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Bioorganic & Medicinal Chemistry Letters 17 (2007) 4630–4634
Bioorganic & Medicinal Chemistry Letters

Discovery of a novel class of benzazepinone $Na_v1.7$ blockers: Potential treatments for neuropathic pain

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Received 18 April 2007; revised 22 May 2007; accepted 24 May 2007
Available online 27 May 2007

Abstract—A series of benzodiazepines and benzazepinones were synthesized and evaluated as potential sodium channel blockers in a functional, membrane potential-based assay. One member of the benzazepinone series, compound **47**, displayed potent, state-dependent block of $hNa_v1.7$, and was orally 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 affects more than 1.6 million people in the United States, 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 such as sedation and impairment.

Neuropathic pain signaling begins with the aberrant firing of action potential bursts in damaged nerve tissue. 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 carbamazepine and lidocaine have shown efficacy in the treatment of neuropathic pain, thereby providing clinical validation for this approach (Fig. 1).[5,6]

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.[7,8] As such, their symptoms resemble those presented by neuropathic pain patients. In contrast, individuals with loss of function mutations in *SCN9A* have a complete inability to sense pain, yet retain all other normal nerve functions.[9,10] Collectively, these studies provide compelling genetic validation for $hNa_v1.7$ as an important pain target.

Channel blockers destined for the clinic must inhibit aberrant neuronal signaling while leaving normal nerve

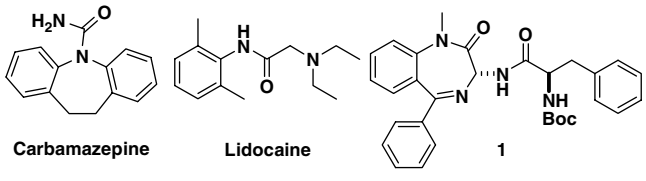

Figure 1. Sodium channel blockers.

Keywords: Sodium channel; Neuropathic pain; Nav1.7; Benzazepinone; Benzodiazepine.
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doi:10.1016/j.bmcl.2007.05.076

functions intact. We believe that this can be achieved, in large part, via 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 damaged nerve tissue, on the other hand, they accumulate in the inactivated state. Compounds that selectively bind and stabilize that inactivated state should block signaling in damaged tissue preferentially, thereby minimizing the potential for mechanism-based adverse effects.

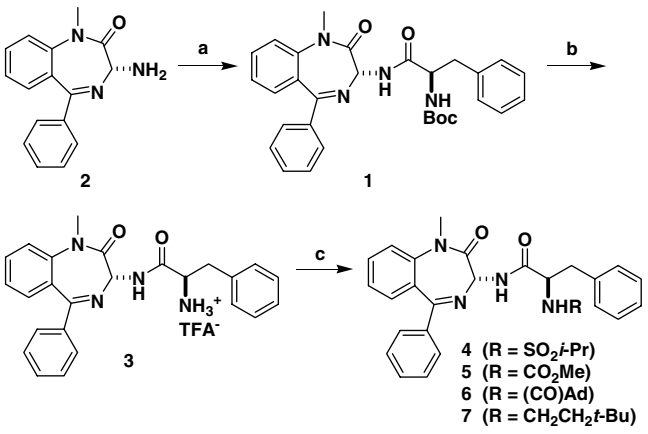
Our goal is to develop potent, state-dependent $hNa_v1.7$ blockers as treatments for neuropathic pain. Toward that end, we initiated a screening of the Merck sample collection and identified benzodiazepine **1** (Fig. 1) as a starting point for optimization studies. The modification of **1**, described herein, has led to the discovery of a potent, state-dependent $hNa_v1.7$ blocker that displays good oral efficacy in a rat model of neuropathic pain.

Initial analogs of **1** were synthesized using the procedures outlined in Scheme 1. The starting material for this sequence, (*R*)-3-amino-1-methyl-5-phenyl-1,3-dihydro-benzo[*e*][1,4]diazepin-2-one **2**, has been described previously.[11] Coupling of **2** with *N*-Boc-D-phenylalanine furnished protected amide **1**. Acid-catalyzed amine deprotection then gave **3**, a central intermediate that could be coupled with various sulfonyl chlorides, chloroformates or carbonyl chlorides to yield products such as **4**, **5**, and **6**. Alternatively, **3** could participate in reductive amination to afford amines such as **7**.

