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SYNTHESIS OF AZIDO DERIVATIVES OF SEMOTIADIL, A NOVEL 1,4-BENZOTHIAZINE CALCIUM ANTAGONIST, FOR PHOTOAFFINITY PROBES OF CALCIUM CHANNELS

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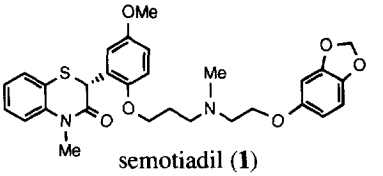
Abstract: Aliphatic and aromatic azido derivatives of semotiadil (**1**), a novel calcium antagonist with a 1,4-benzothiazine skeleton, were synthesized for developing photoaffinity probes of L type calcium channels. The azidophenoxy derivative **12** proved to be a potent calcium antagonist and its [^{3}H]-labeled compound **16** would be a useful tool to clarify the binding sites of **1** to the calcium channels.

Calcium antagonists are classified into three main types based on their structures: dihydropyridines, benzothiazepines and phenylalkylamines, which are represented by nifedipine, diltiazem and verapamil, respectively. Each type has distinct tissue selectivity between blood vessels and cardiac tissues from the others. Those calcium antagonists bind to the different sites of α_1 subunit of L type calcium channels,[1] and thereby they show allosteric interactions to one another. Diltiazem enhances the binding of dihydropyridines and slows their dissociation, while verapamil decreases the binding of dihydropyridines and enhances their dissociation.[2]



semotiadil (**1**)

Figure 1

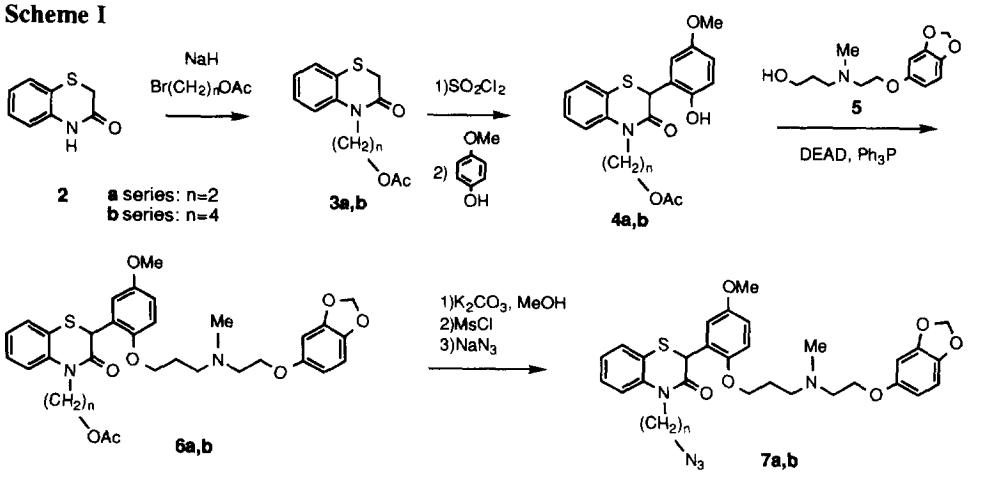
Semotiadil (SD-3211, **1**) is a novel calcium antagonist with a unique 1,4-benzothiazine structure (Figure 1).[3] The compound has longer-lasting activity than diltiazem and nifedipine, and shows higher selectivity for blood vessels against cardiac tissues than diltiazem and lower selectivity than nifedipine.[4] Furthermore, the agent **1** increases the dissociation rate of [^{3}H]-PN200-110, a dihydropyridine derivative, from the specific binding sites, as in the case of verapamil. In contrast, **1** shows no apparent effect on the verapamil-induced inhibition of [^{3}H]-PN200-110 binding to the calcium channels.[5] These results suggest that semotiadil binds to calcium channels at the sites different from those of known calcium antagonists.

