Benzazepinone Calcium Channel Blockers. 5. Effects on Antihypertensive Activity Associated with N1 and Aromatic Substituents

Jagabandhu Das,* David M. Floyd,* S. David Kimball, Keith J. Duff, Michael W. Lago, John Krapcho, Ronald E. White, Richard E. Ridgewell, Mary T. Obermeier, Suzanne Moreland, Diane McMullen, Diane Normandin, S. Anders Hedberg, and Thomas R. Schaeffer

Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-4000.
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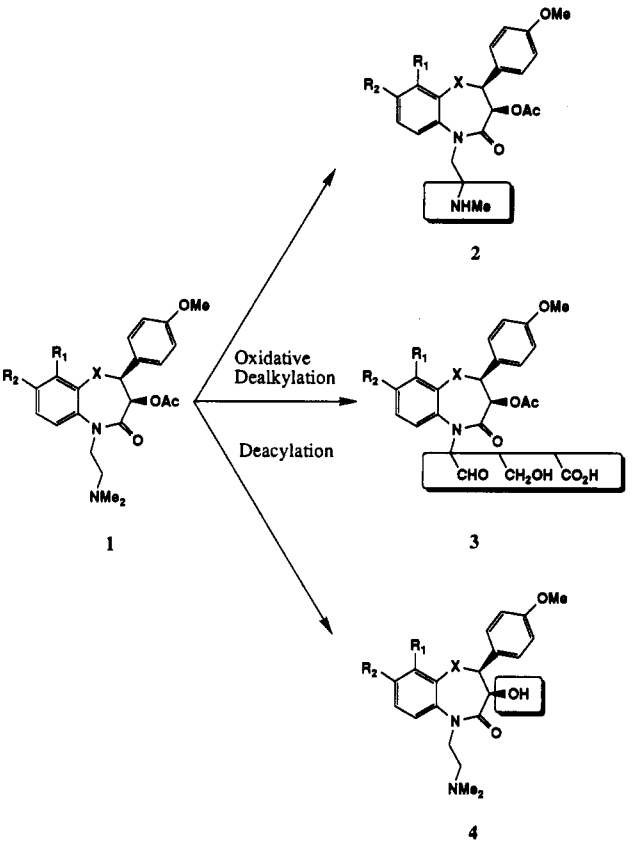
We have shown that the pyrrolidinylmethyl substituent on the lactam nitrogen (N1) of benzazepinone and benzothiazepinone calcium channel blocking agents is resistant to metabolic deamination and generally increases the duration and potency of antihypertensive activity in spontaneously hypertensive rats (SHR) relative to (*N,N*-dimethylamino)ethyl analogs. Additionally, compounds possessing a substituent on the fused aromatic ring are more resistant to metabolic deacylation of the C3 hydroxy function, which may explain why aromatic substituents also frequently increase the potency and/or duration of antihypertensive activity. Our data also indicate the increased antihypertensive activity associated with these structural modifications is independent of any effects of potency in vitro. Overall, we interpret these results to indicate that these structural modifications improve antihypertensive activity as a result of increased metabolic stability and, consequently, oral bioavailability.

Introduction

We have previously described structure–activity studies with a series of benzazepinone calcium channel blocking agents (1) (X = CH_2) which are structural analogs of the benzothiazepinone diltiazem (1e). This work resulted in the discovery of compounds that possessed potent antihypertensive activity when administered orally to spontaneously hypertensive rats (SHR).[1] As a means of focusing our efforts on the discovery of compounds with an extended duration of action, we investigated the metabolic profile of these compounds. As shown in Scheme I, we found the major metabolic pathways involved oxidative dealkylation of the (*N,N*-dimethylamino)ethyl substituent on the lactam nitrogen (N1 using benzazepinone numbering) to give 2 and 3 and deacylation of the C3 acetoxy functionality giving 4, in accord with data published for diltiazem (1e).[2] We found that secondary amines such as 2, resulting from oxidative demethylation of the *N,N*-dimethylamino group, maintained potent calcium channel blocking activity and appeared to be resistant to further metabolic degradation. We also observed the alternate oxidative dealkylation process resulting in the mixture of compounds 3. The desamino metabolites 3 were devoid of calcium channel blocking activity due to the removal of the basic amino functionality from the N1 substituent.[3] These studies led the way to compounds such as 5 (X = CH_2) as long-acting and potent antihypertensive agents in the SHR. The key feature of 5 is the pyrrolidinylmethyl N1 substituent, which proved to be resistant to oxidative

Scheme I. General Metabolic Pathways



(1) Floyd, D. M.; Kimball, S. D.; Krapcho, J.; Das, J.; Turk, C. F.; Moquin, R. V.; Lago, M. W.; Duff, K. J.; Lee, V. G.; White, R. E.; Ridgewell, R. E.; Moreland, S.; Brittain, R. J.; Normandin, D. E.; Hedberg, S. A.; Cucinotta, G. G. Benzazepinone Calcium Channel Blockers. 2. Structure–Activity and Drug Metabolism Studies Leading to Potent Antihypertensive Agents. Comparison with Benzothiazepinones. *J. Med. Chem.* **1992**, *35*, 756–772.

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(3) Kimball, S. D.; Floyd, D. M.; Das, J.; Hunt, J. T.; Krapcho, J.; Rovnyak, G.; Duff, K. J.; Lee, V. G.; Moquin, R. V.; Turk, C. F.; Hedberg, S. A.; Moreland, S.; Brittain, R. J.; McMullen, D. M.; Normandin, D. E.; Cucinotta, G. G. Benzazepinone Calcium Channel Blockers. 4. Structure–Activity Overview and Intracellular Binding Site. *J. Med. Chem.* **1992**, *35*, 780–793.

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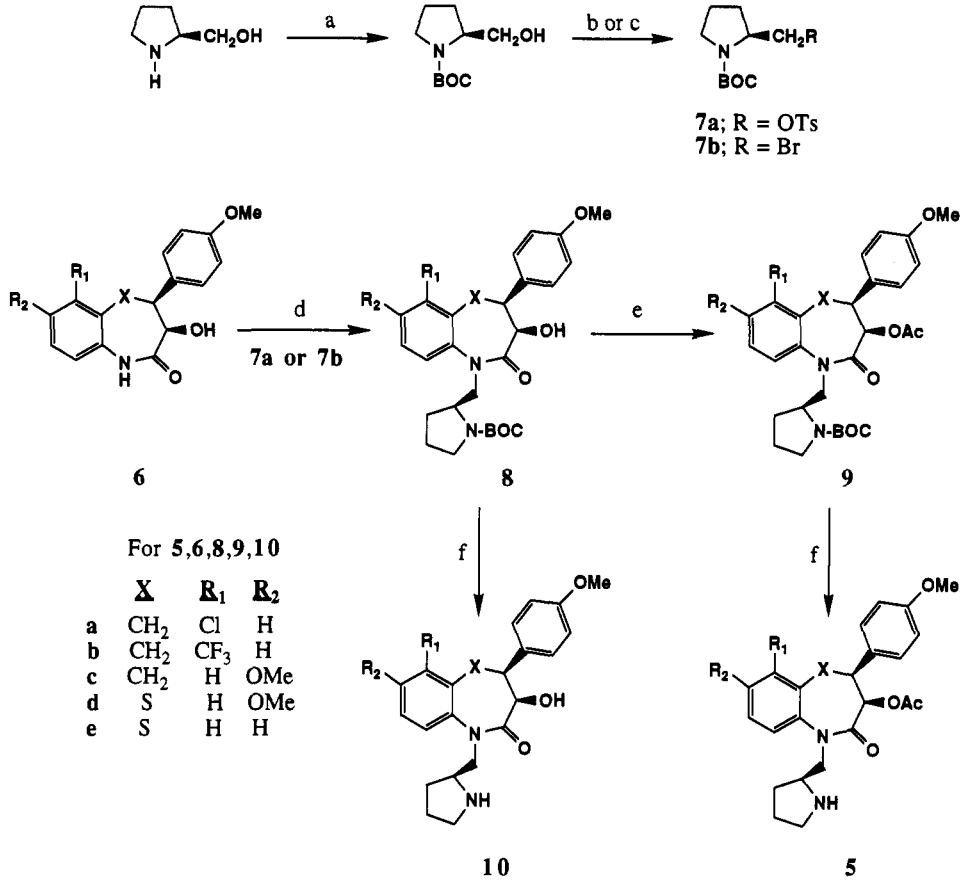
Table I. Physical Properties of Benzazepinones and Benzothiazapinones **5**, **10**, and **1f**

