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Fused Piperidines as a Novel Class of Potent and Orally Available Transient Receptor Potential Melastatin Type 8 (TRPM8) Antagonists

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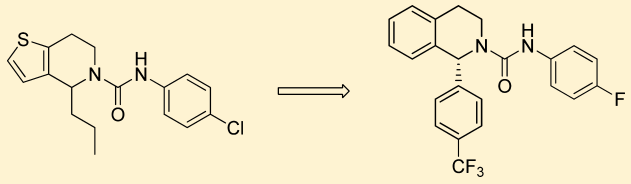
Supporting Information

ABSTRACT: The transient receptor potential melastatin type 8 (TRPM8) is a nonselective cation channel primarily expressed in a subpopulation of sensory neurons that can be activated by a wide range of stimuli, including menthol, icilin, and cold temperatures (<25 °C). Antagonism of TRPM8 is currently under investigation as a new approach for the treatment of pain. As a result of our screening efforts, we identified tetrahydrothienopyridine **4** as an inhibitor of icilin-induced calcium influx in CHO cells expressing recombinant rat TRPM8. Exploration of the structure−activity relationships of **4** led to the identification of a potent and orally bioavailable TRPM8 antagonist, tetrahydroisoquinoline **87**. Compound **87** demonstrated target coverage in vivo after oral administration in a rat pharmacodynamic model measuring the prevention of icilin-induced wet-dog shakes (WDS).



INTRODUCTION

The transient receptor potential melastatin type 8 (TRPM8) is a member of the transient receptor potential (TRP) superfamily of ion channels. Based on amino acid homology, the mammalian members of this family have been classified into six subfamilies: TRPC, TRPV, TRPM, TRPA, TRPP, and TRPML. The TRP channels have six transmembrane polypeptide subdomains flanked by intracellular C- and N-terminal regions. In addition, the TRP proteins assemble as homo- or heterotetramers to form cation-permeable pores.[1] These channels are nonselective cation channels activated by a variety of chemical and physical stimuli. For example, TRPM8 is a ligand-gated, Ca^{2+}-permeable, nonspecific cation channel primarily expressed in a subset of small diameter sensory neurons.[2] TRPM8 is activated by cold temperatures (<25 °C), as well as by natural cooling compounds such as menthol (**1**) and eucalyptol (**2**).[3] The TRPM8 channel is also activated by the synthetic cooling agent icilin (**3**) (Figure 1).[4] The cloning and characterization of the TRPM8 receptor, as well as several studies with knockout mice, revealed its role in cold sensation as well as cold allodynia (pain induced by normally innocuous cold) and its potential utility as a therapeutic target.[5,6] Cold allodynia is one of the predominant clinical symptoms in patients going through chemotherapy,[7] as well as in diseases such as diabetic neuropathy,[8] fibromyalgia,[9] and traumatic neuropathy.[10] Furthermore, correlation of pain with increased expression of TRPM8 in nerve fibers of overactive and painful bladders suggests TRPM8 involvement in bladder pain.[11] Preclinically, an antagonist of TRPM8 has been shown to decrease the frequency of volume-induced bladder contractions, without reducing the amplitude of contraction in rats.[12]

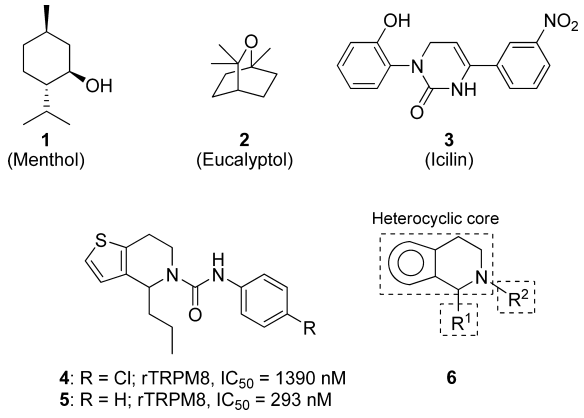


Figure 1. TRPM8 agonists, menthol (**1**), eucalyptol (**2**), and icilin (**3**), the initial high-throughput TRPM8 hit **4**, tetrahydrothienopyridine **5**, and the generic structure **6** used for SAR investigations.

Together, the above studies suggest a potential role for TRPM8 antagonists in chronic pain conditions as well as in painful bladder syndromes.[13] Small molecule antagonists of the TRPM8 channel would provide important pharmacological tools for fully assessing the therapeutic potential of inhibiting this novel target.

At the onset of our efforts to validate TRPM8 as a novel target for pain, there were very few reports of TRPM8 antagonists in the public domain.[14,15] We therefore set out to

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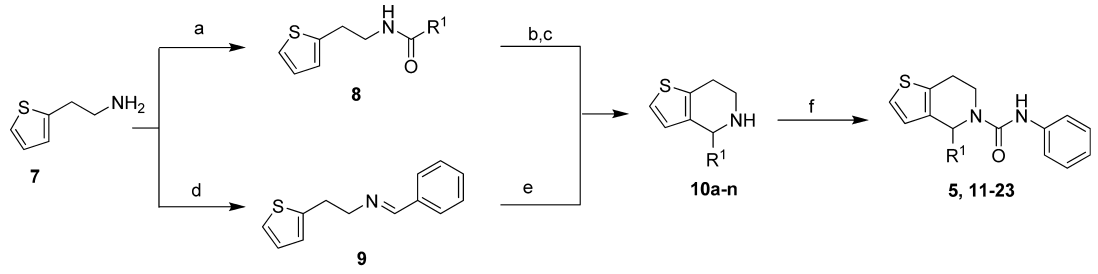
Scheme 1[a]



[a]Reagents and conditions: (a) R^1COCl, Et_3N, CH_2Cl_2, room temperature, 2 h; (b) $POCl_3$, CH_3CN, 60 °C, 18 h; (c) $NaBH_4$, MeOH, room temperature, 2 h; (d) benzaldehyde, toluene, reflux, 16 h; (e) trifluoroacetic acid, room temperature, 72 h; (f) phenyl isocyanate, CH_2Cl_2, room temperature, 1 h.

discover a novel small molecule antagonist by performing a high-throughput screen to identify inhibitors of icilin activation of the rTRPM8 channel. Tetrahydrothienopyridine **4** was identified as a hit from this screening campaign (Figure 1). Compound **4** inhibited the Ca^{2+} influx evoked by **3** in CHO cells transfected with rTRPM8 with an IC_{50} value of 1.39 μM. However, stability data from rat liver microsomal (RLM) preparations predicted that compound **4** would be extensively metabolized (CL_{int} > 399 μL/(min·mg))[16] and therefore, it would not have adequate pharmacokinetic (PK) characteristics necessary for in vivo target validation. An initial substructure search of the corporate database identified several other tetrahyhydrothienopyridines as antagonists of rTRPM8. From this set, compound **5** (Figure 1) was found to be 5-fold more potent than the initial hit, albeit displaying similar instability in RLM (IC_{50} = 293 nM; CL_{int} > 399 μL/(min·mg)).[16] Therefore, we undertook a structure–activity relationship (SAR) investigation to identify analogues of **5** with the goal of improving both the potency and the pharmacokinetic properties of this series.

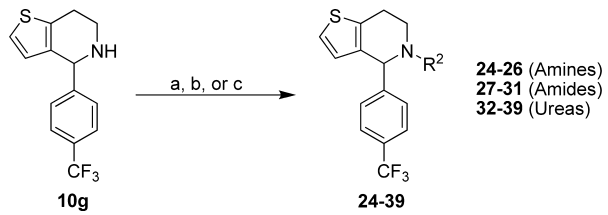
To investigate the SAR around compound **5**, we decided to systematically vary three segments of the molecule: the heterocyclic core, the R^1 group on the 2-position of the piperidine ring, and the R^2 substituent on the piperidine nitrogen (general structure **6**; Figure 1). Toward this goal, novel analogues of **5** were synthesized and tested for their ability to antagonize rTRPM8. The compounds were also evaluated for in vitro metabolic stability in rat liver microsomes (RLM). This investigation provided an understanding of the SAR of this class of compounds and resulted in the discovery of a novel series of rTRPM8 antagonists, exemplified by tetrahydroisoquinoline **87**. This compound potently inhibited rTRPM8 in vitro and demonstrated adequate target coverage in vivo.

CHEMISTRY

Tetrahydrothienopyridine analogues where the R^1 group was varied were prepared via "amide" or "imine" synthetic routes as depicted in Scheme 1. Acylation of 2-(thiophen-2-yl)-ethanamine (**7**) with various acid chlorides led to amides of general structure **8**. Cyclization of the amides with $POCl_3$ and subsequent reduction of the resulting imines with $NaBH_4$ led to the desired tetrahydrothienopyridines **10a–10m**. Alternatively, 4-phenyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**10n**) was prepared via a Pictet–Spengler reaction. Treatment of amine **7** with benzaldehyde formed the imine **9**, which was cylized in the presence of trifluoroacetic acid. The targeted ureas (**5**, **11–23**), were prepared by reacting phenyl isocyanate with tetrahydrothienopyridines **10a–10n**.

To study the role of the urea substituent in compound **5** (R^2 at the piperidine nitrogen), several analogues having amines (**24–26**), amides (**27–31**), or ureas (**32–39**) substituents were prepared from 4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**10g**) (Scheme 2). Reductive

Scheme 2[a]



[a]Reagents and conditions: (a) ketone/aldehyde, trifluoroacetic acid, $NaB(OAc)_3H$, DCE, room temperature, 1 h; (b) acid chloride, Et_3N, CH_2Cl_2, room temperature, 2 h; (c) isocyanate, CH_2Cl_2, room temperature, 1 h.

amination of **10g** with acetone, isobutyraldehyde, or benzaldehyde led to amines **24–26**. Amides (**27–31**) were prepared by the reaction of 4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**10g**) with the corresponding acid chlorides in the presence of triethylamine. Finally, the urea derivatives **32–39** were prepared by condensation of **10g** with various isocyanates (Scheme 2).

To extend our SAR study, we also investigated a variety of replacements of the tetrahydrothienopyridine core. Initially, we examined the nature of the five-membered heterocyclic ring fused to the piperidine. For example, tetrahydrofuropyridine **41** was synthesized by N-acylation of commercially available 2-(furan-2-yl)ethanamine (**40**) with 4-(trifluoromethyl)benzoyl chloride, followed by cyclization with $POCl_3$ and reduction of the cyclic imine intermediate (Scheme 3). The regiosomeric analogues, tetrahydrofuropyridine **42** and tetrahydrothienopyridine **43**, were obtained by previously described procedures,[17,18] and the tetrahydropyrrolo[1,2-*a*]pyrazine **44** was commercially available. The requisite urea analogues **45–48** were synthesized in good yields by treatment of fused

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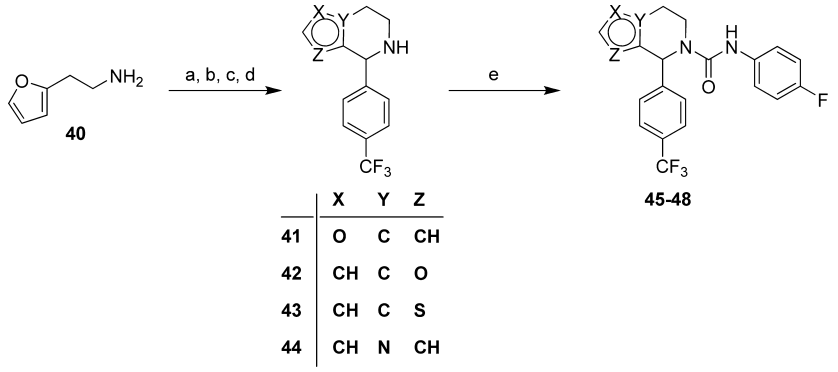
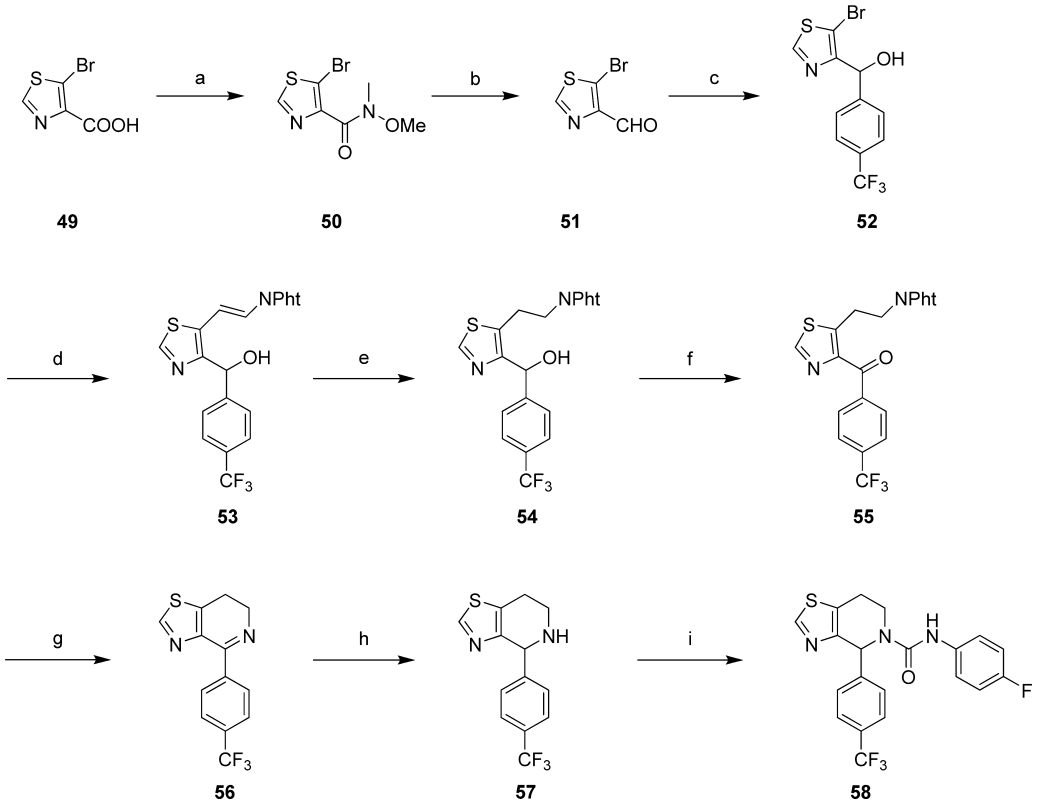
Scheme 3[a]



[a]Reagents and conditions: (a) 4-CF_3COCl, Et_3N, CH_2Cl_2, room temperature, 2 h; (b) $POCl_3$, benzene, reflux, 2 h; (c) $NaB(OAc)_3H$, CH_2Cl_2, room temperature, 18 h; di-*tert*-butyl dicarbonate, Et_3N, CH_2Cl_2, room temperature, 18 h; (d) HCl/dioxane, room temperature, 18 h; (e) 4-F-phenyl isocyanate, Et_3N, CH_2Cl_2, room temperature, 1 h.

Scheme 4[a]



[a]Reagents and conditions: (a) MeONHMe·HCl, EDC, DIEA, CH_2Cl_2, room temperature, 16 h; (b) DIBAL, THF, −78 °C, 1 h; (c) 4-CF_3PhMgBr, THF, 0 °C; (d) *N*-vinylphtalimide, $Pd_2(dba)_3$, X-Phos, Et_3N, DMF, 80 °C, 24 h; (e) Pd/C, H_2, MeOH; (f) MnO_2, CH_2Cl_2, room temperature, 4 h; (g) NH_2NH_2, EtOH, room temperature, 72 h; (h) $NaBH_4$, MeOH, room temperature, 30 min; (i) 4-F-phenyl isocyanate, CH_2Cl_2, room temperature, 1 h.

piperidines **41**−**44** with 4-fluorophenyl isocyanate at room temperature.

The synthesis of the fused 4,5-thiazole derivative **58** needed for this investigation required a longer synthetic route (Scheme 4). Intermediate **51** was synthesized following a two-step procedure starting from commercially available acid **49** via the Weinreb amide **50**. Reaction of 5-bromothiazole-4-carbaldehyde (**51**) with 4-(trifluoromethyl)phenyl Grignard gave the benzylic alcohol **52**, which was then coupled with *N*-vinylphthalimide under palladium-catalyzed conditions to yield **53**. Catalytic hydrogenation of the vinyl group of compound **53**, followed by oxidation with manganese oxide led to ketone **55**. Removal of the phthalimide protecting group with hydrazine in ethanol and reduction of the resulting dihydrothiazolopyridine intermediate **56** gave tetrahydrothiazolopyridine **57**. Finally, compound **57** was treated with 4-fluorophenyl isocyanate to give the desired analogue, **58**.

