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Synthesis and biological evaluation of pyrrolidine derivatives as novel and potent sodium channel blockers for the treatment of ischemic stroke

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ABSTRACT

A novel series of pyrrolidine derivatives as Na^+ channel blockers was synthesized and evaluated for their inhibitory effects on neuronal Na^+ channels. Structure–activity relationship (SAR) studies of a pyrrolidine analogue **2** led to the discovery of **5e** as a potent Na^+ channel blocker with a low inhibitory action against human ether-a-go-go-related gene (hERG) channels. Compound **5e** showed remarkably neuroprotective activity in a rat transient middle cerebral artery occlusion (MCAO) model, suggesting that **5e** would act as a neuroprotectant for ischemic stroke.

Ischemic stroke is a leading cause of death and long-lasting disability in developed countries. Neuroprotection is widely recognized to be a potential strategy for the treatment of ischemic stroke,[1] and considerable efforts have been devoted to the development of neuroprotective agents, such as *N*-methyl-D-aspartate (NMDA) receptor antagonists, α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid (AMPA) receptor antagonists, and Ca^{2+} channel blockers.[2] However, none of them has been approved for the treatment of ischemic stroke because of their limited efficacy or unfavorable risk-benefit ratio in clinical trials.[3]

As an alternative neuroprotectant, Na^+ channel blockers have been reported (Fig. 1).[4] Although several Na^+ channel blockers have been tested in clinical trials, some of them were unsuccessful because of their limited efficacy[5] and/or adverse effects such as heart-conduction disorders, QT prolongation,[6] which was caused by blocking of hERG K^+ channels.[7] Indeed, enecadin,[4c] crobenetine,[4d] SUN N8075,[4e] and our previous lead **1**[4f] displayed the potential risk of QT prolongation.[8] Therefore, potent Na^+ channel blockers with a low risk of QT prolongation are strongly desired. In the course of our study to develop Na^+ channel blockers, we became interested in a novel pyrrolidine analogue **2** as a tractable lead having low molecular weight and three sites available for derivatization (Fig. 2). Here, we describe synthesis and biological evaluation of a series of novel pyrrolidine derivatives.

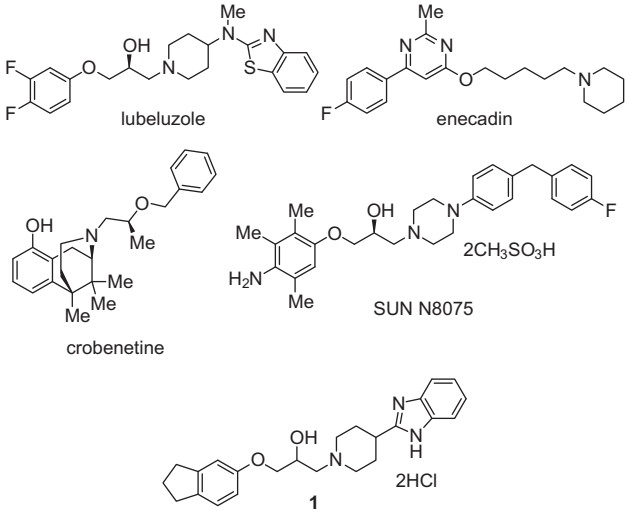

Figure 1. Reported sodium channel blockers.

Scheme 1 illustrates the synthesis of 4-phenylpyrrolidines **5a–e** and **6**. All compounds were prepared as racemates. Stereospecific [3+2]-cycloaddition of *trans*-1-nitro-2-phenylethylene and *N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]benzylamine, an azomethine ylide equivalent, afforded *trans*-3-nitropyrrolidine **3** in a

