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Letter

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Optimization of ADME Properties for Sulfonamides Leading to the Discovery of a T-Type Calcium Channel Blocker ABT-639

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KEYWORDS: *$Ca_v3.2$, T-type calcium channel, pain, Sulfonamides, ADME*

ABSTRACT: The discovery of a novel peripherally acting and selective $Ca_v3.2$ T-type calcium channel blocker, ABT-639 is described. HTS hits **1** and **2** which have poor metabolic stability were optimized to obtain **4,** which has improved stability and oral bioavailability. Modification of **4** to further improve ADME properties led to the discovery of ABT-639. Following oral administration, ABT-639 produces robust antinociceptive activity in experimental pain models at doses that do not significantly alter psychomotor or hemodynamic function in the rat.

Voltage-gated calcium channels (VGCC) play an important role in the regulation of calcium influx into cells in response to change membrane conductance, thereby activating various physiological functions, such as neurotransmitter release, cellular excitability, muscle contraction and many others.[1] These channels can be classified into low-voltage activated T-type and high-voltage activated L-type and P/Q-, N- and R-types calcium channels. N-type calcium channels are found primarily at presynaptic terminals and are involved in neurotransmitter release.[2,3] T-type channels are primarily involved in postsynaptic excitability.[4] Recent studies have shown that T-type calcium channels may be important therapeutic targets for the treatment of several neurophysiological disorders, including as epilepsy,[5] pain,[6,7,8] hypertension,[9] sleep architecture,[10] tremor,[11] and Parkinson's disease.[12, 13]

$Ca_v3.2$ is the predominant T-type calcium channel isoform in sensory nerves that modulate nociception, and is expressed in dorsal root ganglion (DRG) neurons, peripheral receptive fields, spinal cord dorsal horn and brain.[14] Bourinet *et al* demonstrated that silencing of $Ca_v3.2$ channel strongly reduced acute and neuropathic nociception.[15] Intrathecal administration or local injection of $Ca_v3.2$-specific, but not $Ca_v3.1$ and $Ca_v3.3$-specific antisense oligonucleotides produces a significant knockdown of $Ca_v3.2$ T-type currents in nociceptive DRG neurons, and robust long-lasting and reversible mechanical and thermal antinociceptive effects. Jagodic *et al.* demonstrated that following chronic constriction injury (CCI) of the sciatic nerve induced upregulation of T-type calcium channel currents in small rat DRG.[16] Modulation of the $Ca_v3.2$ (α1H) channel controls the sensitization of nociceptors, the peripheral pain-sensing neurons.[17] These results further support $Ca_v3.2$ T-type channels as a mechanism for modulating nociceptive sensitivity.

High throughput screening (HTS) generated a number of sulfonamides hits including **1** (IC_{50} = 3 μM**)** and **2** (IC_{50} = 5 μM) (Figure 1) against $Ca_v3.2$ T-type channel in a FLIPR based Ca^{2+} flux assay.[18,19] However, HTS hits **1** and **2** are metabolically unstable in rats and both have very poor oral bioavailability (*F* = 0.5% and 1.9%, respectively) (Table 1).

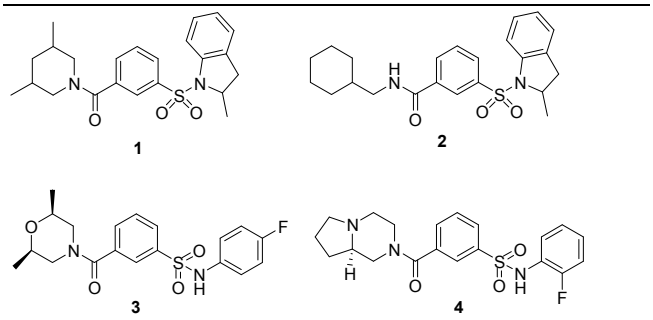


Figure 1. Structures of hits **1**, **2**, and lead **3**, **4**

Since the potency of **1** and **2** were in a similar range to other previously described T/N-type calcium channel blockers, lead optimization efforts were focused on improving ADME properties for these hits.[20] Modification of both sulfonamide and amide sides of these hits led to identification of a new lead **3**, which has a lower cLogP than **1** and **2**. Compound **3** afforded 29% oral bioavailability in rats. Unfortunately, the half-life ($t_{1/2}$) of **3** following i.v. dosing at 5 μmol/kg was only 0.31 hr, mainly due to the high plasma clearance rate (CLp) of 1.66 L/hr/kg and a low volume distribution (V_β) of 0.75 L/kg (Table 1).

