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SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP OF SUBSTITUTED 1,2,3,4-TETRAHYDROISOQUINOLINES AS N-TYPE CALCIUM CHANNEL BLOCKERS

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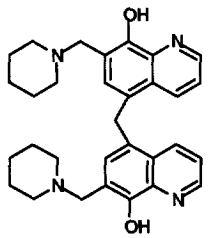
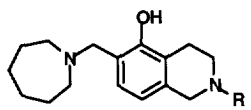
Abstract: Voltage Activated Calcium Channel (VACC) blockers have been demonstrated to have utility in the treatment of pain and stroke. A series of aminomethyl substituted isoquinolinol derivatives with potent functional activity for N-type VACC's have been identified. Their synthesis and preliminary pharmacology are discussed herein.

A number of distinct classes of voltage sensitive calcium channels (VSCC) can be found in neurons. These calcium channels regulate intracellular calcium concentration, which in turn controls various important neuronal functions such as hormone secretion, neurotransmitter release, metabolism, and cyctoskeletal function.[1] It is well documented in the literature that immediately following an ischemic or traumatic event, pathologically high calcium concentrations are reached in the surrounding tissues. Sustained elevation of neuronal calcium concentration initiates a cascade of biochemical events such as formation of free radicals, activation of proteases, and breakdown of neuronal membranes, which ultimately lead to cell death. ω-Conotoxin MVIIA, a 25 amino acid-residue containing peptide with 3 disulfide bonds, is a selective N-type voltage-sensitive calcium channel blocker. Its synthetic equivalent, SNX-111,[2] has demonstrated utility in animal models of traumatic brain injury, focal cerebral ischemia, and pain.[3] It is also currently in clinical trials for the treatment of ischemia-induced brain injury and chronic pain.[4]



PD029361



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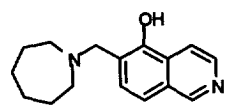

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Due to the promising efficacy shown by N-channel blockers, we initiated a chemistry program to develop small molecule blockers of N-type calcium channels. PD029361[5] was identified as a chemical lead by

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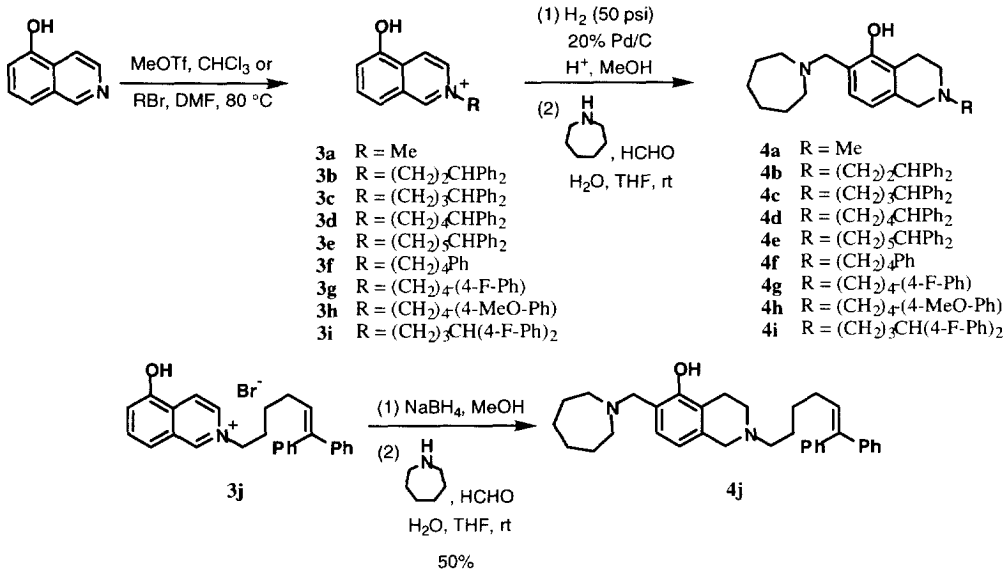
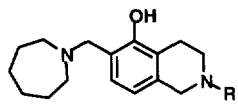
high volume screening of our compound library. It has moderate activity (IC_{50} = 4.4 μM) in blocking N-type calcium channel functionally in the IMR-32 human neuroblastoma cell assay.[6] While investigating the SAR of PD029361, we discovered several *N*-substituted tetrahydroisoquinoline derivatives (**1**) that are also quite potent in the IMR-32 assay.



