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Discovery and Optimization of Selective $Na_v1.8$ Modulator Series That Demonstrate Efficacy in Preclinical Models of Pain

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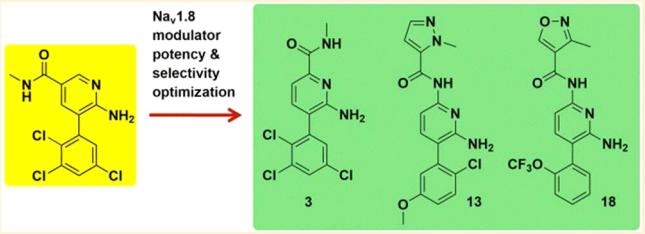
Supporting Information

ABSTRACT: Voltage-gated sodium channels, in particular $Na_v1.8$, can be targeted for the treatment of neuropathic and inflammatory pain. Herein, we described the optimization of $Na_v1.8$ modulator series to deliver subtype selective, state, and use-dependent chemical matter that is efficacious in preclinical models of neuropathic and inflammatory pain.



KEYWORDS: *Voltage-gated sodium channels, sodium channel drugs, $Na_v1.8$, SCN10A, TTX-R*

Voltage-gated sodium channels (Na_v) are a family of transmembrane (TM) ion channel proteins. Structurally, they are members of the 6-TM ion channel family and are composed of a TM α-subunit of approximately 260 kDa with associated transmembrane β-subunits of lower molecular weight. The family comprises nine members, $Na_v1.1$–$Na_v1.9$, which can be subdivided into tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) subtypes. Na_vs play a key role in controlling excitability of neurons by regulating the threshold of firing, underlying the upstroke of the action potential and controlling the duration of interspike interval.[1] Nonselective Na_v blockers (e.g., lamotrigine, lacosamide, and mexilitine) have been successfully used in the clinic to treat pathological firing patterns of neurons that occur in a range of conditions such as chronic pain and epilepsy. However, such drugs have a narrow therapeutic window due to inhibition of sodium channels in the heart and throughout the central nervous system (CNS).

Selective block of Na_v channels as pain targets gained traction with the recognition that some Na_v subtypes showed preferential or exclusive expression in peripheral sensory neurons. A number of preclinical studies have implicated $Na_v1.3$, 1.7, 1.8, and 1.9, which are expressed in DRG (dorsal root ganglion neurons) and trigeminal neurones, in nociceptive processing.[2] $Na_v1.8$ is highly (but not exclusively) expressed in nociceptors,[3,4] and its expression and function is modulated by agents that cause pain[5,6] Genetic ablation of $Na_V1.8$ in rodents results in deficits in nociception following inflammation, but not neuropathic pain,[7−10] while recent human genetic evidence suggest that gain of function mutations in $Na_V1.8$ contributes to painful peripheral neuropathy.[11] A-803467 is one of the first compounds in the public domain that demonstrated selectivity across human Na_v subtypes and attenuated pain sensitivity in models of both nerve injury and inflammation induced pain

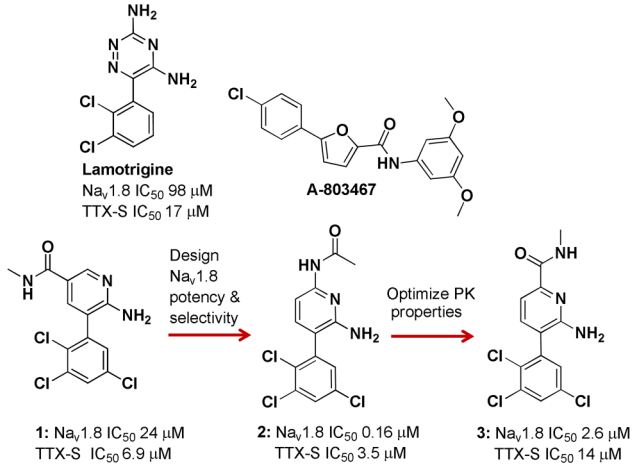


Figure 1. Discovery of candidate compound **3**. IC_{50} data generated in VSP-FRET at hNav1.8 in HEK293 cells (in house cell line) with at least three tests on three different assay runs. TTX-S data generated in VSP-FRET in SHSY5Y neuroblastoma cell line expressing hNav1.2, hNav1.3, and hNav1.7.[16]

