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

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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]

(1) (a) Benzazepinone Calcium Channel Blockers. 2. Structure–Activity and Drug Metabolism Studies Leading to Potent Antihypertensive Agents. Comparison with Benzothiazepinones. 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., previous article in this issue. (b) Benzazepinone Calcium Channel Blockers. 3. Synthesis and Structure–Activity Studies of 3-Alkyl Benzazepinones. Das, J.; Floyd, D. M.; Kimball, S. D.; Duff, K. J.; Vu, T. C.; Moquin, R. V.; Gougoutas, J. Z.; Malley, M. F.; Moreland, S.; Brittain, R. J.; Hedberg, S. A.; Cucinotta, G. G., previous article in this issue.

(2) For a recent review see: Buckley, M.; Grant, S.; Goa, K.; McTavish, D.; Sorkin, E. Diltiazem: A Reappraisal of its Pharmacological Properties and Therapeutic Use. *Drugs* **1990**, *39*, 757–806.

(3) Moreland, S.; McMullen, D. M. Effects of SQ 31,765, a New Calcium Channel blocker, on Stress and Myosin Light chain Phosphorylation in Swine Carotid Media. *J. Cardiovasc. Pharmacol.* **1990**, *16*, 609–615.

(4) (a) Grover, G. J.; Parham, C. S.; Sleph, P. G.; Moreland, S. Anti-Ischemic and Vasorelaxant Effects of the New Benzazepine Calcium Channel Blocker SQ 31,765. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 1020–1025. (b) Grover, G. J.; Sleph, P. G.; Parham, C. S.; Brittain, R. J.; Krapcho, J.; Moreland, S. Anti-Ischemic Activity of the Novel Benzazepine Calcium Antagonist SQ 31,486. *J. Cardiovasc. Pharmacol.* **1990**, *16*, 219–227.

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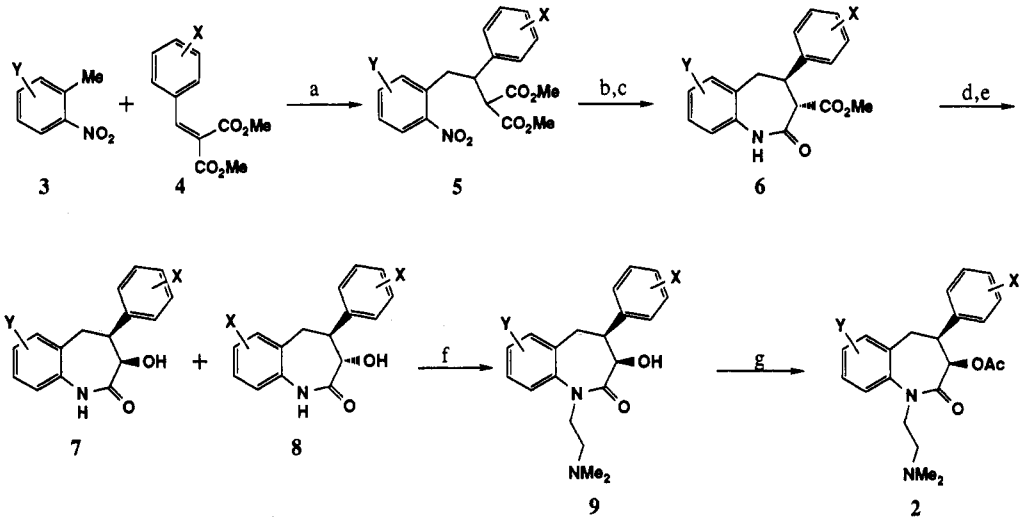
Scheme I[a]



[a] (a) NaH, DMF; (b) H_2, Pd/C; or $SnCl_2$, HCl, MeOH; (c) NaOMe, MeOH, reflux; (d) potassium hexamethyldisilazide $P(OEt)_3$, O_2; or KOt-Am, $P(OMe)_3$, O_2; (e) LiI, pyridine; (f) (*N,N*-dimethylamino)ethyl chloride, NaH, DMF; (g) Ac_2O, 100–120 °C.

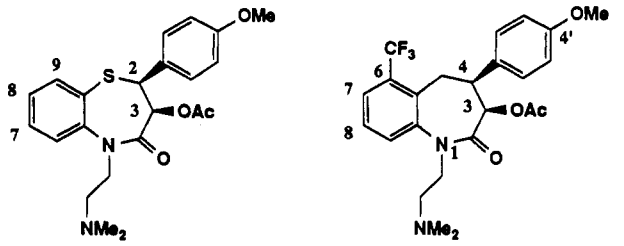
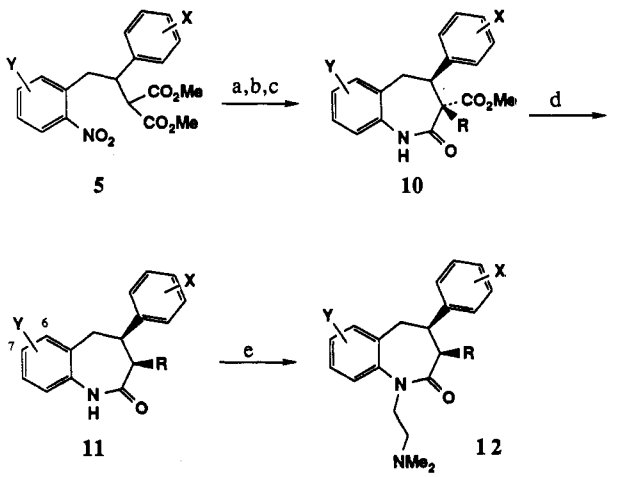


Figure 1.

Thus, the data presented below represents the first comprehensive collection of structure–activity information for diltiazem-like CCBs.[6]

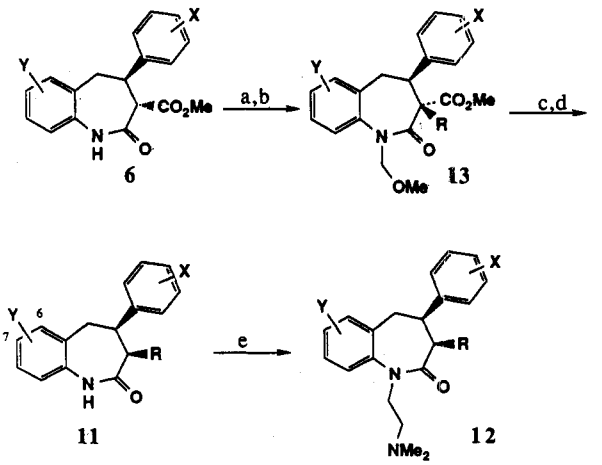
We have found that two pharmacophores are important for activity in vitro and in vivo: a 4′-methoxy substituent on the C4 aryl ring and a basic amino group on the N1 substituent. We find a strong preference for cis stereochemistry at the C3 and C4 positions. The effect of sub-

Scheme II[a]



[a] (a) NaH, DMF, RBr; (b) H_2, Pd/C; or $SnCl_2$, HCl, MeOH; (c) NaOMe, MeOH, reflux; (d) LiI, pyridine; (e) (*N,N*-dimethylamino)ethyl chloride, NaH, DMF.

Scheme III

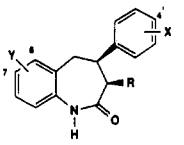


[a] (a) NaH, DMF, MOMBr; (b) NaH, DMF, RBr; (c) H_2SO_4, LiBr, MeOH; (d) LiI, pyridine; (e) (*N,N*-dimethylamino)ethyl chloride, NaH, DMF.

(5) (a) For a recent review see: *Diltiazem*, Tanabe Seiyaku Co. Ltd., Higashiku, Osaka, Japan, 1987, Chapter 1. (b) 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. (c) Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. Studies on a New 1,5-Benzothiazepine Derivative (CRD-401). II. Vasodilator Actions. *Jpn. J. Pharmacol.* **1972**, *22*, 1–10. (d) Takeda, M.; Oh-Ishi, T.; Nagao, T.; Nakajima, H. U.K. Patent Appl. 2154757 A, 1985. (e) Inoue, H.; Gaino, M.; Nagao, T.; Murata, S. Eur. Patent Appl. 0302379 A1, 1989. (f) Takeda, M.; Oh-Ishi, T.; Nakajima, H.; Nagao, T. U.K. Patent Appl. GB 2167063 A, 1986. (g) Eur. Patent Appl. 0353032, 1990. (h) Mohacsi, E.; O'Brien, J. P. U.S. Patent 4,652,561, 1987. (i) Ibid. U.S. Patent 4,640,930, 1987. (j) Ibid. U.S. Patent 4,959,359, 1990. (k) Morimoto, M.; Kohno, H.; Yasuda, K.; Date, T.; Takamura, N.; Sugasawa, S. Synthesis of 2-Substituted Derivatives of Diltiazem. *Heterocycles* **1990**, *30*, 471–486. (l) 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.

(6) For a summary and leading references see: Triggle, D. J. Drugs Acting on Ion Channels and Membranes. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: New York, 1990; Vol. 3, 1047–1099.

Table I. Physical Data for Compounds 7 and 11



compd	X	Y	R	Scheme	% yield from 5	mp, °C	recryst solvent	formula	analysis
7a	4'-OMe	7-Cl	OH	I	59	157–158	EtOAc		
7b	3'-OMe	7-Cl	OH	I	61				
7c	2'-OMe	7-Cl	OH	I	70				
7d	4'-OMe	H	OH	I	13	173–175	Et_2O	$C_{17}H_{17}NO_3$	C,H,N
7e	4'-OMe	6-Cl	OH	I	8	177–179	Et_2O	$C_{17}H_{16}NO_3Cl$	C,H,N,Cl
7f	4'-OMe	6-Me	OH	I	15	182–184	EtOH	$C_{18}H_{19}NO_3$	C,H,N
7g	4'-OMe	6-CF_3	OH	I	39	220–222	CH_3CN	$C_{18}H_{16}NO_3F_3$	C,H,N,F
7h	4'-OMe	6-CN	OH	I	33	205–209	CH_3CN	$C_{18}H_{16}N_2O_3$	C,H,N
7i	4'-OMe	6-NO_2	OH	I	7	198–200	CH_3CN	$C_{17}H_{16}N_2O_5$	C,H,N
7j	4'-OMe	6-OMe	OH	I	17	213–215	CH_3CN	$C_{18}H_{19}NO_4$	C,H,N
7k	4'-OMe	6-CO_2Et	OH	I	20	166–168	EtOH	$C_{20}H_{21}NO_5$	
7o	4'-OMe	7-OBn	OH	I	18	156–159	EtOH	$C_{24}H_{23}NO_4$	
7s	4'-OMe	7-StBu	OH	I	61	184–250 dec	EtOAc		
7t	4'-OMe	7-OCF_2H	OH	I	22	190–192	CH_3CN	$C_{18}H_{17}NO_4F$	C,H,N,F
7v	4'-OMe	7-SPh	OH	I	26	174–176	EtOAc	$C_{25}H_{23}NO_4S$	
7w	4'-OMe	7-OPh	OH	I	6	198–200	EtOAc	$C_{25}H_{23}NO_5$	
7x	4'-OMe	7-CF_3	OH	I	35	204–206	CH_3CN	$C_{18}H_{16}NO_3F_3$	C,H,N
7y	4'-OMe	6-OMe,7-Br	OH	I	52	198–199	CH_3CN	$C_{18}H_{18}NO_4Br$	C,H,N,Br
11a	4'-OMe	6-CF_3	Me	II	66	203–205	EtOAc	$C_{19}H_{18}NO_2F_3$	C,H,N,F
11c	4'-SMe	6-CF_3	Me	II	36	180–181	EtOAc	$C_{22}H_{24}NO_4SF_3$	C,H,N,F,S
11d	4'-Et	6-CF_3	Me	II	34	123–125	MeOH	$C_{20}H_{20}NOF_3$	C,H,N,F
11e	3',4'-$(OMe)_2$	6-CF_3	Me	II	38	143–145	$MeOH/H_2O$	$C_{20}H_{20}NO_3F_3$	C,H,N,F
11g	4'-OMe	6-CF_3	H	II	2[a]	181–183	EtOAc	$C_{18}H_{16}NO_2F_3$	C,H,N,F
11h[f]	4'-OMe	6-CF_3	Et	III	99[b]				
11i	4'-OMe	6-CF_3	allyl	II	70[c]				
11k[f]	4'-OMe	6-CF_3	Bn	III	56[d]				
11n	4'-OMe	7-CF_3	SAc	IV	25[e]	215–216	EtOAc	$C_{20}H_{18}NO_3F_3S$	C,H,N,F,S
11o	4'-OMe	6-OMe	Me	II	24	218–219	EtOAc	$C_{19}H_{21}NO_3$	C,H,N
11p	4'-OMe	6-OMe,7-Br	Me	II	26	219–224	Et_2O	$C_{19}H_{21}NO_3Br$	C,H,N,Br
11q	4'-OMe	H	Me	II	91				
11r	4'-OMe	H	allyl	II	22	169–171	MeOH	$C_{20}H_{21}NO_2$	C,H,N

[a] From 6g. [b] 80:20 cis–trans. [c] 87:13 cis–trans. [d] 50:50 cis–trans. [e] From intermediate 14. [f] Nonracemic compound.

stitution in the fused aryl ring and at C3 is structurally nonspecific, with some limit on the size of the substituent. The most preferred substituents at these positions are those that optimize the overall lipophilicity of the compound. We also demonstrate that CCBs related to diltiazem bind on the intracellular surface of the calcium channel protein. This finding provides a conceptual basis for understanding the profound effect of molecular lipophilicity on activity in this series of compounds.