compd	$[\alpha]_D$,[a] deg	X	R_1	R_2	% yield from 6	mp, °C	recryst solvent	formula	anal.
5a	+148	CH_2	Cl	H	15[b]	80–84	foam	$C_{22}H_{25}ClN_2O_3 \cdot 0.42H_2O$	C,H,N,Cl
10a	+130	CH_2	Cl	H	18[b]	74–78	foam	$C_{24}H_{27}ClN_2O_4 \cdot 0.29H_2O$	C,H,N,Cl
5b	+80.5	CH_2	CF_3	H	57[c]	219–21	acetone/pentane	$C_{25}H_{27}F_3N_2O_4 \cdot HCl \cdot 0.05H_2O$	C,H,N,Cl,F
10b	+130	CH_2	CF_3	H	75[c]	165–67	Et_2O	$C_{23}H_{25}F_3N_2O_3 \cdot HCl \cdot 0.73H_2O$	C,H,N,Cl,F
5c	+103	CH_2	H	OMe	30[d]	287–88	AcCN	$C_{25}H_{30}N_2O_5 \cdot HCl \cdot 0.25H_2O$	C,H,N,Cl
10c	+109	CH_2	H	OMe	20[d]	179–81	Et_2O/EtOAc	$C_{23}H_{28}N_2O_4 \cdot HCl \cdot 0.48H_2O$	C,H,N,Cl
5d	+50.3	S	H	OMe	58[c]	145–46	AcCN	$C_{24}H_{28}N_2O_5S \cdot HCl$	C,H,N,Cl,S
10d	+62.9	S	H	OMe	65[c]	121–24	Et_2O	$C_{22}H_{26}N_2O_4S \cdot HCl \cdot 2H_2O$	C,H,N,Cl,S
5e	+66.1	S	H	H	68[c]	132–35	Et_2O	$C_{23}H_{26}N_2O_4S \cdot HCl \cdot 0.73H_2O$	C,H,N,Cl,S
10e	+91.6	S	H	H	32[c]	>240	Et_2O/CH_2Cl_2	$C_{21}H_{24}N_2O_3S \cdot 1.1HCl \cdot 0.46H_2O$	C,H,N,Cl,S
1f	+117	CH_2	H	Cl	NA[e]	63–65	Et_2O	$C_{23}H_{28}N_2O_4 \cdot HCl \cdot 1.5H_2O$	C,H,N

[a] c = 1, MeOH. [b] Prepared according to Method I. [c] Prepared according to Method II. [d] Prepared according to Method III (see Experimental Section). [e] See Experimental Section.

Scheme II.[a] Synthesis of Compounds **5** and **10**



[a] (a) $(BOC)_2O$, CH_2Cl_2; (b) *p*-TsCl, Py; (c) CBr_4, Ph_3P, Et_2O; (d) NaH, DMF, 80 °C; or Cs_2CO_3, DMF, 50 °C; (e) Ac_2O, DMAP, CH_2Cl_2; (f) (i) TFA, CH_2Cl_2; (ii) Et_2O, HCl.

metabolism and resulted in compounds with very high oral bioavailability in the rat.[1]

In this paper we report cognate studies in which we investigated the effects of the pyrrolidinylmethyl modification on antihypertensive activity in the SHR with a series of benzazepinone and benzothiazepinone analogs **5**. Our data indicate that incorporation of the pyrrolidinylmethyl N-1 substituent generally increases duration and/or potency of antihypertensive activity in SHR without a large or consistent effect on potency in vitro. We also present data indicating that compounds possessing a substituent on the fused aromatic ring are more resistant to metabolic deacylation of the C3 hydroxy function which, in some cases, also results in a significant attenuation in calcium channel blocking activity. These observations appear to explain why aromatic substituents also frequently increase antihypertensive potency and/or duration in the absence of a profound effect on potency in vitro. Taken together, our data indicate general structural modifications in both the benzazepinone and benzothiazepinone series that potentially improve antihypertensive activity as a direct result of increasing oral bioavailability.

Synthesis

Compounds **1** were prepared by previously published methods.[1,4] Nonracemic **1f** (see Table I) was prepared by simple hydrogenolysis (Pd/C, H_2) of the corresponding nonracemic 7-chlorobenzazepinone **1h** (see ref 9).[1]

(4) Floyd, D. M.; Moquin, R. V.; Atwal, K. S.; Ahmed, S. Z.; Spergel, S. H.; Gougoutas, J. Z.; Malley, M. F. Synthesis of Benzazepinone and 3-Methylbenzothiazepinone Analogues of Diltiazem. *J. Org. Chem.* **1990**, *55*, 5572–5579.

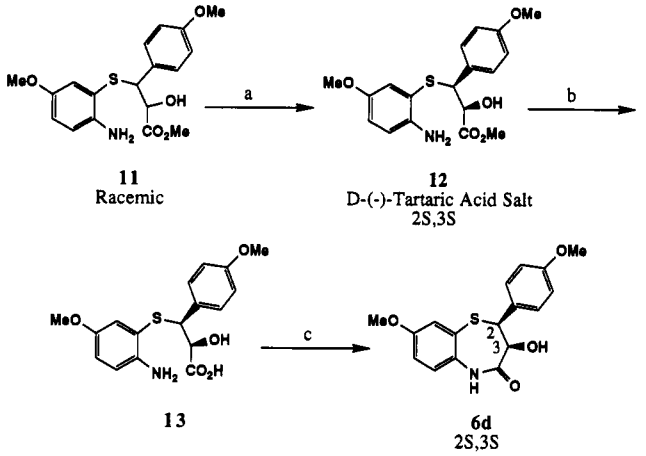
The alkylating agents **7a** or **7b** used to prepare compounds **5** and **10** in Table I were prepared from commercially available (*S*)-pyrrolidine-2-methanol by initial reaction with di-*tert*-butyldicarbonate (BOC_2O) in methylene chloride giving BOC-2-pyrrolidinemethanol followed by treatment with either *p*-toluenesulfonyl chloride in pyridine to form the tosylate **7a** or with carbon tetrabromide and triphenylphosphine in ether to afford the bromide **7a** or with carbon tetrabromide and triphenylphosphine in ether to afford the bromide **7b** (see Scheme II).[5]

