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Design and SAR of selective T-type calcium channel antagonists containing a biaryl sulfonamide core

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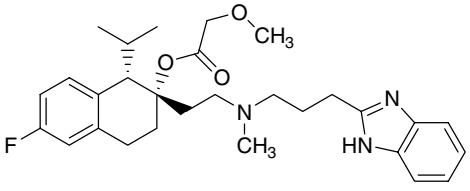
Abstract—T-type calcium channel antagonists were designed using a protocol involving the program SPROUT and constrained by a ComFA-based pharmacophore model. Scaffolds generated by SPROUT were evaluated based on their ability to be translated into structures that were synthetically tractable. From this exercise, a novel series of potent and selective T-type channel antagonists containing a biaryl sulfonamide core were discovered.

Calcium channels open in response to membrane depolarization causing an increase in intracellular calcium, thereby activating many crucial physiological processes such as muscle contraction, hormone secretion, neurotransmission, synaptic plasticity, regulation of enzymatic activities and gene expression.[1] Calcium channels are widely distributed. For example, T-type channels can be found in neurons, heart, kidney, smooth and skeletal muscle, sperm, and endocrine tissues such as the adrenal and pituitary glands and the pancreas. T-type calcium channels are thought to be involved in autonomic nervous functions, and in regulation of cardiovascular activities such as heart rate, arterial and venous smooth muscle innervation and tone.[2]

Drugs such as Mibefradil[3] and Efonidipine[4] (**1** and **2**, respectively, in Fig. 1), which selectively block T-type over L-type calcium channels, have been shown to be useful in treating a variety of disease states. For example, Mibefradil has been shown to be useful for the treatment of hypertension and angina, without showing the side-effects associated with predominant L-type channel blockers such as negative inotropy, reflex tachychardia, vasoconstrictive hormone release or peripheral edema.[5] Furthermore, multiple animal studies with Mibefradil



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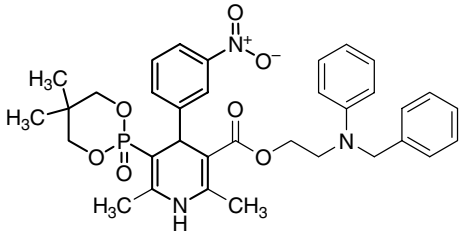

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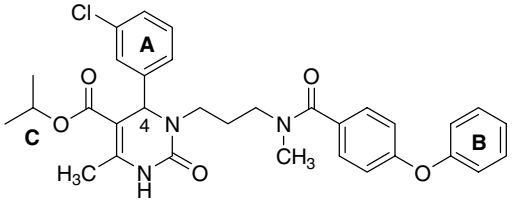

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Figure 1. Structures of Mibefradil[3] (**1**), efonidipine[4] (**2**), and compound **3**.[10]

Keywords: T-type calcium channel antagonists; Molecular modelling; Sulfonamide; COMFA; SPROUT.
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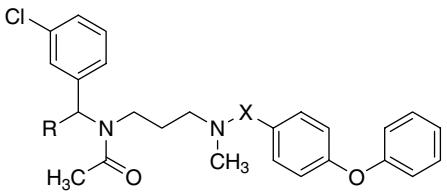
have demonstrated its potential to be cardioprotective. For example, Mibefradil was shown to improve left ventricular remodeling and reduce capillary density in cardiomyopathic hamsters (CMH),[6a] to reduce myocardial fibrosis in aldosterone treated rats,[6b] and to improve myocardial function in dogs following coronary perfusion pressure induced ischemia.[6c] Other studies have pointed to its potential to be renal protective. For example, treatment with Mibefradil caused a greater increase in renal microvascular efferent blood flow versus afferent blood flow in dogs,[7a] reduced glomular damage and protenuria in deoxycorticosterone acetate (DOCA) treated hypertensive rats,[7b,c] and prevented L-NAME-exacerbated nephrosclerosis in spontaneously hypertensive rats.[7d] In addition, unlike L-type calcium blockers, Mibefradil has been shown to be potentially useful in the treatment of heart failure.[8a] For example, Mibefradil improved cardiac function in rat model of chronic heart failure[8b] and helped to normalize Ca^{2+} utilization and improve inotropic effects of β-adrenergic stimulation in hypertrophied rat myocardium.[8c] More recently, both antagonists[9a,b] and dual action agonist/antagonists[9c] of the T-type calcium channel have been shown to have potent anti-proliferative activity against a variety of cancer cell lines. In light of the potential increase in benefit shown by mixed T-type and L-Type calcium channel blockers over predominantly L-type calcium channel blockers in the treatment of hypertension and other disorders, a program to discover proprietary and selective T-type calcium channel blockers was initiated.

