Bioorganic & Medicinal Chemistry Letters 22 (2012) 2052–2062

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

# Discovery and hit-to-lead optimization of pyrrolopyrimidines as potent, state-dependent $Na_v1.7$ antagonists

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ARTICLE INFO

*Article history:*
Received 16 November 2011
Revised 3 January 2012
Accepted 9 January 2012
Available online 18 January 2012

*Keywords:*
$Na_v1.7$
Voltage-gated sodium channels
$Na_v$ channels
Sodium channel blockers
Sodium channel inhibitors
Sodium channel antagonists
Congenital indifference to pain
Paroxysmal extreme pain disorder
Primary erythromelalgia
Pyrrolopyrimidine

ABSTRACT

Herein we describe the discovery, optimization, and structure–activity relationships of novel potent pyrrolopyrimidine $Na_v1.7$ antagonists. Hit-to-lead SAR studies of the pyrrolopyrimidine core, head, and tail groups of the molecule led to the identification of pyrrolopyrimidine **48** as exceptionally potent $Na_v1.7$ blocker with good selectivity over hERG and improved microsomal stability relative to our hit molecule and pyrazolopyrimidine **8** as a promising starting point for future optimization efforts.

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The treatment of chronic pain represents a major unmet medical need. Current pain treatments suffer from poor efficacy and dose limiting toxicity. Recent human genetic evidence implicates the voltage-gated sodium ion channel $Na_v1.7$ (encoded by the SCN9A gene) as a major regulator of human pain.[1] Gain of function mutations of $Na_v1.7$ cause primary erythromelalgia and paroxysmal extreme pain disorder, both characterized by spontaneous chronic pain.[2] In contrast, loss of function mutations in $Na_v1.7$ result in congenital indifference to pain, characterized by complete insensitivity to pain.[2] Existing sodium channel blockers used clinically are neither very potent, nor selective among the nine members of the sodium channel family. Accordingly, $Na_v1.7$ channel is an attractive target for the development of new and effective pain therapeutics.[3] Herein we describe the discovery and structure–activity relationships (SAR) around a potent state-dependent pyrrolopyrimidine scaffold that could contribute to the development of $Na_v1.7$ inhibitors.

It is presumed that sodium channels exist predominantly in three conformational states: resting, open and inactivated. The inactivated states of sodium channels are likely to exist in greater proportion in the hyperexcitable neurons driving chronic pain, therefore inhibition of inactivated channels should selectively target sites of aberrant signaling. Pyrrolopyrimidine **1**[3] (Fig. 1) was identified as a highly potent and state-dependent inhibitor of $hNa_v1.7$ from an electrophysiology-based screening campaign [$IC_{50}$ = 0.06 μM (20% inactivated) and 6.4 μM (non-inactivated) on $Na_v1.7$ channels]. In addition, hit molecule (**1**) possessed a novel structure relative to other published $Na_v$ inhibitors, had reasonable physiochemical properties [MW = 434, Log*D* (pH 7.4) = 4.35, LipE = 2.65] and a modular structure amenable for rapid SAR exploration at each portion of the molecule. Unfortunately, compound **1** suffered from poor intrinsic stability in liver microsomes (HLM/RLM intrinsic clearance (μL/min/mg): >399/>399) and though modestly selective versus hERG (20×) lacked selectivity over cardiac $hNa_v1.5$ channels. Thus, we initiated a medicinal chemistry effort towards generating a compound with improved metabolic stability and selectivity over hERG and $hNa_v1.5$[4] by modulating LipE (PX $IC_{50}$-*c*Log*P*).

Our initial efforts were focused on modifying or replacing the pyrrolopyrimidine core (Table 1) with an emphasis on blocking or removing potential metabolic soft spots and lowering Log*D* (pH 7.4) in an attempt to decrease intrinsic clearance and improve selectivity over hERG. Compounds in which the 2-methyl

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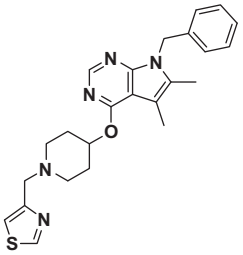
0960-894X/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2012.01.015



| | |
|---|---|
| $hNa_v1.7$ PX $IC_{50}$ (μM) | 0.15[a] |
| $hNa_v1.7$ Manual $IC_{50}$ (μM) | 0.06 [6.4][a] |
| Binding efficiency (kcal/NHA) | 0.3[b] |
| $hNa_v1.5$ PX $IC_{50}$ (μM) | 0.12[a] |
| hERG dofetilide binding Ki derived (μM) / PX $IC_{50}$ (μM) | 2.5 / 0.51 |
| HLM / RLM $CL_{int}$ (μL/min/mg) | >399 / >399 |
| Symyx solubility - SIF, PBS, 0.01 N HCl (μg/mL) | 177 / 65 / >200 |
| logD (pH = 7.4) / PSA / LipE | 4.35 / 56 / 2.65 |

[a]Electrophysiology $IC_{50}$ of partially inactivated channels is shown. Where applicable, bracket indicates $IC_{50}$ against fully noninactivated channels determined with manual electrophysiology. Inhibitory activity represents an average of at least two determinations. [b]Binding efficiency = RT[-log(hNav1.7 PX $IC_{50}$)]*(1x$10^{-6}$)/(number of heavy atoms). LipE = PX $IC_{50}$-cLogP.

