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Tetrahydropyridine-4-carboxamides as novel, potent transient receptor potential vanilloid 1 (TRPV1) antagonists

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ABSTRACT

A series of 1,2,3,6-tetrahydropyridyl-4-carboxamides, exemplified by **6**, have been synthesized and evaluated for in vitro TRPV1 antagonist activity, and in vivo analgesic activity in animal pain models. The tetrahydropyridine **6** is a novel TRPV1 receptor antagonist that potently inhibits receptor-mediated Ca^{2+} influx in vitro induced by several agonists, including capsaicin, *N*-arachidonoyldopamine (NADA), and low pH. This compound penetrates the CNS and shows potent anti-nociceptive effects in a broad range of animal pain models upon oral dosing due in part to its ability to antagonize both central and peripheral TRPV1 receptors. The SAR leading to the discovery of **6** is presented in this report.

1. Introduction

The lipophilic vanilloid capsaicin (**1**) (Fig. 1) activates primary sensory nociceptors via a specific cell surface receptor, designated the transient receptor potential vanilloid 1 receptor (TRPV1).[1–3] The TRPV1 receptor has been called a "polymodal detector" of noxious stimuli since it can be activated in several ways,[4] including vanilloids, heat, and acid (pH < 6).

Knockout mice lacking the TRPV1 receptor revealed a marked absence of responses evoked by noxious stimuli,[1,5] and suggest TRPV1 may be a viable target for the treatment of pain with small molecule antagonists. The capsaicin analogs capsazepine[6] and **2** (BCTC)[7] block activation of the channel in response to ligands, acid, or heat, and reduce inflammation-induced hyperalgesia in animal models. Recent reviews have described significant progress in understanding TRPV1 receptor biology as well as antagonist medicinal chemistry.[8] A growing number of TRPV1 antagonists which display anti-nociceptive effects in vivo have been identified, including our earlier lead heterocyclic urea **3** (A-795614).[9]

Comparison of the analgesic profiles of **2** and **3** showed that **2** exhibited far greater potency in the Chung neuropathic pain model[10] than did **3** despite similar in vitro inhibition of capsaicin-induced calcium influx and similar anti-nociceptive effects in the complete Freund's adjuvant (CFA) model[9] of inflammatory hyperalgesia (Table 1). This difference was hypothesized to be due to the higher CNS distribution of **2** relative to the peripherally-restricted **3**.

High-throughput screening of the Abbott compound library identified the hTRPV1 antagonist **4** (Fig. 2), and hit-to-lead efforts generated a series of biaryl amides, typified by **5**, with improved in vitro potency. Due to the similarity of these compounds to **2**, they were pursued in order to develop analogs possessing a different analgesic profile than that of previous series, and to determine if TRPV1 antagonists with increased central exposure would broaden the scope of anti-nociception.

Other researchers have also reported the discovery of **5**[11] in efforts to improve upon the poor solubility and metabolic instability of **2**. These reports, as well as our own work, demonstrated that a phenyl ring provided a suitable steric replacement for the central piperazine ring, maintaining potent TRPV1 antagonism, but failing to improve aqueous solubility. Our further exploration of this region demonstrated that a central tetrahydropyridine ring offered additional improvements in antagonist potency and physicochemical properties, and yielded compounds with significant distribution into the CNS. Herein we describe our evaluation of this new series of 1-heteroaryl-1,2,3,6-tetrahydropyridyl-4-carboxamides, and the discovery of **6**, a potent, orally bioavailable TRPV1 antagonist that reduces pain-induced behavior in several animal models.

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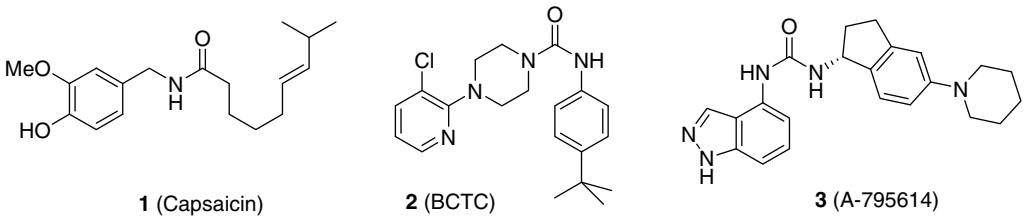


Figure 1. TRPV1 ligands.

Table 1
Potency, CNS distribution, and efficacy comparison of TRPV1 antagonists

Compound	hTRPV1 IC_{50} (cap, nM)[a]	[brain]:[plasma]	CFA ED_{50} (μmol/kg, po)	Chung ED_{50} (μmol/kg, po)
2	5.3 ± 1.0	5	8	8
3	14 ± 1	0.008	12	>300

[a] All values are the mean ± SEM of at least two independent experiments run in triplicate.

2. Chemistry

The target compounds were prepared as shown in Scheme 1. The heteroarylation of **7**,[12] followed by deprotection, enol triflate formation, and carbonylation comprised the preferred route[13] to the corresponding esters. The desired amides were then formed either *via* the acid chlorides following ester hydrolysis and chlorination, or directly by $AlMe_3$-mediated reaction[14] with the appropriate aniline. Heteroarylation of the corresponding cyclic amines followed by amide formation provided compounds **18b**,**c**,[15a] and **22b**[15b], while **20b** was synthesized *via* the above carbonylation route starting from **19**.

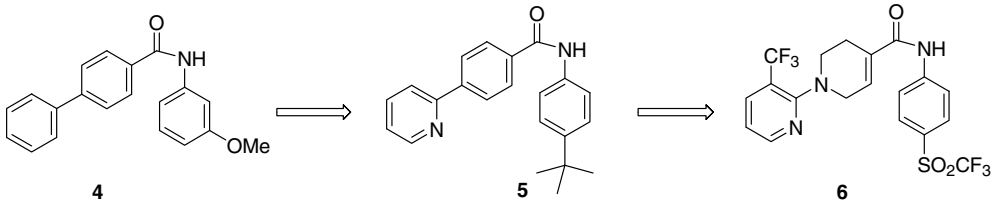
3. Results and discussion

Initial hit-to-lead SAR efforts led to the generation of biaryl analogs such as **5**, which incorporated a benzamide ring as a central aryl moiety and a heterocycle at the phenyl 4-position. As with the prior research on the biaryl analogs,[11] the SAR showed that pyridines bearing electron-withdrawing groups and pyrimidines were the heterocycles that generated the best TRPV1 receptor antagonists. Of the pyridyl substituents examined, 3-fluoro-, 3-chloro-, and 3-trifluoromethyl groups provided the optimal potencies. The three most important interactions for in vitro functional activity involve the antagonist heterocyclic nitrogen atom, amide functionality, and aniline ring substitution. In general, bulky substituents at the aniline 4-position were preferred, showing increased potency with size in the series *t*-Bu > Et > Me > H.

Optimization efforts led to replacement of the central aromatic ring of these biaryl compounds with the non-aromatic, heterocyclic 1,2,3,6-tetrahydropyridyl ring, which afforded compounds with potency comparable to the best biaryl analogs. A comparison of the crystal structures of three compounds with different central rings shows considerable topological similarity between the tetrahydropyridyl ring and the piperazine ring of **2** (Fig. 3). In these cases, the overlap of the extended pi-system leads to a much flatter conformation of the compounds than for the saturated analog **22b**, in which the carbonyl and amide phenyl ring are orthogonal to the central piperidine ring. Although these crystal conformations may not be predictive of receptor-bound conformations, they provide a possible explanation for the potency differences between the series and corroborate earlier reports regarding the importance of structural planarity.[11b] Related studies have shown a similar decrease in potency (~20×) upon replacement of the piperazine urea nitrogen with a carbon to give the corresponding piperidine.[16] That study also demonstrated TRPV1 agonism for a related piperidine regioisomer, but no corresponding hTRPV1 agonist activity was observed for the tetrahydropyridine analogs examined here.

