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Discovery and evaluation of $Ca_v3.1$-selective T-type calcium channel blockers

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ABSTRACT

We identified and characterized a series of pyrazole amides as potent, selective $Ca_v3.1$-blockers. This series culminated with the identification of pyrazole amides **5a** and **12d**, with excellent potencies and/or selectivities toward the $Ca_v3.2$- and $Ca_v3.3$-channels. This compound displays poor DMPK properties, making its use difficult for *in vivo* applications. Nevertheless, this compound as well as analogous ones are well-suited for *in vitro* studies.

A first generation of T-channel blockers was developed in the 1990s, and culminated with the discovery of mibefradil. This drug, developed at Roche for angina pectoris, and meanwhile withdrawn from the market due to unacceptable drug-drug interactions, is a rather potent, but unselective T-type calcium channel blocker.[1] A second generation of T-type calcium channel blocker arose during the last years, with two compounds, MK-8998[2] and Z-944,[3] entering clinical trials. These compounds are *selective* T-type calcium channel blockers, meaning that they block the $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$ channels with similar potencies, while they do not block other channels.

We recently disclosed a series of dihydropyrazole derivatives as selective T-type calcium channel antagonists,[4] and demonstrated their *in vivo* efficacy in two animal models of epilepsy, the WAG/Rij rat model for absence seizures. Simultaneously, we observed in spontaneously hypertensive rats that these compounds induced a prolongation of the PR interval on ECG. Due to the excellent PK/PD correlation and a strong parallelism with the desired antiepileptic effect, we hypothesized that this PR prolongation was directly linked to the blockade of all T-type calcium channel subtypes in the rodent heart. We conjectured that we might be able to dissociate both effects (i.e. desired antiepileptic effect without PR prolongation) by applying *subtype selective* T-type calcium channel blockers, i.e. compounds that would block one of the three T-type calcium channel only. A certain subtype selectivity was possible to achieve. In this paper, we describe the discovery and the study of $Ca_v3.1$-subtype selective blockers, whereas $Ca_v3.2$-subtype selective blockers were described in the previous paper. Furthermore, we described recently a compound with a moderate selectivity for the $Ca_v3.3$ channel.[5]

In the previous paper, we described a series of pyrrole-based $Ca_v3.2$-subtype selective blockers. In an effort to increase the polarity of such compounds, we investigated pyrazole analogues from this series. Indeed, compound **1**[6] (Fig. 1) had appeared as a weak hit in an HTS campaign (Table 1). Two other hits, compounds **2a** and **2b**, prepared via an amide coupling from commercially available starting material, proved to be moderately potent $Ca_v3.1$- and $Ca_v3.2$-blockers, with no measurable potency against $Ca_v3.3$, this in in the FLIPR® assay we had been using previously[4,5] (Table 1). In particular, an *ortho*-substituent seemed to confer a good subtype selectivity for the $Ca_v3.1$ channel. In a first SAR study at the amide position, we introduced an *ortho*-trifluoromethoxy substituent that had been successful in the development of $Ca_v3.2$-blockers, as described in the previous manuscript. Compound **2c** proved to be a slightly more potent and subtype selective $Ca_v3.1$-blocker. Compound **2c** was confirmed using patch-clamp

Abbreviations: AcOH, acetic acid; 9-BBN, 9-borabicyclo(3.3.1)nonane; DAST, diethylaminosulfur trifluoride; DIPEA, *N,N*-diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; DMF, *N,N*-dimethylformamide; EDC·HCl, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; HOBt, hydroxybenzotriazole; NBS, *N*-bromosuccinimide; ^{t}Bu, *tert*-butyl; Tf, trifluorosulfonyl; THF, tetrahydrofuran.

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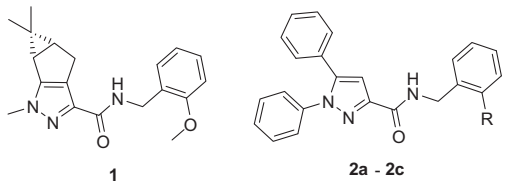


Fig. 1. First pyrazole-based $Ca_v3.1$-blockers.

(>99%, 83%, and 39% block of $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$ at 10,000 nM, respectively).

