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A novel benzazepinone sodium channel blocker with oral efficacy in a rat model of neuropathic pain

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ABSTRACT

A series of benzazepinones were synthesized and evaluated for block of $Na_v1.7$ sodium channels. Compound **30** from this series displayed potent channel block, good selectivity versus other targets, and dose-dependent oral efficacy in a rat model of neuropathic pain.

Neuropathic pain is a chronic pain state resulting from injury to the peripheral or central nervous system.[1] Its onset is typically associated with underlying conditions such as diabetes, shingles, or chemotherapy use that cause nerve damage through a variety of mechanisms. Because few drugs have been developed specifically to treat neuropathic pain, patients are often prescribed anticonvulsants or antidepressants as therapies. Optimized for other indications, these brain-penetrant agents provide inadequate relief for some patients, and elicit dose-limiting CNS side effects such as sedation and coordination impairment.

Neuropathic pain signaling can be initiated by the firing of ectopic, high-frequency action potential bursts in or near damaged neurons. These action potentials are generated and propagated along neuronal axons via the opening of voltage-gated sodium channels ($Na_v1.x$). Of the nine voltage-gated sodium channel isoforms that have been cloned and functionally expressed to date ($Na_v1.1$–$Na_v1.9$), three ($Na_v1.3$, $Na_v1.7$ and $Na_v1.8$) appear to play roles in pain signaling.[2]

Na_v1 sodium channel blockers have been investigated as treatments for neuropathic pain. Weak, non-subtype selective blockers such as lidocaine and carbamazepine have demonstrated clinical efficacy in the treatment of neuropathic pain, thereby providing validation for this approach (Fig. 1).[3,4] Blockers with improved potency and/or selectivity have been more recently reported (**1**, ralfinamide and A-803467, Fig. 1), and have demonstrated efficacy in preclinical pain models.[5–9]

Data from human genetic studies support a key role for $Na_v1.7$ in pain signaling. Gain of function mutations in *SCN9A*, the gene that encodes $Na_v1.7$, have been identified as causal for two inherited pain syndromes, primary erythermalgia (PE) and paroxysmal extreme pain disorder (PEPD).[10,11] In PE, mutations in *SCN9A* alter the kinetics of $Na_v1.7$ activation and deactivation, lower the threshold for action potential firing, and produce hyperexcitability in nociceptive neurons. Affected individuals experience burning pain in their extremities in response to stimuli such as mild warmth or exercise —inflammatory- like symptoms that also recapitulate aspects of neuropathic allodynia. In PEPD, a different set of mutations produce channels with a reduced capacity for fast inactivation. Once activated, the mutant channels remain open much longer than wild-type channels, producing long-duration action potentials and persistent signaling in affected neurons. These mutations yield a phenotype characterized by spontaneous paroxysms of rectal, ocular, or submandibular pain.

Loss of function mutations in *SCN9A* have also been reported, and they lead to a rare and remarkable condition: the complete

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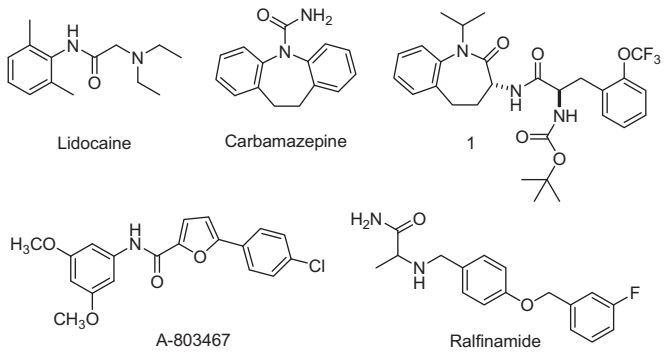


Figure 1. Na_v1 sodium channel blockers.

inability to sense pain.[12,13] Individuals with nonsense mutations in *SCN9A* are healthy and normal in terms of most non-nociceptive sensory functions, but are congenitally unable to sense pain in any form.[14] Given that several Na_v1 isoforms have been implicated in pain signaling, it is striking that loss of function in just one is sufficient to block all pain perception. Together with the gain-of-function findings, these data provide compelling human genetic validation for $Na_v1.7$ as an important pain target.

To be used safely in the clinic, sodium channel blockers must inhibit chronic pain signaling while leaving acute pain perception, motor coordination and other nerve functions intact. We believe that this can be achieved through a combination of subtype selectivity and/or state-dependent channel block. Voltage-gated sodium channels exist in three main conformational states: resting, open and inactivated. In healthy nerve and cardiac tissue, these channels reside predominantly in the resting state. In contrast, the repetitive, high-frequency firing patterns characteristic of some chronic pain syndromes (e.g., trigeminal neuralgia) cause sodium channels to accumulate in the inactivated state. Compounds that selectively bind and stabilize the inactivated state should block chronic pain signaling preferentially, thus minimizing the potential for mechanism-based adverse effects.

