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Novel KCNQ2/Q3 Agonists as Potential Therapeutics for Epilepsy and Neuropathic Pain

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Current drugs for the treatment of seizure disorders, although effective in many patients, still suffer from a number of failures and are not effective in some forms of resistant epilepsies. Historically, many of these drugs have multiple mechanisms of action including calcium and sodium channel blockade as well as GABAergic activity and thus a number of associated side effects. Modulation of the M-current through opening of KCNQ channels has been proposed as a way to attenuate neuroexcitability and have a therapeutic benefit for the treatment of seizure disorders. Therefore, as part of our program to identify new treatments for epilepsy, we set out to identify agonists of KCNQ channels. High throughput screening of our corporate collection led to the identification of **1**, adamantane-1-carboxylic acid (3-methyl-3*H*-benzothiazol-2-ylidine) hydrazide, a potent KCNQ2/Q3 agonist. Herein, we describe the syntheses and structure−activity relationships of analogues of **1** as well as their in vivo activity in animal models of epilepsy and neuropathic pain.

Introduction

Epilepsy and neuropathic pain are disorders characterized by abnormally excessive or ectopic neuronal discharge. Approved drugs for the treatment of epilepsy include modulators of voltage-gated sodium channels, voltage-operated calcium channels, and those that modulate the GABAergic[a] neurotransmission system.[1−4] Drugs used to treat neuropathic pain include gabapentin, pregabalin, carbamazepine, and lamotrigine.[4−8] Although current treatments for epilepsy and neuropathic pain provide adequate care for certain patient populations, there remains a lack of clinical efficacy in a large percentage of patients. Suboptimal side effect profiles also limit their use.[2,9]

Although the drugs described above work through different mechanisms, a common theme is their ability to dampen neuronal excitability. One approach that has more recently received attention is the modulation of KCNQ2/Q3 potassium channels. These channels are the molecular correlate of the M-current, I_M, which is known to play an important role in neuronal excitability.[10] Activation of KCNQ2/Q3 channels hyperpolarize neuronal membranes, resulting in a dampening of action potential firing. Therefore, regulation of neuronal excitability through modulation of KCNQ2/Q3 channels represents a potentially new way to treat disorders such as epilepsy and neuropathic pain. In fact, mutations in the KCNQ2 and KCNQ3 genes have been identified as the genetic basis of benign familial neonatal convulsions, a generalized epilepsy syndrome, and potassium channel openers such as retigabine have anticonvulsant effects in animal models.[4,11−16] There is also a growing body of evidence supporting the hypothesis that nociception can be modulated by KCNQ2/Q3 channels.[4] These channels are expressed at a number of key locations in the pain transmission pathway, including the thalamus, the cerebral cortex, and the spinal cord and both KCNQ2 and KCNQ3 are expressed in rat dorsal root ganglia (DRG) including nociceptive DRG neurons. In fact, studies have shown that firing in these neurons can be inhibited by a KCNQ2/Q3 activator, which have been shown to inhibit nociception in several animal models.[17−21] In addition, the marketed analgesic flupirtine activates KCNQ2/Q3.[22] Clearly the data support the potential of KCNQ2/Q3 channels as targets for the treatment of disorders associated with hyperexcitable neurons.

High throughput screening of Icagen's diverse corporate collection identified adamantane-1-carboxylic acid (3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide **1** (Figure 1) as a potent KCNQ2/Q3 agonist (see Scheme 1 and Table 1). Further screening against the cardiac liability channel and family member KCNQ1 + KCNE1 revealed that the compound possessed >100-fold selectivity against this channel. This initial hit also exhibited anticonvulsant effects in an in vivo model of epilepsy when administered intraperitoneally (IP) but not when administered orally (PO) (see Table 2).

Our initial medicinal chemistry efforts focused on the benzothiazolylidene ring system. Specifically, we were interested in determining the effect of substituting the aryl ring with electron-withdrawing groups would have on potency and more importantly bioavailability. Next, our attention focused on the *N*-methyl, thiazolyl, and amide groups in an effort to understand their contributions to activity.

Chemistry

The syntheses of the adamantane (benzothiazol-2-ylidene)-hydrazides and the adamantane (benzooxazol-2-ylidene)-hydrazide derivatives **4a**−**m** are outlined in Scheme 1 (refer

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[a]Abbreviations: EBSS, Earle's balanced salt solution; EC_{50}, concentration required for 50% of efficiency; EtOAc, ethyl acetate; GABA, γ-aminobutyric acid; HPLC, high performance liquid chromatography; KCNQ, a class of potassium channel; MES, maximal electroshock seizure; PTZ, pentylenetetrazol induced seizure; SAR, structure−activity relationship; SDS, sodium dodecyl sulfate; SNL, spinal nerve ligation.

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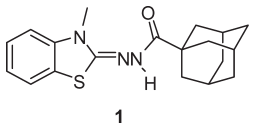

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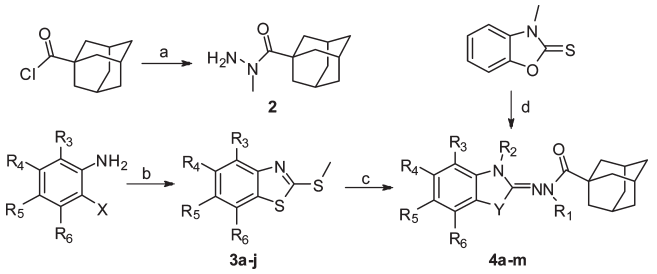
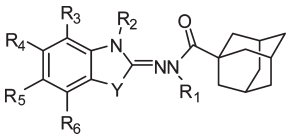
Figure 1. Adamantane-1-carboxylic acid (3-methyl-3*H*-benzothiazol-2-ylidine) hydrazide screening hit.

Scheme 1[a]



[a] Reagents: (a) Methylhydrazine, CH_2Cl_2, −78 °C, 44%. (b) (1) $EtOCS_2K$, NMP, 120 °C, 1 to 18 h; (2) MeI, K_2CO_3, DMF, 23 °C, 2 to 18 h. (c) (1) MeOTf, CH_2ClCH_2Cl, 23 °C, 4 h or EtOTf, CH_2ClCH_2Cl, 23 °C, 6 h; (2) adamantane-1-carboxylic acid hydrazide, Et_3N, EtOH, 80 °C, 8 h or **2**, Et_3N, EtOH, 80 °C, 8 h; (d) (1) MeOTf, CH_2ClCH_2Cl, 23 °C, 1 h; (2) adamantane-1-carboxylic acid hydrazide, Et_3N, EtOH, 80 °C, 82% for 2 steps.

Table 1. KCNQ2/Q3 Activation by Adamantyl Derivatives **1**, **4a**−**m**



compd	Y	R1	R2	R3	R4	R5	R6	KCNQ2/Q3 (efflux) EC_{50} (μM)[a]
1	S	H	Me	H	H	H	H	0.027 ± 0.002
4a	S	H	Me	F	H	H	H	0.38 ± 0.06
4b	S	H	Me	CF_3	H	H	H	0.091 ± 0.003
4c	S	H	Me	F	H	F	H	0.16 ± 0.04
4d	S	H	Me	H	CF_3	H	H	0.053 ± 0.005
4e	S	H	Me	H	H	F	H	0.028 ± 0.004
4f	S	H	Me	H	H	CF_3	H	0.16 ± 0.03
4g	S	H	Me	H	H	OCF_3	H	0.025 ± 0.003
4h	S	H	Me	H	H	H	F	0.098 ± 0.013
4i	S	H	Me	H	F	F	H	0.021 ± 0.005
4j	S	H	Me	H	H	H	CF_3	2.08 ± 1.04
4k	S	H	Et	H	H	H	H	0.57 ± 0.06
4l	S	Me	Me	H	H	H	H	> 10[b]
4m	O	H	Me	H	H	H	H	2.70 ± 0.68

[a] EC_{50} values were determined from eight-point, half log concentration response curves using an KCNQ2/Q3 isotopic efflux assay as described in the Experimental Section. Data shown with standard error (±SEM) represent the mean of 2−4 separate determinations. All active compounds (EC50 < 1 μM) exhibited > 30-fold selectivity compared to KCNQ1 + KCNE1. [b] An EC_{50} value could not be calculated due to low potency.

to Table 1 for Y and R groups). Adamantane-1-carboxylic acid *N*-methylhydrazide, **2**, was prepared from adamantanecarbonyl chloride and methylhydrazine. Commercially available bromo- or fluoroanilines were condensed with potassium ethyl xanthate to afford benzothiazole thiones, which were alkylated with iodomethane to afford methylsulfanylbenzothiazoles **3a**−**j**.[23−27] Further alkylation of **3a**−**j** with methyl trifluoromethanesulfonate afforded triflate salts, which were then treated with adamantane-1-carboxylic acid hydrazide to afford adamantyl derivatives **4a**−**j**.[28] Alkylation of 2-(methylthio)benzothiazole with ethyl trifluoromethanesulfonate followed by treament with adamantane-1-carboxylic acid hydrazide afforded adamantyl derivative **4k**. Methylation of 2-(methylthio)benzothiazole with methyl trifluoromethanesulfonate followed by treatment of the resulting triflate salt with adamantane-1-carboxylic acid *N*-methylhydrazide, **2**, afforded adamantyl derivative **4l**. Compound **4m** was prepared from 3-methyl-2(3*H*)-benzoxazolethione via methylation with methane trifluoromethanesulfonate and reaction of the resulting salt with adamantane-1-carboxylic acid hydrazide.

The 3-methyl-6-trifluoromethoxy derivatives were readily prepared from 2-(methylthio)benzothiazole **3g** (Scheme 2, refer to Table 3 for Y and R groups). Methylation of **3g** afforded the triflate salt, followed by treatment with an ethanolic solution of hydrazine afforded hydrazide **5**.[28,29] Acylation of this material with carboxylic acid chlorides, cyclopentyl 4-nitrophenyl carbonate,[30] isopropyl chloroformate, or di-*tert*-butyl dicarbonate proceeded to afford hydrazides **6a**−**p**.

Table 2. Efficacy of Select Compounds in in Vivo Anticonvulsant Assay, the Mouse Maximal Electroshock Seizure (MES) assay

compd	mouse MES IP 30 mg/kg	mouse MES PO 30 mg/kg
1	5/8[a]	1/8
4d	2/8	0/8
4e	6/8	0/8
4f	6/8	0/8
4g	8/8	8/8
4h	3/8	0/8[b]
4i	6/8	1/8

[a] Number of mice protected from seizure/number of mice tested. [b] Assayed at 20 mg/kg dose.

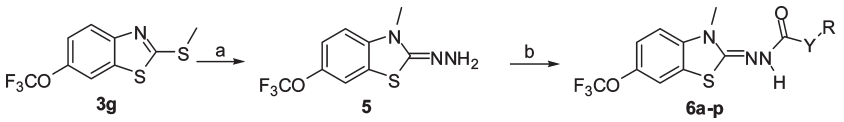
Results and Discussion

Compounds were tested to measure their activity against KCNQ2/Q3.[31−35] The EC_{50} values of compounds **1**, **4a**−**m** are shown in Table 1. The addition of fluoro, trifluoromethyl, and trifluoromethoxy moieties on the aryl ring were generally well-tolerated (**4a**−**i**) with the exception of trifluoromethyl in the R6 position (**4j**). This substitution resulted in a > 10-fold loss in in vitro potency. An increase in size of the *N*-alkyl group (**4k**) was detrimental to potency giving approximately 9-fold less activity. Replacement of sulfur with oxygen resulted in a dramatic loss of activity (**4m**) and, finally, amide *N*-methylation resulted in a compound (**4l**) that lacked agonist activity at 10 μM. This suggests that this part of the molecule plays a critical role this series ability to increase efflux through KCNQ2/Q3 channels.

Select compounds were tested for their anticonvulsant activity in the mouse maximal electroshock seizure (MES) model.[36] The results of this assay are summarized in Table 2. Compounds were initially administered IP and several exhibited pronounced anticonvulsant effects (**1**, **4e**, **4f**, **4g**, **4i**). However, bioavailability issues were found upon oral dosing. In fact, only compound **4g**, the 3-methyl-6-trifluoromethoxy analogue, was efficacious when given orally and thus was chosen for further SAR development.

