarbodiimide (70 µL, 0.45 mmol) was added in small portions over 1 h to a refluxing mixture of **6** (71 mg, 0.15 mmol), boc-GlyOH (79 mg, 0.45 mmol) and 4-(pyrrolidin-1-yl)pyridine (22 mg, 0.15 mmol) in DCM (3 mL). The mixture was refluxed for an additional 0.5 h. The mixture was diluted with DCM, washed sequentially with cold 5% sulfuric acid and saturated sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and concentrated. Subsequently the crude product was subjected to flash chromatography (silica gel/hexane-EtOAc 100:0 to 0:100 gradient) to afford boc-glycine ester of compound **6** (150 mg) as a white solid (contaminated with diisopropylurea as determined by proton NMR). After dissolution of the crude product in DCM (1 mL) and addition of TFA (1 mL), the reaction was allowed to stand at RT for 10 min. After concentration, the residue was partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and concentrated. The crude product was subjected to flash chromatography (silica gel/methylene chloride-methanol 100:0 to 90:10 gradient) to afford **6a** (60 mg, 48 % yield) as a white solid; TLC R_f = 0.28 (silica gel/methylene chloride-methanol 93:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (1 H, s), 7.64 (2 H, d, J=8.6 Hz), 7.52 (1 H, s), 7.43 (2 H, d, J=8.6 Hz), 7.04 (1 H, d, J=8.3 Hz), 6.96 (1 H, d, J=2.3 Hz), 6.92 (1 H, dd, J=8.3, 2.3 Hz), 4.83 (2 H, d, J=7.8 Hz), 4.79 (2 H, d, J=8.1 Hz), 4.60 (2 H, s), 3.86 (3 H, s), 3.47 (2 H, s).

Pro-drug **6a** underwent slow decomposition when stored as a free base in methanol solution at RT to generate the parent alcohol. Therefore conc. HCl (15 µL) was added to a -70 ºC solution of **6a** which had been prepared by dissolution of **6a** in DCM (0.5 mL) followed by addition of methanol (0.3 mL) and rapid cooling to -70 ºC.

The volatiles were removed at RT yielding compound **6a** as a white solid (64 mg, HCl salt). MS (ESI) *m/z* 528 $[M+H]^+$; Analytical HPLC t_R = 2.17 min (method A), 3.89 min (method F), 3.5 min (method D).

6-(4-Chlorophenyl)-3-(4-((1-hydroxycyclobutyl)methoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (7). 17b was converted to **7** following the procedure used to prepare **6**. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.46 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 7.6 Hz, 1H), 6.89 (d, J = 2.2 Hz, 1H), 6.85 (dd, J = 2.2, 7.6 Hz, 1 H), 4.01 (s, 2H), 3.80 (s, 3H), 3.09 (br s, 1H), 2.15 (m, 4H), 1.80 (m, 1H), 1.53 (m, 1H); analytical HPLC (method I) 4.32 min; 28.32 min (method G); MS *m/z* 469 $[M+H]^+$.

1-((4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)methyl)cyclobutyl glycinate (7a). 7 was converted to**7a** following the procedure used to prepare **6a**. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.66 (d, *J*=8.8 Hz, 2H), 7.53 (s, 1H), 7.44 (d, *J*=8.2 Hz, 2H), 7.04 (d, *J*=8.2 Hz, 1H), 6.96 (d, *J*=2.2 Hz, 1H), 6.92 (dd, *J*=8.8, 2.7 Hz, 1H), 4.43 (s, 2H), 3.88 (s, 3H), 3.38 (s, 2H), 2.59 - 2.47 (m, 2H), 2.46 - 2.38 (m, 2H), 2.01 - 1.91 (m, 1H), 1.87 - 1.74 (m, 1H); MS *m/z* 528 $[M+H]^+$; analytical HPLC t_R 2.28 min (method A), 13.88 min (B), 3.52 min (method F), 25.92 min (method G).

6-(4-Chlorophenyl)-3-(4-((1-hydroxycyclopentyl)methoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (8). 18b was converted to **8** following the procedure used to prepare **6**. ^{1}H NMR ($CDCl_3$) 8.14 (s, 1H), 7.67 (d, J = 9.4 Hz, 2H), 7.52 (s, 1H), 7.46 (d, J = 9.4 Hz, 2H), 7.03 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 2.2, 8.2 Hz, 1 H), 4.01 (s, 2H), 3.87 (s, 3H), 2.37 (s, 1H), 1.90-1.60 (m, 8H); MS *m/z* 483 $[M+H]^+$; analytical HPLC t_R 2.13 min (method A), 29.4 min (method G).

