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Substituted biaryl oxazoles, imidazoles, and thiazoles as sodium channel blockers

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ABSTRACT

Voltage-gated sodium channels have been shown to play a critical role in neuropathic pain. With a goal to develop potent peripherally active sodium channel blockers, a series of low molecular weight biaryl substituted imidazoles, oxazoles, and thiazole carboxamides were identified with good in vitro and in vivo potency.

Neuropathic pain is a complex pain state, that is, usually caused by injury to the peripheral or central nervous system. It causes persistent debilitating pain long after the acute injury or disease. Such pain states are associated with hyper-excitability and spontaneous action potential firing in peripheral sensory neurons. Neuropathic pain is associated with shingles, peripheral nerve injury (phantom limb), diabetic neuropathy chemotherapy, post-herpetic neuralgia, and chronic back pain.[1]

Many sodium channels subtypes exist in the nervous system. Subtype $Na_v1.7$ and $Na_v1.8$ are over expressed at the sites of nerve injuries. $Na_v1.7$ is primarily expressed in the peripheral nervous system.[2] Recent human genetic evidence implicates the crucial role of $Na_v1.7$ in noccieptive signaling. Indeed, a loss of function mutation in $Na_v1.7$ has been associated with congenital insensitivity to painful stimuli.[3]

Several of the marketed drugs used in the treatment of neuropathic pain are weak sodium channel antagonists. The efficacy of these drugs is limited by poor tolerability. We believe that a state dependent sodium channel blocker may provide functional selectivity with minimal CNS and cardiac effects.

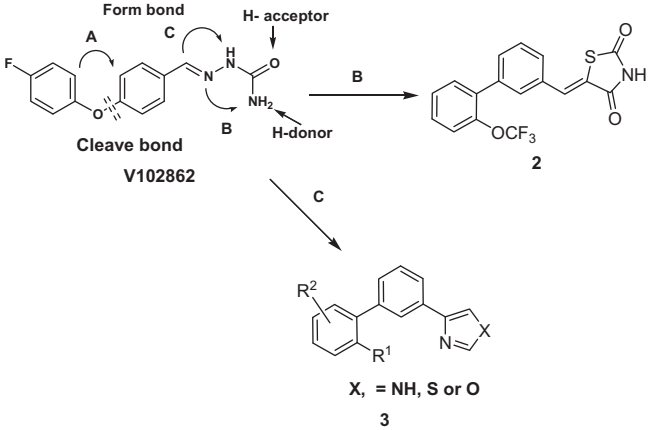

Figure 1. Design concept.

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Our goal is to develop potent, state dependent $hNa_v1.7$ blockers for neuropathic pain. Recently, scientists at Cocensys/Purdue Pharma reported the discovery of the semicarbazone sodium channel blocker **V102862** ($hNa_v1.7$, $K_i = 0.36\ \mu M$), and this compound was considered as a template to design non-semicarbazone based sodium channel blockers.[4]

