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Pyridyl amides as potent inhibitors of T-type calcium channels

Thomas S. Reger [a,*], Zhi-Qiang Yang [a], Kelly-Ann S. Schlegel [a], Youheng Shu [a], Christa Mattern [a], Rowena Cube [a], Kenneth E. Rittle [a], Georgia B. McGaughey [a], George D. Hartman [a], Cuyue Tang [a], Jeanine Ballard [b], Yuhsin Kuo [b], Thomayant Prueksaritanont [b], Cindy E. Nuss [a], Scott M. Doran [c], Steven V. Fox [c], Susan L. Garson [c], Yuxing Li [c], Richard L. Kraus [c], Victor N. Uebele [c], John J. Renger [c], James C. Barrow [a]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, United States
[b] Department of Drug Metabolism and Pharmacokinetics, Merck Research Laboratories, West Point, PA 19486, United States
[c] Department of Depression and Circadian Disorders, Merck Research Laboratories, West Point, PA 19486, United States

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ABSTRACT

A novel series of amide T-type calcium channel antagonists were prepared and evaluated using in vitro and in vivo assays. Optimization of the screening hit **3** led to identification of the potent and selective T-type antagonist **37** that displayed in vivo efficacy in rodent models of epilepsy and sleep.

Voltage-gated calcium channels (VGCCs) are membrane-spanning proteins that allow controlled entry of Ca^{2+} ions into cells. Calcium is the most common signal transduction element in cells and its influx initiates a wide range of physiological processes.[1] VGCCs are divided into three distinct classes based on sequence homology of the critical pore-forming α1 subunit, voltage gating, current kinetics and pharmacology: $Ca_v1.x$ (L-type); $Ca_v2.x$ (N, P/Q, R-type); and $Ca_v3.x$ (T-type).[2] The T-type calcium channel family has three members (α1G/$Ca_v3.1$, α1H/$Ca_v3.2$, and α1I/$Ca_v3.3$) that are differentiated from the L, N, P/Q, and R-type families by their activation at lower membrane potentials, smaller conductance, and faster inactivation. The α1H subtype is broadly expressed in both peripheral and central tissues while the α1G and α1I subtypes are primarily expressed in CNS neurons.[3] As such, T-type calcium channels are implicated in many physiological processes including smooth muscle contraction, hormone secretion, pain processing, and thalamocortical signaling.[4] Given these diverse functions, modulators of T-type channels have significant potential for the treatment of hypertension and CNS disorders such as absence epilepsy,[5] essential tremor,[6] insomnia,[7] schizophrenia,[8] and neuropathic pain.[9]

Despite their potential role in diverse physiological and pathophysiological processes, assessment of the functional role of T-type calcium channels has been hampered by the lack of selective antagonists.[10] The anti-hypertensive agent mibefradil was initially described as a selective T-type calcium channel inhibitor.[11] However, it was later shown that its effects on cardiovascular function likely resulted from L-type channel blockade,[12] and it was ultimately withdrawn from the market due to concerns related to drug–drug interactions.[13] The recent development of α1G knockout mice[14] as well as specific anti-sense knockdown of each T-type sub-type[15] further underscores the channel's potential and interest as a therapeutic target. Several laboratories have utilized pharmacophore models for the rational design of selective T-type small molecule antagonists, but these reports are limited to in vitro studies.[16] We have recently detailed efforts to discover potent, selective, and brain penetrant T-type antagonists.[17,18] Piperidine **1**[17a] and quinazolinone **2**[18] both demonstrated in vivo efficacy in rat models of epilepsy and tremor, while **2** was also shown to suppress active wake in a rat sleep experiment. An additional lead series exemplified by amide **3** was identified in the same high-throughput screen that uncovered the precursors to **1** and **2** (Fig. 1). Compound **3** was an attractive starting point due to its good potency, low molecular weight, and modular structure. Herein, we describe the optimization of this novel series as we sought to identify

* Corresponding author. Tel.: +1 215 652 2438; fax: +1 215 652 3971.
E-mail address: thomas_reger@merck.com (T.S. Reger).

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another distinct class of potent and selective T-type calcium channel inhibitors for evaluation in CNS models.

The potency of compounds on the T-type calcium channel was assessed against the inactivated, or depolarized, state of the α1I channel subtype utilizing a FLIPR assay as we have previously reported.[19] Lead compound **3** is a single enantiomer and, as illustrated in Table 1, displayed good potency in the FLIPR assay with an IP of 235 nM. Moving to either the *S*-enantiomer (**4**) or the gem-dimethyl (**5**) analogs resulted in a significant loss of potency. Likewise, N-methylation of **3** to produce **6** led to an inactive compound.