6-(4-Chlorophenyl)-3-(4-((4-hydroxytetrahydro-2H-pyran-4-yl)methoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (9). 19b was converted to **9** following the procedure used to prepare **6**. ^{1}H NMR ($CDCl_3$) δ ppm 1.70 - 1.87 (m, 4 H), 3.78 - 3.96 (m, 9 H), 6.91 - 6.96 (m, 1 H), 6.97 (d, 1 H), 7.03 (d, 1 H), 7.45 (d, 2 H), 7.51 - 7.57 (m, 1 H), 7.66 (d, 2 H); analytical HPLC t_R 3.13 min (method F), 9.17 (method B), 8.44 min (method C); MS (ESI) *m/z* 499 $[M+H]^+$.

6-(4-Chlorophenyl)-3-(4-((3,3-difluoro-1-hydroxycyclobutyl)methoxy)-3-methoxyphenyl)thieno[3,2-d]pyrimidin-4(3H)-one (10). A stirred mixture of **16** (33.9 g, 105 mmol) and **25b** (27.2 g, 105 mmol) in phenol (200 g) was heated at 135-140 ºC for 45 min.[12] The mixture was diluted with methanol (700 mL) and stirred at RT for 15 min. The mixture was allowed to stand at RT overnight. The precipitated product was isolated by filtration, washed with dry-ice chilled methanol and dried under vacuum giving compound **10** (37 g, 70% yield) as a white solid. The mother liquor was diluted with ether and hexane and the precipitated solid was triturated from MeOH to give a second batch of the desired product (1.8 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.66 (d, J=8.6 Hz, 2H), 7.54 (s, 1H), 7.45 (d, J=8.6 Hz, 2H), 7.08 (d, J=8.6 Hz, 1H), 6.99 (d, J=2.3 Hz, 1H), 6.95 (dd, J=8.3, 2.0 Hz, 1H), 4.14 (s, 2H), 3.89 (s, 3H), 2.87 - 2.76 (m, 4H); MS (ESI) *m/z* 505 $[M+H]^+$; analytical HPLC (method A) t_R = 2.34 min, (method B) t_R = 16.34 min, (method C) t_R = 15.36 min.

1-((4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)methyl)-3,3-difluorocyclobutyl glycinate (10a). *N,N'*-Diisopropylcarbodiimide (44 µL, 0.28 mmol) was added slowly to a refluxing mixture of compound **10** (70 mg, 0.139 mmol), boc-GlyOH (73 mg, 0.416 mmol) and 4-(pyrrolidin-1-yl)pyridine (21 mg, 0.139 mmol) in DCM (3 mL). After the mixture was heated at reflux for 45 min, LC/MS analysis indicated complete conversion to the desired product. The mixture was diluted with DCM, washed sequentially with cold 5% sulfuric acid and saturated sodium bicarbonate solutions. The organic phase was dried ($MgSO_4$) and concentrated to give white solid. To the crude product dissolved in DCM (1 mL), was added TFA (1 mL). After stirring at RT for 5 min, the mixture was concentrated and partitioned between DCM and saturated sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and concentrated. The crude product was subjected to flash chromatography (silica gel/hexane-EtOAc 100:0 to 0:100 gradient then DCM-methanol 100:0 to 85:15 gradient) to afford compound **10a** (65 mg, 0.116 mmol, 83 % yield) as a white solid, TLC R_f = 0.5 (silica gel/DCM-methanol 85:15). ^{1}H NMR of HCl salt (400MHz, DMSO-D6) δ 8.43 (br. s., 3H), 8.41 (s, 1H), 7.99 (s, 1H), 7.93 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.6 Hz, 2H), 7.26 (d, J=2.5 Hz, 1H), 7.17 (d, J=8.6 Hz, 1H), 7.08 (dd, J=8.4, 2.4 Hz, 1H), 4.42 (s, 2H), 3.86 - 3.77 (m, 5H), 3.30 - 3.05 (m, 4H); ^{19}F NMR (376MHz, DMSO-D6) δ -84.80 (d, J=199.3 Hz, 1F), -93.89 (d, J=198.0 Hz, 1F); MS (ESI) *m/z* 562 $[M+H]^+$;

analytical HPLC t_R = 2.04 min (method A), 7.61 min (method B), 8.87 min (method C). The product from above was dissolved in DCM (2 mL), cooled to -30 ºC, prior to addition of a solution of conc. HCl (25 μL) in 0.5 mL MeOH. The mixture was stirred at RT for 5 min and concentrated to give HCl salt of the title compound **10a** (66 mg).

