Benzazepinone Calcium Channel Blockers. 3. Synthesis and Structure-Activity Studies of 3-Alkylbenzazepinones[1]

Jagabandhu Das,* David M. Floyd,* S. David Kimball, Keith J. Duff, Truc Chi Vu, Michael W. Lago, Robert V. Moquin, Ving G. Lee, Jack Z. Gougoutas, Mary F. Malley, Suzanne Moreland, Russell J. Brittain, S. Anders Hedberg, and Gabriella G. Cucinotta

Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-4000.
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As part of a program aimed at identifying novel analogues of diltiazem, we developed several synthetic routes for 3-alkylbenzazepinones, both in racemic and nonracemic form. Structure–activity relationship studies in this series have led to identification of several analogues as potent calcium channel blocking agents, both in vitro and in vivo. Analogues containing a 6-trifluoromethyl substituent (**17a** and **17b**) are the most potent vasorelaxants in vitro. The oral antihypertensive activity of these compounds is comparable to its 3-acetoxy derivative 1 (X = 6-CF_3) and 8-chlorodiltiazem (**2b**). The 3-allyl analogue **17c** is a more potent antihypertensive agent than **17a**, **17b**, or 8-chlorodiltiazem (**2b**), and has a longer duration of action in vivo.

In the preceding paper, we described the synthesis, preliminary, structure–activity, and antihypertensive activity of a series of 3-acetoxy-1-benzazepin-2-one analogues (1) of diltiazem (**2a**) (Figure 1).[2] We demonstrated that, like the benzothiazepinone (diltiazem) series, both the absolute and relative stereochemistry of the C3 and C4 (benzazepinone numbering) substituents are important to calcium channel blocking activity in the benzazepinone series. One of the potential advantages we foresaw with the benzazepinone ring system was the increase in stability of the 7-membered carbocyclic ring relative to the benzothiazepinone ring by removing the possibility for ring cleavage via β-elimination of the thiophenoxide moiety. Consequently, we anticipated the benzazepinone ring system would allow us to explore structure–activity at C3 more fully. Consistent with this expectation, we were easily able to prepare the racemic 3-alkylbenzazepinone derivatives **3**.[3]

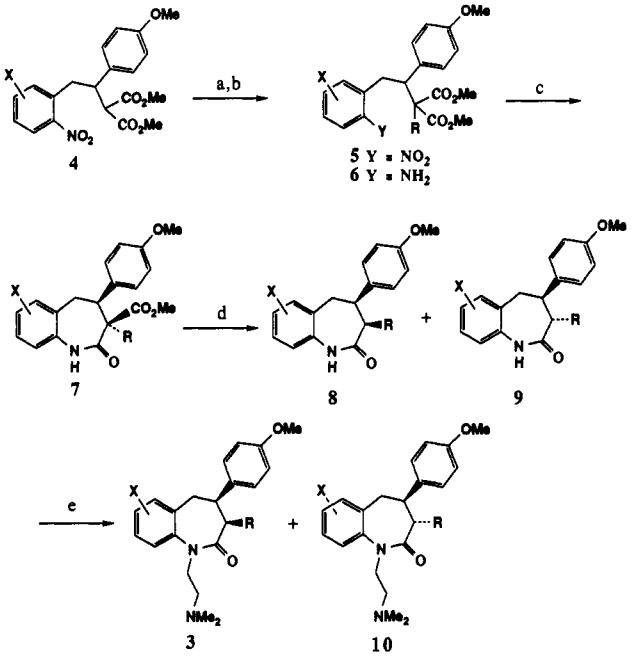
In this paper we report additional synthetic procedures that afford nonracemic 3-alkylbenzazepinones. We also report on the general structure–activity relationships in this series. Analogous to the 3-acetoxybenzazepinones, the 6-trifluoromethyl substituent appears to be important to maximal potency in vitro and antihypertensive activity. These studies have resulted in the identification of some of the most potent benzazepinone/benzothiazepinone calcium channel blocking agents reported to date.

Chemistry

The preparation of racemic 3-alkylbenzazepinones **3** was accomplished by procedures described previously as outlined in Scheme I.[3] Alkylation of intermediate **4** occurred under mild conditions to afford excellent yields of **5**, which was reduced either catalytically or with stannous chloride in acidic media to provide anilines **6** in high yield. Cyclization in the presence of sodium methoxide gave the desired 3,3-disubstituted benzazepinones **7**, again in excellent yields. Decarboxylation of **7** with lithium bromide in hot DMF in the presence of *p*-aminothiophenol (see below) generally afforded the desired cis-3,4-disubstituted benzazepinone **8** as the major product contaminated by its trans isomer **9**. Alkylation of the mixture of **8** and **9** at N1 with (*N,N*-dimethylamino)ethyl chloride (NaH/DMF) gave the C3 epimers **3** and **10**. The desired isomer **3** could be separated from trans isomer **10** by either crystallization or chromatography. Although these methods were generally applicable to the preparation of racemic analogues, we were unable to effect resolution of the 3-alkylbenzazepinone enantiomers using this route. Therefore, it was necessary to develop alternate procedures (Scheme II) based on nonracemic 3-carbomethoxybenzazepinones which are available by the methods previously described for the preparation of nonracemic **11**.[2]

Direct alkylation of **11** was not preparatively useful. For example, treatment of the racemic 7-chlorobenzazepinone analogue of **11** with lithium diisopropylamide (3 equiv) in

Scheme I.[a] Preparation of Racemic Benzazepinones



[a] (a) DMF, NaH, RX; (b) H_2, Pd/C; or $SnCl_2$, HCl, MeOH; (c) NaOMe, MeOH, reflux; (d) LiI, pyridine-H_2O (1%), 100 °C; or LiBr, DMF, 4-aminothiophenol, 135 °C; (e) (*N,N*-dimethylamino)-ethyl chloride, NaH, DMF, 80 °C; or K_2CO_3, KI (cat.), methyl ethyl ketone, (*N,N*-dimethylamino)ethyl chloride, 80 °C.

(1) This work was presented in a preliminary form at the 198th National ACS meeting at Miami Beach, Florida, September 10–15, 1989. See: Das, J.; Floyd, D. M.; Moreland, S.; Hedberg, S. A. Structure Activity of 3-Alkyl-benzazepin-2-ones. *Abstracts of Papers*; American Chemical Society: Washington, DC, 1989; Med Chem 93.

(2) 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. II. Structure–Activity and Drug Metabolism Studies Leading to Potent Antihypertensive Agents. Comparison with Benzothiazepinones, preceeding paper in this issue.

(3) 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.

