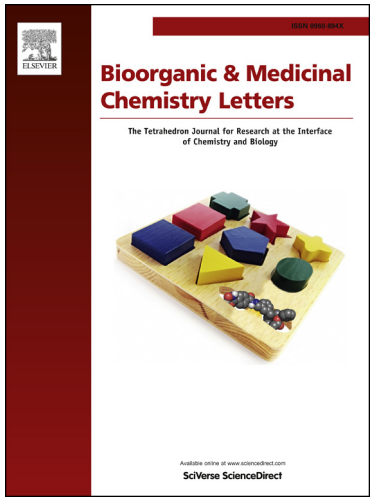

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ABSTRACT

A novel class of $Na_V1.7$ inhibitors has been identified by high-throughput screening followed by structure activity relationship studies. Among this series of compounds, piperidine **9o** showed potent human and mouse $Na_V1.7$ inhibitory activities with fair subtype selectivity over $Na_V1.5$. Compound **9o** successfully demonstrated analgesic efficacy in mice comparable to that of the currently used drug, mexiletine, but with an expanded central nervous system safety margin.

Since pain is known as the most common symptom reported by almost all patients, there are still huge unmet medical needs with regard to treating it. Genetic analysis of congenital insensitivity to pain (CIP) patients revealed that the loss of SCN9A gene function leads to CIP, and the SCN9A gene has been shown to encode voltage-gated sodium channel 1.7 ($Na_V1.7$).[1] On the other hand, the gain of SCN9A gene function was shown to be involved in a wide spectrum of human genetic pain disorders.[2] Moreover, deletion of the SCN9A gene in both sensory and sympathetic neurons in mice is known to result in the same phenotype as in humans.[3] In fact, several Na_V blockers, such as lidocaine (**I**) and mexiletine (**II**) (Figure 1), have been used clinically to treat various types of pain disorder. Consequently, $Na_V1.7$ inhibitors are expected to be promising analgesic agents. Herein, we report the discovery and structure activity relationship of novel $Na_V1.7$ inhibitors with several biological properties.[4]

Through the high-throughput screening (HTS) of our corporate library, piperazine derivative **1** was identified (Figure 1).[5] When *in vitro* evaluations of $Na_V1.7$ inhibitory activity were performed, the inhibitory activities of $Na_V1.1$ and $Na_V1.5$ were also evaluated because inhibiting $Na_V1.1$ is known to cause central nervous system (CNS) side effects such as dizziness and sedation, whereas the inhibition of $Na_V1.5$ leads to cardiac arrhythmias.[6] HTS hit **1** inhibited $Na_V1.7$ at IC_{50} = 3.9 μM with fair subtype selectivity over $Na_V1.1$ and $Na_V1.5$ (over 8.5-fold and 5.1-fold, respectively). Therefore, to acquire potent and highly subtype-selective $Na_V1.7$ inhibitors, the derivatization of HTS hit **1** was commenced.

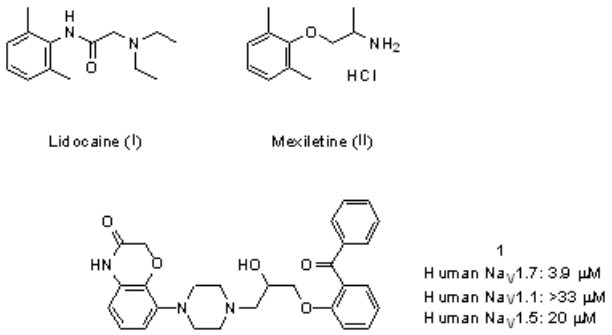
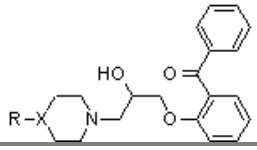


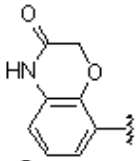
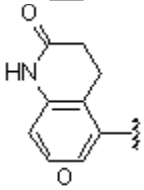
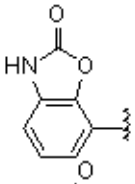
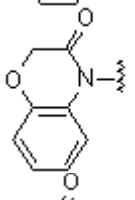
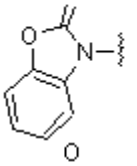
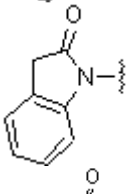
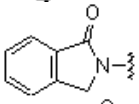
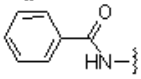
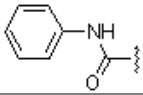
Figure 1. The structures of lidocaine (**I**), mexiletine (**II**) and HTS hit **1** with human Na_V IC_{50} values.