Dibenzyl 1-((4-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)methyl)-3,3-difluorocyclobutyl phosphate (10b). A mixture of compound **10** (50 g, 99 mmol), dibenzyl diisopropylphosphoramidite (113 g, 327 mmol) and 1H-1,2,4-triazole (22.57 g, 327 mmol) in 1,2-dichloroethane (2 L) was heated at reflux for 1 hr. After cooling to RT, 30% hydrogen peroxide (60 mL, 979 mmol) was added over 10 min at while maintaining the reaction temperature between 15-45 ºC (exothermic, used ice-water cooling bath). After stirring for 15 min. at RT, the mixture was diluted with DCM, washed sequentially with water and 5% aq. sodium thiosulfate, dried ($MgSO_4$) and concentrated. The crude residue was subjected to flash chromatography (2 Kg silica gel/DCM-EtOAc 100:0 to 0:100 gradient) to obtain **10b** (70.5 g, 93% yield) TLC R_f = 0.6, silica gel/1:1 DCM-EtOAc; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.67 (d, J=8.6 Hz, 2H), 7.54 (s, 1H), 7.45 (d, J=8.6 Hz, 2H), 7.40 - 7.29 (m, 10H), 6.99 - 6.84 (m, 3H), 5.08 (dd, J=7.9, 1.6 Hz, 4H), 4.32 (s, 2H), 3.76 (s, 3H), 3.27 - 2.94 (m, 4H); MS (ESI) *m/z* 765 $[M+H]^+$; analytical HPLC t_R = 2.54 min (method A), 13.52 min (method B), 12.22 min (method C).

1-((4-(6-(4-Chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-methoxyphenoxy)methyl)-3,3-difluorocyclobutyl dihydrogen phosphate (10c). Compound **10b** (70.5 g) was dissolved in TFA (500 mL) and stirred at RT for 8 h. The mixture was concentrated, re-concentrated twice from DCM prior to recrystallization of the residue from refluxing EtOH (ca. 10 L) to give compound **10c** as a light yellow solid. This material was re-dissolved in refluxing EtOH (ca. 10 L), treated with charcoal and stirred for 10 min. The mixture was filtered through celite while hot and allowed to stand at RT for 24 h and then at 4 ºC for 48 h to afford **10c** as a white crystalline solid (37 g, 1st crop). The celite-charcoal filter cake was extracted with hot DMF (2 X 1.5L), the DMF extract was concentrated and the residue was triturated alternately with EtOH and 1,2-dichloroethane affording additional **10c** (8.4 g); 78.4% combined yield. ^{1}H NMR (400 MHz, DMSO-D6) δ

8.40 (1 H, s), 7.98 (1 H, s), 7.92 (2 H, d, J=8.3 Hz), 7.57 (2 H, d, J=8.3 Hz), 7.23 (1 H, d, J=1.8 Hz), 7.15 (1 H, d, J=8.8 Hz), 7.07 (1 H, d, J=8.1 Hz), 4.27 (2 H, s), 3.79 (3 H, s), 3.21 (2 H, q, J=14.4 Hz), 2.94 - 3.10 (2 H, m); ^{19}F NMR (376MHz, DMSO-d6) δ -84.76 (d, J=196.6 Hz, 1F), -94.38 (d, J=193.8 Hz, 1F). MS (ESI) *m/z* 585 $[M+H]^+$; analytical HPLC t_R = 2.2 min (method A), 9.34 min (method B), 8.56 min (method C).

3-((2-Methoxy-4-nitrophenoxy)methyl)oxetan-3-ol (15a). A solution of aqueous osmium tetroxide (4%, 0.1 mL) and hydrogen peroxide (50%, 1 mL) were sequentially added to a stirred solution of **13** (0.5g, 4.8 mmol)[13] in 1:1 THF-water (2 mL) at 4 ^oC. The mixture was allowed to come to RT and stirred for 1 h. After dilution of the reaction mixture with water (3 mL) and filtration through a pad of celite and charcoal, the filtrate was concentrated *in vacuo* at 40-50 ºC (ca. 30 mm vacuum) to afford 3-(Hydroxymethyl)oxetan-3-ol (**14**) as a thick brown oil (0.6 g, 49 % crude yield).