The design of biaryl sulfonamide calcium channel antagonists grew out of an effort to simplify the core structure of T-type calcium channel antagonists like compound **3** (Fig. 1; T-EP IC_{50} = 0.25 μM, RA IC_{50} = 2.1 μM),[16,17] which contain a chiral dihydropyrimidinone (DHP).[10] Comparative molecular field analysis (CoMFA)[11] of representative examples from the DHP series, including compound **3**, and related series suggested that the DHP core functioned primarily to display peripheral binding elements in the proper orientation, specifically rings **A** and **B** and, to a lesser extent, the ester side chain **C**.[12]

The first attempt to simplify the core and to eliminate the chiral center was carried out by straightforward deletion of portions of the DHP core and the ester side chain. This approach produced compounds **4** and **5** (Fig. 2, synthesis not shown) that were inactive at a concentration of 1.0 μM. Re-installation of the ester side chain, and hence the chiral center, gave compound **6** (Fig. 2, synthesis not shown), which did not show improved potency.

In an attempt to identify a new, more rigid core, a modeling exercise was carried out using the program SPROUT.[13,14] The input was constructed from compound **3**, where the DHP core, the ester side chain, and the first two methylene units of the side chain containing the biaryl ether were deleted, leaving a 5 Å gap to be filled in by SPROUT (Fig. 3A). The retained portions of the structure, which contained binding elements **A** and **B**, were constrained according to the CoMFA



4: R = H, X = CO (5%)
5: R = H, X = SO_2 (30%)
6: R = $CH_2CO_2CH(CH_3)_2$
X = SO_2 (17%)

Figure 2. Structures of compounds **4**–**6**. The values in parentheses represent percent inhibition at 1 μM inhibitor concentration in the T-EP assay.[16]

model.[12] The output contained >1000 hypothetical scaffolds that were categorized into families according to their structural similarity. The largest families were evaluated for their ability to be translated from the hypothetical scaffold provided by SPROUT into real, synthetically accessible chemical structures suitable for SAR evaluation. Two families satisfied this criterion; one was translated into a biphenyl core (Fig. 3B) and the other into a biaryl sulfonamide core (Fig. 3C). Importantly, both provided an attachment point (denoted **X** in Fig. 3B and C) for the ester side chain **C** contained in compound **3**. Thus, these two cores provided the ability to recapitulate and explore each of the key binding elements, **A**–**C**, defined by the CoMFA model.[12]

To corroborate the choice of these two cores, an additional modeling exercise was carried out. First, small molecule X-ray crystal structures from the public domain containing either the biphenyl or biaryl sulfonamide core were surveyed. The most frequently observed conformation for each was used to validate models of the biphenyl series (e.g., structure **7**, Fig. 4A) and of the biaryl sulfonamide series (e.g., structure **8**, Fig. 4B) having key torsion angles in their lowest energy conformation. Each validated structure was overlaid onto compound **3**, which was constrained according to the CoMFA model used to construct the SPROUT query. This study showed that both cores adopted low energy conformations that displayed the key binding elements A–C similarly to compound **3**. However, the atom-for-atom correspondence between the biphenyl core and compound **3** was less than the correspondence for the biaryl sulfonamide core and compound **3** (Fig. 4A and B). In order to compare the two cores experimentally, synthesis of examples of each was initiated.