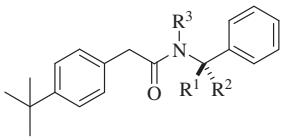
In order to improve T-type potency, we next examined modifications to the benzylamine group and the results are shown in Table 2. *ortho*-, *meta*- and *para*-Substitution was tolerated with compounds **7**–**10** essentially equipotent to **3**. Electronic factors did not significantly influence activity as a 4-chloro and 4-methoxy substituent resulted in similar potency. In an effort to reduce the overall hydrophobicity of the molecules, a nitrogen atom was incorporated at each position of the ring to produce pyridines **11**–**13**. The 2-pyridyl analog maintained modest T-type potency with a FLIPR IP of 427 nM whereas the 3- and 4-pyridyl isomers had reduced activity. The combination of the 4-chloro or 4-methoxy groups with the 2-pyridyl template to generate **14** and **15**, respectively, was synergistic as a dramatic potency enhancement was observed.

In addition to its activity in the functional FLIPR assay, compound **15** (TTA-A1)[20] also had high affinity in an α1I membrane binding assay with a K_i of 5 nM (Fig. 2).[19,21] Counterscreening in binding assays against the hERG potassium channel and L-type calcium channel revealed excellent selectivity as **15** was inactive at the highest tested concentration of 10 μM. Compound **15** was not a substrate for the rat P-glycoprotein transporter (B:A/A:B = 1.2)[22] and exhibited a brain/plasma concentration ratio of 0.27 at 1 h after oral dosing. In vivo CNS activity of **15** was evaluated in a genetic model of absence epilepsy using Wistar albino Glaxo rats bred in Rijswijk, The Netherlands (WAG/Rij).[23] These rats display abnormal thalamocortical oscillatory activities and a characteristic EEG pattern of frequent seizures. Because T-type calcium channels are involved in the regulation of thalamocortical rhythms that underlie these seizures, measurement of EEG in WAG/Rij rats serves as a relevant pharmacodynamic readout for brain penetration and T-type channel efficacy of test compounds. Despite its similar in vitro potency to piperidine **1** and quinazolinone **2**, amide **15** demonstrated inferior WAG/Rij efficacy with a modest 49% inhibition of total seizure duration over the initial 4 h period after a 10 mg/kg oral dose.[17,18] This is likely due to a poor pharmacokinetic profile in rat characterized by high clearance (CL = 52 mL/min/kg) and low bioavailability (*F*% = 6).

Compound **15** was also a potent activator of the Pregnane X Receptor (PXR, 87% of positive control rifampicin) in an in vitro SEAP assay.[24] This activity can lead to induction of the CYP3A4 enzyme which is a potential risk for clinical drug–drug interactions.[25] We sought to reduce this liability as well as to improve oral pharmacokinetics in subsequent analogs.

Molecular modeling suggested that replacement of the *tert*-butyl substituent in **15** with smaller, more polar groups may reduce the propensity for PXR activation.[24] As illustrated in Table 3, however, changes to the *tert*-butyl group generally resulted in reduced T-type potency. Indeed, *para*-substitution with a fluoro (**17**), chloro (**18**), methylsulfone (**22**), cyano (**23**), or methoxy (**24**) group produced less active compounds. Interestingly, a 4-carbomethoxy or

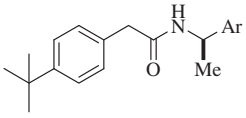
Table 1
Early SAR around HTS lead **3**.



Compd	R^1	R^2	R^3	a1I FLIPR, IP[a] (nM)
3	Me	H	H	235
4	H	Me	H	4678
5	Me	Me	H	5475
6	Me	H	Me	>10,000

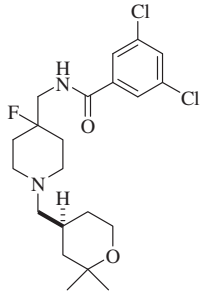
[a] Values are the mean of two or more experiments.

Table 2
Modifications to the benzylamine group

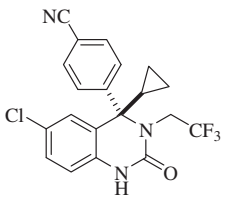


Compd	Ar	a1I FLIPR, IP[a] (nM)
7[b]	2-Chlorophenyl	332
8	4-Chlorophenyl	123
9	3-Methoxyphenyl	146
10	4-Methoxyphenyl	146
11[b]	2-Pyridyl	427
12[b]	3-Pyridyl	5383
13[b]	4-Pyridyl	>10,000
14	5-Chloropyridin-2-yl	30
15	5-Methoxypyridin-2-yl	22

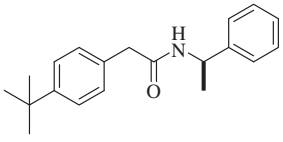
[a] Values are the mean of two or more experiments.
[b] Tested as a racemic mixture.