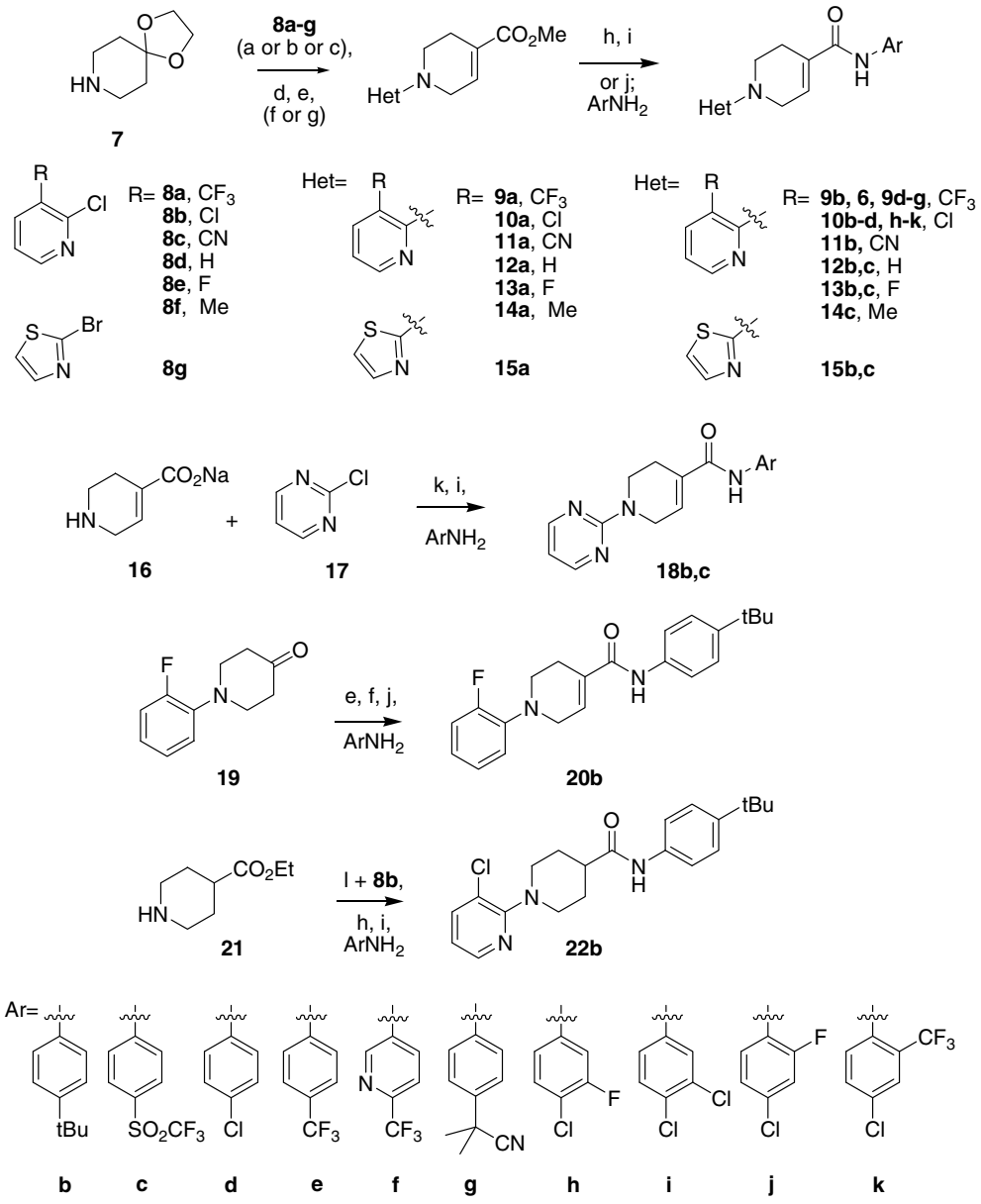
Because of the acrylamide moiety contained within the tetrahydropyridines, compounds **6**, **9g**, and **14c** were examined for reactivity towards covalent modification using the ALARM NMR technique.[17] The lack of reactivity in the assay indicates covalent binding to TRPV1 is unlikely. Additionally, in vitro electrophysiology experiments have also demonstrated reversible binding for **6**.

The 4-*t*-butylaniline amides provided the best in vitro antagonist potencies for each pyridine core, and this moiety was used to optimize the heterocyclic region. Lipophilic, electron-withdrawing groups at the pyridine 3-position gave the greatest potency (Table 2). The benefit of the pyridyl nitrogen is shown by the greater than tenfold loss in potency between compounds **13b** and **20b**. Both pyrimidine and thiazole analogs were also potent. Based on these SAR studies, the 3-(trifluoromethyl)-pyridine arose as the optimal substituent for this region. The analogs in Table 2 with TRPV1 IC_{50} values <50 nM were evaluated for analgesic efficacy using the CFA pain model. However, in vivo efficacies only ranged from 15% to 39% effect at an oral dose of 30 μmol/kg (e.g., 28% for



Compound	4	5	6
hTRPV1 IC_{50} (cap, nM)[a]	147 ± 39	42 ± 9	24 ± 2

Figure 2. TRPV1 antagonists. [a]All values are the mean ± SEM of at least two independent experiments run in triplicate.



Scheme 1. Syntheses of TRPV1 antagonists. Reagents and conditions: (a) K_2CO_3, DMSO; (b) Et_3N, 160 °C, microwave; (c) $Pd_2(dba)_3{\cdot}CHCl_3$, BINAP, KO^{t}Bu, toluene, 80 °C, microwave; (d) HCl; (e) LHMDS, $PhNTf_2$; (f) CO, $PdCl_2(PPh_3)_2$, Et_3N, MeOH; (g) CO, $Pd(OAc)_2$, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, Et_3N, MeOH, DMF; (h) NaOH; (i) $(COCl)_2$, pyr; (j) Me_3Al, CH_2Cl_2; (k) H_2O, 90 °C; (l) EtOH, 80 °C.

9b). These poor efficacies were attributed to metabolic or pharmacokinetic liabilities arising from the *t*-butylaniline group, since the *t*-butylaniline analogs displayed higher in vitro and in vivo clearances than were generally found for other corresponding analogs.

In SAR studies to mitigate the problems with the *t*-butylaniline group, compounds were evaluated both for their in vivo efficacy as well as in vitro potency (Table 3). Replacing the *t*-butyl group in **9b** with a trifluoromethylsulfonyl group to give **6** resulted in a four-fold loss of in vitro potency, but significant anti-nociceptive efficacy. In contrast, the 4-Cl analog **9d** and the CF_3-containing analog **9e** showed better TRPV1 antagonist potency but somewhat lower in vivo activity than **6**. The pyridylamine amide analog **9f** was synthesized to improve physical and pharmacokinetic properties, and to reduce the oxidative liability of the aryl ring. A similar substitution proved effective for related compounds found previously,[16] and this analog did show favorable in vivo efficacy and clearance, but displayed reduced TRPV1 antagonist potency and oral bioavailability (F = 3%). A nitrile group (**9g**) was employed to reduce the metabolism of the *t*-butyl group, but this analog showed reduced in vitro potency, and no improvement of in vivo efficacy relative to **9b**.

Although the chloropyridine **10d** showed good in vivo and in vitro activities, it also possessed poor pharmacokinetic properties ($t_{1/2}$ = 1.7 h, F = 16%, rat, po) and displayed inhibition of hERG. Additional amide SAR studies based on **10d** demonstrated some tolerance for substitution at the aniline 3-position, but low tolerance for substitution at the 2-position.

For the various heterocycles, the 4-(trifluoromethylsulfonyl)aniline containing analogs showed a similar rank-order of the in vitro potencies as the 4-*t*-butylanilines (Table 4), with the 3-(trifluoromethyl)pyridyl compound **6** still providing the most potent analog. Although each compound in this series showed significant anti-nociceptive effects in vivo, compound **6** possessed the lowest efficacious plasma level (EPL) of the compounds examined.