The binding sites of dihydropyridines, benzothiazepines and phenylalkylamines have been determined by defined proteolysis and sequence-directed antibodies after photoaffinity labeling of calcium channels.[6,7,8] In

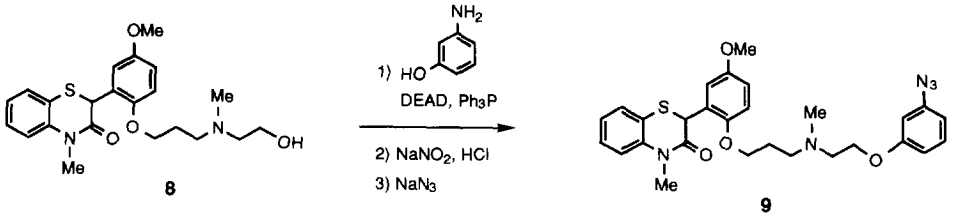
these earlier studies, azido or diazirine derivatives of the calcium antagonists were used for photoaffinity labeling: typical compounds are azidopine,[9] diazipine,[10] azidobutyryldiltiazem[11] and LU49888.[12] To determine the binding sites of compound **1**, we synthesized azido derivatives of **1** and evaluated their calcium antagonist activity.

Information on the structure-activity relationships (SARs) of **1** was limited to the side chain 3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl moiety: namely, substitution of the 3,4-(methylenedioxy)phenoxy moiety with a mono-, di- or tri- methoxyphenoxy group mostly retained the activity, and displacement of the *N*-methyl group on the side chain with an *N*-isopropyl group yielded one-order less potency.[3] These results suggest that displacement of the methylenedioxy moiety with an azido group may retain potency and that substitution of the *N*-methyl group on the side chain with an azidoalkyl group may decrease potency. In contrast, it was of interest to introduce an azidoalkyl group into the 4-position of the benzothiazine skeleton, whereas no SAR data were available on the substituent at that position. Thus, we designed 4-azidoethyl and 4-azidobutyl benzothiazines **7a,b** and 3-azidophenoxy compound **9**. First, we synthesized these compounds in racemic forms and then evaluated their calcium antagonist activity by a literature method.[3] The compounds **7a,b** and **9** showed potent activity (Figure 2). Compound **7a** gradually decomposed to unknown compounds at 4℃. We selected compound **9** and then developed both synthetic routes for its enantiomer **12** with the same *R*-configuration to that of **1** and for the [^{3}H]-labeled compound **16**. The *R*-isomer **12** was twice as potent as the corresponding *RS*-compound **9**. Compounds **1** and **12** replaced [^{3}H]-semotiadil binding to