These tetrahydroisoquinolines were synthesized by *N*-alkylating 5-hydroxyisoquinoline with the appropiate alkyl bromides[7] in DMF at 80 °C, or with methyl triflate in chloroform at 0 °C in the case where R is methyl, to from the corresponding 5-hydroxyisoquinolinium salts **3a-j** in 80-90% yield. The isoquinolinium salts **3a-i** were then reduced to the tetrahydroisoquinoline derivatives by catalytic hydrogenation. In the case of **3j**, the isoquinolinium bromide was reduced with excess sodium borohydride in methanol at 0 °C to the corresponding tetrahydroisoquinoline where the diphenylethene moiety remained intact. These *N*-alkyl-5-hydroxyisoquinolines were then treated with formaldehyde and hexamethyleneimine to give the Mannich products **4a-j** in 50-60% yield.

These *N*-alkyl-5-hydroxy-1,2,3,4-tetrahydroisoquinolines were evaluated in the IMR-32 assay for potencies in blocking N-type calcium channel. Unlike PD029361 (IMR-32 IC_{50} = 4.4 μM), the parent 6-aminomethyl-5-hydroxyisoquinoline **2**[8] showed extremely weak activity in the IMR-32 assay. The methyl analog **4a** is totally inactive. However, when a diphenylalkyl side chain was introduced onto the tetrahydroisoquinoline ring, the calcium channel blocking activity of these compound began to increase. The diphenylbutyl substitution (**4c**) seemed to be optimal. Replacing the diphenylbutyl side chain with the diphenylpentyl group (**4d**) resulted in a 10-fold decrease in potency. However, with the diphenylhexyl substitution in **4e**, the compound did regained some of the lost potency. Introduction of unsaturation on the diphenylhexyl side chain resulted in a small decrease in activity. The diphenylbutyl analogs are more potent than the corresponding

phenylbutyl analogs (**4c** vs **4f**; **4i** vs **4g**). In the phenylbutyl series, the *p*-fluoro substitution on the phenyl ring increased the calcium channel blocking activity of the compound (**4f** vs **4g**). Unfortunately, this increase of activity is not transferable to the diphenylbutyl compounds (**4c** vs **4i**).



Compound	R	IMR-32 IC_{50} (μM)
2	–	35
4a	Me	> 100
4b	$(CH_2)_2CHPh_2$	7.4
4c	$(CH_2)_3CHPh_2$	0.46
4i	$(CH_2)_3CH(4\text{-F-Ph})_2$	1.3
4d	$(CH_2)_4CHPh_2$	4.8
4e	$(CH_2)_5CHPh_2$	1.1
4j	$(CH_2)_4CH{=}CPh_2$	2.5
4f	$(CH_2)_4Ph$	15
4g	$(CH_2)_4$-(4-F-Ph)	5.1
4h	$(CH_2)_4$-(4-MeO-Ph)	10

In summary, a series of 5-hydroxy-1,2,3,4-tetrahydroisoquinoline based N-type calcium channel blockers was discovered. These compounds are potent and in situ active in the IMR-32 assay. Compound **4c**, the diphenylbutyl substituted analog on the tetrahydroisoquinoline nitrogen, is the most active compound in this series with an IC_{50} value of 0.46 μM.

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References and Notes:

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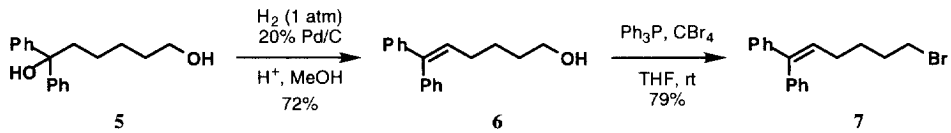
6. N-Type Ca^{2+} channel blocking potencies of compounds were measured using the fluorescent Ca^{2+} indicator Indo-1 in IMR-32 human neuroblastoma cells in the presence of 5 μM of nitrendipine to block L-type channels.

7. 1,1-Diphenyl-6-bromohex-1-ene (**7**) was prepared from 1,1-diphenyl-1,6-hexan-1,6-diol (**5**) in a 2-step sequence. The diol **5** was dehydrated with 20% Pd/C in methanol under hydrogen atmosphere (1 atm) to give the unsaturated alcohol **6** (the saturated alcohol by-product was removed by silica gel chromatography). The alcohol **6** was converted to the bromide **7** by carbon tetrabromide in the presence of triphenylphosphine.[9]



5 6 7

8. The isoquinoline **2** was prepared in 60% yield from 5-hydroxyisoquinoline, formaldehyde and hexamethyleneimine in THF under standard Mannich conditions.

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