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(*cis*)-3-METHYL-1,5-BENZOTHIAZEPINE-4-ONES: POTENT ANALOGS OF THE CALCIUM CHANNEL BLOCKER DILTIAZEM

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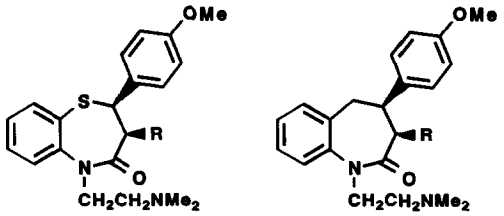
Abstract: 3-Methyl analogs of the calcium channel blocker diltiazem are reported. The title compounds were prepared from readily available amino thiophenols by a six step sequence which involves setting up the desired 2,3-*cis*-stereochemistry through decarboxylation under acidic conditions. To our knowledge, these are the most potent analogs of diltiazem reported to date.

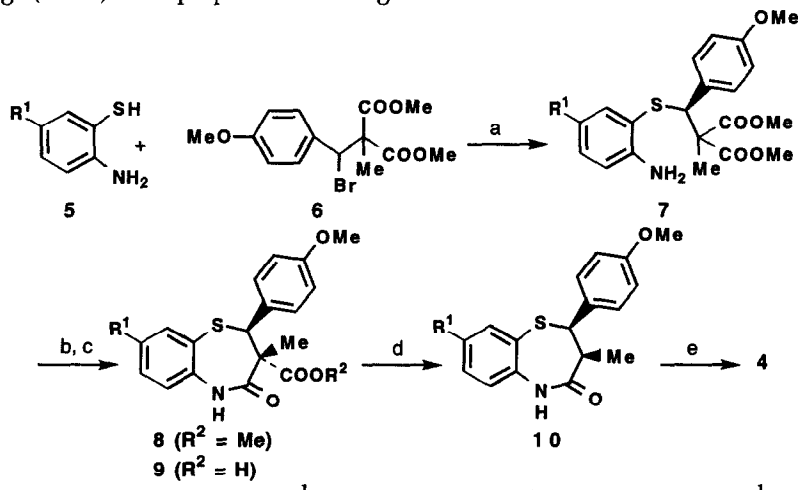
Calcium channel blockers are important therapeutic agents for the treatment of various cardiovascular diseases.[1] Among the currently available agents is the 2,3-*cis*-substituted benzothiazepine derivative diltiazem (**1**). Efforts aimed at the identification of improved analogs of this agent have led to the discovery of benzazepinones (**2**).[2] During structure-activity studies on the benzazepinone calcium channel blockers, we found improvement in potency associated with the replacement of the 3-acetoxy group of **2** with an alkyl substituent (e.g., **3**).[3] Since the benzothiazepines are somewhat more potent *in vitro* than the analogous benzazepinones,[2] we prepared 3-methyl-benzothiazepinone analogs (**4**) for comparison with the corresponding acetoxy-benzothiazepines (**1**) and 3-methyl-benzazepinones (**3**). The results of those studies are reported in this publication.



1 R = OAc (Diltiazem) **2** R = OAc
4 R = Me **3** R = Me

The (*cis*)-3-methyl-benzothiazepinone analogs were prepared according to the synthetic sequence outlined below.[4] Treatment of amino-thiophenol **5** with the bromide **6** gave the intermediate **7** which on treatment with sodium hydride provided the benzothiazepinone **8** as the major product, together with the 2,3-*trans* isomer, in a ratio of 9:1. The ester **8** was saponified and the resulting acid **9** was decarboxylated by heating with *p*-toluenesulfonic acid in dimethylsulfoxide to provide the *cis*-product **10**. The stereochemical outcome for the formation of **10** in this reaction is presumably due to the protonation of the intermediate enol from the least hindered side away from the C2 aryl ring. Alkylation of **10** with dimethylaminoethyl chloride provided **4**

in an uneventful manner. Details of this methodology are described.[4] The racemic diliazem **1** and its analogs (Table) were prepared according to literature methods.[5]

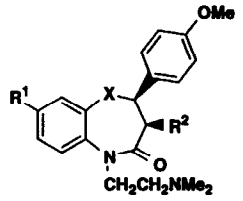


Reaction conditions: [a]NaH, DMF, 60%; [b]NaH, DMSO, 60%; [c]KOH, MeOH, 87%; [d]p-TsOH, DMSO, 57%; [e]K_2CO_3, dimethylaminoethyl chloride hydrochloride, 61%.

