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Design, syntheses, and SAR of 2,8-diazaspiro[4.5]decanones as T-type calcium channel antagonists

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ABSTRACT

It was hypothesized that an appropriately substituted 2,8-diazaspiro[4.5]decan-1-one could effectively approximate a 5-feature T-type pharmacophore model published in the literature. Compounds were designed and synthesized to test our hypothesis and were found to be potent T-type calcium channel inhibitors with modest selectivity over L-type calcium channels. The synthesis and SAR of the series is described.

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Calcium is an important signaling molecule for many physiological processes in the human body. These include electrical signaling in the nervous system, as well as controlling heart and smooth muscle contraction and hormone release. The entry of calcium into cells is regulated by a diverse set of proteins called calcium channels. A fundamental role of Ca²⁺ channels is to translate an electrical signal on the surface membrane into a chemical signal within the cytoplasm, which, in turn, activates many important intracellular processes including contraction, secretion, neurotransmission, regulation of enzymatic activities, and gene expression, as well as cell death.¹

Voltage-gated calcium channels are divided into two primary groups based on electrophysiological characteristics: low voltage activated (LVA or T-type) and high voltage activated (HVA).² The HVA group includes the L-, N-, P-, Q-, and R-types and requires a relatively large membrane depolarization to open and displays slow inactivation kinetics. In contrast, the LVA or T-type channels require a smaller membrane depolarization for activation. These channels are so named because they carry a transient current with a low voltage of activation and rapid inactivation.

The T-type channels are further subdivided into three subtypes based on the amino acid sequences of their pore-forming α_1 subunits.³ Three genes that encode these subunits have been identified: CACNA1G for Ca_V3.1 (α_{1G}), CACNA1H for Ca_V3.2 (α_{1H}), and CACNA1I for Ca_V3.3 (α_{11}). These three α_1 subunits are differentially and widely expressed in the central and peripheral nervous systems, cardiac, and vascular smooth muscle, kidneys, sperm, adrenal, and pituitary glands, as well the pancreas.³ Rapid gating kinetics and smaller membrane depolarization thresholds make T-type channels well suited to control neuronal excitability.^{3,4} For example, the roles of T-type channels in regulating sleep rhythms and in certain forms of epilepsy have been established.⁵ More recent evidence of a link between T-type channels and weight maintenance is intriguing and may suggest a potential for treatment of obesity.⁶

The role of T-type channels in nociception is less established, but evidence has been accumulating. It has been demonstrated that T-type channel-dependent, low-threshold Ca²⁺ spikes regulate excitability in DRG neurons. Furthermore, T-type activity is upregulated in neuropathic animals resulting in spontaneous burst firing of action potentials.⁷

The analgesic nitrous oxide selectively blocks DRG T-type currents with no effect on HVA currents at clinically relevant concentrations. A number of anesthetics including isoflurane were found to block T-type currents.⁸

The modestly selective T-type/L-type calcium channel antagonist mibefradil, briefly marketed as Posicor™ for the treatment of hypertension and angina pectoris, was withdrawn from the market less than a year after its introduction due to problems associated with inhibition of cytochrome P450 enzymes.⁹ Nevertheless, mibefradil has been a useful tool for investigating the role of T-type calcium channels in in vitro and in vivo models.

Mibefradil and the T-type antagonist ethosuximide reduce in vivo hyperalgesic responses to thermal or mechanical stimuli induced by chemical agents or experimental nerve injury. Moreover, selective T-type knock-out animals provide further evidence for the role of Ttype calcium channels in peripheral nerve pain signaling.¹⁰

The desire to find novel mechanisms of action and therapeutic targets for the treatment of hypertension, epilepsy, insomnia, obesity, and neuropathic pain has spurred considerable interest in the

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development of novel and selective antagonists to T-type channels.^{11,12} The 5-feature T-type calcium channel pharmacophore model described by Pae and co-workers, consisting of three hydrophobic regions, one hydrogen bond acceptor and one positive ionizable region, captured our attention.^{11b} It was recognized that 2,8-diazaspiro[4.5]decan-1-one, which contains a hydrogen bond acceptor and a positive ionizable atom could serve as a semi-rigid core from which to attach hydrophobic moieties. Furthermore, the spatial arrangement of the attached hydrophobic moieties, hydrogen bond acceptor, and positive ionizable atom appeared to approximate the model described by Pae and co-workers. It was hypothesized that compounds derived from such a scaffold would be potent inhibitors of the α 1H T-type calcium channel.