Initial studies were focused on the conversion of benzoxazinone and piperazine moieties, as shown in Table 1. For a reference, the *in vitro* profile of mexiletine (**II**) was acquired to confirm that mexiletine (**II**) is a non-selective weak Na_V inhibitor.

The replacement of the piperazine ring with piperidine improved human $Na_V1.7$ inhibitory potency, while this modification also led to the enhancement of $Na_V1.1$ and $Na_V1.5$ activities (**2a**). Piperidine **2a** also enhanced mouse $Na_V1.7$ activity by 2.4-fold. In the modification of the benzoxazinone moiety, replacement of the oxygen atom with carbon was tolerated (**2b**), while the reduction of the ring size was not (**2d**). As carbon analogue **2b** retained $Na_V1.7$ activity, its piperidine analogue **2c** exhibited potent human $Na_V1.7$ activity, as expected. Although **2c** exhibited improved $Na_V1.5$ selectivity, it suffered from poor mouse $Na_V1.7$ activity. Since piperidine derivatives exhibited better human $Na_V1.7$ potency than piperazines, several piperidine analogues were synthesized. Compound **2e**, which is a 4-substituted analogue of **2a**, exhibited potent human $Na_V1.7$ activity (IC_{50} = 1.1 μM). This modification resulted in less $Na_V1.1$ selectivity with $Na_V1.5$ selectivity comparable to that of HTS hit **1**. Interestingly, five-membered analogue **2f** maintained a similar *in vitro* profile to **2e**, even though diminished Na_V activities were observed for **2d**. Although indolinone **2g** is a poor $Na_V1.7$ inhibitor, high *in vitro* activities against human and mouse $Na_V1.7$ were observed for regioisomer **2h**. In addition, isoindolinone **2h** exhibited expanded subtype selectivity against $Na_V1.5$ (16-fold). Decyclization of the isoindolinone ring gave benzamide **2i**, which retained $Na_V1.7$ activities with the reduction of $Na_V1.5$ selectivity. Although anilide **2j** was discovered as a potent $Na_V1.7$ inhibitor, further reduction of $Na_V1.5$ selectivity was observed.