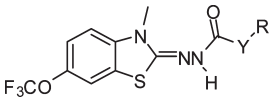
The in vitro and in vivo data for compounds **6a**−**p** is summarized in Table 3. Compound **6d**, which contains a small one-carbon acyl group was not a potent KCNQ2/Q3 agonist. However, compounds with monocyclic alkyl groups (**6a**−**b**) were approximately as potent as the adamantyl compound **1**,

Scheme 2[a]



[a] Reagents: (a) (1) MeOTf, CH_2ClCH_2Cl, 23 °C, 2 h; (2) hydrazine, Et_3N, EtOH, 23 °C, 1 h; 81% for 2 steps. (b) RYCOCl, K_2CO_3, CH_3CN-H_2O, 23−60 °C, 1−4 h or (1) cyclopentanol, 4-nitrophenyl chloroformate, pyridine, 23 °C, 15 h; (2) **5**, NMM, DMF, 75 °C, 6 h, 74% or 1.0 M isopropyl chloroformate solution in toluene, NMM, THF, 23 °C, 6 h, 64% or Boc_2O, THF, 23 °C, 3 h, 69%.

Table 3. KCNQ2/Q3 Activation and Efficacy in the Mouse Maximal Electroshock Seizure (MES) and the Rat Subcutaneous Pentylenetetrazol Induced Seizure (PTZ) Assays by (3-Methyl-6-trifluoromethoxy-3*H*-benzothiazol-2-ylidine)hydrazides **6a−p**



compd	Y	R	KCNQ2/Q3 (efflux) EC_{50} (μM)[a]	mouse MES PO 20 mg/kg	mouse MES PO 10 mg/kg	mouse MES PO EC_{50} (mg/kg)[b]	rat PTZ PO EC_{50} (mg/kg)[b]
6a		*c*hexyl	0.028 ± 0.004	1/8[c]	nt[d]	nt	nt
6b		*c*pentyl	0.062 ± 0.023	0/8	nt	nt	nt
6c		*t*Bu	0.71 ± 0.18	7/8	0/8	nt	3.8
6d		Me	> 10[e]	nt	nt	nt	nt
6e	CH_2	*t*Bu	0.049 ± 0.001	7/8	8/8	4.4	3.8
6f	CH_2	*c*pentyl	0.044 ± 0.004	8/8	5/8	< 10	7.5
6g	CH_2	*i*Pr	0.22 ± 0.04	7/8	2/8	nt	nt
6h		2-THF	5.57 ± 2.84	nt	nt	nt	nt
6i		3-THF	6.73 ± 2.72	nt	nt	nt	nt
6j		3-F Ph	0.10 ± 0.02	4/8	nt	nt	nt
6k		4-F Ph	0.044 ± 0.004	7/8	5/8	nt	nt
6l		Ph	0.26	7/8	1/8	nt	nt
6m		2-furyl	0.50 ± 0.01	2/8	nt	nt	nt
6n	O	*c*pentyl	0.029 ± 0.009	nt	7/8	nt	nt
6o	O	*i*Pr	0.095 ± 0.037	8/8	5/8	8.8	2.6
6p	O	*t*Bu	0.023 ± 0.009	nt	8/8	nt	nt

[a] EC_{50} values were determined from eight-point, half log concentration response curves using an KCNQ2/Q3 isotopic efflux assay as described in the Experimental Section. Data shown with standard error (±SEM) represent the mean of two to four separate determinations. All active compounds (EC_{50} < 1 μM) exhibited > 30-fold selectivity compared to KCNQ1 + KCNE1. [b] EC_{50} values were determined from latency to seizure scores as described in the Experimental Section. [c] Number of mice protected from seizure/number of mice tested. [d] Not tested. [e] An EC_{50} value could not be calculated due to low potency.

but these compounds were not efficacious in the MES model at 20 mg/kg PO dose. Interestingly, the incorporation of oxygen into the monocyclic alkyl groups resulted in compounds (**6h−i**) that were approximately 100-fold less active in vitro than **6b**. The moderately potent *tert*-butyl analogue **6c** was efficacious at a dose of 20 mg/kg in the MES model. The incorporation of aromatic acyl groups produced compounds that were potent KCNQ2/Q3 agonists and also efficacious in vivo. Most notable was compound **6k**, which protected 5 out of 8 animals in the mouse MES model (10 mg/kg, po). The incorporation of a methylene spacer into the branched or monocyclic alkyl appendages resulted in compounds that possessed excellent in vitro potency and oral efficacy in the mouse MES (**6e−g**) and rat pentylenetetrazol induced seizure (PTZ) (**6e−f**) assays.[36] As the methylene spacer had proved beneficial we decided to investigate the possibility of employing the more enzymatically stable carbamates. The carbazate analogues **6n−p** had good KCNQ2/Q3 potency and were found to be orally efficacious in the mouse MES model as well as the rat PTZ model. This suggests that the compounds possessed broad spectrum anticonvulsant activity. Oral ED_{50} values were obtained for select compounds in both the mouse MES and the rat PTZ assays. Compounds **6e**, **6f**, and **6o** displayed good in vivo efficacy in both of the anticonvulsant assays with oral ED_{50} values less than 10 mg/kg. Compounds 6e, **6f**, and **6o** were also evaluated in pain models (Table 4). The compounds reduced the number of flinches in the phase II portion of the rat formalin model, an effect thought to result from secondary spinal sensitization.[37,38] The percent reduction in flinches for compounds **6e**, **6f**, and **6o** was similar to morphine, gabapentin, and retigabine. A 10 mg/kg po dose of

Table 4. Comparison of Icagen KCNQ2/Q3 Agonists and Reference Compounds in the Rat Formalin and Spinal Nerve Ligation (SNL) Models

compd	dose mg/kg	route	reduction in flinches recorded in phase II (formalin), %	reduction in tactile allodynia score (SNL), %
morphine	3	sc	38	77
gabapentin	100	iv	61[a]	70[a]
retigabine	10	po	nt[b]	0[c]
retigabine	17	po	49	nt
6e	17	po	55	nt
6f	34	po	28	nt
6o	10	po	47	100[c]

[a] Data presented by S. Dworetzky, at the IBC 2nd International Ion Channel Meeting (Boston, MA, October 20−22, 2003). [b] Not tested. [c] Experiments performed at Dr. Frank Porreca's laboratory, University of Arizona (Tuscon).

compound **6o** resulted in a complete reduction of tactile allodynia in the spinal nerve ligation (SNL) model of neuropathic pain.[39] Administration of morphine (3 mg/kg sc) and gabapentin (100 mg/kg iv) also resulted in a large reduction of tactile allodynia; however, a 10 mg/kg po dose of retigabine did not result in any reduction of tactile allodynia. In the behavioral assays, no overt effects on behavior were noted that would be considered to confound any findings of efficacy. Effects on motor coordination were specifically examined in mice using the rotarod assay.[36] In this assay, oral ED_{50} values of 20.0 and 16.2 mg/kg were determined for compounds **6e** and **6o**, respectively. In addition, Cerep receptor panel binding assays on compounds **6e**, **6f**, and **6o** did not support off-target mechanisms observed in in vivo efficacy.[40] The results of Cerep receptor panel binding assays are included in the Supporting Information.

In conclusion, adamantane-1-carboxylic acid (3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide **1** was identified as a potent KCNQ2/Q3 agonist that was >100-fold selective against cardiac liability channel and family member KCNQ1 + KCNE1. The SAR of this compound was explored, and an orally active anticonvulsant (**4g**) was found. Further optimization led to novel compounds that were potent, selective against KCNQ1 + KCNE1, and Cerep receptor panel binding assays with oral ED_{50}'s less than 10 mg/kg in two in vivo anticonvulsant models (**6e**, **6f**, **6o**). In addition, these compounds were shown to be orally active in rodent models of pain.

Experimental Section

General Procedures. All reagents and solvents were obtained from commercial sources and used as received. ^1H and ^{13}C NMR spectra were obtained with a Varian Inova spectrometer at 300 and 75 MHz, respectively, in the solvent indicated. Coupling constants (*J*) are in hertz (Hz). Mass spectrometric identification of compounds was performed using standard electrospray ionization methods, MS (ESI), with a Perkin-Elmer SCIEX API 150 EX. Melting points were obtained with a Electrothermal IA9000 digital melting point apparatus. All compounds were assessed as greater than 95% pure by two HPLC columns (C18 and Cyano) on a Michrom Bioresources Magic 2002 system (solvent A = 100% water/1.0 mL/L formic acid; solvent B = 99% CH_3OH/1% water/1.0 mL/L formic acid; gradient of 0% to 100% B over 10 min). CMA80 is solvent mixture that was used as an eluent in chromatography; it is a 2/18/80 mixture of $NH_4OH/CH_3OH/CHCl_3$.

KCNQ2/Q3 Isotopic Efflux Assay. Cells expressing voltage-gated K^+ channels, such as KCNQ2-like channels were loaded with $^{86}Rb^+$ by culture in media containing ^{86}RbCl. Following loading, culture media were removed and the cells were washed in EBSS to remove residual traces of $^{86}RB^+$. Cells were pre-incubated with drug (0.01−30 μM in EBSS) and then $^{86}Rb^+$ efflux was stimulated by exposing cells to EBSS solution supplemented with a submaximal concentration of KCl (generally 7−20 mM) in the continued presence of drug. After a suitable efflux period, the EBSS/KCl solution was removed from the cells and the $^{86}Rb^+$ content determined by Cherenkov counting (Wallac Trilux). Cells were then lysed with a SDS solution and the $^{86}Rb^+$ content of the lysate determined. Percent $^{86}Rb^+$ efflux was calculated according to:

$$(^{86}Rb^+ \text{ content in EBSS}/(^{86}Rb^+ \text{ content in EBSS} + {}^{86}Rb^+ \text{ content of the lysate})) \times 100$$

Efflux was normalized to the maximal $^{86}Rb^+$ efflux (i.e., that induced by a high concentration of KCl, generally 30−135 mM).

Mouse Maximal Electroshock Seizure (MES) Assay. Male CD-1 mice were tested in the MES assay using the electroshock seizure apparatus designed by Walhquist Instrument Co. (Salt Lake City, UT). Compounds were formulated in 5% dimethyl sulfoxide/95% (0.5% hydroxypropylmethylcellulose/1% Tween 80) and were administered in a volume of 10 mL/kg 15 min before electroshock application for ip administration and 30 min before electroshock application for po administration. The shock level was set at 50 mA, and the duration was set at 0.2 s. A drop of 1% proparacaine solution was placed in each eye, electrodes were placed over the eyes, and shock was administered. Latency to hind limb extension was measured to the nearest 0.1 s. If extension did not occur within 6 s, the animal was scored as protected and a latency score of 6 s was recorded.

Rat Subcutaneous Pentylenetetrazol Seizure (PTZ) Assay. Compounds were formulated in 0.5% methylcellulose and administered po in a volume of 1 mL/kg in male Sprague−Dawley rats 30 min before administration of 85 mg/kg PTZ sc. The latency to tonic-clonic seizure was recorded in minutes, using administration of PTZ as time 0. If no seizure was observed within 15 min post-PTZ the animal was considered protected, and a latency score of 15 min was recorded.

Rat Formalin Assay. One hour prior to assay, male Sprague−Dawley rats had a small (0.5 g) loose metal band glued to the right hind paw. Compounds were formulated in 0.5% methylcellulose and administered po. 1 h before assay. Immediately before testing, 50 μL of 2.5% formalin (Richard-Allen Scientific) was administered sc into the dorsal surface of the right hind paw using a 30 gauge needle. Rats were immediately placed without restraint into a plexiglass observation chamber situated over an electromagnetic detector system (Automated Formalin Analyzer, Department of Anesthesiology, University of California, San Diego). Paw flinches of the formalin-injected paw are detected by the electromagnetic system and counted for 60 min following formalin injection. Phase I flinches are defined as flinches occurring within the first 10 min following formalin injection. Phase II flinches occur from 11 to 60 min following formalin injection.

Spinal Nerve Ligation (SNL) Assay. A neuropathic pain condition was induced in male Sprague−Dawley rats using a modification of the nerve injury model described by Kim and Chung.[39] Rats were anesthetized with halothane, and the L5 spinal nerve was exposed, carefully isolated, and tightly ligated with 4.0 silk suture distal to the dorsal root ganglia. The wound was sutured, and the rats were allowed to recover for 2−3 weeks. To test the effect of compounds on tactile allodynia following L5 nerve ligation, Von Frey tactile withdrawal thresholds were determined. Test animals were placed in a box separated by walls with a wire mesh floor allowing access to the plantar surface of the paw. Tactile testing was conducted using a set of calibrated nylon fibers (Von Frey hairs), each approximately 3 cm long and sequentially increasing in diameter and stiffness, mounted on handles. Beginning with a medium hair, the tip of the fiber was placed on the plantar surface of the rat paw and applied with a pressure to make it slightly bend. If the rat responded by lifting its paw, the next descending hair was tested. Failure to lift the hind paw after 4 s was scored a negative response and the next ascending hair was applied. Dixon's Up−Down Method was applied for a total of six responses following and including the first change in response to determine 50% paw withdrawal thresholds. A top threshold was set at 15 g. Baseline measurements of allodynia were performed immediately prior to subject selection and compound administration. Compounds were formulated in 0.5% methylcellulose and were administered po. Behavioral testing was conducted one and two hours following administration.