Sodium hydride (0.384 g, 9.6 mmol) was added in small portions to a stirred solution of 1-chloro-2-methoxy-4-nitrobenzene (0.9 g, 4.80 mmol) and crude 3-(hydroxymethyl)oxetan-3-ol from above (0.5 g, 4.80 mmol) in DMSO (20 mL) at RT. After stirring at RT for 6 h, the reaction mixture was diluted with ether and washed with saturated NH_4Cl solution. The organic phase was dried ($MgSO_4$), concentrated and the crude product was subjected to flash chromatography (silica gel/hexane-EtOAc 100:0 to 0:100 gradient) to afford the title compound (340 mg, 28 % yield) as a yellow gummy solid (TLC R_f = 0.15; silica gel/hexane-EtOAc 1:1). ^{1}H NMR (500 MHz, CDCl3) δ 7.83 (1 H, dd, J=8.9, 2.6 Hz), 7.69 (1 H, d, J=2.7 Hz), 6.95 (1 H, d, J=8.8 Hz), 4.69 (2 H, d, J=7.4 Hz), 4.57 (2 H, d, J=7.4 Hz), 4.31 (2 H, s), 3.88 (3 H, s); analytical HPLC (method A) t_R = 1.66 min.

3-((4-Amino-2-methoxyphenoxy)methyl)oxetan-3-ol (15b). A mixture of **15a** (340 mg, 1.33 mmol) and 10% palladium on carbon (50 mg) was stirred under hydrogen at 50 psi for 3 h, filtered and concentrated to give **15b** (280 mg, 93 % crude yield) as a thick brown oil. ^{1}H NMR (500 MHz, CD_3OD) δ 6.85 (1 H, d, J=8.5 Hz), 6.51 (1 H, d, J=2.5 Hz), 6.34 (1 H, dd, J=8.5, 2.5 Hz), 4.66 (2 H, d, J=7.1 Hz), 4.58 (2 H, d, J=6.9 Hz), 4.05 (2 H, s), 3.80 (3 H, s); MS (ESI) *m/z* 248 $[M+Na]^+$; analytical HPLC t_R = 0.29 min (method A).

1-((2-Methoxy-4-nitrophenoxy)methyl)cyclobutanol (17a). 1-(Hydroxymethyl)cyclobutanol (1.27g, 12.5 mmol)[24] was added to a suspension of NaH (60% mineral oil dispersion, 0.50g, 12.5 mmol) in DMSO (14.6 mL). Subsequently, 30 min after cessation of gas evolution, 2-bromo-4-nitroanisole (1.95g, 8.4 mmol) in DMSO (5.9 mL) was added to the stirred solution. The reaction was stirred for 2.5 h before being poured into 0.1N HCl (300 mL). After extraction of the mixture with ether, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was subjected to flash chromatography (silica gel/DCM-EtOAc 0:100 to 50:50 gradient) to yield 0.65 g of **17a**. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.89 (dd, J=8.9, 2.8 Hz, 1H), 7.74 (d, J=2.5 Hz, 1H), 6.97 (d, J=9.2 Hz, 1H), 4.11 (s, 2H), 3.93 (s, 3H), 3.05 (br. s., 1H), 2.22 (dd, J=9.2, 6.6 Hz, 4H), 1.95 - 1.81 (m, 1H), 1.74 - 1.55 (m, 1H); ^{13}C NMR (101MHz, $CDCl_3$) δ 154.0, 149.3, 141.7, 117.6, 111.8, 106.7, 74.5, 73.3, 56.1, 32.6, 12.2; analytical HPLC (method A) t_R1.56 min; MS *m/z* 254 $[M+H]^+$.

1-((4-Amino-2-methoxyphenoxy)methyl)cyclobutan-1-ol (17b). **17a** was converted to**17b** following the procedure used to prepare **15b**. ^{1}H NMR (400MHz, $CDCl_3$) δ 6.76 (d, J=8.1 Hz, 1H), 6.28 (d, J=2.5 Hz, 1H), 6.20 (dd, J=8.6, 2.5 Hz, 1H), 3.90 (s, 2H), 3.73 (s, 3H), 2.19 - 2.04 (m, 4H), 1.84 - 1.70 (m, 1H), 1.62 - 1.45 (m, 1H); analytical HPLC t_R 0.78 min (method A).