**Figure 1.** Data for pyrrolopyrimidine hit (**1**).

substituent was removed (**2**), and 3-methyl replaced with halogen (**3**) or (**4**) demonstrated a slight increase in potency but no improvement in intrinsic clearance or hERG selectivity. Deletion of both methyl groups (**5**) resulted in retained potency ($Na_v1.7$ $IC_{50}$ = 0.26 μM), with decreased Log*D* (pH 7.4) (3.35 vs 4.35) and improved microsomal stability (130 μL/min/mg), and selectivity over hERG (>10×). Substitution of the 6-position of the pyrrolopyrimidine core, with a methyl (**6**) or trifluoromethyl (**7**) provided no improvements in potency or microsomal stability. Introduction of another nitrogen into the pyrrole ring [pyrazolopyrimidine (**8**) and imidazopyrimidine (**9**)] further decreased Log*D* and accordingly afforded improved microsomal stability (76 and 60 μL/min/mg, respectively), but at the expense of potency (0.83 and 7.2 μM, respectively). Partial saturation of the core and concomitant introduction of *gem*-dimethyl at the 3-position (**10**) or further oxidation of the 2-position (**11**) afforded no improvement in potency or microsomal stability. SAR studies led to the identification of (**5**), which had decreased Log*D*, retained potency and improved microsomal stability and selectivity over hERG (hERG PX $IC_{50}$ = 0.76 μM, LipE = 3.77, BE = 0.31) relative to **1**. Substitution or modification of the core did not yield any further improvement. Hence, this core was locked for SAR explorations on the remainder of the molecule.

Based on the Met ID studies of a similar analog (not reported here), we directed our efforts towards improving metabolic stability by replacing the piperidine ring (Table 2). Contracting the piperidine ring to pyrrolidine (**12**) or azetidine (**13**) or planarizing the ring to a phenyl (**14**) resulted in a drastic decrease in potency. Changing the linker on the 4-position of the piperidine from oxygen to *–NH–* (**15**) or *–NMe–* (**16**) provided improved microsomal stability, but these modifications were accompanied by a large drop in potency. Overall, attempts to replace the alkoxy piperidine ether resulted in a drastic decrease in potency and therefore the alkoxy piperidine ether was retained as the optimal linker for further SAR.

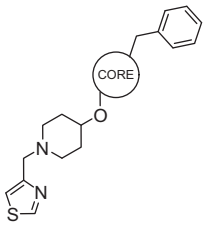
We then separately, but simultaneously, embarked on head group ($R^1$, Table 3) and tail group ($R^2$, Table 4) SAR evaluations. We studied the effect of methylene spacer length between the pyrrole *–N–* and the head group ($R^1$) (Table 3). More drastic changes, for example, deleting the methylene (**17**), homologating (**18**), or saturating the phenyl ring [cyclohexyl analog (**19**)] resulted in large reductions in potency. Based on this evaluation, further analoging in this space focused on the effect of substitution on the benzyl head group. In general, compounds resulting from *ortho*-substitution provided improved potency regardless of the substituent. For example, *ortho*-fluoro analog (**20**) displayed exceptional potency of 20 nM on $hNa_v1.7$, with retained microsomal stability and high selectivity over hERG (76×). Introduction of an *ortho*-chloro substituent (**23**) provided a sixfold improvement in potency but reduced microsomal stability. Introduction of small and large hydrophobic groups [Me (**26**) and $CF_3$ (**29**)] offered improved potency (6× and 3×, respectively), but reduced microsomal stability. Compounds resulting from *meta*-substitution [F (**21**), Cl (**24**), Me (**27**), $CF_3$ (**30**)] showed improved potency relative to (**5**), but less than the *ortho*-substituted analogs, and afforded no advantage in terms of microsomal stability or hERG selectivity. All compounds prepared with *para*-substitution [F (**22**), Cl (**25**), Me (**28**) or $CF_3$ (**31**)] suffered 10× loss in potency. Substitution with polar groups such as pyridine or thiazole resulted in complete loss in potency (data not shown). Evaluation of disubstituted analogs (**32–35**) showed no major gains.

Concurrent with our head group SAR evaluation replacement or substitution of the tail group thiazole was investigated ($R^2$, Table 4) towards improving potency, metabolic stability and/or selectivity over hERG.

Complete removal of the tail group methylene thiazole (**36**) resulted in a substantial drop in potency, as did replacement with a phenyl group (**37**). Replacement with a benzyl group (**38**) resulted in fourfold drop in potency and loss in selectivity over hERG. Introduction of a carbonyl at the methylene junction resulted in amide (**39**) which suffered a complete loss of potency.