Vasorelaxant potencies, presented as IC_{50} values, were determined by relaxation of potassium depolarized rabbit aortic strips.[6] Potencies for receptor binding, represented by K_i values, were determined by displacement of [^{3}H]-diltiazem from guinea pig striated muscle.[2] The biological activity of various analogs prepared is summarized in the Table. Replacement of the 3-acetoxy group of **1a** (racemic diltiazem) with a methyl substituent (**4a**) led to a 20-fold enhancement in vasorelaxant potency. However, the improvement in vasorelaxant potency of 3-methyl-benzothiazepinone analog **4a** over **1a** was not associated with higher affinity for the diltiazem receptor. The reasons for this discrepancy between smooth muscle relaxing potency and binding affinity are not clear but they may be related to the use of different tissues for the two assays. The effect of substitution on the fused aromatic ring of 3-methyl-benzothiazepines, previously shown to enhance potency in diltiazem related compounds,[2] was also examined. Comparison of the vasorelaxant potencies of methoxy analogs **1b**[7] and **4b** supports the conclusion that 3-methyl analogs of diltiazem are generally more potent *in vitro* than their acetoxy counterparts. Replacement of methoxy with a trifluoromethyl group (**4c**) maintained the smooth muscle relaxing potency of **4b**. As shown by the comparison of **4a** with **3**, the 3-methyl-benzothiazepines are an order of magnitude more potent than the corresponding benzazepinones as smooth muscle relaxants. Once again, the higher vasorelaxant potency of **4a** compared to **3** was not associated with enhanced affinity for the diltiazem receptor.

In order to compare the 3-methyl and 3-acetoxy analogs *in vivo*, we administered compounds **1b** and **4b** to spontaneously hypertensive rats at a dose of 135 μmol/kg, po.[8] Both compounds caused equal 33±5% reduction in blood pressure, with the effects lasting for the entire duration (24 hours) of the test. There was a slight tachycardia associated with the fall in blood pressure, which seemed to subside after 1-2 hours. These results show the higher *in vitro* potency of **4b**

Table: Vasorelaxant and Binding Potencies of Benzothiazepinone and Benzazepinone Calcium Channel Blockers



Compound	X	R^1	R^2	Mol. Formula	M.P. °C[a]	IC_{50} (μM)[b]	K_i (μM)[c]
1a	S	H	OAc	-[d]	-	1.8 (0.72-4.6)	0.38±0.04
4a	S	H	Me	-[e]	-	0.082 (0.059, 0.120)	0.54±0.13
1b	S	OMe	OAc	-[f]	-	0.12 (0.072-1.9)	0.042±0.006
4b	S	OMe	Me	$C_{22}H_{28}N_2O_3S$ fumarate. 0.3 H_2O	105-107 (A)	0.010 (0.007, 0.015)	0.085±002
4c	S	CF_3	Me	$C_{22}H_{25}F_3N_2O_2S$ fumarate. 0.9 H_2O	184-186 (B)	0.0.022 (0.018, 0.027)	-
3	CH_2	H	Me	-[g]	-	1.1 (0.61-1.9)	0.65±0.22

[a]Solvent of crystallization in parentheses; A, trituration with isopropyl ether; B, 2-propanol. [b]IC_{50} values were obtained from concentration-response curves using KCl contracted rabbit aortic strips (95% confidence interval). [c]K_i values were calculated by Cheng and Prusoff equation[12] from IC_{50} values for displacement of [^{3}H]-diltiazem in guinea pig striated muscle (±SEM). [d]Reference 5. [e]Reference 4. [f]Reference 7. [g]Reference 3.

does not translate into increased efficacy *in vivo* over **1b**. The reasons for this less than expected *in vivo* potency of **4b** may be related to its pharmacokinetic properties and metabolism profile.

In conclusion, we have shown that 3-methyl-benzothiazepines **4** are 10-20 fold more potent *in vitro* than the corresponding acetoxy compounds (e.g., diltiazem **1**). These compounds are also significantly more potent *in vitro* than the recently reported 3-methyl-benzazepinone (**3**) calcium channel blockers.[2] These data, taken together with previous results[3], demonstrate a variety of substituents are tolerated at C3 of diltiazem. The higher *in vitro* potency of 3-methyl-benzothiazepines may be due to a combination of effects including those associated with increased molecular lipophilicity of methyl*vs.* acetoxy analogs.[10] Higher lipophilicity may account for enhanced delivery of these compounds to their biological target.[11] Whatever the reasons, 3-methyl-benzothiazepines are the most potent analogs of diltiazem reported to date.

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