Compounds **5** and **10** are single enantiomers; 3*R*,4*S* (benzazepinone numbering) for X = CH_2 and 2*S*,3*S* (benzothiazepinone numbering) for X = S in Table I. Benzazepinones **5**/**10a** and **5**/**10c** were prepared from racemic **6** whereas **5**/**10b** and the benzothiazepinones **5**/**10d** and **5**/**10e** were prepared from the nonracemic **6**. Benzazepinones **6a–c** and the benzothiazepinone **6e** were prepared by previously described methods.[1,4] For example, alkylation of racemic **6a** with bromide **7b** in DMF at 80 °C formed a diastereomeric mixture of adducts which were separated by silica gel column chromatography to give the desired diastereomer **8a** in 28% yield (56% of theory). Alternately, nonracemic **6d** (see below for preparation) was alkylated with tosylate **7a** in presence of cesium carbonate in DMF at 50 °C to afford **8d** in 76% isolated yield after silica gel chromatography. In general, removal of the BOC group of **8** in dichloromethane with trifluoroacetic acid and subsequent treatment with anhydrous hydrogen chloride afforded **10**, as hydrogen chloride salts, in excellent yields. The 3-acetoxy derivatives **5** were prepared by initial treatment of **8** with acetic anhydride in dichloromethane in the presence of 4-(dimethylamino)pyridine to form **9**. These compounds were then deprotected and converted to their hydrochloride salts, as described above, to afford **5** in good yields. A third method was employed in the csae of **5**/**10c**. For these compounds, separation of the diastereomeric mixture of **8c** was not synthetically useful. Consequently, the mixture of diastereomers was carried through the sequence shown in Scheme II with final purification effected by recrystallization of **5c**. The corresponding C3 hydroxy compound **10c** was obtained by simple basic hydrolysis of **5c**.

The absolute stereochemical assignments for compounds **5**/**10a** and **5**/**10c**, which were prepared from racemic **6a** and **6c**, were assumed to be 3*R*,4*S* (benzazepinone numbering). This was based on both the sign of the optical rotation, which does not change with the additional stereocenter contained in the pyrrolidinylmethyl group, and their potent biological activity. The enantiomeric 3*S*,4*R* benzazepinones are known to possess very low potency in vitro.[1] The assignment of absolute stereochemistry for **5c** was supported by single crystal X-ray analysis.[6] The absolute stereochemical purity of **5**/**10a** and **5**/**10c** was predicated on the observation that the synthetic precursors, **8a** and **8c** respectively, were chromatographically homogeneous. As noted previously, relative stereochemical purity is easily determined by NMR methods.[4]

Laborious methods have been published for the preparation of nonracemic benzothiazepinone **6d** involving the separation of diastereomers formed by the acylation of racemic **6d**.[7] As described in Scheme III, we have developed a much more efficient method based on resolution at an early stage of the synthesis. This was possible due to the fact that the aromatic amino group of **11** was sufficiently basic to form stable salts with a variety of chiral carboxylic acids, presumably due to the presence of the *p*-methoxy group. The intermediate **11** was prepared in 63% yield by the reaction of 2-amino-5-methoxythiophenol with the requisite methyl *p*-methoxyphenylglycidate in refluxing toluene as described in the patent literature.[7] Treatment of the racemate **11** with D-(−)-tartaric acid in 95% ethanol gave, after a single recrystallization, **12** as its D-(−)-tartaric acid salt in 83% of the theoretical yield. This material was then hydrolyzed to the carboxylic acid **13** and cyclized to **6d** via a carbodiimide-mediated cyclization in aqueous DMF in an overall yield of 96%. None of the enantiomer was detected by NMR by employing chiral shift reagents. Further proof of absolute configuration was obtained from the X-ray crystallographic structure determination of **5d** which was prepared from **6d**.[6]

Scheme III.[a] Synthesis of **6d**



[a] (a) D-(−)-Tartaric acid, 95% EtOH; (b) NaOH, MeOH–H_2O; (c) ethyl-[3-(dimethylamino)propyl]carbodiimide, pH 4.5.

Results and Discussion

The data presented in Table II indicate that for several of the compounds incorporation of the pyrrolidinylmethyl group improves antihypertensive activity in the SHR following oral administration. Furthermore, the effect on antihypertensive potency and/or duration is not consistent with any increase in potency in vitro as a result of this structural modification. For example, the largest increases in potency in vitro associated with the pyrrolidinylmethyl N1 modification are with the chloro-(**1a** vs **5a**) and methoxy-(**1c** vs **5c**) substituted benzazepinones, 7- and 4-fold, respectively.[8] However, despite being 7-fold more potent, **5a** is only slightly more active as an antihypertensive agent than its (*N*,*N*-dimethylamino)ethyl analog **1a**. With the methoxy-substituted benzazepinones, the pyrrolidinylmethyl derivative **5c** demonstrates markedly increased antihypertensive activity compared to **1c**, although it is only about 4-fold more potent in vitro. In

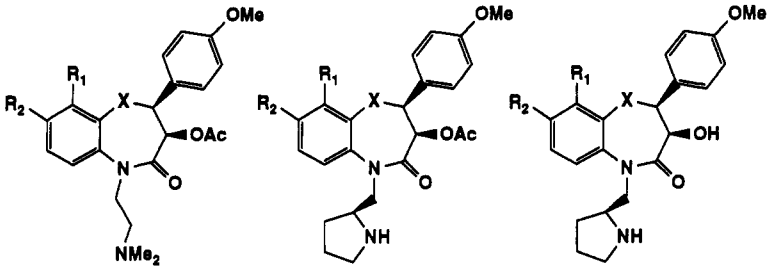
(5) For a related preparation of **7a** see: Jones, K.; Woo, K-C. A Total Synthesis of (−)-Ruspolinone. *Tetrahedron* **1991**, *47*, 7179–7184.

(6) Gougoutas, J. Z.; Malley, M. F. Unpublished results. Both the relative and absolute stereochemical assignments for **5c** and **5d** were confirmed by single crystal X-ray analysis. The absolute stereochemical assignments were based on the known absolute configuration of **7a,b**.

(7) Takeda, M.; Ohishi, T.; Nakajima, H.; Nagao, T. U.S. Patent 4,590,188.

(8) Compounds possessing the wrong absolute stereochemistry are at least 10 times less potent than the biologically most active enantiomers. It is, therefore, an acceptable working assumption that (3*R*,4*S*)-benzazepinones and (2*S*,3*S*)-benzothiazepinones are twice as potent in vitro as their racemates; that is, $IC_{50(racemic)} = 0.5 \times (IC_{50(nonracemic)})$. This assumption is supported by our observations in this series of compounds (see refs 1 and 3).