Adamantane-1-carboxylic Acid *N*-Methylhydrazide (2). A solution of methylhydrazine (1.064 mL, 20.0 mmol) in 20 mL of CH_2Cl_2 at −78 °C was treated over 30 min with adamantanecarbonyl chloride (1.99 g, 10.0 mmol). After addition was complete, the reaction mixture was warmed to rt over a 2 h period. The reaction mixture was diluted with CH_2Cl_2 (100 mL),

washed with 1:1 H_2O/ $NaHCO_3$ (satd aq solution) (2 × 100 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica (elution with a gradient of $CHCl_3$ to 10% CMA80/$CHCl_3$) afforded 916 mg (4.40 mmol, 44%) of **2** as a white powder; mp 146−147 °C. ^{1}H NMR ($CDCl_3$) δ: 1.74 (s, C(CH_2C**H**C**H$_2$)$_3$), 2.03 (s, C(CH_2-C**H**CH_2)$_3$), 2.12 (s, C(C**H$_2$**CHCH_2)$_3$), 3.25 (s, 3 H, C(O)N(C**H$_3$**)-NH_2), 3.88 (b, 2 H, C(O)N(CH_3)N**H$_2$**). ^{13}C NMR (DMSO-d_6) δ: 28.7 (C(CH_2CHCH_2)$_3$), 37.2 (C(CH_2CH**C**H_2)$_3$), 38.7 (C(**C**H_2-$CHCH_2$)$_3$), 40.8 (**C**(CH_2CHCH_2)$_3$), 41.6 (C(O)N(**C**H_3)NH_2), 177.3 (**C**(O)N(CH_3)NH_2). MS (ESI) m/z 209 (M + H)$^+$.

Representative Procedure for Conversion of 2-Fluoro Anilines to 2-(Methylthio)benzothiazoles (Method A). 4-Fluoro-2-(methylthio)benzothiazole (3a). A solution of 2,6-difluoroaniline (2.16 g, 16.73 mmol) in 16.7 mL of NMP was treated dropwise with a solution of potassium ethyl xanthate (2.81 g, 17.57 mmol) in 16.7 mL of NMP and the mixture was heated at 120 °C for 4 h. The reaction mixture was cooled and partitioned between EtOAc (300 mL) and brine (200 mL). The organic phase was washed with brine (2 × 200 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica (elution with $CHCl_3$) followed by recrystallization from $CHCl_3$ afforded 2.02 g (10.9 mmol) of the intermediate 4-fluorobenzothiazole-2(3*H*)-thione. The intermediate was dissolved in 40 mL of DMF and treated with K_2CO_3 (1.81 g, 13.1 mmol) and iodomethane (0.81 mL, 13.1 mmol). The reaction mixture was stirred overnight and partitioned between EtOAc (300 mL) and H_2O (200 mL). The organic phase was washed with brine (2 × 200 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica (elution with 5% EtOAc/hexane) afforded 1.99 g (10.0 mmol, 60% for 2 steps) of **3a** as an oil, which becomes a waxy solid upon standing for a few days; mp 37.1−37.4 °C. ^{1}H NMR ($CDCl_3$−CD_3OD) δ: 2.72 (s, SC**H$_3$**), 7.04 (ddd, J = 0.8, 8.0, 8.1 Hz, Ar**H**), 7.16 (ddd, J = 4.6, 8.1, 8.1 Hz, Ar**H**), 7.43 (d, J = 8.0 Hz, Ar**H**). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 16.0 (**S**CH_3), 111.9 (d, J = 18.0 Hz, CF**C**H), 116.7 (d, J = 4.3 Hz, CFCH-CH**C**H), 124.9 (d, J = 7.4 Hz, CFCH**C**HCH), 137.6 (d, J = 3.7 Hz, CH**C**SCN), 141.8 (d, J = 13.7 Hz, CS**C**NCF), 155.7 (d, J = 254.9 Hz, **C**F), 169.7 (S**C**(N)SCH_3). MS (ESI) m/z 200 (M + H)$^+$.

4-Trifluoromethyl-2-(methylthio)benzothiazole (3b). Prepared from 2-fluoro-6-(trifluoromethyl)aniline according to method A; mp 64.9−65.2 °C. ^{1}H NMR ($CDCl_3$) δ: 2.82 (s, SC**H$_3$**), 7.30 (dd, J = 7.8, 8.0 Hz, C(CF_3)CHC**H**), 7.68 (d, J = 7.7 Hz, C(CF_3)C**H**), 7.90 (d, J = 8.0 Hz, CHC**H**CS). ^{13}C NMR ($CDCl_3$) δ: 16.2 (**S**CH_3), 122.5 (q, J = 32.0 Hz, **C**CF_3), 123.4 (Ar**C**H), 123.7 (q, J = 4.9 Hz, C(CF_3)**C**H), 123.9 (q, J = 273.1 Hz, **C**F_3), 124.8 (Ar**C**H), 137.3 (CH**C**SCN), 149.6 (CS**C**NC(CF_3)), 171.0 (S**C**(N)SCH_3). MS (ESI) m/z 250 (M + H)$^+$.

4,6-Difluoro-2-(methylthio)benzothiazole (3c). Prepared from 2,4,6-trifluoroaniline according to mMethod A; mp 55.9−56.5 °C. ^{1}H NMR ($CDCl_3$) δ: 2.78 (s, SC**H$_3$**), 6.90 (ddd, J = 2.3, 10.0, 10.0 Hz, CFC**H**CF), 7.24 (ddd, J = 1.4, 2.3, 7.6 Hz, CFC**H**CS). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 16.1 (**S**CH_3), 102.0 (dd, J = 21.9, 28.0 Hz, CF**C**HCFCH), 103.3 (dd, J = 14.5, 26.5 Hz, CFCHCF**C**H), 138.0 (dd, J = 4.8, 12.5 Hz, CS**C**NCF), 138.9 (J = 1.8 Hz, CH**C**SCN), 153.7 (dd, J = 13.4, 258.2 Hz, **C**F), 159.4 (dd, J = 10.4, 247.3 Hz, **C**F), 168.3 (d, J = 1.8 Hz, S**C**(N)SCH_3). MS (ESI) m/z 218 (M + H)$^+$.

5-Trifluoromethyl-2-(methylthio)benzothiazole (3d). Prepared from 2-fluoro-5-(trifluoromethyl)aniline according to method A; mp 67.8−68.2 °C. ^{1}H NMR ($CDCl_3$) δ: 2.78(s, SC**H$_3$**), 7.48 (d, J = 8.3 Hz, C(CF_3)C**H**CH), 7.78 (d, J = 8.3 Hz, C(CF_3)CHC**H**CS), 8.09 (s, CNC**H**C(CF_3)). ^{13}C NMR ($CDCl_3$) δ: 15.9 (**S**CH_3), 118.4 (q, J = 4.2 Hz, CN**C**HC(CF_3)), 120.5 (q, J = 3.5 Hz, C(CF_3)**C**HCH), 121.5 (CH**C**HCS), 124.3 (q, J = 272.2 Hz, **C**F_3), 128.7 (q, J = 32.6 Hz, **C**(CF_3)), 138.7 (CH**C**SCN), 153.0 (CS**C**NCH), 170.6 (S**C**(N)SCH_3). MS (ESI) m/z 250 (M + H)$^+$.

6-Fluoro-2-(methylthio)benzothiazole (3e). Prepared from 2,4-difluoroaniline according to mMethod A; mp 69.9−70.2 °C. ^{1}H NMR ($CDCl_3$) δ: 2.75 (s, SC**H$_3$**), 7.11 (ddd, J = 2.6, 8.9, 8.9 Hz, CHC**H**CF), 7.40 (dd, J = 2.5, 8.1 Hz, CFC**H**CS), 7.77 (dd, J = 4.8, 8.9 Hz, CNC**H**CH). ^{13}C NMR ($CDCl_3$) δ: 16.0 (**S**CH_3), 107.5 (d, J = 27.2 Hz, CF**C**HCS), 114.4 (d, J = 24.7 Hz, CH**C**HCF), 122.1 (d, J = 9.1 Hz, CN**C**HCH), 136.1 (d, J = 11.0 Hz, CH**C**SCN), 150.0 (d, J = 1.6 Hz, CS**C**NCH), 159.8 (d, J = 244.7 Hz, **C**F), 167.6 (d, J = 2.8 Hz, S**C**(N)SCH_3). MS (ESI) m/z 200 (M + H)$^+$.

6-Trifluoromethyl-2-(methylthio)benzothiazole (3f). Prepared from 2-fluoro-4-(trifluoromethyl)aniline according to mMethod A; mp 55.8−57.0 °C. ^{1}H NMR ($CDCl_3$) δ: 2.82 (s, SC**H$_3$**), 7.65 (d, J = 8.5 Hz, CHC**H**C(CF_3), 7.94 (d, J = 8.6 Hz, CNC**H**CH), 8.04 (s, C(CF_3)C**H**CS). ^{13}C NMR ($CDCl_3$) δ: 16.0 (**S**CH_3), 118.6 (q, J = 4.3 Hz, Ar**C**H), 121.6 (CN**C**HCH), 123.3 (q, J = 3.4 Hz, Ar**C**H), 124.3 (q, J = 272.2 Hz, **C**F_3), 126.3 (q, J = 33.0 Hz, **C**(CF_3)), 135.4 (CH**C**SCN), 155.4 (CS**C**NCH), 171.9 (S**C**(N)SCH_3). MS (ESI) m/z 250 (M + H)$^+$.

6-Trifluoromethoxy-2-(methylthio)benzothiazole (3g). Prepared from 2-fluoro-4-(trifluoromethoxy)aniline according to method A; mp 35.6−35.9 °C. ^{1}H NMR (DMSO-d_6) δ: 2.78 (s, SC**H$_3$**), 7.35−7.42 (m, CHC**H**C(OCF_3)), 7.88 (d, J = 8.8 Hz, CNC**H**CH), 8.08−8.16 (m, C(OCF_3)C**H**CS). ^{13}C NMR (DMSO-d_6) δ: 16.2 (**S**CH_3), 115.6 (C(OCF_3)**C**HCS), 120.6 (CH**C**HC(OCF_3)), 120.9 (q, J = 254.4 Hz, O**C**F_3), 122.6 (CN**C**HCH), 136.5 (CH**C**SCN), 145.3 (CH**C**(OCF_3)CH), 152.5 (CS**C**NCH), 170.8 (S**C**(N)SCH_3). MS (ESI) m/z 266 (M + H)$^+$.

7-Fluoro-2-(methylthio)benzothiazole (3h). Prepared from 2,3-difluoroaniline according to method A; mp 50.4−50.8 °C. ^{1}H NMR ($CDCl_3$) δ: 2.82 (s, SC**H$_3$**), 7.03 (dd, J = 8.4, 8.8 Hz, CHC**H**CF), 7.38 (ddd, J = 5.5, 8.0, 8.2 Hz, CHC**H**CH), 7.68 (d, J = 8.0 Hz, CNC**H**CH). ^{13}C NMR ($CDCl_3$) δ: 16.2 (**S**CH_3), 109.8 (d, J = 18.6 Hz, CH**C**HCF), 117.2 (d, J = 3.6 Hz, CN**C**HCH), 122.1 (d, J = 16.8 Hz, CF**C**SCN), 127.1 (d, J = 7.3 Hz, CH**C**HCH), 156.2 (d, J = 2.7 Hz, CS**C**NCH), 156.6 (d, J = 249.1 Hz, CH**C**FCS), 169.5 (d, J = 1.8 Hz, S**C**(N)SCH_3). MS (ESI) m/z 200 (M + H)$^+$.

