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Synthesis and SAR of 1,2-*trans*-(1-hydroxy-3-phenylprop-1-yl) cyclopentane carboxamide derivatives, a new class of sodium channel blockers

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Abstract—Novel cyclopentane-based 3-phenyl-1-hydroxypropyl compounds were evaluated for inhibitory activity against the peripheral nerve sodium channel $Na_V1.7$ and off-target activity against the cardiac potassium channel hERG. The stereochemistry of the hydroxyl group and substitution on the phenyl rings with either fluorinated *O*-alkyl or alkyl groups were found to be critical for conferring potency against $Na_V1.7$. A benchmark compound from this series displayed efficacy in rat models of inflammatory and neuropathic pain.

Neuropathic pain is defined as chronic pain that arises from injury to the peripheral or central nervous system or from diseases that affect the nervous system, such as diabetes mellitus and HIV. Neuropathic pain is thought to be associated with hyperexcitability of sensory afferents, leading to abnormal spontaneous firing.[1] Voltage-gated sodium channels (VGSCs) have been shown to accumulate in injured sensory nerves[2], and block of VGSCs inhibits injury-induced spontaneous firing.[3] Several sodium channel blockers are used clinically in the treatment of neuropathic pain. These include local anesthetics (e.g., lidocaine), antiarrhythmics (e.g., mexiletine) and anticonvulsants (e.g., lamotrigine and carbamazepine).[4]

Recently, the structurally novel sodium channel blocker *N*-{[2′-(aminosulfonyl)biphenyl-4-yl]methyl}-*N*′-(2,2′-bithien-5-ylmethyl)succinamide (BPBTS)[5] was identified through high-throughput screening, using a FRET-based membrane potential assay that measures the activity of the $Na_V1.7$ channel subtype. $Na_V1.7$ channels are highly expressed in sensory neurons and are thought to contribute to nociception.[6] BPBTS (compound **1**) has good in vitro potency, blocking the inactivated state of the VGSC subtype $Na_V1.7$ with a K_i of 0.15 μM. When injected locally, BPBTS dose-dependently inhibited pain behavior in a rat model of tonic pain. Recently, we reported the synthesis of CDA54[7] (compound **2**), which has improved pharmacokinetics compared to that of BPBTS and is orally active in the spinal nerve ligation (SNL) model, a rat model of neuropathic pain.[8] Despite a reasonable pharmacokinetic profile in rats (F = 44%, Clp = 14 mL/min/kg, $T_{0.5}$ = 0.98 h), human liver microsomal (HLM) stability studies with CDA54 indicated rapid metabolic oxidation of the *N*-Me amide side chain, leading to dealkylated metabolites, and of the biphenylsulfonamide group. The purpose of the present study was to further define the key structure–activity relationships (SARs) of **2** and identify analogs with improved pharmacokinetic properties.

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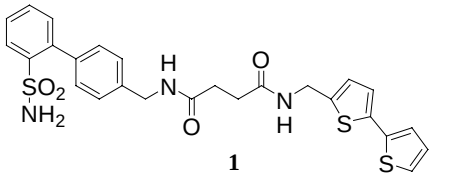

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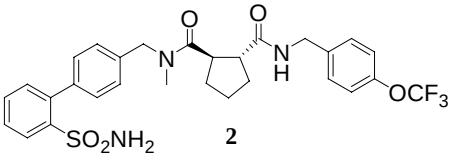

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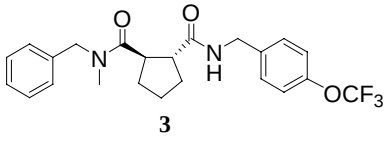

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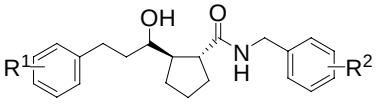
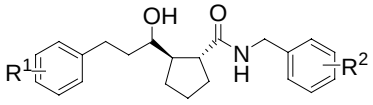


4

Initial SAR studies began with the removal of the metabolically labile biphenylsulfonamide group leading to the *N*-Me benzylamide **3**[9], which showed a 5-fold loss in potency in the functional $Na_V1.7$ assay[10], when compared to that of **2** ($IC_{50} \sim 1.5$ vs 0.29 μM for **2**). We next sought to decrease the peptidyl nature of the compound by replacing an amide bond in **3** with various surrogates. Ether, amine, sulfonamide, reverse amide, and hydroxypropyl tethers led to a further decrease in potency. However, phenyl substitution, and modifications of the right-hand benzyl amide region in molecules containing a 1-hydroxy-3-phenylprop-1-yl tether produced several compounds with $Na_V1.7$ potency similar to that of **2**.