The CNS penetration of these tetrahydropyridyl compounds was generally good. For the SO_2CF_3-containing analogs, the brain expo-

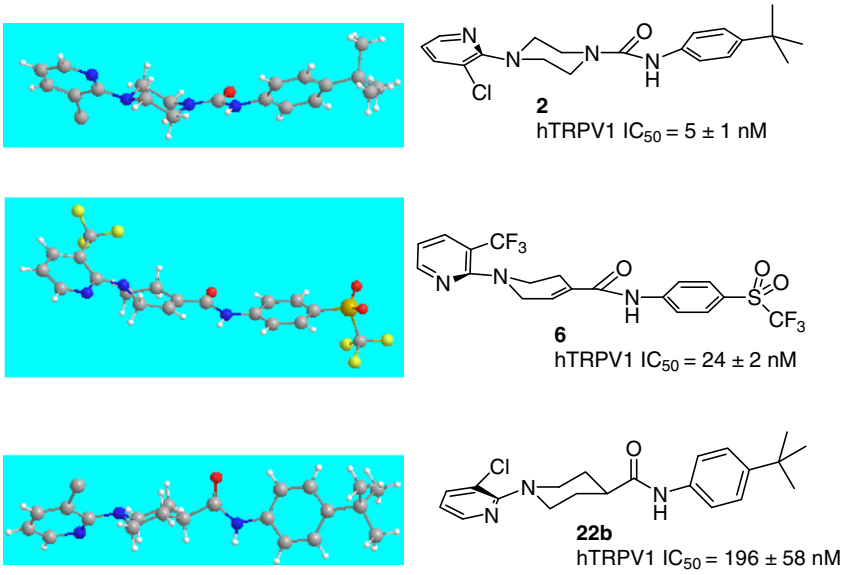


Figure 3. Crystallographic analysis of analog conformations.

Table 2
Effects of heterocycle substitution on 4-*t*-butylaniline analogs

	9b	10b	11b	12b	13b	15b	18b	20b
Ar								
IC_{50} (nM)[a]	6 ± 1	10 ± 2	78 ± 14	27 ± 13	19 ± 3	14 ± 2	10 ± 1	265 ± 44

[a] All values are the mean ± SEM of at least two independent experiments run in triplicate vs. cap.

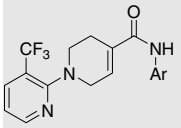
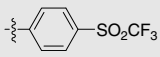
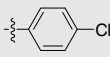
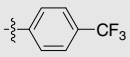
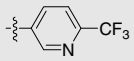
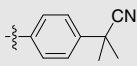
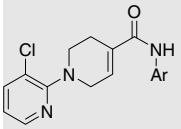
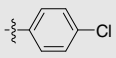
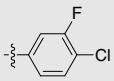
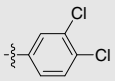
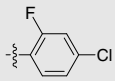
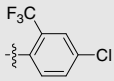
sure of **6** ([brain]:[plasma] = 1.5) was intermediate between that of **14c** (0.7) and **10c** (2.2). The exposure found for **9g** (1.2) showed that the sulfone was not required for good brain penetration. Although **10c** offered the highest degree of CNS penetration, it demonstrated cardiovascular liabilities upon further testing in anesthetized rats. Compound **14c** also caused adverse cardiovascular effects, a property absent in the 3-trifluoromethylpyridyl derivative **6**. The favorable cardiovascular attributes due to the CF_3 group were also conferred on **9g**, but replacement of the aniline SO_2CF_3 group by the isobutyronitrile moiety led to poorer pharmacokinetic properties. Since **6** displayed the best combination of in vitro potency, analgesic efficacy, therapeutic plasma concentration, CNS penetration, and favorable cardiovascular profile, it was chosen for further study.

Compound **6** also potently inhibited Ca^{2+} influx induced by stimuli other than capsaicin, such as the endogenous ligand NADA (IC_{50} = 20.2 ± 7.7 nM, 3 μM NADA) and low pH (IC_{50} = 14.0 ± 2.3 nM, pH 5.5), which may be more relevant to natural pain states. **6** was also evaluated as a ligand for other TRP receptors, but showed little effect at either hTRPM8 or hTRPA1.[9]

Compound **6** was efficacious in a number of preclinical models of both acute and chronic pain.[9] IC_{50} values for rat TRPV1 vs. capsaicin were determined for both **6** (17 ± 2 nM) and **3** (30 ± 2 nM) to provide a better correlation to rat pain models. Although reversed in rank-order, both **6** and **3** displayed similar in vitro potencies both with regard to each other, and to rat and human TRPV1. As previously shown,[9] the CNS penetrant **6** was more potent than the peripherally restricted antagonist **3** in the CFA mechanical allodynia, capsaicin-induced secondary mechanical hyperalgesia, and osteoarthritis pain models (Table 5). In further in vivo studies, **6** also showed full reversal of acute, post-operative pain using a skin-incision model in rats (ED_{50} = 20 μmol/kg), and full efficacy in a rat model of acute inflammatory thermal hyperalgesia produced by carrageenan (ED_{50} = 25 μmol/kg). Interestingly, both compounds were essentially inactive in the Chung model (ED_{50} > 300 μmol/kg), which was the impetus for determining the effects of CNS exposure on the scope of anti-nociception. While this result demonstrates the involvement of multiple factors in pain pathology, the importance of CNS penetration for broad-spectrum efficacy in pain models has been previously elaborated as a result of some of this work.[9] Other studies have also shown the importance of central TRPV1 receptors in the reversal of CFA-induced mechanical hyperalgesia,[18a] and in mediating referred allodynia induced by a visceral stimulus.[18b]

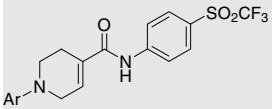
The primary challenge to the development of **6** was its very low aqueous solubility (33 ng/mL). The high permeability of the

Table 3
Effects of aniline substitution

	**6**	**9d**	**9e**	**9f**	**9g**
Ar					
IC_{50} (cap, nM)[a]	24 ± 2	19 ± 2	8 ± 2	42 ± 5	41 ± 5
CFA efficacy[b]	58%**	40%*	35%**	61%**	25%*
	**10d**	**10h**	**10i**	**10j**	**10k**
Ar					
IC_{50} (cap, nM)[a]	33 ± 2	78 ± 9	124 ± 18	618 ± 88	2746 ± 783

[a] All values are the mean ± SEM of at least two independent experiments run in triplicate.
[b] 30 μmol/kg, po dose in rats, with $n = 6$/dose group.
* $p < 0.05$ vs. vehicle.
** $p < 0.01$ vs. vehicle.

Table 4
Effects of heterocycles on 4-(SO_2CF_3)aniline core

	**6**	**10c**	**13c**	**14c**	**15c**	**18c**
Ar						
IC_{50} (cap, nM)[a]	24 ± 2	41 ± 3	67 ± 7	35 ± 2	95 ± 12	44 ± 6
CFA efficacy[b]	58%**	63%**	51%**	53%**	37%**	53%**
EPL [c](ng/mL)	200	280	900	960	2100	380

[a] All values are the mean ± SEM of at least two independent experiments run in triplicate.
[b] 30 μmol/kg, po dose in rats, with $n = 6$/dose group.
[c] Efficacious plasma levels at ED_{50} in rat CFA experiments 1 h after dosing.
** $p < 0.01$ vs. vehicle.

compound, as shown by Caco-2 membrane permeability studies ($P_{app} = 28.5 \times 10^{-6}$ cm/s), likely contributed significantly to its broad oral efficacy. Efforts to find a suitable formulation of **6** revealed that the compound is highly soluble in organic vehicles (>100 mg/mL in PEG-400). A vehicle composed of 10% ethanol, 20% polysorbate-80, and 70% PEG-400 was employed in the in vivo studies described above. However, **6** demonstrated non-linear pharmacokinetic properties on dose escalation, limiting its exposure to levels below those required for toxicology studies, and precluding it from further evaluation as a potential clinical candidate.

In conclusion, 1,2,3,6-tetrahydropyridyl-4-carboxamide TRPV1 antagonists show potent analgesic activity in multiple animal pain models, with **6** displaying enhanced anti-nociceptive effects resulting from its preferential CNS distribution. These findings show **6** to be a useful standard for evaluating TRPV1 antagonists, and provide further support for the viability of such antagonists as potential therapeutics for pain.