5,6-Difluoro-2-(methylthio)benzothiazole (3i). Prepared from 2,4,5-trifluoroaniline according to method A; mp 80.7−81.2 °C. ^{1}H NMR ($CDCl_3$) δ: 2.77 (s, SC**H$_3$**), 7.50 (dd, J = 7.5, 9.3 Hz, C**H**CFCF), 7.62 (dd, J = 7.1, 10.6 Hz, C**H**CFCF). ^{13}C NMR ($CDCl_3$) δ: 16.1 (**S**CH_3), 108.7 (d, J = 22.2 Hz, **C**HCF), 109.3 (d, J = 19.5 Hz, **C**HCF), 130.2 (d, J = 8.8 Hz, CH**C**SCN), 148.4 (dd, J = 14.7, 247.8 Hz, CH**C**FCF), 149.5 (d, J = 12.2 Hz, CS**C**NCH), 150.0 (dd, J = 14.5, 246.3 Hz, CH**C**FCF), 169.8 (S**C**(N)SCH_3). MS (ESI) m/z 218 (M + H)$^+$.

7-Trifluoromethyl-2-(methylthio)benzothiazole (3j). Prepared from 2-fluoro-3-(trifluoromethyl)aniline according to method A; mp 41.3−41.7 °C. ^{1}H NMR ($CDCl_3$) δ: 2.83 (s, SC**H$_3$**), 7.51 (ddd, J = 0.6, 7.8, 7.8 Hz, CHC**H**CH), 7.59 (dd, J = 0.4, 7.5 Hz, CHC**H**C(CF_3)), 8.03 (dd, J = 0.3, 7.8 Hz, CNC**H**CH). ^{13}C NMR ($CDCl_3$) δ: 16.0 (**S**CH_3), 121.5 (q, J = 4.3 Hz, CH**C**HC-(CF_3)), 123.7 (q, J = 272.5 Hz, **C**F_3), 124.2 (q, J = 33.9 Hz, CH**C**(CF_3)CS), 124.7 (Ar**C**H), 126.1 (Ar**C**H), 131.9 (C(CF3)-**C**SCN), 154.7 (CS**C**NCH), 170.4 (S**C**(N)CH_3). MS (ESI) m/z 250 (M + H)$^+$.

Representative Procedure for Conversion of 2-(Methylthio)-benzothiazoles to Adamantane-1-carboxylic Acid (3-Methyl-3*H*-benzothiazol-2-ylidine)hydrazides (Method B). Adamantane-1-carboxylic Acid (3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (1). A solution of 2-(methylthio)benzothiazole (399 mg, 2.20 mmol) in 7.0 mL of 1,2-dichloroethane was treated with methyl trifluoromethanesulfonate (266 μL, 2.42 mmol) and the reaction was stirred at rt for 1 h. The reaction mixture was concentrated in vacuo and dried under vacuum. The crude triflate salt was dissolved in 11 mL of ethanol and added to a solution of adamantane-1-carboxylic acid hydrazide (513 mg, 2.64 mmol) and triethylamine (552 μL, 3.96 mmol) in 11 mL of ethanol. The reaction mixture was heated at 80 °C for 8 h then concentrated in vacuo. The residue was partitioned between EtOAc (100 mL) and H_2O (60 mL). The organic phase was washed with brine (60 mL), dried (Na_2SO_4),

and concentrated. Recrystallization from EtOAc afforded 588 mg (1.72 mmol, 78%) of **1** as a white solid; mp 236.8−237.2 °C. ^{1}H NMR (DMSO-d_6) δ: 1.67 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.85 (s, C(C**H$_2$**CHCH$_2$)$_3$), 1.98 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.47 (s, N**CH$_3$**), 7.05 (ddd, J = 1.0, 7.6, 7.7 Hz, Ar**H**), 7.20 (d, J = 7.8 Hz, CNC**H**CH), 7.30 (ddd, J = 1.1, 8.2, 8.3 Hz, Ar**H**), 7.54 (dd, J = 1.0, 7.6 Hz, 1 H, CHC**H**CS), 9.83 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 28.3 (C(CH$_2$**C**HCH$_2$)$_3$), 31.2 (N**C**H$_3$), 36.8 (C(CH$_2$CH**C**H$_2$)$_3$), 39.4 (C(**C**H$_2$CHCH$_2$)$_3$), 40.4 (**C**(CH$_2$CHCH$_2$)$_3$), 110.4 (CN**C**HCH), 122.2 (Ar**C**H), 122.4 (CH**C**SCN), 123.0 (Ar**C**H), 127.2 (Ar**C**H), 141.6 (CS**C**NCH), 166.8 (S**C**(N)N), 173.7 (NH**C**(O)C). MS (ESI) m/z 342 (M + H)$^+$.

Adamantane-1-carboxylic Acid (4-Fluoro-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4a). Prepared from 4-fluoro-2-(methylthio)benzothiazole (**3a**) according to method B; mp 211.0−211.8 °C. ^{1}H NMR (DMSO-d_6) δ: 1.70 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.90 (s, C(C**H$_2$**CHCH$_2$)$_3$), 2.00 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.66 (d, J = 2.9 Hz, N**CH$_3$**), 7.03 (ddd, J = 3.7, 7.8, 8.2 Hz, CHC**H**CH), 7.15 (dd, J = 8.3, 13.0 Hz, CFC**H**CH), 7.38 (d, J = 7.7 Hz, CHC**H**CS), 9.89 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 28.2 (C(CH$_2$**C**HCH$_2$)$_3$), 33.5 (d, J = 8.9 Hz, N**C**H$_3$), 36.7 (C(CH$_2$CH**C**H$_2$)$_3$), 39.2 (C(**C**H$_2$CHCH$_2$)$_3$), 40.4 (**C**(CH$_2$CHCH$_2$)$_3$), 114.5 (d, J = 19.5 Hz, CF**C**HCH), 119.1 (CH**C**SCN), 122.5 (d, J = 7.0 Hz, CH**C**HCH), 125.1 (d, J = 3.6 Hz, CH**C**HCS), 128.8 (d, J = 9.2 Hz, CS**C**NCF), 148.0 (d, J = 243.3 Hz, **C**F), 166.2 (S**C**(N)N), 173.5 (NH**C**(O)C). MS (ESI) m/z 360 (M + H)$^+$.

Adamantane-1-carboxylic Acid (4-Trifluoromethyl-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4b). Prepared from 4-trifluoromethyl-2-(methylthio)benzothiazole (**3b**) according to method B; mp 203.5−204.4 °C. ^{1}H NMR ($CDCl_3$−CD_3OD) δ: 1.66 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.89 (s, C(C**H$_2$**CHCH$_2$)$_3$), 1.98 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.65 (s, N**CH$_3$**), 7.01 (dd, J = 8.0, 8.0 Hz, CHC**H**CH), 7.42 (d, J = 7.6 Hz, C(CF$_3$)C**H**CH), 7.48 (d, J = 8.0 Hz, CHC**H**CS). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 28.0 (C(CH$_2$**C**HCH$_2$)$_3$), 34.6 (q, J = 7.0 Hz, N**C**H$_3$), 36.4 (C(CH$_2$CH**C**H$_2$)$_3$), 39.0 (C(**C**H$_2$CHCH$_2$)$_3$), 40.6 (**C**(CH$_2$CHCH$_2$)$_3$), 113.3 (q, J = 32.6 Hz, **C**(CF$_3$)), 120.9 (CH**C**HCH), 123.5 (q, J = 271.8 Hz, **C**F$_3$), 125.2 (Ar**C**), 125.3 (Ar**C**), 125.4 (Ar**C**), 125.8 (Ar**C**), 138.5 (CS**C**NC(CF$_3$)), 167.8 (S**C**(N)N), 175.2 (NH**C**(O)C). MS (ESI) m/z 410 (M + H)$^+$.

Adamantane-1-carboxylic Acid (4,6-Difluoro-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4c). Prepared from 4,6-difluoro-2-(methylthio)benzothiazole (**3c**) according to method B; mp 166.3−167.3 °C. ^{1}H NMR ($CDCl_3$) δ: 1.76 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.99 (s, C(C**H$_2$**CHCH$_2$)$_3$), 2.08 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.75 (s, N**CH$_3$**), 6.79 (d,d,d, J = 1.9, 9.7, 9.7 Hz, CFC**H**CF), 6.89 (d, J = 7.0 Hz, CFC**H**CS), 7.94 (s, NN**H**C(O)). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 28.2 (C(CH$_2$**C**HCH$_2$)$_3$), 33.5 (d, J = 9.2 Hz, N**C**H$_3$), 36.6 (C(CH$_2$CH**C**H$_2$)$_3$), 39.1 (C(**C**H$_2$CHCH$_2$)$_3$), 40.7 (**C**(CH$_2$CHCH$_2$)$_3$), 103.1 (dd, J = 24.4, 27.1 Hz, CF**C**HCF), 105.5 (dd, J = 4.0, 26.6 Hz, CF**C**HCS), 125.6 (Ar**C**), 125.7 (Ar**C**), 147.7 (dd, J = 12.2, 248.4 Hz, CN**C**FCH), 157.3 (dd, J = 11.0, 244.5 Hz, CH**C**FCH), 167.1 (S**C**(N)N), 175.5 (NH**C**(O)C). MS (ESI) m/z 410 (M + H)$^+$.

Adamantane-1-carboxylic Acid (5-Trifluoromethyl-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4d). Prepared from 5-trifluoromethyl-2-(methylthio)benzothiazole (**3d**) according to method B; mp 239.8−240.1 °C. ^{1}H NMR (DMSO-d_6) δ: 1.70 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.89 (s, C(C**H$_2$**CHCH$_2$)$_3$), 2.01 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.56 (s, N**CH$_3$**), 7.39 (d, J = 8.2 Hz, C(CF$_3$)C**H**CH), 7.53 (s, CNC**H**C(CF$_3$)), 7.79 (d, J = 8.1 Hz, CHC**H**CS), 9.94 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 28.2 (C(CH$_2$**C**HCH$_2$)$_3$), 31.3 (N**C**H$_3$), 36.7 (C(CH$_2$CH**C**H$_2$)$_3$), 39.2 (C(**C**H$_2$CHCH$_2$)$_3$), 40.9 (**C**(CH$_2$CHCH$_2$)$_3$), 106.7 (CN**C**HC(CF$_3$)), 118.5 (C(CF$_3$)**C**HCH, 123.5 (CH**C**SCN), 124.9 (q, J = 272.3 Hz, **C**F$_3$), 127.5 (CH**C**HCS), 127.8 (q, J = 31.7 Hz, (**C**(CF$_3$)), 142.0 (CS**C**NCH), 166.0 (S**C**(N)N), 173.5 (NH**C**(O)C). MS (ESI) m/z 410 (M + H)$^+$.

Adamantane-1-carboxylic Acid (6-Fluoro-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4e). Prepared from 6-fluoro-2-(methylthio)benzothiazole (**3e**) according to method B; mp 227.5−229.0 °C. ^{1}H NMR (DMSO-d_6) δ: 1.68 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.86 (s, C(C**H$_2$**CHCH$_2$)$_3$), 1.99 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.46 (s, N**CH$_3$**), 7.10−7.22 (m, CH**C**HCF and CFC**H**CS), 7.54 (dd, J = 2.5, 8.8 Hz, CNC**H**CH), 9.82 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 28.2 (C(CH$_2$**C**HCH$_2$)$_3$), 31.1 (N**C**H$_3$), 36.7 (C(CH$_2$CH**C**H$_2$)$_3$), 39.2 (C(**C**H$_2$CHCH$_2$)$_3$), 40.3 (**C**(CH$_2$CHCH$_2$)$_3$), 110.2 (d, J = 27.7 Hz, CH**C**HCF), 110.6 (d, J = 8.6 Hz, CN**C**HCH), 113.6 (d, J = 23.6 Hz, CF**C**HCS), 123.8 (d, J = 10.0 Hz, CH**C**SCN), 138.1 (CSC**N**CH), 157.8 (d, J = 237.4 Hz, CH**C**FCH), 166.4 (S**C**(N)N), 173.5 (NH**C**(O)C). MS (ESI) m/z 360 (M + H)$^+$.