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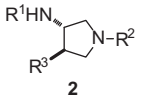
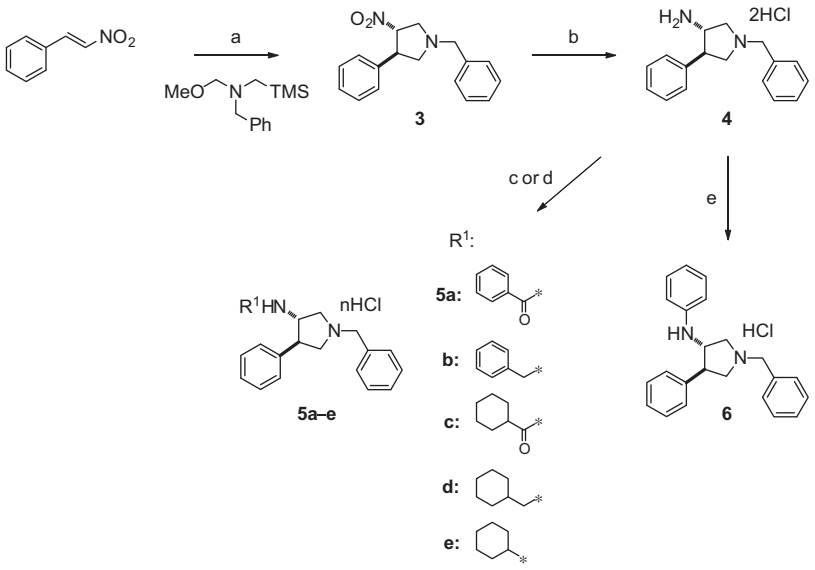
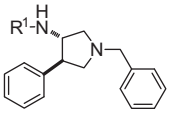


Figure 2. Our new pyrrolidine analogue **2**.



Scheme 1. Reagents and conditions: (a) trifluoroacetic acid, CH_2Cl_2 (62%); (b) (i) Fe, acetic acid, 2-PrOH/H_2O, 80 °C, (ii) 4 N HCl/EtOAc, EtOAc (90%); (c) (i) benzoyl chloride or cyclohexanecarbonyl chloride, Et_3N, CH_2Cl_2, (ii) BH_3·THF, THF, reflux, (iii) 4 N HCl/EtOAc, EtOAc (35–62%); (d) (i) cyclohexanone, $NaBH(OAc)_3$, acetic acid, acetonitrile, (ii) 4 N HCl/EtOAc, EtOAc (65%); (e) (i) iodobenzene, CuI, K_3PO_4, ethylene glycol, 80 °C, (ii) 4 N HCl/EtOAc, EtOAc (35%).

Table 1
Inhibition of Na^+ and hERG channels of 4-phenylpyrrolidines **5a**–**e** and **6**[a]



Compound	R^1	Anti-veratridine[b] IC_{50} (μM)	hERG[c] (% inhibition, 1 μM)
5a		1.90	45
5b		0.64	57
5c		0.48	31
5d		0.32	60
5e		0.51	8.4
6		0.48	43

[a] All compounds are racemic and were tested using the hydrochlorides or dihydrochlorides except **5a** and **5c**.
[b] Inhibitory activity on veratridine-induced depolarization in rat cerebrocortical synaptosomes using voltage-sensitive dye Rhodamine 6G.[10]
[c] Inhibition rates were determined by a voltage patch clamp technique using HEK293 cells expressing hERG channels.

moderate yield.[9] The nitro group of **3** was reduced with iron and acetic acid to give **4**, which was then converted into 3-amidopyrrolidines **5a** and **5c** by acylation with the corresponding acid chlorides. Reduction of the amide group of **5a** and **5c** yielded 3-aminopyrrolidines **5b** and **5d**, respectively, and reductive alkylation of **4** with cyclohexanone provided **5e**. Compound **6** was obtained by copper-catalyzed coupling of **4** and iodobenzene.

The effects of **5a**–**e** and **6** on Na^+ channels were evaluated by inhibitory action on veratridine-induced depolarization in rat cerebrocortical synaptosomes (Table 1).[10] Compounds **5c** and **5d**