Herein we describe the design, syntheses, and structure–activity relationship (SAR) of a series of novel 2,8-diazaspiro[4.5]decanone analogs. To test our hypothesis, we coupled commercially available reagents 2-(4-chlorobenzyl)-2,8-diazospiro[4.5]decan-1-one **1** and 4,4-difluorobenzhydryl chloride to form 2-(4-chlorobenzyl)-8-(4,4-difluorobenzhydryl)-2,8-diazaspiro[4.5]decan-1-one **2** (Scheme 1). Compound **2** was found to inhibit the α 1H T-type calcium channel subtype 58 ± 1% at a concentration of 30 nM in patch clamp electrophysiology assays, thus validating our hypothesis (Table 1).¹³ Compound **2** displayed modest (~10-fold) selectivity (T-type/L-type Ca channels) as it inhibited the α 1C L-type calcium channel 31 ± 5% at 0.1 μ M in our patch clamp assay. The potency and T-type/L-type selectivity of **2** was similar to that of mibefradil.¹⁴ The unsubstituted 2-(4-chlorobenzyl)-2,8-diazospiro[4.5]decan-1-one, **1**, was not active at 3 μ M concentration in the α 1H T-type assay.

Next the amide carbonyl hydrogen bond acceptor was removed by treating compound **2** with lithium aluminum hydride to produce the bis-amine **3**. This compound inhibited $\alpha 1H$ (66 ± 8% at 1 µM) but was far less potent than **2**, indicating the importance of the hydrogen bond acceptor for potent T-type activity. Reductive amination of diazaspirodecanone **1** with aldehydes by treatment with sodium triacetoxyborohydride in 1,2-dichloroethane afforded analogs **4–7**. Compound **4** demonstrated that removal of one of the three hydrophobic regions led to a large decrease in $\alpha 1H$ potency (65 ± 3% at 3 µM). Inserting a methylene spacer between the amine



Scheme 1. Reagents and conditions: (a) 4,4-difluorobenzhydryl chloride, Cs_2CO_3 , DMF, 70 °C, 16 h, 17%; (b) LiAlH₄, THF, rt, 16 h, 7%; (c) RCHO, NaBH(OAc)₃, DCE, 5–16 h, 77–99%; (d) (i) isobutyraldehyde, (CH₃)₃SiCN, CH₃CN, rt, 16 h, 51%; (ii) iPrMgBr, THF, rt, 16 h, 21%; (e) 4-fluorobenzoyl chloride, NaOH, THF, H₂O, rt, 1 h, 81%; (f) 4-fluorophenylsulfonyl chloride, NaOH, THF, H₂O, rt, 12 h, 69%.

Percent Inhibition of α 1H and α 1C at concentration in μ M^a

Compd	R	α1H% inhib @	α1C% inhib @
		(µM)	(µM)
1		NA ^b @ 3	
2		58 ± 1 @ 0.03	31 ± 5 @ 0.1
3		66 ± 8 @ 1	
4	4-FPhCH ₂	65 ± 3 @ 3	59±7@3
5	(4-FPh) ₂ CHCH ₂	59 ± 4 @ 0.1	
6	2-EtOPhCH ₂	67 ± 6 @ 3	
7	3-PhOPhCH ₂	56 ± 14 @ 0.3	
8		40 ± 4 @ 0.3	
9		NA @ 1	
10		45 ± 4 @ 3	54±8@3
11	4-ClPhCH ₂ CH ₂	30 ± 11 @ 0.03	
12	3-Cl PhCH ₂	91 ± 1 @ 0.3	
		NA @ 0.03	
13	3-MeOPhCH ₂	52 ± 1 @ 0.03	67 ± 14 @ 0.3
14	MeOCH ₂ CH ₂	28 ± 2 @ 1	
15	MeOCH ₂ CH ₂ CH ₂	44 ± 9 @ 1	58 ± 8 @ 10
16	iPrOCH ₂ CH ₂ CH ₂	76±3@1	56±5@3
17	O(CH ₂ CH ₂) ₂ NCH ₂ CH ₂ CH ₂	35 ± 2 @ 1	
18	iPr	57±6@3	52 ± 3 @ 3
19	t-BuCH ₂ CH ₂	44 ± 13 @ 0.3	60 ± 13 @ 0.3
20	Н	NA @ 3	
21		68±3@1	42 ± 0 @ 0.1
22		59 ± 4 @ 0.3	44 ± 2 @ 0.1

^a For assay conditions see references.

^b NA (not active) denotes <20% inhibition.

and the benzhydryl moiety (compound **5**) led to a modest decrease in α 1H potency (59 ± 4% at 0.1 μ M).