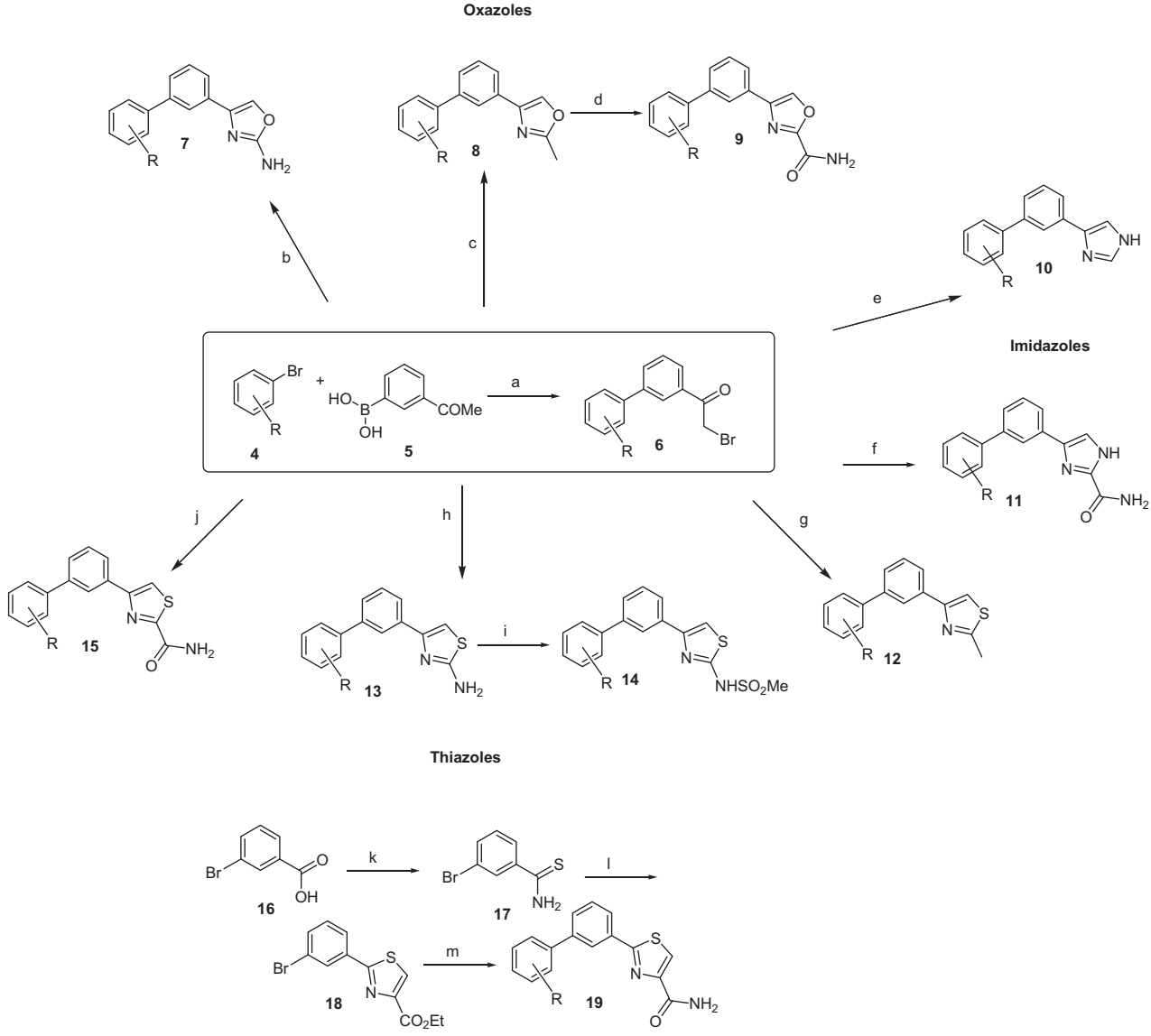
As shown in Figure 1, the phenoxy group of the semicarbazone of **V102862** can be replaced by a biphenyl group and a rigid ring closed analog could be derived via pathways B and C. Pathway B gives a novel series of biphenyl thiazolidin-2,4-diones with potent $hNa_v1.7$ activity ($hNa_v1.7$, $K_i = 0.02\ \mu M$) and has been described separately.[5] Pathway C could give rise to a series of five-membered heterocycles **3** as a potential replacement for the semicarbazone of **V102862**. This modification has led us to the discovery of a series of a new biphenyl heterocycles.

Our exploration focused on three different five-membered heterocyclic replacements of the semicarbazone moiety in **V1028662**: the oxazoles, imidazoles, and thiazoles. These are three different heterocycles with different basic properties.

The compounds were synthesized and evaluated for their ability to block voltage-gated $hNa_v1.7$ via an in vitro functional membrane potential FRET based assay, details of which have recently been described in a separate Letter.[6] Selected compounds were also screened for activity against ancillary targets including hERG (MK-0499 binding), CYP inhibitions and Cav 1.2 (diltiazem (DLZ) binding).[7] Those compounds that were found to be selective in these ancillary assay were then examined in the rat spinal nerve ligation (Chung) model of neuropathic pain and their pharmacokinetic profiles were evaluated.[8]

The syntheses of the biphenyl heterocyclic compounds are outlined in Scheme 1. These analogs were constructed from the biphenyl bromoketone **6**, a common key intermediate. The intermediate **6** was prepared via a palladium catalyzed Suzuki cross-coupling reaction of the aryl bromide **4** with the commercially available 3-acetophenone boronic acids **5** followed by acid-catalyzed bromination.[9]

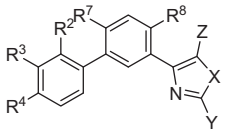
With the bromoketone derivative **6** in hand, the biphenyl heterocycles were synthesized using condensation chemistry.