4. Experimental

4.1. Determination of TRPV1 antagonist activity

The functional antagonist activity of compounds at the TRPV1 receptor was determined with a Ca^{2+} influx assay by measuring the effect on capsaicin evoked increase in intracellular Ca^{2+} levels ($[Ca^{2+}]_i$) using 1321N1 cells stably expressing recombinant human or rat

Table 5
ED_{50} values for oral doses of **3** and **6** in various pain models in rats[9a]

Assay	3	6
hTPRV1 (cap, nM)[a]	14 ± 1	24 ± 2
rTRPV1 (cap, nM)[a]	30 ± 2	17 ± 2
[brain]:[plasma]	0.008	1.5
Nocifensive behavior ED_{50} (μmol/kg)[b]	10	10
CFA-induced thermal hyperalgesia ED_{50} (μmol/kg)	12	6
CFA-induced mechanical allodynia ED_{50} (μmol/kg)	300	76
Secondary mechanical allodynia ED_{50} (μmol/kg)	165	40
MIA-induced osteoarthritis ED_{50} (μmol/kg)	280	8
Chung ED_{50} (μmol/kg)	>300	>300

[a] All values are the mean ± SEM of at least two independent experiments run in triplicate.
[b] Capsaicin-induced.

TRPV1. All compounds were tested over an 11-point half-log concentration range. Compound solutions were prepared in D-PBS (4× final concentration), and diluted serially across 96-well v-bottom tissue culture plates using a Biomek 2000 robotic automation workstation (Beckman–Coulter, Inc., Fullerton, CA). A 0.2 μM solution of the TRPV1 agonist capsaicin was also prepared in D-PBS. The fluorescent Ca^{2+} chelating dye fluo-4 was used as an indicator of the relative levels of $[Ca^{2+}]_i$ in a 96-well format using a Fluorescence Imaging Plate Reader (FLIPR) (Molecular Devices, Sunnyvale, CA). Cells were grown to confluency in 96-well black-walled tissue culture plates. Then, prior to the assay, the cells were loaded with 100 μL per well of fluo-4 AM (2 μM, in D-PBS) for 1–2 h at 23 °C. Following washing of the cells (2 × 1 mL D-PBS per well) to remove extracellular fluo-4 Am, plates containing the cells in 100 μL D-PBS were placed in the reading chamber of the FLIPR instrument. Fifty microliters of the compound solutions were added to the cells at the 10 s time mark of the experimental run. After 3 min, 50 μL of the capsaicin solution was added (0.05 μM final concentration, final volume = 200 μL) to activate the TRPV1 receptor. Fluorescence readings were made at 1 to 5 s intervals over the 240 s course of the experimental run. The peak increase in relative fluorescence units (minus baseline) was calculated and expressed as a percentage of the 0.05 μM capsaicin (control) response. Curve-fits of the data were solved using a four-parameter logistic Hill equation in GraphPad Prism® (GraphPad Software, Inc., San Diego, CA), and IC_{50} values were calculated.

4.2. Animals

Male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA), weighing 200–320 g were group housed, and given food and water ad libitum, except before oral administration of drugs when food was removed for 16 h before dosing.

4.3. Thermal hyperalgesia assessment

Unilateral inflammation was induced by injecting 100 μL of a 1% solution of λ-carrageenan or 150 μL of a 50% solution of complete Freund's adjuvant (CFA) (Sigma Chemical Co., St. Louis, MO) in physiological saline into the plantar surface of the right hindpaw of the rat. The hyperalgesia to thermal stimulation was determined 2 h after carrageenan injections or 48 h after CFA injections using a commercially available paw thermal stimulator (UARDG, University of California, San Diego, CA; Dirig and Yaksh, 1995), modeled after that described by Hargreaves.[19] Animals were placed individually in Plexiglass cubicles mounted on a glass surface maintained at 30 °C, and allowed a 30 min habituation period. A thermal stimulus, in the form of radiant heat emitted from a focused projection bulb, was then applied to the plantar surface of each hindpaw. In each test session, each rat was tested in 3 sequential trials at approximately 5 min intervals. Paw withdrawal latencies were calculated as the mean of the two shortest latencies.

4.4. Skin incision-induced acute thermal hyperalgesia

Paw incision was performed under halothane (2–3%) anesthesia, using procedures previously described.[20] Using aseptic techniques, the plantar aspect of the left hind paw was placed through a hole in a sterile plastic drape. A 1-cm longitudinal incision was made through the skin and fascia, starting 0.5 cm from the proximal edge of the heel and extending towards the toes, the plantar muscle was elevated and injured longitudinally leaving the muscle origin and insertion points intact. After hemostasis with gentle pressure, the skin was apposed with 2 mattress sutures (5–0 nylon). Animals were allowed to recover for 2 h before behavioral testing.

4.5. General methods

^{1}H NMR spectra were obtained at 300 MHz using Me_4Si as an internal standard. Low-resolution mass spectra were recorded on a Finnigin-4000 instrument, and high-resolution were recorded on an Agilent LC/MSDTOF instrument. Elemental analyses were obtained from Quantitative Technologies, Inc., and were within 0.4% of theoretical values unless otherwise noted. Chromatography was performed with EM Science silica gel 60 (230–400 mesh) or Analogix Super Flash columns. Reactions were conducted under an inert N_2 atmosphere using commercial high-purity solvents as received. All materials were obtained and used as-received from commercial sources unless otherwise noted.

4.6. Methyl 1-(3-(trifluoromethyl)pyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxylate (9a)

To a solution of **8a** (14.2 g, 78 mmol) and **7** (15 mL, 117 mmol) in DMSO (155 mL) was added K_2CO_3 (13.0 g, 94 mmol). The reaction mixture was heated to 100 °C for 5 h. After cooling to rt, the mixture was partitioned between H_2O and Et_2O. The organic layer was separated and washed with brine, and then concentrated in vacuo. The residue was dissolved in concentrated HCl (50 mL) and stirred overnight. The mixture was then neutralized with NH_4OH (50 mL) and extracted with ether. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (gradient elution of 10% to 50% Et_2O/Hex) to give the corresponding substituted piperidinone as a white solid (12.4 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 4.6 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.07 (dd, J = 4.6, 7.6 Hz, 1H), 3.59 (t, J = 5.9 Hz, 4H), 2.61 (t, J = 5.9 Hz, 4H).

To a solution of the above 1-(3-(trifluoromethyl)pyridin-2-yl)piperidin-4-one (7.2 g, 29.5 mmol) and $PhNTf_2$ (11.6 g, 31 mmol) in THF (60 mL) at −78 °C was added dropwise LHMDS (1 N in THF, 33 mL, 33 mmol) over 30 min. The mixture was stirred at this temperature for 1 h and then allowed to warm to rt, concentrated, dissolved in 1:1 EtOAc/Hex and then washed with 1 N NaOH. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (10% to 30% Et_2O/Hex gradient elution) to give the vinyl triflate as a clear oil (7.0 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, J = 1.4, 4.7 Hz, 1H), 7.89 (dd, J = 1.4, 7.8 Hz, 1H), 7.01 (ddd, J = 1.4, 4.7, 7.8 Hz, 1H), 5.86 (sept, J = 1.5 Hz, 1H), 3.99 (q, J = 3.7 Hz, 2H), 3.55 (t, J = 5.8 Hz, 2H), 2.59–2.66 (m, 2H).

To a 1:1 mixture of MeOH:DMF (80 mL) that had been saturated with CO, were added the above triflate (7.0 g, 19 mmol), PPh_3 (377 mg, 1.4 mmol), $Pd(OAc)_2$ (105 mg, 0.47 mmol), and Et_3N (5.2 mL, 37 mmol). This mixture was stirred under CO (1 atm) overnight and was then diluted with H_2O and extracted with Et_2O, and the combined organic layers were washed with brine, dried (Na_2SO_4), concentrated, and chromatographed (10% to 30% Et_2O/Hex gradient elution) to give **9a** as a white solid (5.5 g, 19 mmol, quant.): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (dd, J = 1.7, 4.8 Hz, 1H), 7.87 (dd, J = 1.7, 7.8 Hz, 1H), 7.01 (sept, J = 1.7 Hz,

1H), 6.96 (ddd, J = 1.0, 4.8, 7.8 Hz, 1H), 4.03 (q, J = 3.0 Hz, 2H), 3.77 (s, 3H), 3.44 (t, J = 5.4 Hz, 2H), 2.53–2.61 (m, 2H).