1-((2-Methoxy-4-nitrophenoxy)methyl)cyclopentan-1-ol (18a). **18a** was prepared as described for **17a**. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.84 (dd, J=8.7, 2.7 Hz, 1H), 7.70 (d, J=2.7 Hz, 1H), 6.89 (d, J=9.4 Hz, 1H), 4.01 (s, 2H), 3.91 (s, 3H), 1.89 - 1.64 (m, 8H); ^{13}C NMR (126MHz, $CDCl_3$) δ 154.0, 149.1, 141.5, 117.5, 111.6, 106.7, 80.9, 76.2, 56.1, 37.1, 24.0; analytical HPLC t_R 3.55 min (method D), 22.3 min (method G).

1-((4-Amino-2-methoxyphenoxy)methyl)cyclopentan-1-ol (18b). **18b** was prepared as described for **15b**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.79 (d, J=8.65 Hz, 1H), 6.51 (d, J=2.03 Hz, 1H), 6.35 (dd, J=2.54, 8.14 Hz, 1H), 3.81 (s, 2H), 3.79 (s, 3H), 1.48-1.93 (m, 8H); MS *m/z* 238 $[M+H]^+$; analytical HPLC t_R 1.02 min (method A).

4-((2-Methoxy-4-nitrophenoxy)methyl)tetrahydro-2H-pyran-4-ol (19a). 1,6-Dioxaspiro[2.5]octane[25] was converted to **19a** as described for the preparation of **25a**. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.89 (dd, J=9.2, 2.5 Hz,

1H), 7.75 (d, J=2.5 Hz, 1H), 6.92 (d, J=9.2 Hz, 1H), 3.93 (s, 5H), 3.91 - 3.79 (m, 4H), 1.87 - 1.69 (m, 4H); MS *m/z* 301 $[M+H]^+$; analytical HPLC t_R 1.18 min (method H).

4-((4-Amino-2-methoxyphenoxy)methyl)tetrahydro-2H-pyran-4-ol (19b). 19b was prepared as described for **15b**. ^{1}H NMR (400MHz, $CDCl_3$) δ 6.78 (d, J=8.1 Hz, 1H), 6.29 (d, J=2.5 Hz, 1H), 6.21 (dd, J=8.1, 2.5 Hz, 1H), 3.92 - 3.73 (m, 9H), 1.80 - 1.61 (m, 4H); MS *m/z* 276 $[M+Na]^+$; analytical HPLC t_R 0.23 min (method H).

1-(3,3-Difluorocyclobutyl)-*N,N*-dimethylmethanamine (21): Oxalyl chloride (21.7 mL, 248 mmol) was added dropwise to a stirred solution of 3,3-difluorocyclobutanecarboxylic acid (**20**)[14] (26 g, 191 mmol) in dichloromethane (500 mL) and DMF (0.5 mL) at 0 ºC. The reaction mixture was allowed to warm to RT, stirred for 1 h and concentrated *in vacuo* at RT. The residue was dissolved in THF (300 mL) and treated at 0 ºC with 2M dimethylamine (478 mL, 955 mmol) in THF. The reaction mixture was stirred at RT for 0.5 h and partitioned between ether and 5% aq. sodium carbonate. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. After portioning the residue between methylene chloride and water, the organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give 3,3-difluoro-*N,N*-dimethylcyclobutanecarboxamide (24 g, 147 mmol, 77% yield) as a brown semi-solid, used as such in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99-3.12 (1H, m), 2.95 (3H, s), 2.94 (3H, s), 2.78-2.92 (2 H, m), 2.62-2.77 (2H, m). A solution of 3,3-difluoro-*N,N*-dimethylcyclobutanecarboxamide (24 g, 147 mmol) in THF (500 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (7.5 g, 198 mmol) in THF (500 mL) at 0 ºC. Upon completion of addition, the mixture was allowed to warm to RT. After stirring for 18 h, the mixture was cooled to ca. 5 ºC and quenched by slowly adding 6N NaOH (10 mL) and water (5 mL) with stirring. The mixture was allowed to warm to RT, then dried over sodium sulfate and filtered. The filtrate was concentrated to ca. 30 mL by distilling off most of the THF using a vigreux column. The remaining material was distilled under slightly reduced pressure (ca. 100-200 mm Hg) giving a fraction (20 mL, collected at 70-90 ºC) containing the title compound contaminated with THF. This material was carefully purged with a gentle stream of nitrogen to remove the residual THF giving 1-(3,3-difluorocyclobutyl)-*N,N*-dimethylmethanamine (12

g, 80 mmol, 55% yield) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60-2.75 (2H, m), 2.38 (2H, d, J = 6.6 Hz), 2.16-2.28 (9H, m). HRMS (ESI) *m/z* 150.10875 $[M+H]^+$, calcd for $C_7H_{14}NF_2$ 150.10888.

