Pergamon

*Bioorganic & Medicinal Chemistry Letters*, Vol. 4, No. 2, pp. 351-354, 1994

0960-894X/94 $6.00+0.00

0960-894X(93)E0087-H

# Heterocyclic Guanidines as Calcium Antagonists

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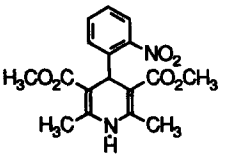
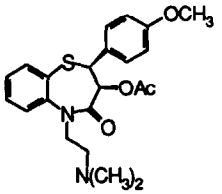
**Abstract:** A series of 2-(1,1-diphenylalkylamino)-1,3-diazaheterocycles was prepared and evaluated as antagonists of L-type calcium channels. Of the eighteen derivatives in this series, tetrahydropyrimidine **6h** and hexahydro-1,3-diazocine **6n** were the most potent calcium antagonists, being essentially equipotent to both diltiazem (**2**) and amidine **5**.

There are currently a substantial number of compounds which have been reported as antagonists of L-type calcium channels. These compounds may interact with six or more discrete binding sites on this channel.[1] In spite of the structural diversity of these agents, from a therapeutic standpoint, the area is still dominated by the 1,4-dihydropyridines, e.g. nifedipine (**1**), the benzothiazepines, e.g. diltiazem (**2**), and the phenylalkylamines, e.g. verapamil (**3**). Our interest in calcium channel antagonists evolved from the pharmacology we observed with a series of heterocyclic amidines. Selected members of this series were shown to possess activity as



**1**



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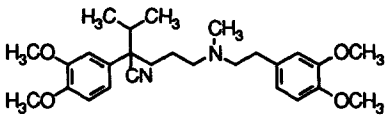

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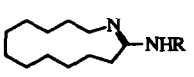
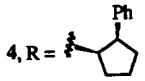
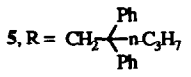
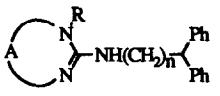




**4**, R =



**5**, R =



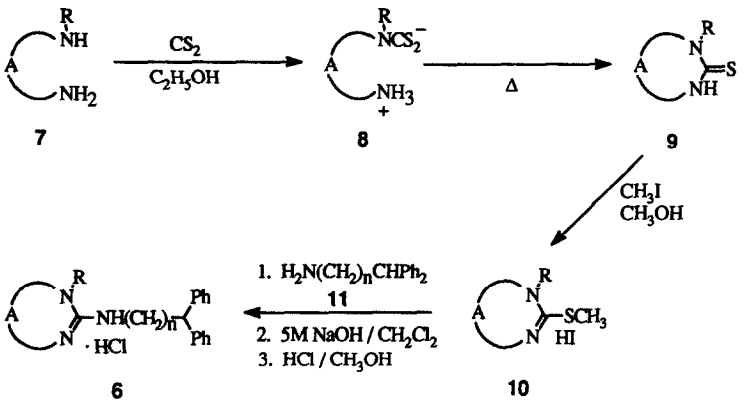
**6**

hypoglycemic,[2-6] diuretic,[6] and antiinflammatory agents[6] as well as inhibiting blood platelet aggregation.[6,7] Subsequent investigations revealed that amidine **4** inhibited stimulated adenylate cyclase activity[8-11] and

produced negative inotropic and chronotropic effects on isolated guinea pig hearts which could be reversed by calcium.[12] More recently we reported[13] that amidine **5** was a calcium antagonist *in vitro*, with an activity profile and potency that was similar to diltiazem (**2**). Pursuant to these investigations, we now report the calcium antagonist properties associated with a related series of heterocyclic guanidines **6**.

The guanidines which were evaluated in this study were prepared as depicted in Scheme I. Thus, reaction of diamines **7** with carbon disulfide afforded the dithiocarbamic acid inner salts **8** which were subsequently thermalized yielding the cyclic thioureas **9**. Methylation of **9** using iodomethane afforded the corresponding isothiourea hydroiodides **10**. Displacement of methyl mercaptan from **10**[14] with various diphenylalkylamines **11** gave the desired guanidine hydroiodides which were neutralized and converted to the corresponding hydrochlorides **6** (Table I).

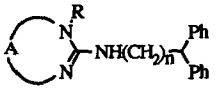
**Scheme I**




The calcium channel-blocking effects of the compounds presented in Table I were assessed in potassium ion depolarized guinea pig ileum strips by recording the contractile responses produced by varying concentrations of calcium chloride. The potencies are expressed as $pA_2$ values which were determined according to either the method of Van Rossum[15] or by Schild plot analysis.[16]

Contained in generic structure **6** are three structural variables. Two of these variables produced a clear impact on the observed activity. First, methylation of a ring nitrogen invariably led to a decrease in activity when compared to the corresponding unsubstituted compounds (compounds **6d**, **6e**, **6i**, **6j** versus compounds **6b**, **6c**, **6g**, **6h**). Second, increasing the length of the alkyl chain connecting the guanidine and benzhydryl moieties generally resulted in an increase in activity. For example, diphenylethyl-substituted guanidine **6b** was more active than the corresponding benzhydryl-substituted guanidine **6a**. Likewise, diphenylpropyl-substituted guanidines (compounds **6c**, **6e**, **6h**, **6j**, **6l**, **6n**, **6r**) were more potent than the corresponding diphenylethyl-substituted guanidines (compounds **6b**, **6d**, **6g**, **6i**, **6k**, **6m**, **6q**). In the only case we examined, this trend seemed to plateau since diphenylbutyl-substituted guanidine **6f** was only slightly more active than the corresponding diphenylpropyl-substituted guanidine **6e**. Finally, changing the size of the guanidine moiety gave