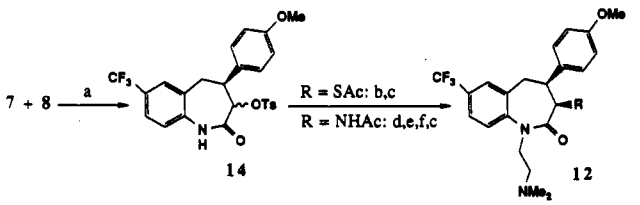
Chemistry

The synthesis of substituted benzazepinones followed the general procedures described previously. Compounds substituted at C-3 by hydroxy or acetoxy were synthesized from the requisite nitrotoluenes (3) and benzylidenemalonates (4) following Scheme I. Nonracemic 3-hydroxy and 3-acetoxy compounds were synthesized from the nonracemic intermediate 6, prepared as described earlier.[1a]

The synthesis of 3-alkyl-substituted derivatives diverged from that of the 3-hydroxy series either by alkylation of intermediate 5 (Scheme II) or modification of 6 as described previously (Scheme III). Nonracemic 3-alkyl compounds were synthesized from nonracemic 6 following Scheme III. These synthetic schemes are described in greater detail in the previous paper in this series.[1b]

Alkylation of intermediates 7 or 11 was routinely carried out using sodium hydride in dimethylformamide, to provide tertiary amides 9 or 12. In cases where the N1 substituent differs from (dimethylamino)ethyl, compounds 15 were prepared via alkylation of 7 or 11 by the appropriate alkyl halide using conditions described in Schemes I–IV

Scheme IV[a]



[a] (a) TsCl, pyridine; (b) KSAc, DMSO, 90 °C; (c) (*N,N*-dimethylamino)ethyl chloride, $KHCO_3$, MEK; (d) NaN_3, Bu_4NHSO_4, DMF, 90 °C; (e) H_2, Pd–C, TFA; (f) Ac_2O, pyridine.

for (*N,N*-dimethylamino)ethyl substituents. Compounds substituted at N1 by secondary aminoalkyl residues were prepared as described in the second paper of this series.[1a] These compounds can be alkylated by alkyl halides to provide variously substituted *N,N*-dialkylamine-substituted benzazepinones such as **15u**. The synthesis of 3-heterosubstituted compounds was carried out by displacement of tosylate 14 (Scheme IV).[7] Physical data for 7 and 11, 2 and 12, and 15 are contained in Tables I–III, respectively.

Structure–Activity Relationships

The biological test methods have been described in detail in the Experimental Section of a previous paper in this series.[1a] The majority of compounds described here were synthesized in racemic form; nonracemic compounds

(7) For additional procedures see: (a) Das, J.; Floyd, D. 3-Substituted Benzazepines. U.S. Patent 4,767,756, 1988. (b) Das, J. Benzazepine Derivatives. U.S. Patent 4,771,047, 1988.

are indicated in the accompanying tables. The data in all tables are reported for the exact form prepared and tested, as indicated in that table (racemic or nonracemic). However, for the purposes of quantitative analysis, in vitro biological data for nonracemic compounds were adjusted to the value expected for a racemic mixture (i.e., IC_{50} and k_d values were doubled) in order to facilitate structure–activity comparisons. Graphical and statistical analysis of the data were performed using the software program DATADESK from Odesta Corp.

We have previously established that benzazepinones are competitive and reversible ligands at the diltiazem binding site on the calcium channel.[1a] These compounds show the same absolute and relative stereochemical preferences as benzothiazepinones. We demonstrate here that the biological activity of benzazepinones is dependent upon two pharmacophores: a 4′-methoxy substituent on the 4-aryl ring and a basic amino substituent appended to N1. Given these two key interactions with the receptor, activity can then be optimized by modifying log *P*.

Definition of 4-Aryl Ether Pharmacophore. Examination of 7-chloro benzazepinones substituted in the 4-aryl ring (**2a**, **2b**, **2c**) shows that the position of the methoxy substituent on the 4-aryl ring is critical (Table IV). Both the 3′- and 2′-substituted methoxy derivatives **2b** and **2c** are inactive relative to **2a**. In the 6-trifluoromethyl series, modification of the 4′-methyl ether **15a** to give the 4′-methoxymethyl ether **15b** and 4′-(methoxyethoxy)methyl ether **15c** derivatives provides inactive compounds.[8]

Further alteration of the 4′-substituent in the 3-methyl-6-trifluoromethyl series reveals that the 4′-methyl ether **12a** is the most active of a series of isosteres. Since activity follows the hydrogen bond acceptor capability of the 4′-substituent, with OMe > NHMe > SMe > CH_2Me, we postulate that this group serves to accept a hydrogen bond from an appropriate residue in the diltiazem receptor binding site. Introduction of a 3′-methoxy substituent in addition to the 4′-substituent (**12e**) attenuates the IC_{50} by a factor of 50 (compare with **12a**). This may be due to steric constraints at the 3′-position in the receptor pocket or the effect of 3′,4′-disubstitution on the orientation of the 4′-methyl ether. From the failure of our attempts to improve activity by modification of the 4′-methyl ether, and the dramatic drop in activity caused by structural alterations at the 4′ position, we conclude that this group is required for an important binding interaction at the receptor.

Definition of Basic Amine Pharmacophore. The basic *N*-1-alkylamino substituent comprises the second essential benzazepinone pharmacophore (Table V). Removal of the basic character of the amine by acylation leads to a significant decrease of activity in vitro. Comparison of **15a** with **15d**,[9] **2g** with **15e**, and **15f** with **15g** show this effect within series of close structural analogues. From these varied examples it is apparent that the decrease of activity in vitro is a function of a loss in basicity and is not due to a steric perturbation.

Additional supporting evidence for the critical contribution of the basic amino substituent comes from a series of N-substituted compounds in which amine basicity is varied. The pK_a values for dimethylpropylamine, dimethylallylamine, and dimethylpropargylamine are 9.99, 8.72, and 7.05, respectively.[10] The *N*-methyl-*N*-propyl (**15h**), *N*-methyl-*N*-allyl (**15i**), and *N*-methyl-*N*-propynyl (**15j**) benzazepinone analogues were synthesized to evaluate the effect of such a change in pK_a. These compounds were found to have differences in pK_a comparable to those of the simple dimethylalkylamines.[11] Biological activity is maintained with *N*-propyl and *N*-allyl substitutions as in **15h** and **15i**, both of which should be protonated at physiological pH. In contrast, the less basic *N*-propynyl derivative **15j** is much less active in vitro. These data support the conclusion that a protonated amino substituent appended to the N1 position provides a critical binding interaction at the receptor.

Effect of Modification of the N-1 Substituent. Varying the distance between N-1 and the basic amine pharmacophore demonstrates that an ethyl linkage is superior to propyl for activity in vitro and in vivo (compare **15s**, **12a**). Substitution at the β position of the *N*-1-ethylamino group (**15l**, **15m**) decreases activity in vitro slightly, but does not affect activity in vivo. However, substitution at the position α to N-1 (**15n**, **15o**) causes a significant reduction of activity both in vitro and in vivo. Introduction of a bulky isopropyl group on the basic nitrogen (**15p**, **15q**, **15r**) reduces calcium channel blocking activity. Incorporation of the basic nitrogen into a pyrrolidinyl ring (**15t**) likewise has a dramatic effect on activity in vitro and in vivo relative to **12a**. In contrast to the sensitivity of benzazepinones towards bulky substitution on the basic nitrogen pharmacophore, large but unbranched substituents on N-1 do not have a deleterious effect on calcium channel blocking activity (**15u**). From these modifications we conclude that increasing the bulk of the substituents around the basic *N*-1-aminoethyl group is deleterious to activity. This further supports the role of the basic amine in receptor binding.

Effect of Substitution in the Fused Aryl Ring. We have synthesized a series of C6 substituted benzazepinones in which lipophilic, electronic, and steric parameters were varied (Table VI). The electron-withdrawing trifluoromethyl (**2g**), cyano (**2h**), and nitro (**2i**) analogues are the most potent compounds in vitro, although **2h** is inactive in vivo. The electron-donating methoxy group (**2j**) provides an analogue with activity some 10–20 times less than the compounds with electron-withdrawing functionality. The 6-carboxy analogue **2m** is much less active relative to the isoelectronic 6-nitro analogue **2i**, demonstrating that an ionizable isostere of the nitro group is not tolerated at the 6-position. In view of the good activity of **2i** it is somewhat surprising to find that carboxylic acid derivatives at C6 (**2k**, **2l**, **2n**) are also relatively inactive. This finding may be related to the larger steric bulk in the plane of the fused phenyl ring, or to the hydrophilicity of these compounds (vida infra).

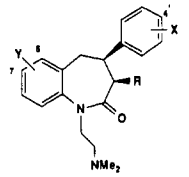
(8) Compounds **15b** and **15c** were synthesized by reacting **15a** with BBr_3. The resulting 3-OH, 4′-OH compound was protected on nitrogen as the CBZ derivative. This compound followed either of two paths. To obtain **15b**, the 3-OH was acetylated (Ac_2O/DMAP), the potassium salt of the phenol alkylated (KHMDS/MOMBr), and deprotected (H_2/Pd/C). Alternatively, **15c** was obtained by selective alkylation of the phenol ($CsCO_3$/MEMBr), acetylation (Ac_2O/DMAP) and nitrogen deprotection (H_2/Pd/C).

(9) Compound **15d** was prepared from **11g** by alkylation with methyl bromoacetate, aminolysis with methylamine, and acetylation (Ac_2O/DMAP).

(10) Hall, H. K. Correlation of the Base Strengths of Amines. *J. Am. Chem. Soc.* **1957**, *79*, 5441–5444.

(11) The pK_a values for several benzazepinones were estimated by titrating the hydrochloride salts in acetonitrile–water with the following results: tertiary NMe_2 benzazepinone pK_a = 7.4, secondary NHMe pK_a = 8.5, N(Me)allyl pK_a = 6.5, N(Me)-propynyl $pK_a \leq 5$. By way of comparison, the pK_a of diltiazem is 7.8; the reduction in basicity of both benzazepinone and benzothiazepinone calcium channel blockers relative to simple tertiary alkylamines is apparently due to the β electron-withdrawing N-1 amide.