1-(3,3-Difluorocyclobutyl)-*N,N*-dimethylmethanamine oxide hydrate (22): Aqueous hydrogen peroxide (30%, 18 mL) was added dropwise to a stirred solution of 1-(3,3-difluorocyclobutyl)-*N,N*-dimethylmethanamine (12 g, 80 mmol) in methanol (100 mL) over 2 h, while maintaining the reaction temperature between 5 and 22ºC. Upon completion of addition, the mixture was kept at RT for 20 h, then additional 30% hydrogen peroxide (18 mL) was added and stirring continued for 3 h. A slurry of palladium black (150 mg) in water (3mL) was then added in small portions carefully to the stirred reaction mixture, maintaining the temperature between 5 to 25 ºC. The reaction mixture was stirred at RT until all of the excess hydrogen peroxide (ca. 1 h) had decomposed. After filtration, the filtrate was concentrated *in vacuo* to give 1-(3,3-difluorocyclobutyl)-*N,N*-dimethylmethanamine oxide (15 g) as a semi-solid hydrate. ^{1}H NMR (400 MHz, CD_3OD) δ 3.47 (2H, d, J = 5.3 Hz), 3.16 (6H, s), 2.75-2.92 (3H, m), 2.42-2.58 (2H, m).

1,1-Difluoro-3-methylenecyclobutane (23): Crude 1-(3,3-difluorocyclobutyl)-*N,N*-dimethylmethanamine oxide hydrate (15 g) was heated under vacuum (ca. 10 mm Hg) at 100 ºC using a distillation setup in order to remove most of the water from the sample. The receiving flask was cooled to -78 ºC as the temperature was gradually increased to 165 ºC. After ca. 1 h, most of the starting material had been pyrolized (a small amount of dark brown residue remained in the distillation flask). Contents of the receiving flask were washed sequentially with 5% aq. HCl (3X3 mL) and saturated sodium bicarbonate (5 mL). The organic layer (olefin **6**) was filtered through a small plug of sodium sulfate giving 1,1-difluoro-3-methylenecyclobutane (5.5 g, 52.8 mmol, 66% yield from **21**) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (2H, quin, J = 2.5 Hz), 2.77-3.57 (4H, m). ^{19}F NMR (376 MHz, chloroform-D) δ -95.16 (2F, s).

5,5-Difluoro-1-oxaspiro[2.3]hexane (24): m-CPBA (70%, 90.0 g, 365 mmol) was added in small portions to a stirred solution of 1,1-difluoro-3-methylenecyclobutane (21.0 g, 202 mmol) in methylene chloride (600 mL) at RT. After ca. 1 h, a slight exotherm was noticed and the mixture was cooled using an ice bath. The reaction

mixture was allowed to warm to RT over 3 h and stirred for additional 18 h. Monitoring of the progress of the reaction by ^{1}H NMR revealed incomplete oxidation. After additional m-CPBA (10 g) was added, the mixture was stirred at RT for additional 24 h. The mixture was filtered to remove solids prior to washing the filtrate with 10% sodium carbonate. The organic layer was dried (sodium sulfate) and concentrated at atmospheric pressure to ca. 250 mL using a vigreux column. The material was flash distilled at ca. 10 mm Hg employing two sequential (in series) traps cooled to -78 ºC to collect the distillate. The combined distillate was further concentrated at atmospheric pressure using a vigreux column to a volume of approximately 50 mL affording 5,5-difluoro-1-oxaspiro[2.3]hexane (71 g, contained ca. 2.5 equivalents of dichloromethane by NMR, quantitative yield). While adequate for most chemical transformations, if desired, this material could be enriched by further distillation. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91-3.16 (4H, m), 2.88 (2H, s). ^{19}F NMR (376 MHz $CDCl_3$) δ -90.84 (1F, m, J = 200.7 Hz), -99.53 (1F, dquin, J = 202.1, 12.37 Hz). HRMS (ESI) *m/z* 162.07237 $[M+CH_3CN+H]+$, calcd for $C_7H_{10}ONF_2$ 162.07250.