Analogs **6** and **7** attempted to fill the third hydrophobic region by attaching a moiety to the benzyl substituent; α 1H potency increased in relation to the size of the moiety off the benzyl group (**6**, EtO, 67 ± 6 at 3 µM and **7**, PhO, 56 ± 14 at 0.3 µM). A Strecker and Bruylants reaction sequence with diazaspirodecanone **1** afforded analog **8**,¹⁵ which replaced the two phenyl rings of the benzhydryl moiety with two isopropyl groups; this analog inhibited α 1H (40 ± 4% at 0.3 µM) but was less potent than **2**. Acylation and sulfonylation of **1** afforded compounds **9** and **10**, which were inactive and weakly active, respectively.

Compounds **11–20** were prepared to explore changes to the hydrophobic region on the amide side of the spirocycle. Alkylation of ethyl 1-*tert*-butoxycarbonylpiperidine-4-carboxylate with allyl bromide followed by oxidative cleavage afforded the ethyl ester aldehyde (Scheme 2). Reductive aminations and concomitant cyclization afforded Boc-protected diazaspirodecanones. Acid catalyzed deprotections and alkylations with 4,4-difluorobenzhyd-ryl chloride afforded compounds **11–19**. Insertion of a methylene spacer into the 4-chlorobenzyl moiety (**11**, $30 \pm 11\%$ at 0.03 µM) or moving the chloro from the ortho to the *meta* position (**12**, 91 ± 1% at 0.3 µM) reduced α 1H potency, however the 3-methoxy-



Scheme 2. Reagents and conditions: (a) (i) ($(CH_3)_3Si$)₂NLi, allyl bromide, THF, -70-0 °C, 4 h, 97%; (ii) NalO₄, OsO₄(cat), dioxane, H₂O, rt, 16 h, 76%; (b) (i) RNH₂, NaBH(OAC)₃, DCE, rt, 1 h then reflux, 16 h, 45–86%; (ii) CF₃CO₂H, DCM, rt, 1 h, 100%; (iii) 4,4-difluorobenzhydryl chloride, K₂CO₃, DMF, 80 °C, 16 h, 11–21%; (c) 4,4-difluorobenzhydryl chloride, K₂CO₃, DMF, 80 °C, 16 h, 10%.

benzyl analog 13 (52 ± 1% at 0.03 μM) was nearly equipotent against $\alpha 1H$ with compound 2. Like compound 2, compound 13 was found to have modest (~eightfold) T-type/L-type calcium channel selectivity.

Compounds **14–17** incorporated alkyl ether moieties into the hydrophobic region on the amide side of the pharmacophore. The α 1H potency increased with the size of the moiety; methoxyethyl (28 ± 2% at 1 μ M, **14**), methoxypropyl (44 ± 9% at 1 μ M, **15**), and isopropoxypropyl (76 ± 3% at 1 μ M, **16**). Incorporation of a basic amine into this region, morpholinopropyl **17**, resulted in decreased α 1H potency (35 ± 2% at 1 μ M).

Alkyl analogs **18** (iPr, $57 \pm 6\%$ at 3μ M) and **19** (tBuCH₂CH₂, 44 ± 13% at 0.3 μ M) also showed increasing α 1H potency with an increase in size of alkyl substituent but remained much less potent that the benzyl analogs. The unsubstituted amide **20** was prepared by alkylation of commercially available 2,8-diazaspiro[4.5]decan-1-one hydrochloride with 4,4-difluorobenzhydryl chloride, the compound was not active at 3 μ M concentration against α 1H.

Additional SAR regarding the position of the amide carbonyl hydrogen bond acceptor was generated through compounds **21** and **22**. Compound **21** was prepared following the procedure of Smith et al.¹⁶ Reaction of 1-*tert*-butoxycarbonyl-4-piperidone with stabilized Wittig reagent (methoxycarbonylmethylene)triphenyl-phosphorane afforded the unsaturated ester, which underwent Michael addition of nitromethane when refluxed in the presence of 1,1,3,3-tetramethylguanidine (Scheme 3). Subsequent reduction with hydrogen and Raney nickel followed by concomitant cyclization afforded the Boc-protected 2,8-diazaspiro[4.5]decan-3-one. Alkylation with 4-chlorobenzyl chloride and sodium hydride afforded **21**.

Compound **22** was prepared in a three-step sequence from commercially available 2,8-diazaspiro[4.5]decane-2-carboxylic acid *tert*-butyl ester. Alkylation of the amine with 4,4-dif-luorobenzhydryl chloride followed by Boc deprotection and acylation with 4-chlorobenzoyl chloride afforded **22** (Scheme 4).