Adamantane-1-carboxylic Acid (6-Trifluoromethyl-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4f). Prepared from 6-trifluoromethyl-2-(methylthio)benzothiazole (**3f**) according to method B; mp 206.1−206.6 °C. ^{1}H NMR (DMSO-d_6) δ: 1.67 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.86 (s, C(C**H$_2$**CHCH$_2$)$_3$), 1.97 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.50 (s, N**CH$_3$**), 7.32 (d, J = 8.4 Hz, CNC**H**CH), 7.60 (d, J = 8.4 Hz, CHC**H**C(CF$_3$)), 7.97 (s, C(CF$_3$)C**H**CS), 9.90 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 28.2 (C(CH$_2$**C**HCH$_2$)$_3$), 31.3 (N**C**H$_3$), 36.7 (C(CH$_2$CH**C**H$_2$)$_3$), 39.2 (C(**C**H$_2$CHCH$_2$)$_3$), 40.4 (**C**(CH$_2$CHCH$_2$)$_3$), 110.1 (CN**C**HCH), 120.0 (d, J = 4.0 Hz, CH**C**HC(CF$_3$)), 122.3 (q, J = 32.0 Hz, **C**(CF$_3$)), 123.6 (CH**C**SCN), 124.4 (d, J = 4.0 Hz, C(CF$_3$)**C**HCS), 124.9 (q, J = 271.3 Hz, **C**F$_3$), 144.5 (CS**C**NCH), 166.1 (S**C**(N)N), 173.5 (NH**C**(O)C). MS (ESI) m/z 410 (M + H)$^+$.

Adamantane-1-carboxylic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4g). Prepared from 6-trifluoromethoxy-2-(methylthio)benzothiazole (**3g**) according to method B; mp 170.1−170.5 °C. ^{1}H NMR (DMSO-d_6) δ: 1.70 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.89 (s, C(C**H$_2$**CHCH$_2$)$_3$), 2.00 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.50 (s, N**CH$_3$**), 7.24−7.30 (m, CNC**H**CH and CHC**H**C(OCF$_3$)), 7.72 (s, C(OCF$_3$)C**H**CS), 9.88 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 28.3 (C(CH$_2$**C**HCH$_2$)$_3$), 31.4 (N**C**H$_3$), 36.8 (C(CH$_2$CH**C**H$_2$)$_3$), 39.4 (C(**C**H$_2$CHCH$_2$)$_3$), 40.4 (**C**(CH$_2$CHCH$_2$)$_3$), 110.8 (CH**C**HC(OCF$_3$)), 116.7 (CN**C**HCH), 120.4 (C(OCF$_3$)**C**HCS), 120.9 (q, J = 255.8, O**C**F$_3$), 124.1 (CH**C**SCN), 140.8 (CS**C**NCH), 143.1 (**C**(OCF$_3$)), 166.4 (S**C**(N)N), 173.6 (NH**C**(O)C). MS (ESI) m/z 426 (M + H)$^+$.

Adamantane-1-carboxylic Acid (7-Fluoro-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4h). Prepared from 7-fluoro-2-(methylthio)benzothiazole (**3h**) according to method B; mp 223.7−224.0 °C. ^{1}H NMR (DMSO-d_6) δ: 1.70 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.89 (s, C(C**H$_2$**CHCH$_2$)$_3$), 2.01 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.51 (s, N**CH$_3$**), 6.97 (dd, J = 8.9, 8.7 Hz, CHC**H**CF), 7.10 (d, J = 8.1 Hz, CNC**H**CH), 7.36 (ddd, J = 8.2, 8.2, 6.0 Hz, CHC**H**CH), 9.95 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 28.2 (C(CH$_2$**C**HCH$_2$)$_3$), 31.7 (N**C**H$_3$), 36.7 (C(CH$_2$CH**C**H$_2$)$_3$), 39.2 (C(**C**H$_2$CHCH$_2$)$_3$), 40.4 (**C**(CH$_2$CHCH$_2$)$_3$), 106.7 (d, J = 2.8 Hz, CN**C**HCH), 108.3 (d, J = 24.3 Hz, CF**C**SCN), 108.5 (d, J = 18.6 Hz, CH**C**HCF), 128.9 (d, J = 7.9 Hz, CH**C**HCH), 143.9 (d, J = 7.0 Hz, CS**C**NCH), 156.5 (d, J = 242.3 Hz, CH**C**FCS), 165.5 (S**C**(N)N), 173.6 (NH**C**(O)C). MS (ESI) m/z 360 (M + H)$^+$.

Adamantane-1-carboxylic Acid (5,6-difluoro-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4i). Prepared from 5,6-difluoro-2-(methylthio)benzothiazole (**3i**) according to method B; mp 145.0−145.9 °C. NMR (DMSO-d_6) δ: 1.68 (s, C(CH$_2$CHC**H$_2$**)$_3$), 1.85 (s, C(C**H$_2$**CHCH$_2$)$_3$), 1.99 (s, CCH$_2$C**H**CH$_2$)$_3$), 3.45 (s, N**CH$_3$**), 7.43 (dd, J = 6.7, 11.6 Hz, CNC**H**CF), 7.75 (dd, J = 7.8, 10.1 Hz, CFC**H**CS), 9.85 (s, NN**H**C(O)). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 28.2 (C(CH$_2$**C**HCH$_2$)$_3$), 31.1 (N**C**H$_3$), 36.5 (C(CH$_2$CH**C**H$_2$)$_3$), 39.1 (C(**C**H$_2$CHCH$_2$)$_3$), 40.6 (**C**(CH$_2$CHCH$_2$)$_3$), 99.1 (d, J = 23.8 Hz, CNC**H**CF), 110.9 (d, J = 22.6 Hz, CFC**H**CS), 117.2 (d, J = 4.9 Hz, CH**C**SCN), 137.5 (d, J = 9.7 Hz, CS**C**NCH), 145.8 (dd, J = 14.0, 243.5 Hz, CF**C**FCHCS), 149.7 (dd, J = 14.0, 245.8 Hz, CH**C**FCF), 167.1 (S**C**(N)N), 175.2 (NH**C**(O)C). MS (ESI) m/z 378 (M + H)$^+$.

Adamantane-1-carboxylic Acid (7-Trifluoromethyl-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4j). Prepared from 7-trifluoromethyl-2-(methylthio)benzothiazole (**3j**) according to method B; mp 189.2−189.4 °C. ^{1}H NMR ($CDCl_3$) δ: 1.77 (s, C(CH$_2$CHC**H$_2$**)$_3$), 2.01 (s, C(C**H$_2$**CHCH$_2$)$_3$), 2.09 (s, C(CH$_2$C**H**CH$_2$)$_3$), 3.59 (s, N**CH$_3$**), 7.11 (d, J = 7.9 Hz, CHC**H**C(CF$_3$)), 7.29 (d, J = 7.7 Hz,

CNC**H**CH), 7.39 (dd, J = 7.8, 7.9 Hz, CHC**H**CH), 7.90 (s, NN**H**C(O)). ^{13}C NMR ($CDCl_3$) δ: 28.2 (C(CH_2CHCH_2)$_3$), 31.3 (N**C**H$_3$), 36.5 (C(CH_2C**H**CH_2)$_3$), 39.2 (C(**C**H_2CHCH_2)$_3$), 40.7 (**C**(CH_2CHCH_2)$_3$), 112.2 (CN**C**HCH), 118.9 (q, J = 4.3 Hz, CH**C**HC(CF_3)), 120.5 (C(CF_3)**C**SCN), 123.5 (q, J = 273.1 Hz, CF_3), 124.5 (q, J = 33.6 Hz, **C**(CF_3)), 127.1 (CH**C**HCH), 142.5 (CS**C**NCH), 164.9 (S**C**(N)N), 174.7 (NH**C**(O)C). MS (ESI) m/z 410 $(M + H)^+$.

Adamantane-1-carboxylic Acid (3-Ethyl-3*H*-benzothiazol-2-ylidine)hydrazide (4k). A solution of 2-(methylthio)benzothiazole (1.24 g, 6.84 mmol) in 20.0 mL of 1,2-dichloroethane was treated with ethyl trifluoromethanesulfonate (0.975 mL, 7.52 mmol) and the reaction was stirred at rt for 6 h. The reaction mixture was concentrated in vacuo and dried under vacuum. The crude triflate salt was dissolved in 20 mL of ethanol and added to a solution of adamantane-1-carboxylic acid hydrazide (1.59 g, 8.21 mmol) and triethylamine (1.72 mL, 12.3 mmol) in 20 mL of ethanol. The reaction mixture was heated at 80 °C for 8 h and then concentrated in vacuo. The residue was partitioned between EtOAc (200 mL) and H_2O (120 mL). The organic phase was washed with brine (120 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica (4:1 EtOAc/hexane eluent) afforded 1.65 g (4.64 mmol, 68%) of **4k** as a white solid; mp 162.6−164.2 °C. ^{1}H NMR ($CDCl_3$−CD_3OD) δ: 1.24 (t, J = 7.1 Hz, NCH$_2$C**H$_3$**), 1.66 (s, C(CH_2CH-C**H$_2$**)$_3$), 1.88 (s, C(C**H$_2$**$CHCH_2$)$_3$), 1.97 (s, C(CH_2C**H**CH_2)$_3$), 3.99 (q, J = 7.2 Hz, NC**H$_2$**CH_3), 6.87−6.96 (m, CNC**H**CH and C**H**CHCS), 7.18 (dd, J = 7.8, 7.8 Hz, CNCHC**H**), 7.24 (d, J = 7.6 Hz, CHC**H**CS). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 11.7 (NCH_2**C**H$_3$), 28.1 (C(CH_2**C**HCH_2)$_3$), 36.4 (C(CH_2C**H**CH_2)$_3$), 39.0 (C(**C**H_2CHCH_2)$_3$), 39.1 (N**C**H_2CH_3), 40.5 (**C**(CH_2CH-CH_2)$_3$), 109.4 (CN**C**HCH), 121.6 (Ar**C**H), 122.1 (Ar**C**H), 122.4 (CH**C**SCN), 126.6 (CNCH**C**HCH), 140.2 (CS**C**NCH), 166.4 (S**C**(N)N), 175.0 (NH**C**(O)C). MS (ESI) m/z 356 $(M + H)^+$.

Adamantane-1-carboxylic Acid (3-Methyl-3*H*-benzothiazol-2-ylidine)hydrazide (4l). A solution of 2-(methylthio)benzothiazole (181 mg, 1.00 mmol) in 3.0 mL of 1,2-dichloroethane was treated with methyl trifluoromethanesulfonate(121 μL, 1.10 mmol) and the reaction was stirred at rt for 1 h. The reaction mixture was concentrated in vacuo and dried under vacuum. The crude triflate salt was dissolved in 5 mL of ethanol and added to a solution of adamantane-1-carboxylic acid *N*-methylhydrazide (**2**) (250 mg, 1.20 mmol) and triethylamine (250 μL, 1.80 mmol) in 5.0 mL of ethanol. The reaction mixture was heated at 80 °C for 8 h then concentrated in vacuo. The residue was partitioned between EtOAc (50 mL) and H_2O (30 mL). The organic phase was washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica (5−33% EtOAc/hexane eluent) afforded 78.7 mg (0.22 mmol, 22%) of **4l** as a white solid; mp 199.0−203.6 °C. ^{1}H NMR ($CDCl_3$−CD_3OD) δ: 1.57 (s, C(CH_2CHCH_2)$_3$), 1.87 (s, C(CH_2-C**H**CH_2)$_3$), 1.94 (s, C(C**H$_2$**$CHCH_2$)$_3$), 3.08 (s, NN(C**H$_3$**)C(O)), 3.53 (s, NC**H$_3$**), 6.99−7.06 (m, CNC**H**CH and C**H**CHCS), 7.27 (ddd, J = 7.7, 7.8 Hz, CNCHC**H**), 7.34 (d, J = 7.8 Hz, CH-C**H**CS). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 28.3 (C(CH_2**C**HCH_2)$_3$), 30.7 (N**C**H_3), 36.7 (C(CH_2C**H**CH_2)$_3$), 36.9 (NN(**C**H_3)C(O)), 37.5 (C(**C**H_2CHCH_2)$_3$), 42.3 (**C**(CH_2CHCH_2)$_3$), 109.7 (CN**C**HCH), 122.1 (Ar**C**H), 122.3 (Ar**C**H), 122.4 (CH**C**SCN), 126.8 (Ar**C**H), 141.1 (CS**C**NCH), 168.8 (S**C**(N)N), 178.4 (NH**C**(O)C). MS (ESI) m/z 356 $(M + H)^+$.