Table 1. *In vitro* profile of $Na_V1.7$ inhibitors **2a–2j**

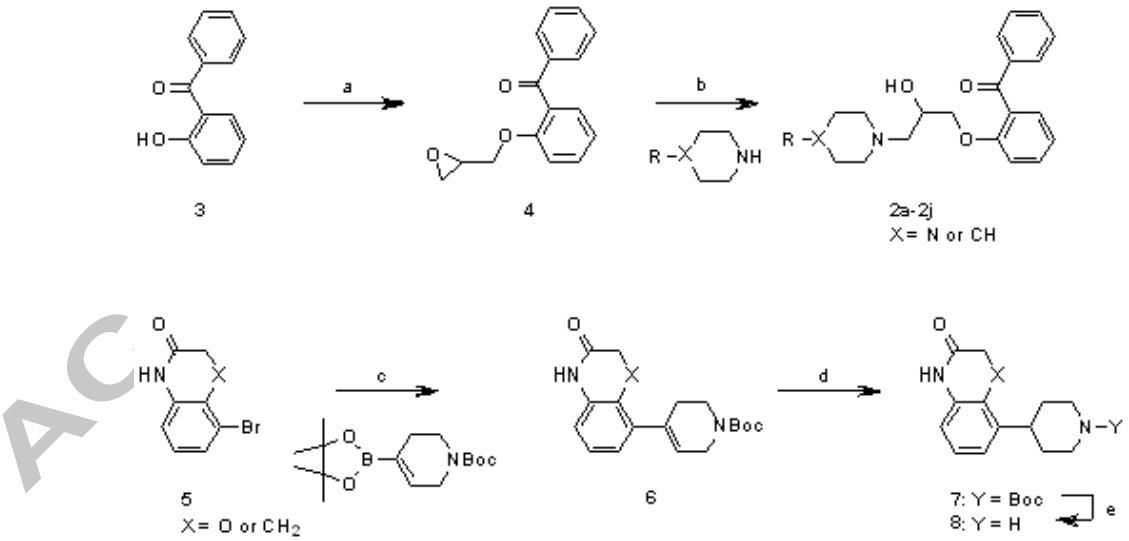


Cmpd	R	X	Human $Na_V1.1$ IC_{50}[a] (μM)	Human $Na_V1.5$ IC_{50}[a] (μM)	Human $Na_V1.7$ IC_{50}[a] (μM)	Mouse $Na_V1.7$ IC_{50}[a] (μM)
II			11	7.8	14	11
1		N	>33	20	3.9	5.0
2a		CH	4.4	7.0	0.78	2.1
2b		N	21	17	3.7	2.4
2c		CH	7.1	18	1.3	16
2d		N	>33	>33	24	31
2e		CH	4.8	5.2	1.1	1.3
2f		CH	5.4	3.4	1.8	3.1
2g		CH	26	33	9.4	5.0
2h		CH	3.3	24	1.5	1.2
2i		CH	3.2	4.9	1.1	0.92
2j		CH	4.3	1.9	1.2	1.0

[a]Values in an inactivated state. Na_V currents were evoked by a depolarizing pulse following a two-second conditioning prepulse to approximately half-inactivating potential. The inhibitory effects were calculated from the difference in Na_V current amplitudes before and after adding the test compound and corrected for the vehicle control response. IC_{50} values were determined by fitting to a sigmoidal dose-response equation.[7]

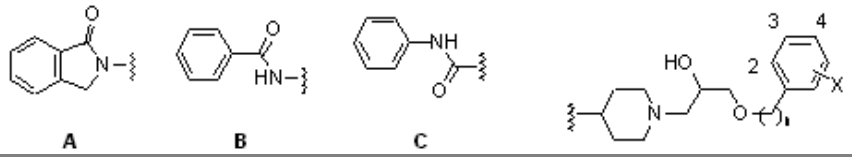
Compounds **2a–2j** listed in Table 1 were synthesized by a nucleophilic epoxide opening reaction as a key step, as shown in Scheme 1. Commercially available benzophenone **3** was reacted with epichlorohydrin to afford epoxide **4**, followed by the treatment with piperazine or piperidine derivatives under basic conditions to furnish compounds **2a–2j**. Piperidine intermediates **8** for the synthesis of **2a** and **2c** were prepared from bromide **5** in the usual manner, utilizing Suzuki coupling as a key step.[8,9]