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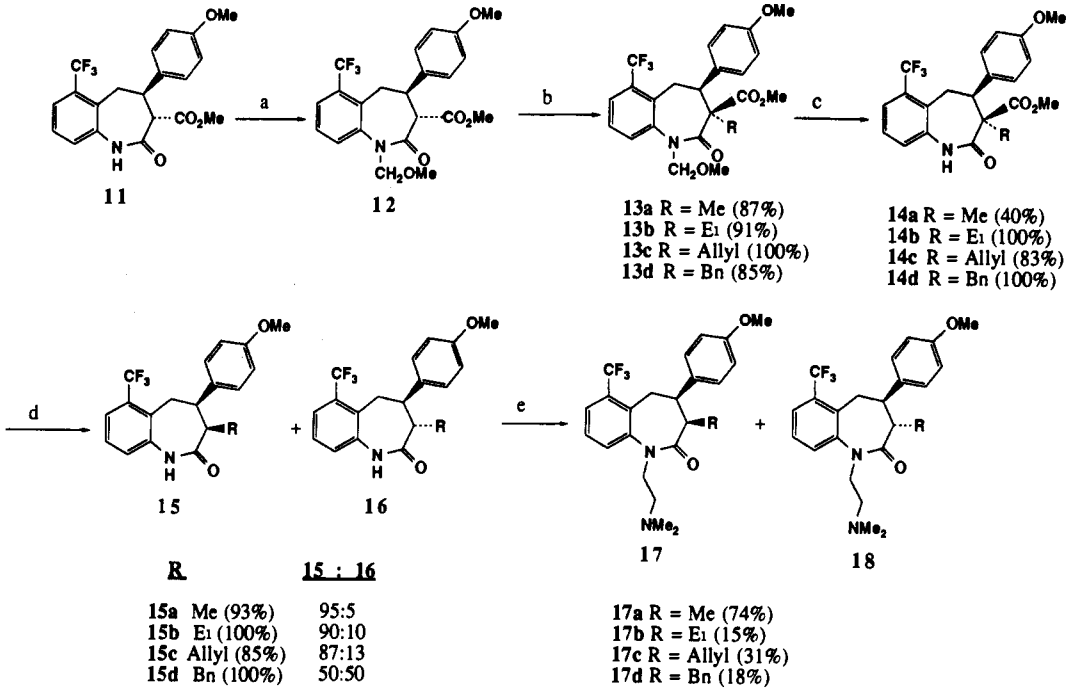
Scheme II.[a] Preparation of Nonracemic 3-Alkyl-6-(trifluoromethyl)benzazepinones



[a] (a) NaH, DMF, $MeOCH_2Br$; (b) DMF, NaH, RX; (c) LiBr, MeOH, H_2SO_4, 80 °C; (d) LiBr, 4-aminothiophenol, DMF, 135 °C; (e) (*N*,*N*-dimethylamino)ethyl chloride, NaH, DMF, 80 °C.

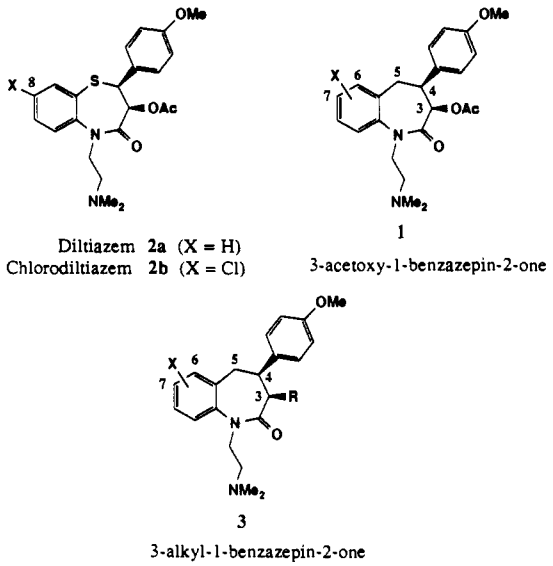


Figure 1.

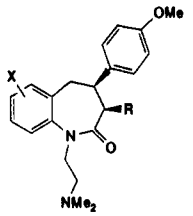
THF at −78 °C followed by the addition of excess iodomethane and allowing the reaction to warm to −20 °C over several hours gave the methylated adduct (7-chloro analogue of **14**) in 45% isolated yield. Under similar conditions, employing a 6-day reaction time, this alkylation procedure afforded only a 19% yield of the 3-ethyl analogue, with 56% recovery of starting material.

More reliable results were obtained by first blocking the amide functionality as shown in Scheme II. In this approach, nonracemic 3-carbomethoxybenzazepinone **11** was first treated with sodium hydride in THF at −78 °C followed by the addition of 1.2 equiv of bromomethyl methyl ether to give the *N*-methoxymethyl adduct **12** in nearly quantitative yield. Deprotonation of **12** was then accomplished with sodium hydride in DMF at 0 °C. The addition of an alkyl halide gave the alkylated adducts (**13a–d**) in high yield as single diastereoisomers.[4] This stereochemical result is analogous to those obtained during the oxidation of **11** and related systems,[3] where we assumed alkylation of **12** occurred exclusively from the least hindered α-face of the molecule. Except for the methyl adduct **13a**, removal of the methoxymethyl protecting group with LiBr in a mixture of hot MeOH and H_2SO_4 proceeded smoothly and in high yield to afford nonracemic 3,3-disubstituted 6-(trifluoromethyl)benzazepinones **14**. With the 3-methyl adduct **13a**, only a 40% isolated yield was obtained during the deprotection step; the major byproducts resulted from partial opening of the lactam ring and ester hydrolysis. The yield for this substrate was improved significantly (83% isolated yield of **14a**) when the crude reaction products were treated with ethereal diazomethane and subsequently recyclized.

Unlike the 3-hydroxy series,[2,3] decarbomethoxylation of **14a–d** using lithium iodide in wet pyridine formed a significant amount of the undesired trans product. For example, reaction of 3-allyl adduct **14c** with LiI in pyridine and water (1%) at 100 °C formed the cis and trans adducts **15c** and **16c** in roughly 3:2 ratio. Changing the solvent to DMF at reflux improved the ratio in favor of **15c**, but also resulted in the formation of ca. 30% of the *N*-methyl adduct which arises from the amide nitrogen trapping methyl iodide generated during the reaction. This problem was partially circumvented by substituting lithium bromide for lithium iodide, and completely eliminated by incorporating 4-aminothiophenol as a scavenger for the methyl halide educt. As shown in Scheme II, the stereochemical outcome of the decarbomethoxylation reaction is dependent on the size of the alkyl group, with the methyl adduct **14a** providing 95% of the cis product **15a**. Under the same conditions, the benzyl analogue **14d** gave a 1:1 mixture of

(4) This stereochemical assignment is based on single-crystal X-ray analyses of **7** (racemic **14b**) and the corresponding acid. The conclusion that only one diastereomer is formed in these reactions is based on the ^1H NMR spectra of the crude alkylated products.