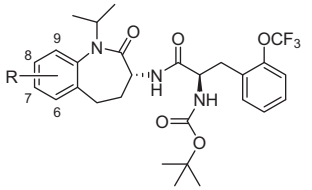
The goal of the present study is to develop state-dependent $Na_v1.7$ blockers as treatments for chronic pain. Toward that end, we recently reported the discovery of a structurally novel class of benzazepinone $Na_v1.7$ blockers. An early example from this class (compound **1**, Fig. 1) displayed potent, state-dependent block of $Na_v1.7$, a moderate pharmacokinetic profile, and oral efficacy in a rat model of neuropathic pain. Subsequent work has targeted the improvement of pharmacokinetic properties and efficacy in this series. These efforts have led to the discovery of **30**, a state-dependent $Na_v1.7$ blocker that is moderately selective against other Na_v isoforms (Na_v 1.5, Na_v 1.6, and Na_v 1.8), and that displays dose-dependent oral efficacy in a preclinical model of neuropathic pain.

Our primary objectives were to improve pharmacokinetics (PK) and efficacy in this series. An initial benchmark compound had displayed a moderate PK profile in rat and dog (compound **1**, Table 1). Incubation of **1** in the presence of rat liver microsomes had revealed metabolic oxidation at the N-Boc *tert*-butyl group, and at one or more unspecified sites on the benzazepinone phenyl ring (C6–C9, Table 1). Prior efforts to block this metabolism via chlorination of the benzazepinone 7-position had led to reduced clearance and improved oral exposure.[15] Intrigued by this initial result, we wanted to systematically examine the effect of blocking positions 6–9 on the benzazepinone core.

Substituted benzazepinones were synthesized as shown in Scheme 1. Known 7-fluorobenzazepinone **2** was prepared in four steps from commercially available 2-bromo-4-fluoroaniline using our recently reported method.[16] Sequential treatment of **2** with sodium hydride and 2-iodopropane effected lactam alkylation to yield *N*-isopropyl derivative **3**. That compound could then be elaborated to amine **4** using a modified version of the process developed by Armstrong et al.[17] Thus, exposure of **3** to tetramethylethylenediamine (TMEDA), iodotrimethylsilane (TMSI) and iodine effected iodination alpha to the lactam carbonyl. Nucleophilic displacement of iodide with azide and subsequent hydrogenation then furnished racemic amine **4**. That amine was coupled with N-Boc-D-2-F-Phe under standard conditions (BOP, *i*-Pr_2NEt) to give two diastereomeric products that were separable via HPLC.[18] Exposure of the fast-eluting (*R,R*) diastereomer **5** to standard conditions for N-Boc deprotection (trifluoroacetic acid in dichloromethane) provided a crude TFA salt that could be coupled with 2-trifluoromethyl-4-fluorobenzoic acid to afford target compound **6**.

N-Cyclopropyl benzazepinones were prepared as outlined in Scheme 2. Known trifluorobenzazepinone **7** was synthesized from 2-bromo-3,4,6-trifluoroaniline using our recently reported method.[16] Upon heating in the presence of 10 mol % copper iodide and *N,N′*-dimethylethylenediamine, **7** underwent Cu(I)-catalyzed Buchwald coupling with vinyl bromide or 2-bromopropene to provide **8a** or **8b**, respectively.[19] Treatment of **8a** or **8b** with diethylzinc, trifluoroacetic acid and diiodomethane then effected cyclopropanation to yield **9a** or **9b**.[20] Those compounds were subjected to the sequence shown in Scheme 1 for the conversion of **3** to **6** to provide target compounds **28**–**31**.

Table 1
Effect of benzazepinone substitution on $Na_v1.7$ potency and rat pharmacokinetics in the 2-OCF_3 Phe series



Compound	R	$Na_v1.7$ (IC_{50}, nM)	MK-0499 (% inh @ 10 μM)	*F* (%)	AUC_N (po, μM h/mpk)	C_{max}	Cl_p (mL/min/kg)	$t_{1/2}$ (h)
1	H	35	17	24	0.31	0.30	24	2.3
10	9-F	70	24	27	0.39	0.38	21	2.7
11	8-F	18	26	20	0.20	0.24	29	2.5
12	7-F	34	24	35	0.66	0.47	16	2.3
13	7-Cl	108	32	31	0.71	0.53	13	3.0
14	7-CF_3	181	7	59	0.41	0.09	39	1.9
15	8-CF_3	494	19	21	0.22	0.01	26	1.3
16	7,9-di-F	57	21	30	0.54	0.32	17	2.7
17	6,7,9-tri-F	67	24	n.d.	n.d.	n.d.	n.d.	n.d.