Replacement of thiazole with alternative five-membered heterocyclic rings that afforded lower Log*D* such as oxazole (**40**), imidazole (**41**), pyrazole (**42**), its isomer (**43**), 1-methyl pyrazole (**44**), and methyl imidazole (**45**) and thiazole isomer (**47**) resulted in decreased intrinsic clearance and in some cases generally led to

**Table 1**
SAR: core substitution and modification



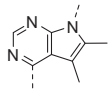
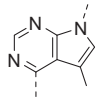
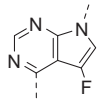
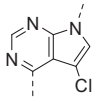
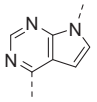
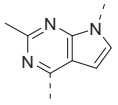
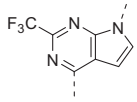
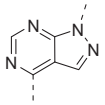
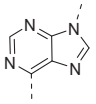
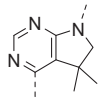
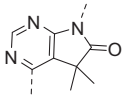
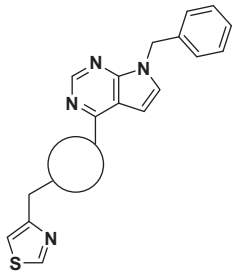
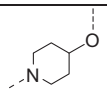
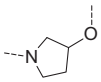
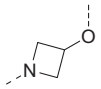
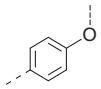
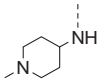
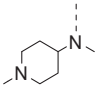

| Entry | CORE | $hNa_v1.7$ PX $IC_{50}$ (μM) | $hNa_v1.5$ PX $IC_{50}$ (μM) | HLM $CL_{int}$ (μL/min/mg) | hERG Ki derived (μM) or % inh (30 μM) | LogD (pH =7.4) |
|---|---|---|---|---|---|---|
| **1** |  | 0.15 | 0.12 | >399 | 2.5 | 4.35 |
| **2** |  | 0.05 | 0.05 | >399 | 1.4 | 3.89 |
| **3** |  | 0.06 | 0.03 | 236 | 2.5 | 3.49 |
| **4** |  | 0.04 | 0.08 | >399 | 1.5 | 4.03 |
| **5** |  | 0.26 | 0.20 | 130 | 41% (PX = 0.76 μM) | 3.77 |
| **6** |  | 0.31 | 0.35 | 332 | 36% | 4.15 |
| **7** |  | 2.29 | 1.57 | >399 | 0.99 | 5.10 |
| **8** |  | 0.83 | 0.93 | 76 | 51% | 2.18 |
| **9** |  | 7.2 | -- | 60 | -- | 2.28 |
| **10** |  | 0.14 | 0.25 | >399 | 23% | 3.94 |
| **11** |  | 0.10 | 0.13 | >399 | 28% | 2.39 |

**Table 2**
SAR: linker group modifications



| Entry | Linker | hNa$_v$1.7 PX IC$_{50}$ (μM) or hNa$_v$1.7 % inh (10 μM) | HLM CL$_{int}$ (μL/min/mg) |
|---|---|---|---|
| **5** |  | 0.26 | 130 |
| **12** |  | 6.6 | 125 |
| **13** |  | >30 | 52 |
| **14** |  | 3.6% | 61 |
| **15** |  | 3.51 | <14 |
| **16** |  | 7.0% | 77 |

a significant drop in potency. Introducing a methyl group on thiazole (**46**) resulted in decreased microsomal stability.

Replacement of the thiazole with a six membered heterocycle led to the discovery of 2-pyridyl analog (**48**), with similar potency and moderate intrinsic clearance with good selectivity over hERG (>100×). The 3-substituted pyridyl (**49**) and 4-substituted pyridyl (**50**) analogs were much less potent.

Once the 2-pyridyl group was identified as a good replacement of the thiazole moiety, further optimization of (**48**) was conducted. Initial efforts were geared towards gauging the influence of introducing small substituents around the pyridine ring. Accordingly, methyl substitution at the 2-, 3-, 4- or 5-positions (**51**–**54**) maintained potency, but with a significant increase in intrinsic clearance. The 2-fluoro substituted 2-pyridyl analog (**55**) displayed a 10-fold loss in potency and reduction in microsomal stability while 3-fluoro substituted analog (**56**) had similar potency and microsomal stability as compared to the lead (**48**) but suffered a reduction in hERG selectivity. The 5-fluoro substituted analog (**57**) showed about a fivefold loss in potency and significant loss in microsomal stability. Replacing the pyridine with other heterocycles such as pyrazine (**58**), to decrease Log*D*, resulted in a significant drop in potency and an increase in intrinsic clearance.

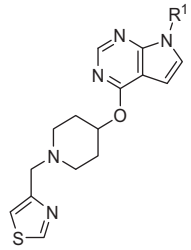
From the SAR that we have evaluated we can conclude that methylene-2-pyridyl moiety (**48**) was the optimal tail group in terms of Na$_v$ 1.7 inhibitory activity, binding efficiency (0.32), metabolic stability and selectivity over hERG.

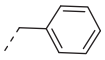
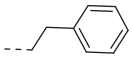
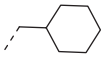
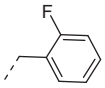
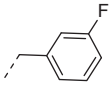
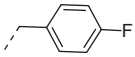
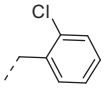
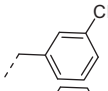
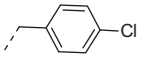
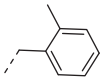
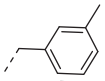
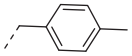
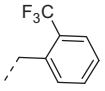
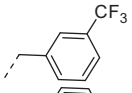
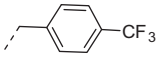
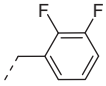
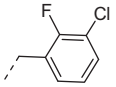
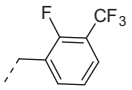
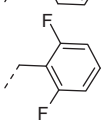
In an attempt to realize a cumulative effect, we combined our optimal head groups and tail group into our next series of analogs (Table 5). Accordingly, *ortho* fluoro analog (**59**) and *ortho*, *meta*-disubstituted derivatives (**60**–**62**) were prepared, demonstrating modestly improved potencies but comparable or decreased stability in HLM and reduced selectivity over hERG relative to lead **48**.