Table I. Physical Data of Final Compounds



compd	isomer	X	R	% yield from 4	mp (°C)	recryst solvent	formula	analysis
3a	racemic	H	Me	7	211–16	Et_2O	$C_{22}H_{28}N_2O_2 \cdot HCl$	C,H,N,Cl
3b	racemic	H	allyl	17	154–57	EtOAc/Et_2O	$C_{24}H_{30}N_2O_2 \cdot HCl$	C,H,N,Cl
3c	racemic	H	propyl	17	178–80	EtOAc/Et_2O	$C_{24}H_{32}N_2O_2 \cdot HCl$	C,H,N,Cl
3d	racemic	7-Cl	Me	22[a]	228–31	Et_2O	$C_{22}H_{27}ClN_2O_2 \cdot HCl$	C,H,N,Cl
3e	racemic	7-Cl	Et	6[a]	108–10	Et_2O	$C_{23}H_{29}ClN_2O_2 \cdot HCl$	C,H,N,Cl
3f	racemic	7-Cl	allyl	13	116–18	EtOAc/Et_2O	$C_{25}H_{29}ClN_2O_2 \cdot HCl$	C,H,N,Cl
3g	racemic	6-Cl	Et	3	179–81	EtOAc/hexane	$C_{27}H_{32}ClN_2O_6 \cdot C_4H_4O_4$	C,H,N,Cl
3h	racemic	6-OMe	Me	25	243–44	Et_2O	$C_{23}H_{30}N_2O_3 \cdot HCl$	C,H,N,Cl
3i	racemic	6-OMe, 7-Br	Me	26	142–46	Et_2O	$C_{23}H_{29}BrN_2O_3 \cdot HCl$	C,H,N,Br,Cl
3j	racemic	6-OMe, 7-SMe	Me	13	200–01	Et_2O	$C_{24}H_{32}N_2O_3S \cdot HCl$	C,H,N,Cl,S
3k	racemic	6-CF_3	Me	54	99–101	Et_2O	$C_{23}H_{27}F_3N_2O_2 \cdot C_4H_4O_4$	C,H,N,F
3l	racemic	6-CF_3	allyl	22	226–28	Et_2O	$C_{25}H_{29}F_3N_2O_2 \cdot HCl$	C,H,N,Cl,F
3m	racemic	6-CF_3	propyl	13	181–83	Et_2O	$C_{25}H_{31}F_3N_2O_2 \cdot HCl$	C,H,N,Cl,F
3n	racemic	7-CF_3	Me	19	130–35	CH_2Cl_2/hexane	$C_{23}H_{27}F_3N_2O_2 \cdot HCl$	C,H,N,Cl,F
3o	racemic	7-CF_3	allyl	11	218–20	Et_2O	$C_{25}H_{29}F_3N_2O_2 \cdot HCl$	C,H,N,Cl,F
3p	racemic	7-CF_3	propyl	27	234–35	Et_2O	$C_{25}H_{31}F_3N_2O_2 \cdot HCl$	C,H,N,Cl,F
17a[b]	3*R*,4*S*	6-CF_3	Me[c]	24	150–51	CH_2Cl_2	$C_{23}H_{27}F_3N_2O_2 \cdot C_4H_4O_4$	C,H,N,F
17b[d]	3*R*,4*S*	6-CF_3	Et[c]	14	162–64	Et_2O	$C_{24}H_{29}F_3N_2O_2 \cdot HCl$	C,H,N,Cl,F
17c[e]	3*R*,4*S*	6-CF_3	allyl[c]	31	225–27	EtOAc/Et_2O	$C_{25}H_{29}F_3N_2O_2 \cdot HCl$	C,H,N,Cl,F
17d[f]	3*R*,4*S*	6-CF_3	Bn[c]	14	155–59	MeOH	$C_{25}H_{29}F_3N_2O_2 \cdot C_4H_4O_4$	C,H,N,F
10k	racemic (trans)	6-CF_3	Me	5	224–25	Et_2O	$C_{23}H_{27}F_3N_2O_2 \cdot HCl$	C,H,Cl,N,F

[a] Overall yield from racemic 7-Cl analogue of 11. [b] $[\alpha]_D$ +108° (c = 1, MeOH). [c] Overall yield from 11. [d] $[\alpha]_D$ +112° (c = 1, MeOH). [e] $[\alpha]_D$ +100° (c = 1, MeOH). [f] $[\alpha]_D$ +55.2° (c = 1, MeOH).

isomers **15d** and **16d**. The ratio of the cis and trans products in this decarbomethoxylation step was determined by analysis of ^1H NMR spectra. By analogy to the 3-hydroxy series, the coupling constant between protons at C3 and C4 ($J_{3,4}$ = 7 Hz for cis and $J_{3,4}$ = 10 Hz for trans) was diagnostic for establishing the relative stereochemistry at these centers.[3,5d] Generally, the cis and trans epimers were not separated at this stage. The crude mixture of **15** and **16** was alkylated with (*N*,*N*-dimethylamino)ethyl chloride in hot DMF (NaH) and the nonracemic cis products **17** were isolated by flash chromatography on a silica gel column and/or crystallization. The corresponding trans products **18** could also be isolated from these mixtures, e.g., **18** (R = Et). The physical properties of the materials prepared by the above procedures are listed in Table I.

The relative stereochemistry of **17a–d**, **18b** (R = Et),[6] and **8** (X = 7-Cl, R = Me) have been determined by single-crystal X-ray analysis and support the assignment of relative stereochemistry based on NMR spectral analysis.[7] The solid-state molecular conformations of the C3 cis

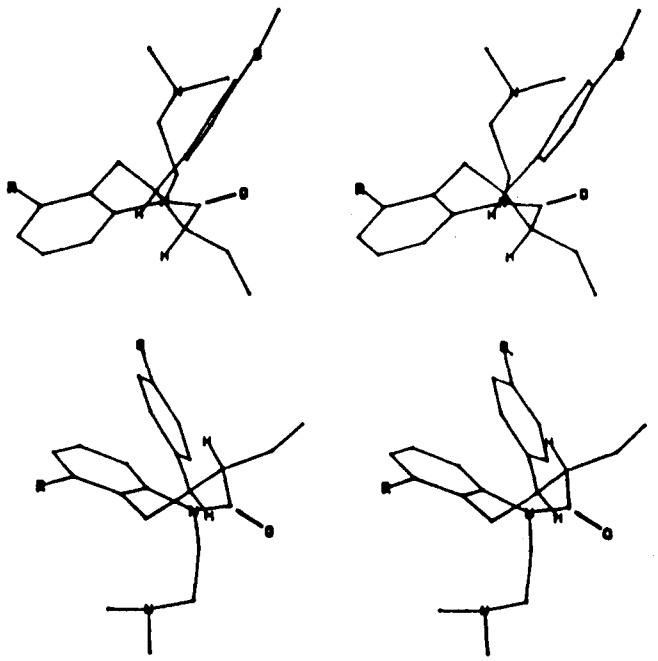


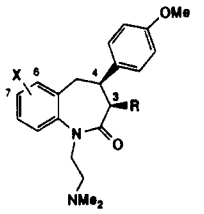
Figure 2. Stereoscopic comparison of the solid-state conformations of the C3 cis (**17b**, top) and C3 trans (**18b**, bottom) ethyl derivatives. The CF_3 group and most hydrogens have been omitted for clarity.

(5) (a) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. Synthesis of 1,5-Benzothiazepine Derivatives. III. *Chem. Pharm. Bull.* **1971**, *19*, 595–602. (b) Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. Studies on a New 1,5-Benzothiazepine Derivative (CRD-401). IV. Coronary Vasodilating Effect and Structure-Activity Relationship. *Chem. Pharm. Bull.* **1973**, *21*, 92–97. (c) Inoue, H.; Konda, M.; Hashiyama, T.; Otsuka, H.; Takahashi, K.; Gaino, M.; Date, T.; Aoe, K.; Takeda, M.; Murata, S.; Narita, H.; Nagao, T. Synthesis of Halogen-Substituted 1,5-Benzothiazepine Derivatives and Their Vasodilating and Hypotensive Activities. *J. Med. Chem.* **1991**, *34*, 675–687. (d) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. Synthesis of 1,5-Benzothiazepine Derivatives. II. *Chem. Pharm. Bull.* **1970**, *18*, 2284.

(6) Compound **18b** (R = Et) was isolated in crystalline form (<1 mg) by repeated recrystallization of a mixture of **17b** and **18b** from hot diethyl ether. The only analytical data available for this compound is the structure, as determined by X-ray crystallography.

(7) The absolute configuration of the biologically active series was established by X-ray analysis of the (*S*)-(−)-α-methylbenzylamine salt of the free acid of **11**. See Experimental Section for details.