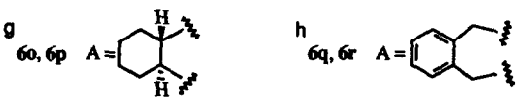
**Table I.** Heterocyclic Diphenylalkylguanidines



6

| Compound[a] | A | R | n | mp, °C | % Yield[b] | $pA_2$ (m)[c] |
|---|---|---|---|---|---|---|
| 6a | $(CH_2)_2$ | H | 0 | 210-212[d] | 31 | 5.60±0.06 (5) |
| 6b | $(CH_2)_2$ | H | 1 | 162-164 | 44 | 6.17±0.08 (5) |
| 6c | $(CH_2)_2$ | H | 2 | 119-120 | 34 | 7.24±0.11 (4) |
| 6d | $(CH_2)_2$ | $CH_3$ | 1 | 238-241[e] | 68 | 5.73±0.06 (5) |
| 6e | $(CH_2)_2$ | $CH_3$ | 2 | 202-204 | 61 | 6.59±0.17 (5) |
| 6f | $(CH_2)_2$ | $CH_3$ | 3 | 158-159 | 32 | 6.77±0.08 (6) |
| 6g | $(CH_2)_3$ | H | 1 | 180-182 | 40 | 6.11±0.17 (4) |
| 6h | $(CH_2)_3$ | H | 2 | 144-146 | 31 | 7.46±0.05 (4) |
| 6i | $(CH_2)_3$ | $CH_3$ | 1 | 155-157 | 22 | 5.96±0.10 (5) |
| 6j | $(CH_2)_3$ | $CH_3$ | 2 | 178-180 | 51 | 6.62±0.23 (5) |
| 6k | $(CH_2)_4$ | H | 1 | 173-175 | 64 | 6.26±0.04 (4) |
| 6l | $(CH_2)_4$ | H | 2 | 151-152 | 43 | 6.62±0.11 (4) |
| 6m | $(CH_2)_5$ | H | 1 | 195-197 | 22 | 6.60±0.02 (4) |
| 6n | $(CH_2)_5$ | H | 2 | 160-162 | 16 | 7.43±0.06 (5) |
| 6o | g | H | 1 | 216-218 | 74 | 6.85±0.06 (6) |
| 6p | g | H | 2 | 155-157 | 32 | 6.88±0.04 (4) |
| 6q | h | H | 1 | 243-245 | 67 | 7.09±0.09 (7) |
| 6r | h | H | 2 | 178-180 | 58 | 7.30±0.09 (5) |
| 2 | | | | | | 7.38±0.13[f] |
| 5 | | | | | | 7.27±0.19[f] |

[a]Satisfactory analyses (C, H, and N ± 0.4% of theoretical values) were obtained for all compounds. [b]Yield for 10 → 6. [c]m = Number of determinations. [d]Literature[17] mp 207-209 °C. [e]Literature[14] mp 235-237 °C. [f]Reference 13.



variable results. For example, imidazoline **6c**, tetrahydropyrimidine **6h**, hexahydro-1,3-diazocine **6n**, and 2,5-dihydro-1*H*-2,4-benzodiazepine **6r** were essentially equiactive with diltiazem (**2**) and amidine **5**.

Lee and coworkers have reported that amidine **4**, like diltiazem, enhanced the specific binding of [$^3$H]nitrendipine in both the rat cerebral cortex and heart with $EC_{50}$ values of 6.1 x $10^{-8}$ and 3.4 x $10^{-8}$ M respectively.[18] We have reported that amidine **5** produced a similar enhancement of [$^3$H]nitrendipine binding.[13] On the other hand, other researchers have found that under certain circumstances amidine **4** and diltiazem have opposing actions on [$^3$H]1,4-dihydropyridine binding.[19] This implies that amidines such as **4** define a site on the the calcium channel that is distinct from that of the benzothiazepines. With these studies in mind the guanidines in Table 1 were examined for effects on [$^3$H]nitrendipine binding in rat heart membranes. These componds displayed weak inhibitory effects on [$^3$H]nitrendipine binding ($IC_{50}$ values > 1 μM) and in no instance was enhancement of binding noted. These results suggest that the guanidines described in Table 1 may bind to a site which is distinct from that of amidines **4** and **5**.

In conclusion, we have prepared a series of heterocyclic guanidines **6** and we have evaluated them as antagonists of L-type calcium channels. Several of the compounds exhibited $pA_2$ values which were essentially equivalent to those of both diltiazem (**2**) and amidine **5**. In contrast to both **2** and **5**, however, none of these compounds potentiated the binding of [$^3$H]nitrendipine in rat heart membranes.

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(*Received in USA* 27 *September* 1993; *accepted* 2 *November* 1993)