Analogues having a fused imidazole ring were readily accessible by thermal cyclization of the Schiff base obtained from histamine (**59**) and 4-trifluoromethylbenzaldehyde

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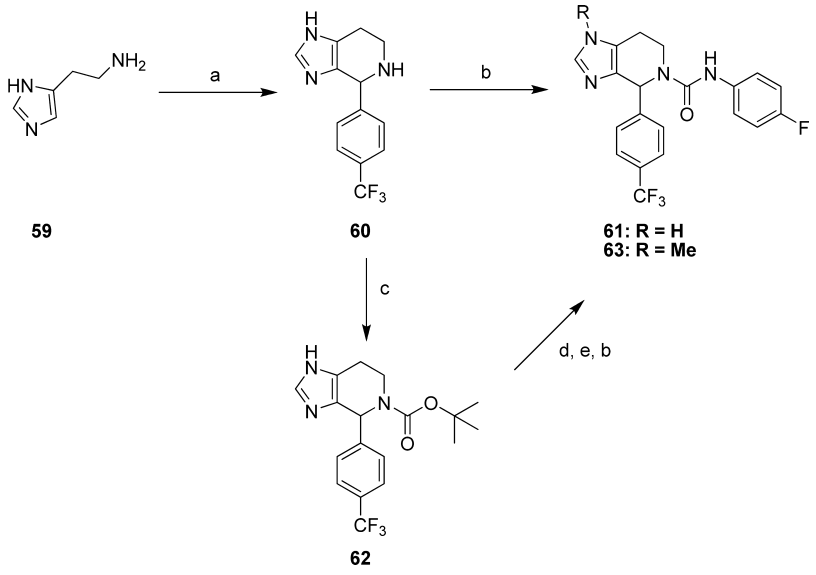
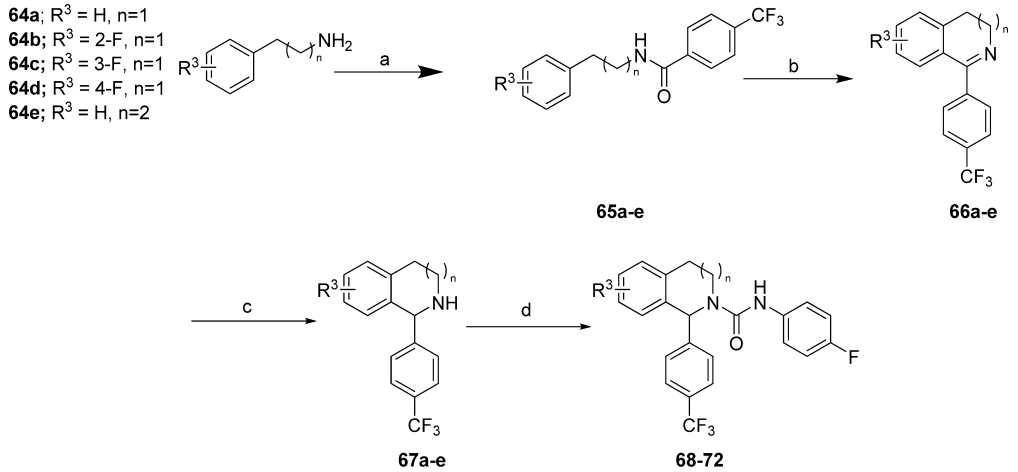
Scheme 5[a]



[a]Reagents and conditions: (a) 4-CF_3PhCHO, KOH, EtOH/H_2O, 100 °C, 4 h; (b) 4-F-phenyl isocyanate, CH_2Cl_2, room temperature, 1 h; (c) di-*tert*-butyl dicarbonate, $NaHCO_3$, MeOH, room temperature, 2 h; (d) MeI, $NaHCO_3$, DMF, room temperature, 2 h; (e) trifluoroacetic acid/CH_2Cl_2, room temperature, 2 h.

Scheme 6[a]



[a]Reagents and conditions: (a) 4-CF_3PhCOCl, DIEA, CH_2Cl_2, room temperature, 16 h; (b) P_2O_5, polyphosphoric acid, 165 °C, 2 h; (c) $NaBH_4$, MeOH, room temperature, 2 h; (d) 4-F-phenyl isocyanate, CH_2Cl_2, room temperature, 1 h.

(Scheme 5). The tetrahydroimidazopyridine **60** was converted to the 4-fluorophenyl urea **61** by reaction with 4-fluorophenyl isocyanate. To prepare analogue **63**, the piperidine amino group of compound **60** was first protected using di-*tert*-butyl carbonate to give intermediate **62**. Methylation of the imidazole ring with methyl iodide in the presence of sodium bicarbonate gave the 1-methyl regioisomer as the major product.[19] The *t*-butoxycarbonyl protecting group was removed by treatment with trifluoroacetic acid in dichloromethane. Further funtionalization with 4-fluorophenyl isocyanate and purification gave the dihydroimidazopyridine, **63**.

We next examined a set of compounds containing either a substituted or an unsubstituted fused six-membered aromatic ring. Compounds having a tetrahydroisoquinoline or benzazepine core substituted with a 4-trifluoromethylphenyl group as R^1 were prepared by standard methods from 4-(trifluoromethyl)benzoyl chloride and the appropriate 2-arylethylamines (**64a**–**64d**) or 2-phenylpropylamine (**64e**) as shown in Scheme 6. The intermediate amides **65a**–**e** underwent a Bischler–Napieralski reaction upon treatment with polyphosporic acid and phosphorus pentoxide. The resulting imines **66a**–**e** were reduced with sodium borohydride. Treatment of tetrahydroisoquinolines **67a**–**d** or benzazepine **67e** with 4-fluorophenyl isocyanate at room temperature gave the corresponding ureas **68**–**72** in good yields.

The synthesis of the final fluorotetrahydroisoquinoline derivative **78** is shown in Scheme 7. In this case, the 4-(trifluoromethyl)phenyl group was introduced at the C-1 position of the isoquinoline ring via activation of 8-fluoroisoquinoline (**73**) with benzyl bromide followed by reaction with (4-(trifluoromethyl)phenyl)magnesium bromide. Reduction of the tetrahydroisoquinoline core, deprotection of the *N*-benzyl amine, and subsequent urea formation led to the 8-fluoro analogue, **78**.

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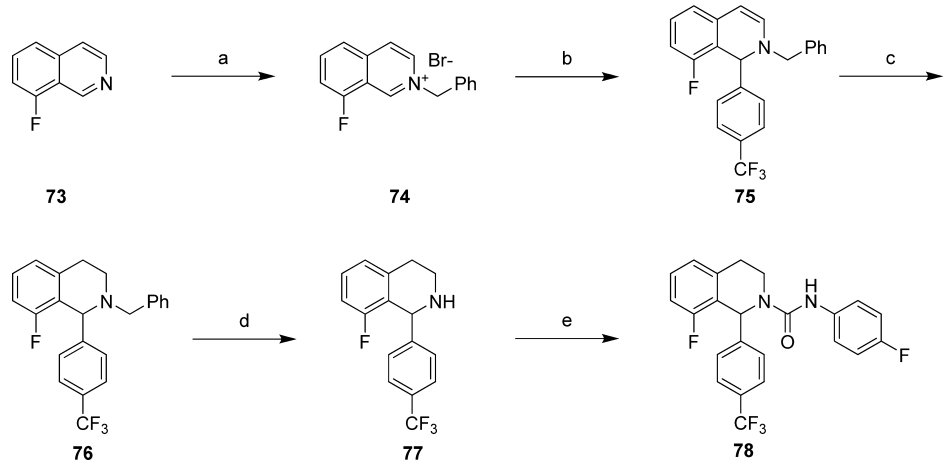
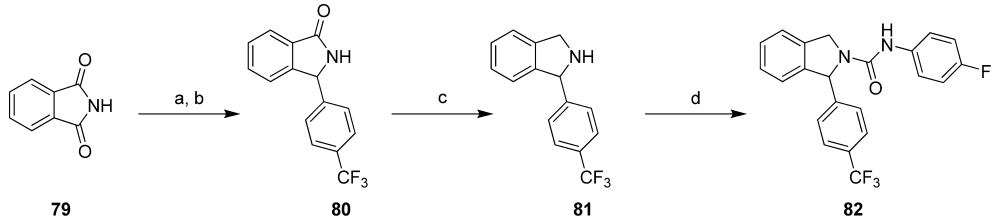
Scheme 7[a]



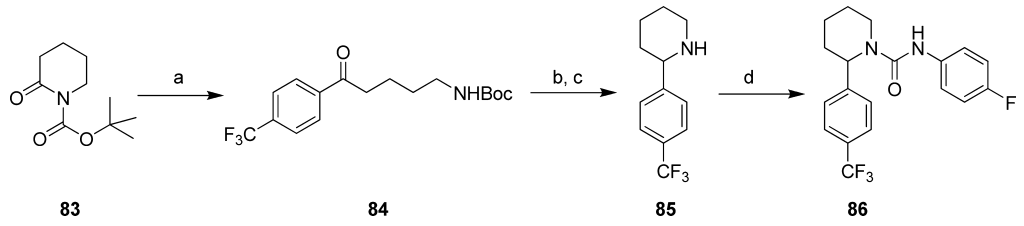
[a]Reagents and conditions: (a) $PhCH_2Br$, CH_3CN, 90 °C, 3 h; (b) 4-$CF_3PhMgBr$, THF, 0 °C to room temperature, 4 h; (c) $NaBH_4$, AcOH, THF, room temperature, 2 h; (d) $Pd(OH)_2$, H_2, EtOH, 50 psi, 3 h; (e) 4-F-phenyl isocyanate, CH_2Cl_2, room temperature, 1 h.

Scheme 8[a]



[a]Reagents and conditions: (a) 4-$CF_3PhMgBr$, THF, 0 °C, 2 h; (b) trifluoroacetic acid, Et_3SiH, CH_2Cl_2, room temperature, 18 h; (c) $LiAlH_4$, THF, 75 °C, 2 h; (d) 4-F-phenyl isocyanate, CH_2Cl_2, room temperature, 2 h.

Scheme 9[a]



[a]Reagents and conditions: (a) 4-$CF_3PhMgBr$, THF, −78 °C to room temperature, 2.5 h; (b) trifluoroacetic acid, room temperature, 4 h; (c) $NaBH_4$, MeOH, room temperature, 18 h; (d) 4-F-phenyl isocyanate, CH_2Cl_2, room temperature, 3 h.

The isoindoline analogue **82** (Scheme 8) was prepared by the addition of 4-trifluoromethylphenyl Grignard to phthalimide (**79**), followed by deoxygenation of the intermediate with triethylsilane and trifluoroacetic acid to give 3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (**80**). Isoindolinone **80** was reduced to isoindoline **81** by treatment with lithium aluminum hydride. The requisite urea analogue, **82**, was obtained by derivatization of **81** with 4-fluorophenyl isocyanate.

To explore the effect of eliminating the fused aromatic ring, the 2-(4-(trifluoromethyl)phenyl)piperidine analogue **86** was prepared (Scheme 9). Nucleophilic addition of 4-trifluoromethylphenyl Grignard to the protected γ-lactam **83** provided ketone **84**.[20] Removal of the *t*-butoxycarbonyl protecting group with trifluoroacetic acid gave the intermediate amine that cyclized readily under the reaction conditions. Reduction of the resulting Schiff base with sodium borohydride gave the piperidine derivative, **85**, which was treated with 4-fluorophenyl isocyanate to provide the piperidine derivative, **86**.

RESULTS AND DISCUSSION

The fused piperidine analogues prepared in this study were evaluated for their ability to block the icilin-induced calcium influx in CHO cells expressing the rTRPM8 channel. The results are shown in Tables 1−4. All compounds reported herein behaved as full antagonists. Additionally, the metabolic stability of the compounds was assayed in rat liver microsomal (RLM) preparations for initial assessment of metabolism, and the data is reported as intrinsic clearance (CL_{int}).[16]

To establish a thorough understanding of the SAR of this series, each of the three variables of general structure **6** were systematically modified including the R^1 and R^2 substituents and the central heterocyclic core. We began our investigation by examining the effect of altering the R^1 group at the 2-

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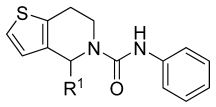
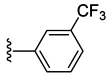
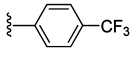
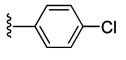
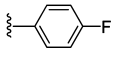
Table 1. In Vitro rTRPM8 Activities and Rat Microsomal Stabilities for Tetrahydrothienopyridines (R^1 Group Modifications)[a]



Compound No.	R^1	rTRPM8 IC_{50} (nM)	CL_{int} (μL/min/mg)
5		293 ± 64	>399
11	H	>20000	180
12	CH_3	6800 ± 110	N.D.
13		5570 ± 940	>399
14		1690 ± 1130	>399
15		240 ± 36	>399
16		1830 ± 440	>399
17		290 ± 74	211
18		140 ± 48	>399
19		2890 ± 2180	>399
20		560 ± 460	>399
21		2270 ± 960	>399
22		1320 ± 820	>399
23		1840 ± 1330	>399

[a] IC_{50} values based on inhibition of icilin (1 μM) induced influx of Ca^{2+} into rTRPM8-expressing CHO cells. Each IC_{50} value reported represents an average of at least two independent experiments with three replicates at each concentration. In vitro microsomal stability measured in a high-throughput automated format.[16]

position of the tetrahydrothienopyridine core structure. Derivatives of lead compound **5** with modifications at R^1 are shown in Table 1. The unsubstituted tetrahydrothienopyridine **11** (R^1 = H) was devoid of activity against the rTRPM8 channel indicating that substitution at the 2-position on the heterocyclic core was required. Decreasing the size of the alkyl group from *n*-propyl (compound **5**) to methyl and cyclopropyl (compounds **12** and **13**) also proved to be detrimental (IC_{50} values of 6800 and 5570 nM, respectively). A loss in potency was also observed for the phenyl, the 3-trifluoromethyl phenyl, and the 3-chlorophenyl substituted derivatives (**14**, **16**, and **19**); however, 2- and 4-trifluoromethyl or chloro substituted phenyl analogues (**15**, **17**, **18**, and **20**) had similar activities as the parent compound **5**. By contrast, no benefit was realized by the addition of the smaller fluoro group at any of the three positions on the phenyl ring (**14** vs **21**–**23**). Although the 2-substituted derivatives **15** and **18** showed good activities, the 4-trifluoromethyl group gave slightly better stability in rat liver microsomes. From this set of analogues, we determined that substituting the *n*-propyl group of compound **5** by a 4-trifluoromethyl phenyl group (to give compound **17**) resulted in an analogue that retained rTRPM8 antagonistic activity but had an improved stability in the rat microsomal assay (CL_{int} = 211 μL/(min·mg)).