1 (TTA-P2)

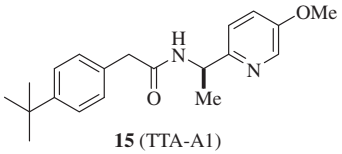


2 (TTA-Q6)



3

Figure 1. Structurally diverse T-type calcium channel antagonists.

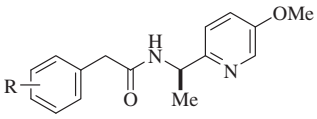


15 (TTA-A1)

a1I FLIPR IP	22 nM
a1I binding Ki	5 nM
hERG binding IC_{50}	>10 uM
L-type binding IC_{50}	>10 uM
PGP (B:A/A:B)	1.2
WAG/Rij (%inh@4h)	49% (10 mg/kg)
PXR (%Rif@10uM)	87%

Figure 2. In vitro/in vivo profile of **15**.

Table 3
Modifications to the phenylacetic acid group



Compd	R	a1I FLIPR, IP[a] (nM)	PXR[b]
15	4-*t*Bu	22	87%
16	H	>10,000	NT
17	4-F	>10,000	NT
18	4-Cl	1331	NT
19	3-Cl	2778	NT
20	2-Cl	>5000	NT
21	3,4-Dichloro	252	35%
22	4-SO_2Me	>10,000	NT
23	4-CN	>5000	NT
24	4-OMe	1742	NT
25	4-OPh	439	29%
26	4-CO_2Me	1452	−2.7%
27		1133	−7.1%
28	4-Isopropyl	45	26%
29	4-Cyclopropyl	70	22%

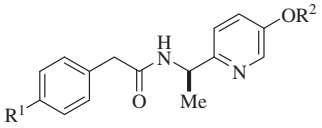
NT = not tested
[a] Values are the mean of two or more experiments.
[b] % response of PXR activation relative to Rifampicin at 10 μM (see Ref. 24).

tertiary alcohol substitution gave **26** and **27** that, while less active against the T-type calcium channel, did not activate PXR. It was ultimately discovered that just slightly reducing the steric bulk of the *tert*-butyl substituent had a significant impact on PXR activation. Compounds **28** and **29** containing an isopropyl and cyclopropyl group, respectively, exhibited reduced PXR activation and were only slightly less potent than **15**.

In an effort to regain some potency, we prepared a series of analogs in which the methoxy substituent of either **28** or **29** was modified (Table 4). Removal of the methyl group gave the hydroxypyridines **30** and **34** that had reduced activity. Incorporation of a benzyloxy, propyloxy, or trifluoroethoxy group on either the isopropyl or cyclopropyl scaffold, however, generated very potent compounds. The trifluorethoxy analogs in particular were extremely potent in the α1I FLIPR assay. The cyclopropyl-containing analogs **35**–**37** showed reduced PXR activation compared to the corresponding isopropyl analogs **31**–**33**. Compound **37** (TTA-A2), therefore, displayed a favorable overall profile as a potent T-type calcium channel antagonist with reduced PXR activation.

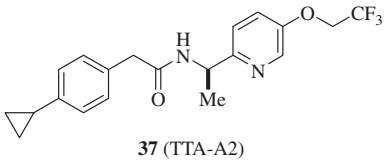
Compound **37** (TTA-A2) also exhibited high affinity in the α1I binding assay with a K_i of 1.2 nM and had excellent selectivity over the hERG potassium channel and L-type calcium channel (Fig. 3).[19]

Table 4
Modifications to the alkoxy group



Compd	R^1	R^2	a1I FLIPR, IP[a] (nM)	PXR[b]
30	*i*Pr	H	920	NT
31	*i*Pr	Benzyl	16	57%
32	*i*Pr	Propyl	10	42%
33	*i*Pr	Trifluoroethyl	5	30%
34	cyPr	H	1722	NT
35	cyPr	Benzyl	21	38%
36	cyPr	Propyl	11	12%
37	cyPr	Trifluoroethyl	6	14%

NT = not tested.
[a] Values are the mean of two or more experiments.
[b] % response of PXR activation relative to Rifampicin at 10 μM (see Ref. 24).



37 (TTA-A2)

a1I FLIPR IP	6 nM
a1I binding Ki	1.2 nM
hERG binding IC_{50}	>10 uM
L-type binding IC_{50}	>10 uM
PGP (B:A/A:B)	0.7
WAG/Rij (%inh@4h)	87% (10 mg/kg)

Figure 3. In vitro/in vivo profile of **37**.