The syntheses of target molecules **2**, **5–8**, **18–35** was accomplished as outlined in Scheme 1. The general procedure involved alkylation of the pyrrole nitrogen of 4-chloro-pyrrolopyrimidine (**63**) with a suitably substituted $R^1CH_2X$ to obtain **64**.[5] Subsequent nucleophilic aromatic substitution ($S_NAr$) reaction[6] with alcohol **65**, which was obtained by reductive amination[7] of thiazole-4-carbaldehyde with piperidin-4-ol, afforded desired compounds **2**, **5–8**, **18–35**.

The synthesis of pyrrolopyrimidines **9**, **38**, **40**–**58** was accomplished in three steps starting from compound **66** (**a** or **b**). Substitution of the chloride was performed with *tert*-butyl 4-

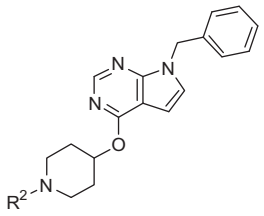
**Table 3**
SAR: head group substitution



| Entry No. | $R^1$ | $hNa_v1.7$ PX $IC_{50}$ (μM) | $hNa_v1.5$ PX $IC_{50}$ (μM) | HLM $CL_{int}$ (μL/min/mg) | hERG $K_i$ derived (μM) or % inh (30 μM) | Log*D* (pH 7.4) |
|---|---|---|---|---|---|---|
| **5** |  | 0.26 | 0.2 | 130 | 41% | 3.44 |
| **17** |  | >30 | – | 71 | – | 3.30 |
| **18** |  | 25.2 | – | >399 | – | 3.87 |
| **19** |  | 3.26 | – | 306 | – | 4.32 |
| **20** |  | 0.02 | 0.02 | 188 | 1.5 | 3.49 |
| **21** |  | 0.12 | – | 89 | 1.1 | 3.49 |
| **22** |  | 7.62 | – | 143 | – | 3.49 |
| **23** |  | 0.05 | 0.11 | 280 | 32% | 4.03 |
| **24** |  | 0.07 | 0.3 | 304 | 1.2 | 4.03 |
| **25** |  | 3.81 | – | 204 | – | 4.03 |
| **26** |  | 0.04 | 0.14 | 264 | 3.2 | 3.90 |
| **27** |  | 0.07 | 0.06 | 237 | 0.93 | 3.90 |
| **28** |  | 2.9 | 2.2 | 156 | 2.75 | 3.90 |
| **29** |  | 0.08 | 0.12 | 249 | 2.46 | 4.01 |
| **30** |  | 0.13 | 0.19 | 246 | 0.6 | 4.01 |
| **31** |  | 3.49 | – | 178 | – | 4.01 |
| **32** |  | 0.02 | 0.07 | 197 | 2.3 | 3.45 |
| **33** |  | 0.02 | 0.05 | 277 | 0.95 | 4.19 |
| **34** |  | 0.03 | 0.04 | 179 | 0.3 | 4.08 |
| **35** |  | 0.16 | 0.04 | 192 | 2.3 | 3.58 |

hydroxypiperidine-1-carboxylate using potassium *tert*-butoxide as a base to obtain **67** (**a** or **b**).[6] Subsequent *tert*-butyloxy-carbonyl (Boc) cleavage under standard conditions (TFA, DCM) provided amine **68** (**a** or **b**) as its TFA salt. In the final step, reductive amination with the appropriate aldehyde in the presence of sodium cyanoborohydride afforded desired compounds **9**, **38**, **40**–**58**. The coupling of **68a** with thiazole-4-carboxylic acid in presence of HATU provided compound **39** and reaction of **68a** with bromobenzene in presence of a base (potassium *tert*-butoxide) provided compound **37**.

**Table 4**
SAR: tail group modification



| Entry No | $R^2$ | $hNa_v1.7$ PX $IC_{50}$ (μM) or $hNa_v1.7$ % inh (10 μM) | $hNa_v1.5$ PX $IC_{50}$ (μM) | HLM $CL_{int}$ (μL/min/mg) | hERG Ki derived (μM) or % inh (30 μM) | LogD (pH =7.4) |
|---|---|---|---|---|---|---|
| **5** |  | 0.26 | 0.2 | 130 | 41% | 3.44 |
| **36** | H | 8.4% | -- | <14 | -- | 1.24 |
| **37** |  | 1.5% | -- | 102 | -- | 5.31 |
| **38** |  | 1.1 | 0.74 | 177 | 1.2 | 4.96 |
| **39** |  | 2.6% | -- | 61 | -- | 3.07 |
| **40** |  | 4.7 | -- | 57 | -- | 3.10 |
| **41** |  | 2.7 | 2.7 | 23 | 36% | 2.35 |
| **42** |  | 1.4 | 0.58 | 61 | 45% | 3.02 |
| **43** |  | 14 | -- | 33 | -- | 3.16 |
| **44** |  | 1.7 | 0.44 | 65 | 46% | 3.01 |
| **45** |  | 4.6 | -- | 184 | -- | 2.93 |