Since compound **17**, which contains a 4-trifluoromethyl phenyl group (R^1 substituent), had the best combination of potency and microsomal stability, this group was maintained at the 2-position in the next phase of our SAR investigations whereby we examined the effect of varying the R^2 substituent on the piperidine nitrogen (Table 2). Removal of the phenyl urea group to give the unsubstituted piperidine derivative **10g** (R^2 = H) completely abolished functional activity against the rTRPM8 channel (IC_{50} > 20 μM). We then explored other functional groups on the piperidyl nitrogen such as alkyl groups, amides, or ureas. The isopropyl, isobutyl, and benzyl derivatives (**24**, **25**, and **26**) did not show any antagonistic activity against the rTRPM8 channel. In contrast, adding a carbonyl group adjacent to the piperidyl nitrogen, by replacing the R^2 isobutyl group (derivative **25**) with an isopropyl amide group (analogue **27**), increased the potency significantly (**27** IC_{50} = 1260 nM), indicating that a carbonyl group in this position was beneficial. Next, we examined analogues bearing aromatic amides at the piperidinyl nitrogen, 2-fluoro (**28**), 3-fluoro (**29**), and 4-fluorophenyl amide (**30**). Interestingly, this substitution was only tolerated when the fluoro was at the 2-position on the phenyl group (**28**, IC_{50} = 510 nM). The 3- and 4-fluorophenyl analogues (**29** and **30**, respectively) had IC_{50} values greater than 20 μM, indicating that the substitution at the phenyl group was very sensitive to substituent's position. Although amide **28** was moderately potent, it had extremely poor rat microsomal stability. Therefore, we turned our attention to ureas and explored the substitution of the phenyl urea of compound **17** by alkyl ureas. Introduction of an isopropyl urea (**32**) or a cyclopropyl urea (**33**) at the piperidinyl nitrogen led to compounds that were 2–5-fold weaker than the parent phenyl urea **17**, indicating that a phenyl group was preferred for activity. Also, the antagonistic activity against rTRPM8 of **17** was abolished when a morpholino urea group was introduced at R^2 (compound **34**). We then explored substitution at the 4-position on the *N*-phenyl urea group with electron-donating (**35**, R^2 = 4-methoxyphenyl urea) and electron-withdrawing groups (**36**, R^2 = 4-chlorophenyl urea). We postulated that introduction of substituents at this position, if tolerated, may improve the in vitro microsomal stability because the 4-position in a phenyl group is often a site for oxidative metabolism. Unfortunately, these substitutions resulted in a loss of activity (**35**, IC_{50} = 2320 nM; **36**, IC_{50} = 1630 nM). In contrast, the 2-, 3-, and 4-fluoro substituted phenyl derivatives were more encouraging, as illustrated by compounds **37**–**39**. Of these analogues, the 4-fluoro derivative, **39**, proved to be both the most potent and the most metabolically stable. As a direct comparison of the 4-fluorophenyl urea, and to interrogate the contribution of the urea NH functionality to potency and microsomal stability, we

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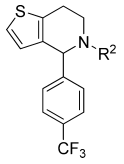
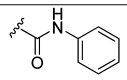
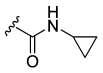
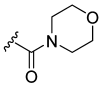
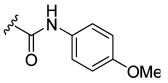
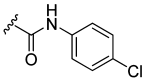
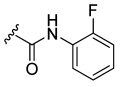
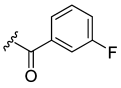
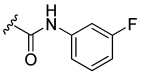
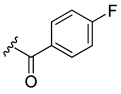
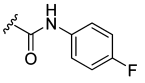
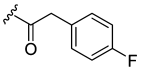
Table 2. In Vitro rTRPM8 Activities and Rat Microsomal Stabilities for Tetrahydrothienopyridines (R^2 Group Modifications)[a]



Compound No.	R^2	rTRPM8 IC_{50} (nM)	CL_{int} (μL/min/mg)	Compound No.	R^2	rTRPM8 IC_{50} (nM)	CL_{int} (μL/min/mg)
17		290 ± 74	211	**33**		1210 ± 260	>399
10g	H	>20000	>399				
24		>20000	<14	**34**		>20000	>399
25		>20000	N.D.				
26		>20000	>399	**35**		2320 ± 1060	203
27		1260 ± 650	>399	**36**		1630 ± 360	162
28		510 ± 67	>399	**37**		600 ± 52	342
29		>20000	>399	**38**		780 ± 63	278
30		>20000	248	**39**		340 ± 210	178
32		550 ± 340	>399	**31**		890 ± 150	>399

[a]IC_{50} values based on inhibition of icilin (1 μM) induced influx of Ca^{2+} into rTRPM8-expressing CHO cells. Each IC_{50} value reported represents an average of at least two independent experiments with three replicates at each concentration (SEM). In vitro microsomal stability measured in a high-throughput automated format.[16]

also prepared the 4-fluorophenylacetamide derivative **31**. This analogue was slightly less potent than urea **39** but was significantly less stable in rat liver microsomes demonstrating the added stability provided by the urea functionality. We therefore continued our investigations using analogue **39** for further optimization studies.

The final SAR examined in this work resulted from modifications of the heterocyclic core of compound **39** (Table 3). Replacement of the fused thiophene ring in **39** with its regioisomeric five-membered ring heterocycle gave 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine **45**. This small modification gave only a 2-fold improvement in potency against rTRPM8; however, it did not improve the microsomal stability. Similarly, substitution of the fused thiophene ring by a furan ring did not result in a significant change in activity with the regioisomeric 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine **46** and 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine **47** having IC_{50} values of 260 and 230 nM, respectively. This suggested that the sulfur atom did not play a critical role in the antagonistic activity against the rTRPM8 channel. Other fused five-membered ring heterocycles such as pyrrole **48**, thiazole **58**, and imidazoles **61** and **63** were also assessed for functional antagonism of rTRPM8. There was not a significant difference in potency between the parent thiophene analogue **39** and compounds **48** and **58**. However, introduction of an additional H-bond donating group such as in imidazole **61** proved detrimental for activity (IC_{50} = 1430 nM). Masking the NH in the imidazole ring by methylation led to analogue **63**, which had improved potency and RLM values. We then examined six-membered rings and a significant improvement in activity was observed when the (5,6)-bicyclic core was replaced with a (6,6)-core. For example, tetrahydroisoquinoline **68** was not only 6-fold more potent than the parent compound, but it was also significantly more metabolically stable with a CL_{int} = 92 μL/(min·mg). This result demonstrated that the tetrahydrothienopyridine moiety, a highly electron-rich ring system and potentially the main source of metabolic instability, could be replaced while enhancing rTRPM8 antagonistic activity.

With the tetrahydroisoquinoline core identified as a superior structural motif, four isomeric monofluoro tetrahydroisoquino-

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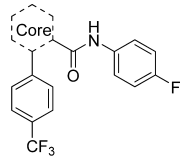
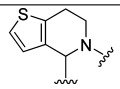
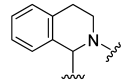
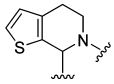
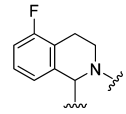
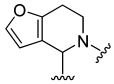
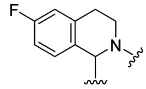
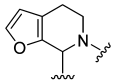
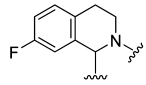
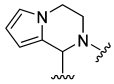
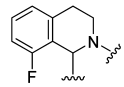
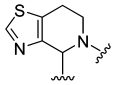
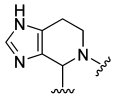
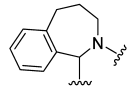
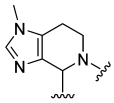
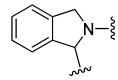
Table 3. In Vitro rTRPM8 Activities and Rat Microsomal Stabilities for Substituted Piperidines (Heterocyclic Core Modifications)[a]



Compound No.	Core	rTRPM8 IC_{50} (nM)	CL_{int} (μL/min/mg)	Compound No.	Core	rTRPM8 IC_{50} (nM)	CL_{int} (μL/min/mg)
39		340 ± 210	178	**68**		53 ± 19	92
45		150 ± 40	206	**69**		100 ± 55	48
46		260 ± 0.1	109	**70**		302 ± 24	40
47		230 ± 3	164	**71**		190 ± 13	34
48		180 ± 110	123	**78**		790 ± 240	43
58		93 ± 81	110	**86**		2664 ± 180	285
61		1430 ± 106	23	**72**		>20000	146
63		260 ± 7	36	**82**		340 ± 31	64

[a] IC_{50} values based on inhibition of icilin (1 μM) induced influx of Ca^{2+} into rTRPM8-expressing CHO cells. Each IC_{50} value reported represents an average of at least two independent experiments with three replicates at each concentration (SEM). In vitro microsomal stability measured in a high-throughput automated format.[16]

line analogues were prepared (i.e., **69**–**71**, **78**) in an effort to further improve in vitro stability by blocking possible sites of metabolism on this new series of compounds (Table 3). Introduction of a fluoro substituent at the 6- or 8-position (**70**, **78**) was not well tolerated for rTRPM8 activity. However, the 5- and 7-fluoro analogues (**69**, **71**) were potent antagonists of rTRPM8, and a moderate improvement in metabolic stability was obtained.

The role of the aromatic ring fused to the piperidine was also investigated with the piperidine analogue **86**. This compound was significantly less potent than the parent tetrahydrothienopyridine **39**, indicating that a fused bicyclic core was preferred for activity.

Next we turned our attention to the fused piperidine ring and examined the effect of the ring size on potency and microsomal stability. Homologation of the piperidine ring to the seven-membered ring analogue resulted in benzazepine **72**, which was not active against rTRPM8 following activation by **3**. In contrast, the indoline analogue **82** was only 6-fold less potent than the parent tetrahydroisoquinoline **68**.

Due to its improved in vitro metabolic clearance, as well as its intrinsic potency at the target, tetrahydroisoquinoline **68** was selected for in vivo evaluation. Separation of the racemic mixture **68** using preparative chiral chromatography provided the two enantiomers (**87** and **88**). The absolute stereochemistries of tetrahydroisoquinolines **87** and **88** were determined by two different methods that compare theoretical and experimental measurements: vibrational circular dichroism (VCD)[21] and optical rotation.[22] In the first method, VCD spectra for each enantiomer were acquired on a chiral infrared (IR) instrument (Figure 2a), and the corresponding theoretical VCD spectra were determined quantum mechanically (B3LYP/6-31G*)[22a−c] (Figure 2b). Experimental and theoretical achiral IR spectra were also obtained and are illustrated in Figure 2c. Alignment of the experimental and theoretical achiral IR spectra allowed for the major absorption transitions (i−iv in

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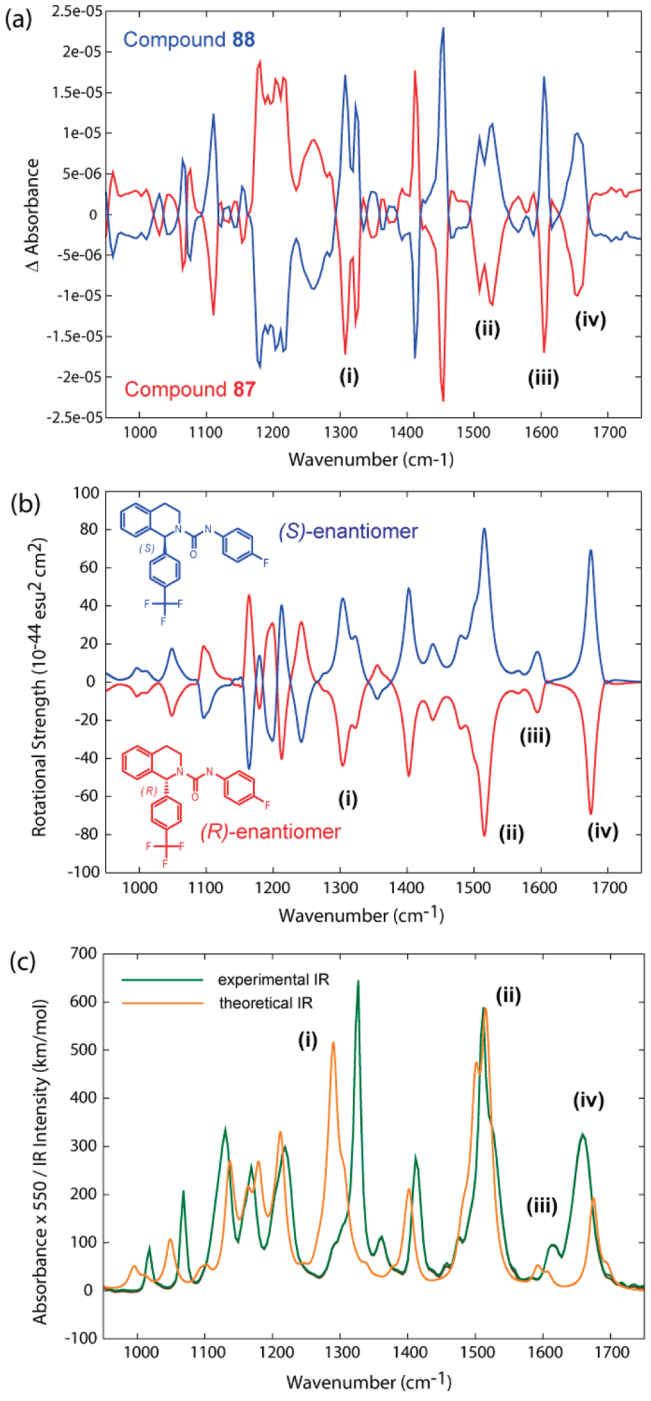
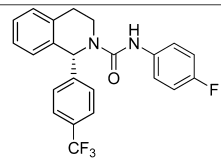
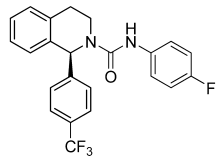


Figure 2. IR and VCD spectra for compounds **87** and **88**: (a) experimental VCD spectra; (b) theoretical VCD spectra; (c) experimental and theoretical achiral IR spectra, superimposed. See Supporting Information for computational details.

Figure 2) to be mapped to their corresponding peaks in the chiral VCD spectra. Comparison of these unambiguous regions of the corresponding experimental VCD traces of **87** and **88** to those computed for the (*R*)- and (*S*)-forms, led to the assignments of compounds **87** and **88** as the (*R*)- and (*S*)-enantiomers, respectively. The second method used to determine the absolute stereochemistries of **87** and **88** utilized optical rotation measurements. In this method, the predicted optical rotation values for the Boltzmann-weighted, conformational average of the (*R*)- and (*S*)-enantiomers (−379° and +379°, respectively; at 589 nm) were in qualitative agreement with the measured optical rotations for **87** and **88** ($[\alpha]^{26}_{D}$ −106.6° and +106.7° [*c* 0.1, chloroform], respectively), thereby corroborating the VCD-based assignments.

Having determined the absolute configuration of compounds **87** and **88**, we analyzed both enantiomers in vitro. The *R*-isomer **87** was a significantly more potent rTRPM8 antagonist and was more stable in rat liver microsomes preparations (IC_{50} = 56 nM, CL_{int} = 42 μL/(min·mg); Table 4). Following

Table 4. In Vitro rTRPM8 Activities and Rat Microsomal Stabilities for Tetrahydroisoquinoline Enantiomers 87 and 88[a]

Compound No.	*Structure*	*rTRPM8 IC_{50} (nM)*	*CL_{int} (μL/min/mg)*
87		56 ± 24	42
88		>20000	151

[a] IC_{50} values based on inhibition of icilin (1 μM) induced influx of Ca^{2+} into rTRPM8-expressing CHO cells. Each IC_{50} value reported represents an average of at least two independent experiments with three replicates at each concentration. In vitro microsomal stability measured in a high-throughput automated format.[16] For selectivity information on other TRP channels as well as potency for the human channel and human liver microsomal data, see Supporting Information.

intravenous administration in Sprague−Dawley rats (Table 5), **87** displayed a relatively high total systemic clearance (2.9 L/(h·kg), ∼88% of hepatic blood flow), a high volume of distribution (15.3 L/kg), and a moderate terminal half-life of 6.7 h. In contrast, an even higher rate of clearance (CL) was observed for compound **88** (5.8 L/(h·kg)). The pharmacokinetic profile of compound **87** after single oral administration (po) is summarized in Table 5. Tetrahydroisoquinoline **87** was well-absorbed, with a bioavailability of 57%. The maximum plasma concentration (C_{max}) following oral administration of compound **87** was 265 ng/mL at 2.7 h. Rat plasma protein binding for compound **87** was determined to be 90.1%.

Although pharmacokinetic properties of tetrahydroisoquinoline **87** were not optimal, its potency and overall profile made it a suitable candidate for in vivo evaluation in an on-target biochemical challenge model. In this model, prevention of icilin-induced wet-dog shakes (WDS) in rats by tetrahydroisoquinolines **87** and **88** was measured (Figure 3).[23] Vehicle or test compounds (**87** and **88**) were administered orally to Sprague−Dawley rats 90 min prior to challenge with **3** (0.5 mg/kg, ip). In the vehicle/**3** group, over 150 shakes were counted during a 30 min period. Pretreatment with compound **87** significantly reduced icilin-induced WDS in a dose-dependent manner. A reduction significantly different from vehicle was observed at 3 mg/kg (30%; $p < 0.01$) and more than 80% reduction was obtained at 30 mg/kg ($p < 0.001$). A

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Table 5. Mean (SD) Pharmacokinetic (PK) Parameters of Compounds 87 and 88 in Male Sprague–Dawley Rats[a]

	route	dose (mg/kg)	AUC_{inf} (ng·h/mL)	CL (L/(h·kg))	Vss (mL/kg)	$t_{1/2}$ (h)	C_{max} (ng/mL)	F (%)
87	iv[b]	2	763(306)	2.9(1.0)	15.3(2.0)	6.7(2.1)		
88	iv[b]	2	347(19.1)	5.8(0.31)	15.8(3.2)	4.4(1.8)		
87	po[c]	10	1747(548)				265(55.7)	57

[a]All PK parameters were reported as mean(SD). [b]Study in fed male Sprague–Dawley rats dosed at 2 mg/kg in DMSO, n = 3 animals per study. [c]Study in fasted male Sprague–Dawley rats dosed at 10 mg/kg as a suspension in 5% Tween 80/Oraplus, n = 3 animals per study.