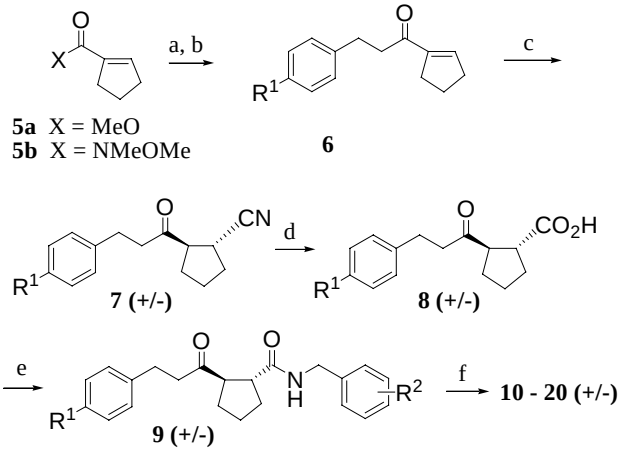
The synthesis of the compounds in Table 1 is described in Scheme 1. Commercially available methyl 1-cyclopentene-1-carboxylate (**5a**) was treated with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropyl magnesium chloride to give Weinreb amide **5b**. This was reacted with excess Grignard reagent to give ketones **6** (range of yields 53–65% from **5a**).[11] In a key step, a high selectivity of the *trans* stereochemistry of nitriles **7** (>88% dec) was obtained in ⩾90% yield via the reaction of **6** with potassium cyanide in refluxing methanol. The nitriles **7** were then hydrolyzed to the corresponding acids **8** (concd HCl, 80 °C, 5 h, dioxane) in quantitative yield.[12] The acids **8** were converted to the benzyl amides **9** using the requisite benzylamine through BOP-mediated amide bond formation. The carbonyl group in **9** was finally reduced with $NaBH_4$ to provide a set of racemic, diastereomeric alcohols **10**–**20**. The two diastereomers were readily separated by standard silica gel chromatography.[13] The faster moving diastereomers were typically more potent against $Na_V1.7$, and all compounds shown in Tables 1 and 2 refer to the faster moving diastereomer, except for **10** which is a mixture of two diastereomers.

Table 1. Potencies in functional $Na_V1.7$ and hERG binding assays



Compound	R^1	R^2	$Na_V1.7$ IC_{50} (μM)	MK-0499 binding (% inhibition at 10 μM)
2			0.29	54
3			1.49	nd[c]
10	H	H	>3	nd[c]
11	2-OCF_3	H	0.32	92
12	3-OCF_3	H	0.23	89
13	4-OCF_3	H	0.64	52
13A[a]	4-OCF_3	H	0.52	68
13B[b]	4-OCF_3	H	0.36	60
14	H	3,5-di-Cl	0.98	91
15	2-OCF_3	3,5-di-Cl	1.15	73
16	3-OCF_3	3,5-di-Cl	0.44	87
17	3-OCF_3	2-CF_3	0.44	78
18	4-OCF_3	3,5-di-Cl	0.87	93
19	4-OCH_3	3,5-di-Cl	1.21	70
20	4-SO_2CH_3	4-OCF_3	>3	nd[c]

[a] **13A**, enantiomer A of **13**.
[b] **13B**, enantiomer B of **13**.
[c] nd, not determined.

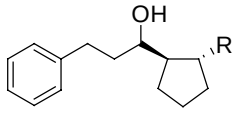


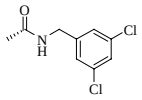
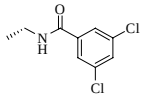
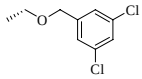
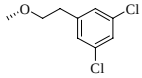
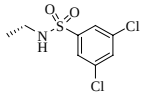
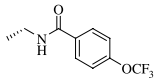
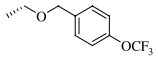
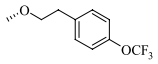
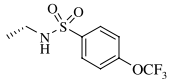
Scheme 1. Reagents and conditions: (a) Me(MeO)NH · HCl, *i*-PrMgCl, THF, 93%; (b) R_1-$Ph(CH_2)_2MgBr$, ether; (c) KCN, CH_3OH, reflux; (d) concd HCl, dioxane, 80 °C, 5 h, quant.; (e) R_2-$PhCH_2NH_2$, HOBT, BOP, *i*-Pr_2NEt; (f) $NaBH_4$, CH_3OH, 95%.