Table II. Physical Data for Compounds 2 and 12



compd	X	Y	R	scheme	% yield	mp, °C	formula	analysis
2a	4′-OMe	7-Cl	OAc	I	42[a]	207–209	$C_{23}H_{27}N_2O_4Cl·HCl·0.40H_2O$	C,H,N,Cl
2b	3′-OMe	7-Cl	OAc	I	67[a]	225–226	$C_{23}H_{27}N_2O_4Cl·HCl·0.35H_2O$	C,H,N,Cl
2c	2′-OMe	7-Cl	OAc	I	38[a]	250–252	$C_{23}H_{27}N_2O_4Cl·HCl$	C,H,N,Cl
2d	4′-OMe	H	OAc	I	96[a]	215–216	$C_{23}H_{28}N_2O_4·HCl·0.70H_2O$	C,H,N,Cl
2e	4′-OMe	6-Cl	OAc	I	93[a]	151–153	$C_{23}H_{27}N_2O_4Cl·HCl·1.13H_2O$	C,H,N,Cl
2f	4′-OMe	6-Me	OAc	I	72[a]	176–178	$C_{24}H_{30}N_2O_4·HCl·0.25H_2O$	C,H,N,Cl
2g[h]	4′-OMe	6-CF_3	OAc	I	89[a]	180–182	$C_{24}H_{27}N_2O_4F_3·HCl$	C,H,N,F,Cl
2h	4′-OMe	6-CN	OAc	I	84[a]	198–200	$C_{24}H_{27}N_3O_4·HCl·1.0H_2O$	C,H,N,Cl
2i	4′-OMe	6-NO_2	OAc	I	84[a]	198–200	$C_{23}H_{27}N_3O_6·HCl·1.0H_2O$	C,H,N,Cl
2j	4′-OMe	6-OMe	OAc	I	86[a]	227–229	$C_{24}H_{30}N_2O_5·HCl·0.25H_2O$	C,H,N,Cl
2k	4′-OMe	6-CO_2Et	OAc	I	66[a]	215–217	$C_{26}H_{32}N_2O_6·HCl$	C,H,N,Cl
2l	4′-OMe	6-CO_2Bn	OAc	I	30[b]	187–188	$C_{31}H_{34}N_2O_6·HCl$	C,H,N,Cl
2m	4′-OMe	6-CO_2H	OAc	I	9[b]	>230	$C_{24}H_{28}N_2O_6·HCl·0.49H_2O$	C,H,N,Cl
2n	4′-OMe	6-$CONH_2$	OAc	I	56[b]	186–190	$C_{24}H_{29}N_3O_5·HCl·1.06H_2O$	C,H,N,Cl
2o	4′-OMe	7-OBn	OAc	I	60[a]	117–120	$C_{30}H_{34}N_2O_5·HCl·2.0H_2O$	C,H,N,Cl
2p	4′-OMe	7-OMe	OAc	I	49[c]	215–217	$C_{24}H_{30}N_2O_5·HCl·0.75H_2O$	C,H,N,Cl
2q	4′-OMe	7-OCONHMe	OAc	I	52[c]	216–218	$C_{25}H_{31}N_3O_6·HCl·1.0H_2O$	C,H,N,Cl
2r	4′-OMe	7-OCOtBu	OAc	I	38[c]	198–200	$C_{28}H_{36}N_2O_6·HCl·1.5H_2O$	C,H,N,Cl
2s	4′-OMe	7-StBu	OAc	I	75[a]	190–214	$C_{27}H_{36}N_2O_4S·HCl·0.28H_2O$	C,H,N,S,Cl
2t	4′-OMe	7-OCF_2H	OAc	I	91[a]	206–208	$C_{24}H_{28}N_2O_5F_2·HCl·0.75H_2O$	C,H,N,F,Cl
2u	4′-OMe	7-SMe	OAc	I	25[d]	235–236	$C_{24}H_{30}N_2O_4S·HCl·0.54H_2O$	C,H,N,S,Cl
2v	4′-OMe	7-SPh	OAc	I	55[a]	192–194	$C_{29}H_{32}N_2O_4S·HCl·0.34H_2O$	C,H,N,S,Cl
2w	4′-OMe	7-OPh	OAc	I	64[a]	155 dec	$C_{29}H_{32}N_2O_5·HCl·3.0H_2O$	C,H,N,Cl
2x	4′-OMe	7-CF_3	OAc	I	18[a]	230–232	$C_{24}H_{27}N_2O_4F_3·HCl·0.25H_2O$	C,H,N,F,Cl
2y	4′-OMe	6-OMe, 7-Br	OAc	I	83[a]	222–223	$C_{24}H_{29}N_2O_5Br·HCl·0.54H_2O$	C,H,N,Br,Cl
12a	4′-OMe	6-CF_3	Me	II	71[e]	99–101	$C_{23}H_{27}N_2O_2F_3·C_4H_4O_4·0.34H_2O$	C,H,N,F
12b	4′-NHMe	6-CF_3	Me	II	14[e]	197–200	$C_{23}H_{28}N_3OF_3·2HCl·1.47H_2O$	C,H,N,Cl,F
12c	4′-SMe	6-CF_3	Me	II	77[e]	234–235	$C_{23}H_{27}N_2OSF_3·HCl·0.07H_2O$	C,H,N,F,Cl,S
12d	4′-Et	6-CF_3	Me	II	84[e]	244–246	$C_{24}H_{29}N_2OF_3·HCl·0.40H_2O$	C,H,N,F,Cl
12e	3′,4′-$(OMe)_2$	6-CF_3	Me	II	83[e]	190–192	$C_{24}H_{29}N_2O_3F_3·HCl$	C,H,N,F,Cl
12f	4′-OH	6-CF_3	Me	II	78[e]	>260	$C_{22}H_{25}N_2O_2F_3·HCl·0.25H_2O$	C,H,N,F,Cl
12g	4′-OMe	6-CF_3	H	II	73[e]	136–138	$C_{22}H_{25}N_2O_2F_3·HCl·0.50H_2O$	C,H,N,F,Cl
12h[h]	4′-OMe	6-CF_3	Et	III	15[e]	162–164	$C_{24}H_{29}N_2O_2F_3·HCl·0.95H_2O$	C,H,N,F,Cl
12i	4′-OMe	6-CF_3	allyl	II	32[e]	226–228	$C_{25}H_{29}N_2O_2F_3·HCl·0.23H_2O$	C,H,N,F,Cl
12j	4′-OMe	6-CF_3	Pr	II	19[e]	180–182	$C_{25}H_{31}N_2O_2F_3·HCl·0.40H_2O$	C,H,N,F,Cl
12k[h]	4′-OMe	6-CF_3	Bn	III	14[e]	155–159	$C_{29}H_{31}N_2O_2F_3·C_4H_4O_4·0.42H_2O$	C,H,N,F
12l	4′-OMe	7-CF_3	NHAc	IV	46[f]	192–196	$C_{24}H_{28}N_3O_3F_3·HCl·1.25H_2O$	C,H,N,F,Cl
12m	4′-OMe	7-CF_3	CH_2Ac		35[g]	209–210	$C_{25}H_{29}N_2O_3F_3·HCl·0.70H_2O$	C,H,N,F,Cl
12n	4′-OMe	7-CF_3	SAc	IV	53[f]	147–150	$C_{24}H_{27}N_2O_3SF_3·HCl·0.69H_2O$	C,H,N,S,Cl
12o	4′-OMe	6-OMe	Me	II	60[e]	243–244	$C_{23}H_{30}N_2O_3·HCl·0.69H_2O$	C,H,N,Cl
12p	4′-OMe	6-OMe, 7-Br	Me	II	72[e]	142–146	$C_{23}H_{29}N_2O_3Br·HCl·0.39H_2O$	C,H,N,Br,Cl
12q	4′-OMe	H	Me	II	47[e]	211–216	$C_{22}H_{28}N_2O_2·HCl·0.44H_2O$	C,H,N,Cl
12r	4′-OMe	H	allyl	II	78[e]	154–157	$C_{24}H_{30}N_2O_2·HCl·0.35H_2O$	C,H,N,Cl
12s	4′-OMe	H	Pr	II	76[e]	178–180	$C_{24}H_{32}N_2O_2·HCl·0.38H_2O$	C,H,N,Cl

[a] From 7. [b] From 7k. [c] From 2o. [d] From 7s. [e] From 11. [f] From 14. [g] From 11i. [h] Nonracemic compound. Optical rotations: **2g** +97.1° (c = 1, MeOH), **12h** +112° (c = 1, MeOH), **12k** +55.2° (c = 1, MeOH).

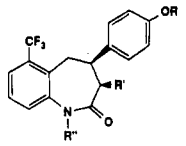
Substitution at C7 reveals that compounds with large, lipophilic groups (**2o**, **2v**, **2w**) are superior in activity in vitro to those with more polar substituents (**2q**). However, extremely hindered branched compounds such as **2r** and **2s** are less active in vitro regardless of their lipophilicity. While the effects of substitution at C7 on activity are much less dramatic than at C6, activity in vitro for C7 substituted compounds tend to correlate with the molecular lipophilicity (log P),[12] with the caveat that compounds with highly branched and hindered C7 substituents are relatively inactive.

Comparison of C6 and C7 substitution provides insight into the subtleties of benzazepinone structure–activity relationships. While the chloro (**2e**, **2a**) and methoxy (**2j**, **2p**) analogues at C6 and C7 did not differ greatly in activity, substitution of trifluoromethyl (**2g**, **2x**) has a pronounced effect at C6 relative to C7. Compound **2g** is a potent antihypertensive agent with a long duration of action. The enhanced activity of compounds containing electron withdrawing C6 substituents may indicate a preference at the receptor for a negative dipole at the 6-position of benzazepinones.

Effect of Substitution at C3. Substitution at C3 by a cis alkyl substituent of moderate size (**12a**, **12h**, **12i**) provides compounds which are potent calcium channel blockers in vitro and in vivo. The benzazepinone lacking substitution at C-3 (**12g**) is significantly less active than

(12) Log P values were estimated from reverse-phase HPLC data using the equation: log P = 4.6 log k' − 0.33. This equation was derived from measured log P values in octanol–water at pH = 6.6 for several representative benzazepinones. These data were linearly related to log k' as determined on a Waters Bondapak C18 column (3.9 mm × 30 cm) with a mobile phase of acetonitrile–water (50:50) containing 1.5 g/L heptanesulfonic acid sodium salt, 8.0 g/L sodium acetate and adjusted to pH = 6.6 with acetic acid.

Table III. Physical Data for Compounds 15



compd	R	R′	R″	yield from 7 or 11	mp, °C	formula	analysis	optical rotation
15a[f]	Me	OAc	CH_2CH_2NHMe	43	83–86	$C_{23}H_{25}N_2O_4F_3 \cdot HCl \cdot 1.5H_2O$	C,H,N,Cl	+95.0° (*c* = 1, MeOH)
15b[f]	MOM	OAc	CH_2CH_2NHMe	13	104–105	$C_{24}H_{27}N_2O_5F_3 \cdot C_4H_4O_4 \cdot 0.39H_2O$	C,H,N	+81.7° (*c* = 1.03, MeOH)
15c[f]	MEM	OAc	CH_2CH_2NHMe	31	93–96	$C_{25}H_{29}N_2O_5F_3 \cdot C_4H_4O_4 \cdot 1.75H_2O$	C,H,N	+82.4° (*c* = 1.02, MeOH)
15d[f]	Me	OAc	$CH_2CONHMe$	65	174–175	$C_{23}H_{23}N_2O_5F_3$[a]	C,H,N,F	+105° (*c* = 5.8, MeOH)
15e[f]	Me	OAc	CH_2CH_2NMeAc	40	73–76	$C_{25}H_{27}N_2O_5F_3 \cdot 2.85H_2O$	C,H,N,F	+76.8° (*c* = 1, MeOH)
15f[f]	Me	OH	$CH_2CH_2NMe_2$	100	192–194	$C_{22}H_{25}N_2O_3F_3 \cdot HCl \cdot 1.25H_2O$	C,H,N,F,Cl	+97° (*c* = 1, MeOH)
15g[f]	Me	OH	CH_2CH_2NMeAc	37	70–71	$C_{23}H_{25}N_2O_4F_3 \cdot 2.01H_2O$	C,H,N,F	+135° (*c* = 1, MeOH)
15h[f]	Me	OAc	CH_2CH_2NMePr	26	105–125	$C_{26}H_{31}N_2O_4F_3 \cdot HCl \cdot 0.25H_2O$	C,H,N,Cl	+96.2° (*c* = 0.58, MeOH)
15i[f]	Me	OAc	$CH_2CH_2NMeallyl$	32	100–115	$C_{26}H_{29}N_2O_4F_3 \cdot HCl$	C,H,N,Cl	+97.3° (*c* = 0.58, MeOH)
15j[f]	Me	OAc	$CH_2CH_2NMepropynyl$	28	194–196	$C_{26}H_{27}N_2O_4F_3 \cdot HCl$	C,H,N,Cl	+95.5° (*c* = 0.67, MeOH)
15k[b]	Me	Me	$CH_2CH_2NMe_3{}^+I^-$	84[c]	>220	$C_{24}H_{30}N_2O_2F_3I \cdot 0.19H_2O$	C,H,N,I	
15l[b]	Me	Me	$CH_2CH(Me)NMe_2$ (A)	23	101–104	$C_{24}H_{29}N_2O_2F_3 \cdot HCl \cdot 0.50H_2O$	C,H,N,Cl	
15m[b]	Me	Me	$CH_2CH(Me)NMe_2$ (B)	13	83–86	$C_{24}H_{29}N_2O_2F_3 \cdot HCl \cdot 0.50H_2O$	C,H,N,Cl	
15n[b]	Me	Me	$CH(Me)CH_2NMe_2$ (A)	14	>220	$C_{24}H_{29}N_2O_2F_3 \cdot HCl$	C,H,N,Cl,F	
15o	Me	Me	$CH(Me)CH_2NMe_2$ (B)	10	>220	$C_{24}H_{29}N_2O_2F_3 \cdot HCl \cdot 0.60H_2O$	C,H,N,Cl,F	
15p	Me	Me	CH_2CH_2NH-2-Pr	70[d]	278–280	$C_{24}H_{29}N_2O_2F_3 \cdot HCl$	C,H,N,Cl	
15q	Me	Me	CH_2CH_2N-2-PrMe	84	226–228	$C_{25}H_{31}N_2O_2F_3 \cdot HCl \cdot 0.25H_2O$	C,H,N,Cl	
15r	Me	Me	CH_2CH_2-2-Pr_2	91	81–84	$C_{27}H_{35}N_2O_2F_3 \cdot HCl \cdot 0.50H_2O$	C,H,N,Cl	
15s	Me	Me	$CH_2CH_2CH_2NMe_2$	24	78	$C_{24}H_{29}N_2O_2F_3 \cdot C_4H_4O_4 \cdot 10.50H_2O$	C,H,N	
15t	Me	Me	CH_2CH_2Npyrrolidinyl	73	>250	$C_{25}H_{29}N_2O_2F_3 \cdot HCl \cdot 0.33H_2O$	C,H,N,Cl,F	
15u	Me	OAc	$CH_2CH_2NMe(CH_2)_4Ph$	24[e]	90–95	$C_{33}H_{37}N_2O_4F_3 \cdot HCl \cdot 0.50H_2O$	C,H,N,Cl	

[a] Crystallizes with 0.1 equiv toluene. [b] Preparation described in Experimental Procedures. [c] From **12a**. [d] From **15r**. [e] From **15a**. [f] Nonracemic compounds.

comparable cis benzazepinones such as methyl-substituted **12a**. From this result and previous data for the diastereomers of **2g**[1a] we conclude that active benzazepin-2-one calcium channel blockers are optimally substituted at C3 with a cis substituent. We believe that one effect of the cis substitution is to stabilize the active "M" (syn) conformation relative to the inactive "U" (anti) conformation.[13]

Effect of Partition Coefficient (log *P*). Inspection of the data in Table VI indicates that substitution at either C3 or C7 with moderately lipophilic groups provides maximal activity in vitro. This observation, combined with the data from substitution at C6 led us to the hypothesis that molecular lipophilicity (as measured by log *P*) may play an important role in determining activity in vitro and in vivo.

An analysis of the relationship between the log *P* and log IC_{50} for the compounds of Table VI is shown in Figure 2. Note that compounds of Table VI all satisfy the minimum prerequisites for activity: the presence of the two important pharmacophores and a 3-substituent in the cis configuration. While a great deal of scatter is apparent in the data, linear regression analysis reveals a significant trend ($F_{1,33} = 7.19$, $p < 0.025$, $R^2 = 18\%$) of increasing activity in vitro with increasing log *P*.

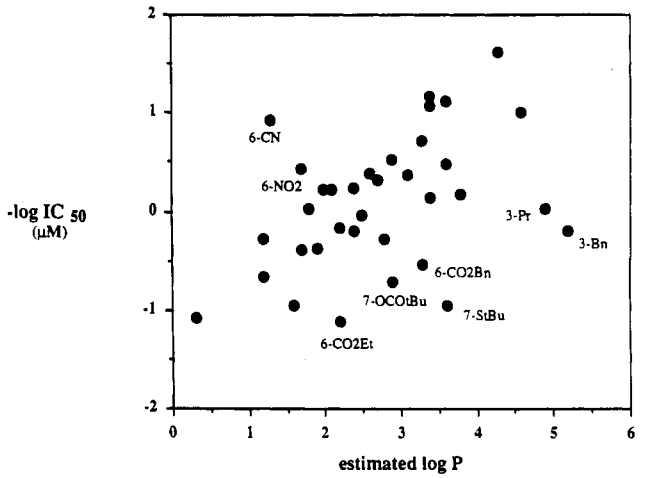
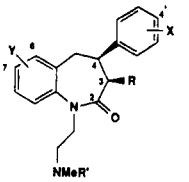


Figure 2. Vasorelaxant activity vs log *P* for compounds of Table VI.