Table II. Activity of Racemic 3-Alkyl-Substituted Benzazepinones in Vitro and in Vivo



compd	X	R	IC_{50} (μM)[a]	k_d (μM)[b]	% decrease in BP @ 135 μmol/kg po[c] 0–6 h	6–12 h	12–18 h
3a	H	Me	1.10 (0.61–1.90)	0.65 (±0.22)	6	4	8
3b	H	allyl	0.19 (0.12–0.32)	0.05 (±0.01)	25	23	18
3c	H	Pr	0.34 (0.23–0.52)	0.25 (±0.08)	10	11	12
3d	7-Cl	Me	0.15 (0.06–0.41)	0.67 (±0.13)	12	13	11
3e	7-Cl	Et	0.28 (0.16–0.50)	NT	20	22	21
3f	7-Cl	allyl	0.16 (0.09–0.29)	5.04 (±3.86)	23	23	25
3g	6-Cl	Et	0.08 (0.06–0.10)	NT	14	18	7[d]
3h	6-OMe	Me	0.42 (0.31–0.58)	0.40[e]	7	10	8
3i	6-OMe, 7-Br	Me	0.09 (0.06–0.12)	0.12 (±0.04)	9	12	14
3j	6-OMe, 7-SMe	Me	0.07 (0.04–0.13)	NT	18	15	14
3k	6-CF_3	Me	0.08 (0.04–0.14)	90% @ 1 μM	28	22	22
3l	6-CF_3	allyl	0.10 (0.06–0.17)	NT	24	27	29[d]
3m	6-CF_3	Pr	0.95 (0.01–63)	NT	14	19	24[d]
3n	7-CF_3	Me	1.23 (0.85–1.80)	NT	23	23	25
3o	7-CF_3	allyl	0.24 (0.15–0.37)	NT	23	28	30[d]
3p	7-CF_3	Pr	1.20 (0.88–1.50)	NT	6	5	8[d]
10k	6-CF_3	Me (trans)	3.29 (2.02–5.36)	NT	12	9	8

[a] IC_{50} in rabbit aorta strips contracted with KCl (95% confidence interval). [b] k_d determined by displacement of radiolabeled diltiazem in guinea pig striated muscle (±SEM). [c] In spontaneously hypertensive rats, $n = 5$. [d] Dosed at 45 μmol/kg po. [e] Based on concentration-effect curve using tissue from one animal.

substituted alkyl derivatives (see Figure 2, structure of **17b**) are essentially identical to that of diltiazem[8] ("M" twist-boat conformation of the heptagonal ring with equatorial cis C3-substituent), and are in accord with our X-ray analyses of twenty variously substituted cis C3-derivatives. By contrast, most trans derivatives studied (see Figure 2, structure of **18b** (R = Et)) adopted a solid-state conformation in which the heptagonal ring is inverted ("P" twist-boat conformation with an equatorial trans C3-substituent). The spatial relationship of the C4 methoxyphenyl ring and the N1 substituent of the essentially planar amide group is markedly different for these conformers. This gross dissimilarity in the overall molecular shape of the two isomers may be an important basis for the significant difference in biological activity observed between cis and trans epimers in this and the benzothiazepinone series.[3]

Structure–Activity Relationships

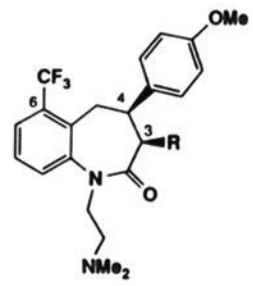
The pharmacological test procedures summarized in Table II have been described in the preceding paper.[2] These data indicate that the effects on biological activity of aromatic substituents at either C6 or C7 are similar to those observed in the 3-acetoxy series.[2] With 3-methyl analogues, substitution at C6 with either a trifluoromethyl (**3k**) or a methoxy group (**3h**) results in an increase in potency in vitro relative to **3a**, which contains no aromatic substituent. The incorporation of a C7 chlorine substituent (**3d**) in the 3-methyl series results in a significant increase in potency, whereas the 7-trifluoromethyl analogue **3n** is equipotent to unsubstituted **3a**. These results are essentially identical to those obtained in the 3-acetoxy series.[2] Comparing the potency of the 6,7-disubstituted analogues **3i** and **3j** to either **3a** or the monosubstituted 6-methoxy derivative **3h** demonstrates that the addition of a lipophilic C7 substituent to the 6-methoxy nucleus results in an increase of potency in vitro. This effect is most likely indicative of a general relationship between lipophilicity and potency in vitro which will be discussed in the following publication in this series. For 3-allyl substituted analogues, there is little effect of aromatic substitution (compare **3b** with **3f**, **3l**, and **3o**) on either potency in vitro or antihypertensive activity in SHR. Although less potent than the 3-methyl or 3-allyl analogues, compounds containing a propyl group at C3 (**3c**, **3m**, and **3p**) also show little effect of aromatic substitution. Thus, it appears that increasing the size of the C3 alkyl group eliminates the potency-enhancing effects of C6 or C7 substitution seen in either the 3-acetoxy or 3-methyl series.

Consistent with our previous results is the observation that compounds containing a trifluoromethyl substituent consistently show good antihypertensive activity in SHR upon oral dosing. Also in agreement with our previous work, analogues with a trifluoromethyl substituent at C6 show optimal vasorelaxant potency in vitro and antihypertensive activity in vivo.

Comparing the potency of **3k** to its trans isomer **10** (R = Me) in Table II clearly demonstrates the importance of cis relative stereochemistry, in agreement with previous results.[2] Upon the basis of these observations, we assumed the 3*R*,4*S* absolute configuration would also be favored for 3-alkylbenzazepinones. Therefore, we prepared additional nonracemic 3*R*,4*S* benzazepinones (Table III) in order to evaluate their activity in vitro and in vivo. In this series, the 3-methyl (**17a**) and 3-ethyl (**17b**) analogues are the most potent compounds, being about 10 times more potent than its 3-acetoxy analogue **1** (X = CF_3), diltiazem (**2a**), or its 8-chloro derivative (**2b**). The 3-allyl analogue **17c**

(8) Kojie-Prodic, B.; Ruzic-Toros, Z.; Sunjie, V.; Decorte, E.; Moimas, F. Absolute Conformation and Configuration of (2*S*,3*S*)-3-Acetoxy-5-(dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one Chloride (Dilthiazem Hydrochloride). *Helv. Chim. Acta* **1984**, *67*, 916–926.

Table III. Comparison of Nonracemic 6-Trifluoromethyl-3-alkylbenzazepinones in Vitro and in Vivo



compd	R	chirality	IC_{50} (μM)[a]	% decrease in BP @ 45 μmol/kg po[b] 0–6 h	6–12 h	12–18 h
17a	Me	3*R*,4*S*	0.017 (0.012–0.025)	24	23	17
17b	Et	3*R*,4*S*	0.012 (0.009–0.017)	24	19	15
17c	allyl	3*R*,4*S*	0.077 (0.049–0.12)	33	32	27
17d	Bn	3*R*,4*S*	0.79 (0.55–1.10)	14	8	6[c]
18b	Et	3*S*,4*S* (trans)	NT	NT		
1	OAc	3*R*,4*S*	0.15 (0.11–0.20)	17	12	12
2a	diltiazem		0.21 (0.13–0.36)	23	12	17[c]
2b	8-chlorodiltiazem		0.10 (0.06–0.18)	29	16	22

[a] IC_{50} in rabbit aorta strips contracted with KCl (95% confidence interval). [b] In spontaneously hypertensive rats, $n = 5$. [c] Dosed @ 135 μmol/kg po.