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.[12] Selected compounds were also screened against several 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-labeled MK-0499, a known hERG blocker.[13] Similarly, because block of $Ca_v1.2$ Ca^{2+} channels can lead to unsafe decreases in mean arterial pressure, compounds were screened in a binding assay that measures displacement of ^3H-diltiazem (DLZ), a known $Ca_v1.2$ blocker.[14]

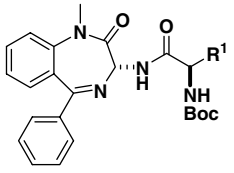
Initial SAR efforts were aimed at paring **1** down to the minimum structure required for potent $hNa_v1.7$ block. We began by varying the sidechain R^1 substituent. As shown in Table 1, when the R^1 phenyl present in **1** was replaced with a cyclohexyl group (compound **9**) or deleted entirely (compound **8**), a dramatic loss in $hNa_v1.7$ potency was observed. If the alkyl tether connecting R^1 to the molecule was shortened or lengthened (**10** and **11**), potency was also diminished. While fluorination of the R^1 phenyl was tolerated (**12** and **13**), replacement of the phenyl with various aromatic heterocycles led to weaker channel block (**14**–**16**). Taken together, these data indicate that a lipophilic aromatic group is required at this site.

Having elucidated the requirements for R^1, we turned our attention toward the sidechain R^2 site. In a bid to reduce structural complexity, we prepared analogs wherein the *N*-Boc group (Table 2, compound **17**) or the entire –NH(Boc) moiety (compound **18**) had been excised. Unfortunately, each of these afforded only weak $hNa_v1.7$ functional block. An *N*-methylated derivative (**19**), a series of sulfonamides (**20**, **4**, and **21**) and an amine (**7**) that retained the terminal *tert*-butyl group of **1** were also prepared and found to be much less potent than *N*-Boc derivative **1**. These results suggested that the sidechain N–H might play an important role in channel binding, and might need to be maintained within a specific pK_a range. With that in mind, we narrowed the scope of our efforts and prepared a series of carbamates and amides. In the carbamate series, methyl derivative **5** displayed only weak channel block, but benzyl



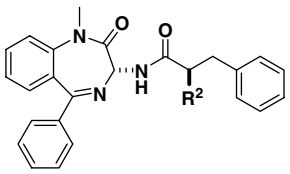
Scheme 1. Reagents and condition: (a) *N*-Boc-D-Phe, CDI, DMF, 60 °C (89%); (b) TFA, CH_2Cl_2; (c) *i*-$PrSO_2Cl$, *i*-Pr_2NEt, CH_2Cl_2; or MeO_2CCl, K_2CO_3, CH_2Cl_2; or 1-adamantyl carbonyl chloride, K_2CO_3, CH_2Cl_2; or 3,3-dimethylbutyraldehyde, $NaCNBH_3$, MeOH.

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



Compound	R^1	$hNa_v1.7$ (IC_{50}, nM)
1	CH_2Ph	125
8	Me	>1000
9	CH_2(c-Hex)	>1000
10	Ph	375
11	CH_2CH_2Ph	238
12	CH_2(2-F-Ph)	87
13	CH_2(4-F-Ph)	71
14	CH_2(4-thiazolyl)	684
15	CH_2(3-pyridyl)	978
16	CH_2(4-imidazolyl)	>1000

Table 2. Effect of the R^2 group on $hNa_v1.7$ potency



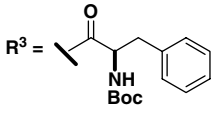
Compound	R^2	$hNa_v1.7$ (IC_{50}, nM)
1	NH(Boc)	125
17	NH_2	>1000
18	H	>1000
19	NMe(Boc)	>1000
20	$NH(SO_2Me)$	>1000
4	$NH(SO_2i\text{-Pr})$	>1000
21	$NH(SO_2Ph)$	>1000
7	$NH(CH_2CH_2t\text{-Bu})$	>1000
5	$NH(CO_2Me)$	>1000
22	$NH(CO_2Bn)$	150
23	NH(CO)*c*-Pr	>1000
24	NH(CO)*t*-Bu	380
6	NH(CO)Ad	420