Table 1. RLM and PK Parameters of Compounds 1, 2, 3 and 4

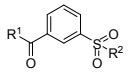
	RLM [a] (%)	cLogP	V_β (L/kg)	CLp (L/hr/kg)	$t_{1/2}$ (hr)	F (%) (p.o.)
1	0.3	4.4	4.94	1.90	1.80	0.5 [b]
2	0.1	5.3	11.1	3.47	2.16	1.9 [b]
3	46	3.1	0.75	1.66	0.31	29.0 [c]
4	68	2.8	0.65	1.79	0.25	31.3 [c]

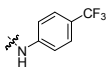
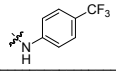
[a]Rat Liver Microsomal stability. Percentage remaining after 30 min at 1μM. [b]3 μM/kg iv and po. [c]5 μM/kg iv and 30 μM/kg po. Oral formulation: PEG400: Cremophor EL: Oleic Acid (10:10:80, by weight 2 ml/kg).

After evaluating several diamines, a rigid bicyclic diamine was identified to replace dimethylmorpholine in **3**. Compound

4 demonstrated better stability in rat liver microsomes compared to **1, 2** and **3**. However, the plasma clearance rate of **4** is still high (1.79 L/hr/kg) with a volume distribution (V_β) of 0.65 L/kg in rats. In order to further improve the ADME properties and PK profile of **4**, compounds **5** to **9** and the (*S*)-enantiomers **4b** to **6b** with different R_2 groups which have electron-withdrawing substituents on anilines were investigated to compare their plasma clearance (CLp) and oral bioavailability (Table 2). We observed that the plasma clearance (CLp) rate of the (*R*)-enantiomers (**4**, **5**, and **6**) is lower than the (*S*)-enantiomers (**4b**, **5b** and **6b**), and the oral bioavailability in rats is improved for the (*R*)-enantiomers. i.e. compound **4b**, the (*S*)-enantiomer of **4** shows higher plasma clearance (3.36 L/hr/kg) than (*R*)-enantiomer **4**. Compound **7** with 2-chloroaniline had increased CLp, and decreased bioavailability compared to **4**, but compounds **5**, **8, 6** and **9** with 2,3-, 2,6-difluoroaniline, 4- and 2-(trifluoromethyl)aniline had lower CLp and higher bioavailability. Compounds **6** and **6b** have an excellent PK profile with CLp of 0.45 - 0.81 L/hr/kg and oral bioavailability of 76 - 100%. However, compound **4** is the only one in the Table 2 which shows IC_{50} = 10.6 μM potency, other compounds in Table 2 are weak $Ca_v3.2$ T-type calcium channel blockers (<30% inhibition @10 μM). Our next attempt was to add the halogen atoms to the central aromatic ring since it is possible that the high plasma clearance rate was also due to the metabolic oxidation of the central aromatic ring.

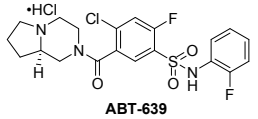
Table 2.[a] **Pharmacokinetic Parameters of Compounds 4 to 9 and 4b to 6b**



Compound	R^1	R^2	Plasma clearance CLp (L/hr/kg)	bioavailability (p.o.) F (%)
4			1.79	31
4b			3.36	28
5			1.21	44
5b			2.28	29
6			0.45	100
6b			0.81	76
7			1.93	5.8
8			0.92	54
9			0.74	57

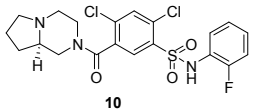
[a]5 μM/kg iv and 30 μM/kg po. Oral formulation: PEG400: Cremophor EL: Oleic Acid (10:10:80, by weight 2 ml/kg).