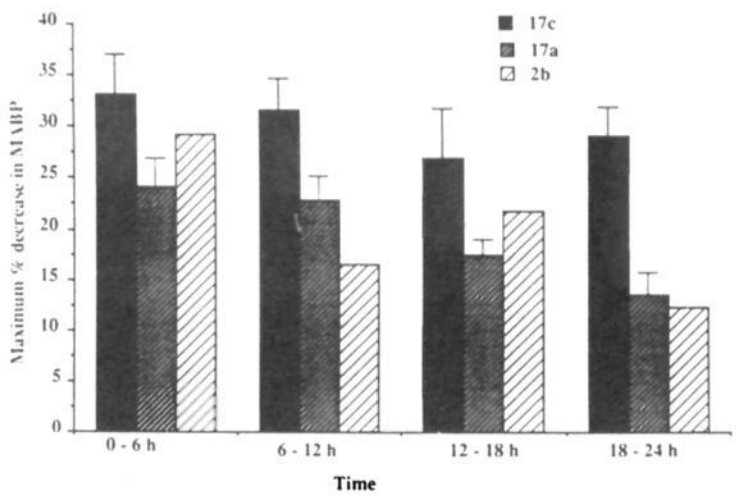


Figure 3. Comparison of oral antihypertensive effects of **17a**, **17c**, and **2b** in SHR at a dose of 45 μmol/kg ($n = 5$).

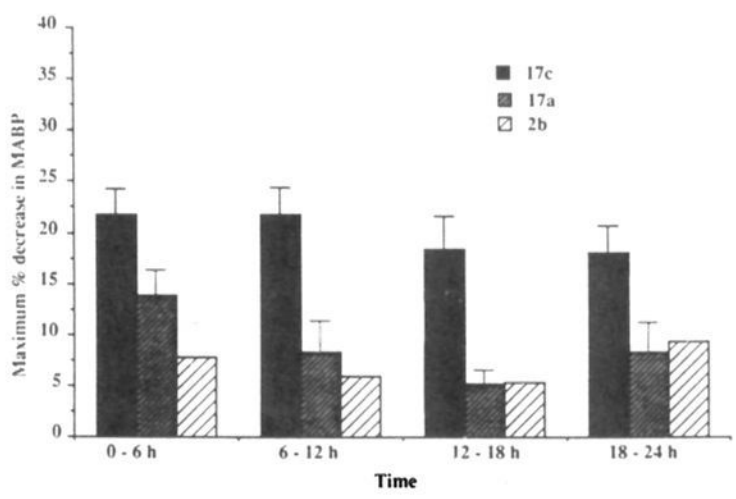


Figure 4. Comparison of oral antihypertensive effects of **17a**, **17c**, and **2b** in SHR at a dose of 15 μmol/kg ($n = 5$).

is somewhat less potent than either **17a** or **17b**, while benzyl adduct **17d** is the least potent compound in this series. As noted above, compounds containing a C3 propyl group also show attenuated activity in vitro and in vivo (compare **3b**, **3l**, **3o** with **3c**, **3m**, **3p**). Upon the basis of these data it appears that increased molecular volume of the C3 substituent may decrease activity in vitro and in vivo.

The antihypertensive activity of **17a**, **17b**, and **17c** is consistent with their potency in vitro and similar to that of 8-chlorodiltiazem (**2b**).[5c] These compounds are somewhat more potent antihypertensive agents than the analogous 3-acetoxybenzazepinone **1** (X = 6-CF_3). As predicted from its reduced potency in vitro, 3-benzyl analogue **17d** demonstrated only marginal antihypertensive activity at the dose noted in Table III. Examination of the data in Figures 3 and 4 reveals that the duration of antihypertensive activity demonstrated by allyl analogue **17c** is superior to other compounds. This distinction is highlighted by comparing the antihypertensive effects of **17c** with that of either **17a** or **2b** at an oral dose of 15 μmol/kg (Figure 4). At this dose, **17c** shows ca. 20% reduction in blood pressure that is maintained throughout the 24-h test period, whereas **2b** is essentially devoid of effect, and **17a** shows an effect only during the first few hours of the test. The difference between **17c** and **2b** may be rationalized by noting that deacetylation of the 3-acetoxy function of **2b** is an important metabolic process that is expected to reduce its calcium channel blocking activity.[9] The fact that **17c** cannot undergo this metabolic process may explain the different duration of action observed between the two compounds. However, the basis for the discrepancy in antihypertensive potency between **17c** and its 3-methyl analogue **17a** is obscure, especially in view of the fact that **17a** is significantly more potent in vitro. Regardless, the 3-allylbenzazepinone **17c** remains one of the most potent antihypertensive agents containing an (*N*,*N*-dimethylamino)ethyl N1 substituent that we have encountered in our extensive studies of diltiazem-like calcium channel blockers.

Summary

We have developed methods to prepare 3-alkylbenzazepinones that take advantage of the increased chemical stability of the benzazepinone ring system compared to the benzothiazepinone system. Pharmacological studies in this series demonstrate that the 3-acetoxy group can be replaced with an alkyl substituent, resulting in an improvement of potency in vitro. Analogues containing a 6-trifluoromethyl substituent are the most potent benzazepinones in vitro and demonstrate marked antihypertensive activity in SHR upon oral administration. The

(9) (a) Montamat, S. C.; Abernethy, D. R.; Mitchell, J. R. High-performance Liquid Chromatographic Determination of Diltiazem and Its Major Metabolites, N-monodemethyldiltiazem and Desacetyldiltiazem, in Plasma. *J. Chromatogr.* **1987**, *415*, 203–207. (b) LeBoeuf, E.; Grech-Belanger, O. Deacetylation of Diltiazem by Rat Liver. *Drug Metab. Dispos.* **1987**, *15*, 122–126.

Table IV. Crystal Structure Data

	8 (X = 7-Cl; R = Me)	11 (acid salt, ref 5)	7 (X = 6-CF_3; R = Et)	17a	17b	17c	17d	18b (R = Et)
a, Å	18.750 (4)	17.717 (8)	10.936 (8)	14.742 (4)	10.244 (2)	10.277 (1)	9.255 (2)	10.048 (4)
b, Å	7.518 (1)	6.455 (2)	11.621 (2)	22.151 (5)	12.837 (2)	12.829 (2)	14.895 (3)	12.479 (3)
c, Å	25.473 (5)	22.23 (1)	8.409 (2)	8.143 (2)	17.527 (1)	17.728 (1)	19.040 (3)	18.186 (5)
α°			82.19 (1)					
β°	97.95 (1)		98.75 (2)					
γ°			85.61 (3)					
V, Å^3	3556 (2)	2543 (3)	1041 (1)	2659 (2)	2304.9 (9)	2337.4 (7)	2625 (2)	2280 (2)
space group	C2/c	$p2_12_12_1$	P1bar	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
d_{obs}, g cm^{-3}	N/A	1.31	1.38	1.33	N/A	1.27	N/A	1.27
d_{calc}, g cm^{-3}	1.34	1.31	1.38	1.34	1.25	1.27	1.14	1.27
Z	8	4	2	4	4	4	4	4
formula	$C_{18}H_{18}NO_2Cl \cdot 0.5CH_2Cl_2$	$C_{27}H_{27}N_2O_4F_3$	$C_{23}H_{22}NO_4F_3$	$C_{27}H_{31}N_2O_6F_3$	$C_{24}H_{29}N_2O_2F_3$	$C_{25}H_{29}N_2O_2F_3$	$C_{25}H_{31}N_2O_2F_3$	$C_{24}H_{29}N_2O_2F_3$
NREFL[a]	3728	2045	4101	2109	2476	2519	2799	2449
NUNI[b]	3567	2019	3875	2085	2451	2479	2772	2421
NOBS[c]	1403	1385	2124	925	1499	1395	1764	1611
NV[d]	214	320	272	153	281	290	326	281
R	0.078	0.061	0.049	0.081	0.042	0.045	0.046	0.043
R_w	0.112	0.079	0.050	0.085	0.049	0.052	0.054	0.050