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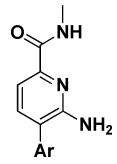
Table 1. Compounds 2, 3, 13, and 18: Pharmacokinetic Studies in Rat (R) and Dog (D)

Cmpd	Dose (mg/kg) route	$T_{1/2}$ (h)	T_{max} (h)	Plasma CL[a]	V_d (L/kg)	Oral F (%)
2 (R)	3, p.o.	4.1	0.75	204		N.D.
3 (R)	2, i.v.	4.0		11.7	3.0	
	5, p.o.	4.6	1.0	13.3		91
13 (R)	1, i.v.	3.9		6.7	2.25	
	2, p.o.	N.D.	1.3	11.4		59
18 (D)	0.1, i.v.	9.7		6.2	5.3	
	0.25, p.o.	N.D.	3.5	10.0		63

[a]Plasma CL (i.v.) or CL/F (p.o.) in mL/min/kg.

Table 2. Aryl Ring SAR in Picolinamide Series[a]



Cmpd	Aryl	$Na_v1.8$ IC_{50} (μM)	cLogP	LipE
3	2,3,5-trichlorophenyl	2.6	3.8	1.8
4	2-chlorophenyl	>32	2.5	NA
5	3-chlorophenyl	>32	2.8	NA
6	4-chlorophenyl	>32	2.8	NA
7	2,5-dichlorophenyl	12	3.3	1.6
8	3,5-dichlorophenyl	>32	3.5	NA

[a]IC_{50} data generated in VSP-FRET at hNav1.8 in HEK293 cells (in house cell line) with at least three tests on three different assay runs.[16] cLogP was calculated using BioByte program version 4.3.

(the latter with the exception of the formalin challenge paw withdrawal assay).[12] This provided the first pharmacological evidence supporting a role for $Na_v1.8$ in both inflammatory and neuropathic pain.

Existing subtype selective $Na_v1.8$ inhibitors, for example, A-803467, exhibit poor oral pharmacokinetics in preclinical species.[12] In this article, we discuss the discovery of subtype selective $Na_v1.8$ modulators with good oral pharmacokinetics in preclinical studies.

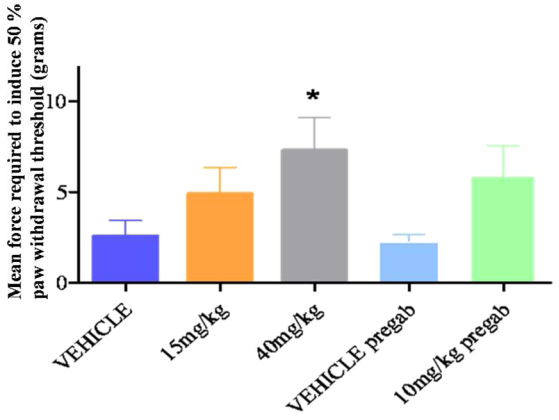


Figure 2. Antiallodynic effects of **13** in the TNT model of neuropathic pain. Error bars represent the SEM. A single dose of 40 mg/kg of **13** equivalent to a free plasma exposure of 0.2 μM, significantly shifted the 50% paw withdrawal threshold in the ipsilateral paw from a baseline of 1.7 ± 0.3 to 7.3 ± 1.8 g, 1.5 h after dosing (*P < 0.05). These effects were comparable to 10 mg/kg of Pregabalin, which shifted the 50% paw withdrawal threshold in the ipsilateral hindpaw from 1.7 ± 0.2 to 5.8 ± 1.7 g, 1.5 h after dosing (P = 0.07).

Lamotrigine is a first generation sodium channel modulator and an anticonvulsant used in the treatment of epilepsy and bipolar disorder (Figure 1). Lamotrigine is a weak $Na_v1.8$ inhibitor and shows no selectivity for $Na_v1.8$ over TTX-S channels (measured in fluorescence based assays). Compound **1** was identified through file screening and suggested that trichloroaryl and aminopyridine units offered a potent $Na_v1.8$ and TTX-S channel inhibition profile. Modification of the core to a diaminopyridine unit coupled with the introduction of 6-acetamide led to compound **2**, which displayed a significant improvement in $Na_v1.8$ potency together with approximately 20-fold selectivity over TTX-S channels.