Further analysis of this data set for trends was performed using the DATA DESK program (version 3.0, Odesta Corp.). Plotting predicted values against the residuals from the linear regression in Figure 2 allowed us to identify four structural subsets that are outliers from the regression. First, highly branched substituents at C7 (**2r**, 7-OCOtBu; **2s**, 7-StBu) are much less active than predicted from the regression. This may indicate that the presence of large branched groups at C7 interferes with drug binding to the calcium channel protein. Second, as previously noted, all carboxylic acid derivatives at C6 (**2k**, 6-CO_2Et; **2l**, 6-CO_2Bn) are much less active than predicted from the regression. In fact, two compounds of Table VI not included in the quantitative analysis are the 6-carboxylic acid **2m**

(13) A detailed discussion of this point will be presented in a future manuscript. See: (a) 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. (b) Glaser, R.; Sklarz, B. Stereochemistry and Conformation in Solution of Diltiazem Hydrochloride, a 1,5-Benzothiazepine Coronary Vasodilator. *J. Chem. Soc., Perkin Trans. II* **1989**, 1031–1036.

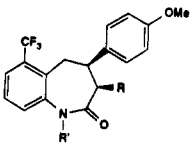
Table IV. Effect of Substitution in 4-Aryl Position



compd	X	Y	R	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
2a	4′-OMe	7-Cl	OAc	Me	1.5 (0.84–2.8)	1.4 (±0.51)	13	14	18[d]
2b	3′-OMe	7-Cl	OAc	Me	18 (13–26)	3.5 (±1.1)	5	2	3
2c	2′-OMe	7-Cl	OAc	Me	16 (9.5–26)	5.8 (±2.3)	2	2	0
12a	4′-OMe	6-CF_3	Me	Me	0.076 (0.041–0.14)	0.075 (±0.043)	28	22	22
12b	4′-NHMe	6-CF_3	Me	Me	0.33 (0.20–0.56)	0.57 (±0.23)	14	18	20
12c	4′-SMe	6-CF_3	Me	Me	0.73 (0.38–1.4)	1.1 (±0.40)	12	8	5
12d	4′-CH_2Me	6-CF_3	Me	Me	2.4 (1.5–3.9)	1.0 (±0.20)	20	14	13
12e	3′,4′-$(OMe)_2$	6-CF_3	Me	Me	3.8 (1.9–7.5)	2.0 (±0.83)	3	5	5
12f	4′-OH	6-CF_3	Me	Me	0.16 (0.087–0.28)	1.6[e]	10	5	7
15a[f]	4′-OMe	6-CF_3	OAc	H	0.18 (0.12–0.28)	0.16 (±0.024)	32	34	32
15b[f]	4′-OMOM	6-CF_3	OAc	H	21 (16–27)	155 (±95)	6	8	8
15c[f]	4′-OMEM	6-CF_3	OAc	H	39 (28–56)	5.8 (±0.51)	5	5	7

[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 270 μmol/kg. [e] Based on concentration–effect curve from one animal; data not used in analysis. [f] Nonracemic compound.

Table V. Effect of Substitution at N-1



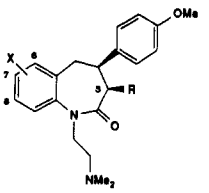
compd	R	R′	IC_{50} (μM)[a]	k_d (μM)[b]	% decrease in BP @ 135 μmol/kg po[c] 0–6 h	6–12 h	12–18 h
2g[e]	OAc	$CH_2CH_2NMe_2$	0.15 (0.11–0.20)	0.12 (±0.018)	31	27	20
12a	Me	$CH_2CH_2NMe_2$	0.076 (0.041–0.14)	0.075 (±0.043)	28	22	22
15a[e]	OAc	CH_2CH_2NHMe	0.18 (0.12–0.28)	0.16 (±0.024)	32	34	32
15d[e]	OAc	$CH_2CONHMe$	6.2 (3.7–10)	15 (±6.0)	13	8	10
15e[e]	OAc	$CH_2CH_2N(Me)COCH_3$	4.5 (3.3–6.2)		2	1	5
15f[e]	OH	$CH_2CH_2NMe_2$	0.30 (0.19–0.46)	0.66[d]	21	26	28
15g[e]	OH	$CH_2CH_2N(Me)COCH_3$	2.2 (1.4–3.4)	13 (±1.6)			
15h[e]	OAc	$CH_2CH_2N(Me)CH_2CH_2CH_3$	0.19 (0.10–0.37)	0.52[d]	27	26	28
15i[e]	OAc	$CH_2CH_2N(Me)CH_2CH{=}CH_2$	0.17 (0.095–0.29)	0.42[d]	28	26	25
15j[e]	OAc	$CH_2CH_2N(Me)CH_2CCH$	3.3 (2.4–4.6)	1.8[d]	26	25	25
15k	Me	$CH_2CH_2NMe_3^+$	6.2 (4.9–7.9)	0.84 (±0.041)	25	22	21
15l	Me	$CH_2CH(Me)NMe_2$ (isomer A)	0.36 (0.20–0.62)		26	17	14
15m	Me	$CH_2CH(Me)NMe_2$ (isomer B)	0.40 (0.22–0.70)	0.32 (±0.013)	26	16	12
15n	Me	$CH(Me)CH_2NMe_2$ (isomer A)	5.9 (3.0–12)	0.54 (±0.075)	15	16	16
15o	Me	$CH(Me)CH_2NMe_2$ (isomer B)	2.3 (1.4–3.7)	0.61 (±0.11)	16	16	16
15p	Me	CH_2CH_2NH-2-Pr	0.95 (0.57–1.6)		17	15	10
15q	Me	CH_2CH_2NMe-2-Pr	0.81 (0.38–1.7)	0.13 (±0.014)	18	15	14
15r	Me	CH_2CH_2N-2-Pr_2	4.2 (2.5–6.8)		14	8	8
15s	Me	$CH_2CH_2CH_2NMe_2$	1.1 (0.79–1.6)		24	22	24
15t	Me	CH_2CH_2Npyrrolidinyl	1.1 (0.52–2.4)		8	10	11
15u	OAc	$CH_2CH_2NMe(CH_2)_4Ph$	0.073 (0.033–0.16)	0.22[d]	28	23	24

[a] IC_{50} in rabbit aorta strips contracted with KCl (95% confidence interval). [b] k_d determined by displacement of radiolabeled diltiazem in guina pig striated muscle (±SEM). [c] In spontaneously hypertensive rats, $n = 5$. [d] Based on concentration–effect curve using tissue of one animal; data not used in analysis. [e] Nonracemic compound.

and the primary amide **2n**; their IC_{50} values are too large for accurate determination under our experimental conditions. The third group includes the most lipophilic compounds (**12j**, 3-Pr; **12k**, 3-Bn), which are less active than anticipated from a simple linear model. It is possible that highly lipophilic and relatively water-insoluble molecules are less able to access the diltiazem receptor. This finding would not be surprising in view of the fact that a parabolic relationship between log *P* and drug concentration is a well-established phenomenon for passive transport processes.[14] Further support for this contention is our belief that the water solubility of **12j** may have been limiting in the determination of its activity in vitro, as evidenced by the large confidence interval for its IC_{50}. On a more positive note, the 6-CN derivative **2h** is more active

(14) Dearden, J. C. Molecular Structure and Drug Transport. In *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: New York, 1990, *4*, 375–409.

Table VI. Effect of Substitution in Fused Aryl Ring and at C3



compd	X	R	log p^a	IC_{50} (μM)^b	k_d (μM)^c	% decrease in BP @ 135 μmol/kg po^d 0–6 h	6–12 h	12–18 h
2a	7-Cl	OAc	2.2	1.5 (0.84–2.8)	1.4 (±0.51)	13	14	18[e]
2d	H	OAc	1.2	4.7 (2.9–7.8)	5.1 (±1.4)	8	8	13[e]
2e	6-Cl	OAc	2.4	1.6 (0.71–3.4)		9	8	11
2f	6-Me	OAc	1.7	2.5 (1.9–3.3)		6	10	12
2g[i]	6-CF_3	OAc	2.9	0.15 (0.11–0.20)	0.12 (±0.018)	31	27	30
2h	6-CN	OAc	1.3	0.12 (0.067–0.20)		9	7	9
2i	6-NO_2	OAc	1.7	0.37 (0.24–0.58)		16	12	14
2j	6-OMe	OAc	1.9	2.4 (1.8–3.2)	1.8 (±0.44)	0	0	1
2k	6-CO_2Et	OAc	2.2	13 (7.3–23)	2.0 (±0.64)	4	6	5
2l	6-CO_2Bn	OAc	3.3	3.5 (1.8–7.0)	1.4 (±0.11)	4	8	8
2m	6-CO_2H	OAc	−4.1	>30		8	9	10
2n	6-$CONH_2$	OAc	−1.0	>30		13	12	12
2o	7-OBn	OAc	3.4	0.73 (0.42–1.3)		8	10	11
2p	7-OMe	OAc	1.2	1.9 (0.88–4.0)	1.6 (±0.28)	15	8	10
2q	7-OCONHMe	OAc	0.31	12 (7–19)		7	10	12
2r	7-OCOtBu	OAc	2.9	5.2 (4.0–6.7)		13	14	16
2s	7-StBu	OAc	3.6	9.0 (6.1–13)		10	11	14
2t	7-OCF_2H	OAc	1.8	0.96 (0.63–1.5)		12	13	16
2u	7-SMe	OAc	2.0	0.60 (0.37–0.98)		19	20	21
2v	7-SPh	OAc	3.8	0.69 (0.42–1.1)		15	17	19
2w	7-OPh	OAc	3.1	0.44 (0.22–0.87)		16	12	16
2x	7-CF_3	OAc	2.8	1.9 (0.95–4.0)		19	19	18
2y	6-OMe,7-Br	OAc	2.4	0.58 (0.41–0.78)	0.12[h]	18	12	11
12a	6-CF_3	Me	3.6	0.076 (0.041–0.14)		28	22	22
12g	6-CF_3	H	3.1	1.1 (0.75–1.7)		2	3	3
12h[i]	6-CF_3	Et	4.3	0.012 (0.093–0.017)	0.60 (±0.17)	21	19	15[f]
12i	6-CF_3	allyl	4.6	0.10 (0.064–0.17)		24	27	29[f]
12j	6-CF_3	Pr	4.9	0.95 (0.014–63)[g]		14	19	24[f]
12k[i]	6-CF_3	Bn	5.2	0.79 (0.55–1.1)		14	8	6
12l	7-CF_3	NHAc	1.6	9.2 (6.4–13)		12	12	10
12m	7-CF_3	CH_2Ac	2.7	0.48 (0.32–0.71)		23	28	28
12n	7-CF_3	SAc	3.4	0.068 (0.053–0.087)		13	18	23
12o	6-OMe	Me	2.6	0.42 (0.31–0.58)	0.40[h]	7	10	8
12p	6-OMe, 7-Br	Me	3.4	0.085 (0.058–0.12)	0.12 (±0.036)	9	12	14
12q	H	Me	2.5	1.1 (0.61–1.9)	0.65 (±0.22)	6	4	8
12r	H	allyl	3.3	0.19 (0.12–0.32)	0.052 (±0.008)	25	23	18
12s	H	Pr	3.6	0.34 (0.23–0.52)	0.25 (±0.08)	10	11	12
15f[i]	6-CF_3	OH	2.1	0.30 (0.19–0.46)	0.66[h]	21	26	28

[a] log *P* determined as described in ref 12. [b] IC_{50} in rabbit aorta strips contracted with KCl (95% confidence interval). [c] k_d determined by displacement of radiolabeled diltiazem in guina pig striated muscle (±SEM). [d] In spontaneously hypertensive rats, $n = 5$. [e] Dosed at 270 μmol/kg. [f] Dosed at 45 μmol/kg. [g] Wide confidence interval probably due to lack of solubility. [h] Based on concentration–effect curve using tissue of one animal; data not used in analysis. [i] Nonracemic compound.

in vitro than would be predicted from its log *P*. Although **2h** is inactive as an antihypertensive agent, we have already noted that the presence of an electron-withdrawing group at C-6 can have a marked effect on activity in vitro and in vivo (e.g., **2g**, **2i**). When these structural constraints are included in our structure–activity hypothesis, a highly significant linear regression is obtained between −log IC_{50} and log *P* for the remaining compounds (Figure 3). This regression implies that, for this set of compounds, log *P* is the primary determinant of activity in vitro.