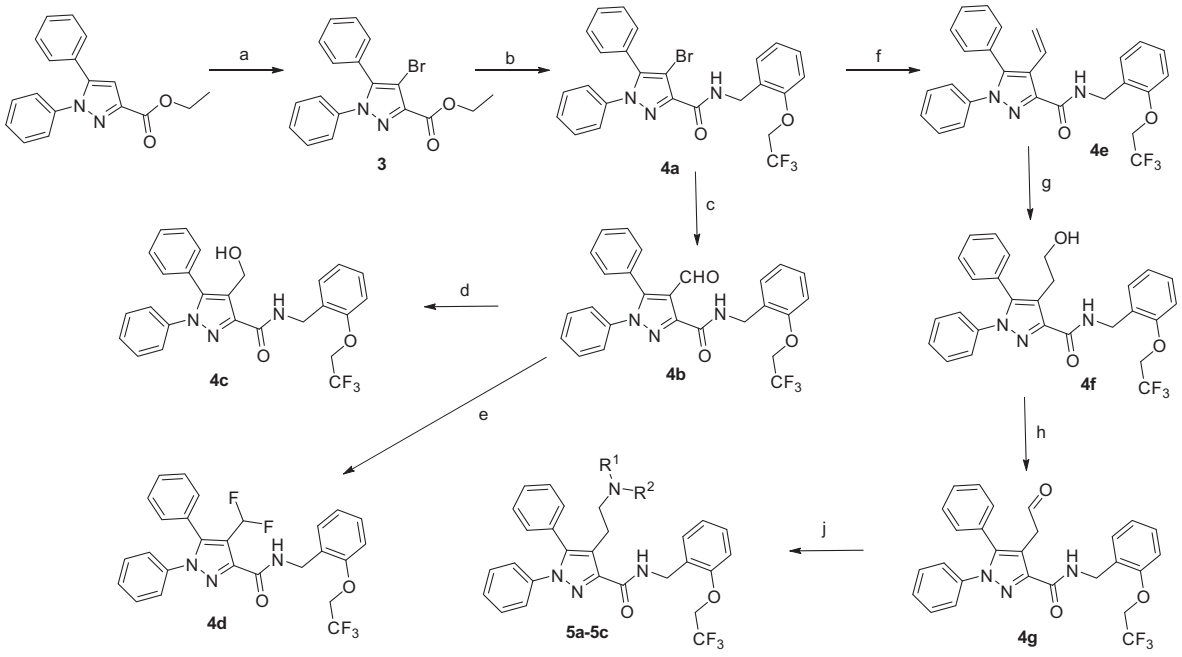
In a next step, we explored at first the position 4 of the pyrazole ring. From commercial starting material, a bromination led to compound **3** (Scheme 1). Saponification and amide coupling led to a first derivative **4a**. Formylation, reduction, and fluorination led to compounds **4b**, **4c**, and **4d**, respectively. Vinylation of compound **4a** led to derivative **4e**, which was transformed into compounds **4f** and **4g** via hydroboration and oxidation. Eventually, reductive aminations of compounds **4g** led to secondary and tertiary amines **5a**–**5c**.

The bromine substituent (compound **4a** Table 2) increased slightly the potency on the $Ca_v3.1$- and $Ca_v3.2$-channel compared to compound **2c**, while no potency was measurable on the $Ca_v3.3$-channel. Overall, subtype selectivity toward the $Ca_v3.2$-channel, the most difficult one to achieve, was maintained. From compounds **4c**–**4f**, we concluded that polarity at this position is

Table 1
Potencies of a few T-channel blockers (FLIPR®).

Compound	R-substituent	$Ca_v3.1$ IC_{50} (nM)[a]	$Ca_v3.2$ IC_{50} (nM)[a]	$Ca_v3.3$ IC_{50} (nM)[a]	Ratio $Ca_v3.2/Ca_v3.1$
1	–	2100	5800	9000	–
2a	–H	200	510	>10,000	2.6
2b	–F	130	1900	>10,000	15
2c	CF_3CH_2O–	59	1000	>10,000	17

[a] Geometric mean of at least two measurements.



Scheme 1. Preparation of $Ca_v3.1$-subtype selective blockers **4a**–**4g** and **5a**–**5c**. (a) NBS, AcOH, microwave, 150 °C, 10 min, 87%; (b) (i) 2.5 M aq. NaOH, EtOH, reflux, 1 h; (ii) *ortho*-trifluoroethoxybenzylamine, EDC·HCl, HOBt, DMAP, DIPEA, CH_2Cl_2, rt, overnight, 50% over two steps; (c) 3 M MeMgCl in THF, 1.6 M ^{t}BuLi in pentanes, DMF, THF, −78 °C to rt, 2 h, 46%; (d) $NaBH_4$, MeOH, rt, 1 h, 73%; (e) DAST, CH_2Cl_2, rt, 2 weeks, 39%; (f) vinylboronic anhydride pyridine complex, $Pd(^tBu_3P)_2$, K_2CO_3, H_2O, dioxane, 80 °C, overnight, 85%; (g) 0.5 M 9-BBN in THF, 70 °C, overnight, 6 M aq. NaOH, 30% H_2O_2, 50 °C, 1 h, 93%; (h) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 3 h, 64%; (j) amine, $NaBH(OAc)_3$, CH_2Cl_2, rt, 6 h, 71–94%.

Table 2
Potencies of first $Ca_v3.1$-subtype selective blockers (FLIPR®).

Compound	R^1R^2N-substituent	$Ca_v3.1$ IC_{50} (nM)[a]	$Ca_v3.2$ IC_{50} (nM)[a]	$Ca_v3.3$ IC_{50} (nM)[a]	Ratio $Ca_v3.2/Ca_v3.1$
4a	–	20	350	>10,000	17
4c	–	55	410	1370	7.4
4d	–	49	820	>10,000	17
4e	–	71	850	>10,000	12
4f	–	46	310	650	6.8
5a	EtNH–	52	280	1900	5.3
5b	Cyclopropyl-NH	200	590	900	2.9
5c	Et_2N–	240	2150	4370	9.0

[a] Geometric mean of at least two measurements.