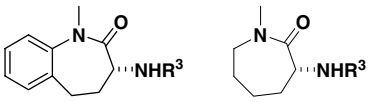
carbamate **22** proved to be as potent as **1**. Likewise, in the amide series, the smaller cyclopropyl analog **23** proved weak, while the larger *tert*-butyl and adamantyl amides **24** and **6** were more potent. This initial survey suggested that a range of amides and carbamates might be tolerated at R^2, so long as they terminated in a bulky alkyl or aryl group.

We next probed the effect of alterations to the benzodiazepine core. With an eye toward simplification, we truncated the tricyclic core of **1** and obtained **25**, a compound that maintained potent $hNa_v1.7$ block (Table 3). Taking this approach a step further, we deleted the left-hand phenyl ring from **25**. The resulting derivative **26** proved less potent, thus underscoring the importance of that ring in binding and/or conformational constraint. Because it seemed to offer numerous advantages, the benzazepinone core embodied in **25** was employed in all subsequent designs.

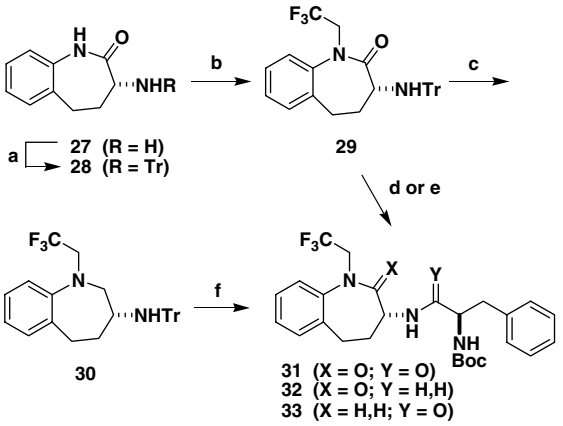
Analogs in this new benzazepinone series were synthesized according to the procedures outlined in Scheme 2. The requisite starting material, (*R*)-3-amino-2,3,4,5-

Table 3. Modifications to the benzodiazepine core





Compound	**25**	**26**
$hNa_v1.7$ (IC_{50}, nM)	192	>1000

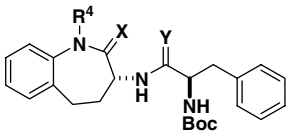


Scheme 2. Reagents and conditions: (a) TrCl, Et_3N, DMF (60%); (b) NaH, THF, CF_3CH_2OTf, 0 °C to RT (82%); (c) LAH, THF, 0–60 °C (99%); (d) HCl, MeOH; *N*-Boc-D-Phe, CDI, DMF, 60 °C; (e) HCl, MeOH; *N*-Boc-D-phenylalaninal, $NaCNBH_3$, MeOH; (f) HCl, MeOH; *N*-Boc-D-Phe, BOP, *i*-Pr_2NEt, THF (64%—2 steps).

tetrahydro-1*H*-[1]-benzazepin-2-one **27**, was prepared according to the procedure of Armstrong and coworkers, then tritylated to yield compound **28**.[15] Sequential treatment of **28** with sodium hydride and trifluoroethyl triflate resulted in lactam alkylation to give **29**. Acid-catalyzed N-detritylation of **29** then furnished an amine that could undergo amide coupling with *N*-Boc-D-phenylalanine to yield **31** (step d), or reductive amination with *N*-Boc-D-phenylalaninal to provide **32** (step e). Alternatively, intermediate **29** could be treated with lithium aluminum hydride to afford **30**, the product of lactam reduction. Acid-catalyzed amine deprotection followed by BOP-mediated amide coupling then delivered **33**. Compounds listed in Tables 3–5 were synthesized according to these procedures using the appropriate commercially available starting materials. In several instances (**46** and **47**), compounds were prepared using non-commercially available amino acids that had been synthesized via the method of Scholkopf.[16] Analogs with (*S*) stereochemistry at the 3-amino stereocenter (e.g., **48**) were prepared from the enantiomer of **27**, known compound (*S*)-3-amino-2,3,4,5-tetrahydro-1*H*-[1]-benzazepin-2-one.[17]