[a] Total number of reflections collected within 2θ max (140° for all except 11 (115°). [b] Number of symmetry-independent reflections. [c] Number of observed reflections with $I \geq 3\sigma(I)$ used in least-squares refinements. [d] Number of refined variables.

antihypertensive effects of **17a** and **17b** are greater than the corresponding 3-acetoxy derivative **1** (X = CF_3) and similar to that of 8-chlorodiltiazem (**2b**). The 3-allyl analogue **17c** appears to be the most potent and long-acting antihypertensive agent in this series and is clearly more potent than its 3-acetoxy analogue **1** (X = 6-CF_3) or **2b**. We believe these compounds could prove useful in the clinic as orally active, long-acting antihypertensive agents.

Experimental Section

Crystallographic Studies. Crystal data and some details of the structure refinements are given in Table IV. Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 15 high-angle reflections. Crystal densities were measured by flotation methods. Intensities were measured diffractometrically using Cu Kα radiation (λ = 1.5418 Å) at 23 °C with the θ–2θ variable scan technique and were corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. Except for 8 (X = 7-Cl, R = Me), no appreciable crystal decomposition was observed during data acquisition. No attempt was made to correct for the ~30% observed intensity decay for the CH_2Cl_2 solvate of 8 (0.38 instead of the idealized 0.5 site occupancy of CH_2Cl_2 was found in the structure analysis). The structures were solved by direct methods[10] and refined on the basis of observed reflections [$I \geq 3\sigma(I)$], using the SDP[11] software package. Least-squares weights $w = \sigma^{-2}(F_o)$ were calculated with the assumption that $\sigma^2 = \epsilon^2 + (pI)^2$, where ϵ is the statistical counting error and p = 0.02–0.04. The function minimized in the least-squares refinements is $\sum_w(|F_o| - |F_c|)^2$. R is defined as $\sum||F_o| - |F_c||/\sum|F_o|$, while R_w is defined as $[\sum_w(|F_o| - |F_c|)^2/\sum_w|F_o|^2]^{1/2}$. Most hydrogen positions were evident during the latter stages of refinement. All hydrogens on carbon were introduced in idealized positions; those on heteroatoms were introduced only if they were observed on difference maps. Although the scattering of hydrogens was included in the terminal stages of refinement, no hydrogen parameters were varied. Final difference maps contained no significant features.

General Chemical Procedures. Melting points were recorded on a Thomas-Hoover capillary apparatus and are 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. Optical rotations were recorded with a Perkin-Elmer 241 spectrophotometer. All reactions were conducted under an atmosphere of dry nitrogen or argon using anhydrous solvents unless noted otherwise. Table V contains physical data for synthetic intermediates.

α-Methyl-[1-(4-methoxyphenyl)-2-[2-nitro-5-(trifluoromethyl)phenyl]ethyl]propanedioic Acid, Dimethyl Ester (5n). Sodium hydride (890 mg, 18.4 mmol, 50% in oil) was added to a solution of **4n** (7 g, 15.4 mmol; see ref 2 and 3 for preparation) in dry DMF (35 mL). The suspension was stirred for 20 min, and iodomethane (11.6 g, 81.5 mmol) was added. After 4.5 h, the mixture was partitioned between ethyl acetate and 1 N HCl solution. The ethyl acetate extract was washed with saturated potassium carbonate and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a silica gel column and eluted with 10% and 20% EtOAc in hexanes to provide **5n** (6.9 g, 97%) as a viscous oil.

α-Methyl-[2-[2-amino-5-(trifluoromethyl)phenyl]-1-(4-methoxyphenyl)ethyl]propanedioic Acid, Dimethyl Ester (6n). A stirred solution of **5n** (6.8 g, 14.9 mmol) in methanol (200 mL) was treated with powdered stannous chloride dihydrate (17.48 g, 77.5 mmol) and concentrated HCl (19 mL). The resulting solution was stirred at room temperature for 1.5 h, treated with Celite, and diluted with ethyl acetate (500 mL) and saturated potassium carbonate solution. The suspension was filtered through a Celite pad and washed thoroughly with EtOAc. The filtrate was concentrated, and the residual solid was triturated with 10% methanol in water to give **6n** (6.02 g, 95%), mp 154–157 °C.

1,3,4,5-Tetrahydro-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-3-methyl-7-(trifluoromethyl)-2*H*-1-benzazepin-2-one (7n). A solution of sodium methoxide in methanol (14.2 mL, 25% by weight solution, 0.063 mol) was added to a stirred solution of **6n** (5.96 g, 13.56 mmol) in methanol (30 mL) and DMF (35 mL). The solution was heated to 95 °C overnight, cooled, and acidified with 1 N HCl solution. The precipitated solid was filtered, washed with water, and dried in vacuo to provide **7n** (4.88 g, 95%), mp 211–214 °C.

***cis*- and *trans*-1,3,4,5-Tetrahydro-4-(4-methoxyphenyl)-3-methyl-7-(trifluoromethyl)-2*H*-1-benzazepin-2-one (8n and 9n).** A solution of **7n** (4.0 g, 9.82 mmol) and anhydrous LiI (5.26 g, 39.3 mmol) in pyridine (40 mL) was heated under reflux for 8.5 h. The reaction mixture was cooled, diluted with EtOAc (200 mL), and washed with 1 N HCl (3×). The EtOAc extract was dried ($MgSO_4$), filtered, and concentrated to afford a colorless solid (3.43 g, a 4:1 mixture of **8n** and **9n**). The crude mixture was used in the next step without further purification.

***cis*-1-[2-(Dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-3-methyl-7-(trifluoromethyl)-2*H*-1-benzazepin-2-one, Monohydrochloride (3n).** Sodium hydride (556

(10) Main, P., Lessinger, L., Woolfson, M. M., Germain, G. and Declercq, J. P. MULTAN 78; University of York (England) and Louvain (Belgium), 1978.

(11) SDP, Structure Determination Package, A. Frenz & Associates, College Station, TX 77840. Scattering factors, including f' and f'', in the SDP software were taken from the *International Tables for Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol 4: Tables 2.2A and 2.3.1.