Adamantane-1-carboxylic Acid (3-methyl-3*H*-benzoxazol-2-ylidine)hydrazide (4m). A solution of 3-methyl-2(3*H*)-benzoxazolethione (165 mg, 1.00 mmol) in 3.0 mL of 1,2-dichloroethane was treated with methyl trifluoromethanesulfonate (136 μL, 1.20 mmol) and the reaction was stirred at rt for 1 h. The reaction mixture was concentrated in vacuo and dried under vacuum. The crude triflate salt was dissolved in 5 mL of ethanol and added to a solution of adamantane-1-carboxylic acid hydrazide (233 mg, 1.20 mmol) and triethylamine (250 μL, 1.80 mmol) in 5.0 mL of ethanol. The reaction mixture was heated at 80 °C for 7 h then concentrated in vacuo. The residue was partitioned between EtOAc (50 mL) and H_2O (30 mL). The organic phase was washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Recrystallization from EtOAc afforded 268 mg (0.823 mmol, 82%) of **4m** as a white solid; mp 157.3−159.7 °C. ^{1}H NMR ($CDCl_3$−CD_3OD) δ: 1.67 (s, C(CH_2CH-C**H$_2$**)$_3$), 1.88 (s, C(C**H$_2$**$CHCH_2$)$_3$), 1.99 (s, C(CH_2C**H**CH_2)$_3$), 3.28 (s, NC**H$_3$**), 6.81 (d, J = 7.6 Hz, CNC**H**CH), 6.91 (dd, J = 7.7, 7.8 Hz, CNCHC**H**CH), 7.05−7.10 (m, CHC**H**CHCO and CHC**H**CO). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 28.0 (C(CH_2**C**H-CH_2)$_3$), 28.4 (N**C**H_3), 36.4 (C(CH_2C**H**CH_2)$_3$), 39.0 (C(**C**H_2CH-CH_2)$_3$), 40.3 (**C**(CH_2CHCH_2)$_3$), 107.4 (Ar**C**H), 109.2 (Ar**C**H), 120.9 (CH**C**HCH), 124.6 (CHC**H**CH), 133.1 (CO**C**NCH), 144.7 (CH**C**OCN), 152.0 (O**C**(N)N), 173.4 (NH**C**(O)C). MS (ESI) m/z 326 $(M + H)^+$.

(6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)-hydrazone (5). A solution of 6-trifluoromethoxy-2-(methylthio)benzothiazole (**3g**) (3.32 g, 12.53 mmol) in 25 mL of 1,2-dichloroethane was treated with methyl trifluoromethanesulfonate (1.70 mL, 15.04 mmol) and the reaction was stirred at rt for 2 h. The reaction mixture was concentrated in vacuo and dried under vacuum. The crude triflate salt was dissolved in 50 mL of ethanol and slowly added dropwise to a solution of hydrazine (1.97 mL, 62.6 mmol) in 50 mL of ethanol. After addition was complete, the reaction mixture was stirred at rt for 1 h. Most of the ethanol was removed in vacuo and the residue was dissolved in $CHCl_3$ (500 mL), washed with satd $NaHCO_3$ solution (250 mL), brine (250 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography on silica (1/4 CH_3CN/$CHCl_3$ eluent) afforded 2.80 g (10.64 mmol, 85%) of **5** as a white solid; mp 113.4−113.6. ^{1}H NMR (DMSO-d_6) δ: 3.34 (s, NC**H$_3$**), 5.10 (s, NN**H$_2$**), 7.04 (d, J = 8.7 Hz, CNC**H**CH), 7.18 (ddd, J = 0.8, 2.3, 8.6 Hz, CHC**H**C(OCF_3)), 7.58 (d, J = 1.7 Hz, C(OCF_3)C**H**CS). ^{13}C NMR (DMSO-d_6) δ: 30.9 (N**C**H_3), 109.0 (CH**C**HC(OCF_3)), 116.4 (CN**C**HCH), 119.8 (C(OCF_3)**C**HCS), 120.8 (q, J = 256.1 Hz, C(O**C**F_3)), 124.8 (CH**C**SCN), 141.4 (CS**C**NCH), 142.5 (q, J = 2.1 Hz, **C**(OCF_3)), 157.0 (S**C**(N)N). MS (ESI) m/z 264 $(M + H)^+$.

Representative Procedure for Conversion of (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (5) to Carboxylic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazides (Method C). Cyclohexylcarboxylic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)-hydrazide (6a). A solution of (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) (80.5 mg, 0.306 mmol) and K_2CO_3 (47 mg, 0.336 mmol) in 6 mL of 9:1 CH_3CN/H_2O was treated with cyclohexanecarbonyl chloride (45 μL, 0.336 mmol) and stirred at rt for 1 h. The reaction mixture was concentrated in vacuo. The residue was partitioned between EtOAc (15 mL) and water (15 mL). The organic phase was washed with 1 M HCl solution (15 mL) and brine (15 mL) and then dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica (15−25% CH_3CN/$CHCl_3$ eluent) afforded 82.7 mg (0.221 mmol, 72%) of **6a** as a white solid; mp 198.6−199.3. ^{1}H NMR (DMSO-d_6) δ: 1.03−1.50 (m, 5 Alkyl**H**), 1.56−1.78 (m, 5 Alkyl**H**), 2.20 (m, NHC(O)C**H**), 3.43 (s, NC**H$_3$**), 7.19−7.29 (m, CNC**H**CH and CHC**H**C(OCF_3)), 7.68 (s, C(OCF_3)C**H**CS), 10.11 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 25.9 (C(O)CHCH$_2$-**C**H$_2$), 26.1 (C(O)CHCH$_2$CH$_2$**C**H$_2$), 30.0 (C(O)CH**C**H$_2$), 31.3 (N**C**H_3), 43.3 (NHC(O)**C**H), 110.7 (CH**C**HC(OCF_3)), 116.6 (CN**C**HCH), 120.4 (C(OCF_3)**C**HCS), 120.9 (q, J = 255.5, O**C**F_3), 124.0 (CH**C**SCN), 140.8 (CS**C**NCH), 143.1 (**C**(OCF_3)), 164.9 (S**C**(N)N), 172.0 (NH**C**(O)C). MS (ESI) m/z 374 $(M + H)^+$.

Cyclopentylcarboxylic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6b). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and cyclopentanecarbonyl chloride according to method C; mp 215.5−216.0. ^{1}H NMR (DMSO-d_6) δ: 1.50−1.82 (m, 8 Alkyl**H**), 2.63−2.72 (m, NHC(O)C**H**), 3.47 (s, NC**H$_3$**), 7.23−7.30 (m, CNC**H**CH and CHC**H**C(OCF_3)), 7.72 (d, J = 0.9 Hz,

C(OCF$_3$)C**H**CS), 10.2 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 26.3 (C(O)CHCH$_2$**C**H$_2$), 30.6 (C(O)CH**C**H$_2$CH$_2$), 31.2 (N**C**H$_3$), 43.3 (NHC(O)**C**H), 110.6 (CH**C**HC(OCF$_3$)), 116.5 (CN**C**HCH), 120.3 (C(OCF$_3$)**C**HCS), 120.7 (q, J = 255.7 Hz, O**C**F$_3$), 123.9 (CH**C**SCN), 140.6 (CS**C**NCH), 142.9 (**C**(OCF$_3$)), 164.7 (S**C**(N)N), 172.1 (NH**C**(O)C). MS (ESI) m/z 360 (M + H)$^+$.

2,2-Dimethylpropanoic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6c). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and trimethylacetyl chloride according to method C except that the reaction mixture was heated at 60 °C for 4 h; mp 214.7−216.9. ^{1}H NMR ($CDCl_3$) δ: 1.29 (s, C(O)C(C**H$_3$**)$_3$), 3.50 (s, NC**H$_3$**), 6.89 (d, J = 8.8 Hz, CNC**H**CH), 7.11 (d, J = 8.9 Hz, CHC**H**C(OCF$_3$)), 7.19 (s, C(OCF$_3$)C**H**CS), 7.85 (s, NN**H**C(O)). ^{13}C NMR ($CDCl_3$) δ: 27.5 (C(O)C(**C**H$_3$)$_3$), 31.2 (N**C**H$_3$), 38.9 (C(O)**C**(CH$_3$)$_3$), 109.6 (CH**C**HC(OCF$_3$)), 115.9 (CN**C**HCH), 120.2 (C(OCF$_3$)**C**HCS), 120.7 (q, J = 256.9 Hz, O**C**F$_3$), 123.8 (CH**C**SCN), 140.1 (CS**C**NCH), 143.8 (**C**(OCF$_3$)), 166.2 (S**C**(N)N), 175.1 (NH**C**(O)C). MS (ESI) m/z 348 (M + H)$^+$.

Acetic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6d). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and acetyl chloride according to method C; mp 209.0−209.2 °C. ^{1}H NMR (DMSO-d_6, 60 °C) δ: 1.93 (s, NHC(O)C**H$_3$**), 3.48 (s, NC**H$_3$**), 7.22−7.30 (m, CNC**H**CH and CHC**H**C(OCF$_3$)), 7.70 (s, C(OCF$_3$)C**H**CS), 10.02 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6, 60 °C) δ: 21.7 (C(O)**C**H$_3$), 31.4 (N**C**H$_3$), 110.7 (CH**C**HC(OCF$_3$)), 116.4 (CN**C**HCH), 120.3 (C(OCF$_3$)**C**HCS), 120.9 (q, J = 256.0 Hz, O**C**F$_3$), 124.1 (CH**C**SCN), 140.8 (CS**C**NCH), 143.2 (**C**(OCF$_3$)), 163.9, 166.0 (S**C**(N)N and NH**C**(O)C). MS (ESI) m/z 306 (M + H)$^+$.

3,3-Dimethylbutanoic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6e). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and *tert*-butylacetyl chloride according to method C; mp 209.0−209.4 °C. ^{1}H NMR (DMSO-d_6) δ: 1.01 (s, C(O)CH$_2$C(C**H$_3$**)$_3$), 2.03 (s, C(O)C**H$_2$**C(CH$_3$)$_3$), 3.44 (s, NC**H$_3$**), 7.18−7.32 (m, CNC**H**CH and CHC**H**C(OCF$_3$)), 7.72 (s, C(OCF$_3$)C**H**CS), 10.1 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 30.5 (C(O)CH$_2$C(**C**H$_3$)$_3$), 31.3 (C(O)CH$_2$**C**(CH$_3$)$_3$), 31.4 (N**C**H$_3$), 47.9 (C(O)**C**H$_2$C(CH$_3$)$_3$), 110.8 (CH**C**HC(OCF$_3$), 116.7 (CN**C**HCH), 120.5 (C(OCF$_3$)**C**HCS), 120.9 (d, J = 256.7 Hz, O**C**F$_3$), 124.0 (CH**C**SCN), 140.8 (CS**C**NCH), 143.1 (**C**(OCF$_3$)), 164.5, 167.7 (S**C**(N)N and NH**C**(O)C). MS (ESI) m/z 362 (M + H)$^+$.

Cyclopentylacetic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6f). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and cyclopentylacetyl chloride according to method C; mp 214.7−215.3 °C. ^{1}H NMR (DMSO-d_6, 80 °C) δ: 1.16−1.32 (m, 2 Alkyl**H**), 1.45−1.70 (m, 4 Alkyl**H**), 1.73−1.85 (m, 2 Alkyl**H**), 2.18−2.30 (m, 3 Alkyl**H**), 3.47 (s, NC**H$_3$**), 7.18−7.30 (m, CNC**H**CH and CHC**H**C(OCF$_3$)), 7.65 (s, C(OCF$_3$)C**H**CS), 9.90 (bs, NN**H**C(O)). ^{13}C NMR (DMSO-d_6, 80 °C) δ: 25.3 (C(O)CH$_2$CHCH$_2$**C**H$_2$), 31.5 (N**C**H$_3$), 32.8 (C(O)CH$_2$CH**C**H$_2$CH$_2$), 37.4 (C(O)CH$_2$**C**HCH$_2$CH$_2$), 41.5 (C(O)**C**H$_2$CHCH$_2$CH$_2$), 110.7 (CH**C**HC(OCF$_3$), 116.4 (CN**C**HCH), 120.2 (C(OCF$_3$)**C**HCS), 121.0 (q, J = 255.9 Hz, O**C**F$_3$), 124.3 (CH**C**SCN), 140.9 (CS**C**NCH), 143.4 (**C**(OCF$_3$), 164.3, 168.7 (S**C**(N)N and NH**C**(O)C). MS (ESI) m/z 374 (M + H)$^+$.