4.7. 1-(3-(Trifluoromethyl)pyridin-2-yl)-N-(4-(trifluoromethylsulfonyl)phenyl)-1,2,3,6-tetrahydropyridine-4-carboxamide (6)

To a solution of 4-(trifluoromethylsulfonyl)-aniline (8.38 g, 37.2 mmol) in CH_2Cl_2 (90 mL) was added Me_3Al (2 N in toluene, 18.6 mL, 37.2 mmol) dropwise. After 30 min, **9a** (5.5 g, 18.6 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred at rt for 2 h. The mixture was then diluted with EtOAc and then quenched with 0.5 N HCl. The organic layer was washed with 1 N NaOH, H_2O, and brine, and dried (Na_2SO_4). The product was chromatographed (0% to 30% EtOAc/(1:1 CH_2Cl_2:Hex) gradient elution) and triturated with Et_2O to give **6** as a white solid (7.24 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, J = 1.7, 4.6 Hz, 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.88–7.92 (m, 3H), 7.75 (br s, 1H), 7.02 (dd, J = 4.6, 7.5 Hz, 1H), 6.85 (sept, J = 1.7 Hz, 1H), 4.09 (q, J = 3.0 Hz, 2H), 3.52 (t, J = 5.4 Hz, 2H), 2.64–2.72 (m, 2H); MS (ESI+) m/z 480.3 $(M+H)^+$. Anal ($C_{19}H_{15}F_6N_3O_3S$) C, H, N.

4.8. *N*-(4-*tert*-Butylphenyl)-1-(3-(trifluoromethyl)pyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (9b)

Ester **9a** (3.89 g, 13.5 mmol) was dissolved in MeOH (15 mL) and THF (30 mL), and stirred with 1 N NaOH (27 mL) for 2 h. Additional 1 N NaOH (16 mL) was added and stirred for 1 h, followed by another aliquot (14.5 mL) for 1 h. The mixture was then diluted with water, and extracted with CH_2Cl_2. The aqueous layer was then acidified with conc HCl and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated to give the corresponding acid as a tan solid (3.00 g, 11.0 mmol, 81%): ^{1}H NMR (300 MHz, CD_3OD) δ 8.45 (m, 1H), 7.99 (dd, J = 2.4, 7.8 Hz, 1H), 7.08-7.14 (m, 1H), 7.02 (sept, J = 1.7 Hz, 1H), 3.99 (q, J = 3.1 Hz, 2H), 3.39 (t, J = 5.6 Hz, 2H), 2.45–2.53 (m, 2H); MS (ESI+) m/z 273.1 $(M+H)^+$.

To a suspension of the acid (0.300 g, 1.10 mmol) and DMF (cat) in CH_2Cl_2 (4 mL) was added $(COCl)_2$ (0.14 mL, 1.6 mmol). The mixture was stirred for 90 min, diluted with PhMe (1 mL), concentrated to dryness, and dissolved in CH_2Cl_2 (4 mL). To the solution were added pyridine (0.14 mL, 1.7 mmol), DMAP (cat), and 4-*t*-butylaniline (0.21 mL, 1.3 mmol). The mixture was stirred 1 h, diluted with water and extracted with CH_2Cl_2, dried (Na_2SO_4), and purified by flash chromatography (3% EtOAc/CH_2Cl_2) to give **9b** as a white solid (0.33 g, 0.82 mmol, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, J = 1.6, 4.4 Hz, 1H), 7.89 (dd, J = 1.6, 7.5 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 3H), 6.98 (dd, J = 4.4, 7.5 Hz, 1H), 6.76 (sept, J = 1.7 Hz, 1H), 4.06 (q, J = 2.8 Hz, 2H), 3.53 (t, J = 5.4 Hz, 2H), 2.63–2.70 (m, 2H), 1.31 (s, 9H); MS (ESI+) m/z 404.4 $(M+H)^+$. Anal ($C_{22}H_{24}F_3N_3O$) C, H, N.

4.9. *N*-(4-Chlorophenyl)-1-(3-(trifluoromethyl)pyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (9d)

As for **9b** (45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dd, J = 1.8, 5.0 Hz, 1H), 7.89 (dd, J = 1.8, 7.8 Hz, 1H), 7.51 (d, J = 9.1 Hz, 2H), 7.43 (br s, 1H), 7.30 (d, J = 9.1 Hz, 2H), 6.99 (dd, J = 5.0, 7.8 Hz, 1H), 6.77 (sept, J = 1.7 Hz, 1H), 4.05 (q, J = 3.0 Hz, 2H), 3.51 (t, J = 5.4 Hz, 2H), 2.62–2.70 (m, 2H); HRMS (ESI-TOF) calc for $C_{18}H_{15}ClF_3N_3O$ $(M+H)^+$ m/z 382.09285; found 382.09363.

4.10. *N*-(4-(Trifluoromethyl)phenyl)-1-(3-(trifluoromethyl)-pyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (9e)

As for **9b** (54%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.43 (dd, J = 4.7, 1.4 Hz, 1H), 7.89 (dd, J = 7.8, 1.7 Hz, 1H), 7.70 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.54 (s, 1H), 7.00 (dd, J = 7.8, 4.7 Hz, 1H), 6.81 (sept, J = 1.7 Hz, 1H), 4.08 (q, J = 3.1 Hz, 2H), 3.52 (t, J = 5.6 Hz, 2H), 2.64–2.72 (m, 2H); HRMS (FAB) calc for $C_{19}H_{15}F_6N_3O$ (M^+) m/z 415.1119; found 415.1117.

4.11. 1-(3-(Trifluoromethyl)pyridin-2-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (9f)

As for **9b** (96%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.01 (d, J = 2.2 Hz, 1H), 8.53 (dd, J = 1.7, 4.8 Hz, 1H), 8.40 (dd, J = 2.2, 8.3 Hz, 1H), 8.10 (dd, J = 1.7, 7.8 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.19 (ddd, J = 1.0, 4.8, 7.8 Hz, 1H), 6.90 (sept, J = 1.7 Hz, 1H), 4.02 (q, J = 2.8 Hz, 2H), 3.40 (t, J = 5.4 Hz, 2H), 2.53–2.61 (m, 2H); MS (CI) m/z 417.1 $(M+H)^+$. Anal ($C_{18}H_{14}F_6N_4O$) C, H, N.

4.12. *N*-(4-(2-Cyanopropan-2-yl)phenyl)-1-(3-(trifluoromethyl)pyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (9g)

As for **9b** using 1,1-dimethyl-(4-aminophenyl)-acetonitrile[21] (51%): ^{1}H NMR (300 MHz,$CDCl_3$) δ ppm 8.43 (dd, J = 4.7, 2.0 Hz, 1H), 7.89 (dd, J = 7.8, 2.0 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.42–7.47 (m, 3H), 7.00 (dd, J = 7.8, 4.7 Hz, 1H), 6.79 (sept, J = 1.7 Hz, 1H), 4.07 (q, J = 3.1 Hz, 2H), 3.53 (t, J = 5.4 Hz, 2H), 2.64-2.71 (m, 2H), 1.72 (s, 6 H); HRMS (ESI-TOF) calc for $C_{22}H_{21}F_3N_4O$ $(M+H^+)$ m/z 415.17402; found 415.17443.

4.13. *N*-(4-*tert*-Butylphenyl)-1-(3-chloropyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (10b)

The method used for **9a**,**b** was also used starting with 2,3-dichloropyridine to give the corresponding acid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.36 (br s, 1H), 8.20 (dd, J = 1.7, 4.8 Hz, 1H), 7.81 (dd, J = 1.7, 7.8 Hz, 1H), 6.98 (dd, J = 4.8, 7.8 Hz, 1H), 6.94 (sept, J = 1.7 Hz, 1H), 3.98 (q, J = 3.0 Hz, 2H), 3.41 (t, J = 5.4 Hz, 2H), 2.37–2.45 (m, 2H). A mixture of the acid (120 mg, 70%, 0.35 mmol), 4-*t*-butylaniline (90.0 mg, 0.6 mmol) and EDCI (145 mg, 0.75 mmol) in dichloromethane (3 mL) were placed in a flask under N_2. The mixture was stirred at rt overnight, and quenched with water. The organic layer was separated, and the solvent was removed. The crude product was then purified via column chromatography (25% EtOAc/hex) to give **10b** (95 mg, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 ppm (dd, J = 1.7, 4.7 Hz, 1H), 7.61 (dd, J = 1.7, 7.8 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.38 (br s, 1H), 7.35 (d, J = 8.7 Hz, 2H), 6.85 (dd, J = 4.7, 7.8 Hz, 1H), 6.75–6.78 (m, 1H), 4.10 (q, J = 2.8 Hz, 2H), 3.58 (t, J = 5.6 Hz, 2H), 2.67–2.71 (m, 2H), 1.30 (s, 9H). HRMS (ESI-TOF) calc for $C_{21}H_{24}ClN_3O$ $(M+H)^+$ m/z 370.16807; found 370.16883.