The effect of lipophilicity on activity in vitro is better exemplified by two sets of closely related compounds. In the 7-trifluoromethyl series, we synthesized four isosteres at C3, substituting the 3-acetoxy oxygen of **2x** with nitrogen, carbon, and sulfur (**12l**, 3-NHAc; **12m**, 3-CH_2Ac; **12n**, 3-SAc). The synthesis of these compounds has been described previously.[7a,b] In addition, a series of 6-methoxy-substituted compounds varying both the C3 and C7 substituents was prepared (**2j**, 3-OAc; **2y**, 3-OAc, 7-Br; **12o**,

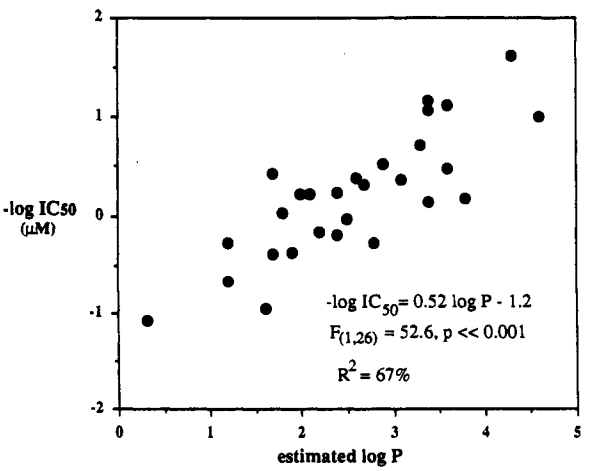


Figure 3. Vasorelaxant activity vs log *P* for compounds of Table VI without outliers.

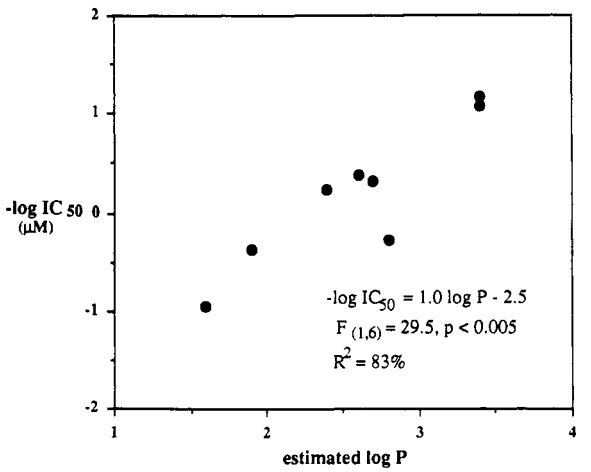


Figure 4. Vasorelaxant activity vs log P for eight isosteres.

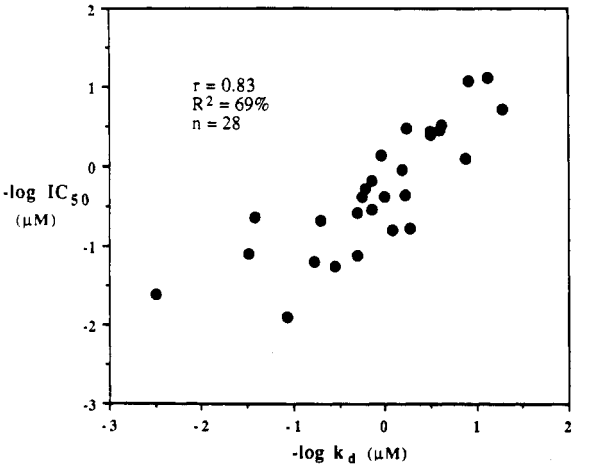


Figure 5. Correlation between in vitro tests for all compounds.

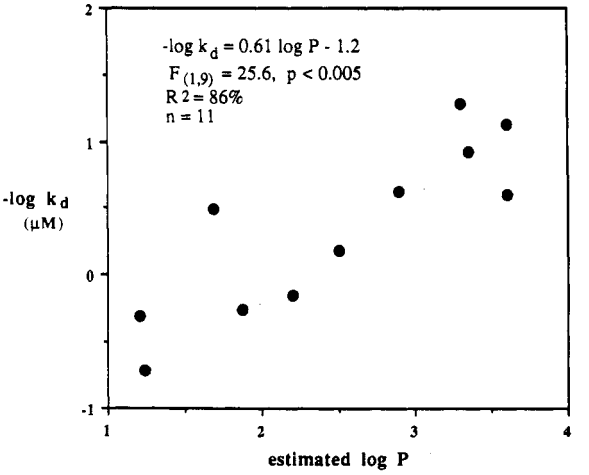


Figure 6. Radioligand displacement vs log P for compounds of Table VI.

3-Me; **12p**, 3-Me, 7-Br). These two isosteric series exhibit a linear relationship between $-\log IC_{50}$ in vitro and log P as shown in Figure 4. These data support the hypothesis that increasing log P by substitution at C3, C6, and C7 can translate directly into an increase of biological activity in vitro.

Test of the Lipophilicity Hypothesis. A logical consequence of the hypothesis that log P is a major determinant of activity in vitro and in vivo is that the *site* of substitution (C3 or C7) may be much less important than the effect of the substituent on log P. Up to this point, substitution at C6 or C7 had provided us with all of the compounds that possessed activity in vitro and in vivo. We therefore proposed to test the hypothesis by synthesizing benzazepinones unsubstituted at C6 or C7, predicting that appropriate substitution at C3 should afford compounds with activity in vitro and possibly in vivo.

This expectation was borne out, as shown in Table VI. The unsubstituted, 3-methylbenzazepinone **12q** is 6-fold more potent than the analogous 3-acetoxybenzazepinone **2d** in vitro. Further, allyl (**12r**) and propyl analogues (**12s**) demonstrate higher levels of activity in vitro. The 3-allyl analogue **12r** is also antihypertensive in the spontaneously hypertensive rat model. The estimated log P values for these compounds (2.5–3.6) are close to those of the most active compounds in Table VI.

Implications of the Lipophilicity Hypothesis: Drug Binding Site. The above results lead us directly to propose that the high dependence of activity in vitro and in vivo on molecular lipophilicity is due to the location of the benzazepinone (diltiazem) binding site on the calcium channel protein. If the binding site is either within the phospholipid membrane domain or requires transport through it to an intracellular binding site, we would expect that activity in vitro should be dependent upon the concentration of drug in the cell membrane. This concept has been previously advanced for drugs binding to receptors *within* the phospholipid bilayer.[15] From the linear dependence of activity in vitro on log P it also follows that structural modifications at C3 and C7 must not have changed significantly the intrinsic affinity (k_d) of these analogues for the calcium channel protein. Instead, these modifications appear to have served primarily to provide more efficient delivery of the drug to, and concentration of the drug at, its receptor.

In order to test the possibility that access to the benzazepinone (diltiazem) binding site requires transport through the cell membrane, we synthesized **15k** (Table V), the quaternary ammonium salt of **12a**.[16] Since **15k** is permanently charged, it should not be able to traverse biological membranes. The quaternary ammonium salt **15k** is almost 100 times less active than **12a** in the rabbit aorta test in vitro. Most interestingly, **15k** does possess modest activity in the radioligand binding assay, a fact which can be put into context when the details of the binding protocol are understood. The tissue preparation used in this assay is subjected to conditions that fragment

(15) (a) For an overview see: Mason, R. P.; Rhodes, D. G.; Herbette, L. G. Reevaluating Equilibrium and Kinetic Binding Parameters for Lipophilic Drugs Based on a Structural Model for Drug Interaction with Biological Membranes. *J. Med. Chem.* **1991**, *34*, 869–877. (b) Herbette, L. G. Techniques for Determining Membrane Structure: The Necessity for Understanding Cardiovascular Drug-Membrane Interactions at the Molecular Level. In *The Heart and Cardiovascular System*; Fozzard, H. A., Ed.; Raven Press: New York, 1986; 263–288.

(16) The quaternary ammonium salt **15k** was synthesized by treating **12a** with methyl iodide. Similar experiments have been carried out with verapamil analogues: (a) Mannhold, R.; Kaufmann, R. The Cellular Site of Action of Heart-active Drugs. *Arch. Pharm. (Weinheim, Ger.)* **1986**, *319*, 1028–36. (b) Hescheler, J.; Pelzer, D.; Trube, G.; Trautwein, W. Does the Organic Calcium Channel Blocker D600 Act from Inside or Outside on the Cardiac Cell Membrane? *Pfluegers Arch.* **1982**, *393*, 287–291. (c) White, E. J.; Bradford, H. F. Participation of Intracellular Sites in the Action of Ca^{+2} Channel Blockers. *Eur. J. Pharmacol.* **1986**, *130*, 243.

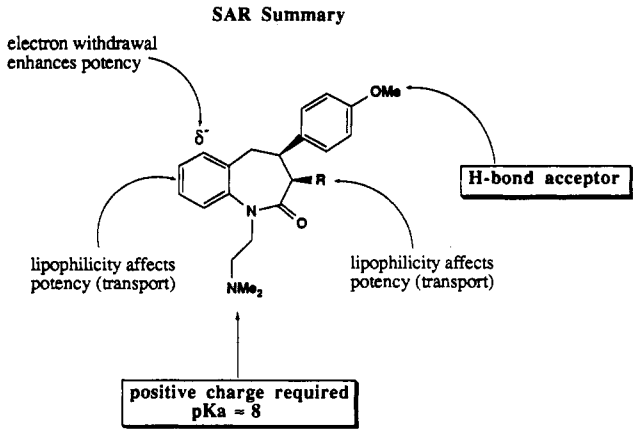


Figure 7. SAR summary.

the cell membranes. The membrane-spanning calcium channel protein should remain associated with the fragmented cell membranes, which may reassemble to produce vesicles that contain a statistical mixture of inside-out and outside-out voltage-operated calcium channel proteins. The fact that **15k** is essentially inactive in the rabbit aorta assay in vitro excludes the possibility of the diltiazem receptor binding site being on the external face of the voltage-operated calcium channel protein. The finding that we observe a significant displacement of diltiazem by **15k** in the radioligand binding assay, in combination with a lack of activity in the rabbit aorta functional test, is consistent *only* with the locus of the diltiazem binding site being on the intracellular face of the calcium channel protein.

Comparison of in Vitro Tests. It is important to validate the biological assays used to evolve our structure–activity relationships. Further, the structure–activity relationships that we have developed here based on both radioligand binding (k_d) and functional calcium antagonism in rabbit aorta strips (IC_{50}) are expected, a priori, to parallel each other. Figure 5 shows the correlation between log k_d values and log IC_{50} values, while Figure 6 shows the anticipated relationship between $-\log k_d$ and log P.

An examination of the structure–activity relationships of benzazepinones in vivo indicates that, as a general rule, calcium channel blocking potency in vitro is a necessary but not sufficient condition for the expression of antihypertensive activity in the spontaneously hypertensive rat. This finding is consistent with calcium channel blockade being the mode of antihypertensive activity in this series of compounds.

Summary

As demonstrated in this paper (Figure 7), the calcium channel blocking activity of benzazepinones is dependent upon two pharmacophores: a 4′-OMe substituted phenyl ring at C4 and a basic residue attached to the N1 benzazepinone amide nitrogen. Most substitutions at C3 and in the fused aryl ring appear to affect delivery of the compound to its biological receptor. For these modifications, activity in vitro is highly correlated with log P. The addition of an electron-withdrawing substituent at C6 may enhance potency in vitro and in vivo.

Binding to the diltiazem receptor, as determined by displacement of radiolabeled diltiazem, is highly correlated with functional activity in vitro. Antihypertensive potency in the spontaneously hypertensive rat requires activity in vitro as a necessary but not sufficient precondition. We have also demonstrated that the binding site for benzazepinone calcium channel blockers is on the intracellular face of the calcium channel protein.

From the above data we conclude that the benzazepinones are specific and reversible calcium channel blockers that act at the diltiazem site on the calcium channel. This work represents the first thorough structure–activity analysis for compounds of this type. Further work is being directed at defining the relative orientation of the two critical pharmacophores more precisely.

Experimental Section

General Procedures. The pharmacological test procedures have been described in detail in a previous paper in this series.[1a] The IC_{50} value reported represents the concentration of compound necessary to cause 50% relaxation of maximal contraction (circumferential rabbit aorta strips) in response to 100 mM KCl. The k_d values reported were calculated from concentration–response curves for the inhibition of specific [^{3}H]-diltiazem binding in guinea pig skeletal muscle. 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 per os. The maximum antihypertensive effect was noted for the 0–6, 6–12, and 12–18 h time periods after dosing. These data allow comparison of both the peak potency and duration of action of the test compounds. All blood pressure measurements were obtained by direct recording.

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. Optical rotations were recorded with a Perkin-Elmer 241 spectrophotometer. All reactions were carried out under an atmosphere of nitrogen or argon.

Representative Synthesis Using Scheme I:

2-Nitro-5-phenylthiotoluene (3v). To a solution of thiphenol (9.87 mL, 96.2 mmol) in DMF (189 mL) at 0 °C was added sodium hydrogen (2.52 g, 105 mmol, 60% mineral oil dispersion) in several increments. When hydrogen gas evolution had subsided, 2-nitro-5-chlorotoluene (15 g, 987 mmol) was added in several increments, and the reaction was allowed to stir overnight at room temperature. Ethyl acetate and 1 N hydrochloric acid were added at 0 °C, the aqueous layer was washed with ethyl acetate, and the ethyl acetate layers were washed with 1 N NaOH solution (3×) and brine, dried over magnesium sulfate, and concentrated in vacuo to give 30.47 g of a yellow oil. Flash chromatography on silica gel (hexane, then 90:10 hexane–ethyl acetate) followed by recrystallization from hexane provided light yellow crystals (14.69 g, 69%), mp 69.5–70.5 °C.

[1-(4-Methoxyphenyl)-2-[2-nitro-5-(phenylthio)phenyl]-ethyl]propanedioic Acid, Dimethyl Ester (5v). A solution of (4-methoxybenzylidene)malonate 4 (13.6 g, 54.4 mmol) in DMF (273 mL) was treated with sodium hydride (3.59 g, 89.8 mmol, 60% mineral oil dispersion). A solution of **3v** (14.68 g, 59.85 mmol) in DMF (10 mL) was added over 1 h, and the reaction was stirred at room temperature overnight and then quenched by the addition of glacial acetic acid (175 mL) at 0 °C. A total of 500 mL of 70:30 water–methanol was added with stirring, ethyl acetate was added, the aqueous layer was washed with ethyl acetate, and the combined ethyl acetate layers were washed with saturated aqueous potassium carbonate solution (2×) and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give a dark brown oil. Mineral oil was removed by washing and decanting several times with hexane. Flash chromatography on silica gel (75:25 hexane–ethyl acetate, then 50:50 hexane–ethyl acetate) provided 23.78 g of a red-brown solid. Trituration from ether–hexane (two crops) gave a light yellow solid (18.04 g, 67%), mp 93.5–95 °C.