*(continued on next page)*

**Table 4.** *(continued)*

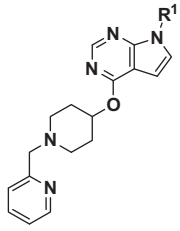
| Entry No | $R^2$ | $hNa_v1.7$ PX $IC_{50}$ (μM) or $hNa_v1.7$ % inh (10 μM) | $hNa_v1.5$ PX $IC_{50}$ (μM) | HLM $CL_{int}$ (μL/min/mg) | hERG Ki derived (μM) or % inh (30 μM) | LogD (pH =7.4) |
|---|---|---|---|---|---|---|
| **46** |  | 0.27 | 0.08 | 294 | 32% | 4.10 |
| **47** |  | 6.5 | -- | 62 | -- | 4.81 |
| **48** |  | 0.11 | 0.16 | 130 | 37% | 3.70 |
| **49** |  | 9.7 | -- | 121 | -- | 3.67 |
| **50** |  | 9.6 | -- | 152 | -- | 3.69 |
| **51** |  | 0.33 | 0.09 | >399 | 2.4 | 4.08 |
| **52** |  | 0.30 | 0.06 | 306 | 0.98 | 4.15 |
| **53** |  | 0.95 | 0.04 | >399 | 2.2 | 4.15 |
| **54** |  | 0.19 | 0.15 | 399 | 0.73 | 4.15 |
| **55** |  | 1.13 | 0.55 | 227 | 2.9 | 3.83 |
| **56** |  | 0.18 | 0.11 | 156 | 1.1 | 3.76 |
| **57** |  | 0.51 | 0.09 | 355 | 44% | 3.77 |
| **58** |  | 5.15 | -- | 115 | -- | 2.71 |

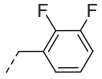
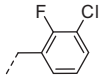
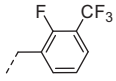
The synthesis of pyrrolopyrimidines **3** and **4** was accomplished in three steps (Scheme 2). Halogenation of 4-chloro-pyrrolopyrimidine (**63**) afforded 3-fluoro[8] or 3-chloro[9] analog **69** (**a** or **b**) in the presence of selectfluor or *N*-chloro-succinimide (NCS), respectively. Subsequent alkylation[5] of the pyrrole nitrogen and $S_NAr$ reaction[6] with the alkoxide of **65** provided compounds **3** and **4**. Compound **17** was prepared by coupling of pyrrole nitrogen **63** with phenyl boronic acid in presence of copper acetate followed by $S_NAr$ reaction[6] with **66a**.

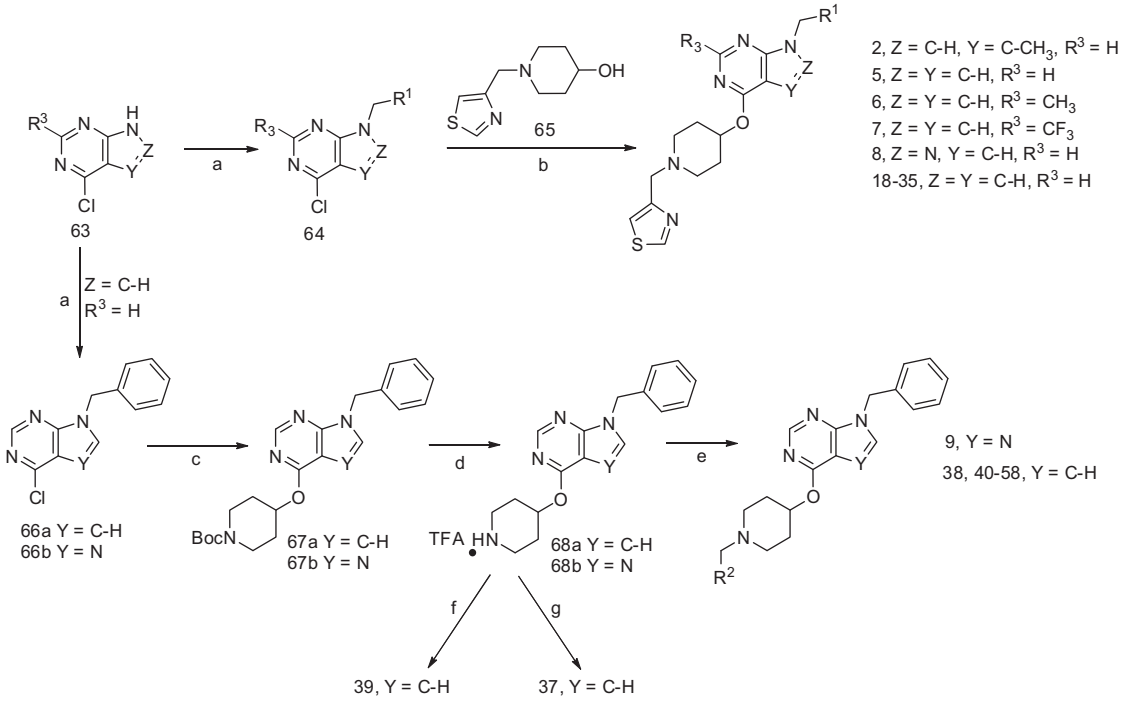
The synthesis of pyrrolopyrimidines **12** and **13** was accomplished in two steps as described in scheme 3. Reductive amination of thiazole-4-carbaldehyde with cyclic amino alcohol **71** (**a** or **b**) gave compound **72** (a or b), followed by $S_NAr$ reaction[6] with **66a** afforded desired compounds **12** and **13**.