4.14. 1-(3-Chloropyridin-2-yl)-*N*-(4-(trifluoromethylsulfonyl)-phenyl)-1,2,3,6-tetrahydropyridine-4-carboxamide (10c)

As for **9b** (75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, J = 1.7, 4.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.82 (br s, 1H), 7.65 (dd, J = 1.7, 7.8 Hz, 1H), 6.85–6.92 (m, 2H), 4.15 (q, J = 3.1 Hz, 2H), 3.60 (t, J = 5.4 Hz, 2H), 2.66–2.73 (m, 2H). MS (ESI) m/z 446 $(M+H)^+$. Anal. ($C_{18}H_{15}ClF_3N_3O_3S$) C, H, N.

4.15. *N*-(4-Chlorophenyl)-1-(3-chloropyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (10d)

As for **9b** (49%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20(dd, J = 1.7, 5.0 Hz, 1H), 7.70 (dd, J = 1.7, 7.5 Hz, 1H), 7.62 (br s, 1H), 7.54 (d,

J = 9.1 Hz, 2H), 7.30 (d, *J* = 9.1 Hz, 2H), 6.92 (dd, *J* = 5.0, 7.5 Hz, 1H), 6.76 (sept, *J* = 1.9 Hz, 1H), 4.16 (q, 2.8 Hz, 2H), 3.64 (t, *J* = 5.6 Hz, 2H), 2.66–2.72 (m, 2H). MS (ESI) *m/z* 350 $(M+H)^+$. Anal ($C_{17}H_{15}Cl_2N_3O$·HCl+0.75 CH_2Cl_2) C, H, N.

4.16. *N*-(4-Chloro-3-fluorophenyl)-1-(3-chloropyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (10h)

As for **9b** (44%): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.05 (s, 1H), 8.22 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.83–7.85 (m, 2H), 7.50–7.53 (m, 2H), 7.01 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.80–6.85 (m, 1H), 4.02 (q, *J* = 2.9 Hz, 2H), 3.45 (t, *J* = 5.4 Hz, 2H), 2.52–2.59 (m, 2H); MS (ESI+) *m/z* 366 $(M+H)^+$. Anal ($C_{17}H_{14}Cl_2FN_3O$+0.6 CH_2Cl_2) C, H, N.

4.17. 1-(3-Chloropyridin-2-yl)-*N*-(3,4-dichlorophenyl)-1,2,3,6-tetrahydropyridine-4-carboxamide (10i)

As for **9b** (47%): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.01 (s, 1H), 8.22 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.67 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.01 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.80–6.84 (m, 1H), 4.02 (q, *J* = 2.8 Hz, 2H), 3.45 (t, *J* = 5.4 Hz, 2H), 2.52–2.59 (m, 2H); MS (ESI+) *m/z* 382 $(M+H)^+$. Anal ($C_{17}H_{14}Cl_3N_3O$+0.65 CF_3CO_2H) C, H, N.

4.18. *N*-(4-Chloro-2-fluorophenyl)-1-(3-chloropyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (10j)

As for **9b** (19%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.60 (s, 1H), 8.22 (d, *J* = 1.5 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.58 (t, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 10.4, 2.5 Hz, 1H), 7.26–7.29 (m, 1H), 7.00 (dd, *J* = 7.7, 4.6 Hz, 1H), 6.84–6.88 (m, 1H), 4.02 (q, *J* = 2.8 Hz, 2H), 3.46 (t, *J* = 5.5 Hz, 2H), 2.52–2.58 (m, 2H); MS (ESI+) *m/z* 366 $(M+H)^+$. Anal ($C_{17}H_{14}Cl_2FN_3O$+0.45 CF_3CO_2H) C, H, N.

4.19. *N*-(4-Chloro-2-(trifluoromethyl)phenyl)-1-(3-chloropyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (10k)

As for **9b** (9%): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.57 (s, 1H), 8.22 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.81–7.84 (m, 2H), 7.78 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.00 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.81–6.84 (m, 1H), 4.02 (q, *J* = 2.8 Hz, 2H), 3.46 (t, *J* = 5.4 Hz, 2H), 2.52–2.57 (m, 2H); HRMS (ESI-TOF) calc for $C_{18}H_{14}Cl_2F_3N_3O$ $(M+H)^+$ *m/z* 416.05388; found 416.05440.

4.20. *N*-(4-*tert*-Butylphenyl)-1-(3-cyanopyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (11b)

As for **9a,b** (21%): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.66 (br s, 1H), 8.42 (dd, *J* = 2.0, 4.7 Hz, 1H), 8.09 (dd, *J* = 2.0, 7.8 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.93 (dd, *J* = 4.7, 7.8 Hz, 1H), 6.73–6.78 (m, 1H), 4.28 (q, *J* = 3.0 Hz, 2H), 3.81 (t, *J* = 5.4 Hz, 2H), 2.53–2.61 (m, 2H), 1.26 (s, 9H); HRMS (ESI-TOF) calc for $C_{22}H_{24}N_4O$ $(M+H)^+$ *m/z* 361.20229; found 361.20228.

4.21. *N*-(4-*tert*-Butylphenyl)-1-(pyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (12b)

As for **9a,b** (33%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (br s, 1H), 8.14 (dd, *J* = 1.7, 4.8 Hz, 1H), 7.52–7.61 (m, 3H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.76–6.80 (m, 1H), 6.65 (dd, *J* = 4.8, 6.8 Hz, 1H), 4.14 (q, *J* = 3.0 Hz, 2H), 3.73 (t, *J* = 5.4 Hz, 2H), 2.44–2.52 (buried m, 2H), 1.26 (s, 9H); MS (CI) *m/z* 336 $(M+H)^+$. Anal ($C_{21}H_{25}N_3O$+0.11 CF_3CO_2H) C, H, N.

4.22. 1-(Pyridin-2-yl)-*N*-(4-(trifluoromethylsulfonyl)phenyl)-1,2,3,6-tetrahydropyridine-4-carboxamide (12c)

As for **9a,b** (37%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.48 (br s, 1H), 8.12–8.17 (m, 3H), 8.08 (d, *J* = 9.1 Hz, 2H), 7.57 (ddd, *J* = 2.0, 7.1, 9.2 Hz, 1H), 6.91–6.96 (m, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.66 (ddd, *J* = 0.7, 5.1, 7.1 Hz, 1H), 4.20 (q, *J* = 3.1 Hz, 2H), 3.74 (t, *J* = 5.8 Hz, 2H), 2.49 (buried); MS (CI) *m/z* 412 $(M+H)^+$. Anal ($C_{18}H_{16}F_3N_3O_3S$+0.15 CF_3CO_2H) C, H, N.

4.23. *N*-(4-*tert*-Butylphenyl)-1-(3-fluoropyridin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (13b)

As for **9a,b** (37%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dt, *J* = 1.7, 4.8 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.39 (br s, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.27 (ddd, *J* = 1.4, 7.8, 13.2 Hz, 1H), 6.73–6.80 (m, 2H), 4.22 (q, *J* = 3.1 Hz, 2H), 3.72 (t, *J* = 5.4 Hz, 2H), 2.61–2.69 (m, 2H), 1.31 (s, 9H); MS (ESI+) *m/z* 354 $(M+H)^+$. Anal ($C_{21}H_{24}FN_3O$+0.21 CF_3CO_2H) C, H, N.