Table V. Physical Data for Synthetic Intermediates

compd	mp (°C)	% yield[a]	recrystn solvent	formula	analysis
5a	82–84	65	MeOH	$C_{22}H_{22}F_3NO_7$	C,H,N,F
5b	oil	80		$C_{23}H_{25}NO_7$	MS (CI): $(M + H)^+$
5g	95.5–97	78	MeOH	$C_{23}H_{24}ClNO_7$	C,H,Cl,N
5k	99.5–101.5	94	MeOH–H_2O	$C_{22}H_{22}F_3NO_7$	C,H,N,F
5l	oil	98		$C_{24}H_{24}F_3NO_7$	C,H,N,F
6a	165–167	77	MeOH	$C_{21}H_{25}NO_5$	C,H,N
6b	117–118	83	MeOH	$C_{23}H_{27}NO_5$	C,H,N
6h	168–168.5	87	EtOAc–hexane	$C_{22}H_{27}NO_6 \cdot 0.29H_2O$	C,H,N
6i	195–197	100	*b*	$C_{22}H_{26}BrNO_6$	C,H,Br,N
6k	145–146	100	*b*	$C_{22}H_{24}F_3NO_5$	C,H,N,F
7a	198–200.5	47	EtOAc–hexane	$C_{20}H_{21}NO_4$	C,H,N
7b	175–176.5	58	MeOH–H_2O	$C_{22}H_{23}NO_4$	C,H,N
7g	190–192	30	EtOAc	$C_{21}H_{22}ClNO_4 \cdot 0.22H_2O$	C,H,Cl,N
7h	192–193.5	68	EtOAc	$C_{21}H_{23}NO_5$	C,H,N
7k	173–174	97	MeOH–H_2O	$C_{21}H_{20}F_3NO_4 \cdot 1.45H_2O$	C,H,N,F
7l	174–178	69	*b*	$C_{23}H_{22}F_3NO_4 \cdot 1.13H_2O$	C,H,N,F
8b	169–171	79	MeOH	$C_{20}H_{21}NO_2$	C,H,N
8h[c]	218–219	71	EtOAc	$C_{19}H_{21}NO_3 \cdot 0.14H_2O$	C,H,N
8i[c]	219–224	41	Et_2O	$C_{19}H_{20}BrNO_3$	C,H,N,Br
8k	203.5–205.5	84	EtOAc	$C_{19}H_{18}F_3NO_2$	C,H,N,F
9k	143.5–144	1	iPE	$C_{19}H_{18}F_3NO_2$	C,H,N,F
12	142–143	100	*b*	$C_{22}H_{22}NF_3O_5 \cdot 0.5H_2O$	C,H,N,F
14b	83–86	100	*b*	$C_{22}H_{22}F_3NO_4 \cdot 0.5H_2O$	C,H,N,F
14d	97–100	100	*b*	$C_{27}H_{24}F_3NO_4 \cdot 1.6H_2O$	C,H,N,F
15b[d]	65–66	100	*b*	$C_{20}H_{20}F_3NO_2 \cdot 0.65H_2O$	C,H,N,F

[a] Yields were not optimized in most cases. [b] No recrystallization was performed. [c] Contains 5% of trans isomer. [d] Contains 10% of trans isomer **16b**.

mg, 11.58 mmol, 50% in oil) was added to a stirred solution of crude **8n** and **9n** (3.37 g, 9.65 mmol) in DMF (75 mL). The mixture was stirred for 20 min, and a solution of (*N,N*-dimethylamino)ethyl chloride in toluene (1.7 M, 24 mL, 40.8 mmol) was added. The reaction mixture was heated to 85 °C for 4 h, cooled, diluted with water, and then extracted with EtOAc (3×). The EtOAc extracts were combined, dried ($MgSO_4$), filtered, and concentrated. The dark oil was chromatographed on a silica gel column and eluted with 1% and 3% methanol in dichloromethane to give the free amine of **3n**, which was dissolved in ether and then treated with excess saturated ether solution of HCl. The precipitated solid was filtered, washed with ether, and dried in vacuo to provide **3n** (1.06 g, 26% overall yield from **7n**) as a colorless solid, mp 130–135 °C. ^1H NMR: δ 7.66 (bs, 2 H), 7.55 (s, 1 H), 7.14 (d, 2 H), 6.91 (d, 2 H), 4.51 (m, 2 H), 3.82 (s, 3 H), 3.65 (m, 1 H), 3.33 (m, 3 H), 3.01 (d, 3 H), 2.96 (d, 3 H), 2.92 (t, 1 H), 2.72 (q, 1 H, J = 6.9 Hz), 0.76 (d, 3 H, J = 6.9 Hz). IR (KBr): 1669, 1515 cm^{-1}. MS (CI): $(M + H)^+$ 421.

(3*S*,4*S*)-1,3,4,5-Tetrahydro-3-(methoxycarbonyl)-1-(methoxymethyl)-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one (12). A suspension of NaH (3.04 g, 63.5 mmol, 50% in oil) in dry THF (300 mL) was treated with solid methyl ester **11** (16.5 g, 42.3 mmol; see ref 2 for preparation) at 0–5 °C. After 20 min, the mixture was cooled to −78 °C, and distilled bromomethyl methyl ether (4.2 mL, 51.5 mmol) was added dropwise via syringe. The mixture was stirred at −78 °C for additional 45 min and was then quenched by addition of water. The organic layer was separated, and the aqueous layer was extracted with ether. The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated to give **12** (18.4 g, 100% crude yield), which was used directly in the next reaction without further purification. A portion of the crude product was purified by chromatography on a silica gel column and eluted with 10–20% EtOAc in hexane to provide analytically pure **12**: mp 142–143 °C; $[\alpha]_D$ +27.6° (c = 1, MeOH). MS (CI): $(M + H)^+$ 438.

[3*S*-(3α,3β,4β)]-1,3,4,5-Tetrahydro-3-(methoxycarbonyl)-1-(methoxymethyl)-4-(4-methoxyphenyl)-3-methyl-6-(trifluoromethyl)-2*H*-benzazepin-2-one (13a). Solid **12** (5.2 g, 12 mmol) was added in portions to a stirred suspension of NaH (1.2 g, 25 mmol) in anhydrous THF (50 mL) cooled to 0–5 °C in an ice–water bath. After 20 min, iodomethane (16 mL, 25 mmol) was added. The mixture was allowed to warm to room temperature over 3 h and was then quenched with water and extracted with ether (2×). The ether extracts were combined, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil which was chromatographed on a silica gel column, eluting with 5–20% EtOAc in hexanes to afford **13a** (4.68 g, 87%), $[\alpha]_D$ −54.8° (c = 1, MeOH).

[3*S*-(3α,3β,4β)]-1,3,4,5-Tetrahydro-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-3-methyl-6-(trifluoromethyl)-2*H*-benzazepin-2-one (14a). Anhydrous lithium bromide (2.7 g, 31 mmol) and concentrated sulfuric acid (20 mL) were added to a stirred solution of **13a** (4.37 g, 9.7 mmol) in methanol (100 mL) at 0–5 °C. The mixture was heated at reflux for 4 h, cooled, diluted with ice-cold water, and neutralized by careful addition of sodium bicarbonate. The mixture was extracted with EtOAc, and the EtOAc extract was washed with brine and dried ($MgSO_4$), filtered, and concentrated to provide a yellow oil which was chromatographed on a silica gel column, eluting with 5–25% EtOAc in hexanes to afford **14a** (1.6 g, 40%): mp 79–85 °C; $[\alpha]_D$ +308° (c = 1, MeOH).

(3*R*,4*R*)-1,3,4,5-Tetrahydro-4-(4-methoxyphenyl)-3-methyl-6-(trifluoromethyl)-2*H*-benzazepin-2-one (15a). A solution of **14a** (1.5 g, 4 mmol), anhydrous lithium bromide (2 g, 23 mmol), and *p*-aminothiophenol (920 mg, 7.35 mmol) in anhydrous DMF (12 mL) was heated to 135 °C for 5 h. The mixture was cooled, diluted with water and extracted with ether (3×), and the combined ether extracts were washed with water, 1 N HCl solution, and brine. The ether extract was dried ($MgSO_4$), filtered, and concentrated to afford **15a** (93%, contained 5% of trans isomer **16a**) as an oil.