The synthesis of target molecules **10** and **11** was accomplished as outlined in Scheme 4. Oxidation of **66a** in the presence of oxone gave compound **73** which was bis-alkylated using methyl iodide to provide **74**. Subsequent $S_NAr$ reaction[6] of **74** with *tert*-butyl 4-hydroxypiperidine-1-carboxylate under basic conditions followed by Boc cleavage and reductive amination with thiazole-4-carbaldehyde afforded compound **10**. The lactam moiety of **10** was reduced to alcohol **75** in the presence of lithium aluminum hydride. Com-

**Table 5**
SAR: optimal tail and head group combinations



| Entry No. | $R^1$ | $hNa_v1.7$ PX $IC_{50}$ (μM) | $hNa_v1.5$ PX $IC_{50}$ (μM) | HLM $CL_{int}$ (μL/min/mg) | hERG $K_i$ derived (μM) or % inh (30 μM) | Log*D* (pH 7.4) |
|---|---|---|---|---|---|---|
| **48** |  | 0.11 | 0.16 | 130 | 37% | 3.70 |
| **59** |  | 0.04 | 0.03 | 145 | 1.8 | 3.75 |
| **60** |  | 0.04 | 0.02 | 209 | 1.0 | 3.71 |
| **61** |  | 0.03 | 0.08 | 248 | 0.68 | 4.46 |
| **62** |  | 0.06 | 0.19 | 153 | 0.32 | 4.35 |

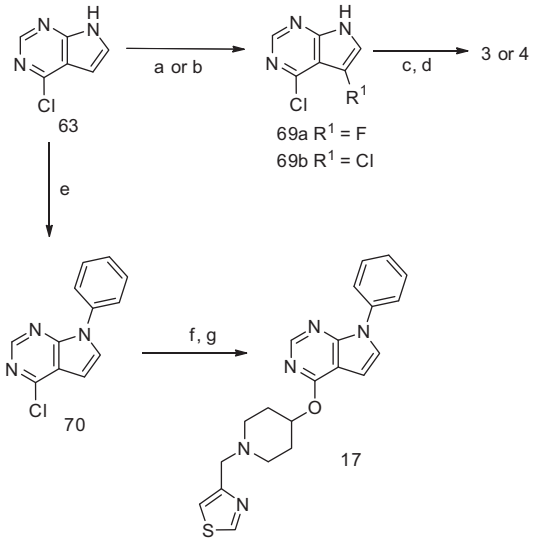



**Scheme 1.** Reagents and conditions: (a) $R^1CH_2X$, $K_2CO_3$, ACN, rt, 2–18 h (23–99%); (b) NaH, DMSO, 0 °C to rt, 16 h (10–41%); (c) *tert*-butyl 4-hydroxypiperidine-1-carboxylate, KO$^t$Bu, ACN, rt, 2 h (56%); (d) TFA, DCM, rt, 2 h (Y = C–H, N, 99%); (e) $R^2CHO$, $NaBH_3(CN)$ (35–60%); (f) thiazole-4-carboxylic acid, HATU, diea, DMF, rt, 20 h (48%); (g) bromobenzene, KO$^t$Bu, toluene, 135 °C, 4 days (7%).

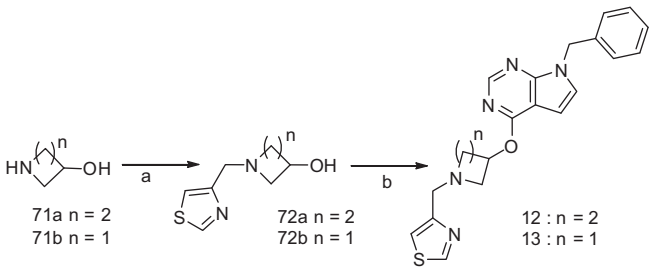
pound **11** was then obtained by reducing alcohol (**75**) in presence of TFA and triethyl silane.

Reductive amination of thiazole-4-carbaldehyde with piperidine **76** followed by Boc cleavage yielded compound **77**. Subsequent $S_NAr$[10] reaction with compound **66a** provided target compounds **15** and **16** (scheme 5).

The Grignard reagent generated from phenyl bromide **78** was added to thiazole-4-carbaldehyde to provide alcohol **79**. Reductive




**Scheme 2.** Reagents and conditions: (a) selectfluor, AcOH, ACN, 70 °C, 12 h (50%); (b) NCS, THF, rt, 1 h (79%); (c) benzyl bromide, NaH, DMF, 0 °C to rt, 16 h ($R^1$ = F, 50%, $R^1$ = Cl, 63%); (d) **65**, NaH, DMSO, 0 °C to rt, 16 h ($R^1$ = F, 18%, $R^1$ = Cl, 16%); (e) $Cu(OAc)_2$, pyridine, phenyl boronic acid, DCM, rt, 16 h (13%); (f) **65**, KO$^t$Bu, ACN, rt, 16 h (13%); (g) **65**, KO$^t$Bu, ACN, rt, 16 h (43%).