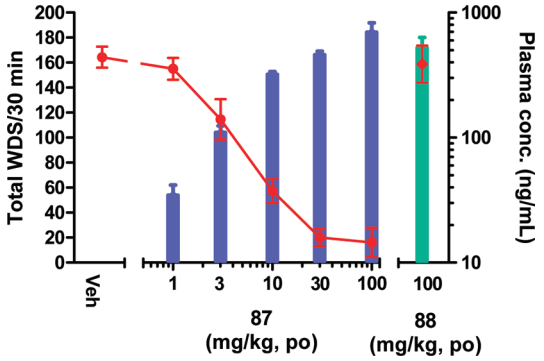

Figure 3. Inhibition of icilin-induced wet-dog shakes (WDS) in rats and corresponding plasma levels (bar graph) of compounds 87 and 88, dosed po in 5% Tween 80/Oraplus 90 min prior to challenge by 3; n = 8 per group of Sprague–Dawley male rats. Plasma samples were collected 2 h after oral dosing.

nonlinear regression model (log inhibitor versus response with variable slope) of plasma concentrations of compound 87 versus WDS yielded an EC_{50} of 209 ng/mL. In the same study, animals were also predosed with 100 mg/kg of compound 88, the enantiomer of 87 (rTRPM8 IC_{50} > 20 μM). Plasma levels of compound 88 at 100 mg/kg (521 ng/mL) were comparable to 30 mg/kg of 87 (460 ng/mL); however, no inhibition of icilin-induced WDS was observed. These results demonstrated that 87 was a potent antagonist of TRPM8 in vivo and that the inhibition of WDS in rats induced by 3 was due to TRPM8 antagonism.

SUMMARY

Following the identification of tetrahydrothienopyridine 4 as a TRPM8 antagonist hit from a high-throughput screening campaign, we undertook a detailed SAR investigation aimed at improving potency as well as increasing metabolic stability of this compound. SAR studies aimed at improving potency and microsomal stability established a 4-trifluorophenyl group as the preferred R^1 substituent and a 4-fluorophenyl urea as the R^2 substituent of choice on the piperidine nitrogen, leading to tetrahydrothienopyridine 39. Subsequent modifications of the central heterocyclic core led to of a new series of tetrahydroisoquinolines as potent TRPM8 antagonists with increased metabolic stability, exemplified by compound 87. The overall profile of this TRPM8 antagonist (87), potency and pharmacokinetic properties, made it a suitable candidate for in vivo studies. Compound 87 showed a dose-dependent reduction of icilin-induced WDS in rats, an on-target biochemical challenge model. Although optimization of potency and overall PKDM profile is still required in this new series, these data represent an encouraging starting point for the discovery of TRPM8 antagonists as novel therapies for pain.

EXPERIMENTAL SECTION

Chemistry. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich or EM Science and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. All microwave-assisted reactions were conducted with a Smith synthesizer from Personal Chemistry, Uppsala, Sweden. All final compounds were purified to >95% purity, as determined by LC/MS obtained on Agilent 1100 and HP 1100 spectrometers. Silica gel chromatography was performed using either glass columns packed with silica gel (200–400 mesh, Aldrich Chemical) or prepacked silica gel cartridges (Biotage or RediSep). ^{1}H NMR spectra were determined with a Bruker 300 MHz or DRX 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ units).

The following 4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivatives were commercially available: 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**10b**), 4-cyclopropyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**10d**), 4-(4-chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**10j**), 1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (**44**), and 4-methyl-*N*-phenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-carboxamide (**12**).

(a). General Procedure for the Preparation of Tetrahydrothienopyridines. *Amide Route.* (Step 1) To a solution of 2-(thiophen-2-yl)ethanamine (7, 20 g, 0.16 mol) and triethylamine (17.8 g, 0.18 mol, 1.1 equiv) in CH_2Cl_2 (120 mL) was added the acid chlorides (1.05 equiv) dropwise at 0 °C. The mixture was stirred until completion of the reaction was determined by TLC (~2 h). The reaction mixture was diluted with EtOAc and washed with 10% aq HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The EtOAc solution was dried over Na_2SO_4, and the solvent was eliminated under vacuum to afford the target amides, **8**.

(Step 2) To a stirred solution of the amide (**8**) in CH_3CN was added $POCl_3$ (4 equiv) dropwise, and the reaction mixture was stirred at 60 °C overnight. The reaction mixture was cooled to room temperature, and the solvent was removed under vacuum. The residue obtained was dissolved in EtOAc, and the mixture was washed with saturated aqueous $NaHCO_3$. The organic layer was separated, washed with water and saturated aqueous NaCl, and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography eluting with EtOAc/hexanes mixtures.

(Step 3) To a stirred solution of the tetrahydrothienopyridines (1.5 mmol) in dry MeOH (10 mL) was added $NaBH_4$ (2 equiv) at room temperature. Stirring was continued until the completion of the reaction as determined by TLC, ~2 h. The reaction mixture was concentrated under vacuum, and the residue was dissolved in EtOAc. The organic layer was washed with water and saturated aqueous NaCl and dried over Na_2SO_4, and the solvent was eliminated under vacuum. The crude product was purified by silica gel column chromatography eluting with EtOAc/hexanes mixtures.

The following compounds were prepared according to this general procedure (amide route).

*4-Propyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**10a**).* ^{1}H NMR (400 MHz, $CDCl_3$): 1.03 (t, J = 7.34 Hz, 3 H), 1.70 (dq, J = 15.28, 7.56 Hz, 2 H), 1.98–2.19 (m, 2 H), 3.07–3.19 (m, 1 H), 3.26–3.43 (m, 2 H), 3.64–3.73 (m, 1 H), 4.43 (t, J = 6.16 Hz, 1 H), 6.81 (d, J = 5.28 Hz, 1 H), 7.20 (d, J = 5.28 Hz, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{10}H_{15}NS$ 182.1; found 182.1.

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*4-(2-(Trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine (**10e**).* ^{1}H NMR (400 MHz, $CDCl_3$): 2.79−2.92 (m, 1 H), 2.99−3.22 (m, 2 H), 3.29−3.41 (m, 1 H), 5.45 (s, 1 H), 6.33 (d, J = 5.09 Hz, 1 H), 6.99 (d, J = 5.28 Hz, 1 H), 7.29−7.39 (m, 2 H), 7.40−7.49 (m, 1 H), 7.68 (d, J = 7.63 Hz, 1 H), 10.20 (br s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{14}H_{12}F_3NS$ 284.1; found 284.0.

*4-(3-(Trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine (**10f**).* ^{1}H NMR (400 MHz, $CDCl_3$): 2.82−2.91 (m, 1 H), 2.96−3.06 (m, 1 H), 3.09−3.18 (m, 1 H), 3.26−3.35 (m, 1 H), 5.08 (s, 1 H), 6.43 (d, J = 5.09 Hz, 1 H), 7.03 (d, J = 5.09 Hz, 1 H), 7.40−7.50 (m, 2 H), 7.54 (d, J = 7.63 Hz, 1 H), 7.58 (br s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{14}H_{12}F_3NS$ 284.1; found 284.0.

*4-(4-(Trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine (**10g**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.70−2.80 (m, 1 H), 2.81−2.99 (m, 2 H), 3.04−3.16 (m, 1 H), 5.01 (s, 1 H), 6.41 (d, J = 5.28 Hz, 1 H), 7.19 (d, J = 5.09 Hz, 1 H), 7.51 (d, J = 8.02 Hz, 2 H), 7.67 (d, J = 8.02 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{14}H_{12}F_3NS$ 284.1; found 284.0.

*4-(2-Chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**10h**).* ^{1}H NMR (400 MHz, $CDCl_3$): 2.82−3.00 (m, 2 H), 3.06−3.14 (m, 1 H), 3.15−3.24 (m, 1 H), 5.55 (s, 1 H), 6.50 (d, J = 5.09 Hz, 1 H), 7.05 (d, J = 1.00 Hz, 1 H), 7.18 (dtd, J = 18.34, 7.41, 7.41, 1.47 Hz, 2 H), 7.40 (dd, J = 7.73, 1.47 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{13}H_{12}ClNS$ 249.0; found 249.0.

*4-(3-Chlorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**10i**).* ^{1}H NMR (400 MHz, $CDCl_3$): 2.75−2.90 (m, 1 H), 2.92−3.05 (m, 1 H), 3.06−3.17 (m, 1 H), 3.29 (dt, J = 12.13, 4.79 Hz, 1 H), 5.00 (s, 1 H), 6.46 (d, J = 5.09 Hz, 1 H), 7.02 (d, J = 5.09 Hz, 1 H), 7.13−7.21 (m, 1 H), 7.23−7.30 (m, 3 H). MS (ESI pos. ion) m/z: calcd for $C_{13}H_{12}ClNS$ 249.0; found 249.0.

*4-(2-Fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**10k**).* ^{1}H NMR (400 MHz, $CDCl_3$): 2.78−3.02 (m, 2 H), 3.07−3.17 (m, 1 H), 3.20−3.32 (m, 1 H), 5.44 (s, 1 H), 6.51 (d, J = 5.09 Hz, 1 H), 6.99−7.13 (m, 4 H), 7.19−7.30 (m, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{13}H_{12}FNS$ 234.1; found 234.1.

*4-(3-Fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**10l**).* ^{1}H NMR (400 MHz, $CDCl_3$): 2.79−2.89 (m, 1 H), 2.93−3.04 (m, 1 H), 3.06−3.16 (m, 1 H), 3.29 (dt, J = 12.18, 4.87 Hz, 1 H), 5.02 (s, 1 H), 6.47 (d, J = 5.28 Hz, 1 H), 6.93−7.04 (m, 3 H), 7.08 (d, J = 7.63 Hz, 1 H), 7.27−7.32 (m, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{13}H_{12}FNS$ 234.1; found 234.1.

*4-(4-Fluorophenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**10m**).* ^{1}H NMR (400 MHz, $CDCl_3$): 2.78−2.90 (m, 1 H), 2.93−3.03 (m, 1 H), 3.06−3.16 (m, 1 H), 3.23−3.36 (m, 1 H), 5.01 (s, 1 H), 6.44 (d, J = 5.09 Hz, 1 H), 6.95−7.06 (m, 3 H), 7.16−7.29 (m, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{13}H_{12}FNS$ 234.1; found 234.1.

*(b). Amine Route. 4-Phenyl-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine (**10n**).* A solution of 2-(thiophen-2-yl)ethanamine (2.2 mL, 17.4 mmol) and benzaldehyde (1.8 g, 17.4 mmol) in toluene (50 mL) was heated at reflux (Dean−Stark trap, H_2O removed) for 16 h. The reaction mixture was then concentrated in vacuo, and trifluoroacetic acid (30 mL) was cautiously added to the residue. The mixture was stirred at room temperature for 3 d. The reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc (50 mL), and the solution was washed with 2 M aqueous NaOH solution (50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography using a mixture of 2% to 4% MeOH in CH_2Cl_2 to give the title compound as an off-white solid (1.46 g, 39%). ^{1}H NMR (400 MHz, DMSO-d_6): 2.63−2.97 (m, 4 H), 3.12 (dt, J = 11.54, 4.50 Hz, 1 H), 4.90 (s, 1 H), 6.38 (d, J = 5.09 Hz, 1 H), 7.16 (d, J = 5.09 Hz, 1 H), 7.20−7.36 (m, 5 H). MS (ESI pos. ion) m/z: calcd for $C_{13}H_{13}NS$ 216.1; found 216.1.

*4-(4-(Trifluoromethyl)phenyl)-4,5,6,7-tetrahydrofuro[3,2-c]-pyridine hydrochloride (**41**).* (Step 1) To a solution of 2-(furan-2-yl)ethanamine (**40**, 6.39 g, 0.06 mol) and triethylamine (12 mL, 0.08 mol) in CH_2Cl_2 (100 mL) at 0 °C was added 4-(trifluoromethyl)-benzoyl chloride (8.5 mL, 0.06 mol) dropwise. The solution was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc and washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification by column chromatography using a mixture of 1:5 to 1:4 EtOAc/hexanes afforded *N*-(2-(furan-2-yl)ethyl)-4-(trifluoromethyl)benzamide as a yellow solid (3.5 g, 22%).

(Step 2) To a stirred solution of phosphorus oxide (5.0 g, 35 mmol) and phosphorus trichloride (5.4 mL, 59 mmol) in benzene (100 mL) at reflux was added *N*-(2-(furan-2-yl)ethyl)-4-(trifluoromethyl)-benzamide (3.4 g, 12 mmol). The reaction mixture was heated at reflux for 2 h and then allowed to cool to room temperature. The solution was poured into crushed ice, basified with potassium carbonate to pH = 10−11, and extracted with benzene. The organic layer was separated, washed with water, and dried over Na_2SO_4, and the solvent was eliminated under vacuum. Purification by column chromatography using a mixture of 1:5 to 1:4 EtOAc/hexanes afforded 4-(4-(trifluoromethyl)phenyl)-6,7-dihydrofuro[3,2-*c*]pyridine as a red oil (0.94 g, 30%).

(Step 3) To a stirred solution of the 4-(4-(trifluoromethyl)phenyl)-6,7-dihydrofuro[3,2-*c*]pyridine (0.61 g, 2.3 mmol) in dry CH_2Cl_2 (15 mL) was added $NaB(OAc)_3H$ (1.63 g, 7.7 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight, diluted with CH_2Cl_2, and cooled to 0 °C. An aqueous solution of NaOH (10%) was added slowly to this solution. The organic layer was separated and dried over Na_2SO_4, and the solvent was eliminated under vacuum. This material was used in the next step without further purification. To a solution of 4-(4-(trifluoromethyl)-phenyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (0.61 g, 2.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added triethylamine (0.47 mL, 3.4 mmol) and di-*tert*-butyl dicarbonate (0.55 g, 2.5 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using a mixture of 1:9 EtOAc/hexanes as eluent to give *tert*-butyl 4-(4-(trifluoromethyl)phenyl)-6,7-dihydrofuro[3,2-*c*]pyridine-5(4*H*)-carboxylate as a yellow oil (0.7 g, 83%).

(Step 4) To a solution of *tert*-butyl 4-(4-(trifluoromethyl)phenyl)-6,7-dihydrofuro[3,2-*c*]pyridine-5(4*H*)-carboxylate (0.65 g, 1.8 mmol) in Et_2O (10 mL) was added HCl/dioxane (4.85 M, 5 mL). The reaction mixture was stirred at room temperature overnight, and the resulting white precipitate was filtered, washed with Et_2O, and dried under vacuum to give the title compound as a white solid (0.52 g, 96%). ^{1}H NMR (400 MHz, DMSO-d_6): 2.92−3.04 (m, 1 H), 3.07−3.21 (m, 1 H), 3.37−3.53 (m, 2 H), 5.76 (br s, 1 H), 6.17 (s, 1 H), 7.68 (d, J = 8.53 Hz, 2 H), 7.71 (s, 1 H), 7.86 (d, J = 8.53 Hz, 2 H), 9.73 (br s, 1 H), 10.47 (br s, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{14}H_{12}F_3NO$ 268.1; found 268.1.

General Procedure for the Preparation of Ureas (4−5, 11−23, 32−39, and 45−48). To a solution of the tetrahydrothieno/furanopyridine (1.9 mmol) in CH_2Cl_2 (4 mL) at room temperature was added 1 equiv of the appropriate isocyanate. The reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The compounds were purified by silica gel chromatography.

*N-(4-Chlorophenyl)-4-propyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**4**).* ^{1}H NMR (400 MHz, $CDCl_3$): 1.00 (t, J = 7.34 Hz, 3 H), 1.47−1.62 (m, 2 H), 1.75−1.87 (m, 2 H), 2.79 (dd, J = 16.14, 2.84 Hz, 1 H), 2.93−3.05 (m, 1 H), 3.21−3.35 (m, 1 H), 4.33 (dd, J = 13.79, 5.18 Hz, 1 H), 5.03 (t, J = 6.75 Hz, 1 H), 6.38 (s, 1 H), 6.81 (d, J = 5.09 Hz, 1 H), 7.12 (d, J = 5.09 Hz, 1 H), 7.23 (d, J = 9.00 Hz, 2 H), 7.27−7.33 (m, 2 H). HRMS calcd for $C_{17}H_{19}ClN_2OS$ (M + H): 335.0976; found 335.0970.

*N-Phenyl-4-propyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**5**).* ^{1}H NMR (400 MHz, $CDCl_3$): 1.00 (t, J = 7.34 Hz, 3 H), 1.55 (sxt, J = 7.43 Hz, 2 H), 1.75−1.92 (m, 2 H), 2.78 (dd, J = 16.04, 2.93 Hz, 1 H), 2.90−3.09 (m, 1 H), 3.27 (ddd, J = 13.64, 12.08, 3.81 Hz, 1 H), 4.35 (dd, J = 13.69, 5.09 Hz, 1 H), 5.06 (t, J = 6.85 Hz, 1 H), 6.40 (br s, 1 H), 6.81 (d, J = 5.28 Hz, 1 H), 6.99−7.06 (m, 1 H), 7.11 (d, J = 5.28 Hz, 1 H), 7.29 (d, J = 7.43 Hz, 2 H), 7.32−7.39 (m, 2 H). HRMS calcd for $C_{17}H_{20}N_2OS$ (M + H): 301.1360; found 301.1365.