[1-(4-Methoxyphenyl)-2-[2-amino-5-(phenylthio)phenyl]-ethyl]propanedioic Acid, Dimethyl Ester. Pulverized $SnCl_2 \cdot 2H_2O$ (41.54 g, 184 mmol) was suspended in methanol (560 mL) and the suspension was degassed several times. Concentrated HCl (57 mL) was added, followed by the addition of compound **5v** as a suspension in hot methanol (266 mL). The reaction

mixture was immersed in a hot water bath (40–52 °C) for 4.5 h. Celite was added, followed by ethyl acetate (680 mL) and saturated aqueous potassium carbonate (275 mL). The reaction mixture was filtered through a Celite pad, and the organic solvents were removed in vacuo. Ethyl acetate and saturated aqueous potassium carbonate solution were added, and the ethyl acetate layer was washed with saturated aqueous potassium carbonate solution (3×), dried over magnesium sulfate, filtered through a Celite pad, and concentrated in vacuo to give a tan gum (17.89 g). Recrystallization from methanol–2-propanol provided off-white crystals (14.26 g, 85%), mp 141–142.5 °C.

1,3,4,5-Tetrahydro-7-(phenylthio)-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (6v). A degassed solution of [1-(4-methoxyphenyl)-2-[2-amino-5-(phenylthio)-phenyl]ethyl]propanedioic acid, dimethyl ester (8.0 g, 17.2 mmol) in methanol (42 mL) was treated with sodium methoxide (9.8 mL, 43 mmol, 2.5 equiv). The reaction was heated to reflux for 3 h, cooled to room temperature, and acidified with 1 N hydrochloric acid. The methanol was evaporated in vacuo, the residue was extracted with ethyl acetate, and the extract was washed with brine, 1 N hydrochloric acid, and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product thus obtained (9.12 g) was purified by trituration from 1:1 ether–ethyl acetate to give a colorless solid (4.04 g, 54%). The mother liquor was chromatographed on silica gel (1:1 hexane–ethyl acetate, with ether trituration) to provide an additional 1.92 g of a colorless solid. Total yield 5.96 g (80%), mp 174–175 °C.

1,3,4,5-Tetrahydro-7-(phenylthio)-3-hydroxy-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one. A solution of **6v** (5.38 g, 12.8 mmol) in THF (275 mL) was cooled to −78 °C under argon. Potassium hexamethyldisilazide (9.88 g, 49.5 mmol, 4 equiv) was added, and the reaction mixture was stirred for 1 h at −78 °C. Trimethyl phosphite (5.84 mL, 49.5 mmol, 4 equiv) was added, and oxygen gas was bubbled through the solution, which was then allowed to warm to 0 °C. After 30 min, the reaction was quenched with acetic acid (170 mL), the solvents were partially removed in vacuo, ethyl acetate was added, and the organic layer was washed with 1 N hydrochloric acid (2×), saturated potassium carbonate (2×), and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to provide a yellow tar (6.48 g). The crude product was chromatographed on silica gel (50:50 hexane–ethyl acetate) to provide a colorless solid (4.81 g, 80%) with no discernible melting point (gradual foaming/decomposition was observed above 68 °C).

***cis*-1,3,4,5-Tetrahydro-7-(phenylthio)-3-hydroxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (7v).** A solution of the 3-hydroxy-3-(methoxycarbonyl)benzazepinone (4.77 g, 10.6 mmol) and LiI (5.68, 42.4 mmol) in pyridine (68 mL) with water (0.68 mL) was heated to reflux for 1.5 h. Pyridine was removed in vacuo, ethyl acetate was added, and the ethyl acetate solution was washed with 1 N hydrochloric acid (3×), saturated aqueous potassium carbonate solution, and brine, dried over magnesium sulfate, and filtered. A small amount of insoluble material was filtered out of the separatory funnel, washed several times with water and then ether, and used to seed the aforementioned ethyl acetate solution. Refrigeration provided an off-white solid which was collected by filtration (1.91 g, 46%), mp 174–175.5 °C. The filtrate was concentrated in vacuo to give 2.05 g of a tan solid (49%, cis/trans mixture).

***cis*-1,3,4,5-Tetrahydro-7-(phenylthio)-3-hydroxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (9v).** To a cloudy suspension of **7v** (2.09 g, 4.83 mmol) in DMF (47 mL) was added sodium hydride (0.21 g, 5.31 mmol, 1.1 equiv). The reaction was stirred for 1 h, (*N*,*N*-dimethylamino)ethyl chloride (3.37 mL, 7.24 mmol, 1.5 equiv) was added as a solution in toluene, and stirring was continued for 3 h at 80 °C. DMF was then removed in vacuo, ethyl acetate and water were added, and the ethyl acetate layer was washed with water (2×) and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to provide 2.09 g of a tan solid. The solid was recrystallized from methanol, and the crude free amine thus obtained was chromatographed on silica gel to give an oil (1.75 g), which was dissolved in a minimal amount of chloroform, treated with saturated ethereal hydrochloric acid, concentrated in vacuo, and triturated with ether to give **9v** as a colorless solid (1.59 g, 66%), mp 240–241 °C dec.

***cis*-1,3,4,5-Tetrahydro-7-(phenylthio)-3-acetoxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Hydrochloride (2v).** A solution of **9v** (1.55 g, 3.11 mmol) in acetic anhydride (53.5 mL) and pyridine (5.35 mL) was heated to 78 °C for 3 h. Pyridine and acetic anhydride were removed in vacuo, the product was partitioned between ethyl acetate and water, and the aqueous layer was back-extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to provide a light yellow solid (1.69 g). Trituration with ether provided the free base (1.49 g) which was dissolved in a minimal amount of chloroform, cooled to 0 °C, and acidified with hydrochloric acid–ether. The solvent was concentrated in vacuo, and the product was triturated with ether to provide a colorless solid (1.40 g, 83%), mp 192.5–194.5 °C. ^{1}H NMR ($CDCl_3$): δ 7.30–7.46 (m, 8 H), 7.22 (d, 2 H, J = 8.4); 6.88 (d, 2 H, J = 8.4), 5.08 (d, 1 H, J = 7.9), 4.27 (m, 2 H), 3.79 (s, 3 H), 3.65–3.85 (m, 1 H), 3.58 (m, 1 H), 3.41 (m, 1 H), 2.98 (s, 6 H), 2.85–3.10 (m, 2 H), 1.86 (s, 3 H). ^{13}C NMR (CD_3OD): δ 171.8, 171.0, 160.4, 140.1, 140.0, 137.6, 136.5, 135, 133.3, 132.4, 132.0, 130.6, 129.1, 124.6, 114.7, 73.1, 56.3, 55.7, 51.2, 45.3, 44.1, 37.8, 20.4. MS (CI): $(M + H)^+$ 505. IR (KBr): 1739, 1680 cm^{-1}.

***cis*-1,3,4,5-Tetrahydro-7-[[(methylamino)carbonyl]oxy]-3-acetoxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Hydrochloride (2q).** A solution of **2o** (0.50 g, 0.87 mmol) in methanol (30 mL) was treated with Pd–C (10%, 0.15 g) and shaken on a Parr hydrogenator at 50 psi for 5 h. The catalyst was filtered off and washed with methanol, and the combined filtrates were evaporated in vacuo. The residue was triturated several times with ether, and the product was dried in vacuo to provide the 7-hydroxy derivative (0.40 g, 96%), mp 229–231 °C.

A stirred suspension of the 7-hydroxybenzazepinone (0.5 g, 1.11 mmol) in MeCN (10 mL) was treated at room temperature with triethylamine (0.65 mL, 4.66 mmol), followed by methyl isocyanate (0.70 mL, 11.9 mmol). The reaction was allowed to stir overnight, the solvents were removed in vacuo, and the residue was partitioned between ethyl acetate (20 mL) and 3% sodium bicarbonate (7 mL). The aqueous phase was back-extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to provide an oil (0.72 g). The oil was dissolved in ethyl acetate and treated with ethanolic hydrochloric acid (5.8 N, 0.2 mL). The hydrochloride salt separated as a gum which crystallized on seeding. The solid was triturated with ether (2×), washed with ether, and filtered, and the resulting solid was dried to provide **2q** (0.51 g, 91%), mp 216–218 °C. ^{13}C NMR (CD_3OD): δ 171.8, 171.1, 160.4, 157.3, 151.5, 138.2, 136.8, 132.5, 130.7, 124.8, 124.1, 123.0, 114.7, 73.1, 56.4, 55.7, 51.2, 45.4, 44.2, 43.9, 37.9, 27.7, 20.3.

***cis*-1,3,4,5-Tetrahydro-7-(methylthio)-3-hydroxy-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (7u).** A solution of **7s** (4.0 g, 10.8 mmol) at 0 °C in trifluoroacetic acid (79 mL) with anisole (2.8 mL) was treated with mercury(II) acetate (3.43 g, 10.8 mmol). After stirring for 2.5 h, the reaction mixture was concentrated in vacuo to ca. 50% of its original volume. Ether was added, and the resulting yellow precipitate was collected by filtration and washed with ether to give the (phenylthio)mercury salt (6.47 g).

The mercurial salt was suspended in degassed ethanol (200 mL) at 0 °C, and sodium borohydride 0.71 g, 18.9 mmol) was added. After 1 h, methyl iodide (0.74 mL, 11.8 mmol) was added, and the reaction was stirred for an additional 1 h. The reaction was quenched with 1 N hydrochloric acid, ethyl acetate was added, and the mixture was filtered through a pad of Celite. The organic layer was washed with hydrochloric acid (2×), saturated potassium carbonate (2×), and brine, dried over magnesium sulfate, and concentrated in vacuo to provide a solid (3.00 g). Flash chromatography on silica gel provided **7u** as a colorless solid (2.49 g, 70%), mp 189–190 °C.

Representative Synthesis Using Scheme II:

[1-(4-Ethylphenyl)-2-[2-nitro-6-(trifluoromethyl)-phenyl]ethyl]propanedioic Acid, Dimethyl Ester (5d). A solution of (4-ethylbenzylidene)malonate **4** (Y = 4′-Et; 17.87 g, 71.2 mmol) in DMF (171 mL) was treated with sodium hydride (4.32 g, 108 mmol, 60% dispersion), and a solution of 2-nitro-6-(trifluoromethyl)toluene (16.24 g, 79.17 mmol) in DMF (13 mL)

was added over 1 h. The internal temperature reached a maximum of 35 °C during the addition. After 5 h, the reaction was quenched by the addition of cold (0 °C) aqueous acetic acid (156 mL of 33% v/v) followed by water (180 mL). Further incremental additions of water (100 mL) led to complete precipitation of the product. The crude product was collected by filtration and washed with 70:30 water–methanol followed by 1:1 hexane–ether to give an off-white solid (23.90 g, 73%), mp 113–114 °C.

[1-Methyl-1-(4-ethylphenyl)-2-[2-nitro-6-(trifluoromethyl)phenyl]ethyl]propanedioic Acid, Dimethyl Ester. A solution of [1-(4-ethylphenyl)-2-[2-nitro-6-(trifluoromethyl)-phenyl]ethyl]propanedioic acid, dimethyl ester (23.77 g, 52.42 mmol) in DMF (95 mL) was treated with sodium hydride (3.15 g, 78.6 mmol, 60%) at 0 °C. After 20 min, iodomethane (16.3 mL, 262 mmol) was added, and the reaction was stirred for 4 h at 0 °C. The reaction was quenched by the addition of acetic acid (190 mL of 20%) at 0 °C, methanol (20 mL) was added, and a solid formed upon standing. Water was added in several increments until crystallization of the product was complete (total solvent volume 500 mL). The crude product was collected by filtration, rinsed with 70:30 water–methanol, and recrystallized from methanol to provide an off-white solid (22.16 g, 90%), mp 84.5–86 °C.

[1-Methyl-1-(4-ethylphenyl)-2-[2-amino-6-(trifluoromethyl)phenyl]ethyl]propanedioic Acid, Dimethyl Ester. A solution of the nitro dimethyl ester (22.08 g, 47.24 mmol) in CH_3CN (180 mL) with 10% Pd–C (2.21 g) was hydrogenated on a Parr apparatus at 40 psi for 4 h. Chloroform was added to redissolve precipitated product. The solution was filtered through a pad of Celite and concentrated in vacuo to give a yellow solid (22.45 g). Trituration from hexane provided the amino compound as a colorless solid (19.03 g, 92%), mp 164.5–165.5 °C.

1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-methyl-3-(methoxycarbonyl)-4-(4-ethylphenyl)-2*H*-1-benzazepin-2-one (10d). A suspension of the amino dimethyl ester (18.87 g, 43.1 mmol) in methanol (109 mL) was treated with a solution of sodium methoxide in methanol (24.66 mL, 25 wt %, 107.8 mmol) and heated to reflux under Ar for 3 h. The reaction was quenched by the addition of aqueous acetic acid (305 mL, 50%) followed by water (260 mL). Upon standing 48 h, the resulting taffy solidified, and the crude product was collected by filtration and washed with 60:40 water–methanol to give a light tan solid. Recrystallization from methanol provided **10d** as an off-white solid (13.05 g, 75%), mp 177–178 °C.