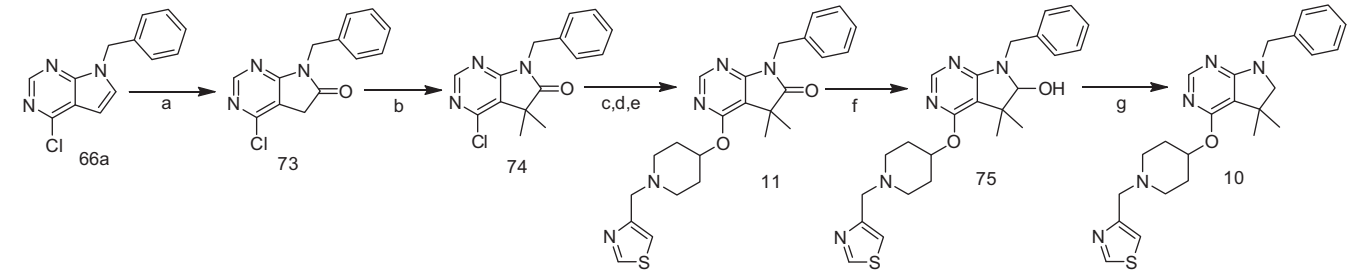

**Scheme 3.** Reagents and conditions: (a) thiazole-4-carbaldehyde, $NaBH_3(CN)$, 1,2 dichloroethane ($n$ = 1, 92%; $n$ = 2, 46%); (b) **66a**, NaH, DMSO, 0 °C to rt, 16 h ($n$ = 1, 2, 10%).

dehydroxylation in the presence of TFA and triethyl silane and subsequent demethylation using $BBr_3$ afforded compound (**80**). Finally $S_NAr$ reaction[11] with **66a** yielded **14** (scheme 6).

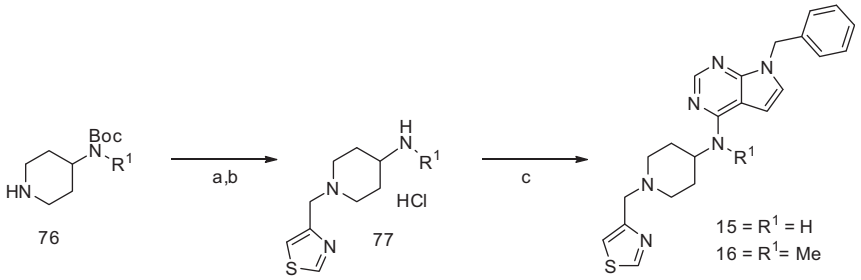
In conclusion, we have described the discovery, synthesis and hit-to-lead optimization of a novel class of potent pyrrolopyrimidines as $Na_v1.7$ antagonists. Removal of two methyl groups from the pyrrolopyrimidine core of hit molecule **1** resulted in lead molecule **5** with reduced Log*D*, improved microsomal stability and hERG selectivity. Exceptional $Na_v1.7$ potency was realized by replacing the benzyl head group of **5** with an *ortho* fluoro-benzyl (**20**) and *ortho*, *meta* difluoro-benzyl (**32**). Replacement of the thiazole tail group of **5** with an *ortho* pyridine (**48**) afforded a modest improvement in potency. Combining the optimized head and tail groups (**59**–**62**) yielded slightly improved potency, but reduced hERG selectivity and provided no improvements in microsomal stability. Inhibitory potency on $hNa_v1.5$ was routinely monitored for all potent compounds throughout this SAR exploration and generally tracked with $hNa_v1.7$ potency such that no gains in selectivity over $Na_v1.5$ were realized.

Analysis of the visualization of described analogs (Fig. 2) reveals that the lipophilic compounds [Log*D* (pH 7.4) >3.5] generally had good potency (<10 nM) but poor microsomal stability (HLM >150 (μL/min/mg)). Less lipophilic compounds [Log*D* (pH 7.4) <3.5] generally exhibited weak potency (>1 μM) and moderate to good microsomal stability (HLM <150 μL/min/mg). In light of these trends, the identification of highly potent compounds which were also highly stable in human liver microsomes was challenging. One promising lead was pyrazolopyrimidine **8**, which had moderate potency ($Na_v1.7$ $IC_{50}$ = 0.83 μM) and good microsomal stability (76 μL/min/mg).

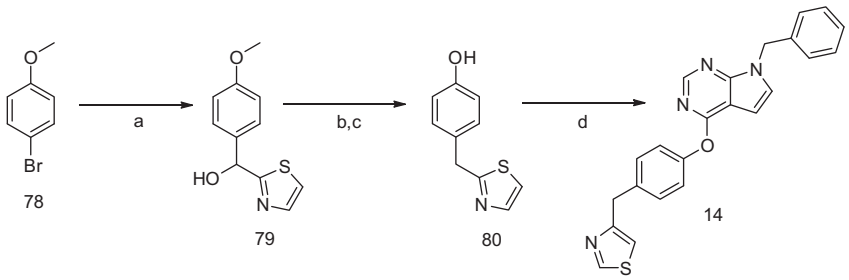
The visualization in Fig. 3 compares Log*D* (pH 7.4) with $Na_v1.7$ potency with compounds sized by microsomal stability and further breakdown by lipophilic efficiency (LipE). In addition to the previously described potency and microsomal stability properties, compound **8** possesses high lipophilic efficiency. As a moderately potent, lipophilically efficient and intrinsically stable lead with good selectivity over hERG, pyrazolopyrimidine **8** is a promising lead for further exploration.