*N-Phenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**11**).* ^{1}H NMR (400 MHz, $CDCl_3$): 2.95 (t, J = 5.58 Hz, 2 H), 3.84 (t, J = 5.67 Hz, 2 H), 4.60 (s, 2 H), 6.40 (br s, 1 H), 6.82 (d, J = 5.09 Hz, 1 H), 7.05 (t, J = 7.34 Hz, 1 H), 7.16 (d, J = 5.09 Hz, 1 H), 7.30 (t, J = 7.92 Hz, 2 H), 7.37 (d, J = 7.61 Hz, 2 H). HRMS calcd for $C_{14}H_{14}N_2OS$ (M + H): 259.0897; found 259.0900.

*4-Cyclopropyl-N-phenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**13**).* ^{1}H NMR (300 MHz, $CDCl_3$): 0.57−0.78 (m, 4 H), 1.15−1.34 (m, 1 H), 2.77−2.89 (m, 1 H), 2.91−3.09 (m, 1 H), 3.40−3.56 (m, 1 H), 4.29 (dd, J = 13.96, 5.33 Hz, 1 H), 4.67 (d, J = 8.33 Hz, 1 H), 6.39 (s, 1 H), 6.92 (d, J = 5.12 Hz, 1 H), 6.98−7.07 (m, 1 H), 7.12 (d, J = 5.12 Hz, 1 H), 7.27−7.39 (m, 4 H). HRMS calcd for $C_{17}H_{18}N_2OS$ (M + H): 299.1209; found 299.1210.

*N,4-Diphenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**14**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.84−3.02 (m, 2 H), 3.03−3.15 (m, 1 H), 4.28 (dd, J = 13.89, 4.50 Hz, 1 H), 6.56 (s, 1 H), 6.83 (d, J = 5.28 Hz, 1 H), 6.95 (t, J = 7.34 Hz, 1 H), 7.19−7.30 (m, 5 H), 7.30−7.36 (m, 2 H), 7.39 (d, J = 5.09 Hz, 1 H), 7.48 (d, J = 7.63 Hz, 2 H), 8.67 (s, 1 H). HRMS calcd for $C_{20}H_{18}N_2OS$ (M + H): 335.1209; found 335.1220.

*N-Phenyl-4-(2-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]-pyridine-5(4H)-carboxamide (**15**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.79−3.01 (m, 2 H), 3.33−3.45 (m, 1 H), 4.11−4.25 (m, 1 H), 6.63 (d, J = 5.12 Hz, 1 H), 6.82 (s, 1 H), 6.88−6.98 (m, 1 H), 7.16 (s, 1 H), 7.23 (d, J = 7.45 Hz, 2 H), 7.36 (d, J = 5.26 Hz, 1 H), 7.41 (dd, J = 8.55, 1.10 Hz, 2 H), 7.52 (t, J = 7.50 Hz, 1 H), 7.56−7.64 (m, 1 H), 7.79 (d, J = 6.72 Hz, 1 H), 8.87 (s, 1 H). HRMS calcd for $C_{21}H_{17}F_3N_2OS$ (M + H): 403.1083; found 403.1090.

*N-Phenyl-4-(3-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]-pyridine-5(4H)-carboxamide (**16**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.82−3.19 (m, 3 H), 4.20−4.41 (m, 1 H), 6.63 (s, 1 H), 6.88 (d, J = 5.26 Hz, 1 H), 6.92−7.02 (m, 1 H), 7.25 (t, J = 7.89 Hz, 2 H), 7.43 (d, J = 5.1 Hz, 1 H), 7.44 − 7. 48 (m, 2 H), 7.51 − 7.64 (m, 3 H), 7.68 (d, J = 8.90 Hz, 1 H), 8.75 (s, 1 H). HRMS calcd for $C_{21}H_{17}F_3N_2OS$ (M + H): 403.1083; found 403.1080.

*N-Phenyl-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]-pyridine-5(4H)-carboxamide (**17**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.81−3.18 (m, 3 H), 4.24−4.35 (m, 1 H), 6.63 (s, 1 H), 6.88 (d, J = 5.26 Hz, 1 H), 6.92−7.01 (m, 1 H), 7.19−7.29 (m, 2 H), 7.43 (d, J = 5.26 Hz, 1 H), 7.48 (d, J = 7.60 Hz, 3 H), 7.72 (d, J = 8.18 Hz, 2 H), 8.73 (s, 1 H). HRMS calcd for $C_{21}H_{17}F_3N_2OS$ (M + H): 403.1083; found 403.1088.

*4-(2-Chlorophenyl)-N-phenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**18**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.84−2.97 (m, 2 H), 3.17−3.26 (m, 1 H), 4.15−4.29 (m, 1 H), 6.73−6.77 (m, 2 H), 6.90−6.96 (m, 2 H), 7.22 (t, J = 7.92 Hz, 2 H), 7.27 (dd, J = 7.53, 1.47 Hz, 1 H), 7.33 (dd, J = 7.5, 1.9 Hz, 1 H), 7.38 (d, J = 5.28 Hz, 1 H), 7.41−7.46 (m, 2 H), 7.49 (dd, J = 7.83, 1.37 Hz, 1 H), 8.82 (s, 1 H). HRMS calcd for $C_{20}H_{17}ClN_2OS$ (M + H): 369.0820; found 369.0830.

*4-(3-Chlorophenyl)-N-phenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**19**).* ^{1}H NMR (400 MHz, $CDCl_3$): 2.87−2.98 (m, 1 H), 3.02−3.17 (m, 1 H), 3.31−3.45 (m, 1 H), 4.08 (dd, J = 14.38, 4.21 Hz, 1 H), 6.38 (s, 1 H), 6.44 (s, 1 H), 6.73 (d, J = 5.28 Hz, 1 H), 7.01−7.08 (m, 1 H), 7.17 (d, J = 5.28 Hz, 1 H), 7.27−7.37 (m, 8 H). HRMS calcd for $C_{20}H_{17}ClN_2OS$ (M + H): 369.0820; found 369.0820.

*4-(4-Chlorophenyl)-N-phenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**20**).* ^{1}H NMR (300 MHz, $CDCl_3$): 2.85−2.99 (m, 1 H), 3.01−3.17 (m, 1 H), 3.36 (ddd, J = 14.03, 11.69, 3.95 Hz, 1 H), 4.07 (dd, J = 13.96, 4.17 Hz, 1 H), 6.39 (s, 1 H), 6.44 (s, 1 H), 6.70 (d, J = 5.26 Hz, 1 H), 7.05 (tt, J = 6.36, 2.19 Hz, 1 H), 7.16 (d, J = 5.26 Hz, 1 H), 7.27−7.35 (m, 8 H). HRMS calcd for $C_{20}H_{17}ClN_2OS$ (M + H): 369.0820; found 369.0829.

*4-(2-Fluorophenyl)-N-phenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**21**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.92 (d, J = 4.38 Hz, 2 H), 3.13−3.31 (m, 1 H), 4.24−4.36 (m, 1 H), 6.73 (d, J = 5.1 Hz, 1 H), 6.77 (s, 1 H), 6.90−6.98 (m, 1 H), 7.01 (dd, J = 7.51, 1.43 Hz, 1 H), 7.09−7.19 (m, 1 H), 7.19−7.28 (m, 3 H), 7.30−7.40 (m, 2 H), 7.41−7.50 (m, 2 H) 8.73 (s, 1 H). HRMS calcd for $C_{20}H_{17}FN_2OS$ (M + H): 353.1115; found 353.1120.

*4-(3-Fluorophenyl)-N-phenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**22**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.79−3.22 (m, 3 H), 4.20−4.35 (m, 1 H), 6.55 (s, 1 H), 6.87 (d, J = 5.12 Hz, 1 H), 6.92−7.05 (m, 2 H), 7.06−7.18 (m, 2 H), 7.25 (t, J = 7.89 Hz, 2 H), 7.34−7.44 (m, 2 H), 7.48 (dd, J = 8.55, 0.95 Hz, 2 H), 8.71 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{20}H_{17}FN_2OS$ 353.1; found 353.0.

*4-(4-Fluorophenyl)-N-phenyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**23**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.81−3.18 (m, 3 H), 4.19−4.36 (m, 1 H), 6.55 (s, 1 H), 6.82 (d, J = 5.26 Hz, 1 H), 6.91−7.01 (m, 1 H), 7.11−7.32 (m, 6 H), 7.40 (d, J = 5.12 Hz, 1 H), 7.47 (dd, J = 8.55, 0.95 Hz, 2 H), 8.69 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{20}H_{17}FN_2OS$ 353.1; found 353.0.

*N-Isopropyl-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**32**).* ^{1}H NMR (300 MHz, DMSO-d_6): 1.07 (dd, J = 6.50, 2.56 Hz, 6 H), 2.72−3.03 (m, 3 H), 3.38 − 3.59 (m, 1 H), 3.82 (d, J = 6.87 Hz, 1 H), 4.08 (d, J = 9.50 Hz, 1 H), 6.43 (d, J = 7.60 Hz, 1 H), 6.49 (s, 1 H), 6.83 (d, J = 5.26 Hz, 1 H), 7.37−7.44 (m, 3 H), 7.70 (d, J = 8.18 Hz, 2 H). HRMS calcd for $C_{18}H_{19}F_3N_2OS$ (M + H): 369.1239; found 369.1230.

*N-Cyclopropyl-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno-[3,2-c]pyridine-5(4H)-carboxamide (**33**).* ^{1}H NMR (300 MHz, DMSO-d_6): 0.33−0.43 (m, 2 H), 0.50−0.61 (m, 2 H), 2.53−2.62 (m, 1 H), 2.68−3.01 (m, 3 H), 3.99 (d, J = 8.92 Hz, 1 H), 6.46 (s, 1 H), 6.83 (d, J = 5.26 Hz, 2 H), 7.35−7.44 (m, 3 H), 7.70 (d, J = 8.04 Hz, 2 H). HRMS calcd for $C_{18}H_{17}F_3N_2OS$ (M + H): 367.1083; found 367.1090.

*Morpholino(4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methanone (**34**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.95 (d, J = 4.68 Hz, 2 H), 3.03−3.39 (m, 5 H), 3.46−3.74 (m, 5 H), 6.03 (s, 1 H), 6.75 (d, J = 5.12 Hz, 1 H), 7.35 (d, J = 5.12 Hz, 1 H), 7.46 (d, J = 8.18 Hz, 2 H), 7.69 (d, J = 8.18 Hz, 2 H). HRMS calcd for $C_{19}H_{19}F_3N_2O_2S$ (M + H): 397.1188; found 397.1190.

*N-(4-Methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**35**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.81−3.15 (m, 3 H), 3.71 (s, 3 H), 4.27 (d, J = 10.82 Hz, 1 H), 6.60 (s, 1 H), 6.79−6.91 (m, 3 H), 7.31−7.39 (m, 2 H), 7.42 (d, J = 5.26 Hz, 1 H), 7.47 (d, J = 8.18 Hz, 2 H), 7.72 (d, J = 8.18 Hz, 2 H), 8.58 (s, 1 H). HRMS calcd for $C_{22}H_{19}F_3N_2O_2S$ (M + H): 433.1188; found 433.1198.

*N-(4-Chlorophenyl)-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**36**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.84−3.18 (m, 3 H), 4.20−4.37 (m, 1 H), 6.61 (s, 1 H), 6.88 (d, J = 5.12 Hz, 1 H), 7.01 (dd, J = 7.89, 1.32 Hz, 1 H), 7.27 (t, J = 8.11 Hz, 1 H), 7.40−7.53 (m, 4 H), 7.65−7.69 (m, 1 H), 7.73 (d, J = 8.18 Hz, 2 H), 8.91 (s, 1 H). HRMS calcd for $C_{21}H_{16}ClF_3N_2OS$ (M + H): 437.0694; found 437.0700.

*N-(2-Fluorophenyl)-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**37**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.83−3.22 (m, 3 H), 4.16−4.33 (m, 1 H), 6.58 (s, 1 H), 6.87 (d, J = 5.26 Hz, 1 H), 7.07−7.27 (m, 3 H), 7.36−7.45 (m, 2 H), 7.49 (s, 2 H), 7.73 (d, J = 8.18 Hz, 2 H), 8.57 (s, 1 H). HRMS calcd for $C_{21}H_{17}F_4N_2OS$ (M + H): 421.0989; found 421.0990.

*N-(3-Fluorophenyl)-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**38**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.82−3.21 (m, 3 H), 4.19−4.39 (m, 1 H), 6.62 (s, 1 H), 6.69−6.83 (m, 1 H), 6.88 (d, J = 5.12 Hz, 1 H), 7.21−7.34 (m, 2 H), 7.38−7.55 (m, 4 H), 7.73 (d, J = 8.18 Hz, 2 H), 8.93 (s, 1 H). HRMS calcd for $C_{21}H_{17}F_4N_2OS$ (M + H): 421.0989; found 421.0980.

*N-(4-Fluorophenyl)-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxamide (**39**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.81−3.22 (m, 3 H), 4.18−4.37 (m, 1 H), 6.61 (s, 1 H), 6.88 (d, J = 5.26 Hz, 1 H), 7.01−7.16 (m, 2 H), 7.36−7.58 (m, 5 H), 7.72 (d, J = 8.18 Hz, 2 H), 8.77 (s, 1 H). HRMS calcd for $C_{21}H_{17}F_4N_2OS$ (M + H): 421.0989; found 421.0990.

*N-(4-Fluorophenyl)-7-(4-(trifluoromethyl)phenyl)-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-carboxamide (**45**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.81−3.17 (m, 3 H), 4.23−4.32 (m, 1 H), 6.61 (s, 1 H), 6.88 (d, J = 5.52 Hz, 1 H), 7.09 (t, J = 8.78 Hz, 2 H), 7.42 (d, J = 5.02 Hz, 1 H), 7.43 (s, 1 H), 7.45−7.53 (m, 4 H), 7.72 (d,

J = 8.03 Hz, 2 H), 8.77 (s, 1 H). HRMS calcd for $C_{21}H_{17}F_4N_2OS$ (M + H): 421.0989; found 421.1000.

*N-(4-Fluorophenyl)-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrofuro[3,2-c]pyridine-5(4H)-carboxamide (**46**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.69 (dd, J = 16.31, 3.26 Hz, 1 H), 2.81−2.97 (m, 1 H), 2.98−3.14 (m, 1 H), 4.31 (dd, J = 14.05, 5.02 Hz, 1 H), 6.50 (d, J = 14.56 Hz, 2 H), 7.09 (t, J = 9.03 Hz, 2 H), 7.48 (dd, J = 8.53, 5.02 Hz, 2 H), 7.56 (d, J = 8.03 Hz, 2 H), 7.64 (s, 1 H), 7.73 (d, J = 8.03 Hz, 2 H), 8.78 (s, 1 H). HRMS calcd for $C_{21}H_{16}F_4N_2O_2$ (M + H): 405.1217; found 405.1210.

*N-(4-Fluorophenyl)-7-(4-(trifluoromethyl)phenyl)-4,5-dihydrofuro[2,3-c]pyridine-6(7H)-carboxamide (**47**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.53 (dd, J = 13.7, 3.01 Hz, 1 H), 2.63−2.79 (m, 1 H), 2.93−3.09 (m, 1 H), 4.28 (dd, J = 14.31, 4.77 Hz, 1 H), 6.51 (d, J = 11.04 Hz, 2 H), 7.09 (t, J = 8.78 Hz, 2 H), 7.43−7.54 (m, 4 H), 7.67 (s, 1 H), 7.76 (d, J = 8.03 Hz, 2 H), 8.81 (s, 1 H). HRMS calcd for $C_{21}H_{16}F_4N_2O_2$ (M + H): 405.1217; found 405.1234.

*N-(4-Fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxamide (**48**).* ^{1}H NMR (300 MHz, $CDCl_3$): 3.62 (ddd, J = 12.79, 8.92, 3.87 Hz, 1 H), 3.95−4.29 (m, 3 H), 5.89−6.07 (m, 1 H), 6.20 (dd, J = 3.51, 2.78 Hz, 1 H), 6.30 (s, 1 H), 6.41 (s, 1 H), 6.68 (dd, J = 2.63, 1.61 Hz, 1 H), 6.92−7.04 (m, 2 H), 7.17−7.25 (m, 2 H), 7.45−7.54 (m, 2 H), 7.56−7.67 (m, 2 H). HRMS calcd for $C_{21}H_{17}F_4N_3O$ (M + H): 404.1377; found 404.1370.