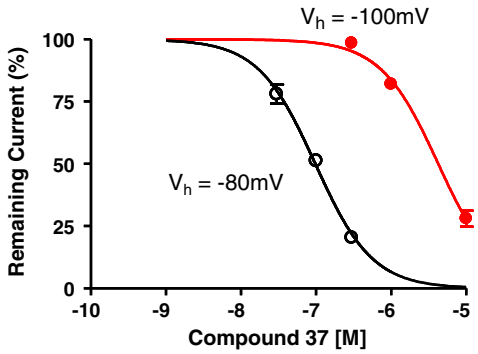


Figure 4. Inhibition of the T-type calcium channel α1I subtype by **37** (TTA-A2) as determined by standard voltage clamp. Data points reflect means ± SEs of three determinations. IC_{50} values of 98 nM and 3.7 μM were determined at −80 and −100 mV, respectively. In some cases, error bars are hidden behind the symbols.

Like compound **15**, it was not a substrate for the rat P-glycoprotein transporter (B:A/A:B = 0.7). When tested in the in vivo WAG/Rij epilepsy model, compound **37** displayed robust efficacy with an 87% reduction in total seizure time over the initial 4 h period after a 10 mg/kg oral dose.

The functional potency of **37** (TTA-A2) was confirmed in a standard voltage-clamp electrophysiology assay.[26] Similar to the previously described quinazolinone **2**,[18] amide **37** exhibited state-dependent inhibition of α1I with potencies of 98 nM and 3.7 μM at membrane holding potentials of −80 and −100 mV, respectively (Fig. 4).[27] As an additional screen for selectivity towards T-type

Table 5
Pharmacokinetic parameters of **37** (TTA-A2)

Species	CLp (mL/min/kg)	$T_{1/2}$ (h)	Vd_{ss} (L/kg)	F (%)
Rat[a]	6	1.5	0.8	68
Dog[b]	0.9	11	0.7	43
Rhesus[c]	17	0.9	0.9	7

[a] 2 mg/kg iv, DMSO, $n = 2$; 10 mg/kg p.o., 1% methylcellulose, $n = 3$.
[b] 0.5 mg/kg iv, DMSO, $n = 2$; 1 mg/kg p.o., 1% methylcellulose, $n = 2$.
[c] 0.5 mg/kg iv, DMSO, $n = 2$; 3 mg/kg p.o., 1% methylcellulose, $n = 2$.

channels, compound **37** was submitted to an external panel of 170 binding and functional assays. No activities with an IC_{50} of less than 10 μM were identified.[28]

A summary of pharmacokinetic (PK) parameters is shown in Table 5. Compound **37** exhibited a favorable PK profile in rat and dog with low clearance, low volume of distribution, and good bioavailability. These data, coupled with excellent in vitro potency and selectivity and in vivo efficacy in the Wag/Rij epilepsy model, prompted us to evaluate the effects of **37** on sleep and wake in rodents. Regulation of arousal includes a significant thalamocortical component and T-type channels play a role in maintaining normal signaling activities.[29] In the experiment, telemetry implanted rats were dosed with compound or vehicle 30 min prior to the inactive phase in a seven-day crossover design. Electrocorticogram (ECoG) and electromyogram (EMG) recordings were collected and scored for the amount of time spent awake or in each state of arousal