(3*R*,4*R*)-1-[2-(Dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-3-methyl-6-(trifluoromethyl)-2*H*-benzazepin-2-one, Fumarate (1:1) Salt (17a). A mixture of **15a** and **16a** (4.66 g, 13.3 mmol, 19:1 mixture) was added to a suspension of NaH (350 mg, 15 mmol) in DMF (134 mL). After 1 h, a solution of (*N,N*-dimethylamino)ethyl chloride in toluene (2.15 M, 9.3 mL, 20 mmol) was added. The mixture was heated to 90 °C for 2.5 h. DMF was removed by distillation in vacuo, and the residue was partitioned between EtOAc and water. The EtOAc extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide the crude free amine of **17a**, which was dissolved in MeOH (20 mL) and treated with fumaric acid (1.54 g, 13.3 mmol). The mixture was concentrated and crystallized from a minimal amount of hot CH_2Cl_2 to afford **17a** (5.26 g, 74%): mp 99–102 °C; $[\alpha]_D$ +112° (c = 1, MeOH). ^1H NMR (CD_3OD): δ 7.69 (d, 1 H), 7.68 (d, 1 H), 7.58 (t, 1 H), 7.17 (d, 2 H), 6.89 (d, 2 H), 6.70 (s, 2 H), 4.42 (m, 1 H), 4.11 (m, 1 H), 3.80 (s, 3 H), 3.27 (m, 2 H), 3.16 (m, 2 H), 3.05 (t, 1 H), 2.77 (s, 6 H), 2.69 (q, 1 H, J = 7. Hz), 0.70 (d, 3 H, J = 7 Hz). ^{13}C NMR: δ

176.1, 170.6, 160.1, 144.8, 135.7, 134.9, 133.7, 130.0, 129.7, 129.0, 127.8, 125.1, 114.5, 56.2, 55.4, 53.6, 45.3, 43.6, 39.3, 35.6, 13.8. IR (KBr): 1668, 1514 cm^{-1}. MS (CI): $(M + H)^+$ 421.

***cis*- and *trans*-1,3,4,5-Tetrahydro-4-(4-methoxyphenyl)-3-methyl-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one (8k and 9k).** A mixture of **7k** (202 g, 0.50 mol, prepared as for **7n**), *p*-aminothiophenol (100 g, 0.99 mol), and lithium bromide (180 g, 2.07 mol) in DMF (1.3 L) was heated at 140 °C for 5 h. The solution was cooled to room temperature and concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water, 1 N hydrochloric acid, sodium bicarbonate, and brine, dried over magnesium sulfate, and evaporated in vacuo to provide a colorless solid (200 g). This compound was dissolved in warm ethyl acetate and allowed to crystallize. Filtration and washing with ethyl acetate provided cis isomer **8k** (123.6 g), mp 203.5–205.5 °C. The filtrate was evaporated, and the residue was applied to an HP-20 reverse-phase polymer column in 40% MeCN/water. The column was eluted with a 60%–80% MeCN gradient, the trans isomer **9k** was identified by analytical HPLC, and the fractions were combined and concentrated in vacuo. The product was recrystallized from diisopropyl ether (iPE) to afford **9k** (1.3 g), mp 143.5–144 °C.

***trans*-1-[2-(Dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-3-methyl-6-(trifluoromethyl)-2*H*-1-benzazepin-2-one, Hydrochloride Salt (10k).** To a solution of **9k** (0.50 g, 1.43 mmol) in dry DMF (5 mL) was added sodium hydride (60%, 0.06 g, 1.43 mmol). The reaction was stirred at room temperature for 1 h and a solution of (*N,N*-dimethylamino)ethyl chloride in toluene (1.91 M, 0.75 mL, 1.43 mmol) was added. The solution was heated to 70 °C for 4.5 h and then cooled to room temperature. The reaction was concentrated in vacuo, the residue was partitioned between ethyl acetate and water, and the organic phase was washed with water, brine, dried over magnesium sulfate, and evaporated in vacuo. The product was dissolved in ether (30 mL), and saturated ethereal HCl (5 mL) was added. The resulting hydrochloride salt was filtered and washed with ether to afford **10k** (0.63 g, 97%), mp 223.5–224.5 °C. ^1H NMR (CD_3OD): δ 7.74–7.82 (m, 1 H), 7.56–7.66 (m, 2 H), 6.60–6.90 (m, 4 H), 4.20–4.30 (m, 2 H), 3.75–3.80 (s, 3 H), 3.50–3.65 (m, 1 H), 3.30–3.50 (m, 1 H), 3.30 (s, 2 H), 3.20–3.28 (d, 1 H), 3.15 (s, 6 H), 2.85–2.95 (m, 1 H), 0.90 (d, 3 H). ^{13}C NMR (CD_3OD): δ 177.4, 160.1, 144.9, 134.5, 133.7, 129.6, 129.0, 125.8, 114.9, 56.9, 55.6, 54.3, 46.1, 44.0, 40.9, 34.7, 14.4. MS: $(M + H)^+$ 421. IR (KBr): 1668 cm^{-1}.

Acknowledgment. Microanalyses, IR spectra, and mass spectra were kindly provided by the Bristol-Myers Squibb Department of Analytical Research and Development.

Supplementary Material Available: Tables of unit cell data, atomic coordinates, and thermal parameters for **7**, **7** (free acid), **8**, **11**, **17a–d**, and **18b** (41 pages). Ordering information is given on any current masthead page.

Benzazepinone Calcium Channel Blockers. 4. Structure–Activity Overview and Intracellular Binding Site

S. David Kimball,* David M. Floyd,* Jagabandhu Das, John T. Hunt, John Krapcho, George Rovnyak, Keith J. Duff, Ving G. Lee, Robert V. Moquin, Chester F. Turk, S. Anders Hedberg, Suzanne Moreland, Russell J. Brittain, Diane M. McMullen, Diane E. Normandin, and Gabriella G. Cucinotta

Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-4000.
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We have synthesized a series of benzazepinones (**2**) in order to determine the structure–activity relationships (SAR) for calcium channel blockers related to diltiazem. A prerequisite for calcium channel blocking activity in vitro and in vivo is the presence of two pharmacophores: a 4′-aryl methyl ether and a basic substituent appended to N1 with a pK_a in the physiological range. When these constraints are satisfied, a wide variety of substitution is tolerated at C6, C7, and C3. The presence of an electron-withdrawing group at C6 appears to enhance potency in vitro and in vivo. For such benzazepinones, activity is primarily dependent upon lipophilicity, as measured by log *P*. We believe these compounds must partition into the cell membrane in order to access their receptor. The quaternary methiodide **15k** was used to demonstrate that the binding site for benzazepinones is on the intracellular face of the membrane. This work represents the first comprehensive SAR of diltiazem-like calcium channel blockers.

Introduction

In the two accompanying papers[1] we have described the preliminary structure–activity relationships of 3-hydroxylated and 3-alkylbenzazepinone calcium channel blockers (CCBs). These compounds are structural analogues of the clinically important[2] benzothiazepinone diltiazem (**1**, Figure 1). We have demonstrated that the benzazepinone class of calcium channel blockers are competitive and reversible ligands at the diltiazem binding site on the voltage dependent L-channel. Benzazepinones are potent CCBs in vitro[3] and also possess antihypertensive and anti-ischemic activity in vivo.[4]

In this paper, we present the major conclusions of our structure–activity studies on benzazepinone CCBs, which were prompted by the lack of information regarding structure–activity relationships for benzothiazepinones.[5]

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