Owing to potent *in vitro* activities against human and mouse $Na_V1.7$ as well as high $Na_V1.5$ selectivity, isoindolinone **2h** was selected as the scaffold for further modifications, and the modifications of the benzophenone moiety are summarized in Table 2. When the 2-benzoyl group was replaced with a 3-benzoyl group, compound **9a** exhibited human $Na_V1.7$ activity enhanced by 1.7-fold, while this modification also enhanced $Na_V1.1$ and $Na_V1.5$ activities. Further enhancement of human $Na_V1.7$ activity was observed for 4-benzoyl derivative **9b**, which exhibited the best human $Na_V1.7$ potency in this series (IC_{50} = 0.38 μM). However, 4-substitution caused the reduction of subtype selectivity. Since unsubstituted phenyl derivative **9c** possessed fair human $Na_V1.7$ activity, the introduction of several functional groups was explored. When a 3- or 4-methoxy group was introduced, the enhancement of $Na_V1.7$ activities was observed (**9e** and **9f**). In contrast, human $Na_V1.7$ activity was decreased for 2-methoxy derivative **9d**. In terms of the selectivity, 3- and 4-methoxy derivatives (**9e** and **9f**) lost $Na_V1.1$ selectivity, while better $Na_V1.1$ selectivity was confirmed for 2-methoxy derivative **9d**. 2-Methoxy derivative **9d** also exhibited high subtype selectivity against $Na_V1.5$ (15-fold), while 3- and 4-methoxy derivatives (**9e** and **9f**) showed diminished $Na_V1.5$ selectivity. Trifluoromethyl substitution enhanced human $Na_V1.7$ activity, and excellent activity was achieved for 4-trifluoromethyl derivative **9i** (IC_{50} = 0.50 μM). However, trifluoromethyl substitution resulted in the enhancement of other Na_V activities (**9g–9i**). As described above, 4-substitution increased three human Na_V activities, while 2-substition increased the subtype selectivity over $Na_V1.5$ when a benzoyl or methoxy group was employed. These results encouraged us to synthesize 2-methoxy-4-trifluoromethyl derivatives. As expected, compound **9j** exhibited high human $Na_V1.7$ activity with good $Na_V1.5$ selectivity. Compared with 4-trifluoromethyl derivative **9i**, 2-methoxy-4-trifluoromethyl derivatives **9j** improved $Na_V1.5$ selectivity from 5.6-fold to 12-fold with potent human and mouse $Na_V1.7$ activities. Since 4-trifluoromethyl benzyl derivative **9k** retained $Na_V1.7$ activities, 2-methoxy-4-trifluoromethyl substitution led to compound **9l** with an *in vitro* profile similar to that of **9j**. By the introduction of a 2-methoxy group, compound **9l** showed better $Na_V1.5$ selectivity than **9k**. Decyclization of the isoindolinone ring was then explored. By the introduction of a 4-trifluoromethyl group, all Na_V activities were increased for benzamide **9m** and anilide **9n**, compared with those of unsubstituted derivatives **2i** and **2j** (Table 1). As expected, introducing a 2-methoxy group in **9n** resulted in the enhancement of $Na_V1.5$ selectivity, and anilide **9o** exhibited potent $Na_V1.7$ activities with fair $Na_V1.5$ selectivity.



Scheme 1. Reagents and conditions: (a) epichlorohydrin, NaOH, reflux, 87%; (b) DIPEA, MeOH; (c) $Pd(dppf)Cl_2$, K_2CO_3, DMF, microwave, 110 °C; (d) H_2, Pd/C, EtOH; (e) TFA, CH_2Cl_2.

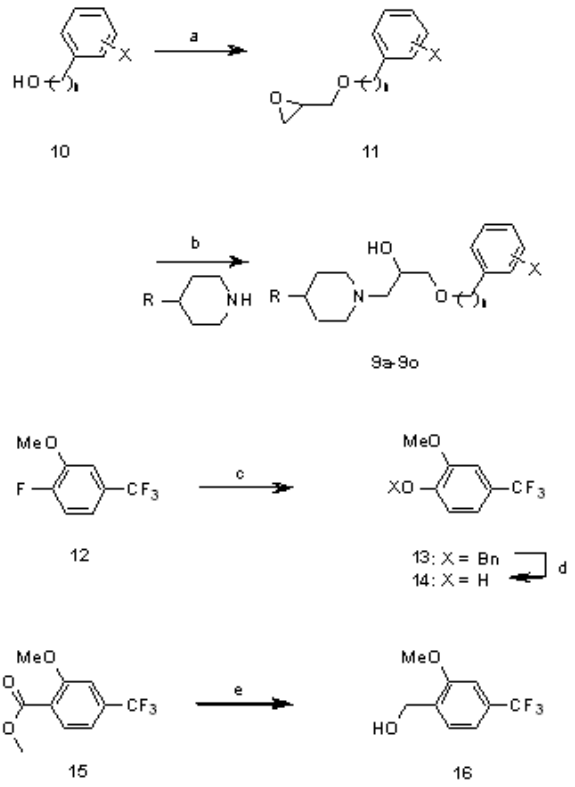
Table 2. *In vitro* profile of $Na_V1.7$ inhibitors **9a–9o**