**Scheme 4.** Reagents and conditions: (a) oxone, ACN/$H_2O$ (1:1), 50 °C, 3 h (56%); (b) NaH, DMSO, MeI, 0 °C to rt, 1 h (68%); (c) *tert*-butyl 4-hydroxypiperidine-1-carboxylate, KO$^t$Bu, ACN, rt, 2 h (34%); (d) TFA, DCM, rt, 2 h (64%) (e) thiazole-4-carbaldehyde, $NaBH_3(CN)$, 1,2 dichloroethane (39%); (f) LAH, THF, 0 °C to rt, 2 h (66%); (g) DCM, TFA, triethyl silane, 0 °C to rt, 2 h (31%).




**Scheme 5.** Reagents and conditions: (a) thiazole-4-carbaldehyde, $NaBH(OAc)_3$, 1,2 dichloroethane rt, 16 h ($R^1$ = H, 34%; $R^1$ = Me, 42%); (b) dioxane, HCl, rt, 0 °C to rt, 16 h, ($R^1$ = H, 24%; $R^1$ = Me, 57%); (c) **66a**, $Cs_2CO_3$, DMF, 0–80 °C, 16 h, ($R^1$ = H, 8%; $R^1$ = Me, 10%).




**Scheme 6.** Reagents and conditions: (a) Mg/THF, thiazole-4-carbaldehyde (42%); (b) DCM, TFA, triethyl silane, 0 °C to rt, 2 h (80%); (c) $BBr_3$, DCM (28%); (d) **66a**, $Cs_2CO_3$, DMF, 0–80 °C, 16 h, (45%).

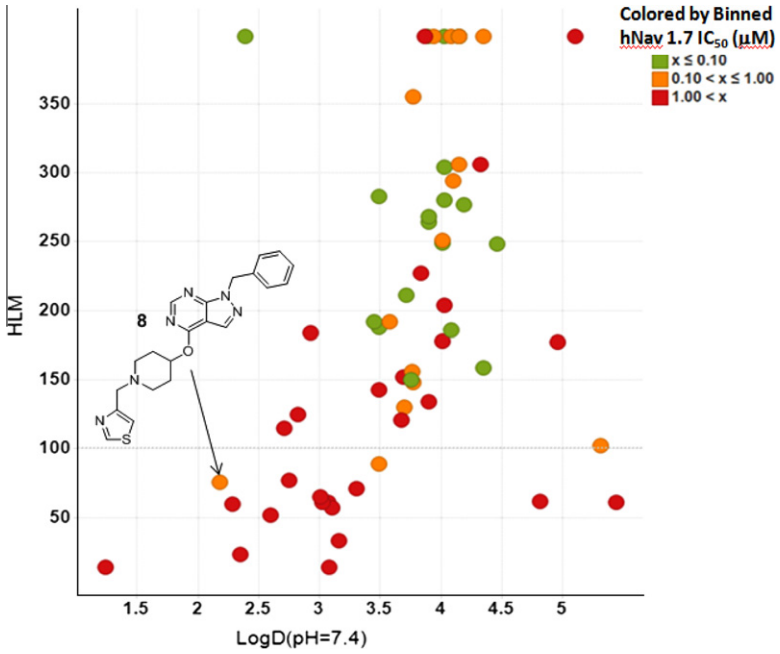



**Figure 2.** Visualization of Log*D* (pH 7.4) versus HLM (µL/min/mg) for described compounds colored by $hNa_v1.7$ potency (PX, µM).

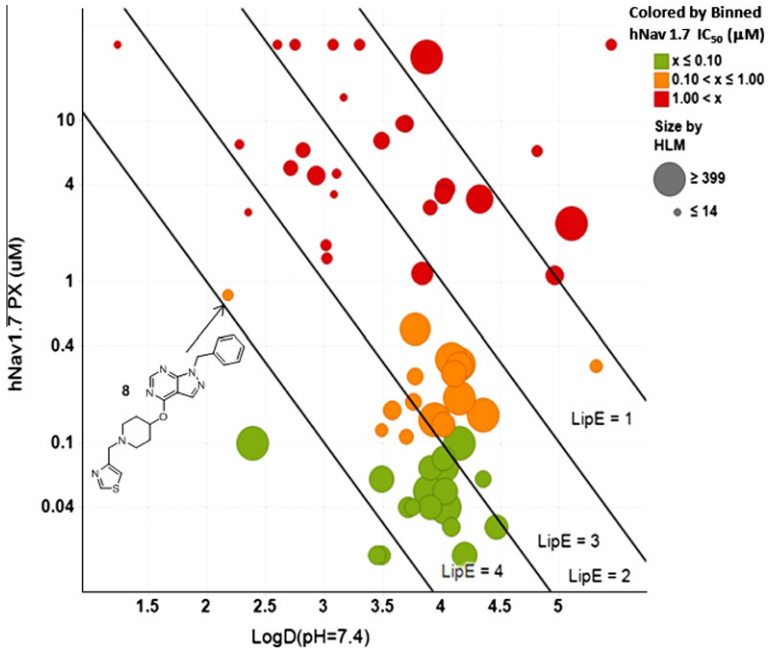



**Figure 3.** Visualization of Log*D* (pH 7.4) versus potency for described compounds sized by microsomal stability with lines representing lipophilic efficiencies (LipE), colored by $hNa_v1.7$ $IC_{50}$ (PX, µM).

## Acknowledgments

The authors would like to thank Grace Bi for purification support and Dr. Margaret Y. Chu-Moyer for proofreading the manuscript.

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