4.24. 1-(3-Fluoropyridin-2-yl)-*N*-(4-(trifluoromethylsulfonyl)-phenyl)-1,2,3,6-tetrahydropyridine-4-carboxamide (13c)

As for **9a,b** (35%): ^{1}H NMR (300 MHz, $CDCl_3$) δ *7.97–8.05* (m, 3H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.83 (br s, 1H), 7.30 (ddd, *J* = 1.7, 7.8, 13.2 Hz, 1H), 6.84–6.88 (m, 1H), 6.80 (ddd, *J* = 3.0, 4.7, 7.8 Hz, 1H), 4.25 (q, *J* = 3.0 Hz, 2H), 3.74 (t, *J* = 5.8 Hz, 2H), 2.62–2.69 (m, 2H); MS (ESI+) *m/z* 430 $(M+H)^+$. Anal ($C_{18}H_{15}F_4N_3O_3S$+0.25 CF_3CO_2H) C, H, N.

4.25. 1-(3-Methylpyridin-2-yl)-*N*-(4-(trifluoromethylsulfonyl)phenyl)-1,2,3,6-tetrahydropyridine-4-carboxamide (14c)

A mixture of **8f** (5.0 mL, 45.8 mmol), Pd_2dba_3·$CHCl_3$ (0.958 g, 0.926 mmol), *rac*-BINAP (1.43 g, 2.30 mmol), NaO*t*Bu (8.51 g, 88.6 mmol), and **7** (5.6 mL, 44 mmol) in PhMe (135 mL) was heated to 100 °C for 3.5 h, diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), and filtered through silica with 70% Et_2O/Hex to give 11.5 g of impure substituted pyridine as a red oil. This material was stirred in conc. HCl (60 mL) for 6 h, quenched with conc NH_4OH (80 mL), diluted with EtOAC, washed with water and brine, dried (Na_2SO_4), and filtered through silica with 80% Et_2O/Hex to give the impure corresponding ketone as a red oil (7.35 g), which was used without further purification.

To a solution of the crude ketone (7.35 g, 38.6 mmol) and $PhNTf_2$ (13.9 g, 39.0 mmol) in THF (60 mL) at −78 °C was added a solution of LHMDS in THF (1 N, 33 mL, 33 mmol) dropwise. The mixture was stirred at this temperature for 5 min and allowed to warm to rt with stirring for 2 h. The mixture was then concentrated, dissolved in 1:1 EtOAc/Hex, washed with 1 N NaOH, sat aq NaHCO3, and brine. The organic layer was dried (Na_2SO_4), and concentrated to give the crude triflate as a brown solid (13.2 g, ∼quant), which was used without purification. This residue, $Pd(OAc)_2$ (0.263 g, 1.17 mmol), 2-dicyclohexylphosphino-2′-(*N,N*-dimethylamino)biphenyl (0.921 g. 2.34 mmol), and Et_3 N (12 mL, 86 mmol) was dissolved in a 1:1 solution of MeOH:DMF (80 mL) that had been saturated with CO, and the mixture was stirred under CO (1 atm) overnight. The mixture was concentrated, diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), concentrated, and chromatographed (10–40% Et_2O/Hex) to give **14a** as a black gummy oil (4.73 g, 20.4 mmol, 53%).

To a solution of 4-(trifluoromethylsulfonyl) aniline (3.79 g, 16.8 mmol) in CH_2Cl_2 (17 mL) was added Me_3Al (2 N in Hex, 8.4 mL, 16.8 mmol) dropwise. After 1 h, **14a** (1.95 g, 8.4 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred at 40 C for 2 h,

diluted with EtOAc and quenched with 1 N HCl. The organic layer was washed with 1 N NaOH, sat aq $NaHCO_3$, and then brine, dried (Na_2SO_4), concentrated, and chromatographed (40–100% Et_2O/Hex) to give **14c** as a yellow solid (1.24 g, 2.90 mmol, 35%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 4.4 Hz, 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 7.1 Hz, 1H), 6.94 (dd, J = 5.4, 7.5 Hz, 1H), 6.86–6.91 (m, 1H), 4.04 (q, J = 2.7 Hz, 2H), 3.88 (t, J = 5.4 Hz, 2H), 2.59–2.67 (m, 2H), 2.34 (s, 3H); MS (ESI+) m/z 426 $(M+H)^+$. Anal ($C_{19}H_{18}F_3N_3O_3S$) H, N, C: calcd, 53.64; found, 53.21.

4.26. *N*-(4-*tert*-Butylphenyl)-1-(thiazol-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (15b)

As for **9a,b** (29%): ^1H NMR (300 MHz, DMSO-d_6) δ ppm 9.71 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 3.7 Hz, 1H), 6.86 (d, J = 3.7 Hz, 1H), 6.71–6.76 (m, 1H), 4.10 (q, J = 2.7 Hz, 2H), 3.62 (t, J = 5.8 Hz, 2H), 2.50–2.56 (buried m, 2H), 1.26 (s, 9H); MS (DCI+) m/z 342 $(M+H)^+$. Anal ($C_{19}H_{23}N_3OS$+0.25 CF_3CO_2H) C, H, N.

4.27. 1-(Thiazol-2-yl)-*N*-(4-(trifluoromethylsulfonyl)phenyl)-1,2,3,6-tetrahydropyridine-4-carboxamide (15c)

As for **9a,b** (14%): ^1H NMR (300 MHz, DMSO-d_6) δ ppm 10.52 (s, 1H), 8.05–8.16 (m, 4H), 7.20 (d, J = 3.4 Hz, 1H), 6.86–6.90 (m, 2H), 4.15 (q, J = 2.5 Hz, 2H), 3.63 (t, J = 5.8 Hz, 2H), 2.52–2.59 (buried m, 2H); HRMS (ESI-TOF) calcd for $C_{16}H_{14}F_3N_3O_3S_2$ $(M+H)^+$ m/z 418.05014; found 418.05059.

4.28. *N*-(4-*tert*-Butylphenyl)-1-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxamide (18b)

A mixture of **17** (0.570 g, 4.98 mmol), and isoguvacine, sodium salt (1.2 g, 8.2 mmol) in water (7 mL) was heated to 90 °C and stirred for 4 h. Additional isoguvacine, sodium salt (0.52 g, 3.3 mmol) was then added and stirred overnight. The mixture was diluted with water and extracted with CH_2Cl_2. The aqueous layer was acidified with conc HCl (pH 3) and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and concentrated to give 1-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxylic acid as a white solid (0.564 g, 2.75 mmol, 55%): ^1H NMR (300 MHz, CD_3OD) δ 8.43 (d, J = 4.8 Hz, 2H), 7.02 (sept, J = 1.7 Hz, 1H), 6.74 (t, J = 4.8 Hz, 1H), 4.39 (q, J = 3.0 Hz, 2H), 3.97 (t, J = 5.8 Hz, 2H), 2.40–2.47 (m, 2H).

A solution of 1-(pyrimidin-2-yl)-1,2,3,6-tetrahydropyridine-4-carboxylic acid (0.282 g, 1.37 mmol) and oxalyl chloride (0.17 mL, 1.9 mmol) in CH_2Cl_2 (9 mL) with DMF (2 drops) was stirred for 30 min and concentrated. The tan solid was dissolved in CH_2Cl_2 (9 mL) to which was added pyridine (0.16 mL, 2.0 mmol) and 4-*t*-butylaniline (0.26 mL, 1.6 mmol). The mixture was stirred 3 h, concentrated, and partitioned between 1 N HCl and EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and chromatographed (15% EtOAc/CH_2Cl_2) to give **18b** as a tan solid (0.360 g, 1.07 mmol, 78%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J = 4.8 Hz, 2H), 7.47 (dt, J = 2.0, 8.8 Hz, 2H), 7.35 (dt, J = 2.0, 8.8 Hz, 2H), 7.35 (buried br s, 1H), 6.75 (sept, J = 1.7 Hz, 1H), 6.54 (t, J = 4.8 Hz, 1H), 4.44 (q, J = 3.0 Hz, 2H), 4.04 (t, J = 5.5 Hz, 2H), 2.55–2.63 (m, 2H), 1.31 (s, 9H); MS (ESI+) m/z 337 $(M+H)^+$. Anal ($C_{20}H_{24}N_4O$) C, H, N.