Cmpd	A, B or C	n	X	Human $Na_V1.1$ IC_{50}[a] (μM)	Human $Na_V1.5$ IC_{50}[a] (μM)	Human $Na_V1.7$ IC_{50}[a] (μM)	Mouse $Na_V1.7$ IC_{50}[a] (μM)
2h	A	0	2-COPh	3.3	24	1.5	1.2
9a	A	0	3-COPh	0.92	3.7	0.90	0.96
9b	A	0	4-COPh	0.67	1.2	0.38	0.59
9c	A	0	H	8.0	38	3.4	5.0
9d	A	0	2-OMe	19	77	5.3	4.8
9e	A	0	3-OMe	3.0	10	1.4	0.91
9f	A	0	4-OMe	2.7	13	1.8	1.3
9g	A	0	2-CF_3	4.5	7.1	2.8	4.8
9h	A	0	3-CF_3	1.2	4.4	1.0	0.79
9i	A	0	4-CF_3	1.8	2.8	0.50	0.10
9j	A	0	2-OMe, 4-CF_3	0.91	5.6	0.48	0.33
9k	A	1	4-CF_3	3.0	3.0	1.1	1.5
9l[b]	A	1	2-OMe, 4-CF_3	1.5	6.1	1.2	0.79
9m	B	0	4-CF_3	0.80	1.1	0.70	0.40
9n	C	0	4-CF_3	3.1	3.4	1.0	0.80
9o	C	1	2-OMe, 4-CF_3	3.3	16	1.7	1.3

[a]Values in an inactivated state. The same assay condition as described in Table 1. [b]Fumaric acid salt.

A synthetic route analogous to that for compounds **2** was utilized for the preparation of compounds **9a–9o** (Scheme 2). Phenols or benzyl alcohols **10** were converted to corresponding epoxides **11**, followed by a reaction with piperidines that provided compounds **9a–9o**.[10] Phenol **14** was prepared from fluoride **12** with S_NAr reaction followed by deprotection, while benzyl alcohol **16** was prepared from ester **15**.



Scheme 2. Reagents and conditions: (a) epichlorohydrin, NaOH, reflux or epichlorohydrin, 4 mol% Bu_4NHSO_4, aq. NaOH; (b) DIPEA, MeOH; (c) BnOH, NaH, DMF, 69%; (d) H_2, Pd/C, EtOH, 98%; (e) DIBAL, toluene, 99%.

Several potent and selective compounds were selected for further evaluations. The pharmacokinetics (PK) profile of the compounds was acquired by oral administration to mice at a dose of 30 mg/kg (Table 3). When 2-benzophenone **2h** was administered to mice, it showed poor PK profile. Improved plasma exposure was observed for 3-benzophenone **9a** and anilide **9o**, and they exhibited 29- and 17-fold increases in AUC value, respectively. Further improvement of PK parameters was confirmed for 2-methoxy derivative **9d** and 2-methoxy-4-trifluoromethyl derivative **9l**. In particular, **9l** showed the best plasma exposure in this series of compounds. Consequently, compounds **9d** and **9l** were selected for evaluations of their *in vivo* efficacy. The *in vivo* evaluation of **9o** was also performed because this compound possessed a large free fraction in mouse plasma (4.18%), even though it exhibited modest PK parameters similar to those of compound **9a**.

The preliminary *in vivo* evaluation was performed by measuring the ability to suppress writhing responses to the i.p. administration of AcOH in mice (Table 3).[11] Compound **9d** successfully demonstrated a reduction of writhing behavior in a dose-dependent manner, with a 50% effective dose (ED_{50}) of 7.0 mg/kg. At the same time, the locomotor activity of **9d** was assessed with the oral administration of 30 mg/kg and 100 mg/kg **9d** to find the suppression of locomotor activity with a 50% inhibitory dose (ID_{50}) of 20 mg/kg. Therefore, **9d** showed the CNS safety margin by 2.9-fold on a dose basis, while compound **9d** was shown to possess mouse $Na_V1.1$ selectivity by 7.1-fold *in vitro*. The mouse writhing efficacy of compound **9l** was determined, and the EC_{50} value was calculated to be 10 mg/kg. The locomotor activity of **9l** could not be determined because the administration of 100 mg/kg **9l** was lethal. Although the plasma exposure of **9o** needs to be improved, **9o** affected writhing efficacy with ED_{50} = 19 mg/kg. The evaluation of locomotor activity provided an expanded CNS safety margin with ID_{50} = 111 mg/kg, which means a 5.8-fold CNS safety margin on a dose basis. For reference, the writhing ED_{50} value and the locomotor ID_{50} value of mexiletine (**II**) were determined to confirm that mexiletine (**II**) showed writhing efficacy with ED_{50} = 21 mg/kg, with only a 2.1-fold CNS safety margin *in vivo*. Therefore, compound **9o** was successfully proven to possess analgesic efficacy comparable to that of mexiletine (**II**), but with a wider CNS safety margin.