Table II. Vasorelaxant and Antihypertensive Activity of Compounds 1, 5, and 10



1 5 10

compd[a]	R_1	R_2	X	IC_{50} (μM)[b]	% decrease in BP ca. 135 μmol/kg po 0–6 h	6–12 h	12–18 h	n[c]
1a[d]	Cl	H	CH_2	1.60 (0.71–3.40)	10 (±4)	8 (±5)	11 (±3)	5
5a	Cl	H	CH_2	0.12 (0.08–0.17)	18 (±3)	17 (±1)	20 (±4)	6
10a	Cl	H	CH_2	0.13 (0.09–0.20)	19 (±4)	15 (±4)	13 (±4)	5
1b	CF_3	H	CH_2	0.15 (0.11–0.20)	29 (±3)	29 (±2)	29 (±3)	10
5b	CF_3	H	CH_2	0.09 (0.07–0.12)	44 (±2)	38 (±2)	38 (±2)	6
10b	CF_3	H	CH_2	0.10 (0.07–0.13)	32 (±3)	21 (±1)	21 (±4)	6
1c[d]	H	OMe	CH_2	1.90 (0.88–4.00)	15 (±3)	8 (±4)	10 (±3)	5
5c	H	OMe	CH_2	0.23 (0.15–0.36)	39 (±2)	33 (±1)	31 (±2)	5
10c	H	OMe	CH_2	1.12 (0.68–1.84)	18 (±3)	19 (±3)	18 (±4)	5
1d[d]	H	OMe	S	0.13 (0.11–0.20)	34 (±3)	21 (±6)	19 (±6)	5
5d	H	OMe	S	0.12 (0.08–0.19)	42 (±2)	39 (±3)	37 (±3)	6
10d	H	OMe	S	0.37 (0.23–0.60)	32 (±3)	33 (±4)	23 (±3)	6
1e	H	H	S	0.21 (0.13–0.36)	20 (±7)	12 (±8)	19 (±6)	10
5e	H	H	S	0.34 (0.23–0.50)	18 (±2)	8 (±3)	10 (±3)	9
10e	H	H	S	1.32 (0.79–2.22)	10 (±3)	10 (±2)	9 (±2)	8
1f	H	H	CH_2	2.99 (1.69–5.30)	8 (±3)	8 (±2)	13 (±4)[e]	5

[a] All compounds are the biologically most active enantiomers unless noted otherwise; 2*S*,3*S* for X = S and 3*R*,4*S* for X = CH_2. [b] Average value from at least four experiments; 95% confidence range shown in parentheses. [c] Data reported as % fall in blood pressure (± standard error) from control levels where n = the number of SHR from which data was recorded. [d] Racemic compound. [e] SHR data from racemic compound dosed at 270 μmol/kg po.

other examples, significant increases in antihypertensive activity are observed with no effects on potency in vitro, i.e., **1b** vs **5b** and **1d** vs **5d**. Consequently, we ascribe the increase in antihypertensive potency and/or duration of action observed with pyrrolidinylmethyl-containing compounds as being associated with increased metabolic stability compared to their (*N*,*N*-dimethylamino)ethyl analogs and not to an effect on intrinsic calcium channel blocking activity. This assumption is supported by the results obtained from metabolism studies with the trifluoromethyl-substituted benzazepinones **1b** and **5b**.[1]

For the methoxy-substituted benzazepinone and benzothiazepinone analogs, incorporation of the pyrrolidinylmethyl N1 substituent resulted in compounds (**5c**,**5d**) that possessed potency and duration of action similar to the trifluoromethyl-substituted benzazepinone **5b**. The benzazepinone **1c** demonstrates a small antihypertensive effect which essentially dissappears after 6 h. By comparison, the pyrrolidinylmethyl analog **5c** shows marked antihypertensive activity throughout the 18 h test. The effect of the pyrrolidinylmethyl modification in the methoxy-substituted benzothiazepinone series becomes clearer on comparing the apparent duration of action of **1d** and **5d**. Although **1d** is a potent antihypertensive agent in this test, the magnitude of its antihypertensive effect decreased by approximately 50% over the duration of the test in SHR. In contrast, **5d**, which incorporates the pyrrolidinylmethyl N1 functionality, maintains an antihypertensive effect that is essentially unchanged over 18 h. Thus, the increased metabolic stability of the pyrrolidinylmethyl group compared to the (*N*,*N*-dimethylamino)-ethyl moiety can manifest itself as an effect on the duration of action and/or the potency of the compound under study.

With the chloro-substituted benzazepinones **1a** and **5a**, the effect is much less pronounced.[9] Furthermore, despite the fact that the chlorobenzazepinone **5a** is equipotent in vitro compared to the benzazepinones **5b**,**c** and benzothiazepinone **5d**, it is much less active in the SHR. Similarly, the benzothiazepinone **5e**, the pyrrolidinylmethyl analog of diltiazem (**1e**), shows reduced antihypertensive activity compared to **5b–d**, despite similar potency in vitro. Although there are many factors that affect oral activity and that could explain these results, based on the studies described below, we believe **5a** and **5e** possess lower antihypertensive activity as a result of additional metabolic processes.

Our overall conclusion from these studies is that incorporation of the pyrrolidinylmethyl N1 substituent is a rational approach to generating compounds with increased oral antihypertensive activity as a result of the increased resistance to oxidative metabolism of this functionality compared to the (*N*,*N*-dimethylamino)ethyl

(9) In general, we believe the comparison of antihypertensive activity in SHR between racemic and nonracemic compounds is valid for this series of compounds. We find the theoretical 2-fold increase in potency in vitro between nonracemic and racemic compounds does not have a marked effect on antihypertensive activity. This is based on data from ref 1 shown in the following table (for compound 1, X = CH_2).

Compound	R_1	R_2	R_3	Chirality	IC_{50}(μM)	% Decrease in BP @ 135 μmol/kg p.o. 0-6 hr	6-12 hr	12-18 hr
1g	H	Cl	Ac	Racemic	1.5 (0.84-2.8)	13	14	18[a]
1h	H	Cl	Ac	3R,4S	0.82 (0.54-1.3)	12	12	12
1i	H	CF_3	Ac	Racemic	1.9 (0.95-3.6)	19	19	18
1j	H	CF_3	Ac	3R,4S	1.6 (0.87-3.1)	19	22	19
1k	CF_3	H	Ac	Racemic	0.24 (0.13-0.45)	24	26	24
1b	CF_3	H	Ac	3R,4S	0.15 (0.11-0.20)	31	27	30

a. Dosed at 270 μmol/kg p.o.

N1 substituent. With analogs containing the latter substituent, oxidative deamination is a significant metabolic process and results in metabolites devoid of calcium channel blocking activity (see Scheme I).[1]

The notable exceptions to the generalization stated above are with diltiazem (**1e**) and the chloro-substituted benzazepinone **1a**. In these examples, incorporation of the pyrrolidinylmethyl group did not result in an increase in antihypertensive activity in the SHR. As noted above, one hypothesis to explain this observation is metabolic deacylation. In the case of diltiazem (**1e** and **5e**, loss of the C3 acetyl group significantly attenuates potency in vitro.[10] However, this hypothesis is not generally supported by examination of the data for other C3 hydroxyl analogs (**10**) shown in Table II.

The data from the compounds in Table II that demonstrate an increase in antihypertensive potency and/or duration of action with the incorporation of the pyrrolidinylmethyl group give little insight into the importance of metabolic deacylation. For (trifluoromethyl)benzazepinone **5b**, loss of the C3 acetyl group does not attenuate potency in vitro. Further, the C3 hydroxyl analog **10b** demonstrates significant, although somewhat reduced, antihypertensive activity relative of **5b**. With the methoxybenzothiazepinone **5d**, the desacetyl derivative **10d** is only 3-fold less potent in vitro and retains a level of antihypertensive activity relative to **5d** similar to that observed with the trifluoromethyl analogs. The largest effect on potency in vitro resulting from C3 deacylation is observed for the methoxybenazepinone **5c**. In this case, the desacetyl derivative **10c** is 5-fold less potent than the parent **5c**. However, like the examples above, **10c** retains significant antihypertensive activity. Thus, none of these examples supply clear data regarding the potential for metabolic deacylation to attenuate the antihypertensive activity of the C3 acetyl derivatives **5**.