Substituent on aromatic ring can influence the microsomal stability and pharmacokinetic properties of the compounds .[21] Introduction of the F or Cl atom to the central aromatic ring of **4** led to the discovery of ABT-639 (Figure 2), which has a significantly decreased plasma clearance rate of 0.55 L/hr/kg. The volume distribution (V_β) was increased to 2.7 L/kg, and the half-life ($t_{1/2}$) of ABT-639 was improved to 3.3 hr in rats. The oral bioavailability in rats was also significant improved (F = 73%). The increase in volume distribution in rat and monkey may be due to the increase of tissue-binding or partitioning into fat since the cLogP (3.8) of ABT-639 is larger than the cLogP (1.79) of **4**.[22] Compound **10** with dichloro-substitutes on the central aromatic ring was prepared and showed weaker potency (IC_{50} = 19 μM) against $Ca_v3.2$ T-type calcium channel with 44% oral bioavailability. Addition of a methyl group to the sulfonamide side of ABT-639 gives compound **11** (Figure 2). Remarkably, compound **11** had decreased stability in rat (RLM) and human liver microsomes (HLM) from 81 - 95% to less than 0.01%. The (*S*)-enantiomer of ABT-639 was also synthesized, it has 57% oral bioavailability in rats.



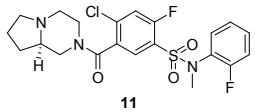
ABT-639

RLM = 81%, HLM = 95%
F = 73%, $t_{1/2}$ = 3.3 hr



10

F = 44%; $t_{1/2}$ = 2.99 hr

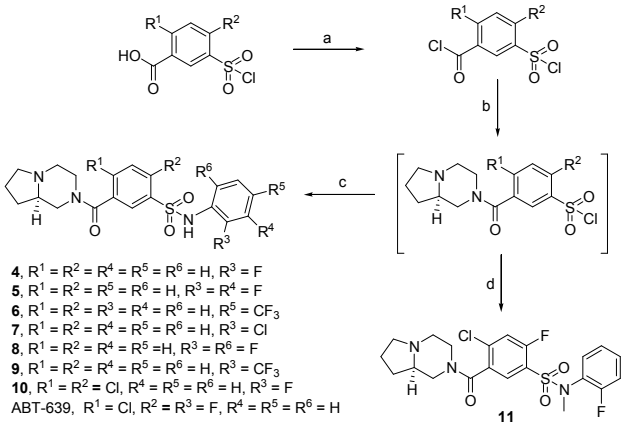


11

RLM = 0.04%, HLM < 0.01%

Figure 2. ABT-639 and its analogs **10** and **11**

Scheme 1. Synthesis of ABT-639 and Compounds **4 -11**[a]



4, $R^1 = R^2 = R^4 = R^5 = R^6$ = H, R^3 = F
5, $R^1 = R^2 = R^5 = R^6$ = H, $R^3 = R^4$ = F
6, $R^1 = R^2 = R^3 = R^4 = R^6$ = H, $R^5 = CF_3$
7, $R^1 = R^2 = R^4 = R^5 = R^6$ = H, R^3 = Cl
8, $R^1 = R^2 = R^4 = R^5$ =H, $R^3 = R^6$ = F
9, $R^1 = R^2 = R^4 = R^5 = R^6$ = H, $R^3 = CF_3$
10, $R^1 = R^2$ = Cl, $R^4 = R^5 = R^6$ = H, R^3 = F
ABT-639, R^1 = Cl, $R^2 = R^3$ = F, $R^4 = R^5 = R^6$ = H

[a]Reagents and conditions: (a) oxalyl chloride, CH_2Cl_2, RT, overnight; (b) (R)-octahydropyrrolo[1,2-*a*]pyrazine, Na_2CO_3, CH_2Cl_2, RT, 5-18 hrs; (c) 2-fluoroaniline or other substituted-anilines , RT, overnight. (d) 2-fluoro-*N*-methylaniline, RT, overnight.

Synthesis of ABT-639 and its analogs is outlined in Scheme 1. ABT-639 was obtained in 77% overall yield in 3 steps with one step purification from commercially available starting materials. 2-chloro-5-(chlorosulfonyl)-4-fluorobenzoyl chloride was prepared by reaction of 2-chloro-5-(chlorosulfonyl)-4-fluorobenzoic acid with oxalyl chloride at room temperate in the presence of DMF as a catalyst.