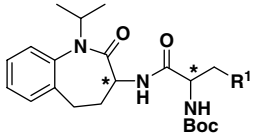
Our final set of core modifications focused on the benzazepinone lactam region. We began by replacing the lactam *N*-methyl of **25** with a set of small alkyl groups (Table 4, compounds **31**, **34**, and **35**). Of these, the *N*-isopropyl analog **35** displayed optimal $hNa_v1.7$ blockade. We also probed the importance of the lactam carbonyl in channel binding. When compared with *N*-methyl lactam **25**, the reduced derivative **36** was notably less potent. In contrast, the *N*-trifluoroethyl lactam **31** and its reduced counterpart **33** were essentially equipotent. Thus, it may be that while the lactam carbonyl is not required per se, electron density on the lactam nitrogen must be attenuated in order to maintain potent $hNa_v1.7$ block. Finally, we investigated the role of the exocyclic amide in channel binding. When compared with amide **31**, the corresponding amine **32** showed both reduced $hNa_v1.7$ potency and increased MK-0499 activity. From these studies, it appeared that an optimal

Table 4. Modifications to the benzazepinone lactam region



Compound	R^4	X	Y	$hNa_v1.7$ (IC_{50}, nM)	MK-0499 (% inhibition at 10 μM)
25	CH_3	0	0	192	16
31	CH_2CF_3	0	0	150	16
34	CH_2*c*-Pr	0	0	78	15
35	*i*-Pr	0	0	45	6
36	CH_3	H,H	0	>1000	28
33	CH_2CF_3	H,H	0	145	40
32	CH_2CF_3	0	H,H	885	79

Table 5. Optimization of the benzazepinone R^1 substituent



Compound	R^1	*/*	$hNa_v1.7$ (IC_{50}, nM)	(% inhibition at 10 μM)	
				MK-0499	DLZ
35	Ph	*R*,*R*	45	6	
37	2-F-Ph	*R*,*R*	44	8	11
38	3-F-Ph	*R*,*R*	9	8	0
39	4-F-Ph	*R*,*R*	98	0	0
40	2,5-di-F-Ph	*R*,*R*	23	6	24
41	2,6-di-F-Ph	*R*,*R*	14	4	36
42	2-CF_3-Ph	*R*,*R*	137	34	
43	3-CF_3-Ph	*R*,*R*	295	15	19
44	4-CF_3-Ph	*R*,*R*	>1000		
45	2-CF_3-3-F-Ph	*R*,*R*	65	39	87
46	2-CF_3-6-F-Ph	*R*,*R*	32	43	81
47	2-OCF_3-Ph	*R*,*R*	35	18	3500[a]
48	2-OCF_3-Ph	*S*,*R*	32	20	1725[a]
49	2-OCF_3-Ph	*R*,*S*	214	0	

[a] IC_{50}, nM.

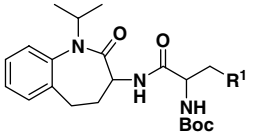
design would incorporate an *N*-isopropyl benzazepinone core coupled to an amide sidechain.

At this point, we had identified the essential structural features required for potent block of $hNa_v1.7$. Because substitution at the R^1 position was known to affect binding, and because we had made significant changes to the lead structure since our first survey of R^1, we ran a focused re-optimization of that domain. Consistent with our earlier results, fluorination of the R^1 phenyl ring was well tolerated (compounds **37**–**41**), with the 3-fluorophenyl and 2,6-difluorophenyl derivatives **38** and **41** proving particularly potent (Table 5). Incorporation of the larger trifluoromethyl group at the 2-, 3- or 4-positions (**42**–**44**) led, in each case, to derivatives less potent than their fluorinated counterparts. Potency of the 2-trifluoromethyl analog could, however, be improved by additional fluorination at the 3- or 6-position (**45** and **46**), or by conversion to a 2-trifluoromethoxy group (**47**). In accordance with trends that have been observed generally in this series, the *S*,*R* diastereomer of **47** (compound **48**) maintained good $hNa_v1.7$ block, while the *R*,*S* diastereomer **49** proved to be less potent. In general, compounds from this series were notably free of activity in the MK-0499 and DLZ counterscreens.