General Procedure for the Preparation of Amines (24−26). To a stirred solution of 4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**10g**, 0.7 mmol) in dichloroethane (DCE) (5 mL) at room temperature was added 1 equiv of trifluoroacetic acid (TFA) followed by 1 equiv of the corresponding ketone/aldehyde and then 3 equiv of $NaB(OAc)_3H$. The reaction mixture was stirred at room temperature for 3 h and quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, concentrated, and evaporated under reduced pressure vacuum to give the crude compound. Purifications were carried out by chromatography on silica gel eluting with EtOAc/hexanes mixtures.

*5-Isopropyl-4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**24**).* ^{1}H NMR (300 MHz, DMSO-d_6): 0.97 (dd, J = 12.20, 6.65 Hz, 6 H), 2.55−2.75 (m, 2 H), 2.82−2.94 (m, 2 H), 3.10−3.22 (m, 1 H), 4.84 (s, 1 H), 6.25 (d, J = 5.12 Hz, 1 H), 7.13 (d, J = 5.12 Hz, 1 H), 7.58 (dd, J = 8.04, 1.00 Hz, 2 H), 7.68 (d, J = 8.48 Hz, 2 H). HRMS calcd for $C_{17}H_{18}F_3NS$ (M + H): 326.1181; found 326.1180.

*5-Isobutyl-4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**25**).* ^{1}H NMR (300 MHz, DMSO-d_6): 0.74 (dd, J = 9.43, 6.50 Hz, 6 H), 1.73−1.90 (m, 1 H), 1.95−2.08 (m, 1 H), 2.18 (dd, J = 12.28, 5.26 Hz, 1 H), 2.53−2.57 (m, 1 H), 2.79−3.01 (m, 2 H), 3.18 (dt, J = 11.73, 4.51 Hz, 1 H), 4.52 (s, 1 H), 6.28 (d, J = 5.12 Hz, 1 H), 7.18 (d, J = 5.12 Hz, 1 H), 7.51 (d, J = 8.04 Hz, 2 H), 7.68 (d, J = 8.04 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{18}H_{20}F_3NS$ 340.1; found 340.1.

*5-Benzyl-4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine (**26**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.56 (dt, J = 11.40, 4.60 Hz, 1 H), 2.75−2.92 (m, 2 H), 2.96−3.06 (m, 1 H), 3.39 (d, J = 12.30 Hz, 1 H), 3.64 (d, J = 13.74 Hz, 1 H), 4.70 (s, 1 H), 6.33 (d, J = 5.12 Hz, 1 H), 7.20 (d, J = 5.26 Hz, 1 H), 7.22−7.36 (m, 5 H), 7.64 (dd, J = 8.33, 1.00 Hz, 2 H), 7.73 (dd, J = 8.18, 1.00 Hz, 2 H). HRMS calcd for $C_{21}H_{18}F_3NS$ (M + H): 374.1181; found 374.1190.

General Procedure for the Preparation of Amides (27−31). To a solution of 4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**10g**, 100 mg, 0.35 mmol) in CH_2Cl_2 (4 mL) at room temperature were added 1.1 equiv of triethylamine and 1.05 equiv of the corresponding acid chloride. The reaction mixture was stirred at room temperature for 2 h and then concentrated in vacuo. Purifications were carried out by chromatography on silica gel eluting with 50% EtOAc/hexanes.

*2-Methyl-1-(4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)propan-1-one (**27**).* ^{1}H NMR (300 MHz, DMSO-d_6): 1.03 (dd, J = 15.27, 6.65 Hz, 6 H), 2.87−3.05 (m, 3 H), 3.09−3.26 (m, 1 H), 4.13 (d, J = 13.45 Hz, 1 H), 6.77 (s, 1 H), 6.87 (d, J = 5.41 Hz, 1 H), 7.30−7.47 (m, 3 H), 7.71 (d, J = 8.04 Hz, 2 H). HRMS calcd for $C_{18}H_{18}F_3NOS$ (M + H): 354.1130; found 354.1130.

*(2-Fluorophenyl)(4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methanone (**28**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.87−2.96 (m, 1 H), 3.02−3.14 (m, 1 H), 3.20−3.28 (m, 1 H), 4.07 (br s, 1 H), 6.54 (br s, 1 H), 6.85 (d, J = 5.28 Hz, 1 H), 7.43 (d, J = 5.09 Hz, 1 H), 7.46−7.57 (m, 3 H), 7.57−7.64 (m, 1 H), 7.75 (d, J = 8.22 Hz, 2 H), 7.86 (d, J = 7.43 Hz, 2 H). HRMS calcd for $C_{21}H_{15}F_4NOS$ (M + H): 406.0880; found 406.0870.

*(3-Fluorophenyl)(4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methanone (**29**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.80−2.92 (m, 1 H), 2.95−3.08 (m, 1 H), 3.19−3.31 (m, 1 H), 3.66−3.69 (m, 1 H), 6.84 (br s, 1 H), 6.91 (d, J = 5.28 Hz, 1 H), 7.25 (d, J = 7.04 Hz, 1 H), 7.30−7.38 (m, 2 H), 7.41−7.59 (m, 4 H), 7.75 (d, J = 8.02 Hz, 2 H). HRMS calcd for $C_{21}H_{15}F_4NOS$ (M + H): 406.0880; found 406.0870.

*(4-Fluorophenyl)(4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methanone (**30**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.82−2.94 (m, 1 H), 2.95−3.09 (m, 1 H), 3.18 − 3.33 (m, 1 H), 3.67 (br s, 1 H), 6.84 (br s, 1 H), 6.90 (d, J = 5.09 Hz, 1 H), 7.29 (t, J = 8.90 Hz, 2 H), 7.42−7.58 (m, 5 H), 7.75 (d, J = 8.22 Hz, 2 H). HRMS calcd for $C_{21}H_{15}F_4NOS$ (M + H): 406.0880; found 406.0890.

*2-(4-Fluorophenyl)-1-(4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanone (**31**).* ^{1}H NMR (300 MHz, DMSO-d_6): 2.76−2.94 (m, 2 H), 3.08−3.22 (m, 1 H), 3.32 (s, 3 H), 4.13 (dd, J = 13.88, 3.65 Hz, 1 H), 6.76 (s, 1 H), 6.85 (d, J = 5.26 Hz, 1 H), 7.06−7.16 (m, 2 H), 7.22−7.31 (m, 2 H), 7.34−7.45 (m, 3 H), 7.70 (d, J = 8.18 Hz, 2 H). HRMS calcd for $C_{22}H_{17}F_4NOS$ (M + H): 420.1036; found 420.1030.

*5-Bromo-N-methoxy-N-methylthiazole-4-carboxamide (**50**).* To a 100 mL round-bottomed flask were added 5-bromothiazole-4-carboxylic acid (**49**; 0.98 g, 4.7 mmol), CH_2Cl_2 (20 mL), and *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (11.08 g, 5.6 mmol). The reaction mixture was stirred at room temperature for 20 min. To this mixture, *N*,*O*-dimethylhydroxylamine hydrochloride (0.55 g, 5.6 mmol) and *N*,*N*-diisopropylethylamine (0.98 mL, 5.6 mmol) were added. The reaction mixture was stirred at room temperature for 16 h, diluted with water (40 mL), and extracted with EtOAc (50 mL). The organic extract was washed with water (20 mL) and saturated aqueous NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography eluting with 50% EtOAc/hexanes to give the title compound (0.68 g, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.37 (s, 3 H), 3.73 (s, 3 H), 8.76 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_6H_7BrN_2O_2S$ 250.9; found 250.9.

*5-Bromothiazole-4-carbaldehyde (**51**).* To a 100 mL round-bottomed flask were added 5-bromo-*N*-methoxy-*N*-methylthiazole-4-carboxamide (**50**, 0.63 g, 2.5 mmol) and THF (10 mL). The reaction mixture was cooled to −78 °C, and diisobutylaluminum hydride (2.7 mL, 2.7 mmol, 1 M in THF) was added. The reaction mixture was stirred at −78 °C for 1 h and then quenched by the addition of MeOH (1 mL). The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (10 mL), saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give the title compound (0.42 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.85 (s, 1 H), 10.12 (s, 1 H). MS (ESI pos. ion) m/z: calcd for C_4H_2BrNOS 192.9; found 192.9.

*(5-Bromothiazol-4-yl)(4-(trifluoromethyl)phenyl)methanol (**52**).* To a suspension of magnesium turnings (0.11 g, 4.4 mmol) in THF (10 mL) was added 1-bromo-4-(trifluoromethyl)benzene (0.62 mL, 4.4 mmol). The reaction mixture was stirred at 60 °C for 2 h and cooled to 0 °C. To this solution, 5-bromothiazole-4-carbaldehyde (**51**, 0.42 g, 2.2 mmol) in THF (10 mL) was added dropwise. After the addition was completed, the reaction mixture was stirred at 0 °C for 30 min, then the reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (40 mL). The organic extract was washed with water and saturated aqueous NaCl,

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dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 40% EtOAc/hexanes to give the title compound (0.51 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.28 (d, J = 7.75 Hz, 1 H), 6.03 (d, J = 7.75 Hz, 1 H), 7.50−7.70 (m, 4 H), 8.78 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{11}H_7BrF_3NOS$ 338.9; found 338.9.

*(E)-2-(2-(4-(Hydroxy(4-(trifluoromethyl)phenyl)methyl)thiazol-5-yl)vinyl)isoindoline-1,3-dione (**53**).* To a 50 mL round-bottomed flask were added (5-bromothiazol-4-yl)(4-(trifluoromethyl)phenyl)-methanol (**52**, 0.25 g, 0.75 mmol), *N*-vinylphthalimide (0.14 g, 0.82 mmol), acetato(2′-di-*t*-butylphosphino-1,1′-biphenyl-2-yl)palladium-(II) (35 mg, 75 μmol), triethylamine (0.10 mL, 0.75 mmol), and DMF (2 mL). The reaction mixture was stirred at 80 °C for 24 h and cooled to room temperature. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with water and saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with 40% EtOAc/hexanes to give the title compound (56 mg, 17%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.19 (d, J = 4.24 Hz, 1 H), 3.55 (d, J = 7.02 Hz, 1 H), 6.00−6.16 (m, 2 H), 7.14 (dd, J = 1.97, 0.80 Hz, 1 H), 7.20 (d, J = 1 4.76 Hz, 1 H), 7.52−7.68 (m, 6 H), 7.79 (dd, J = 5.48, 3.14 Hz, 2 H), 7.89−7.96 (m, 2 H), 8.63 (s, 1 H), 8.80 (d, J = 1.90 Hz, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{21}H_{13}F_3N_2O_3S$ 431.1; found 431.0.

*2-(2-(4-(Hydroxy(4-(trifluoromethyl)phenyl)methyl)thiazol-5-yl)-ethyl)isoindoline-1,3-dione (**54**).* To a 50 mL round-bottomed flask were added (*E*)-2-(2-(4-(hydroxy(4-(trifluoromethyl)phenyl)methyl)-thiazol-5-yl)vinyl)isoindoline-1,3-dione (**53**, 0.12 g, 0.27 mmol), 10% palladium on carbon (2.9 mg, 27 μmol), and MeOH (2 mL). The reaction mixture was hydrogenated under 1 atm of hydrogen for 6 days. The solution was filtered to remove the catalyst through a pad of Celite, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography, eluting with 50% EtOAc/hexanes to give the title compound (28 mg, 24%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.29 (t, J = 7.09 Hz, 2 H), 3.49 (d, J = 6.87 Hz, 1 H), 3.88−4.00 (m, 2 H), 6.01 (d, J = 6.72 Hz, 1 H), 7.52 (s, 4 H), 7.55−7.66 (m, 1 H), 7.67−7.76 (m, 2 H), 7.76−7.87 (m, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{21}H_{15}F_3N_2O_3S$ 433.1; found 433.0.

*2-(2-(4-(4-(Trifluoromethyl)benzoyl)thiazol-5-yl)ethyl)isoindoline-1,3-dione (**55**).* To a 50 mL round-bottomed flask were added 2-(2-(4-(hydroxy(4-(trifluoromethyl)phenyl)methyl)thiazol-5-yl)ethyl)-isoindoline-1,3-dione (**54**, 26 mg, 60 μmol), CH_2Cl_2 (2 mL), and manganese(IV) oxide (104 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 4 h. The solid was removed by filtration, washed with EtOAc, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography, eluting with 30% EtOAc/hexanes to give the title compound (22 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.71 (t, J = 6.43 Hz, 2 H), 4.11 (t, J = 6.43 Hz, 2 H), 7.60−7.71 (m, 4 H), 7.72−7.83 (m, 2 H), 8.06 (d, J = 8.04 Hz, 2 H), 8.64 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{21}H_{13}F_3N_2O_3S$ 431.1; found 431.0.

*4-(4-(Trifluoromethyl)phenyl)-6,7-dihydrothiazolo[4,5-c]pyridine (**56**).* To a 50 mL round-bottomed flask were added 2-(2-(4-(4-(trifluoromethyl)benzoyl)thiazol-5-yl)ethyl)isoindoline-1,3-dione (**55**, 22 mg, 51 μmol), EtOH (1 mL), and anhydrous hydrazine (8 μL, 0.26 mmol). The reaction mixture was stirred at room temperature for 3 days, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography, eluting with 80% EtOAc/hexanes to give the title compound (6 mg, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 3.03−3.19 (m, 2 H), 3.99−4.15 (m, 2 H), 7.70 (d, J = 8.18 Hz, 2 H), 8.11 (d, J = 8.18 Hz, 2 H), 8.68 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{13}H_9F_3N_2S$ 283.0; found 283.0.

*4-(4-(Trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothiazolo[4,5-c]-pyridine (**57**).* To a 50 mL round-bottomed flask were added 4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothiazolo[4,5-*c*]pyridine (**56**, 6 mg, 21 μmol), MeOH (1 mL), and $NaBH_4$ (1 mg, 21 μmol). The reaction mixture was stirred at room temperature for 30 min, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography, eluting with 10% MeOH/EtOAc to give the title compound (5 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): 2.85−3.36 (m, 4 H), 5.27 (s, 1 H), 7.44 (d, J = 8.33 Hz, 2 H), 7.59 (d, J = 8.18 Hz, 2 H), 8.60 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{13}H_{11}F_3N_2S$ 285.0; found 285.0.

*N-(4-Fluorophenyl)-4-(4-(trifluoromethyl)phenyl)-6,7-dihydrothiazolo[4,5-c]pyridine-5(4H)-carboxamide (**58**).* To a 25 mL round-bottomed flask were added 4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrothiazolo[4,5-*c*]pyridine (**57**, 5 mg, 18 μmol), CH_2Cl_2 (1 mL), and 4-fluorophenyl isocyanate (2 mg, 18 μmol). The solution was stirred at room temperature for 1 h, and the solvent was removed in vacuo. The residue was purified by silica gel chromatography, eluting with 40% EtOAc/hexanes to give the title compound (5 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): 2.92−3.06 (m, 1 H), 3.08−3.24 (m, 1 H), 3.28−3.44 (m, 1 H), 4.36 (dd, J = 13.88, 4.68 Hz, 1 H), 6.36 (s, 1 H), 6.53 (s, 1 H), 6.93−7.07 (m, 2 H), 7.19−7.36 (m, 2 H), 7.52−7.70 (m, 4 H), 8.73 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{20}H_{15}F_4N_3OS$ 422.0942; found 422.0951.

*4-(4-(Trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine (**60**).* To a 100 mL round-bottomed flask were added histamine dihydrochloride (**59**, 0.19 g, 1.03 mmol), potassium hydroxide (0.18 g, 3.2 mmol), and water (1 mL). The reaction mixture was treated with 4-(trifluoromethyl)benzaldehyde (0.14 mL, 1.03 mmol) in EtOH (2.5 mL) followed by the addition of water (12.5 mL). The reaction mixture was heated at 100 °C for 4 h. The mixture was allowed to cool to room temperature, and the resulting precipitate was collected by filtration. The crude product was dissolved into $MeOH/H_2O$ and filtered. The filtrate was concentrated in vacuo to give the title compound as a white solid (94 mg, 34%). ^{1}H NMR (300 MHz, CD_3OD): 2.59−2.88 (m, 2 H), 3.02 (ddd, J = 12.61, 7.20, 5.19 Hz, 1 H), 3.08−3.23 (m, 1 H), 5.07 (s, 1 H), 7.38−7.55 (m, 3 H), 7.56−7.68 (m, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{13}H_{12}F_3N_3$ 268.1; found 268.0.

