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Benzazepinone $Na_v1.7$ blockers: Potential treatments for neuropathic pain

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Abstract—A series of benzazepinones were synthesized and evaluated as $hNa_v1.7$ sodium channel blockers. Several compounds from this series displayed good oral bioavailability and exposure and were efficacious in a rat model of neuropathic pain.

Neuropathic pain is a chronic, debilitating pain state that results from injury to the peripheral or central nervous system. It is estimated to affect 4 million people in the US, and can be triggered by a variety of events or conditions, including diabetes, shingles and chemotherapy.[1] Because few effective therapies exist, patients suffering neuropathic pain are often prescribed anticonvulsants or topical anesthetics as treatment. Optimized for other indications, these agents typically offer only modest pain relief, and frequently elicit dose-limiting CNS-based side effects.

Neuropathic pain signaling begins with the aberrant firing of action potential bursts in damaged axons. The initiation and propagation of these action potentials typically require the opening of voltage-gated sodium channels ($Na_v1.x$). Because they can inhibit action potential firing, Na_v1 blockers have been investigated as treatments for neuropathic pain.[2–4] Weak blockers such as lidocaine, carbamazepine and ralfinamide have shown preclinical and/or clinical efficacy in the treatment of neuropathic pain, thereby providing validation for this approach.[5–8]

Recent data from human genetic studies have implicated $hNa_v1.7$, a subtype located primarily in the PNS, as a key constituent in pain signaling. Individuals with gain of function mutations in *SCN9A*, the gene that encodes $hNa_v1.7$, experience bouts of intense pain that are either evoked by mild stimuli or spontaneous in nature.[9,10] As such, their symptoms resemble those presented by neuropathic pain patients. In contrast, individuals with loss of function mutations in *SCN9A*—human $Na_v1.7$ knockouts—are viable, healthy, and normal in seemingly every regard, save one: they have a complete inability to sense pain.[11,12] Collectively, these studies provide compelling genetic validation for $hNa_v1.7$ as an important pain target.

Our goal is to develop $hNa_v1.7$ blockers as treatments for neuropathic pain. Toward that end, we recently reported the discovery of a structurally novel class of benzazepinone $hNa_v1.7$ blockers.[13] An exemplar of this class, compound **1**, displayed potent, state-dependent block of $hNa_v1.7$ in vitro, blocked spontaneous

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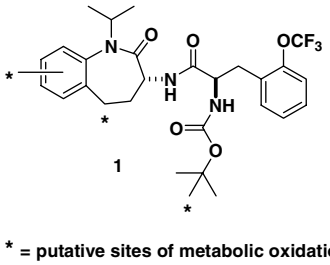
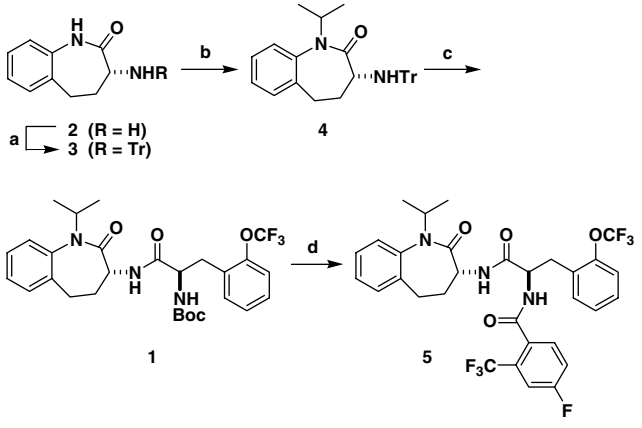


Figure 1. Benzazepinone $Na_v1.7$ sodium channel blocker **1**.

neuronal firing in vivo, and was orally efficacious in a rat model of neuropathic pain (Fig. 1). Because **1** exhibited modest pharmacokinetics (PK) in rat and dog, subsequent work in this series has focused specifically on improving PK. These efforts, described herein, have led to the discovery of compounds that display improved oral bioavailability and exposure as well as increased efficacy in a rat model of neuropathic pain.