***cis*-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-methyl-4-(4-ethylphenyl)-2*H*-1-benzazepin-2-one (11d).** A solution of **10d** (12.88 g, 31.77 mmol) in DMF (97 mL) with LiBr (15.73 g, 181 mmol) was heated to 142 °C (oil bath temperature) for 4 h. The reaction mixture was cooled to room temperature, ethyl acetate and 1 N hydrochloric acid were added, the aqueous layer was washed with ethyl acetate, and the combined ethyl acetate layers were washed with 1 N hydrochloric acid (3×), saturated aqueous potassium carbonate, and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give a colorless glass (9.55 g). ^{1}H NMR revealed a cis/trans isomer ratio of 93:7. Recrystallization from methanol gave a colorless crystalline solid (8.44 g, 76%), mp 123.5–125.5 °C. ^{1}H NMR indicated a cis/trans ratio of 97:3.

***cis*-1,3,4,5-Tetrahydro-6-(trifluoromethyl)-3-methyl-1-[2-(dimethylamino)ethyl]-4-(4-ethylphenyl)-2*H*-1-benzazepin-2-one, Hydrochloride (12d).** A solution of **11d** (1.5 g, 4.32 mmol) in DMF (43 mL) was treated with sodium hydride (0.19 g, 6.48 mmol, 60%). The reaction was stirred at room temperature for 1 h, (*N*,*N*-dimethylamino)ethyl chloride solution was added (3.39 mL of a 1.91 M toluene solution, 6.48 mmol), and the reaction was heated at 90 °C (oil bath temperature) for 2 h. DMF was removed in vacuo, water and ethyl acetate were added, the aqueous layer was washed with ethyl acetate, and the combined ethyl acetate layers were washed with water (3×) and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a viscous tan oil. The oil was dissolved in ethyl acetate, treated with saturated hydrochloric acid–ether solution, concentrated in vacuo, and coevaporated with ether to give an off-white solid. Trituration with ether–ethyl acetate afforded an off-white solid (1.71 g, 84%), mp 244–246 °C. ^{1}H NMR ($CDCl_3$): δ 7.48–7.66 (m, 3 H), 7.17 (d, 2 H, J = 8.4), 7.12 (d, 2 H, J = 8.4), 4.52 (m, 2 H), 3.49 (m, 1 H), 3.30 (m, 3 H), 2.96 (d, 3 H, J = 4.2), 2.88 (d, 3 H, J = 4.2), 2.67 (m, 4 H), 1.24 (t, 3 H, J = 7), 0.78 (d, 3 H, J = 7). ^{13}C NMR (CD_3OD): δ 176.7, 145.1, 144.6, 139.2, 135.0, 129.4, 129.3, 128.9, 128.2, 125.4, 56.8, 54.3, 45.6, 44.2, 43.7, 39.5, 35.9, 29.4, 16.1, 14.1. MS (CI) $(M + H)^+$ 419. IR (KBr): 1662, 1513, 1464 cm^{-1}.

***cis*-1,3,4,5-Tetrahydro-4-(4-methoxyphenyl)-3-methyl-6-(trifluoromethyl)-1-[2-(trimethylammonio)ethyl]-2*H*-1-benzazepin-2-one, Iodide (15k).** The synthesis of **12a** is described in ref 1b. To obtain the free base, **12a** (0.6 g, 1.31 mmol) was suspended in ethyl acetate and washed with saturated potassium carbonate solution (2×) and brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give a light tan oil (0.55 g, 100%). The free base was dissolved in dry THF (13 mL) and iodomethane (0.41 mL, 6.55 mmol) was added. The reaction was stirred for 1.5 h at room temperature. An additional portion of iodomethane (0.82 mL, 13.1 mmol) was added, and the reaction was continued for 1 h. Concentration of the solvent in vacuo provided a yellow solid (0.74 g), which was triturated with ethyl acetate–ether (15 mL:30 mL) to provide an off-white solid (0.62 g, 84%), mp >221 °C. ^{1}H NMR (CD_3OD): δ 7.57–7.76 (m, 3 H), 7.14 (d, 2 H, J = 9.0), 6.91 (d, 2 H, J = 9.0), 4.46 (m, 2 H), 3.93 (m, 1 H), 3.80 (s, 3 H), 3.59 (m, 1 H), 3.25 (s, 9 H), 3.15–3.40 (m, 1 H), 2.92 (dd, 1 H, J = 13.2), 2.70 (dq, 1 H, J = 6.9), 0.71 (d, 3 H, J = 6.9). ^{13}C NMR (CD_3OD): δ 176.0, 160.3, 144.7, 135.0, 133.9, 130.4, 129.5, 128.3, 125.5, 114.9, 63.4, 55.8, 54.2, 53.9, 44.2, 39.6, 36.0, 14.1. MS (CI): $(M + H)^+$ 421. IR (KBr): 1666, 1466 cm^{-1}.

***cis*-1,3,4,5-Tetrahydro-3-methyl-6-(trifluoromethyl)-1-[2-(dimethylamino)propyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Hydrochloride (15l).** A stirred solution of **11a** (3.0 g, 8.69 mmol) in methyl ethyl ketone (90 mL) was treated with 1.7 g (10.8 mmol) of 2-chloro-1-methyl-1-(dimethylamino)-ethane,[17] followed by pulverized potassium carbonate (3.0 g, 21.7 mmol), and then it was heated to reflux. TLC analysis showed two isomeric products gradually forming. After 48 h, additional 2-chloro-1-methyl-1-(dimethylamino)ethane (1.2 g) and potassium carbonate (2.2 g) were added. After an additional 24 h, the reaction was cooled, the solids were filtered and washed with methyl ethyl ketone, and the combined filtrates were concentrated. The residue was shaken with ethyl acetate (90 mL) and water (30 mL), and the organic layer was separated, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was taken up in ether and concentrated again, and the residue was dried in vacuo to give a mixture of isomeric products as a solid (3.86 g). Two crystallizations from isopropyl ether afforded a solid (1.05 g) which contained predominantly the faster moving isomer on TLC (R_f 0.51 in 90:10 dichloromethane–methanol). This solid was chromatographed on silica gel, as were the mother liquors from the crystallization. The two batches were combined, suspended in methanol (25 mL), and treated with ethanolic HCl (0.45 mL of 5 N), and the solvents were removed in vacuo. The syrupy residue was rubbed under ether and concentrated in vacuo two times to afford isomer A as a colorless solid (0.92 g, 23%), mp 101–104 °C. ^{1}H NMR ($CDCl_3$): δ 7.64 (m, 1 H), 7.49 (m, 2 H), 7.08 (d, 2 H, J = 8.8), 6.93 (d, 2 H, J = 8.8), 4.80 (d, 1 H, J = 12.3), 3.82 (s, 3 H), 3.70–3.93 (m, 2 H), 3.30 (m, 2 H), 2.99 (s, 3 H), 2.97 (s, 3 H), 2.71 (m, 2 H), 2.14 (bs, 2 H), 1.32 (d, 3 H, J = 6.4), 0.76 (d, 3 H, J = 6.4). ^{13}C NMR ($CDCl_3$): δ 173.3, 158.6, 143.8, 136.0, 133.8, 129.5, 126.8, 126.6, 123.5, 123.4, 113.7, 56.8, 55.2, 52.9, 49.6, 39.9, 38.3, 33.8, 13.9, 8.9. IR (KBr): 1669 cm^{-1}. MS $(M + H)^+$ 435.

***cis*-1,3,4,5-Tetrahydro-3-methyl-6-(trifluoromethyl)-1-[2-(dimethylamino)-1-methylethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Hydrochloride, Isomer A (15n).** To a suspension of sodium hydride (0.22 g, 5.37 mmol, 60%) in dry DMF (15 mL) was added **11a** (1.50 g, 4.29 mmol). The solution was stirred for 15 min at room temperature, cooled to 0 °C and 2-chloropropionitrile (0.42 mL, 5.37 mmol) was added. The solution was stirred at 0 °C for 10 min, warmed to room temperature for 15 min, and heated to 45 °C for 90 min. Additional sodium

(17) Schultz, E. M.; Sprague, J. M. The Preparation and Rearrangements of 1,2-Dimethylaminochloropropanes. *J. Am. Chem. Soc.* **1948**, *70*, 48–52.

hydride (50 mg) and 2-chloropropionitrile (0.15 mL) were added, and the solution was stirred for 20 min at 45 °C. The reaction was quenched with 1 M ammonium chloride, and DMF was removed in vacuo. The residue was partitioned between ether and ammonium chloride, and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated to afford a brown foamy solid. The crude product consisted of the two diastereomers, designated as the faster-moving isomer (FMI) and slower-moving isomer (SMI) by their relative mobility on TLC. The product was chromatographed on silica gel to afford the pure FMI and nearly pure SMI. Rechromatographing and combining the mixed fractions provided FMI (1.02 g) and SMI (0.46 g, 25%).

The SMI (0.60 g, 1.49 mmol) was dissolved in methanol with saturated ammonia–methanol (125 mL, 1:1) and was hydrogenated using rhodium on alumina (0.49 g, 5%) for 20 h at 50 psi hydrogen. The solution was filtered through Celite, the Celite was rinsed twice with methanol, and the combined filtrates were concentrated. The semisolid residue was taken up in dichloromethane, filtered through Celite, and concentrated to afford the primary amine as a colorless solid (0.56 g), which was used directly in the next step.

The primary amine was dissolved in acetonitrile (10 mL) containing aqueous formaldehyde (1.2 mL of 37%), and then solid sodium cyanoborohydride (0.28 g, 4.44 mmol) and acetic acid (0.145 mL) were added. The solution was stirred for 2 h, additional acetic acid (0.145 mL) was added, and the solution was stirred for an additional 30 min. The reaction was partitioned between ether and 10% potassium carbonate, and the organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to afford an oil (0.70 g). The oil was chromatographed on silica (1% methanol–0.5% triethylamine–dichloromethane) to afford the free base as a colorless foamy solid (0.32 g). This material was dissolved in ether, and ethereal hydrochloric acid was added to provide a precipitate. The solid was dissolved in methanol, concentrated twice, filtered through Celite, and dissolved in warm methanol (2 mL), and isopropyl ether was added to effect crystallization. Filtration provided the hydrochloride salt as a colorless crystalline solid (0.27 g, 42%), mp >220 °C. ^{1}H NMR (CD_3OD): δ 7.60–7.85 (m, 3 H), 7.18 (d, 2 H, J = 9), 6.92 (d, 2 H, J = 9), 4.39 (m, 1 H), 4.15 (dd, 1 H, J = 6.4, 13.5), 3.80 (s, 3 H), 3.75 (m, 1 H), 3.2–3.3 (m, 2 H), 3.06 (s, 6 H), 2.99 (t, 1 H, J = 13.5), 2.64 (m, 1 H), 1.67 (d, 3 H, J = 6.4), 0.69 (d, 3 H, J = 7.0). ^{13}C NMR (CD_3OD): δ 177.2, 160.5, 145.6, 135.6, 134.0, 130.4, 129.6, 126.0, 114.9, 62.8, 57.8, 55.8, 53.7, 45.1, 40.5, 35.9, 17.3, 14.0. IR (KBr): 1667 cm^{-1}. MS (M + H)$^+$ 435.

***cis*-1,3,4,5-Tetrahydro-3-acetoxy-6-(trifluoromethyl)-1-[2-[methyl(4-phenylbutyl)amino]ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Hydrochloride (15u).** For the preparation of secondary amine analogues such as **15a**, see ref 1a. A stirred mixture of the free base of **15a** (0.90 g, 2.0 mmol) and 1-chloro-4-phenylbutane (1.40 g, 8.3 mmol) in acetonitrile (15 mL) was treated with pulverized potassium carbonate (6.0 g) and sodium iodide (0.20 g). The mixture was heated to reflux for 7 h, the solvent was removed in vacuo, and the residue was treated with ethyl acetate (150 mL) and water (25 mL). The organic layer was washed with water (2×), dried over magnesium sulfate, and filtered, and the filtrate was treated with a solution of oxalic acid (0.44 g, 4.9 mmol) in ether (40 mL). The salt slowly crystallized from the solution. After cooling overnight, the product was filtered to give the oxalate (1.08 g, 80%), mp 166–168 °C. The oxalic acid salt was converted to the free base by suspending the salt in ethyl acetate and water and treating with excess sodium bicarbonate. The organic phase was separated and washed with water (2×), dried over magnesium sulfate, and filtered, and the filtrated was treated with ethereal hydrochloric acid to give a granular foam (1.13 g). This solid was triturated with water (5 mL), the aqueous phase was decanted, and the process was repeated with 3 mL of water. The resulting gummy solid was dried in vacuo to give **15u** as a colorless solid (0.99 g, 57%): mp 90–95 °C; $[\alpha]_D$ +77.4° (c = 1.0, methanol). ^{1}H NMR ($CDCl_3$): δ 7.52–7.66 (m, 3 H), 7.26 (m, 3 H), 7.18 (m, 4 H), 6.92 (d, 2 H, J = 8.8), 5.02 (d, 1 H, J = 8.8), 4.40–4.65 (m, 2 H), 3.82 (s, 3 H), 3.77 (m, 1 H), 3.35 (m, 1 H), 2.85–3.45 (m, 4 H), 2.84 (s, 3 H), 2.68 (m, 1 H), 1.91 (s, 3 H), 1.71 (bs, 6 H). ^{13}C NMR (DMSO-d_6): δ 169.3, 167.1, 158.4, 142.0, 141.6, 131.9, 130.7, 129.3, 128.7, 128.2, 127.7, 127.4, 126.0, 125.7, 124.4, 122.2, 113.6, 70.7, 55.0, 51.4, 48.6, 43.0, 40.1, 34.5, 32.6, 27.9, 22.9, 20.2. IR (KBr): 1740, 1684 cm^{-1}. MS (M + H)$^+$ 583.