Scheme 1. Reagents and conditions: (a) (i) Ph_3P, $Pd(OAc)_2$, *n*-propanol, H_2O, 2 M Na_2CO_3, reflux; (ii) Br_2, HBr (cat), MeOH; (b) urea, *t*-BuOH; (c) (i) AcOH, K_2CO_3, EtOH, H_2O; (ii) BF_3-Et_2O, $MeCONH_2$, xylene; (d) (i) SeO_2, pyridine; (ii) CDI, NH_4OAc, THF; (e) $HCONH_2$, 210 °C; (f) (i) methyl glyoxalate, NH_4OAc, MeCN; (ii) ammonia, EtOH; (g) $MeCSNH_2$, toluene, reflux; (h) H_2NCSNH_2, toluene, reflux; (i) $MeSO_2Cl$, pyridine, THF; (j) (i) ethyl thioxamate, EtOH; (ii). ammonia, EtOH; (k) (i) CDI, NH_4OAc; (ii) Lawesson's reagent, THF; (l) ethyl bromopyruvate, dioxane; (m) (i) $ArB(OH)_2$, Ph_3P, $Pd(OAc)_2$, *n*-propanol, H_2O, 2 M Na_2CO_3, reflux; (ii) ammonia, MeOH.

Cyclization of the bromo ketone **6** with urea afforded the 2-amino oxazoles **7**. Biphenyl oxazole **9** was prepared from the 2-methyl oxazole analog **8**, which was, in turn derived from the corresponding acetate. Cyclization of the bromo ketone **6** with formamide gave the biphenyl imidazole, **10**. The 2-carboxamide imidazole **11** was derived from condensation with methyl glyoxalate. The thiazoles were prepared according to the method described by Wright and coworkers.[10] The biphenyl thiazoles **12** were derived from the cyclization of bromo ketone **6** with ethanethioamide. Similarly, thiourea cyclization afforded the 2-thiazolamine **13** which was then functionalized to the sulfonamide **14**. Cyclization of **6** with ethyl thioxamate afforded the ester which was converted to the 2-thiazolecarboxamides **15**. A different synthetic route was utilized to synthesize 4-thiazolecarboxamides **19**. Commercially available 3-bromo acetic acid **16** was converted to the thioamide **17** which was cyclized to 4-thiazole ethyl ester **18**. The carboxamide **19** was prepared from the corresponding ester **18**.

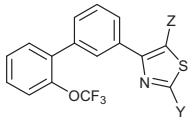
Table 1
SAR of the oxazoles and imidazoles



Entry	R^2	R^7	R^8	Z	X	Y	$Na_v1.7$ VIPR[a]
20	CF_3	H	H	H	O	H	5.31
21	OCF_3	H	H	H	O	H	1.94
22	OCF_3	H	H	H	O	Me	2.14
23	OCF_3	H	H	H	O	NH_2	37%[b]
24	OCF_3	H	H	H	O	$CONH_2$	2.36
25	CF_3	H	H	H	NH	H	2.1
26	OCF_3	H	H	H	NH	H	14%[b]
27	CF_3	H	H	H	NH	$CONH_2$	55%[b]
28	CF_3	H	H	Cl	NH	$CONH_2$	2.77
29	CF_3	H	H	H	NMe	$CONH_2$	1.25
30	OCF_3	H	F	H	NMe	$CONH_2$	15%[b]
31	OCF_3	F	H	H	NMe	$CONH_2$	0.49

[a] IC_{50}, μM.
[b] % inh @ 1 μM.

Table 2
SAR around the thiazole ring



Entry	Z	Y	$Na_v1.7$ VIPR (IC_{50}, μM or % inh @ 1 μM)
32	H	H	2.16
33	H	Me	2.99
34	H	NH_2	84%
35	H	NH_2SO_2Me	65%
36	H	NHCOMe	5%
37	H	$NHCONMe_2$	6.6%
38	H	$CONH_2$	0.23
39	H	$CONMe_2$	1.37
40	Me	$CONH_2$	0.43
41	H	CH_2CONH_2	0.62
42	H	CH_2OH	1.80
43	Me	CO_2Et	8%
44	H	CH_2CN	8%
45	H	2,3-Pyrazine	1.26
46	H	2-Pyridyl	−21%
47	H	Oxazole	27%
48	H	Imidazole	0.95
49	H	Pyrimidine	6.3%

Initial SAR efforts were directed towards the biphenyl oxazoles. Earlier work in the area of biphenyl thiazolidine-2,4-diones had shown that *meta* arrangement of the biphenyl (1,3) is preferred to the *para* biphenyl (1,4).[5,11] In case of the biphenyl heterocycles, the same relationship was maintained.