The first set of compounds evaluated for antagonist activity against the T-type calcium channel were designed to extend incrementally a phenyl ring away from the core by varying the length of the linker to a position that would be likely to overlap with ring **B** in compound **3** (see Fig. 3A–C). In addition, a few examples in each series were designed to potentially extend beyond ring **B** in compound **3**. The selection of the **X**-group was based on the preference for an isopropyl ester in the DHP series as in compound **3**.[10] Thus, **X** in the biphenyl series was chosen to be the carboxy

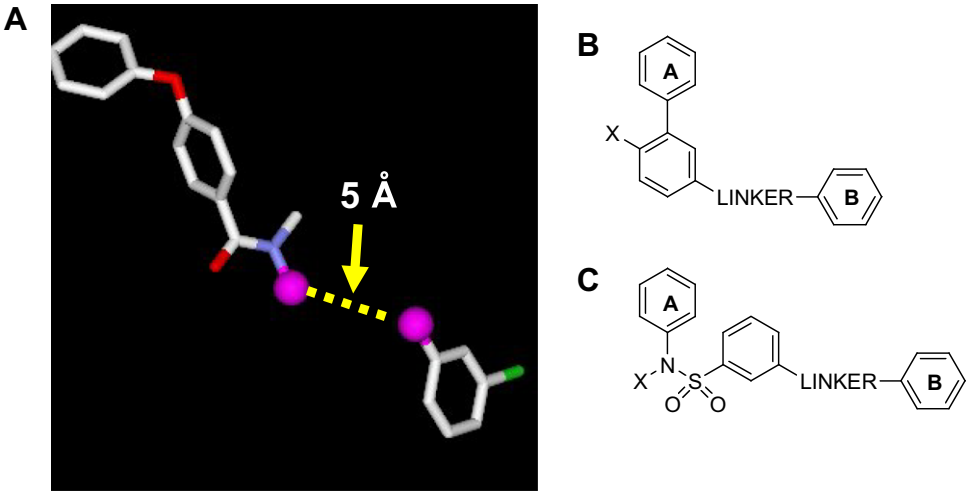


Figure 3. (A) SPROUT input showing the portion of compound **3** retained where the atoms connected by SPROUT are depicted as purple spheres. (B) Biphenyl series. (C) Biaryl sulfonamide series.