Representative Synthesis Using Scheme IV:

1,3,4,5-Tetrahydro-7-(trifluoromethyl)-3-[(tolylsulfonyl)oxy]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (14). To a mixture of epimeric alcohols **7x** and **8x** (11.28 g, 30 mmol) in pyridine (50 mL) was added *p*-toluenesulfonyl chloride (11.4 g, 60 mmol). The reaction mixture was allowed to stand for 24 h at room temperature, and it was then diluted with dichloromethane (500 mL), and washed several times with aqueous saturated copper sulfate. The dichloromethane extract was washed with water (3×), dried over magnesium sulfate, filtered, and concentrated in vacuo. The oily residue was then triturated with ether (100 mL), filtered, and dried in vacuo to provide **14** (11.78 g, 78%) as a mixture of the cis and trans isomers.

1,3,4,5-Tetrahydro-7-(trifluoromethyl)-3-(acetylthio)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one (11n). To a solution of **14** (1.06 g, 2.0 mmol) in dimethyl sulfoxide (10 mL) under argon was added potassium thioacetate (0.57 g, 5.0 mmol). The reaction mixture was heated to 90 °C for 1 h, cooled, diluted with ethyl acetate, and washed thoroughly with water. The organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo to provide a yellow residue. Trituration with ether provided the cis thioacetate **11n** of ca. 95% purity (215 mg, 25%).

***cis*-1,3,4,5-Tetrahydro-7-(trifluoromethyl)-3-(acetylthio)-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, Hydrochloride (12n).** A solution of **11n** (0.74 g, 1.81 mmol) was dissolved in methyl ethyl ketone (9 mL) and DMF (2 mL) and treated with potassium bicarbonate (0.71 g, 7.2 mmol). After the mixture was stirred for 15 min, a solution of (*N*,*N*-dimethylamino)ethyl chloride (1.67 mL of 2.15 M solution in toluene) was added, and heating (85–90 °C) was continued for 4 h. The mixture was cooled, diluted with ethyl acetate, and washed with water, 1 N sodium bicarbonate, and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude free amine was purified by preparative TLC (10% methanol–dichloromethane), dissolved in ethyl acetate, and treated with ethereal hydrochloric acid to provide **12n** as a colorless solid (0.50 g, 53%), mp 147.5–150.5 °C. ^{1}H NMR ($CDCl_3$): δ 7.72 (s, 2 H), 7.56 (s, 1 H), 7.16 (d, 2 H, J = 8.4), 6.90 (d, 2 H, J = 8.4), 4.64 (m, 1 H), 4.39 (m, 2 H), 3.82 (s, 3 H), 3.59 (m, 2 H), 3.33 (m, 1 H), 2.94 (m, 8 H), 2.17 (s, 3 H). ^{13}C NMR (CD_3OD): δ 194.8, 170.0, 159.3, 144.1, 134.2, 131.8, 128.9, 126.6, 123.1, 114.1, 55.2, 54.4, 51.0, 50.2, 45.0, 43.9, 42.6, 39.8, 29.0. IR (KBr): 1677, 1614 cm^{-1}. MS (CI): (M + H)$^+$ 481.

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Registry No. **2a** free base, 138334-33-5; **2a**·HCl, 138334-34-6; **2b** free base, 138334-35-7; **2b**·HCl, 138334-36-8; **2c** free base, 138334-37-9; **2c**·HCl, 138334-38-0; **2d** free base, 129151-95-7; **2d**·HCl, 129151-94-6; **2e** free base, 138334-39-1; **2e**·HCl, 138334-40-4; **2f** free base, 138334-41-5; **2f**·HCl, 138334-42-6; **2g** free base, 138383-07-0; **2g**·HCl, 125762-03-0; **2h** free base, 138334-43-7; **2h**·HCl, 138334-44-8; **2i** free base, 138334-45-9; **2i**·HCl, 138334-46-0; **2j** free base, 138334-47-1; **2j**·HCl, 138334-48-2; **2k** free base, 138334-49-3; **2k**·HCl, 138352-84-8; **2l** free base, 138334-50-6; **2l**·HCl, 138334-51-7; **2m** free base, 138334-52-8; **2m**·HCl, 138334-53-9; **2n** free base, 138334-54-0; **2n**·HCl, 138334-55-1; **2o** free base, 138334-56-2; **2o**·HCl, 138334-57-3; **2p** free base, 138334-58-4; **2p**·HCl, 138334-59-5; **2q** free base, 138334-60-8; **2q**·HCl, 138334-61-9; **2r** free base, 138334-62-0; **2r**·HCl, 138334-63-1; **2s** free base, 138334-64-2; **2s**·HCl, 138334-65-3; **2t** free base, 138334-66-4; **2t**·HCl, 138334-67-5; **2u** free base, 138334-68-6; **2u**·HCl, 138334-69-7; **2v** free base, 138334-70-0; **2v**·HCl, 138334-71-1; **2w** free base, 138334-72-2; **2w**·HCl, 138334-73-3; **2x** free base, 138383-08-1; **2x**·HCl, 138383-09-2; **2y** free base,

138334-74-4; **2y**·HCl, 138353-24-9; **3v**, 60326-45-6; **4** (X = 4-Et), 138334-75-5; **4** (X = 4-OMe), 7443-25-6; **5** (X = 4′-OMe, Y = 7-Cl), 138334-76-6; **5** (X = 3′-OMe, Y = 7-Cl), 138334-77-7; **5** (X = 2′-OMe, Y = 7-Cl), 138334-78-8; **5** (X = 4′-OMe, Y = H), 129151-87-7; **5** (X = 4′-OMe, Y = 6-Cl), 138334-79-9; **5** (X = 4′-OMe, Y = 6-Me), 138334-80-2; **5** (X = 4′-OMe, Y = 6-CF_3), 138334-81-3; **5** (X = 4′-OMe, Y = 6-CN), 138334-82-4; **5** (X = 4′-OMe, Y = 6-NO_2), 138334-83-5; **5** (X = 4′-OMe, Y = 6-OMe), 138334-84-6; **5** (X = 4′-OMe, Y = 6-CO_2Et), 138334-85-7; **5** (X = 4′-OMe, Y = 7-OBn), 138334-86-8; **5** (X = 4′-OMe, Y = 7-S-*t*-Bu), 138352-85-9; **5** (X = 4′-OMe, Y = 7-OCF_2H), 138334-87-9; **5** (X = 4′-OMe, Y = 7-SPh), 138334-88-0; **5** (X = 4′-OMe, Y = 7-OPh), 138334-89-1; **5** (X = 4′-OMe, Y = 7-CF_3), 138334-90-4; **5** (X = 4′-OMe, Y = 6-OMe, 7-Br), 138334-91-5; **5** (X = 4′-SMe, Y = 6-CF_3), 138384-04-0; **5** (X = 4′-Et, Y = 6-CF_3), 138384-05-1; **5** (X = 3′,4′-$(OMe)_2$, Y = 6-CF_3), 138334-92-6; **6g**, 138383-10-5; **6v**, 138334-93-7; **7** (X = 4′-OMe, Y = 7-SHgSPh, R = OH), 138334-94-8; **7a**, 138334-95-9; **7b**, 138334-96-0; **7c**, 138334-97-1; **7d**, 129151-91-3; **7e**, 128574-37-8; **7f**, 138334-98-2; **7g**, 133963-42-5; **7h**, 138334-99-3; **7i**, 138335-00-9; **7j**, 138335-01-0; **7k**, 138335-02-1; **7o**, 138335-03-2; **7s**, 138335-04-3; **7t**, 138335-05-4; **7u** free base, 128510-87-2; **7v**, 138335-06-5; **7w**, 138335-07-6; **7x**, 138335-08-7; **7y**, 138335-09-8; **8x**, 138335-10-1; **9v**, 138335-11-2; **10d**, 138352-86-0; **11a**, 128510-83-8; **11c**, 138335-12-3; **11d**, 138335-13-4; **11e**, 138335-14-5; **11g**, 138335-15-6; *cis*-**11h**, 111605-16-4; *trans*-**11h**, 138383-11-6; *cis*-**11i**, 138335-16-7; *trans*-**11i**, 138335-17-8; *cis*-**11k**, 119217-65-1; *trans*-**11k**, 138383-12-7; **11n**, 138335-18-9; **11o**, 138335-19-0; **11p**, 138335-20-3; **11q**, 129151-99-1; **11r**, 119217-62-8; **12a** free base, 138335-21-4; **12a**·fumarate, 138335-22-5; **12b** free base, 138335-23-6; **12b**·2HCl, 138335-24-7; **12c** free base, 138335-25-8; **12c**·HCl, 138335-26-9; **12d** free base, 138335-27-0; **12d**·HCl, 138335-28-1; **12e** free base, 138335-29-2; **12e**·HCl, 138335-30-5; **12f** free base, 138335-31-6; **12f**·HCl, 138335-32-7; **12g** free base, 138353-25-0; **12g**·HCl, 138335-33-8; **12h** free base, 119217-15-1; **12h**·HCl, 119217-31-1; **12i** free base, 119217-13-9; **12i**·HCl, 119217-30-0; **12j** free base, 119217-14-0; **12j**·HCl, 119217-29-7; **12k** free base, 138383-13-8; **12k**·fumarate, 138456-70-9; **12l** free base, 138335-34-9; **12l**·HCl, 138335-35-0; **12m** free base, 138335-36-1; **12m**·HCl, 138335-37-2; **12n** free base, 138335-38-3; **12n**·HCl, 138335-39-4; **12o** free base, 138335-40-7; **12o**·HCl, 138335-41-8; **12p** free base, 138335-42-9; **12p**·HCl, 138335-43-0; **12q** free base, 119217-37-7; **12q**·HCl, 119217-36-6; **12r** free base, 119217-39-9; **12r**·HCl, 119217-38-8; **12s** free base, 138335-44-1; **12s**·HCl, 119217-40-2; *cis*-**14**, 138335-45-2; *trans*-**14**, 138335-46-3; **15a** free base, 132201-65-1; **15a**·HCl, 129524-09-0; **15b** free base, 138335-47-4; **15b**·fumarate, 138383-14-9; **15c** free base, 138335-48-5; **15c**·fumarate, 138383-15-0; **15d** free base, 138335-49-6; **15e** free base, 138335-50-9; **15f** free base, 138335-51-0; **15f**·HCl, 138383-16-1; **15g** free base, 138335-52-1; **15h** free base, 138335-53-2; **15h**·HCl, 138383-17-2; **15i** free base, 138335-54-3; **15i**·HCl, 138383-18-3; **15j** free base, 138335-55-4; **15j**·HCl, 138383-19-4; **15k** free base, 138335-56-5; **15l** free base, 128573-80-8; **15l**·HCl, 128509-61-5; **15m** free base, 128573-81-9; **15m**·HCl, 128656-27-9; **15n** free base, 128573-82-0; **15n**·HCl, 128509-64-8; **15n** (R″ = CH(Me)CN) free base, 128510-18-9; **15n** (R″ = CH(Me)CH_2NH_2) free base, 138383-20-7; **15o** free base, 138383-21-8; **15o**·HCl, 128573-83-1; **15o** (R″ = CH(Me)CN) free base, 128574-18-5; **15o** (R″ = CH(Me)CH_2NH_2) free base, 138383-22-9; **15p** free base, 138335-57-6; **15p**·HCl, 138335-58-7; **15q** free base, 138335-59-8; **15q**·HCl, 138335-60-1; **15r** free base, 119217-19-5; **15r**·HCl, 119217-35-5; **15s** free base, 138335-61-2; **15s**·fumarate, 138335-62-3; **15t** free base, 138335-63-4; **15t**·HCl, 138335-64-5; **15u** free base, 138335-65-6; **15u**·HCl, 138383-23-0; **15u**·oxalate, 138383-24-1; $Me_2N(CH_2)_2Cl$, 107-99-3; $MeCH(NMe_2)CH_2Cl$, 53309-35-6; thiophenol, 108-98-5; 2-nitro-5-chlorotoluene, 5367-28-2; [1-(4-methoxyphenyl)-2-[2-amino-5-(phenylthio)phenyl]-ethyl]propanedioic acid, dimethyl ester, 138335-66-7; 1,3,4,5-tetrahydro-7-(phenylthio)-3-hydroxy-3-(methoxycarbonyl)-4-(4-methoxyphenyl)-2*H*-1-benzazepin-2-one, 138335-67-8; 2-nitro-6-(trifluoromethyl)toluene, 6656-49-1; [1-methyl-1-(4-ethylphenyl)-2-[2-nitro-6-(trifluoromethyl)phenyl]ethyl]propanedioic acid, dimethyl ester, 138335-68-9; [1-methyl-1-(4-ethylphenyl)-2-[2-amino-6-(trifluoromethyl)phenyl]ethyl]propanedioic acid, dimethyl ester, 138353-26-1.

Communications to the Editor

Inhibitors of Sterol Synthesis. 3β,25-Dihydroxy-5α-cholest-8(14)-en-15-one, an Active Metabolite of 3β-Hydroxy-5α-cholest-8(14)-en-15-one

Oxygenated sterols are potent regulators of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity in mammalian cells.[1,2] 15-Oxygenated sterols are particularly active in the regulation of HMG-CoA reductase activity and of cholesterol biosynthesis.[1-7] One 15-oxygenated sterol, 3β-hydroxy-5α-cholest-8(14)-en-15-one (**1**), is highly active in lowering not only the levels of HMG-CoA reductase activity in cultured mammalian cells but also that of two other key enzymes involved in the formation of mevalonic acid, i.e., cytosolic acetoacetyl-CoA thiolase and HMG-CoA synthase.[5] In addition to its inhibitory action on cholesterol biosynthesis, **1** has been shown to be a potent inhibitor of cholesterol absorption in intact rats.[8,9] The 15-ketosterol serves as a substrate

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