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Structure and activity relationship in the (S)-*N*-chroman-3-ylcarboxamide series of voltage-gated sodium channel blockers

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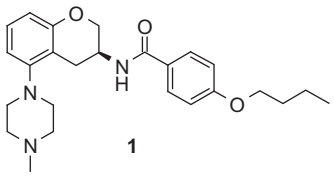
ABSTRACT

Recent findings showing a relation between mutations in the $Na_V1.7$ channel in humans and altered pain sensation has contributed to increase the attractiveness of this ion channel as target for development of potential analgesics. Amido chromanes **1** and **2** were identified as blockers of the $Na_V1.7$ channel and analogues with modifications of the 5-substituent and the carboxamide part of the molecule were prepared to establish the structure–activity relationship. Compounds **13** and **29** with good overall in vitro and in vivo rat PK profile were identified. Furthermore, **29** showed in vivo efficacy in a nociceptive pain model.

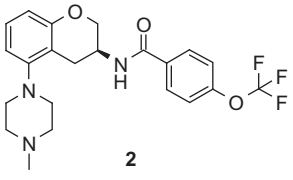
Voltage-gated sodium channels (VGSC) play a critical role in electrical signaling in the nervous system and are responsible for the initiation and propagation of action potentials caused by variations in membrane potentials.[1] Nerve signal transduction can be affected by altered rapid opening and closing of VGSCs and these channels are important targets in the pharmaceutical industry in regards to finding treatment for cardiac conductance disturbances, epilepsy and pain disorders.[2] Inherited loss of function mutations of $Na_V1.7$ in humans were reported to cause congenital inability to experience pain.[3,4] In addition, gain of function mutations have been connected to inheritable pain conditions erythromelalgia and familial rectal pain.[5] These observations make $Na_V1.7$ an attractive target for development of potential analgesics. Current sodium channel blocker therapies available have issues with tolerability and finding more potent compounds with higher subtype selectivity have potentially an important impact on treatment options for neuropathic pain.[6]

As a part of our preclinical $Na_V1.7$ channel blocker program aimed to discover novel analgesic drug candidates we examined a series of amido chromanes substituted at C-5 position. The initial hit series is represented by **1** and **2** (Fig. 1). The compounds were initially identified through HTS screening using a Li^+ flux atomic absorption spectroscopy assay.[7] Compound **1** showed moderate potency on $Na_V1.7$ and moderate selectivity over $Na_V1.5$, as measured in a whole-cell voltage clamp electrophysiology assays.[8,9] The $Na_V1.5$ channel is widely expressed in heart muscle and inhibition leads to ventricular arrhythmia, therefore very high



1

$Na_V1.7$ pIC_{50} 6.0
$Na_V1.5$ pIC_{50} <5.2
clogP 4.64
hERG pIC_{50} 5.2
Solubility 1 μM
RLM Clint 82 μL/min/μg
HLM Clint 361 μL/min/μg



2

$Na_V1.7$ pIC_{50} 5.7
$Na_V1.5$ pIC_{50} 5.7
clogP 4.2
hERG pIC_{50} 5.1
Solubility 27 μM
RLM Clint 18 μL/min/μg
HLM Clint 2.5 μL/min/μg

Figure 1. Profile of initial hits, chromanes **1** and **2**.

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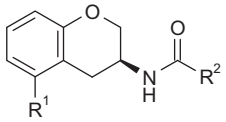
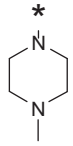
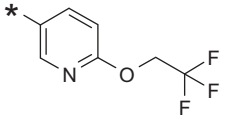
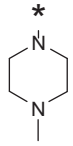
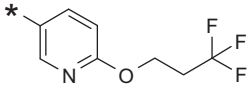
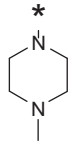
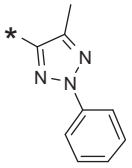
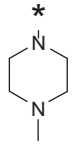
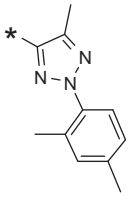
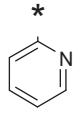
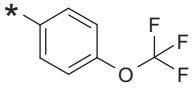
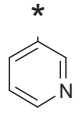
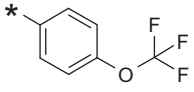
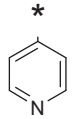
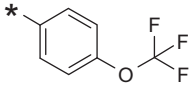
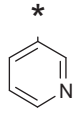
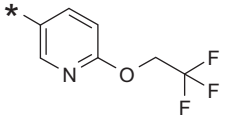
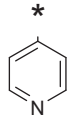
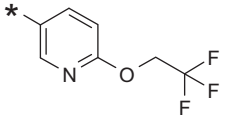
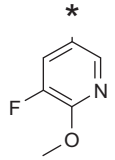
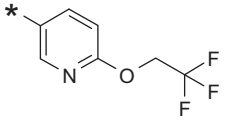
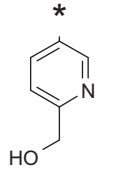
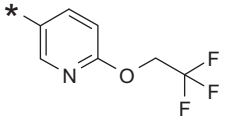
Table 1
Chromanes with piperazine or pyridine as R^1 substituent

	R^1	R^2	NaV1.7 pIC_{50}	NaV1.5 pIC_{50}	hERG pIC_{50}	c*Log*P	Solubility (μM)	RLM/HLM Clint (μl/min/μg)
3			6.1	5.3	5.1	3.82	82	<10/<10
4			6.2	5.3	4.9	3.80	379	<10/<10
5			6.5	5.3	5.1	3.53	211	4/14
6			6.8	5.6	5.0	4.53	4	9/stable
7			5.8	ND[a]	ND[a]	4.86	ND[a]	ND[a]
8			5.9	5.5	ND[a]	4.65	5	ND[a]
9			6.	5.4	5.6	4.65	2	ND[a]/78
10			7.1	5.5	4.6	4.19	29	64/161
11			7.0	5.5	5.2	4.19	9	77/59
12			6.4	5.4	4.6	4.99	1.1	10/19
13			6.8	5.2	5.0	3.60	58	<10/10

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