In the examples where there is a clear failure of the pyrrolidinylmethyl group to increase antihypertensive potency compared to the corresponding (*N*,*N*-dimethylamino)ethyl analogs, the data can be interpreted to indicate a role for additional metabolic pathways. For example, metabolic deacylation of **5a** would give the 3-hydroxy derivative **10a**. In this case, the experimental results could be explained by the rapid metabolic conversion of **5a** to **10a** since both compounds demonstrate the same moderate level of antihypertensive activity. It is important to note, however, that both compounds possess identical potency in vitro and the lack of potent antihypertensive activity could be due to a variety of other factors including inherently poor oral absorption. The effect on potency in vitro from loss of the C3 acetyl group from **5e** in the diltiazem (**1e**) series is more notable. In this case the desacetyl derivative **10e** shows a 4-fold attenuation of vasorelaxant potency. However, as in the above example, both **5e** and **10e** lack potent antihypertensive activity which could be interpreted to indicate that upon oral dosing, **5e** is rapidly converted to **10e**. Thus, in both of these examples, the failure of the pyrrolidinylmethyl analogs **5a,e** to demonstrate improved antihypertensive activity over their (*N*,*N*-dimethylamino)ethyl derivatives **1a,e** could be explained by rapid metabolism to the C3 hydroxy materials **10a,e** which show reduced antihypertensive activity.

Table III. Hydrolysis of C3 Acetyl Group by Rat Liver Homogenate

compd	R_1	R_2	X	extent of hydrolysis (%)[a] 5 min[b]	30 min
1e	H	H	S	68	100
5e	H	H	S	32	57
1f	H	H	CH_2	18	53
5a	H	Cl	CH_2	7	17
5d	H	OMe	S	3	7
5c	H	OMe	CH_2	3	3
1b	CF_3	H	CH_2	0	2
5b	CF_3	H	CH_2	0	0

[a] (Amount of 3-hydroxy product/total amount of substrate-related compound) × 100. [b] Incubation period.

In an attempt to explain the apparent discrepancies in our data we investigated the ability of rat liver homogenate to hydrolyze the C3 acetyl group of several compounds in Table II. The data from this study are summarized in Table III and indicate that the presence of an aromatic substituent generally inhibits hydrolysis of the C3 acetyl group by the liver homogenate esterases. Comparison of the extent of hydrolysis of **1e** and **1f** at 5 and 30 min indicates that the benzazepinone system may be hydrolyzed somewhat more slowly compared to an analogous benzothiazepinone. Nevertheless, both compounds are significantly hydrolyzed after 30 min. Similarly, independent of the class of compounds, neither the methoxybenzothiazepinone **5d** nor the analogous benzazepinone **5c** is extensively hydrolyzed, indicating that the methoxy substituent inhibits deacylation under these conditions. The data also demonstrate that the nature of the N1 substituent does not affect the ability of these compounds to act as substrates for the liver homogenate esterases. Both of the benzothiazepinones **1e** and **5e**, which differ only in the structure of the N1 substituent, are significantly hydrolyzed under these conditions. Also, independent of the N1 substituent, the C3 acetyl groups of the (trifluoromethyl)benzazepinones **1b** and **5b** are resistant to esterase activity. From Table III, it appears that the most important factor determining susceptibility to enzymatic deacylation is the presence or absence of an aromatic substituent, with the degree of protection being possibly dependent on the nature of the substituent (compare the data for the chlorobenzazepinone **5a** to those of **5b** or **5c** in Table III).

The results of this study appear to explain some of the discrepancies in Table II. These data support the hypothesis that the unsubstituted benzothiazepinone **5e** shows no increase in antihypertensive activity compared to its (*N*,*N*-dimethylamino)ethyl analog **1e** as a result of extensive metabolism to the less active 3-hydroxy derivative **10e**. Conversely, the methoxy-substituted benzazepinone **5c** demonstrates a high level of antihypertensive activity because it is resistant to metabolic deacylation to the 3-hydroxy analog **10c**. The studies summarized in Table III are also consistent with our previous observations that replacement of the C3 acetyl group of benzazepinone **1f** with alkyl substituents that are resistant to metabolism results in analogs with good antihypertensive activity in the SHR.[3,11] In this case, C3 metabolism to a less active

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analog is precluded by the alkyl group, and the presence of an aromatic substituent is not necessary for the expression of antihypertensive activity in SHR. This study also appears to explain why simple methoxylation of the diltiazem nucleus (compare **1d** to **1e**), while having no significant effect on intrinsic potency, results in a marked increase in antihypertensive activity. A similar effect is noted by comparing diltiazem to its 8-chloro analog TA 3090.[1]

The data in Table III may also explain the weaker antihypertensive activity of chlorobenzazepinone **5a** relative to the other aromatic-substituted derivatives in Table II. Although the chloro substituent apparently affords some protection against enzymatic deacylation compared to compounds lacking an aromatic substituent, **5a** is still deacylated significantly more than either the methoxy- or trifluoromethyl-substituted benzazepinones. These observations are consistent with the hypothesis that **5a** is metabolized to the C3 hydroxy derivative **10a** and may explain why, despite similar potency in vitro to the other aromatic substituted analogs **5** in Table II, **5a** produces a lower antihypertensive effect in SHR. Thus, based on this observation and the fact that **5a** and **10a** possess identical antihypertensive activities when orally administered to SHR, we conclude that the metabolic deacylation of **5a** attenuates its antihypertensive activity also.

In summary, the studies described above illustrate that increased antihypertensive activity is obtained with diltiazem-like calcium channel blockers by limiting metabolic degradation of the critical basic amino functionality in the N1 substituent. We have shown that incorporation of the pyrrolindinylmethyl N1 substituent is consistent wiht both significantly increased metabolic stability of the basic amino group and maintenance of high biological activity and results in compounds demonstrating potent and long-lasting antihypertensive activity in the SHR.[1] In addition, for compounds containing a C3 acetoxy substituent, maximal antihypertensive activity also requires the presence of a substituent on the fused aromatic ring. Although we can not rationalize this observation on mechanistic grounds, the aromatic substituent appears to inhibit metabolic deacetylation of the C3 acetoxy group and, consequently, the formation of 3-hydroxy metabolites which are frequently less active antihypertensive agents than their corresponding 3-acetoxy analogs. The degree of this effect is, however, dependent on the nature of the substituent. We believe the combined results from these studies indicate general methods to improve the pharmacokinetic profile, and hence, the oral antihypertensive activity, of diltiazem-like calcium channel blocking agents. More generally, the approach we have taken to increasing the potency in vivo of diltiazem–like compounds by having our synthetic effort driven in part by an understanding of important metabolic pathways would be applicable to a variety of medicinal chemistry programs.

Experimental Section

Biological Testing. To determine the effects of structural modifications in the benzazepinone and benzothiazepinone series on potency in vitro we have measured the vasorelaxant effects of compounds in circumferential strips of potassium-depolarized rabbit aorta. The IC_{50} value reported represents the concentration of compound necessary to cause 50% relaxation of a maximal contraction in response to 100 mM KCl. Antihypertensive activity was calculated as the percent fall in systolic blood pressure from predrug control value and is reported as the mean value acquired from five rats at a standard dose of 135 μmol/kg po unless otherwise noted. The maximum antihypertensive effect is reported for the 0–6-h, 6–12-h, and 12–18-h time periods after oral dosing to give an indication of both the potency and duration of action of the test compounds. All blood pressure measurements were obtained by direct recording. A more detailed description of these biological test methods has been reported previously.[1]

Rat Liver Homogenate Deacylations. Enzymatic hydrolysis of the C3 acetyl functionality was performed by exposing the test compound (0.4 mM final concentration) to rat liver homogenate (2 mL, 0.3 g of liver/mL) in the presence of phosphate buffer (5 μM, final concentration, pH 7.4) in a total volume of 2.5 mL at 37 °C. The mixture was incubated for either 5 or 30 min and diluted with acetonitrile (2.5 mL), centrifuged to remove precipitated protein, and analyzed for the expected hydrolysis product by HPLC with an isocratic mobile phase (50 mM ammonium acetate buffer, pH 5–acetonitrile, 60:40 by volume; flow rate 1 mL/min). HPLC analysis was performed using a Beckman Ultrasphere-ODS column (5 m, 4.6 × 250 mm; Beckman Instruments, Inc., San Ramon, CA) on a Perkin-Elmer Series 410 pump system, equipped with an LC-235 diode array detector (Perkin-Elmer Corp., Norwalk, CT) set at 230 nm.