As shown in Table 1, biphenyl oxazoles were found to be modest sodium channel blockers. Liphophilic substituents such as the trifluoromethyl or the trifluoromethoxy were found to be optimal at the R^2 position of the biphenyl group. The trifluoromethoxy derivative **21** had improved $hNa_v1.7$ functional block compared to the trifluoromethyl analog **20**. Introduction of a methyl substituent **22** maintained the same level of $hNa_v1.7$ functional block while a basic amino group **23** had diminished $hNa_v1.7$ block. Introduction of a carboxamide group **24** at the C-2 position of the oxazole improved the $hNa_v1.7$ functional block. In the imidazoles series, the trifluoromethyl analog **25** was more potent on $hNa_v1.7$ than the trifluoromethoxy analog **26**. Imidazole analogs **25** and **27** blocked $hNa_v1.7$ in a state dependent manner with a K_i of 15 nM and 270 nM, respectively. Substitution of the central ring with a fluoro group in the R^8 position **30** diminished potency, but potency was significantly improved by fluoro substitution in R^7 as in **31**.

The thiazole series displayed improved $hNa_v1.7$ block when compared to the corresponding oxazoles and imidazoles. As shown in Table 2, the unsubstituted thiazole, **32** displayed good $hNa_v1.7$ functional block.

Introduction of a methyl group **33** retained the same level of activity, but introduction of a basic amine group at C-2 position **34** again led to a diminished $hNa_v1.7$ activity. The methylsulfonamide **35** and the urea **37** analogs were not tolerated. The thiazole analog **38** with a carboxamide at C-2 displayed excellent $hNa_v1.7$ functional block. A secondary carboxamide **39** or an acetamide **41** at the same position resulted in a diminished $hNa_v1.7$ activity. Analogs with a hydroxymethyl **42** or the nitrile **44** exhibited reduced $hNa_v1.7$ functional block. Introduction of a heterocycle at C-2 position of the thiazole, **45**–**49**, diminished $hNa_v1.7$ activity.

As shown in Table 2, a primary carboxamide at the 2-position of the thiazole imparts good $hNa_v1.7$ functional block in this series. The SAR around the phenyl ring with a thiazole carboxamide at C-2 position was explored. Consistent with earlier results in the other heterocyclic series, the *meta* biphenyl thiazole (1,3) **38** displayed significantly better $hNa_v1.7$ functional block than the *para* biphenyl thiazole (1,4) **50** (Table 3). Liphophilic substitutents such as the trifluoromethyl or the trifluoromethoxy were found to be optimal at the R^2 position of the biphenyl group. Compound **38** is one of the most potent thiazoles investigated.

A representative group of compounds were evaluated for $hNa_v1.7$ block using electrophysiology and their binding inhibition to the Ikr channel and CYP enzymes were evaluated (Table 4). The unsubstituted imidazole **25** though fairly potent on $hNa_v1.7$, exhibited strong CYP inhibition of all the three isoforms tested. Reducing

Table 3
Meta versus para thiazole carboxamides

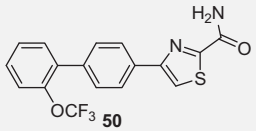
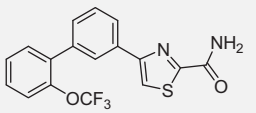
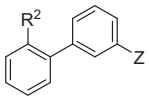
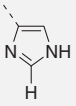
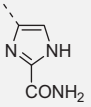
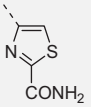
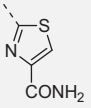
	$Na_v1.7$ VIPR IC_{50} (μM) or % inh at 10 μM
 **50**	6.1%
 **38**	0.228

Table 4
Pharmacokinetic data for selected compounds



Entry	R^2	Z	$Na_V1.7$ VIPR[a]	$Na_v1.7$ EP[a]	MK-0499[a]	CYP 3A4[b]	CYP 2C9[b]	CYP 2D6[b]	Rat dose[c]	*F*%	AUC_N[d]	Clp[e]	$t_{1/2}$ (h)
25	CF_3		2.1	0.15	75%	<0.05	<0.05	<0.05	1.0/2.0	71	1.81	32	0.63
27	CF_3		55%	0.27	25%	>40	>40	>40	1.0/3.0	46	2.23	23	0.5
38	OCF_3		0.23	0.015	0.5%	18	16	48	1.0/2.0	20	0.36	52	1.33
51	OCF_3		0.26	0.05	55%	>50	8.79	>50	1.0/3.0	22	0.27	112	0.74

[a] IC_{50} (μM) or % inh at 1 μM.
[b] IC_{50}, μM.
[c] mg/kg.
[d] mMh/mpk.
[e] mL/min/kg.