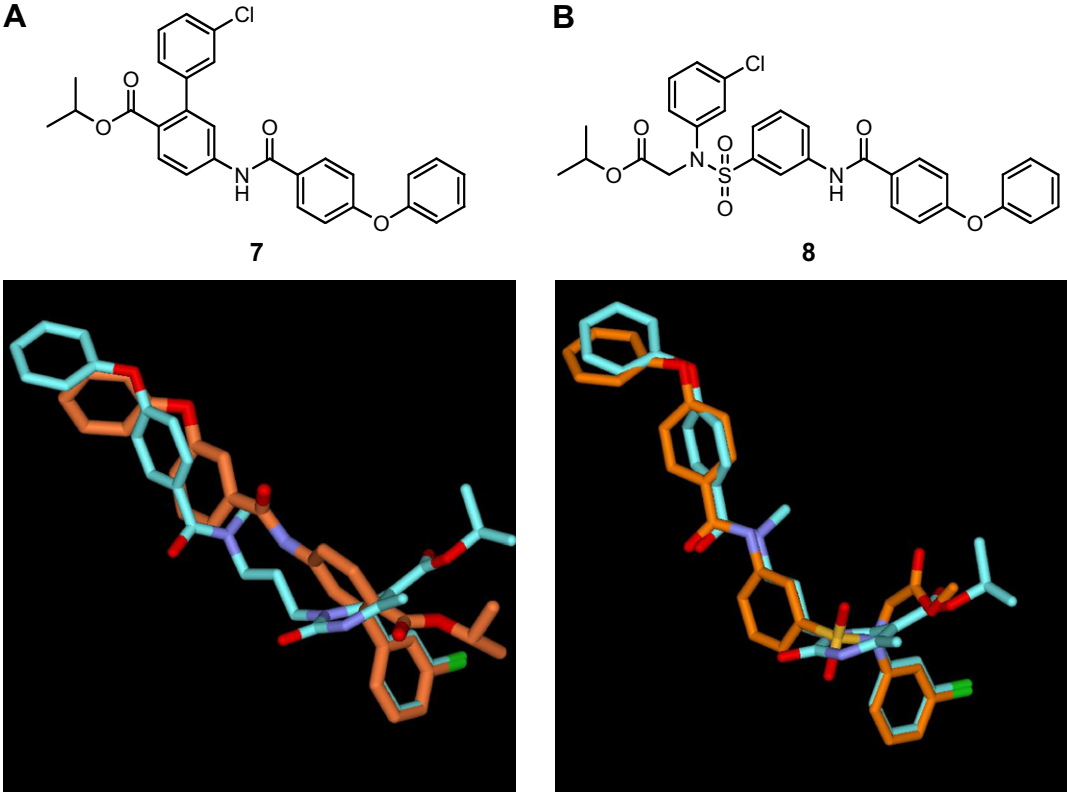


Figure 4. (A) Overlay of compound **3** (magenta) with structure **7** (salmon). (B) Overlay of compound **3** (magenta) with structure **8** (salmon).

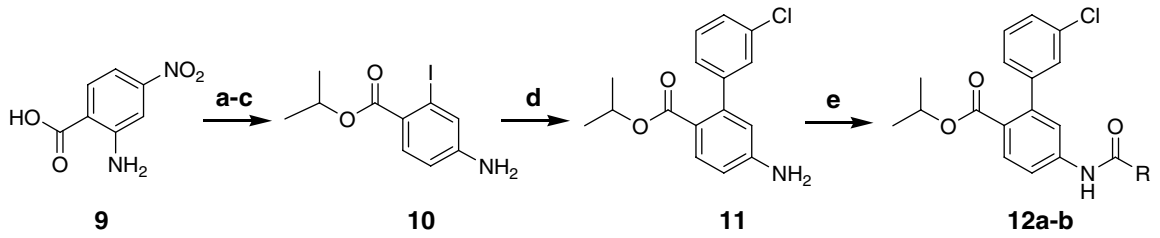
isopropyl group, whereas it was chosen to be the isopropyl acetate group in the biaryl sulfonamide series (Table 1).

Synthesis of the biphenyl series (Scheme 1) began with conversion of 2-amino-4-nitrobenzoic acid (**9**) to 2-iodo-4-nitrobenzoic acid.[15] The resulting iodobenzoic acid was converted to the isopropyl ester and the nitro group was reduced to provide isopropyl 4-amino-2-iodobenzoate (**10**). Coupling of **10** with 3-chlorophenyl boronic acid provided the biphenyl aniline **11**, which was condensed with a diverse set of carboxylic acids,

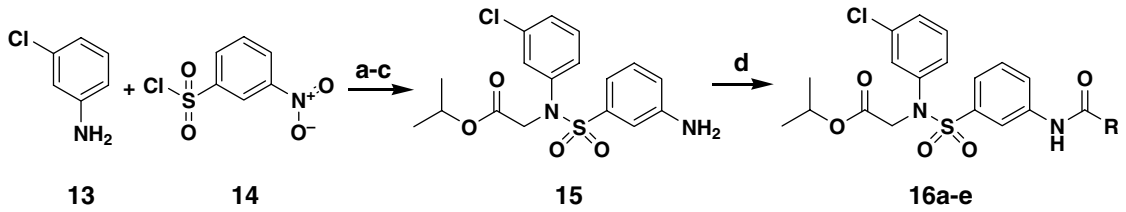
Table 1. T-type patch clamp and rat aorta strip data

Compound	R	IC_{50}[a] (μM)		RA/T-EP
		T-EP[16]	RA[17]	
12a	CH_2CH_2Ph	(6)		
12b	$CH_2N(CH_3)CO_2CH_2Ph$	(24)		
16a	CH_3	(0)		
16b	CH_2Ph	(40)		
16c	CH_2CH_2Ph	0.54	>30	>55
16d	$CH_2N(CH_3)CO_2CH_2Ph$	0.24	15	62
16e	$CH_2CH_2NHCO_2CH_2Ph$	0.42	17	41

[a] Values contained in parentheses are percent inhibition at 1 μM inhibitor concentration.