The oral exposure of **1** was modest in rat and dog (rat: PO AUC_N = 0.31 μM h/mpk; dog: PO AUC_N = 0.27 μM h/mpk) and was limited by relatively high rates of oxidative metabolism and clearance (rat: Cl_p = 24 mL/min/kg; dog: Cl_p = 15 mL/min/kg). We thus sought to increase exposure by improving metabolic stability and reducing clearance. To determine its primary sites of metabolic oxidation, we incubated **1** in the presence of rat liver microsomes. Mass spectral analysis of the major metabolites revealed oxidation at the *N*-Boc *tert*-butyl group, at one or more sites on the benzazepinone phenyl ring (Fig. 1, C6–C9) and/or at the benzazepinone benzylic position (C5). Blocking or deactivating those sites became the main focus of our chemistry efforts, described below.

Analogs of **1** wherein the *N*-Boc group had been replaced were synthesized as shown in Scheme 1. The requisite starting material, (*R*)-3-amino-2,3,4,5-tetrahydro-1*H*-[1]-benzazepin-2-one **2**, was prepared according to the procedure of Armstrong and coworkers, then tritylated to yield compound **3**.[14] Treatment of **3** with sodium hydride and 2-iodopropane effected lactam alkylation to give *N*-isopropyl derivative **4**. Acid-catalyzed detritylation of **4** then furnished an amine that was coupled with *N*-Boc-D-2-OCF_3-phenylalanine to yield **1**.[15] Finally, exposure of **1** to standard conditions for *N*-Boc deprotection (TFA, CH_2Cl_2) gave an amine salt that could be coupled with 4-fluoro-2-(trifluoromethyl)benzoic acid to afford **5**, or with other commercially available carboxylic acids to provide products **6**–**19** (Table 1).

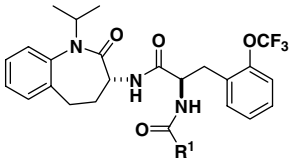


Scheme 1. Reagents and conditions: (a) TrCl, Et_3N, DMF (60%); (b) NaH, DMF, 2-iodopropane, 0–60 °C (72%); (c) HCl, MeOH; *N*-Boc-D-2-OCF_3Phe, EDC, HOBt, *i*-Pr_2NEt, THF; (d) TFA, CH_2Cl_2; 4-F-2-CF_3-benzoic acid, EDC, HOBt, *i*-Pr_2NEt, THF.

Once synthesized, compounds were then assayed for their ability to block $hNa_v1.7$. The extent of channel block was determined in a functional, membrane potential-based assay that measures the fluorescence resonance energy transfer (FRET) between two membrane-associated dyes. Specific details of the experimental protocols employed have recently been described.[16] Target compounds were also screened against other ion channels that are known to impact cardiac function. Because block of hERG K^+ channels has been associated with potentially lethal ventricular arrhythmias, compounds were tested in a binding assay that measures displacement of ^{35}S-labelled MK-0499, a known hERG blocker.[17]

Prior work had shown that $hNa_v1.7$ block was optimized when the side chain incorporated a secondary amide or carbamate. Knowing that, we synthesized a series of analogs wherein the *N*-Boc group of **1** was replaced by a variety of secondary amides. In the alkylamide series, analogs with sterically smaller R^1 groups (Table 1, compounds **6**–**7**) displayed weak $hNa_v1.7$ block, while those with bulkier R^1 groups (compounds **8**–**10**) proved more potent. In the arylamide series, the simple benzamide derivative **11** exhibited best-in-class potency, but suffered from high activity in the MK-0499 counterscreen. Several substituted benzamides (compounds **12**–**15**), albeit less potent, were consider-

Table 1. Effect of the R^1 group on $hNa_v1.7$ potency



Compound	R^1	$hNa_v1.7$ (IC_{50}, nM)	MK-0499 (% inh at 10 μM)
6	CH_3	>1000	9
7	CF_3	868	40
8	$C(CH_3)_3$	131	18
9	$C(CF_3)_2CH_3$	203	10
10	(*c*-Pr)CH_3	172	39
11	Ph	22	83
12	4-F-Ph	94	26
13	4-CF_3-Ph	175	43
14	2-CF_3-Ph	98	0
15	2-CF_3-4-F-Ph	128	31
16	2-Pyridyl	177	61
17	4-Pyridyl	453	44
18	2-Pyrimidinyl	>1000	15
19	5-Pyrimidinyl	>1000	