Compound **2** was assessed in an oral pharmacokinetic (PK) study in rat where it demonstrated high in vivo clearance (CL) (Table 1). The high CL was likely to be mediated by amide

Table 3. $hNa_v1.8$ Potency (IC_{50}), Selectivity (IC_{50}), and Antiallodynic Effects in Rodent Models of Neuropathic Pain for 3, 13, and 18[a]

	$hNa_v1.8$		hNa_v subtype selectivity		TTX-r Rat DRG		TTX-R human DRG		hERG			
Cmpd	IC_{50} (μM)	n	IC_{50} (μM)	n	IC_{50} (μM)	n	IC_{50} (μM)	n	IC_{50} (μM)	Model	Effect significance	Unbound exposure (μM)
3	0.19	5	$Na_v1.1$ = 13	5	0.44	4	0.31	4	30	SNL hypersensitivity	P < 0.05 (equal to 100 mg/kg gabapentin)	0.25
			$Na_v1.2$ = 12.8	5								
			$Na_v1.5$ = 9.0	5								
			$Na_v1.7$ = 19	5								
13	0.19	2	$Na_v1.1$ = 37	2	0.54	4	0.20	3	>30	TNT mechanical allodynia	SP < 0.05 (comparable to 10 mg/kg pregabalin)	0.20
			$Na_v1.5$ = 37	2								
			$Na_v1.7$ = 36	2								
18	0.26	4	SHSY5Y[b] = 10	5	0.33	6	ND		>30	TNT mechanical allodynia	P < 0.05 (comparable to 10 mg/kg pregabalin)	0.19
			$Na_v1.5$ = 12	4								

[a]IC_{50} values for **3**, **13**, and **18** at recombinantly expressed hNav1.8/β1 (Merck Millipore) and at TTX-R in rat and human DRG were determined using manual patch clamp electrophysiology. hNav subtype selectivity for **3** was also measured using manual patch clamp electrophysiology. IC_{50} values determined using manual patch clamp electrophysiology were determined at the respective V0.5 of inactivation for TTX-R and each channel isoform. For **13** and **18**, human sodium channel subtype selectivity was measured using IonWorks Quattro and FRET, respectively. [b]SHSY5Y cells expressing hNav1.2, 1.3, and 1.7 were also used. The voltage protocol for the IonWorks Quattro and assay methodology for the FRET assay is detailed in the Supporting Information.

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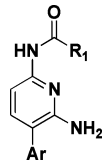
Table 4. Aryl Ring and Amide Moiety SAR Observed in the Acetamide Series[a]



Cmpd	Aryl	R_1	$Na_v1.8$ IC_{50} (μM)	cLogP	LipE
9	2-3-5-trichlorophenyl		0.75	3.7	2.4
10	2-3-5-trichlorophenyl		0.67	3.6	2.6
11	2-5-dichlorophenyl		0.92	3.1	2.9
12	2-chloro-5-methoxyphenyl		0.50	2.4	3.9
13	2-chloro-5-methoxyphenyl		0.70	2.4	3.8
14	2-methoxy-5-chlorophenyl		7.4	2.1	3.0
15	2-chlorophenyl		4.9	2.4	2.9
16	2-chloro-5-methoxyphenyl		4.0	3.5	1.9
17	2-trifluoromethoxyphenyl		2.4	2.4	3.2
18	2-trifluoromethoxyphenyl		0.53	2.4	3.9
19	2-trifluoromethoxyphenyl		7.0	1.8	3.4
20	2-trifluoromethoxyphenyl		3.2	4.1	1.4
21	2-chloro-4-fluorophenyl		> 31	2.5	NA

[a]IC_{50} data generated in VSP-FRET at hNav1.8 in HEK293 cells (in house cell line) with at least three tests on three different assay runs.[16] cLogP was calculated using BioByte program version 4.3.

deacetylation as evidenced by rapid formation of the corresponding diaminopyridine metabolite in vivo. Reversal of the amide produced **3**, which was more stable toward amide hydrolysis based on in vitro ADME data. Compound **2** readily underwent metabolism in rat and human liver microsomes (RLM and HLM), with intrinsic clearance (CL_{int}) values of 29 and 41 μL/min/mg protein in RLM and HLM, respectively, while **3** displayed very little turnover (CL_{int} < 9 and 7.1 μL/min/mg protein in RLM and HLM, respectively).