Addition of one equivalent of (*R*)-octahydropyrrolo[1,2-*a*]pyrazine to this resulting benzoyl chloride slowly over 1 hr generated the amide intermediate, (*R*)-4-chloro-2-fluoro-5-(octahydropyrrolo[1,2-a]pyrazine-2-carbonyl)benzene-1-sulfonyl chloride. Since the amide formation is at a much faster rate than the sulfonamide formation, very little or no side products were detected by LC-MS. Subsequent sulfonamide formation was completed overnight by addition of 2-fluoroaniline to afford ABT-639 after purification by chromatography. Compound **10** was prepared starting from commercially available 2,4-dichloro-5-(chlorosulfonyl)benzoic acid by following the same synthetic route of preparation of ABT-639. Compound **11** was obtained in 71% overall yield by using the same procedures. 2-fluoro-*N*-methylaniline was used at the last step (Scheme 1, step d). Compounds **3 to 9** and **4b** to **6b** were synthesized in 50 - 89% yield by a one-pot reaction from the commercially available 3-(chlorosulfonyl)benzoyl chloride by following the same procedures (Scheme 1, steps b and c).

ABT-639 is a selective voltage-dependent $Ca_v3.2$ T-type calcium channel blocker. It blocks human T-type ($Ca_v3.2$) channels with IC_{50} = 2.3 μM, and also blocks low voltage activated currents in native rat DRG neurons (IC_{50} = 7.6 μM).[17] ABT-639 shows little or no activity at other calcium channels (L-type, N-type, and P/Q-type) and is inactive (IC_{50} > 10 μM) across a wide array of cell surface receptors and ion channels.[18]

Table 3. Pharmacokinetic profile of ABT-639 across species

species	CLp (L/hr/kg)	V_β (L/kg)	$t_{1/2}$ (hr)	F (%)[a]	Microsomal Stability (%)
rat[b]	0.55	2.7	3.3	73	81
dog[c]	0.045	0.3	4.9	88	100
monkey[c]	0.11	1.35	8.3	95	88

[a]Oral formulation: PEG400: Cremophor EL: Oleic Acid (10:10:80, by weight 2 ml/kg). [b]5 μM/kg iv and 30 μM/kg po. [c]1 mg/kg iv and po.

The pharmacokinetic profile of ABT-639 was evaluated in rat, dog and monkey, respectively. The data are shown in Table 3. ABT-639 exhibits moderate to low plasma clearance (CLp) ranging from 0.55 L/hr/kg in rat to 0.045 L/hr/kg in dog. It also demonstrates moderate to low-moderate volume distribution values in these three animal species. The half-life (3.3, 4.9 and 8.3 hrs) and high oral bioavailability (73, 88 and 95%) in rat, dog and monkey are in agreement with the liver microsomal stability data (81-100% remaining after 30 min). ABT-639 shows good aqueous solubility of 489 μM in phosphate buffer (pH = 7.4) and over 9.5 mM in 0.1 HCl solution. In rats, the plasma concentration of ABT-639 was increased proportionally in dose escalation at 30, 100 and 300 mg/kg. ABT-639 has low protein binding (88.9% in rat and 85.2% in human). The brain to plasma concentration ratio was 1:20 in rats. ABT-639 is a not a competitive inhibitor of CYP1A2, 2C9, 2C19, 2D6 and 3A4 (IC_{50} > 10 μM). ABT-639 showed no CYP3A4 (PXR) induction (EC_{50} >10 μM), no CYP1A2 mRNA induction (EC_{50} >10 μM).

ABT-639 dose-dependently attenuates nociception in a capsaicin-induced secondary mechanical hyperalgesia model (Cap-SMH) (Figure 3). The antinociceptive activity of ABT-639 in this model is consistent with its dose-dependent antinociceptive activity in multiple models of neuropathic pain.[18, 23] Additionally, ABT-639 did not produce any decrement in balance or motor performance in the rat Edge (ED_{50} > 300 mg/kg or rat plasma 114 μg/ml, p.o.). In rat cardiovascular (CV) studies, intravenous administration (i.v.) of ABT-639 yielded negligible changes from vehicle control on mean arterial pressure (MAP), heart rate (HR), left ventricular contractility (dP/dt_{50}), and vascular resistance (VR) at concentrations (30 mg/kg, plasma concentration of 43.9 μg/ml).[18]