Several members from this series were submitted to pharmacokinetic (PK) assays. The first compound to be profiled, 2-F-phenyl derivative **37**, displayed rather modest oral bioavailability and exposure (Table 6). Fortunately, analogs of **37** that incorporated larger groups at the phenylalanine 2-position fared better. The 2-CF_3-phenyl derivative **42**, for instance, exhibited a two-fold increase in oral exposure. Related compounds **46** and **47** maintained or improved upon that exposure level and also featured reduced rates of clearance. The derivative with the best overall profile, **47**, was submitted for PK determination in dog and showed similar results, albeit with lower bioavailability, in that species.

Because it was the most promising compound to emerge from this series, **47** was selected for further study. For reasons outlined above, it was important to determine

Table 6. Pharmacokinetic data for selected compounds



Target	R^1	Species	Dose[a] (iv/po)	F%	AUC_N[b]	C_{max}[c]	Cl_p[d]	$T_{1/2}$[e]
37	2-F-Ph	Rat	1.0/3.0	14	0.12	0.10	41	1.5
42	2-CF_3-Ph	Rat	1.0/3.0	35	0.22	0.30	50	2.1
46	2-CF_3-6-F-Ph	Rat	1.0/3.0	28	0.24	0.33	32	2.5
47	2-OCF_3-Ph	Rat	1.0/3.0	24	0.31	0.30	24	2.3
48	2-OCF_3-Ph	Rat	1.0/3.0	15	0.09	0.14	55	2.1
47	2-OCF_3-Ph	Dog	0.38/1.5	9	0.27	0.07	15	4.2

[a] mg/kg.
[b] μM h/mpk.
[c] μM.
[d] mL/min/kg.
[e] Hours.

whether **47** blocked $hNa_v1.7$ in a state-dependent manner. Compound **47** was therefore analyzed by whole cell electrophysiology to determine its binding to $hNa_v1.7$ inactive and resting states (K_i and K_r, respectively).[18] Analysis via this technique yielded a $K_i = 40$ nM and a K_r of >3 μM, indicating that block of $hNa_v1.7$ by **47** is highly state-dependent.

The ability of **47** to inhibit neuronal firing in vivo was examined in the rat peripheral axotomy model.[19] In this assay, the sciatic nerve was sectioned at mid-thigh to generate a neuroma. Three to 10 days later, the nerve was exposed and electrodes were connected to neuronal filaments that were firing spontaneously. After the baseline firing frequency was established, test compound was administered as an iv infusion. Firing frequency was then measured for an additional 60 min post-dose. When dosed iv at 2 mg/kg, **47** produced essentially complete block of spontaneous neuronal firing at all time-points studied (% inhibition at 10, 30, and 60 min = 100%, 100%, 93%, $n = 6$).

Finally, compound **47** was submitted for pharmacodynamic profiling in a rat spinal nerve ligation model of neuropathic pain.[20] In that assay, rats underwent surgical ligation and transection of the L5 spinal nerve as a means of initiating neuropathy. Tactile allodynia was assessed both before and 1 week after surgery using calibrated Von Frey filaments. In rats that presented significant allodynia, test compound was administered orally, and reversal of allodynia was then determined. When dosed orally at 10 mg/kg, compound **47** elicited significant reversal of allodynia at both 2 and 4 h post-dose (% reversal at 2, 4 h = 43%, 40%, $n = 8$), indicating that it is indeed efficacious in a rat model of neuropathic pain.

In summary, we have discovered a structurally novel class of benzazepinone-based sodium channel blockers. An exemplar of this class displayed potent, state-dependent block of $hNa_v1.7$ in vitro, blocked spontaneous neuronal firing in vivo, and was orally efficacious in a rat model of neuropathic pain. Future work in this series will focus on further improvements to pharmacokinetics and pharmacodynamics, and will be reported in due course.

Acknowledgments

We thank Ramona Gray and Joe Leone for their outstanding technical contributions to this work. We also thank Joseph L. Duffy, Deborah E. Pan, and Christian Stevenson for their valuable assistance in proofreading this document.

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