3-Methylbutanoic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6g). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and isovaleryl chloride according to method C; mp 189.1−189.4 °C. ^{1}H NMR (DMSO-d_6) δ: 0.95 (d, J = 15.7, C(O)CH$_2$CH(C**H$_3$**)$_2$), 1.98−2.10 (m, C(O)C**H$_2$**CH(CH$_3$)$_2$ and C(O)CH$_2$C**H**(CH$_3$)$_2$), 3.47 (s, NC**H$_3$**), 7.24−7.34 (m, CNC**H**CH and CHC**H**C(OCF$_3$)), 7.75 (s, C(OCF$_3$)C**H**CS), 10.2 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 22.9 (C(O)CH$_2$CH(**C**H$_3$)$_2$), 26.2 C(O)CH$_2$**C**H(CH$_3$)$_2$), 31.3 (N**C**H$_3$), 43.7 (C(O)**C**H$_2$CH(CH$_3$)$_2$), 110.7 (CH**C**HC(OCF$_3$), 116.5 (CN**C**HCH), 120.4 (C(OCF$_3$)**C**HCS), 120.5 (d, J=255.6 Hz, O**C**F$_3$), 123.8 (CH**C**SCN), 140.7 (CS**C**NCH), 142.9 (**C**(OCF$_3$), 164.6, 168.9 (S**C**(N)N and NH**C**(O)C). MS (ESI) m/z 348 (M + H)$^+$.

2-Tetrahydrofuroic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6h). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and 2-tetrahydrofuroyl chloride[40] according to method C; mp 169.7−170.0 °C. ^{1}H NMR ($CDCl_3$) δ: 1.96−2.05 (m, OCH$_2$C**H$_2$**), 2.23−2.42 (m, OCH$_2$CH$_2$C**H$_2$**), 3.59 (s, NC**H$_3$**), 3.96 (m, OC**H**H′CH$_2$), 4.07 (m OCH**H**′CH$_2$), 4.58 (dd, J = 5.3, 8.4 Hz, C(O)C**H**), 6.97 (d, J = 8.8 Hz, CNC**H**CH), 7.20 (d, J = 8.8 Hz, CHC**H**C(OCF$_3$)), 7.29 (s, C(OCF$_3$)C**H**CS), 8.60 (s, NN**H**C(O)). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 25.2 (OCH$_2$**C**H$_2$), 30.2 (N**C**H$_3$), 30.6 (OCH$_2$CH$_2$**C**H$_2$), 69.4 (O**C**H$_2$CH$_2$), 77.8 (C(O)**C**H), 109.7 (CH**C**HC(OCF$_3$), 115.5 (CN**C**HCH), 120.0 (C(OCF$_3$)**C**HCS), 120.3 (q, J = 256.6 Hz, O**C**F$_3$), 123.0 (CH**C**SCN), 139.8 (CS**C**NCH), 143.5 (**C**(OCF$_3$), 165.9, 170.3 (S**C**(N)N and NH**C**(O)C). MS (ESI) m/z 362 (M + H)$^+$.

3-Tetrahydrofuroic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6i). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and 3-tetrahydrofuroyl chloride[40] according to method C; mp 199.4−199.6 °C. ^{1}H NMR (DMSO-d_6, 60 °C) δ: 2.00−2.08 (m, OCH$_2$C**H$_2$**), 2.96−3.12 (m, C(O)C**H**), 3.45 (s, NC**H$_3$**), 3.65−3.80 (m, O**C**H$_2$CH$_2$ and OC**H**H′CH), 3.90 (dd, J = 8.1, 16.3 Hz, OCH**H**′CH), 7.19−7.25 (m, CNC**H**CH and CHC**H**C(OCF$_3$)), 7.65 (s, C(OCF$_3$)C**H**CS), 10.2 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6, 60 °C) δ: 30.6 (N**C**H$_3$), 31.4 (OCH$_2$**C**H$_2$), 43.3 (C(O)**C**H), 68.3 (O**C**H$_2$CH$_2$), 70.9 (O**C**H$_2$CH), 110.8 (CH**C**HC(OCF$_3$), 116.4 (CN**C**HCH), 120.3 (C(OCF$_3$)**C**HCS), 120.9 (q, J=256.0 Hz, O**C**F$_3$), 124.1 (CH**C**SCN), 140.8 (CS**C**NCH), 143.3 (**C**(OCF$_3$), 164.7, 169.5 (S**C**(N)N and NH**C**(O)C). MS (ESI) m/z 362 (M + H)$^+$.

3-Fluorobenzoic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6j). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and 3-fluorobenzoyl chloride according to method C; mp 151.2−151.6 °C. ^{1}H NMR ($CDCl_3$−CD_3OD) δ: 3.39 (s, NC**H$_3$**), 6.83 (d, J=8.9 Hz, CNC**H**CH), 7.01−7.12 (m, 3 Ar**H**), 7.26 (ddd, J= 2.3, 7.8, 7.9 Hz, Ar**H**), 7.51 (d, J=9.3 Hz, Ar**H**), 7.58 (d, J=7.8 Hz, Ar**H**). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 30.8 (N**C**H$_3$), 109.6 (CH**C**HC(OCF$_3$), 114.5 (d, J = 23.2 Hz, C(O)C**C**HCF), 115.6 (CN**C**HCH), 118.5 (d, J = 21.3 Hz, C(O)CCHCF**C**H), 120.1 (C(OCF$_3$)**C**HCS), 120.4 (q, J = 256.9 Hz, O**C**F$_3$), 123.0 (d, J = 2.7 Hz, C(O)C**C**HCH), 123.4 (CH**C**SCN), 130.1 (d, J = 7.9 Hz, C(O)CCHCFC**H**CH), 135.3 (d, J = 7.0 Hz, C(O)**C**), 139.7 (CS**C**NCH), 143.6 (q, J = 2.2 Hz, **C**(OCF$_3$), 162.5 (d, J = 247.2 Hz, **C**F), 164.4, 166.6 (S**C**(N)N and NH**C**(O)C). MS (ESI) m/z 386 (M + H)$^+$.

4-Fluorobenzoic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6k). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and 4-fluorobenzoyl chloride according to method C; mMp 166.9−168.5 °C. ^{1}H NMR ($CDCl_3$) δ: 3.56 (s, NC**H$_3$**), 6.94 (d, J=8.8 Hz, CNC**H**CH), 7.07−7.21 (m, 3 Ar**H**), 7.24 (s, C(OCF$_3$)C**H**CS), 7.82−7.90 (m, 2 Ar**H**), 8.25 (s, NN**H**C(O)). ^{13}C NMR ($CDCl_3$−CD_3OD) δ: 30.8 (N**C**H$_3$), 109.8 (CH**C**HC(OCF$_3$), 115.4 (d, J = 22.0 Hz, CF**C**H), 115.7 (CN**C**HCH), 120.1 (C(OCF$_3$)**C**HCS), 120.6 (q, J = 256.7 Hz, O**C**F$_3$), 123.5 (CH**C**SCN), 129.4 (d, J = 3.1 Hz, C(O)**C**), 129.8 (d, J = 8.9 Hz, CFCH**C**H), 139.9 (CS**C**NCH), 143.7 (q, J = 2.1 Hz, **C**(OCF$_3$), 164.8 (d, J = 252.1 Hz, **C**F), 165.0, 166.8 (S**C**(N)N and NH**C**(O)C). MS (ESI) m/z 386 (M + H)$^+$.

Benzoic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6l). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and benzoyl chloride according to method C; mp 158.0−158.2 °C. ^{1}H NMR (DMSO-d_6) δ: 3.55 (NC**H$_3$**), 7.27−7.38 (m, 2 Ar**H**), 7.43−7.57 (m, 3 Ar**H**), 7.74 (d, J = 1.2 Hz, C(OCF$_3$)C**H**CS), 7.88 (d, J = 6.7 Hz, C(O)C(C**H**)$_2$), 10.96 (s, NN**H**C(O)). ^{13}C NMR (DMSO-d_6) δ: 31.0 (N**C**H$_3$), 110.6 (CH**C**HC(OCF$_3$), 116.2 (CN**C**HCH), 120.1 (C(OCF$_3$)**C**HCS), 120.3 (q, J = 255.8 Hz, O**C**F$_3$), 123.5

(CHCSCN), 127.4 (ArCH), 128.5 (ArCH), 131.4 (C(O)CCH), 133.8 (C(O)C), 140.3 (CSCNCH), 142.7 (q, J = 1.9 Hz, $C(OCF_3)$), 163.3, 165.7 (SC(N)N and NHC(O)C). MS (ESI) m/z 368 $(M + H)^+$.

2-Furoic Acid (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazide (6m). Prepared from (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) and furoyl chloride[41] according to method C; mp 199.4−201.0 °C. ^{1}H NMR ($CDCl_3$) δ: 3.57 (s, NCH_3), 6.56 (dd, J = 1.7, 3.5 Hz, C(O)CCHCHCH), 6.94 (d, J = 8.9 Hz, CNCHCH), 7.13−7.27 (m, CHCHC(OCF_3), C(O)CCHCHCH and C(O)CCHCHCH), 7.48 (s, C(OCF_3)CHCS), 8.40 (s, NNHC(O)). ^{13}C NMR ($CDCl_3$) δ: 30.9 (NCH_3), 109.8 (CHCHC(OCF_3), 112.1 (C(O)CCHCHCH), 115.1 (C(O)CCHCHCH), 115.7 (CNCHCH), 120.2 (C(OCF_3)CHCS), 120.4 (q, J = 257.0 Hz, OCF_3), 123.4 (CHCSCN), 139.9 (CSCNCH), 143.7 (q, J = 1.8 Hz, C(OCF_3)), 144.6 (C(O)CCHCHCH), 146.6 (C(O)CCHCHCH), 156.4, 166.4 (SC(N)N and NHC(O)C). MS (ESI) m/z 358 $(M + H)^+$.

Cyclopentyl (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazine carboxylate (6n). A solution of cyclopentanol (0.290 mL, 3.20 mmol) in 15 mL of CH_2Cl_2 was treated with 4-nitrophenyl chloroformate (645 mg, 3.20 mmol) and pyridine (0.259 mL, 3.20 mmol) and stirred at rt for 15 h. The reaction mixture was washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated. Chromatography on silica gel (hexanes to 20% EtOAc/hexanes eluent) afforded 508 mg (2.02 mmol, 63%) of cyclopentyl 4-nitrophenyl carbonate as an colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.60−2.00 (m, 8 H), 5.20−5.28 (m, 1 H), 7.39 (d, J = 9.0 Hz, 1 H), 8.28 (d, J = 9.0 Hz, 1 H). A solution of cyclopentyl 4-nitrophenyl carbonate (403 mg, 1.60 mmol) and 4-methylmorpholine (0.882 mL, 8.02 mmol) in 5.0 mL of DMF was treated with a solution of (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) (422 mg, 1.60 mmol) in 5.0 mL of DMF. The reaction mixture was stirred at 75 °C for 15 h, concentrated, and partitioned between EtOAc and water. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica ($CHCl_3$ to 15% $CH_3CN/CHCl_3$ eluent) afforded 448 mg (1.193 mmol, 74%) of **6n** as an off-white solid; mp 124.4−125.2 °C. ^{1}H NMR ($CDCl_3$) δ: 1.53−1.95 (m, OCH(CH_2CH_2)$_2$), 3.52 (s, NCH_3), 5.17−5.26 (m, (OCH(CH_2CH_2)$_2$), 6.76 (s, NNHC(O)O), 6.91 (d, J = 8.8 Hz, CNCHCH), 7.15 (d, J = 2.2, 8.8 Hz, CHCHC(OCF_3)), 7.25 (d, J = 2.2 Hz, C(OCF_3)CHCS). ^{13}C NMR ($CDCl_3$) δ: 23.5 (OCH(CH_2CH_2)$_2$), 30.9 (NCH_3), 32.6 (OCH(CH_2CH_2)$_2$), 78.5 (OCH(CH_2CH_2)$_2$), 109.1 (CHCHC(OCF_3), 115.6 (CNCHCH), 119.8 (C(OCF_3)CHCS), 120.4 (q, J = 256.7 Hz, OCF_3), 123.7 (CHCSCN), 140.0 (CSCNCH), 143.4 (C(OCF_3)), 155.6 (NHC(O)O), 165.5 (SC(N)N). MS (ESI) m/z 376 $(M + H)^+$.