4.29. 1-(Pyrimidin-2-yl)-*N*-(4-(trifluoromethylsulfonyl)-phenyl)-1,2,3,6-tetrahydropyridine-4-carboxamide (18c)

As for **18b** (65%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 4.8 Hz, 2H), 8.00 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H), 7.72 (br s, 1H), 6.82–6.87 (m, 1H), 6.57 (t, J = 4.8 Hz, 1H), 4.48 (q, J = 2.7 Hz, 2H), 4.06 (t, J = 5.8 Hz, 2H), 2.57–2.64 (m, 2H); MS (ESI+) m/z 413 $(M+H)^+$. Anal ($C_{17}H_{15}F_3N_4O_3S$) C, H, N.

4.30. *N*-(4-*tert*-Butylphenyl)-1-(2-fluorophenyl)-1,2,3,6-tetrahydropyridine-4-carboxamide (20b)

To a solution of 1-(2-fluoro-phenyl)-piperidin-4-one (0.98 g, 5.1 mmol) and $PhNTf_2$ (1.89 g, 5.3 mmol) in THF (10 mL) at −78 °C was added LHMDS (1 N in THF, 5.6 mL, 5.6 mmol) dropwise over 30 min. The mixture was stirred at this temperature for 30 min and then allowed to warm to RT over 1 h. The solvent was then removed in vacuo and the residue was dissolved in a 1:1 mixture of EtOAc and Hex and then washed with 1 N NaOH. The organic layer was dried over Na_2SO_4 and then filtered through a plug of silica gel eluted with 1:1 EtOAc/Hex, which was used without further purification. To a solution of this crude triflate in 1:1 MeOH/DMF (20 mL) that had been saturated with CO was added 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (177 mg, 0.45 mmol), $Pd(OAc)_2$ (34 mg, 0.15 mmol), and Et_3N (1.6 mL, 10.2 mmol). This mixture was stirred under CO (1 atm) overnight and then partitioned between H_2O and Et_2O. The organic layer was washed with brine and then dried over Na_2SO_4, and concentrated in vacuo. The product was passed through a plug of silica gel eluting with CH_2Cl_2 to give 1.09 g of the corresponding ester as pale oil (4.63 mmol, 91%).

To a solution of 4-*t*-butylaniline (158 μL, 1.0 mmol) in CH_2Cl_2 (7.5 mL) was added Me_3Al (2 N, in toluene, 0.5 mL, 1.0 mmol) dropwise. The mixture was stirred for 30 min. and then the above methyl ester (117 mg, 0.497 mmol) was added and the mixture was heated to reflux overnight. After cooling to 0 °C the reaction was quenched by the careful addition of 1 N HCl and then extracted with EtOAc. The organic layer was then washed with 1 N NaOH, brine, dried (Na_2SO_4), concentrated, and chromatographed (0% to 4% EtOAc/CH_2Cl_2 gradient elution) to give **20b** as a white solid (167 mg, 0.473 mmol, 95%): ^1H NMR (300 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 7.09–7.19 (m, 3H), 6.94–7.02 (m, 1H), 6.73–6.75 (m, 1H), 3.76 (q, J = 3.0 Hz, 2H), 3.24 (t, J = 5.8 Hz, 2H), 2.53 (buried m, 2H), 1.27 (s, 9H); MS (DCI) m/z 353 $(M+H)^+$. Anal ($C_{22}H_{25}N_2OF$+0.20 CF_3CO_2H) C, H, N.

4.31. *N*-(4-*tert*-Butylphenyl)-1-(3-chloropyridin-2-yl)piperidine-4-carboxamide (22b)

A solution of **21** (2.9 mL, 19 mmol) and **8b** (1.4 g, 9.5 mmol) in EtOH (50 mL) was stirred at 85 °C for 3 days, concentrated, and chromatographed (20% EtOAc/Hex) to give the corresponding aminopyridine as a yellow oil (1.84 g, 6.85 mmol, 72%). A mixture of the aminopyridine (0.202 g, 0.75 mmol) and 1 N NaOH (2.25 mL, 2.25 mmol) in MeOH (5 mL) was stirred for 2 h, concentrated, and quenched with 1 N HCl (3 mL). The suspension was dissolved in EtOAc and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated to give the crude acid as a clear oil (203 mg, 0.84 mmol) which was used without purification. A solution of the crude acid and oxalyl chloride (0.22 mL, 2.5 mmol) in CH_2Cl_2 (10 mL) with DMF (2 drops) was stirred for 30 min and concentrated. The tan solid was dissolved in THF (20 mL), to which was added Et_3N (0.18 mL, 1.3 mmol) and 4-*t*-butylaniline (0.138 g, 0.93 mmol). The mixture was stirred overnight, concentrated, and partitioned between 1 N HCl and EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and chromatographed (30% EtOAc/Hex) to give **22b** as a yellow film (0.157 g, 0.42 mmol, 50%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, J = 1.4, 4.9 Hz, 1H), 7.59 (dd, J = 1.7, 7.6 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.15 (br s, 1H), 6.84

(dd, J = 4.9, 7.6 Hz, 1H), 3.90–3.95 (m, 2H), 2.85–2.95 (m, 2H), 2.39–2.50 (m, 1H), 2.01–2.09 (m, 4H), 1.31 (s, 9H); MS (DCI) m/z 372.1 $(M+H)^+$. Anal. ($C_{21}H_{26}ClN_3O$ + 0.05 H_2O) C, H, N.

Combustion analyses

Compound	Calculated			Found		
	C	H	N	C	H	N
6 ($C_{19}H_{15}F_6N_3O_3S$)	47.60	3.15	8.77	47.60	2.90	8.69
9b ($C_{22}H_{24}F_3N_3O$)	65.50	6.00	10.42	65.47	5.67	10.16
9f ($C_{18}H_{14}F_6N_4O$)	51.86	3.09	13.28	51.93	3.39	13.46
10c ($C_{18}H_{15}ClF_3N_3O_3S$)	48.49	3.39	9.42	48.35	3.08	9.29
10d ($C_{17}H_{15}Cl_2N_3O$.HCl+0.75 CH_2Cl_2)	47.55	3.93	9.37	47.39	3.85	9.16
10h ($C_{17}H_{14}Cl_2FN_3O$+0.6 CH_2Cl_2)	50.67	3.67	10.07	50.54	3.95	10.25
10i ($C_{17}H_{14}Cl_3N_3O$+0.65 CF_3CO_2H)	48.12	3.23	9.20	48.01	3.38	9.18
10j ($C_{17}H_{14}Cl_2FN_3O$+0.45 CF_3CO_2H)	51.49	3.49	10.06	51.57	3.53	9.91
12b ($C_{21}H_{25}N_3O$+0.11 CF_3CO_2H)	73.24	7.27	12.08	73.27	6.88	12.15
12c ($C_{18}H_{16}F_3N_3O_3S$+0.15 CF_3CO_2H)	51.29	3.80	9.81	51.31	3.40	9.64
13b ($C_{21}H_{24}FN_3O$+0.21 CF_3CO_2H)	68.17	6.47	11.13	68.29	6.85	10.73
13c ($C_{18}H_{15}F_4N_3O_3S$+0.25 CF_3CO_2H)	48.53	3.36	9.18	48.17	3.03	9.07
14c ($C_{19}H_{18}F_3N_3O_3S$)	53.64	4.26	9.88	53.21	3.91	9.65
15b ($C_{19}H_{23}N_3OS$+0.25 CF_3CO_2H)	63.30	6.33	11.36	63.31	6.33	11.20
18b ($C_{20}H_{24}N_4O$)	70.27	7.25	16.39	70.57	7.56	16.00
18c ($C_{17}H_{15}F_3N_4O_3S$)	49.51	3.67	13.59	49.28	3.50	13.35
20b ($C_{22}H_{25}N_2OF$+ 0.20 CF_3CO_2H)	71.70	6.77	7.47	71.88	6.68	7.57
22b ($C_{21}H_{26}ClN_3O$+0.05 H_2O)	67.66	7.06	11.27	67.27	7.02	11.10

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