*N-(4-Fluorophenyl)-4-(4-(trifluoromethyl)phenyl)-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxamide (**61**).* To a 5 mL microwave vial, 4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (**60**, 94 mg, 0.35 mmol), 4-fluorophenyl isocyanate (0.040 mL, 0.36 mmol), and CH_2Cl_2 (3 mL) were added. The reaction mixture was stirred at room temperature for 30 min. The resulting precipitate was collected via filtration and washed with CH_2Cl_2 to yield the title compound as a white solid (87 mg, 61%). ^{1}H NMR (300 MHz, DMSO-d_6): 2.54−2.66 (m, 1 H), 2.70−3.10 (m, 2 H), 4.29−4.44 (m, 1 H), 6.40 (s, 1 H), 7.08 (t, J = 8.92 Hz, 2 H), 7.41−7.55 (m, 2 H), 7.58−7.80 (m, 5 H), 8.78 (s, 1 H), 12.02 (br s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{20}H_{16}F_4N_4O$ 405.1; found 405.0.

*tert-Butyl 4-(4-(Trifluoromethyl)phenyl)-6,7-dihydro-1H-imidazo-[4,5-c]pyridine-5(4H)-carboxylate (**62**).* To a 100 mL round-bottomed flask, 4-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine (**60**, 0.58 g, 2.2 mmol), di-*tert*-butyl dicarbonate (0.54 g, 2.5 mmol), $NaHCO_3$ (0.28 g, 3.2 mmol), and MeOH (10 mL) were added. The mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was dissolved in EtOAc (20 mL). The organic phase was washed with water (20 mL) and saturated aqueous NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (iPrOH (w/10% NH_4OH) in $CHCl_3$ 0−10%) to afford the title compound as a pale-yellow solid (0.59 g, 74%). ^{1}H NMR (300 MHz, DMSO-d_6): 1.43 (s, 9 H), 2.54−2.80 (m, 2 H), 2.84−2.99 (m, 1 H), 4.34 (d, J = 4.09 Hz, 1 H), 6.03 (br s, 1 H), 7.52−7.60 (m, 3 H), 7.71 (d, J = 8.18 Hz, 2 H), 12.02 (br s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{18}H_{20}F_3N_3O_2$ 368.2; found 368.0.

*N-(4-Fluorophenyl)-1-methyl-4-(4-(trifluoromethyl)phenyl)-6,7-dihydro-1H-imidazo[4,5-c]pyridine-5(4H)-carboxamide (**63**).* To a 5 mL microwave vial were added iodomethane (0.18 mL, 2.91 mmol), $NaHCO_3$ (0.16 g, 1.95 mmol), *tert*-butyl 4-(4-(trifluoromethyl)-phenyl)-6,7-dihydro-1*H*-imidazo[4,5-*c*]pyridine-5(4*H*)-carboxylate (**62**, 0.36 g, 0.97 mmol), and DMF (4 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was partitioned between water (20 mL) and EtOAc (20 mL). The organic phase was taken and washed with saturated aqueous $NaHCO_3$ (2 × 20 mL). The

organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was taken into CH_2Cl_2 (5 mL), and TFA (2 mL) was added. The yellow solution was stirred at room temperature for 2 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (30 mL) and CH_2Cl_2 (50 mL). The aqueous phase was taken and extracted with CH_2Cl_2 (20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL), and 4-fluorophenyl isocyanate (0.05 mL, 0.13 mmol) was added. The resulting yellow solution was stirred at room temperature for 3 h. The reaction mixture was directly purified by silica gel chromatography (eluent iPrOH (w/ 10% NH_4OH) in $CHCl_3$ 0−10%) to afford the title compound as a white solid (19 mg, 5%). ^{1}H NMR (300 MHz, DMSO-d_6) 2.59 (dd, J = 15.35, 3.22 Hz, 1 H) 2.68−3.05 (m, 2 H) 3.56 (s, 3 H) 4.32−4.51 (m, 1 H) 6.38 (s, 1 H) 7.02−7.14 (m, 2 H) 7.43−7.55 (m, 2 H) 7.57−7.76 (m, 5 H) 8.80 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{21}H_{18}F_4N_4O$ 419.1486; found 419.1490.

*N-Phenethyl-4-(trifluoromethyl)benzamide (**65a**).* To a solution of phenethylamine (**64a**, 14.6 mL, 0.12 mol) and *N*-ethyl-*N*-isopropylpropan-2-amine (20.1 mL, 0.12 mol) in CH_2Cl_2 (500 mL) at 0 °C was added 4-(trifluoromethyl)benzoyl chloride (17.2 mL, 0.12 mol) dropwise. The reaction was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with water, and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, and the solvent was eliminated under vacuum to give the title compound as an off-white solid (31.8 g, 94%). ^{1}H NMR (400 MHz, CD_3OD): 2.94 (t, J = 7.34 Hz, 2 H), 3.63 (t, J = 7.34 Hz, 2 H), 7.15−7.35 (m, 5 H), 7.76 (d, J = 8.22 Hz, 2 H), 7.93 (d, J = 8.22 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{16}H_{14}F_3NO$ 294.1; found 294.1.

*1-(4-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**67a**).* To a round-bottomed flask were added *N*-phenethyl-4-(trifluoromethyl)benzamide (**65a**, 5.0 g, 17.0 mmol), phosphorus(V) oxide (1.21 g, 8.5 mmol), and polyphosphoric acid (60 g). The reaction mixture was heated at 165 °C for 2 h and allowed to cool to room temperature. The reaction mixture was carefully poured into an ice-cold solution of 20% KOH, adjusting the pH to 7. The reaction mixture was extracted with EtOAc (2×), the combined organic extracts were dried over Na_2SO_4, and the solvent was eliminated under vacuum to give **66a**, which was used without further purification. To a crude solution of 1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline (**66a**, 4.69 g, 17.0 mmol) in MeOH (25 mL) at 0 °C was added $NaBH_4$ (1.93 g, 51.1 mmol). The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 2 h. The solvent was removed under vacuum, and the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc (2×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude material. Purification by silica gel chromatography with 20−100% EtOAc/hexanes as eluent provided the title compound as a white solid (1.99 g, 42%). ^{1}H NMR (400 MHz, CD_3OD): 2.84−2.95 (m, 1 H), 2.99−3.10 (m, 2 H), 3.16−3.25 (m, 1 H), 5.19 (s, 1 H), 6.69 (d, J = 7.82 Hz, 1 H), 7.05 (dd, J = 8.02, 2.15 Hz, 1 H), 7.13−7.23 (m, 2 H), 7.44 (d, J = 8.22 Hz, 2 H), 7.64 (d, J = 8.02 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{16}H_{14}F_3N$ 278.1; found 278.1

Compounds **67b−e** were prepared in an analogous manner to that described for **67a**.

*5-Fluoro-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**67b**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.66−2.82 (m, 2 H), 2.85−2.97 (m, 1 H), 3.00−3.11 (m, 2 H), 5.11 (s, 1 H), 6.49 (d, J = 7.63 Hz, 1 H), 6.99 (t, J = 9.00 Hz, 1 H), 7.04−7.12 (m, 1 H), 7.49 (d, J = 8.22 Hz, 2 H), 7.68 (d, J = 8.22 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{16}H_{13}F_4N$ 296.1; found 296.1

*6-Fluoro-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**67c**).* ^{1}H NMR (400 MHz, CD_3OD): 2.82−2.94 (m, 1 H), 2.96−3.11 (m, 2 H), 3.13−3.23 (m, 1 H), 5.16 (s, 1 H), 6.70 (dd, J = 8.51, 5.77 Hz, 1 H), 6.80 (dt, J = 8.40, 2.70 Hz, 1 H), 6.94 (dd, J = 9.59, 0.39 Hz, 1 H), 7.44 (d, J = 8.02 Hz, 2 H), 7.65 (d, J = 8.02 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{16}H_{13}F_4N$ 296.1; found 296.1

*7-Fluoro-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**67d**).* MS (ESI pos. ion) m/z: calcd for $C_{16}H_{13}F_4N$ 296.1; found 296.1

*1-(4-(Trifluoromethyl)phenyl)-2,3,4,5-tetrahydro-1H-benzo[c]-azepine (**67e**).* MS (ESI pos. ion) m/z: calcd for $C_{17}H_{16}F_3N$ 292.1; found 292.1

General Procedure for the Preparation of *N*-(4-Fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinolines (68−72). To a solution of the tetrahydroisoquinoline/benzoazepine, **67a−e** (1.9 mmol) in CH_2Cl_2 (4 mL) at room temperature was added 1 equiv of 4-fluorophenyl isocyanate. The reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo. Purification was carried out by chromatography on silica gel to give compounds **68−72**.

*N-(4-Fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide (**68**).* ^{1}H NMR (400 MHz, CD_3OD): 2.82 (dt, J = 16.24, 5.58 Hz, 1 H), 2.96−3.10 (m, 1 H), 3.60 (ddd, J = 12.96, 8.17, 5.09 Hz, 1 H), 3.88 (dt, J = 12.62, 6.02 Hz, 1 H), 6.64 (s, 1 H), 6.93−7.07 (m, 2 H), 7.19−7.33 (m, 4 H), 7.35−7.48 (m, 4 H), 7.61 (d, J = 8.22 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{23}H_{18}F_4N_2O$ 415.1424; found 415.1420.

The mixture was resolved using chiral SFC (OJH column, 21 × 250 mm^2, 5 μM) using 70% supercritical CO_2/30% iPrOH (0.2% diethylamine) at a flow rate of 65 mL/min) to give two products with enantiomeric excesses greater than 99%.

*(R)-N-(4-Fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide (**87**).* First eluting peak. ^{1}H NMR (400 MHz, CD_3OD): 2.82 (dt, J = 16.04, 5.58 Hz, 1 H), 2.94−3.09 (m, 1 H), 3.60 (ddd, J = 12.91, 8.12, 5.18 Hz, 1 H), 3.81−3.93 (m, 1 H), 6.64 (s, 1 H), 6.96−7.07 (m, 2 H), 7.20−7.32 (m, 4 H), 7.34−7.47 (m, 4 H), 7.61 (d, J = 8.22 Hz, 2 H). Anal. ($C_{23}H_{18}F_4N_2O$): C, H, N.

*(S)-N-(4-Fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide (**88**).* Second eluting peak. ^{1}H NMR (400 MHz, CD_3OD): 2.82 (dt, J = 16.19, 5.60 Hz, 1 H), 3.03 (ddd, J = 16.09, 8.17, 5.67 Hz, 1 H), 3.60 (ddd, J = 13.01, 8.12, 5.09 Hz, 1 H), 3.88 (dt, J = 12.47, 5.99 Hz, 1 H), 6.64 (s, 1 H), 6.96−7.08 (m, 2 H), 7.20−7.33 (m, 4 H), 7.36−7.46 (m, 4 H), 7.61 (d, J = 8.41 Hz, 2 H). Anal. ($C_{23}H_{18}F_4N_2O$): C, H, N.

*5-Fluoro-N-(4-fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide (**69**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.74−2.86 (m, 1 H), 2.88−3.01 (m, 1 H), 3.23−3.40 (m, 1 H), 3.95−4.13 (m, 1 H), 6.66 (s, 1 H), 7.02−7.20 (m, 4 H), 7.25−7.36 (m, 1 H), 7.39−7.52 (m, 4 H), 7.71 (d, J = 8.53 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{23}H_{17}F_5N_2O$ 433.1330; found 433.1320.

*6-Fluoro-N-(4-fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide (**70**).* ^{1}H NMR (400 MHz, CD_3OD): 2.83 (dt, J = 16.38, 5.40 Hz, 1 H), 2.98−3.10 (m, 1 H), 3.55 (ddd, J = 13.20, 8.41, 4.99 Hz, 1 H), 3.84−3.95 (m, 1 H), 6.65 (s, 1 H), 6.96−7.09 (m, 4 H), 7.26 (dd, J = 8.31, 5.58 Hz, 1 H), 7.34−7.47 (m, 4 H), 7.62 (d, J = 8.22 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{23}H_{17}F_5N_2O$ 433.1330; found 433.1340.

*7-Fluoro-N-(4-fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide (**71**).* ^{1}H NMR (400 MHz, DMSO-d_6): 2.70−2.82 (m, 1 H), 2.89−3.01 (m, 1 H), 3.45 (ddd, J = 13.16, 8.46, 4.99 Hz, 1 H), 3.86−3.96 (m, 1 H), 6.65 (s, 1 H), 7.05−7.16 (m, 3 H), 7.20 (dd, J = 9.59, 2.54 Hz, 1 H), 7.33 (dd, J = 8.41, 5.87 Hz, 1 H), 7.43 (d, J = 8.22 Hz, 2 H), 7.46−7.54 (m, 2 H), 7.70 (d, J = 8.22 Hz, 2 H), 8.68 (s, 1 H). MS (ESI pos. ion) m/z: calcd for $C_{23}H_{17}F_5N_2O$ 433.1330; found 433.1320.

*N-(4-Fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-benzo[c]azepine-2(3H)-carboxamide (**72**).* ^{1}H NMR (400 MHz, CD_3OD): 1.71−1.82 (m, 1 H), 1.83−1.96 (m, 1 H), 2.80−2.88 (m, 2 H), 3.21−3.29 (m, 1 H), 4.04 (dt, J = 15.36, 3.77 Hz, 1 H), 6.78 (s, 1 H), 6.96−7.02 (m, 2 H), 7.12 (d, J = 7.43 Hz, 1 H), 7.22 (td, J = 6.75, 2.74 Hz, 1 H), 7.26−7.35 (m, 5 H), 7.37−7.42 (m, 1 H), 7.68 (d, J = 8.22 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{24}H_{20}F_4N_2O$ 429.1580; found 429.1605.

*2-Benzyl-8-fluoro-1-(4-(trifluoromethyl)phenyl)-1,2-dihydroisoquinoline (**75**).* To a 25 mL round-bottomed flask were added 8-

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fluoroisoquinoline (**73**, 0.40 g, 2.7 mmol), CH_3CN (5 mL), and benzyl bromide (0.37 mL, 3.0 mmol). The reaction mixture was heated at reflux for 3 h and cooled to room temperature, and the solvent was removed under vacuum to give 2-benzyl-8-fluoroisoquinolinium bromide (**74**) as a yellow solid that was used without further purification. To a 100 mL round-bottomed flask were added magnesium turnings (0.28 g, 11 mmol), THF (10 mL), and a crystal of iodine. The reaction mixture was placed under an argon atmosphere, and 4-bromobenzotrifluoride (1.16 mL, 8.3 mmol) was added. The reaction mixture was stirred at room temperature for 3 h during which (4-(trifluoromethyl)phenyl)magnesium bromide was formed. A separate 100 mL round-bottomed flask was charged with 2-benzyl-8-fluoroisoquinolinium bromide (**74**, 0.87 g, 2.7 mmol) and THF (15 mL). The solution was cooled to 0 °C. To this flask was added (4-(trifluoromethyl)phenyl)magnesium bromide over a period of 5 min, and the solution was allowed to stir at 0 °C for 1 h and at room temperature for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (35 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with water and saturated aqueous NaCl and dried over Na_2SO_4, and the solvent was removed under vacuum. The title compound was obtained as brown oil and used without further purification. MS (ESI pos. ion) *m*/*z*: calcd for $C_{23}H_{17}F_4N$ 384.2; found 384.1.

*2-Benzyl-8-fluoro-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**76**).* To a 250 mL round-bottomed flask were added 2-benzyl-8-fluoro-1-(4-(trifluoromethyl)phenyl)-1,2-dihydroisoquinoline (**75**, 1.2 g, 3.1 mmol), THF (20 mL), and $NaBH_4$ (0.32 g, 8.4 mmol) at room temperature. After 20 min, acetic acid (3.3 mL) was added, and the reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was concentrated and dissolved in EtOAc (150 mL), and water (25 mL) was added. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated to yield the crude product. Purification by flash silica gel chromatography (eluent EtOAc/hexanes gradient) gave the title compound as a colorless oil (0.78 g, 65%). ^{1}H NMR (400 MHz, DMSO-d_6): 2.61 (dt, *J* = 12.55, 5.27 Hz, 1 H), 2.72−2.87 (m, 2 H), 2.89−3.02 (m, 1 H), 3.55 (d, *J* = 13.55 Hz, 1 H), 3.72 (d, *J* = 13.55 Hz, 1 H), 5.06 (s, 1 H), 6.89−6.98 (m, 1 H), 7.11 (d, *J* = 7.53 Hz, 1 H), 7.21−7.42 (m, 8 H), 7.68 (d, *J* = 8.03 Hz, 2 H). MS (ESI pos. ion) *m*/*z*: calcd for $C_{23}H_{19}F_4N$ 386.2; found 386.1.