Moreover, this analogue retained $Na_v1.8$ activity (albeit weaker activity when compared with **2**) and was $Na_v1.8$ selective. Oral and i.v. rat PK studies with **3** exhibited low CL with high oral bioavailability of 91% (Table 1). Allometric scaling from rat data predicted low CL in human, oral bioavailability >90%, and half-life 8−28 h.[13] Compound **3** was profiled through manual electrophysiology in order to assess potency and selectivity across multiple ion channels. The IC_{50} value for **3** at $hNa_v1.8$, was 0.19 μM with ≥50-fold selectivity for $Na_v1.8$ over the other ion channels studied, including hERG. Furthermore, **3** inhibited native TTX-R currents in both human and rat DRG neurons (Table 3). The block of both human recombinant $Na_v1.8$ and TTX-R currents from rat DRG neurons was found to be frequency and state dependent.[14] State dependence of Na_V modulators results from different affinities for each channel state, whereby binding to the inactivated state is often preferred. Many Na_V modulators also demonstrate use dependence, which occurs when potency increases with Na_V channel firing frequency. As **3** was both state and frequency dependent, it may be possible to achieve functional selectivity by preferentially targeting high frequency firing rates associated with neuroma ectopic activity and sparing the low frequency firing rates of the normal somatosensory system leading to an improved therapeutic index.[15]

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In order to improve the lipophilic efficiency (LipE) of **3** above 1.8, the trichloroaryl ring was varied (Table 2).[17] In this picolinamide series, $Na_v1.8$ potency was found to be highly dependent on aryl polychlorination with **3** being one of the most potent and LipE efficient compounds synthesized.[18]

In a parallel effort, the instability of the acetamide in **2** was also addressed. Through variation of the amide moiety (Table 4) pyrazole **9** and isoxazole **10** were found to be two of the most potent amides identified. Both of these heterocyclic amides retained potency and $Na_v1.8$ subtype selectivity over TTX-S while demonstrating improved amide stability in in vitro systems.[18−20] These amides may be chemically stable due to increased conjugation between the carbonyl and heterocycle in comparison to the acetamide group. However, **9** and **10** were poorly soluble (<0.1 μg/mL at pH 7.2), which was attributable to their combination of high cLogP and planar shape.[21] In order to reduce lipophilicity, the pyridyl core was replaced by a pyrazine core. Although cLogP was reduced by the pyridine to pyrazine switch (data not shown), the simultaneous potency loss of greater than 10-fold led to $Na_v1.8$ inhibitors that were too weak to permit progression.

The aryl unit was also varied (Table 4). Substitution at the 2- and 5-aryl positions with lipophilic groups tended to offer profiles with potency in the submicromolar range, e.g., **11**, **12**, and **13**. In the case of **18**, the larger 2-trifluoromethoxy moiety is sufficient to achieve submicromolar potency without the requirement of a 5-aryl substituent. Moreover, the observed SAR exhibited relatively steep activity cliffs, whereby, for instance, addition of a 4-F atom to compound **15** to give **21** decreased $Na_v1.8$ potency from 4.9 to >31 μM.[22]

The amide group was optimized further (Table 4). Aliphatic amides were less stable to amide hydrolysis in vitro than aromatic amides as exemplified by **16**, which readily underwent amide hydrolysis in buffer solutions at pH 7.4 such that in vitro ADME measurements were precluded. As before, this may be attributed to increased conjugation between the carbonyl and aromatic amides in comparison to the aliphatic amides. Furthermore, it appeared that the optimal heterocyclic amide was heavily dependent on the aryl unit it was combined with. For instance, a comparison of compounds **17**−**20** suggested that the ideal heterocyclic amide to combine with the 2-trifluoromethoxyaryl moiety was 3-methylisoxazole. However, analysis of the 2-chloro, 5-methoxy, and 2,3,5-trichlorophenyl aryl groups present in **9**, **10**, **12**, **13**, and **16** indicated very little difference in $Na_v1.8$ potency between the 1-methyl-1*H*-pyrazole amides and 3-methylisoxazole amides.