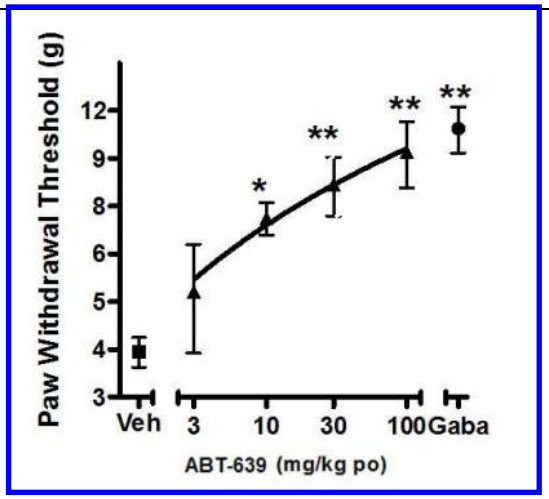


Figure 3. ABT-639 dose dependently reduces tactile allodynia in the rat Cap-SMH model. ABT-639 was administered 1 hr before behavioral testing. Gabapentin (Gaba, 500 μM/kg, i.p.) was included as a positive control for assay sensitivity.

We have described here the discovery of a novel selective T-type calcium channel blocker, ABT-639. Starting from HTS hits **1** and **2** with poor metabolic stability, we replaced the 2-methylindoline with aniline to improve the rat (RLM) and human liver (HLM) microsomal stability. Subsequently, we optimized the new lead **3** by incorporating a novel bicyclic fused diamine. We then introduced the F and Cl atoms to the central aromatic ring to improve the oral bioavailability, metabolic stability, decrease the plasma clearance rate, increase the half-life ($t_{1/2}$), and led to discovery of a novel T-type calcium channel blocker ABT-639. ABT-639 displayed good selectivity against N-type, P/Q-type, L-type calcium channel and hERG channel. ABT-639 has an excellent PK profile with high oral bioavailability in all species. *In vivo*, ABT-639 dose-dependently reduces nociception in a chronic pain model, with no significant cardiovascular effects at analgesic doses.

ASSOCIATED CONTENT

Supporting Information

Experimental and characterization data for all compounds and the Capsiacin-induced secondary mechanical hyperalgesia assay are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version.

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ABBREVIATIONS

HTS, high throughput screening; VGCC, Voltage-gated calcium channels, RLM, rat liver microsomes; HLM, human liver microsomes; HT-ADME, high throughput-absorption, distribution, metabolism, and excretion; FLIPR, fluorescent imaging plate reader; EP, electrophysiology; DMF, *N***,** *N*-dimethylformamide, DRG, dorsal root ganglion; PK, pharmacokinetics.

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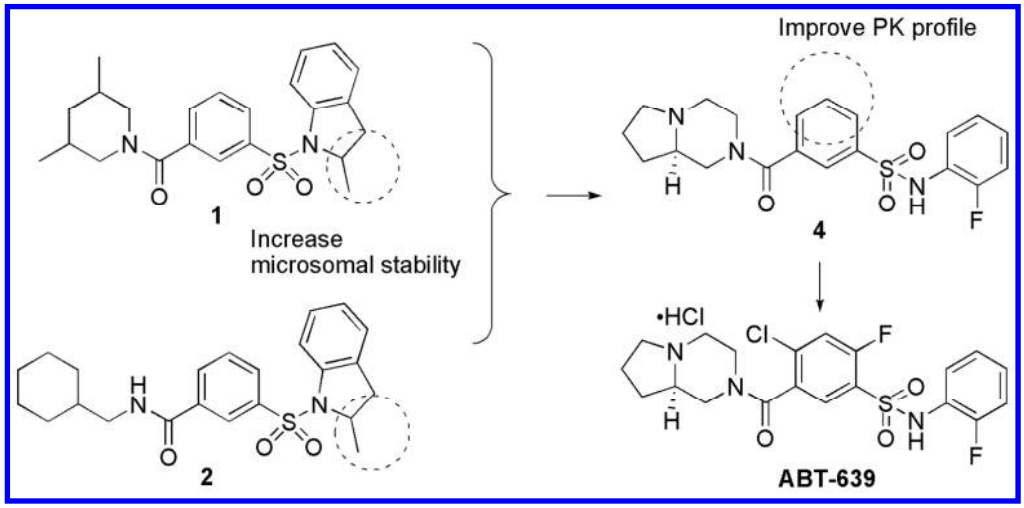

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