Scheme 1. Synthesis of the biphenyl series. Reagents and conditions: (a)[15] $NaNO_2$, 9 N H_2SO_4, NaI, urea (50%); (b) isopropanol, cat. H_2SO_4, reflux (66%); (c) Fe°, HOAc, H_2O, rt (80%); (d) 3-chlorophenyl boronic acid, $PdCl_2$(dppf), K_3PO_4, dioxane, 100 °C (67%); (e) diverse acids, EDCI, HOAt, *N*-Me-morpholine, CH_2Cl_2/DMF 5:2, rt (50–90%).



Scheme 2. Synthesis of the biaryl sulfonamide series. Reagents and conditions: (a) TEA, CH_2Cl_2, rt (85%); (b) isopropyl bromoacetate, NaH, DMF, rt (50%); (c) Fe°, HOAc, H_2O, rt (90%); (d) diverse acids, EDCI, HOAt, 4-Me-morpholine, CH_2Cl_2, rt, 12 h (40–70%).

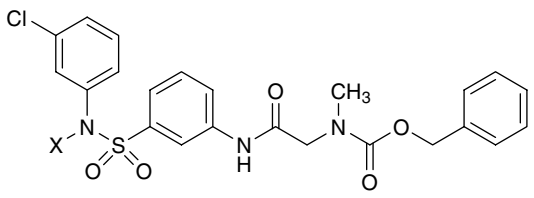
herein exemplified by compounds **12a** and **12b**. Synthesis of the biaryl sulfonamide series (Scheme 2) was initiated by coupling 3-chloroaniline (**13**) with 3-nitrophenyl-sulfonyl chloride (**14**) followed by sequential alkylation of the sulfonamide nitrogen with isopropyl bromoacetate and reduction of the nitro group to give aniline **15**, which was coupled with a diverse set of acids to provide compounds **16a–e**. Synthesis of compounds **17a–g** (see Table 2), where the isopropyl acetate group is replaced by other side chains, was accomplished by straightforward extension of the chemistry used to synthesize compounds **16a–e**.

Compounds were first evaluated for their ability to inhibit the T-type calcium channel at a concentration of 1.0 μM using a patch clamp assay (T-EP).[16] T-EP IC_{50} values were determined for compounds that gave percent inhibition $\geqslant$50% at this concentration. Compounds with IC_{50} values <1 μM were further evaluated in a rat aorta strip assay (RA),[17] which served to measure functional L-type calcium channel antagonist activity. Selectivity of the compounds for the T-type calcium channel was estimated by calculating the ratio (RA IC_{50})/(T-EP IC_{50}).

The first set of compounds from the biphenyl series showed poor inhibition. Two examples, compounds **12a** and **12b**, are representative of the entire set, and showed only 6% and 24% inhibition at 1 μM concentration, respectively. The percent inhibition of all other compounds submitted from the biphenyl series fell within this range, and no clear SAR was apparent. This series was discontinued as a result. In contrast, the first set of compounds submitted from the biaryl sulfonamide series contained potent T-type channel antagonists. For example, compounds **16d** and **16e** gave 78% and 73% inhibition, respectively, at 1 μM concentration, and had IC_{50} values equal to 0.24 and 0.42 μM, respectively. Importantly, both were selective for the T-type channel (62- and 42-fold, respectively). For comparison, Mibefradil inhibits the T-type and L-type channels with IC_{50} values of 0.13 and 7 μM, respectively (data for each obtained by patch clamp technique),[3] whereas the T-EP and RA values for the individual enantiomers of compound **3** were 0.18 and 2.1 μM and 0.65 and 3.8 μM, respectively.[18] Importantly, this series provided a clear SAR, which was absent from the biphenyl series. For example, compounds **16a**–**16c**, which contain aliphatic side chains of increasing length, showed incremental improvement in antagonist potency from inactive (**16a**) to having an IC_{50} = 0.54 μM (**16c**). While the SAR is limited to relatively few examples, there was also an indication that there exists an optimal R-group length, which is suggested by comparing compounds **16c–e** (T-EP IC_{50} = 0.54, 0.24, and 0.42 μM, respectively).