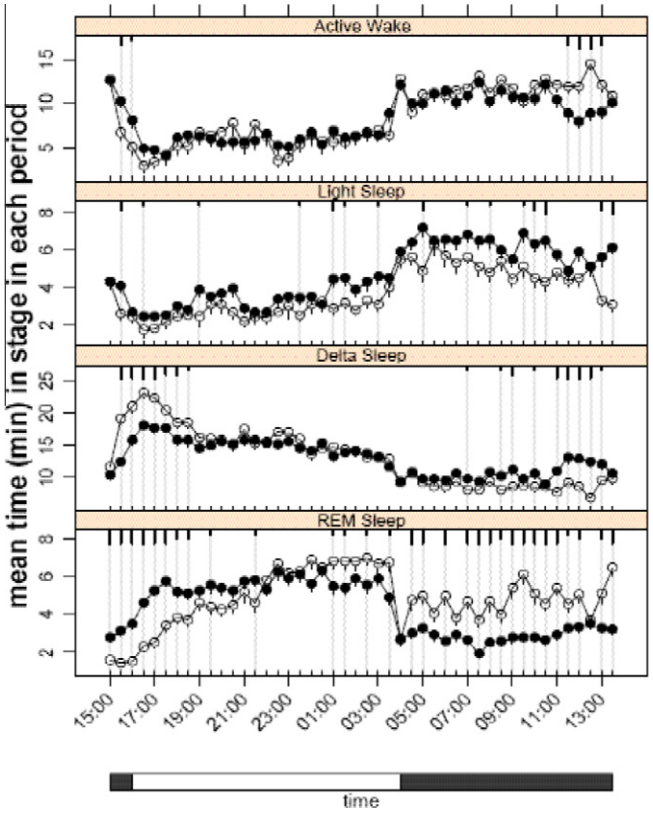
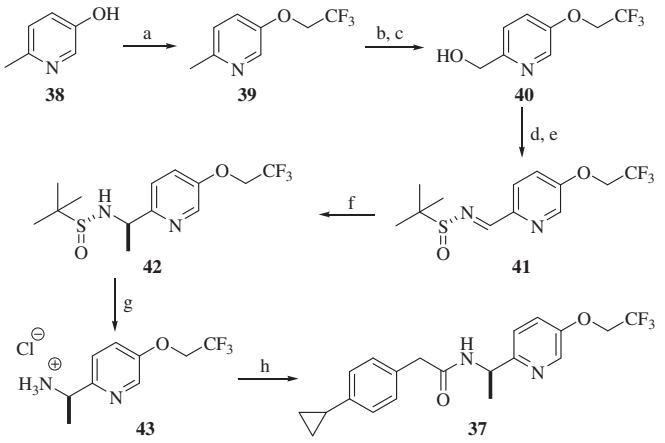


Figure 5. Effects of a 3 mg/kg dose of **37** (TTA-A2) on sleep architecture in rats. The duration of time spent in Active Wake, Light Sleep, Delta sleep, and REM sleep in vehicle (●) vs. drug (○) treated animals following a 3 mg/kg p.o. dose of **37** in 0.5% methylcellulose administered at 15:00. Values are mean ± SEM. The time bar below the *x*-axis denotes periods of lights on (□, inactive phase) and lights off (■, active phase). Vertical gray lines represent statistically significant differences from vehicle treatment as determined using mixed-model ANOVAs at each time point. Significance levels are indicated by length of tic marks (short <0.5, medium <0.01, long <0.001).



Scheme 1. Synthesis of T-type calcium channel inhibitor **37** (TTA-A2). Reagents and Conditions: (a) CF_3CH_2OTf, Cs_2CO_3, DMF; (b) *m*CPBA, $CHCl_3$; (c) Ac_2O, 100 °C, then K_2CO_3, MeOH; (d) NaOCl, TEMPO, KBr, $NaHCO_3$, CH_2Cl_2, H_2O; (e) (R)-2-methyl-2-propanesulfinamide, $CuSO_4$, CH_2Cl_2; (f) MeMgBr, CH_2Cl_2, −78 °C; (g) HCl, MeOH; (h) 4-cyclopropylphenylacetic acid, EDC, HOAt, iPr_2NEt, CH_2Cl_2.

(light sleep, delta sleep, REM) and binned into 30 min intervals. As shown in Figure 5, a 3 mg/kg dose of **37** produced significant changes in sleep architecture in rats.[30] A reduction in active wake soon after dosing was observed with a concurrent increase in delta sleep and decrease in REM sleep. These effects persisted for up to 4 h post-dose. This pattern is consistent with the effects observed with piperidine **1** and quinazolinone **2**, suggesting the common involvement of T-type calcium channels.[31] A parallel PK study performed in non-implanted satellite animals revealed that **37** reached a C_{max} of ~4 μM in plasma at 1.2 h post-dose where the changes in vigilance state were the most pronounced.

The synthesis of compound **37** (TTA-A2) is described in Scheme 1. Commercially-available 5-hydroxy-2-methylpyridine (**38**) was O-alkylated with trifluoroethyl triflate to give **39**. Treatment with mCPBA produced the pyridine N-oxide which underwent rearrangement in acetic anhydride to generate an acetoxymethyl pyridine intermediate. Hydrolysis of the acetate with potassium carbonate in methanol gave the hydroxymethyl compound **40**. A TEMPO-mediated oxidation to the corresponding aldehyde was followed by condensation with (R)-2-methyl-2-propanesulfinamide to provide **41**. In the key step, a highly diastereoselective addition of MeMgBr to **41** afforded **42** as the major isomer (14:1; R,R:R,S) that was readily separated from the minor isomer.[32] Deprotection of the *tert*-butyl sulfinyl group with HCl gave amine **43**[33] that was coupled to 4-cyclopropylphenylacetic acid[34] under standard conditions to furnish amide **37**.