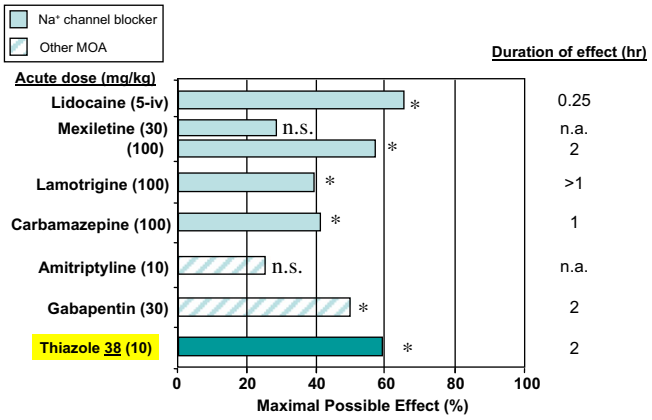


Figure 2. Comparison of thiazole **38** with standards: SNL model of neuropathic pain.

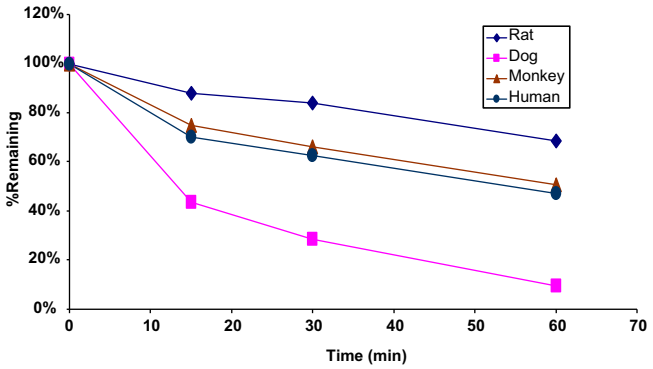


Figure 3. Compound **38** in microsomal incubation.

the basicity of the imidazole with the introduction of a carboxamide group **27** improved the selectivity against CYPs and IKr channel significantly but also had vastly diminished $Na_v1.7$ potency. The thiazole **38** exhibited selectivity against various isoforms of CYPs and the IKr channel. Thiazole **51** was more selective towards IKr channel. The pharmacokinetic properties of the compounds in Table 4 were also evaluated in rats. Imidazole **27** exhibited better clearance and exposure compared to imidazole **25** but was considerably less potent on $hNa_v1.7$. In comparison to compound **51**, thiazole **38** displayed significantly lower clearance and improved half life.

In the rat spinal nerve ligation (Chung) model of neuropathic pain (SNL), thiazole **38** exhibited excellent efficacy.[8] When dosed orally in rats at 10 mg/kg, **38** reversed mechanical allodynia by 61% (p <0.05) (at 2 h post-dose) significantly more than mexiletine, lamotrigine or carbamazepine at 100 mg/kg (Fig. 2).[12] In comparison, thiazole **38** had significantly better reversal of allodynia than most commercial sodium channel blockers.

Pharmacokinetic metabolite analysis of compound **38** revealed significant in vivo hydrolysis of the amide to the corresponding acid. When subjected to rat, dog, and human liver S9 microsomal incubation for 60 min, thiazole **38** had 68%, 10%, and 47% of the parent remaining (Fig. 3). Biphenyl thiazole **38** is extensively metabolized in dog hepatocytes (2 h, 10 μM substrate), with very small amount (<5%) of the parent remaining.

In summary, a new class of biphenyl heterocyclic sodium channel blockers has been developed. Biphenyl oxazoles are modest sodium channel blockers. Biphenyl imidazoles exhibit improved in vitro and in vivo efficacy but have CYP related issues. In comparison, biphenyl thiazoles displayed increased $hNa_v1.7$ functional block. Biphenyl thiazole **38** is a potent state dependent sodium channel blocker with good in vivo efficacy in the Chung model. However, this thiazole analog undergoes extensive hydrolysis of the amide and is rapidly metabolized in dog hepatocytes.

Improvements to the pharmacokinetics and pharmacodynamics of this thiazole series will be focus of future work and will be reported in due course.

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12. Treatment with compound **38** (10 mg/kg) 14 days after surgery in the Chung pain model.