Additional SAR studies (Table 2) with the biaryl sulfonamide series focused on replacing the acetic ester side chain (**X** in Fig. 3C). Replacing the isopropyl ester of **16d** with a carboxylic acid (**17a**) or ethyl ester (**17b**) resulted in compounds with significantly lower potency. Isosteric replacement of the isopropyl acetate of **16d** with a purely aliphatic side chain (**17c**) gave a compound equal in potency (IC_{50} = 0.18 μM, 67-fold T-type selective), whereas replacement of the isopropyl ester with *N*-isopropyl amide (**17d**) reduced the potency by almost 10-fold. Addition of a basic side chain (**17f**) resulted in a substantial loss in potency. The most potent and selective compound discovered in this series (**17e**; IC_{50} = 0.11 μM, 109-fold T-type selective) contained a benzyl group in place of the isopropyl acetic acid side chain.

Table 2. T-type patch clamp and rat aorta strip data



Compound	X	IC_{50}[a] (μM)		RA/ T-EP
		T-EP[16]	RA[17]	
16d	CH_2CO_2i-Pr	0.24	15	62
17a	CH_2CO_2H	(11)		
17b	CH_2CO_2Et	(35)		
17c	$CH_2CH_2CH_2CH(CH_3)_2$	0.18	12	67
17d	CH_2CONi-Pr	1.7	>30	>17
17e	CH_2Ph	0.11	12	109
17f	$CH_2CON(H)CH_2CH_2N(CH_3)_2$	(22)		

[a] Values contained in parentheses are percent inhibition at 1 μM inhibitor concentration.

Application of the design paradigm described in this paper resulted in the discovery of novel, potent T-type calcium channel antagonists, the biaryl sulfonamides, which are selective for the T-type calcium channel.[19] The successful translation from design to identification of potent antagonists may be attributed to combining the CoMFA constrained SPROUT design work with validation of the low energy conformations through comparison with X-ray crystal structures of small molecules containing the biaryl sulfonamide core. Thus, the biaryl sulfonamides disclosed herein provide an additional chemotype that may be used to discover T-type selective antagonists for the treatment of cardiovascular and other disorders.

Acknowledgment

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16. **T-type calcium channel assay conditions** (T-EP): Whole cell currents were recorded from a HEK-293 stable cell line transfected with the human α1H clone using standard whole cell patch clamp techniques. Cells were held at −80 mV and stepped to −30 mV at 0.1 Hz frequency to activate inward Ca^{2+} current using 5 mM Ca^{2+} as the charge carrier. All records were obtained at room temperature (21 °C). Data were digitized at 5 kHz and sampled at 10 kHz. Peak inward currents were measured before and after addition of compound to the bathing solution.
17. **Rat aorta strip assay conditions** (RA): Aortas from rats were dissected, cut into rings, and the endothelium denuded by rubbing. The rings were then attached to force transducers in a tissue bath containing a physiological saline solution. The rings were incubated with KCl to achieve a near maximal contraction, and test compounds were added at increasingly higher doses to determine the IC_{50} for inhibition of force.
18. NOTE: The absolute configurations for the individual enantiomers of compound **3** were not determined.
19. Additional selective T-type calcium channel antagonists have been reported since the completion of this work: (a) Ku, I. W.; Cho, W.; Doddareddy, M. R.; Jang, M. S.; Keum, G.; Less, J.-H.; Chung, B. Y.; Kim, Y.; Rhim, H.; Kang, S. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5244; (b) Kim, H. S.; Kim, Y.; Doddareddy, M. R.; Seo, S. H.; Rhim, H.; Tae, J.; Pae, A. N.; Choo, H.; Cho, Y. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 476.