In summary, we have described the evolution of the promising HTS lead compound **3** into the potent and selective T-type calcium channel antagonist **37** (TTA-A2). By varying the substitution of the two aromatic rings flanking the central amide bond, compounds with improved T-type potency and pharmacokinetics were identified. The optimized amide **37** exhibited robust efficacy in rodent models of epilepsy as well as sleep, and it represents a useful preclinical tool for further investigation of the physiological role of T-type calcium channels.[35,36]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.01.089.

References and notes

1. (a) Zamponi, G. W. *Voltage-Gated Calcium Channels*; Kluwer Academic/Plenum, 2005; (b) Tsien, R. W.; Wheeler, D. B. Voltage-Gated Calcium Channels. In *Calcium as a Cellular Regulator*; Carafoli, E., Klee, C., Eds.; Oxford University Press, 1999; pp 171–199.
2. (a) Ertel, E. A.; Campbell, K. P.; Harpold, M. M.; Hofmann, F.; Mori, Y.; Perez-Reyes, E.; Schwartz, A.; Snutch, T. P.; Tanabe, T.; Birnbaumer, L.; Tsien, R. W.; Catterall, W. A. *Neuron* **2000**, *25*, 533; (b) Perez-Reyes, E. *Physiol. Rev.* **2003**, *83*, 117.
3. (a) Catterall, W. A.; Perez-Reyes, E.; Snutch, T. P.; Striessnig, J. *Pharmacol. Rev.* **2005**, *57*, 411; (b) Talley, E. M.; Cribbs, L. L.; Lee, J. H.; Daud, A.; Perez-Reyes, E.; Bayliss, D. A. *J. Neurosci.* **1999**, *19*, 1895.
4. (a) Zamponi, G. W.; Lewis, R. J.; Todorovic, S. M.; Arneric, S. P.; Snutch, T. P. *Brain Res. Rev.* **2009**, *60*, 84; (b) Steriade, M.; McCormick, D. A.; Sejnowski, T. J. *Science* **1993**, *262*, 679; (c) Iftinca, M. C.; Zamponi, G. W. *Trends Pharmacol. Sci.* **2009**, *30*, 32; (d) Crunelli, V.; Cope, D. W.; Hughes, S. W. *Cell Calcium* **2006**, *40*, 175.
5. Varela, D.; Khosravani, H.; Heron, S. E.; Bladen, C.; Williams, T. C.; Newman, M.; Berkovic, S. F.; Scheffer, I. E.; Mulley, J. C.; Zamponi, G. W. *Biophys. J.* **2007**, 601.
6. Tröster, A. I.; Woods, S. P.; Fields, J. A.; Lyons, K. E.; Pahwa, R.; Higginson, C. I. *Eur. J. Neurol.* **2002**, *9*, 143.
7. Llinas, R. R.; Steriade, M. *J. Neurophysiol.* **2006**, *95*, 3297.
8. Zhang, Y.; Llinas, R. R.; Lisman, J. E. *Front. Neural Circuits* **2009**, *3*. doi: 10.3389/neuro.04.020.2009.
9. Todorovic, S. M.; Jevtovic-Todorovic, V. *CNS Neurol. Disord.: Drug Targets* **2006**, *5*, 639.
10. Lory, P.; Chemin, J. *Expert Opin. Ther. Targets* **2007**, *11*, 717.
11. (a) Clozel, J. P.; Ertel, S. I.; Ertel, E. A. *J. Hypertens.* **1997**, *15*, S17; (b) Massie, B. M. *Am. J. Cardiol.* **1997**, *80*, 23I.
12. Moosmang, S.; Haider, N.; Bruderl, B.; Welling, A.; Hofmann, F. *Circ. Res.* **2006**, *98*, 105.
13. Mullins, M. E.; Horowitz, B. Z.; Linden, D. H. J.; Smith, G. W.; Norton, R. L.; Stump, J. *J. Am. Med. Assoc.* **1998**, *280*, 157.
14. (a) Kim, D.; Song, I.; Keum, S.; Lee, T.; Jeong, M. J.; Kim, S. S.; McEnery, M. W.; Shin, H. S. *Neuron* **2001**, *31*, 3; (b) Lee, J.; Kim, D.; Shin, H. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 18195.
15. Bourinet, E.; Alloui, A.; Monteil, A.; Barrére, C.; Couette, B.; Poirot, O.; Pages, A.; McRory, J.; Snutch, T. P.; Eschalier, A.; Nargeot, J. *EMBO J.* **2005**, *24*, 315.