General Synthetic Procedures. Melting points were recorded on a Thomas-Hoover capillary apparatus and are reported uncorrected. Proton NMR (^{1}H NMR) spectra were obtained on JEOL FX-270 or GX-400 spectrometers and are reported relative to tetramethylsilane (TMS) reference. Carbon NMR (^{13}C NMR) data were obtained on the JEOL FX–270 or FX-60Q spectrometers and are also reported relative to TMS. Analysis by TLC was performed on E. Merck Kieselgel 60, F-254 silica-gel plates. Flash chromatography was done on either Whatman LPS-1 or E. Merck Kieselgel 60 (240–400 mesh) silica gel.

Unless otherwise stated, concentrations of solutions were done in vacuo. All reactions were conducted under an atmosphere of argon employing reagent grade solvents. The DMF was dried by storage over 3-Å molecular sieves. Anhydrous THF was prepared by distillation from sodium benzophenone prior to use.

(*S*)-[*N*-[(*tert*-Butyloxy)carbonyl]-2-pyrrolidinyl]methyl *p*-Toluenesulfonate (7a). A solution of (*S*)-2-pyrrolidinemethanol (25 g, 247 mmol) and di-*tert*-butyl dicarbonate (64.7 g, 297 mmol) in dichloromethane (700 mL) was stirred at room temperature for 5 h. Removal of solvent afforded the desired BOC-protected intermediate (49.7 g) as an oil. A solution of this crude product (20.6 g, 102.4 mmol) in pyridine (100 mL) was treated with *p*-toluenesulfonyl chloride (23.4 g, 122.8 mmol) and the resulting solution was stirred at room temperature for 5 h. Additional *p*-toluenesulfonyl chloride (9.8 g, 51.2 mmol) was added. After 23 h, the mixture was diluted with EtOAc and washed with saturated $CuSO_4$ solution (3×). The EtOAc extract was dried ($MgSO_4$), filtered, and concentrated. The crude oil was chromatographed on a silica gel column and eluted with 10–30% EtOAc in hexanes to obtain **7a** (32.1 g, 88% overall yield) as a viscous oil: $[\alpha]_D = -40°$ (c = 1, methylene chloride), lit.[5] $[\alpha]_D = -39.6°$ (c = 0.74, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 2 H), 7.25 (d, 2 H), 4.10 (m, 1 H), 3.90 (bs, 2 H), 3.30 (m, 2 H), 2.45 (s, 3 H), 1.70–1.95 (m, 4 H), 1.40 (bs, 9 H).

(*S*)-[*N*-[(*tert*-Butyloxy)carbonyl]-2-pyrrolidinyl]methyl Bromide (7b). A solution of crude (*S*)-*N*-[(*tert*-butyloxy)-carbonyl]-2-pyrrolidinemethanol (49.7 g), carbon tetrabromide (129.5 g, 494 mmol) and triphenylphosphine (164 g, 494 mmol) in ether (1 L) was stirred overnight at room temperature. The precipitated solids were then filtered and washed with ether. The filtrate was concentrated to obtain a yellow oil which was chromatographed on a silica gel column. Elution with hexanes, followed by 30% EtOAc in hexanes gave **7b** (36.99 g, 57% overall yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.00 (m, 1 H), 3.36 (m, 1 H), 3.37 (m, 3 H), 2.1–1.85 (m, 4 H), 1.47 (s, 9 H). This material was used without further characterization.

(3*R*,4*S*)-6-Chloro-1,3,4,5-tetrahydro-3-hydroxy-4-(4-methoxyphenyl)-1-[[*N*-[(*tert*-butyloxy)carbonyl]-2-pyrrolidinyl]methyl]-2*H*-1-benzazepin-2-one (8a). Method I. Solid (*cis*)-6-Chloro-1,3,4,5-tetrahydro-3-hydroxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (**6a**, 3 g, 9.44 mmol) was added to a suspension of NaH (270 mg, 11.33 mmol) in DMF (95 mL). After 1 h, **7b** (3 g, 11.33 mmol) was added and the mixture was heated to 80 °C for 3 h. Additional NaH (110 mg, 4.58 mmol) and **7b** (1.25 g, 4.72 mmol) were added, and heating was continued for another 2 h. The mixture was cooled, diluted with water, and extracted with EtOAc (3×). The EtOAc extracts were combined, washed with 10% aqueous LiCl solution (3×), dried ($MgSO_4$),

filtered, and concentrated. The residual oil was chromatographed on a silica gel column and eluted with 5–20% EtOAc in hexanes to obtain **8a** (650 mg, 28%) as an oil: $[\alpha]_D$ = +135.2° (*c* = 1, MeOH); TLC R_f = 0.60 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 3 H), 7.19 (d, 2 H), 6.91 (d, 2 H), 4.55 (m, 1 H), 4.21 (t, 1 H), 3.81 (s, 3 H), 3.75 (m, 1 H), 3.45 (m, 3 H), 3.10 (q, 1 H), 2.82 (m, 2 H), 2.47 (t, 1 H), 2.20–1.70 (m, 4 H), 1.44 (bs, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.3, 158.9, 140.5, 130.5, 129.5, 120.9, 113.9, 69.6, 55.2, 54.9, 51.4, 32.8, 28.5, 28.4. A sample of the diastereomer of **8a** (foam, 420 mg, 18%) was also isolated: $[\alpha]_D$ = –60.5° (*c* = 1, MeOH); TLC R_f = 0.53 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$) δ 7.40–7.15 (m, 5 H), 6.90 (d, 2 H), 4.40–4.25 (m, 2 H), 4.18 (t, 1 H), 3.81 (s, 3 H), 3.70 (m, 1 H), 3.45 (m, 2 H), 3.15 (q, 1 H), 2.80 (m, 2 H), 2.47 (t, 1 H), 2.20–1.70 (m, 4 H), 1.44 (bs, 9 H); ^{13}C NMR ($CDCl_3$) δ 158.9, 154.5, 140.5, 132.0, 129.7, 128.3, 127.8, 121.2, 113.9, 69.6, 56.3, 55.2, 51.1, 32.9, 28.5, 28.3.

[2*S*-[2α,3α,5(*R)]]-5-[[1-[(1,1-Dimethylmethoxy)carbonyl]-2-pyrrolidinyl]methyl]-2,3-dihydro-3-hydroxy-8-methoxy-2-(4-methoxyphenyl)-1,5-benzazothiazepin-4(5*H*)-one (8d). Method II.** A solution of (2*S*,3*S*)-2,3-dihydro-3-hydroxy-8-methoxy-2-)4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**6d**, 1 g, 3.02 mmol), **7a** (340 mg, 0.97 mmol), and cesium carbonate (2.15 g, 6.05 mmol) in DMF (10 mL) was heated to 50 °C overnight. The mixture was cooled, diluted with water (10 mL), and extracted with ether (30 mL, 3×). The ether extracts were combined, washed with 10% aqueous LiCl solution (30 mL, 3×), dried ($MgSO_4$), filtered, and concentrated. The residual foam was chromatographed on a silica gel column and eluted with 50% EtOAc in hexanes to obtain **8d** (1.19 g, 76%): mp 75–80 °C; $[\alpha]_D$ = +119° (*c* = 1, MeOH).