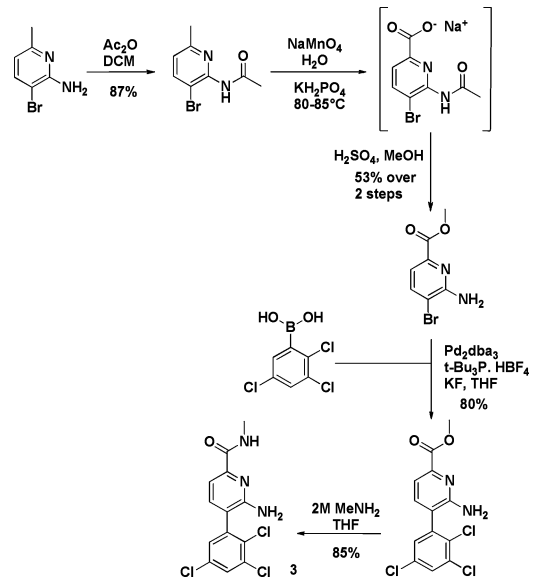
SAR development led to the selection of **13** and **18** as compounds of interest to progress based on highest LipE (**13** and **18** have a LipE two units greater than **3**), $Na_v1.8$ potency and acceptable solubility of ∼10 μg/mL. PK studies in rat with **13** indicated a low CL compound with good bioavailability ∼60% (Table 1). Allometric scaling predicted low CL of **13** in human (CL < 5 mL/min/kg).[13] Preclinical oral PK studies of **18** also yielded low human CL estimates. Compounds **13** and **18** were profiled through manual electrophysiology. In a consistent manner to **3**, **13** and **18** were selective for $hNa_v1.8$ over the other human sodium channel subtypes studied and the hERG channel. Compounds **13** and **18** also inhibited native TTX-R currents in rodent DRG neurons and the IC_{50} for the inhibition of TTX-R currents in human DRG neurons was determined for **13** (Table 3). The block of both human recombinant $Na_v1.8$ and TTX-R currents from rat DRG neurons by both **13** and **18** were found to be frequency and state dependent.[14,15]

Compounds **3**, **13**, and **18** were efficacious in preclinical in vivo models of neuropathic pain: **3** was efficacious in the rat model of spinal nerve injury, while **13** and **18** were efficacious in the tibial nerve transection (TNT) induced mechanical allodynia model in rat (see Table 3 and Figure 2). Analysis of compound concentrations in plasma and cerebrospinal fluid samples suggested that **13** readily crossed the blood−brain barrier in rats (cerebrospinal fluid: unbound plasma concentration ratio 0.75:1). Moreover, an oral dose of **13** (250 mg/kg) achieving unbound exposures up to 0.33 μM in rats had no effect on either horizontal or vertical movements when compared to vehicle control animals indicating little or no effect of **13** on either the peripheral or central nervous system.

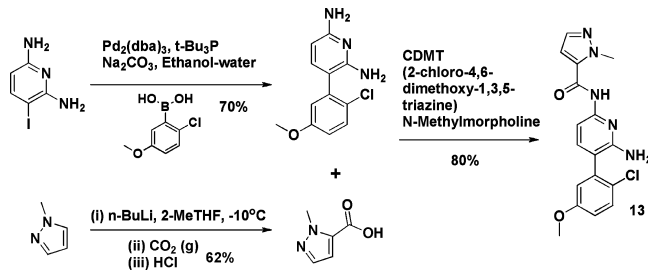
Based on the favorable $Na_v1.8$ potency, LipE, selectivity and in vivo PK profiles of **3**, **13**, and **18** these compounds were selected as candidates for further progression.

Schemes 1 and 2 demonstrate a typical synthetic route for both the picolinamide and acetamide series, in this case illustrated by

Scheme 1. Preparation of Compound 3



Scheme 2. Preparation of Compound 13



the synthesis of analogues **3** and **13**. Further synthesis details are available in the Supporting Information.[23]

In conclusion, optimization of a biaryl lead has led to highly selective $Na_v1.8$ series. Three key compounds **3**, **13**, and **18** have also demonstrated good pharmacokinetics in preclinical species leading to low human CL projections. Moreover, these compounds are efficacious in preclinical studies of neuropathic and inflammatory pain. Further data on the progression of **3**, **13**, and **18** will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for the preparation of compounds **2**−**21**, additional biological data, PK and efficacy study information, and experimental details for the in vitro assays. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.5b00059.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This publication is dedicated to the memory of Bill Million.