16. (a) Jung, H. K.; Doddareddy, M. R.; Cha, J. H.; Rhim, H.; Cho, Y. S.; Koh, H. Y.; Jung, B. Y.; Pae, A. N. *Bioorg. Med. Chem.* **2004**, *12*, 3965; (b) McCalmont, W. F.; Heady, T. N.; Patterson, J. R.; Lindenmuth, M. A.; Haverstick, D. M.; Gray, L. S.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3691; (c) Ku, I. W.; Cho, S.; Doddareddy, M. R.; Jang, M. S.; Keum, G.; Lee, J. H.; Chung, B. Y.; Kim, Y.; Rhim, H.; Kang, S. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5244; (d) Doddareddy, M. R.; Choo, H.; Cho, Y. S.; Rhim, H.; Koh, H. Y.; Lee, J. H.; Jeong, S. W.; Pae, A. N. *Bioorg. Med. Chem.* **2007**, *15*, 1091; (e) Seo, H. N.; Choi, J. Y.; Choe, Y. J.; Kim, Y.; Rhim, H.; Lee, S. H.; Kim, J.; Joo, D. J.; Lee, J. Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5740; (f) Hangeland, J. J.; Cheney, D. L.; Friends, T. J.; Swartz, S.; Levesque, P. C.; Rich, A. J.; Sun, L.; Bridal, T. R.; Adam, L. P.; Normandin, D. E.; Murugesan, N.; Ewing, W. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 474; (g) Gu, S. J.; Lee, J. K.; Pae, A. N.; Chung, H. J.; Rhim, H.; Han, S. Y.; Min, S. J.; Cho, Y. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2705.
17. (a) Shipe, W. D.; Barrow, J. C.; Yang, Z. Q.; Lindsley, C. W.; Yang, F. V.; Schlegel, K. S.; Shu, Y.; Rittle, K. E.; Bock, M. G.; Hartman, G. D.; Tang, C.; Ballard, J. E.; Kuo, Y.; Adarayan, E. D.; Prueksaritanont, T.; Zrada, M. M.; Uebele, V. N.; Nuss, C. E.; Connolly, T. M.; Doran, S. M.; Fox, S. V.; Kraus, R. L.; Marino, M. J.; Graufelds, V. K.; Vargas, H. M.; Bunting, P. B.; Hasbun-Manning, M.; Evans, R. M.; Koblan, K. S.; Renger, J. J. *J. Med. Chem.* **2008**, *51*, 3692; (b) Yang, Z. Q.; Barrow, J. C.; Shipe, W. D.; Schlegel, K. S.; Shu, Y.; Yang, F. V.; Lindsley, C. W.; Rittle, K. E.; Bock, M. G.; Hartman, G. D.; Uebele, V. N.; Nuss, C. E.; Fox, S. V.; Kraus, R. L.; Doran, S. M.; Connolly, T. M.; Tang, C.; Ballard, J. E.; Kuo, Y.; Adarayan, E. D.; Prueksaritanont, T.; Zrada, M. M.; Marino, M. J.; Graufelds, V. K.; DiLella, A. G.; Reynolds, I. J.; Vargas, H. M.; Bunting, P. B.; Woltmann, R. F.; Magee, M. M.; Koblan, K. S.; Renger, J. J. *J. Med. Chem.* **2008**, *51*, 6471.
18. Barrow, J. C.; Rittle, K. E.; Reger, T. S.; Yang, Z. Q.; Bondiskey, P.; McGaughey, G. B.; Bock, M. G.; Hartman, G. D.; Tang, C.; Ballard, J.; Kuo, Y.; Prueksaritanont, T.; Nuss, C. E.; Doran, S. M.; Fox, S. V.; Garson, S. L.; Kraus, R. L.; Li, Y.; Marino, M. J.; Graufelds, V. K.; Uebele, V. N.; Renger, J. J. *ACS Med. Chem. Lett.* **2010**, *1*, 75.
19. Uebele, V. N.; Nuss, C. E.; Fox, S. V.; Garson, S. L.; Cristescu, R.; Doran, S. M.; Kraus, R. L.; Santarelli, V. P.; Li, Y.; Barrow, J. C.; Yang, Z. Q.; Schlegel, K. S.; Rittle, K. E.; Reger, T. S.; Bednar, R. A.; Lemaire, W.; Mullen, F. A.; Ballard, J. E.; Tang, C.; Dai, G.; McManus, O. B.; Koblan, K. S.; Renger, J. J. *Cell Biochem. Biophys.* **2009**, *55*, 81.
20. The TTA-Ax nomenclature is provided for consistency across publications, such as Refs. 18 and 19.
21. Due to its potency, favorable physical properties, and ease of preparation compound **15** was labeled with tritium and demonstrated to be an effective radioligand for binding assays. See Ref. 19 for more details.
22. (a) Hochman, J. H.; Yamazaki, M.; Ohe, T.; Lin, J. H. *Curr. Drug Metab.* **2002**, *3*, 257; (b) Lin, J. H.; Yamazaki, M. *Drug Metab. Rev.* **2003**, *23*, 417.
23. Coenen, A. M. L.; Drinkenburg, W. H. I. M.; Inoue, M.; Vanluijtelaar, E. L. J. M. *Epilepsy Res.* **1992**, *12*, 75.