3,3-Difluoro-1-((2-methoxy-4-nitrophenoxy)methyl)cyclobutanol (25a). A mixture of potassium 2-methoxy-4-nitrophenolate (12.43 g, 0.06 mol), 5,5-difluoro-1-oxaspiro[2.3]hexane (contains 3 moles DCM/mole of **24**, 22.52 g, 0.06 mol) and sodium dihydrogen phosphate monohydrate (7.45 g, 0.054 mol) in 85:15 acetonitrile-water (50 mL) was heated at 130 ºC in a steel bomb for 3.5 h. The reaction mixture was diluted with EtOAc, washed with 5% sodium carbonate, dried ($MgSO_4$) and concentrated. The crude product was recrystallized from MTBE (150 mL) giving **25a** (12.4 g, 73 % yield) as a light yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, dd, J = 8.9, 2.6 Hz), 7.76 (1H, d, J = 2.8 Hz), 6.95 (1H, d, J = 9.1 Hz), 4.16 (2H, s), 3.94 (3H, s), 3.36 (1H, s), 2.73-2.92 (4H, m); MS (ESI) *m/z* 312 $[M+Na]^+$; analytical HPLC (method A) t_R = 1.71 min.

1-((4-Amino-2-methoxyphenoxy)methyl)-3,3-difluorocyclobutanol (25b). A mixture of 3,3-difluoro-1-((2-methoxy-4-nitrophenoxy)methyl)cyclobutanol (32.0 g, 111 mmol) and 10% palladium on carbon (2.0 g) in methanol (700 mL) was stirred under hydrogen at 50 psi for 1.5 h, filtered and the filtrate was concentrated to give **25b** (28.8 g, 111 mmol, 100 % yield) as a light purple solid. ^{1}H NMR (400MHz, CD_3OD) δ 6.78 (d, J=8.6

Hz, 1H), 6.45 (d, J=2.5 Hz, 1H), 6.27 (dd, J=8.3, 2.5 Hz, 1H), 3.88 (s, 2H), 3.79 (s, 3H), 2.99 - 2.77 (m, 2H), 2.64 - 2.50 (m, 2H). MS (ESI) *m/z* 260 $[M+H]^+$; analytical HPLC (method A) t_R = 1.33 min.

Biological Assays. See reference 10 for detailed description of all biological assays.

Acknowledgment. We greatly appreciate the support of Bristol-Myers Squibb Department of Discovery Analytical Sciences.

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Notes.

The authors declare no competing financial interest.

Abbreviations Used.

EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; V_{ss}, volume of distribution at steady state; *F*, % oral bioavailability; CL, Clearance; CYP, cytochrome P450; boc-GlyOH, *N*-(tert-butoxycarbonyl)glycine.

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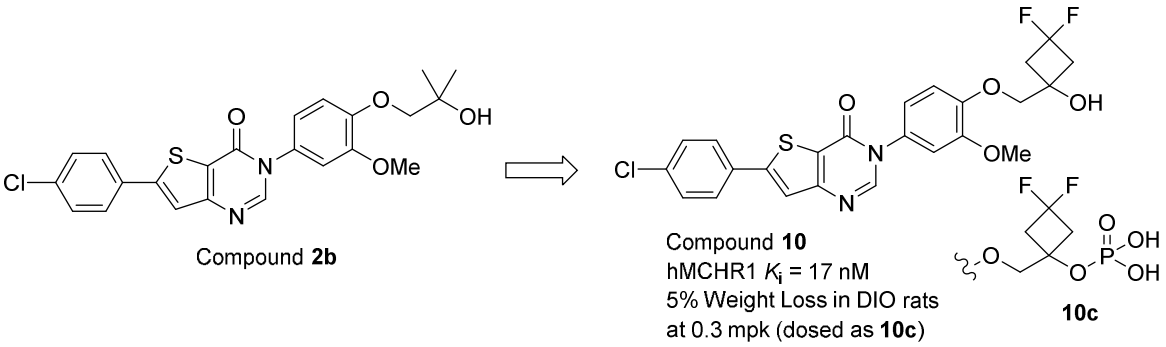

Compound **2b**

Compound **10**
hMCHR1 K_i = 17 nM
5% Weight Loss in DIO rats
at 0.3 mpk (dosed as **10c**)

10c