■ ABBREVIATIONS

Cmpd, compound; PK, pharmacokinetics; ADME, absorption distribution, metabolism, excretion; CL, clearance; PK, pharmacokinetics; DRG, dorsal root ganglion neuron; TNT, tibial nerve transection; TM, transmembrane; TTX-S, tetrodotoxin-sensitive; TTX-R, tetrodotoxin-resistant; LipE, lipophilic efficiency; SNL, spinal nerve injury; CNS, central nervous system; L/kg, liters per kilogram; μg/mL, microgram per milliliter; h, hour; i.v., intravenous; p.o., pharmacokinetic study with oral administration; $T_{1/2}$, pharmacokinetic half-life; T_{max}, time of maximum concentration in vivo; V_d, volume of distribution; oral *F*, oral bioavaibility

■ REFERENCES

(1) Lampert, A.; Eberhardt, M.; Waxman, Stephen G. Altered sodium channel gating as molecular basis for pain: contribution of activation, inactivation, and resurgent currents. *Handb. Exp. Pharmacol.* **2014**, *221*, 91−110.

(2) Dib-Hajj, S. D.; Cummins, T. R.; Black, J. A.; Waxman, S. G. Sodium channels in normal and pathological pain. *Annu. Rev. Neurosci.* **2010**, *33*, 325−347.

(3) Amaya, F.; Decosterd, I.; Samad, T. A.; Plumpton, C.; Tate, S.; Mannion, R. J.; Costigan, M.; Woolf, C. J. Diversity of expression of the sensory neuron-specific TTX-resistant voltage-gated sodium ion channels SNS and SNS2. *Mol. Cell. Neurosci.* **2000**, *15*, 331−342.

(4) Shields, S. D.; Ahn, H.-S.; Yang, Y.; Han, C.; Seal, R. P.; Wood, J. N.; Waxman, S. G.; Dib-Hajj, S. D. Nav1.8 expression is not restricted to nociceptors in mouse peripheral nervous system. *Pain* **2012**, *153*, 2017−2030.

(5) England, S.; Bevan, S.; Docherty, R. J. PGE2 modulates the tetrodotoxin-resistant sodium current in neonatal rat dorsal root ganglion neurons via the cyclic AMP-protein kinase A cascade. *J. Physiol.* **1996**, *495*, 429−440.

(6) Dib-Hajj, S. D.; Fjell, J.; Cummins, T. R.; Zheng, Z.; Fried, K.; LaMotte, R.; Black, J. A.; Waxman, S. G. Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain. *Pain* **1999**, *83*, 591−600.

(7) Akopian, A. N.; Souslova, V.; England, S.; Okuse, K.; Ogata, N.; Ure, J.; Smith, A.; Kerr, B. J.; McMahon, S. B.; Boyce, S.; Hill, R.; Stanfa, L. C.; Dickenson, A. H.; Wood, J. N. The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways. *Nat. Neurosci.* **1999**, *2*, 541−548.

(8) Kerr, B. J.; Souslova, V.; McMahon, S. B.; Wood, J. N. A role for the TTX-resistant sodium channel Nav 1.8 in NGF-induced hyperalgesia, but not neuropathic pain. *NeuroReport* **2001**, *12*, 3077−3080.

(9) Minett, M. S.; Falk, S.; Santana-Varela, S.; Bogdanov, Y. D.; Nassar, M. A.; Heegaard, A.-M.; Wood, J. N. Pain without nociceptors? Nav1.7-independent pain mechanisms. *Cell Rep.* **2014**, *6*, 301−312.

(10) Nassar, M. A.; Levato, A.; Stirling, L. C.; Wood, J. N. Neuropathic pain develops normally in mice lacking both Nav1.7 and Nav1.8. *Mol. Pain* **2005**, *1*, 24.

(11) Faber, C. G.; Lauria, G.; Merkies, I. S. J.; Cheng, X.; Han, C.; Ahn, H.-S.; Persson, A.-K.; Hoeijmakers, J. G. J.; Gerrits, M. M.; Pierro, T.; Lombardi, R.; Kapetis, D.; Dib-Hajj, S. D.; Waxman, S. G. Gain-of-function Nav1.8 mutations in painful neuropathy. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 19444−19449.