Isopropyl (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazine carboxylate (6o). A solution of (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) (127 mg, 0.482 mmol) in 4.0 mL of THF was treated with 4-methylmorpholine (106 μL, 0.965 mmol) and a 1.0 M solution of isopropyl chloroformate in toluene (579 μL, 0.579 mmol). The reaction was stirred at rt for 6 h, concentrated, and partitioned between EtOAc and water. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica ($CHCl_3$ to 15% $CH_3CN/CHCl_3$ eluent) afforded 107 mg (0.306 mmol, 64%) of **6o** as an off-white solid; mp 119.7−120.0 °C. ^{1}H NMR ($CDCl_3$) δ: 1.30 (d, J = 6.4 Hz, OCH(CH_3)$_2$), 3.59 (s, NCH_3), 5.03 (m, J = 6.4 Hz, OCH(CH_3)$_2$), 6.83 (s, NNHC(O)O), 6.95 (d, J = 8.8 Hz, CNCHCH), 7.18 (dd, J = 2.4, 8.8 Hz, CHCHC(OCF_3)), 7.29 (dd, J = 2.4 Hz, C(OCF_3)CHCS). ^{13}C NMR ($CDCl_3$) δ: 22.0 (OCH(CH_3)$_2$), 31.0 (NCH_3), 69.4 (OCH(CH_3)$_2$), 109.2 (CHCHC(OCF_3), 115.8 (CNCHCH), 119.9 (C(OCF_3)CHCS), 120.5 (q, J = 257.3 Hz, OCF_3), 123.7 (CHCSCN), 140.1 (CSCNCH), 143.5 (C(OCF_3)), 155.4 (NHC(O)O), 165.6 (SC(N)N). MS (ESI) m/z 350 $(M + H)^+$.

***tert*-Butyl (6-Trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazine carboxylate (6p).** A solution of (6-trifluoromethoxy-3-methyl-3*H*-benzothiazol-2-ylidine)hydrazone (**5**) (127 mg, 0.482 mmol) in 2.0 mL of THF was treated with a solution of di-*tert*-butyldicarbonate (116 mg, 0.531 mmol) in 1.0 mL of THF. The reaction mixture was stirred at rt for 3 h and then concentrated. Chromatography on silica ($CHCl_3$ to 15% $CH_3CN/CHCl_3$ eluent) afforded 120.5 mg (0.332 mmol, 69%) of **6p** as a white solid; mp 133.3−133.5 °C. ^{1}H NMR ($CDCl_3$) δ: 1.52 (s, OC(CH_3)$_3$), 3.59 (s, NCH_3), 6.74 (s, NNHC(O)O), 6.95 (d, J = 8.8 Hz, CNCHCH), 7.17 (dd, J = 2.4, 8.8 Hz, CHCHC(OCF_3)), 7.29 (d, J = 2.2 Hz, C(OCF_3)CHCS). ^{13}C NMR ($CDCl_3$) δ: 28.2 (OC(CH_3)$_3$), 30.8 (NCH_3), 80.8 (OC(CH_3)$_3$), 109.0 (CHCHC(OCF_3), 115.6 (CNCHCH), 119.7 (C(OCF_3)CHCS), 120.4 (q, J = 256.6 Hz, OCF_3), 123.7 (CHCSCN), 140.0 (CSCNCH), 143.3 (C(OCF_3)), 154.7 (NHC(O)O), 165.1 (SC(N)N). MS (ESI) m/z 308 $(M\text{-}C_4H_8)^+$.

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Supporting Information Available: Data for Cerep receptor binding assays on compounds **6e**, **6f**, and **6o**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Rogawski, M. A.; Loescher, W. The neurobiology of antiepileptic drugs. *Nature Rev. Neurosci.* **2004**, *5*, 553–564.
(2) Schmidt, D.; Rogawski, M. A. New strategies for the identification of drugs to prevent the development or progression of epilepsy. *Epilepsy Res.* **2002**, *50*, 71–78.
(3) Kwan, P.; Sills, G. J.; Brodie, M. J. The mechanisms of action of commonly used antiepileptic drugs. *Pharmacol. Ther.* **2001**, *90*, 21–34.
(4) Wickenden, A. D.; Roeloffs, R.; McNaughton-Smith, G.; Rigdon, G. C. KCNQ potassium channels: drug targets for the treatment of epilepsy and pain. *Expert Opin. Ther. Patents* **2004**, *14*, 1–13.
(5) Gandolfo, G.; Romettino, S.; Gottesman, C.; Van Luijtelaer, G.; Coenen, A.; Bidard, J.-N.; Lazdunski, M. K^+ channel openers decrease seizures in genetically epileptic rats. *Eur. J. Pharmacol.* **1989**, *167*, 181–183.
(6) Rostock, A.; Tober, C.; Runfeldt, C.; Bartsch, R.; Engel, J.; Polymeropoulos, E. E.; Kutscher, B.; Löscher, W.; Hönack, D.; White, H. S.; Wolf, H. H. D-23129: a new anticonvulsant with a broad spectrum activity in animal models of epileptic seizures. *Epilepsy Res.* **1996**, *23*, 211–223.
(7) Rogawski, M. A.; Loescher, W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. *Nature Med.* **2004**, *10*, 685–692.
(8) Eisenberg, E.; Lurie, Y.; Braker, C.; Daoud, D.; Ishay, A. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. *Neurology* **2001**, *57*, 505–509.
(9) Chen, Q.; King, T.; Vanderah, T. W.; Ossipov, M. H.; Malan, T. P.; Lai, J.; Porreca, F. Differential blockade of nerve injury-induced thermal and tactile hypersensitivity by systemically administered brain-penetrating and peripherally restricted local anesthetics. *J. Pain* **2004**, *5*, 281–289.
(10) Wang, H.-S.; Pan, Z.; Shi, W.; Brown, B. S.; Wymore, R. S.; Cohen, I. S.; Dixon, J. E.; McKinnon, D. KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. *Science* **1998**, *282*, 1890–1893.
(11) Biervert, C.; Schroeder, B. C.; Kubisch, C.; Berkovic, S. F.; Propping, P.; Jentsch, T. J.; Steinlein, O. K. A potassium channel mutation in neonatal human epilepsy. *Science* **1998**, *279*, 403–406.
(12) Charlier, C.; Singh, N. A.; Ryan, S. G.; Lewis, T. B.; Reus, B. E.; Leach, R. J.; Leppert, M. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat. Genet.* **1998**, *18*, 53–55.
(13) Singh, N. A.; Charlier, C.; Stauffer, D.; SuPont, B. R.; Leach, R. J.; Melis, R.; Ronen, G. M.; Bjerre, I.; Quattlebaum, T.; Murphy, J. V.; McHarg, M. L.; Gagnon, D.; Rosales, T. O.; Peiffer, A.; Anderson, V. E.; Leppert, M. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. *Nat. Genet.* **1998**, *18*, 25–29.
(14) Rundfeldt, C.; Netzer, R. The novel anticonvulsant retigabine activates M-currents in Chinese hamster ovary-cells transfected with human KCNQ2/3 subunits. *Neurosci. Lett.* **2000**, *282*, 73–76.

(15) Main, J. M.; Cryan, J. E.; Dupere, J. R.; Cox, B.; Clare, J. J.; Burbidge, S. A. Modulation of KCNQ2/3 potassium channels by the novel anticonvulsant retigabine. *Mol. Pharmacol.* **2000**, *58*, 253–262.
(16) Wickenden, A. D.; Yu, W.; Jegla, T.; Wagoner, P. K. Retigabine, a novel anti-convulsant, enhances activation of KCNQ2/Q3 potassium channels. *Mol. Pharmacol.* **2000**, *58*, 591–600.
(17) Passmore, G. M.; Selyanko, A. A.; Mistry, M.; Al-Qatari, M.; Marsh, S. J.; Matthews, E. A.; Dickenson, A. H.; Brown, T. A.; Burbidge, S. A.; Main, M.; Brown, D. A. KCNQ/M currents in sensory neurons: significance for pain therapy. *J. Neurosci.* **2003**, *23*, 7227–7236.
(18) Wickenden, A. D.; Rigdon, G. C.; McNaughton-Smith, G. A.; Gross, M. F. Methods for treating or preventing pain. U.S. Patent 6,326,385, **2002**.
(19) Blackburn-Munro, G.; Jensen, B. S. The aniticonvulsant retigabine attenuates nociceptive behaviours in rat models of persistent and neuropathic pain. *Eur. J. Pharmacol.* **2003**, *460*, 109–116.
(20) Rundfeldt, C.; Bartsch, R.; Rostock, A.; Tober. C.; Dost, R. Use of retigabine for the treatment of neuropathic pain. U.S. Patent 6,117,900, **2000**.
(21) Dost, R.; Rostock, A.; Rundfeldt, C. The anti-hyperalgesic activity of retigabine is mediated by KCNQ potassium channel activation. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2004**, *369*, 382–390.
(22) Ilyin, V. I.; Carlin, K. P.; Hodges, D. D.; Robledo, S.; Woodward, R. M. Flupertine. A positive modulator of heteromeric KCNQ2/Q3 channels. *Soc. Neurosci. Abstr.* **2002**, *758*, 10.
(23) Singh, B.; Pennock, P. O.; Lesher, G. Y.; Bacon, E. R.; Page, D. F. An efficient and novel synthesis of fused thiazol-2(3*H*)-ones. *Heterocycles* **1993**, *36*, 133–144.
(24) Chaudhuri, N. C. Convenient strategies for the preparation of modified 2(3*H*)-benzothiazolethiones. *Synth. Commun.* **1996**, *26*, 3783–3790.
(25) Zhu, L.; Zhang, M. Ortho-selective nucleophillic aromatic substitution reactions of polyhaloanilines with potassium/sodium *O*-ethylxanthate: a convenient access to halogenated 2(3*H*)benzothiazolethiones. *J. Org. Chem.* **2004**, *69*, 7371–7374.
(26) Minami, I.; Kozai, Y.; Nomura, H.; Tashiro, T. Cyanine dyes, new potent antitumor agents. *Chem. Pharm. Bull.* **1982**, *30*, 3106–3120.
(27) Karlsson, H. J.; Berqvist, M. H.; Lincoln, P.; Westman, G. Syntheses and DNA-binding studies of a series of unsymmetrical cyanine dyes: structural influence on the degree of minor groove binding to natural DNA. *Bioorg. Med. Chem.* **2004**, *12*, 2369–2384.
(28) Sutoris, V.; Malovikova, A.; Jakubcova, J.; Foltinova, P.; Blockinger, G. Benzothiazole compounds. XV. Nucleophillic substitution reactions on benzothiazolium salts. *Chem. Zvesti* **1979**, *33*, 558–568.
(29) Suzuki, N.; Kadoya, S.; Dohmori, R. Synthetic chemotherapeutic agents. IV. Synthesis of 3-substituted thiazolo[5,4,-*f*]quinoline derivatives. *Chem. Pharm. Bull.* **1976**, *24*, 1050–1058.
(30) Prepared from cyclopentanol and 4-nitrophenyl chloroformate as described in the Experimental Section.
(31) For screening protocol see McNaughton-Smith, G. A.; Gross, M. F.; Wickenden, A. D. Benzanilides as potassium channel openers. U.S. Patent 6,372,767, **2002**.
(32) Work was completed prior to the issuing of patents covering KCNQ2 and/or KCNQ3 and uses thereof.
(33) Blanar, M. A.; Levesque, P. C.; Little, W. A.; Neubauer, M. G.; Yang, W.-P. KCNQ potassium channels and methods of modulating same. U.S. Patent 6,403,360, **2002**.
(34) Singh, N. A.; Leppert, M. F.; Charlier, C. KCNQ2 and KCNQ3-potassium channel genes which are mutated in benign familial neonatal convulsions (BFNC) and other epilepsies. U.S. Patent 6,413,719, **2002**.
(35) Runfeldt, C.; Netzer, R. Modulatory binding site in potassium channels for screening and finding new active ingredients. U.S. Patent 6,472,165, **2002**.
(36) Roeloffs, R.; Wickenden, A. D.; Crean, C.; Werness, S.; McNaughton-Smith, G.; Stables, J.; McNamara, J. O.; Ghodadra, N.; Rigdon, G. C. In vivo profile of ICA-27243 [*N*-(6-chloropyridin-3-yl)-3,4-difluoro-benzamide], a potent and selective KCNQ2/Q3 (Kv7.2/Kv7.3) activator in rodent anticonvulsant models. *J. Pharmacol. Exp. Ther.* **2008**, *326*, 818–828.
(37) Wang, L. W.; Wang, Z. J. Animal and cellular models of chronic pain. *Adv. Drug Delivery Rev.* **2003**, *55*, 949–965.
(38) Dubuisson, D.; Dennis, S. G. The formalin test: a quantitative study of the analgesic effects of morphine, meperidine, and brain stem stimulation in rats and cats. *Pain* **1977**, *4*, 161–174.
(39) Kim, S. H.; Chung, J. M. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. *Pain* **1992**, *50*, 355–363.
(40) Cerep Poitiers, LeBois l'Eveque, 86600 CELLE L'EVESCAULT, France.
(41) Prepared from the corresponding carboxylic acid and oxalyl chloride.