*8-Fluoro-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**77**).* To a 25 mL reaction vial were added 2-benzyl-8-fluoro-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**76**, 0.20 g, 0.52 mmol), palladium hydroxide and carbon (20%, 0.14 g, 0.19 mmol), and EtOH (10 mL). The reaction mixture was stirred at room temperature under a 50 psi hydrogen atmosphere for 3 h. The catalyst was removed by filtration through a Celite pad, and the solvent was eliminated under vacuum. The crude product was purified by prep-HPLC using a gradient of CH_3CN/water (0.1% TFA) and a PHENOMENEX Gemini Axia-5 C-18 column (100 × 21.2 mm^2). The solvent was removed under vacuum, and the resulting product was dissolved in MeOH (5 mL) and neutralized by passing the solution through a Polymer Lab-HCO_3 macroporous resin cartridge. The filtrate was concentrated under vacuum to give the title compound as a colorless oil (0.13 g, 86%). ^{1}H NMR (400 MHz, DMSO-d_6): 2.82−2.95 (m, 3 H), 2.96−3.03 (m, 1 H), 5.53 (s, 1 H), 6.99 (t, *J* = 9.10 Hz, 1 H), 7.13 (d, *J* = 7.63 Hz, 1 H), 7.28−7.36 (m, 1 H), 7.40 (d, *J* = 8.02 Hz, 2 H), 7.72 (d, *J* = 8.22 Hz, 2 H). MS (ESI pos. ion) *m*/*z*: calcd for $C_{16}H_{13}F_4N$ 296.1; found 296.1.

*8-Fluoro-N-(4-fluorophenyl)-1-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxamide (**78**).* To a 25 mL round-bottomed flask were added 8-fluoro-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**77**, 0.41 g, 1.4 mmol), DCE (10 mL), and 4-fluorophenyl isocyanate (0.18 mL, 1.6 mmol). The reaction was stirred at room temperature for 16 h, and the solvent was eliminated under vacuum. The product was purified by prep-HPLC using a gradient of CH_3CN/water (0.1% TFA) and a PHENOMENEX Gemini Axia-5 C-18 column (100 × 21.2 mm^2). The solvent was removed under vacuum, and the resulting product was dissolved in MeOH (5 mL) and neutralized by passing the solution through a Polymer Lab-HCO_3 macroporous resin cartridge. The filtrate was concentrated under vacuum to give the title compound as a white film (0.42 g, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) 2.79−2.89 (m, 1 H) 2.96−3.09 (m, 1 H) 3.20−3.26 (m, 1 H) 4.00−4.06 (m, 1 H) 6.82 (s, 1 H) 7.11 (q, *J* = 8.80 Hz, 3 H) 7.18 (d, *J* = 7.63 Hz, 1 H) 7.35 − 7.42 (m, 3 H) 7.50 (dd, *J* = 9.00, 5.09 Hz, 2 H) 7.72 (d, *J* = 8.22 Hz, 2 H) 8.81 (s, 1 H). MS (ESI pos. ion) *m*/*z*: calcd for $C_{23}H_{17}F_5N_2O$ 433.1330; found 433.1358.

*3-(4-(Trifluoromethyl)phenyl)isoindolin-1-one (**80**).* To a solution of phthalimide (**79**, 22.4 g, 16.3 mmol) in THF (20 mL) under N_2 atmosphere at 0 °C was added a solution of (4-(trifluoromethyl)-phenyl)magnesium bromide in THF (1M, 60 mL), followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (2 mL). The reaction mixture was stirred at 0 °C for 2 h and quenched by the addition of an aqueous solution of sodium phosphate. The resulting mixture was diluted with EtOAc and stirred at room temperature for 15 min. The organic layer was separated, washed with water and saturated aqueous NaCl, and dried over Na_2SO_4. Evaporation of the solvent under vacuum gave 3-hydroxy-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (5.1 g) as an orange solid that was used without further purification. To a solution of 3-hydroxy-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (3.0 g, 10.2 mmol) in CH_2Cl_2 (60 mL) was added TFA (5.3 mL, 71.6 mmol), and the reaction mixture was stirred at room temperature for 5 min. Triethylsilane (3.3 mL, 20.5 mmol) was added, and the solution was stirred at room temperature for 16 h. The reaction was quenched by the addition of water (50 mL), and CH_2Cl_2 (20 mL) was added. The mixture was stirred at room temperature for 5 min, the organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic extracts were dried over $MgSO_4$ and partially concentrated in vacuo. A white precipitate was obtained, filtered, and dried in vacuo to give the title compound as a white solid (1.15 g, 53%). ^{1}H NMR (400 MHz, CD_3OD): 5.85 (s, 1 H), 7.35 (d, *J* = 7.83 Hz, 1 H), 7.52 (d, *J* = 8.41 Hz, 2 H), 7.56 (d, *J* = 7.04 Hz, 1 H), 7.60 (dt, *J* = 6.30, 1.40 Hz, 1 H), 7.70 (d, *J* = 8.22 Hz, 2 H), 7.86 (d, *J* = 7.24 Hz, 1 H). MS (ESI pos. ion) *m*/*z*: calcd for $C_{15}H_{10}F_3NO$ 278.1; found 278.1.

*1-(4-(Trifluoromethyl)phenyl)isoindoline (**81**).* To a solution of 3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (**80**, 0.50 g, 1.80 mmol) in THF (7 mL) was added lithium aluminum hydride (1 M in THF, 5.41 mL, 5.41 mmol). The reaction mixture was heated at 75 °C for 2 h. The mixture was allowed to cool to room temperature, and the reaction was quenched by the addition of $Na_2SO_4 \cdot H_2O$ until no bubbling was observed. The mixture was stirred at room temperature overnight and filtered, and the solid was washed with EtOAc. The combined filtrates were concentrated, and the residue was purified first by silica gel column chromatography (0−20% MeOH in CH_2Cl_2), then by prep HPLC (0−100% CH_3CN/water, 0.1% TFA). The CH_3CN was removed in vacuo, saturated aqueous $NaHCO_3$ (15 mL) was added, and the solution was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, concentrated, and dried under vacuum to give the title compound as a white solid (63 mg, 13%). ^{1}H NMR (400 MHz, CD_3OD): 4.30 (d, *J* = 15.06 Hz, 1 H), 4.42 (d, *J* = 14.28 Hz, 1 H), 5.53 (s, 1 H), 7.00 (d, *J* = 7.63 Hz, 1 H), 7.19−7.34 (m, 2 H), 7.39 (d, *J* = 7.63 Hz, 1 H), 7.50 (d, *J* = 8.22 Hz, 2 H), 7.66 (d, *J* = 8.02 Hz, 2 H). MS (ESI pos. ion) *m*/*z*: calcd for $C_{15}H_{12}F_3N$ 264.1; found 264.1.

*N-(4-Fluorophenyl)-1-(4-(trifluoromethyl)phenyl)isoindoline-2-carboxamide (**82**).* To a solution of 1-(4-(trifluoromethyl)phenyl)-isoindoline (**81**, 58 mg, 0.22 mmol) and diisopropylethylamine (38 μL, 0.22 mmol) in CH_2Cl_2 (1 mL) was added 4-fluorophenyl isocyanate (25 μL, 0.22 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (2 mL) and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude material. The product was purified by prep-HPLC (0−100% CH_3CN/water, 0.1% TFA). The solvents were removed, and a saturated aqueous solution of $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried over $MgSO_4$, concentrated, and dried under vacuum to give the title compound as a white solid (36 mg, 41%). ^{1}H

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NMR (400 MHz, CD_3OD): 5.01 (d, J = 13.89 Hz, 1 H), 5.18 (dd, J = 13.79, 2.45 Hz, 1 H), 6.30 (d, J = 2.15 Hz, 1 H), 6.94−7.03 (m, 2 H), 7.12 (d, J = 7.63 Hz, 1 H), 7.28 (t, J = 7.43 Hz, 1 H), 7.31−7.39 (m, 3 H), 7.44 (d, J = 7.43 Hz, 1 H), 7.54 (d, J = 8.22 Hz, 2 H), 7.64 (d, J = 8.22 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{22}H_{16}F_4N_2O$ 401.1; found 401.1.

*tert-Butyl 5-Oxo-5-(4-(trifluoromethyl)phenyl)pentylcarbamate (**84**).* To a solution of *tert*-butyl 2-oxopiperidine-1-carboxylate (**83**, 2.11 g, 10.6 mmol) in THF (20 mL) under N_2 atmosphere at −78 °C was added a solution of (4-(trifluoromethyl)phenyl)magnesium bromide in THF (1 M, 11.7 mL). The reaction mixture was stirred at −78 °C for 30 min, allowed to warm to room temperature, and stirred at room temperature for an additional hour. The reaction mixture was quenched by the addition of a 10% aqueous solution of HCl, and the resulting mixture was extracted with CH_2Cl_2 (2×). The combined organic extracts were dried over Na_2SO_4, and the solvent was eliminated under vacuum. The crude product was purified by silica gel column chromatography (eluent EtOAc/hexanes 20%) to afford the title compound as an off-white solid (2.41 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.44 (s, 9 H), 1.53−1.64 (m, 4 H), 1.70−1.89 (m, 2 H), 3.03 (t, J = 7.24 Hz, 2 H), 3.17 (q, J = 6.46 Hz, 2 H), 4.59 (br s, 1 H), 7.73 (d, J = 8.22 Hz, 2 H), 8.06 (d, J = 8.22 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{17}H_{22}F_3NO_3$ 345.1; found 246.1.

*2-(4-(Trifluoromethyl)phenyl)piperidine (**85**).* *tert*-Butyl 5-oxo-5-(4-(trifluoromethyl)phenyl)pentylcarbamate (**84**, 2.31 g, 6.7 mmol) was dissolved in TFA (15 mL), and the reaction mixture was stirred at room temperature for 4 h. To the reaction mixture was added 50% NaOH until the pH was 12−13, and then the mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over Na_2SO_4, and the solvent was eliminated under vacuum. The residue obtained was dissolved in a 4:1 MeOH/H_2O mixture (10 mL), and $NaBH_4$ (0.31 g, 8.0 mmol) was added. The reaction mixture was stirred at room temperature overnight. The mixture was acidified with 10% HCl and stirred at room temperature for 30 min. To the reaction mixture was added 5 N NaOH until the pH was 12−13, and the solution was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over Na_2SO_4, and the solvent was eliminated under vacuum to give the title compound as a yellow solid (1.44 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.39−1.60 (m, 3 H), 1.65−1.72 (m, 2 H), 1.75−1.82 (m, 1 H), 1.86−1.94 (m, 1 H), 2.80 (td, J = 11.54, 2.93 Hz, 1 H), 3.17−3.26 (m, 1 H), 3.62−3.69 (m, 1 H), 7.48 (dd, J = 8.22, 1.00 Hz, 2 H), 7.57 (d, J = 8.22 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{12}H_{14}F_3N$ 230.1; found 230.1.

*N-(4-Fluorophenyl)-2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxamide (**86**).* To a solution of 2-(4-(trifluoromethyl)phenyl)-piperidine (**85**, 0.37 g, 1.64 mmol) in DCE (4 mL) was added 4-fluorophenyl isocyanante (0.20 mL, 1.80 mmol). The reaction mixture was stirred at room temperature for 3 h, and the solvents were evaporated under vacuum. The crude material was absorbed onto a plug of silica gel and purified by silica gel chromatography eluting with CH_2Cl_2. The title compound was obtained as a white solid (0.59 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): 1.40−1.54 (m, 1 H), 1.63−1.78 (m, 3 H), 1.99−2.12 (m, 1 H), 2.33 (dd, J = 14.18, 3.42 Hz, 1 H), 2.97−3.14 (m, 1 H), 3.94 (br d, J = 13.10 Hz, 1 H), 5.49 (br s, 1 H), 6.32 (br s, 1 H), 6.93−7.02 (m, 2 H), 7.26−7.32 (m, 2 H), 7.42 (d, J = 8.22 Hz, 2 H), 7.63 (d, J = 8.41 Hz, 2 H). MS (ESI pos. ion) m/z: calcd for $C_{19}H_{18}F_4N_2O$ 367.1424; found 367.1430.

Biological Assays. *In Vitro Rat TRPM8 Functional Assay.* Chinese Hamster Ovary (CHO) cells stably expressing rat TRPM8 were generated using the tetracycline-inducible T-REx expression system from Invitrogen, Inc. (Carlsbad, CA). To enable a luminescence readout based on intracellular increase in calcium, each cell line was also cotransfected with pcDNA3.1 plasmid containing jellyfish aequorin cDNA.[24] Cells were seeded in 96-well plates 24 h before the assay, and TRPM8 channel expression was induced with 0.5 μg/mL of tetracycline. On assay day, the growth medium was removed, and cells were incubated with assay buffer for 2 h. Cells were then exposed to test compounds (at varying concentrations) and incubated for 2.5 min prior to adding the agonist (**3**, 1 μM). The luminescence was measured by a charged-couple device (CCD) camera-based FLASH-luminometer built by Amgen, Inc. Compound activity was calculated using GraphPad Prism 4.01 (GraphPad Software Inc., San Diego, CA).

Rat Liver Microsomal Stability. Test compounds (1 μM) were incubated with male CD1 rat liver microsomes (1 mg/mL) in the presence of NADPH (1 mM) in phosphate-buffered saline (66.7 mM) at 37 °C. Incubations were conducted for 30 min. Control incubations were generated by the omission of NADPH from the incubation reaction. Under these conditions, a cut off of <100 μL/(min·mg) was considered desirable.

Rat PK Study. Nine male Sprague−Dawley rats were randomized to dose groups as shown in Table 5. Animals in groups 1 and 2 were dosed via intravenous injection, and animals in group 3 were dosed via oral gavage. Plasma samples were collected for PK analysis predose and at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, and 16 h post-iv dose and predose and 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 16 h post-po dose. Plasma concentrations for compounds **87** and **88** were measurement using sensitive LC/MS/MS methods. Noncompartmental analysis was conducted on compound **87** and **88** plasma concentrations using WinNonlin Enterprise v.5.1.1 (Pharsight Corporation, Mountain View, CA).

In Vivo Assay. *Icilin-Induced "Wet-Dog" Shaking in Rats.* Male Sprague−Dawley rats (220−300 g, n = 5−13/treatment) were first habituated to the testing room for 30 min and then to a transparent Plexiglas observation cylinder for 20 min. The cylinders were placed on a custom opaque plastic apparatus such that one rat could not view any other rats.[25] A TRPM8 antagonist or vehicle control was administered po 90 min prior to administration of **3** (0.5 mg/kg, ip, 100% PEG 400), and wet-dog shakes (WDS) were counted for a duration of 30 min postadministration. Antagonists were tested to assess the ability to block the spontaneous wet-dog shake phenomena induced by **3**.

Absolute Sterochemical Determination. Vibrational circular dichroism (VCD) spectra of **87** and **88** were recorded on a BioTools/Bomem Dual PEM *ChiralIR* spectrometer (Biotools, Inc., Jupiter, FL) as $CDCl_3$ solutions (50 mg/mL, BaF_2 cell, 100 μM path length, 8 cm^{-1} resolution) and are solvent subtracted. Optical rotation measurements were performed at 26 °C in $CHCl_3$ at 589 nm. Quantum mechanical geometry optimizations and harmonic frequency/VCD analysis were performed with the B3LYP hybrid density functional and the 6-31G* basis set. Optical rotation calculations were performed with the B3LYP functional and the 6-311++G(2d,2p) basis upon the B3LYP/6-31G* geometries, utilizing the frequency-dependent polarizability at 589.0 nm. All quantum mechanical calculations were performed with the *Gaussian 03* program system. Please see Supporting Information for full details.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Computed geometric parameters, total and free energies, Boltzmann populations, and predicted optical rotations for the conformational ensemble of (*R*)-**87**; complete *Gaussian 03* reference; TRP selectivity data, human TRPM8 activity, and human liver microsomal clearance for compounds **87** and **88**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS

TRPM8, transient receptor potential melastatin type 8; WDS, wet-dog shakes; TRP, transient receptor potential; TRP subtype C, canonical; TRP subtype V, vanilloid; TRP subtype A, ankyrin; TRP subtype P, polycystin; ML, mucolipin; CHO, chinese hamster ovary; SAR, structure−activity relationship; RLM, rat liver microsomes; ND, not determined; VCD, vibrational circular dichroism; AUC_{inf}, area under the serum concentration time curve from time 0 to infinity; CL, total body clearance; V_{ss}, volume of distribution at steady state; $t_{1/2}$, terminal half-life; C_{max}, maximum observed serum concentration

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