24. Gao, Y. D.; Olson, S. H.; Balkovec, J. M.; Zhu, Y.; Royo, I.; Yabut, J.; Evers, R.; Tan, E. Y.; Hartley, D. P.; Moseley, R. T. *Xenobiotica* **2007**, *37*, 124.
25. Bertilsson, G.; Heidrich, J.; Svensson, K.; Asman, M.; Jendeberg, L.; Sydow-Backman, M.; Ohlsson, R.; Postlind, H.; Blomquist, P.; Berkenstam, A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12208.
26. Kraus, R. L.; Li, Y.; Gregan, Y.; Gotter, A. L.; Uebele, V. N.; Fox, S. V.; Doran, S. M.; Barrow, J. C.; Yang, Z.-Q.; Reger, T. S.; Koblan, K. S.; Renger, J. J. *J. Pharmacol. Exp. Ther.* **2010**, *335*, 409.
27. Compound **37** was equally potent against the $Ca_v3.1$ (α1G) and $Ca_v3.2$ (α1H) channels in the standard voltage-clamp electrophysiology assay with IC_{50} values of 89 nM and 92 nM, respectively, at a holding potential of −80 mV. Compound **37** exhibited excellent selectivity against the $Ca_v1.2$ (L-type), $Ca_v2.1$ (P/Q-type), $Ca_v2.2$ (N-type), and $Ca_v2.3$ (R-type) channels which all had IC_{50} values of >30 μM at −80 mV. See Ref. 26 for details.
28. For a partial list of assays, see: Uebele, V. N.; Gotter, A. L.; Nuss, C. E.; Kraus, R. L.; Doran, S. M.; Garson, S. L.; Reiss, D. R.; Li, Y.; Barrow, J. C.; Reger, T. S.; Yang, Z. Q.; Ballard, J. E.; Tang, C.; Metzger, J. M.; Wang, S. P.; Koblan, K. S.; Renger, J. J. *J. Clin. Invest.* **2009**, *119*, 1659.
29. (a) Llinás, R. R.; Ribary, U.; Jeanmonod, D.; Kronberg, E.; Mitra, P. P. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 15222; (b) Contreras, D. *CNS Neurol. Disord.: Drug Targets* **2006**, *5*, 571; (c) Deleuze, C.; Huguenard, J. R. *J. Neurosci.* **2006**, *26*, 8633.
30. We have previously reported that the effects of **37** on active wake in rat are dose-dependent when the compound is dosed during the active phase. See Ref. 28 for details.
31. Compound **37** (TTA-A2) and quinazolinone **2** (TTA-Q6) are both state-dependent T-type channel blockers while piperidine **1** (TTA-P2) is a state-independent blocker. The consistent effect of all three compounds on sleep and wake in rodents suggests that binding to the inactivated state of the channel is sufficient for pharmacological effects.
32. For a discussion on the diastereoselectivity of Grignard additions to chiral 2-pyridyl *tert*-butyl (Ellman) sulfinimines, see: Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641–6643.
33. The absolute stereochemistry of a closely related analog of **43** was firmly established by X-ray crystallographic analysis. See Supplementary data for details.
34. The synthesis of 4-cyclopropylphenylacetic acid is described in the Supplementary data. For a leading reference on the use of cyclopropylboronic acid in Suzuki cross-coupling reactions, see: Wallace, D. J.; Chen, C. Y. *Tetrahedron Lett.* **2002**, *43*, 6987–6990.
35. We have recently reported that **37** inhibits high-fat diet-induced weight gain in mice. See Ref. 28 for details.
36. The further optimization of **37** into a clinical candidate is described here: Yang, Z.-Q.; Schlegel, K. S.; Shu, Y.; Reger, T. S.; Cube, R.; Mattern, C.; Coleman, P. J.; Small, J.; Hartman, G. D.; Ballard, J.; Tang, C.; Kuo, Y.; Prueksaritanont, T.; Nuss, C. E.; Doran, S.; Fox, S. V.; Garson, S. L.; Li, Y.; Kraus, R. L.; Uebele, V. N.; Taylor, A. B.; Zeng, W.; Fang, W.; Chavez-Eng, C.; Troyer, M. D.; Luk, J. A.; Laethem, T.; Cook, W. O.; Renger, J. J.; Barrow, J. C. *ACS Med. Chem. Lett.* **2010**, *1*, 504.