[3*R*-[1*S,3α,4α]]-6-Chloro-1,3,4,5-tetrahydro-3-hydroxy-4-(4-methoxyphenyl)-1-(2-pyrrolidinylmethyl)-2*H*-1-benzazepin-2-one (10a).** A solution of **8a** (670 mg, 1.34 mmol) and trifluoroacetic acid (1 mL, 13.1 mmol) in dichloromethane (10 mL) was stirred at room temperature for 6 h. The mixture was diluted with saturated $KHCO_3$ solution and extracted with ethyl acetate (3×). The ethyl acetate extract was dried ($MgSO_4$), filtered, and concentrated. The crude residue was chromatographed on silica gel plates and eluted with 10% MeOH in dichloromethane to obtain **10a** (280 mg, 52%): mp 80–84 °C, $[\alpha]_D$ = +148° (*c* = 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 1 H), 7.23 (t, 1 H), 7.21 (d, 2 H), 7.20 (dd, 1 H), 6.90 (d, 2 H), 4.46 (dd, 1 H), 4.18 (t, 1 H), 3.81 (s, 3 H), 3.65 (m, 2 H), 3.50 (m, 2 H), 2.99 (t, 1 H), 2.90 (m, 2 H), 2.65 (bs, 2 H), 2.00–1.50 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.0, 159.0, 142.4, 134.0, 132.5, 130.8, 129.8, 128.2, 127.8, 121.2, 113.9, 69.6, 58.0, 55.2, 52.5, 51.3, 46.5, 32.7, 29.9, 25.2. Anal. ($C_{24}H_{27}ClN_2O_4$·0.29H_2O) C, H, N, Cl.

[2*S*-[2α,3α,5(*R)]]-3-(Acetyloxy)-5-[[1-[(1,1-dimethylethoxy)carbonyl]-2-pyrrolidinyl]methyl]-2,3-dihydro-8-methoxy-2-(4-methoxyphenyl)-1,5-benzazothiazepin-4(5*H*)-one (9d).** A solution of **8d** (1.23 g, 2.4 mmol), acetic anhydride (1.25 g, 12.2 mmol), and 4-(dimethylamino)pyridine (640 mg, 5.2 mmol) in dichloromethane (25 mL) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residual oil was chromatographed on a silica gel column. Elution with methylene chloride–methanol (60:1) afforded **9d** (1.17 g, 89%): mp 65–70 °C; $[\alpha]_D$ = +98.5° (*c* = 1, MeOH).

[2*S*-[2α,3α,5(*R)]]-3-(Acetyloxy)-2,3-dihydro-8-methoxy-2-(4-methoxyphenyl)-5-(2-pyrrolidinylmethyl)-1,5-benzothiazepin-4(5*H*)-one, Monohydrochloride (5d).** A solution of **9d** (1.13 g, 2.03 mmol) in dichloromethane (10 mL) and trifluoroacetic acid (10 ml) was stirred at room temperature for 30 min. The solution was concentrated and the residual pale orange oil was dissolved in EtOAc (30 mL) and treated with saturated aqueous $KHCO_3$. The EtOAc extract was dried ($MgSO_4$), filtered, and concentrated. The pale yellow solid was dissolved in acetonitrile (10 mL) and treated with a 5.1 N solution of hydrogen chloride in ethanol (0.40 mL). The solution was diluted with ether (50 mL) to obtain a solid (870 mg, 80%) which was recrystallized from acetonitrile (150 mL) to obtain **5d** (780 mg): mp 228–230 °C, $[\alpha]_D$ = +49° (*c* = 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1 H), 7.34 (d, 2 H), 7.27 (d, 1 H), 7.10 (dd, 1 H), 6.90 (d, 2 H), 5.18 (d, 1 H), 5.03 (d, 1 H), 4.44 (dd, 1 H), 4.25 (dd, 1 H), 4.00 (m, 1 H), 3.85 (s, 3 H), 3.82 (s, 9 H), 3.41 (m, 2 H), 2.25–2.17 (m, 6 H), 1.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.5, 170.2, 160.4, 159.3, 137.2, 131.0, 129.3, 126.4, 126.0, 121.0, 118.0, 114.4, 71.7, 59.6, 56.3, 55.7, 54.7, 50.6, 45.5, 28.9, 24.2, 20.9. Anal. ($C_{24}H_{28}N_2O_5S$·HCl) C, H, N, Cl, S.

[3*R*-[1*S,3α,4α]]-3(Acetyloxy)-1,3,4,5-tetrahydro-7-methoxy-4-(4-methoxyphenyl)-1-(2-pyrrolidinylmethyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (5c). Method III.** A solution of *cis*-1,3,4,5-tetrahydro-3-hydroxy-7-methoxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (see ref 1 for method of preparation) (**6c**; 3 g, 9.57 mmol), **7a** (6.8 g, 19.13 mmol), and cesium carbonate (6.24 g, 19.15 mmol) in DMF (30 mL) was heated to 50 °C overnight. Extractive workup, following the procedure described in preparation of **8d**, and subsequent chromatography on a silica gel column with 33% EtOAc in hexanes as eluent afforded a 1:1 mixture of **8c** and its diastereomer (4.58 g, 96%) as a foam. A solution of this mixture (4.55 g, 9.16 mmol), acetic anhydride (4.32 mL, 45.79 mmol), and 4-(dimethylamino)pyridine (2.24 g, 18.34 mmol) in dichloromethane (142 mL) was stirred at room temperature for 24 h. The reaction was concentrated, and the residual oil was chromatographed on a silica gel column (50% EtOAc in hexanes) to give a mixture of **9c** and its diastereomer (4.05 g, 82%) as a yellow foam. A solution of **9c** and its diastereomer (4.25 g, 7.89 mmol) and trifluoroacetic acid (36 mL) in dichloromethane (36 mL) was stirred at room temperature for 1 h. The reaction was then concentrated and the residual oil dissolved in EtOAc (150 mL) and washed with saturated $NaHCO_3$ solution (100 mL, 2×). The EtOAc extract was dried ($MgSO_4$), filtered, and concentrated by coevaporation with ether. The yellow solid was crystallized from acetonitrile to obtain enantiomerically pure **5c** (910 mg, 53% of theory: mp 287–288 °C, $[\alpha]_D$ = +102.7° (*c* = 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 1 H), 7.16 (d, 2 H), 6.89 (m, 4 H), 5.17 (d, 1 H), 4.48 (dd, 1 H), 4.27 (bs, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.52 (m, 1 H), 3.37 (m, 1 H), 2.89 (m, 2 H), 2.22 (m, 2 H), 1.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 20.1, 22.9, 28.3, 37.5, 46.4, 49.9, 54.8, 55.2, 58.8, 71.3, 113.5, 114.8, 123.8, 128.8, 131.4, 133.9, 134.6, 158.2, 158.5, 169.6, 170.1. Anal. ($C_{25}H_{30}N_2O_5$·HCl·0.25H_2O) C, H, N, Cl.