Table 3. Mouse Na_V activities, PK parameters and *in vivo* efficacy of selected compounds

Cmpd	Mouse $Na_V1.1$ IC_{50}[a] (μM)	Mouse $Na_V1.7$ IC_{50}[a] (μM)	PB free[b] (%)	T_{max} (hr)	C_{max} (ng/mL)	AUC (hr•ng/mL)	Writhing ED_{50} (mg/kg)	Locomotor activity ID_{50} (mg/kg)
II	21	11	NT[c]	NT[c]	NT[c]	NT[c]	21	45
2h	3.1	1.2	NT[c]	0.50[d]	16[d]	18[d]	NT[c]	NT[c]
9a	0.69	0.96	1.99	0.50[d]	169[d]	525[d]	NT[c]	NT[c]
9d	34	4.8	NT[c]	0.50[e]	467[e]	692[e]	7.0	20
9l[f]	0.67	0.79	5.55	0.50[g]	445[g]	1906[g]	10	ND[h]
9o	2.4	1.3	4.18	0.50[g]	161[g]	303[g]	19	111

[a]Values in an inactivated state. [b]Unbound fractions (%) in mouse plasma. [c]Not tested. [d]Average of three CD mice dosed at 30 mg/kg p.o. in *N,N*-dimethylacetamide/Tween 80/saline: 10/10/80. [e]Average of three CD mice dosed at 30 mg/kg p.o. in 0.5% methylcellulose suspension. [f]Fumaric acid salt. [g]Average of three db/db mice dosed at 30 mg/kg p.o. in *N,N*-dimethylacetamide/Tween 80/saline: 10/10/80. [h]Not determined.

In summary, the discovery and optimization of novel $Na_V1.7$ inhibitors have been described. The replacement of a benzoxazinone moiety with an isoindolinone ring resulted in the improvement of $Na_V1.5$ selectivity, while the replacement of piperazine with piperidine led to the enhancement of three human Na_V activities. In the modification of the right-hand side of the phenyl ring, 4-substitution increased three human Na_V activities, while 2-methoxy substitution increased $Na_V1.5$ selectivity. These findings led to the identification of 2,4-substituted compound **9o** with potent human and mouse $Na_V1.7$ inhibitory activities, as well as fair $Na_V1.5$ selectivity. Compound **9o** reduced writhing behavior in a dose-dependent manner, with ED_{50} = 19 mg/kg, and exhibited an expanded CNS safety margin. This biological profile is superior to that of the currently used drug, mexiletine. The optical resolution of compound **9o**, followed by the evaluation of adverse cardiac effects is underway and will be reported in the near future.

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3.56 (2H, ddd, *J* = 5.0, 10.1, 17.5 Hz), 3.88 (3H, s), 3.93-4.00 (1H, m), 4.64 (2H, s), 7.05 (1H, s), 7.11 (1H, t, *J* = 7.4 Hz), 7.17 (1H, s), 7.23 (1H, d, *J* = 7.4 Hz), 7.32 (2H, t, *J* = 7.8 Hz), 7.49-7.54 (3H, m).; MS(ESI/APCI) *m/z*: 467[M+H]$^+$.

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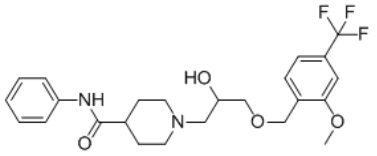

9o
HumanNa$_V$1.7: 1.7 μM
Mouse Na$_V$1.7: 1.3 μM
Writhing ED_{50}: 19 mg/kg
Locomotor activity ID_{50}: 111 mg/kg