(12) Jarvis, M. F.; Honore, P.; Shieh, C.-C.; Chapman, M.; Joshi, S.; Zhang, X.-F.; Kort, M.; Carroll, W.; Marron, B.; Atkinson, R.; Thomas, J.; Liu, D.; Krambis, M.; Liu, Y.; McGaraughty, S.; Chu, K.; Roeloffs, R.; Zhong, C.; Mikusa, J. P.; Hernandez, G.; Gauvin, D.; Wade, C.; Zhu, C.; Pai, M.; Scanio, M.; Shi, L.; Drizin, I.; Gregg, R.; Matulenko, M.; Hakeem, A.; Gross, M.; Johnson, M.; Marsh, K.; Wagoner, P. K.; Sullivan, J. P.; Faltynek, C. R.; Krafte, D. S. A-803467, a potent and selective Nav1.8 sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 8520−8525.

(13) Caldwell, G. W.; Masucci, J. A.; Yan, Z.; Hageman, W. Allometric scaling of pharmacokinetic parameters in drug discovery: Can human CL, Vss and t1/2 be predicted from in-vivo rat data? *Eur. J. Drug Metab. Pharmacokinet.* **2004**, *29*, 133−143.

(14) Payne, C. E. Brown, A. R.; Theile, J. W.; Mahoney, J. H.; Loucif, A. J. C.; Alexandrou, A. J.; Fuller, M. D.; Antonio, B. M.;. Gerlach, A. C.; Prime, R. L.; Stockbridge, G.; Kirkup, A. J.; Bagal, S. K.; Bannon, A. W.; England, S.; Chapman, M. L.; Roeloffs, R.; Bungay, P.; Anand, U.; Anand, P.; Kemp, M.; Butt, R. P.; Stevens, E. B. A novel oral NaV 1.8 blocker PF-01247324 attenuates nociception and neuronal excitability. *Br. J. Pharmacol.* **2015**, *172* (10), 2654−2670; DOI: 10.1111/bph.13092.

(15) Bagal, S. K.; Brown, A. D.; Cox, P. J.; Omoto, K.; Owen, R. M.; Pryde, D. C.; Sidders, B.; Skerratt, S. E.; Stevens, E. B.; Storer, R. I.; Swain, N. A. Ion channels as therapeutic targets: a drug discovery perspective. *J. Med. Chem.* **2013**, *56* (3), 593−624.

(16) hNav1.8 data generated in VSP-FRET hNav1.8 in HEK293 cells with at least three tests on three different assay runs. TTX-S data generated in VSP-FRET in SHSY5Y neuroblastoma cell line expressing hNav1.2, hNav1.3, and hNav1.7.

(17) Freeman-Cook, K. D.; Hoffman, R. L.; Johnson, T. W. Lipophilic efficiency: the most important efficiency metric in medicinal chemistry. *Future Med. Chem.* **2013**, *5* (2), 113−115.

(18) Lane, C. A. L.; Maw, G. N.; Rawson, D. J.; Thompson, L. R. Pyridine derivatives. WO2006011050, 2006.

(19) Bagal, S. K.; Gibson, K. R.; Kemp, M. I.; Poinsard, C.; Stammen, B. L.; Denton, S. M.; Glossop, M. S. Pyridine derivatives. WO2008135826, 2008.

(20) Kemp, M. I. 2,6-Diaminopyrazine-amide derivatives as NaV1.8 channel modulators and their preparation, pharmaceutical compositions and use in the treatment of pain. WO2008135830, 2008.

(21) Ran, Y.; Jain, N.; Yalkowsky, S. H. Prediction of aqueous solubility of organic compounds by the general solubility equation (GSE). *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1208−1217.

(22) Hu, X.; Hu, Y.; Vogt, M.; Stumpfe, D.; Bajorath, J. MMP-Cliffs: systematic identification of activity cliffs on the basis of matched molecular pairs. *J. Chem. Inf. Model.* **2012**, *52*, 1138−45.

(23) Fray, M. J.; Gillmore, A. T.; Glossop, M. S.; McManus, D. J.; Moses, I. B.; Praquin, C. F. B.; Reeves, K. A.; Thompson, L. R. Optimization of permanganate oxidation and Suzuki-Miyaura coupling steps in the synthesis of a Nav1.8 sodium channel modulator. *Org. Process Res. Dev.* **2010**, *14*, 263−271.

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