***threo*-2-Hydroxy-3-[(2-amino-5-methoxyphenyl)thio]-3-(4-methoxyphenyl)propionic Acid, Methyl Ester (11).** A suspension of *trans*-3-(4-methoxyphenyl)oxiranecarboxylic acid, methyl ester (50.5 g, 243 mmol) and 2-amino-5-methoxythiophenol (42.9. g. 276 mmol) in toluene (300 mL) was refluxed for 6 h with a slow stream of nitrogen passing over the reaction. The resulting solution was then cooled and concentrated to a yellow-brown solid which was recrystallized from ethanol twice to yield the desired adduct **11** (52.7 g, 63% yield): mp 101–103 °C (lit.[7] 99.5–102.5 °C). Anal. ($C_{18}H_{21}NO_5S$) C, H, N, S.

(2*S*,3*S*)-2-Hydroxy-3-[(2-amino-5-methoxyphenyl)thio]-3-(4-methoxyphenyl)propionic Acid, Methyl Ester, D-(–)-**Tartaric Acid Salt (12).** A mixture of **11** (5.45 g, 15 mmol) and D-(–)-tartaric acid (2.50 g, 16.7 mmol) was slurried in 95% ethanol (50 mL) and heated to effect solution. The warm solution was cooled in a water bath which resulted in the formation of a crystalline product. After standing for 3 h, the solid was filtered, washed with cold 95% ethanol, and dried. This material (3.73 g) was recrystallized once from 95% ethanol (40 mL) to afford 3.20 g (83% of theory) of the desired product: mp 168–169 °C; $[\alpha]_D$ = +140° (*c* = 1, methanol). Subsequent recrystallizations did not change either the rotation or the mp of this material. Anal. ($C_{18}H_{21}NO_5S$·$C_4H_6O_6$) C, H, N, S.

(2*S*,3*S*)-2-Hydroxy-3-[(2-amino-5-methoxyphenyl)thio]-3-(4-methoxyphenyl)propionic Acid (13). A sample of **12** (8.0 g, 15.6 mmol) was added to a solution of sodium hydroxide (4.0 g, 100 mmol) in water (80 mL) followed by the addition of methanol (80 mL) which resulted in the rapid formation of a clear solution. After 1 h, the reaction was diluted with water (120 mL) and cooled with stirring while 1 N HCl (80 mL) was slowly added. After continued cooling for 2 h, the resulting heavy precipitate was filtered and dried to afford 5.35 g of **13** (98%): mp 188–189 °C dec; $[\alpha]_D$ = +286° (*c* = 1, DMF). Anal. ($C_{17}H_{19}NO_5S$) C, H, N, S.

(2*S*,3*S*)-2,3-Dihydro-3-hydroxy-8-methoxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (6d). A solution of **13** (5.25 g, 10.2 mmol) in DMF (150 mL) was treated with a solution of ethyl [3-(dimethylamino)propyl]carbodiimide hydrochloride (3.40 g, 17.8 mmol) in water (20 mL). The pH of the solution was maintained at 4.5 to 5.0 by the dropwise addition of 1 N HCl (ca. 10 drops) during the course of the reaction which appeared to

be complete after ca. 3 min (no further addition of HCl required). The mixture was stirred for an additional 50 min and poured into 800 mL of ice–water resulting in the formation of a precipitate. The mixture was cooled in an ice bath for an additional 4 h and filtered, and the solids were washed with additional water. After drying, **6d** (4.87 g, 98%) was obtained as a colorless solid: mp 190–191 °C; $[\alpha]_D$ = +95° (c = 1, methanol), [lit. mp 187–190 °C, $[\alpha]_D$ = +99° (c = 0.26, DMF)].[7] Anal. ($C_{17}H_{17}NO_4S$) C, H, N, S.

(3*R*-*cis*)-3-(Acetyloxy)-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (1f). A solution of (3*R*-*cis*)-3-(acetyloxy)-7-chloro-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one monohydrochloride (**1h**, 170 mg, 0.36 mmol, see ref 1 for preparation) was neutralized in ether by washing with with saturated $NaHCO_3$. The ether solution of the free base was then concentrated and the residue redissolved in acetic acid (10 mL). Catalyst was then added (80 mg of 10% Pd/C), and the mixture was shaken overnight under 30 psi of hydrogen gas at room temperature. The mixture was then filtered through Celite and the filtrate, plus washes, was washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated. The residue was dissolved in ether and treated with HCl-saturated ether. The resulting white precipitate was filtered and dried to yield 0.13 g (83%) of the desired product: mp 63–65 °C; $[\alpha]_D$ = +117.2° (c = 1, MeOH); ^1H NMR (CD_3OD) δ 7.45 (m, 3 H), 7.35 (m, 1 H), 7.25 (d, 2 H), 6.90 (d, 2 H), 5.05 (d, 1 H), 4.30 (m, 2 H), 3.80 (m, 4 H), 3.65 (m, 1 H), 3.45 (m, 1 H), 3.00 (m, 8 H), 1.85 (s, 3 H); ^{13}C NMR (CD_3OD) δ 20.35, 37.94, 44.05, 45.34, 51.53, 55.74, 56.46, 73.19, 114.71, 123.76, 128.88, 129.95, 130.67, 130.96, 132.63, 135.51, 141.38, 160.41, 171.07, 171.79. Anal. ($C_{23}H_{29}N_2O_4$·HCl·1.5H_2O) C, H, N.

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Studies on Antidiabetic Agents. 11.[1] Novel Thiazolidinedione Derivatives as Potent Hypoglycemic and Hypolipidemic Agents[2]

Takashi Sohda,* Katsutoshi Mizuno, Yu Momose, Hitoshi Ikeda, Takeshi Fujita, and Kanji Meguro

Research and Development Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan. *Received January 13, 1992*

In the course of further chemical modification of the novel antidiabetic pioglitazone (AD-4833, U-72, 107), a series of 5-[4-(2- or 4-azolylalkoxy)benzyl- or -benzylidene]-2,4-thiazolidinediones was prepared and evaluated for hypoglycemic and hypolipidemic activities in insulin-resistant, genetically obese, and diabetic KKA^y mice. Replacement of the 2-pyridyl moiety of pioglitazone by a 2- or 4-oxazolyl or a 2- or 4-thiazolyl moiety greatly enhanced in vivo potency. The corresponding 5-benzylidene-type compounds, in which a methine was used as a linker between the benzene ring and the thiazolidinedione ring, also had potent biological activity. Among the compounds synthesized, 5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-thiazolidinedione (**18**) exhibited the most potent activity, more than 100 times that of pioglitazone. The synthesis and structure–activity relationships for this novel series of derivatives are detailed.

Introduction

Insulin resistance is a characteristic feature of non-insulin-dependent diabetes mellitus (NIDDM), in particular when it is associated with obesity. This insulin-resistant state at the peripheral tissue level causes impaired glucose utilization leading to hyperglycemia.[3] Therefore, amelioration of insulin resistance with a drug would provide a novel and useful means of treating NIDDM. With regard to this concept[3,4] few drugs have, however, been studied, and exercise and calorimetric restriction are still the fundamental modes of treating NIDDM patients. It has been reported that sulfonylureas, the most commonly used oral hypoglycemics, potentiate insulin action in peripheral tissues by increasing the number of insulin receptors;[5] however, their main mechanism of action actually involves insulin secretion. This insulin secretion can bring about undesired effects such as induction of hypoglycemia.

In 1982, we reported a series of 5-(4-alkoxybenzyl)-2,4-thiazolidinediones[6a] as novel antidiabetic agents which were shown to effectively reduce insulin resistance or potentiate insulin action in genetically diabetic and/or obese animals. Ciglitazone, a prototypical compound of the series (Chart I), was shown to normalize hyperglycemia, hyper-

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