The compounds listed in Tables 1 and 2 were screened at 1 μM in the functional $Na_V1.7$ assay. IC_{50} determinations were obtained on compounds exhibiting >50% inhibition at 1 μM. In parallel, compounds were examined for activity on the cardiac potassium channel hERG using a ^{35}S-labeled MK-0499 binding assay (MK-0499 binding)[14], since blockade of hERG can lead to delayed cardiac repolarization and cause a potentially lethal arrhythmia termed torsades de pointes.[15]

Extensive SAR studies were carried out to assess optimal substitution patterns of the phenyl groups of **4** in order to maximize $Na_V1.7$ potency, while limiting

Table 2. Potencies in the $Na_V1.7$ functional assay and the hERG binding assay



Compound	R	$Na_V1.7$ IC_{50} (μM)	MK-0499 binding (% inhibition at 10 μM)
14		0.98	91
22		>3	79
24		1.11	59
28		>3	40
29		>3	90
30		0.33	84
31		0.82	65
32		>3	70
33		0.63	90

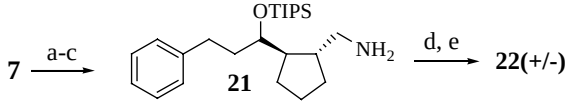
hERG activity (Table 1). Block of $Na_V1.7$ occurred with different substituents at various positions in the aromatic rings, but most compounds also had substantial hERG binding activity.

In general, potency of the unsubstituted lead **10** was increased by substitution at various positions on the phenyl rings with an OCF_3 group, as illustrated by analogs **11**–**13**, which all exhibited improved $Na_V1.7$ activity compared to that of **10**. The 3,5-di-Cl analog (**14**) also resulted in an increase in potency over **10**, suggesting that these substituents may contribute to hydrophobic interaction surfaces. However, simultaneous substitutions on both phenyl rings generally led to a loss of activity as compared to substitutions with a single OCF_3 group (for example, compare **16** and **12**), pointing to potential steric effects. In contrast to $-CF_3$ and $-OCF_3$ substituents, 4-methoxy **19** or sulfone **20** substitutions were not well tolerated.

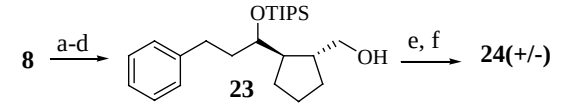
Of the compounds in Table 1, **13** displayed the greatest selectivity for block of $Na_V1.7$ over binding to hERG. To characterize the individual enantiomers of **13**, the racemic parent was resolved by chiral HPLC[16] to yield **13A** and **13B**, as the faster and slower eluting enantiomers, respectively. Enantiomer B (**13B**) displayed slightly better properties with respect to $Na_V1.7$ and hERG activity.

To examine the other benzylic amide moiety, a series of compounds containing modifications on the amide chain of **14** were synthesized (Schemes 2–4) and tested (Table 2). The 3,5-di-Cl compound **22**, a reverse amide analog of **14**, was practically inactive. However, the OCF_3analog of **22** (compound **30**) exhibited a 3-fold increase in activity as compared to **14**. In fact, compound **30** is one of the most potent $Na_V1.7$ blockers prepared in the alcohol series, but inhibited MK-0499 binding to hERG by 45% and 84% at 1 μM and 10 μM, respectively. The interesting effect of the OCF_3 group is not confined to the reverse amide analog **30**, but is also found in the corresponding sulfonamide analogs. While 3,5-di-Cl sulfonamide analog **29** was devoid of activity, the OCF_3 analog **33** exhibited similar activity to **14**. The SAR also shows that replacement of the amide with an ether linkage was well tolerated (**24** and **31**), while the isomeric ether analogs (**28** and **32**) showed a greatly diminished activity.

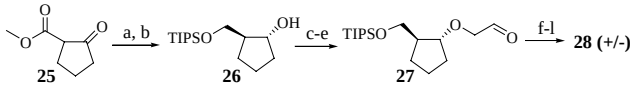
The data in Tables 1 and 2 show that many of the compounds containing a hydroxypropyl tether have similar potency on $Na_V1.7$ as **2**. Apparently, the amide moieties are not critical determinants of potency, and can be replaced with no appreciable loss of activity. However,



Scheme 2. Reagents and conditions: (a) $NaBH_4$, CH_3OH (97%); (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2 (90%); (c) H_2, Raney Ni, NH_3 (50 atm), CH_3OH, 50 °C, 3 h (95%); (d) 3,5-$Cl_2C_6H_3COOH$, HOBT, BOP, *i*-Pr_2NEt, CH_2Cl_2; (e) *n*-Bu_4NF, THF.



Scheme 3. Reagents and conditions: (a) HCl (g), CH_3OH (92%); (b) $NaBH_4$, CH_3OH; (c) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (d) $LiAlH_4$, ether (87%); (e) NaH, 3,5-$Cl_2C_6H_5CH_2Br$, DMF; (f) *n*-Bu_4NF, THF.