Compounds **21** and **22** demonstrated the importance of the position of the amide carbonyl for α 1H T-type inhibition. Moving the amide carbonyl from the 1-position of the 2,8-diazaspiro[4.5]decanone to the 3-position, compound **21**, or shifting the amide carbonyl outside of the 2,8-diazaspirodecane, compound **22**, resulted in at least a 10-fold loss in potency (68 ± 3% at 1 μ M,



Scheme 3. Reagents and conditions: (a) (i) Ph₃PCHCO₂CH₃, toluene, reflux, 16 h, 93%; (ii) CH₃NO₂, *N*,*N*,*N'*,*N'*-tetramethylguanidine, reflux, 16 h, 30%; (iii) H₂, Raney Ni, EtOH, 3 d, 75%; (b) (i) NaH, 4-ClBnCl, THF, rt then reflux, 12 h, 99%; (ii) CF₃CO₂H, DCM, rt, 1 h, 94%; (iii) 4,4-difluorobenzhydryl chloride, K₂CO₃, DMF, 80 °C, 5 h, 6%.



Scheme 4. Reagents and conditions: (a) (i) 4,4-difluorobenzhydryl chloride, Cs₂CO₃, DMF, 70 °C, 16 h, 20%; (ii) CF₃CO₂H, DCM, rt, 1 h, 100%; (iii) 4-chlorobenzoyl chloride, NaOH, THF, H₂O, rt, 1 h, 98%.

21) and $(59 \pm 4\%$ at 0.3 μ M, **22**) against the α 1H T-type channel. Analysis against α 1C showed that moving the amide carbonyl position had little effect on the L-type calcium channel. Indeed compounds **21** (42 ± 0% at 0.1 μ M) and **22** (44 ± 2% at 0.1 μ M) were slightly more potent against α 1C than compound **2**.

Based on the 5-feature T-type calcium channel pharmacophore model described by Pae and co-workers, a series of compounds derived from a 2,8-diazaspiro[4.5]decan-1-one core was designed that appeared to approximate the spatial arrangement of the pharmacophore model. Our initial compound to test this hypothesis, **2**, was a potent inhibitor of the α 1H T-type calcium channel and was approximately 10-fold selective over the α 1C L-type calcium channel. Evaluation of the SAR indicated the importance of the amide carbonyl hydrogen bond acceptor and its position in the 2,8-diazaspiro[4.5]decane core for optimal α 1H inhibition. The size of the moiety attached to the 8-N appeared to correlate with α 1H inhibition. Large groups (such as benzhvdrvl) that could effectively fill two hydrophobic regions contributed to increased potency. Moieties that were less effective at interacting with two hydrophobic regions gave less potent compounds. With respect to groups attached to the 2-N (amide nitrogen), the best activity was obtained from benzyl groups; as other groups, in general, afforded decreased potency in relation to the size of the substituent. The 2,8-diazaspiro[4.5]decanones disclosed herein appear to validate the 5-feature T-type pharmacophore model and provide new insights for the development of potent and selective T-type calcium channel antagonists.

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- 13 α1H (Ca_v3.2, T-type) and α1C (Ca_v2.2, L-type) currents were recorded using standard whole-cell electrophysiology with cell lines prepared in house. The subunits for the L-type channel are $\alpha 1C/\alpha 2\delta 1/\beta 2$. 10 mM DMSO solutions of compounds were diluted with external solution. Test compounds were superfused until steady-state inhibition was reached (typically within 1-2 min). Data are reported as percent inhibition compared to control. Protocol for α1H: external solution in mM NaCl (132), KCl (5.4), CaCl₂ (1.8), MgCl₂ (0.8), 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid (HEPES) (10), glucose (5); pH to 7.4 with NaOH. Internal solution in mM CsAsp (110), CsCl (20), ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid (EGTA) (5), MgCl₂ (1), MgATP (5), Na-GTP (0.2), HEPES (10), pH to 7.3 with CsOH. The halfinactivation potential was determined by the potential needed to generate half-maximal current. The cell was held at the half-inactivation potential then stepped to -20 mV for 200 ms at 15 s intervals. Protocol for α 1C: external solution in mM NaCl (132), KCl (5.4), BaCl₂ (10), MgCl₂ (0.8), HEPES (10), glucose (5); pH to 7.4 with NaOH. Internal solution in mM CsAsp (110), CsCl (20), EGTA (5), MgCl₂ (1), MgATP (5), Na-GTP (0.2), HEPES (10), pH to 7.3 with CsOH. The half-inactivation potential was determined by the potential needed to generate half-maximal current. For compound testing the cell was held at -90 mV then stepped to the half-inactivation potential for 8 s. Current was activated by stepping to +25 mV for 200 ms. The protocol was repeated every 20 s.
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