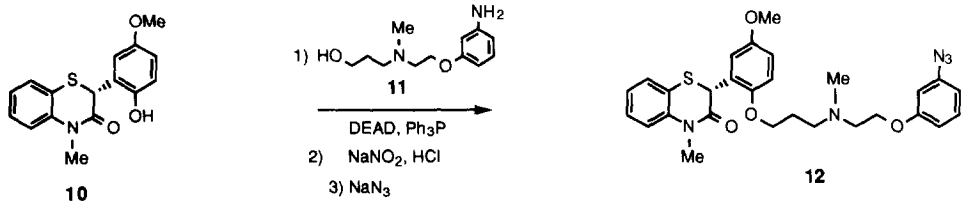
Scheme I



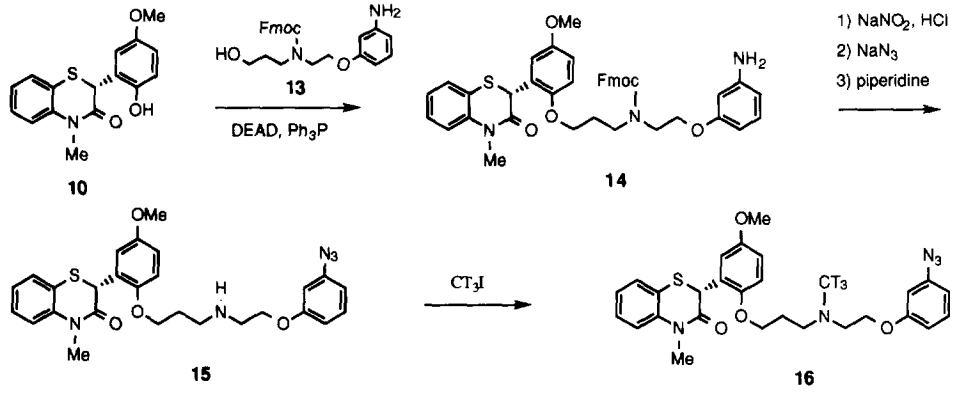
Scheme II



Scheme III



Scheme IV



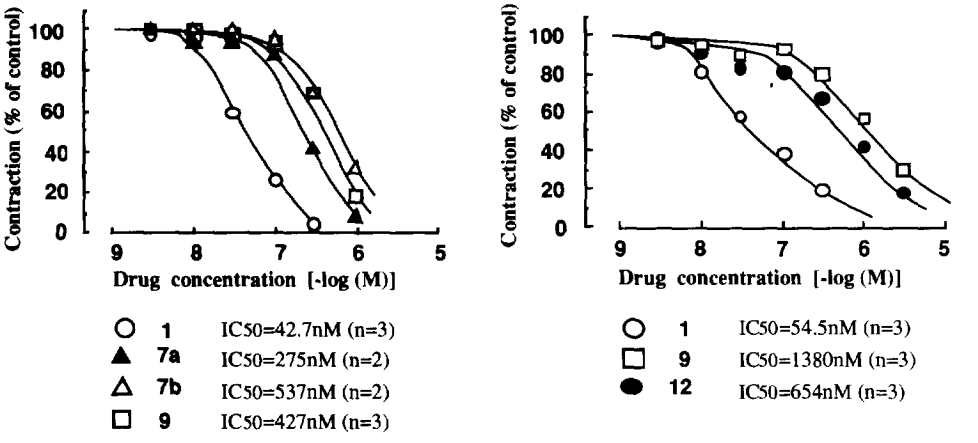


Figure 2. Calcium antagonist activity

membrane preparation of rabbit skeletal muscles, indicating that both drugs bind to calcium channels at the same sites (Figure 3).

Synthetic routes of those compounds are outlined in Schemes I-IV. ω-Acetoxyalkylbenzothiazines **3a,b**, prepared from **2**, were converted into 2-phenylbenzothiazines **4a,b** by treatment with sulfuryl chloride

and subsequent Friedel-Crafts type reaction.[13] The compounds **4a,b** were condensed with the propanol derivative **5** under the Mitsunobu reaction to give **6a,b**. After hydrolysis of **6a,b**, the resulting compounds were successively treated with methanesulfonyl chloride and sodium azide to afford **7a,b** (Scheme I). The azidophenoxy derivative **9** was synthesized through the diazonium salt intermediate derived from compound **8** by two steps (Scheme II). The enantiomer **12** was prepared from the optically active compound **10**[3] (Scheme III). The [^{3}H]-labeled compound **16** was synthesized as follows. The Mitsunobu reaction of **10** with *N*-Fmoc-aminopropanol **13** gave **14**, which was converted into **15**. Alkylation of the compound **15** with [^{3}H]-iodomethane afforded **16** (Scheme IV).

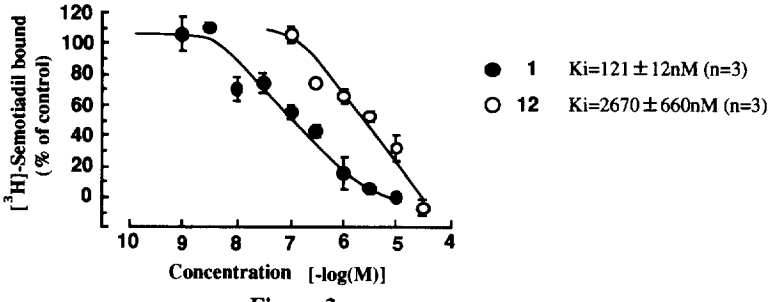


Figure 3

The [^{3}H]-labeled compound **16** could bind to skeletal muscle calcium channels when irradiated by UV light. Analysis of the binding sites of **16** to the α_1 subunit of calcium channels will be reported elsewhere.

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