Scheme 4. Reagents and conditions: (a) $LiAlH_4$, ether (87%); (b) TIPSCl, imidazole, CH_2Cl_2 (95%) and separation of *cis* and *trans* isomers (approximately 1:1); (c) NaH, $CH_2{=}CHCH_2Br$, DMF (70%); (d) 4-Methylmorpholine *N*-oxide, OsO_4, CH_2Cl_2; (e) $Pb(OAc)_4$, pyridine, CH_3OH; (f) 3,5-$Cl_2C_6H_3MgBr$, ether; (g) H_2, Pd/C, CH_3OH (92%); (h) n-Bu_4NF, THF; (i) Jones reagent, acetone (80%); (j) Me(MeO)NHHCl, HOBT, BOP, *i*-Pr_2NEt, CH_2Cl_2; (k) $PhCH_2CH_2MgCl$, THF; (l) $NaBH_4$, CH_3OH.

Table 3. Pharmacokinetic properties and anti-allodynic efficacy

	2	13	13B
HLM stability[a]			
% remaining after 1 h	4	13	49
Pharmacokinetics (1 mg/kg iv)			
Oral bioavailability (%)	44	40	65
Clp (mL/min/kg)	14.0	9.0	9.0
$T_{0.5}$ (h)	1.0	1.6	1.6
C_{max}[b] (μM)	1.0	1.9	2.3
AUC[b] (μM/h)	1.8	5.3	9.0
Anti-allodynic efficacy (3 mg/kg po)			
Maximal reversal (%)	43	25	31

[a] Human liver microsomal preparation.
[b] C_{max} and [b]AUC determined after oral dosing with 2 mg/kg for **2** or 3 mg/kg for **13** and **13B**.

$Na_V1.7$ activity is strongly influenced by the nature of the substituents on both phenyl rings. The alcohols in Tables 1 and 2 are a structurally simplified design and lack one of the metabolic liabilities of compound **2**. Compounds **13** and **13B** were chosen to examine the effect of the hydroxypropyl substitution on the rat pharmacokinetic profile (Table 3).

Compounds **13** displayed a slightly greater stability than compound **2** in human liver microsome incubation studies and stability was greatly improved for **13B**. Oral bioavailability of **13** was comparable to that of **2**, whereas the single enantiomer **13B** displayed improved bioavailability, C_{max}, and AUC. Compounds **13** and **13B** showed reduced clearance rates and increased half-lives compared to **2**, suggesting that removal of the *N*-Me amide did indeed eliminate a site for metabolism. Compounds **2**, **13**, and **13B** were evaluated for anti-allodynic efficacy in a rat model of chronic pain. In the CFA model (intradermal injection of complete Freund's adjuvant)[17], **13** and **13B** significantly reversed CFA-induced allodynia but failed to show an improvement in efficacy over **2**, possibly owing to their somewhat lower in vitro potency against $Na_V1.7$, although other factors such as local tissue concentration or protein binding cannot be ruled out.

In summary, replacement of the *N*-Me amide group of the diamide **2** with an alcohol moiety has afforded a number of potent amide–alcohol hybrids with in vitro activity comparable to that of diamide **2** and with an improved pharmacokinetic profile. Two benchmark amide–alcohols are efficacious in a rat model of chronic pain, and additional experiments will determine the therapeutic potential of these compounds for the treatment of chronic pain.

Acknowledgments

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9. Compound **3** was prepared according to a method for the synthesis of **2** described in Ref. 7.
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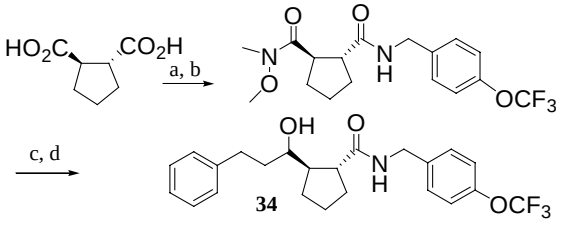
12. The stereochemistry of the cyclopentane has been unequivocally confirmed to be *trans* by an independent synthesis of **34**, which was prepared in a 4-step procedure from commercially available *trans*-DL-1,2-cyclopentane dicarboxylic acid.



Synthesis of **34**: (a) CDI, $C_6H_5CH_2NH_2$, THF; (b) Me(MeO)NH · HCl, HOBT, BOP, *i*-Pr_2NEt; (c) $PhCH_2CH_2MgBr$, ether; (d) $NaBH_4$, CH_3OH.
13. Spectral (^1H NMR, LC–MS) data on all intermediates and final compounds were consistent with the proposed structures.
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16. Column used: ChiralCel OD 4.6 × 250 mm, 10 μm. UV detection at 300 nm. Elution (.75 ml/min) with heptane: isopropyl alcohol (90:10) afforded successively the enantiomers **13A** (7.5 min) and **13B** (8.9 min).
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