(B^+); IR (KBr) 3600–3000 (NH_2, OH), 1750, 1600 cm^{-1} (C=C, C=N); UV λ_{max} 253 nm in 0.1 N HCl; NMR (dimethyl-d_6 sulfoxide) δ 11.05–10.95 (s, 1 H, 7-OH, D_2O exchangeable), 7.10–6.90 (br, 2 H, NH_2, D_2O exchangeable), 4.95–4.80 (m, 1 H, H-1'), 4.70–4.50 (br, 1 H, CH_2OH, D_2O exchangeable), 3.50–3.40 (d, 2 H, CH_2OH), 2.32–1.55 (m, 7 H, H-4', CH_2CH_2, CHH'). Anal. ($C_{10}H_{14}N_6O_2 \cdot 1.25H_2O$) C, H, N.

(±)-*cis*-[4-(5,7-Diamino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)-2-cyclopentenyl]carbinol (11a). Compound **9a** (267 mg, 1 mmol) was processed as described for compound **6a** with a reaction time of 20 h at 60 °C. The residual mixture was absorbed onto silica gel (2 g); it was packed into a column (2.0 × 10 cm) and eluted by $CHCl_3$–MeOH (15:1) to yield **11a** as white crystals, 204 mg (83%). The crude product was recrystallized from ethanol–water (2:1) to yield **11a**: mp 240–242 °C dec; MS (30 eV, 240 °C) *m/e* 247 (M^+), 229 ($M^+ - 18$), 217 ($M^+ - 30$), 151 (B^+); IR (KBr) 3600–3100 (NH_2, OH), 1700, 1650, 1600 cm^{-1} (C=O, C=C, C=N); UV λ_{max} 253, 283 nm in 0.1 N HCl; NMR (dimethyl-d_6 sulfoxide) δ 7.80–7.20 (br, 2 H, NH_2, D_2O exchangeable), 6.50–6.30 (s, 2 H, NH_2, D_2O exchangeable), 6.15–6.10 and 5.95–5.90 (dd, 2 H, CH=CH vinyl, J = 5.0 Hz), 5.65–5.55 (m, 1 H, H-1'), 4.75–4.65 (t, 1 H, CH_2OH, D_2O exchangeable), 3.55–3.40 (m, 2 H, CH_2OH), 2.95–2.85 (m, 1 H, H-4'), 2.65–2.55 (m, 1 H, CHH'), 1.90–1.80 (m, 1 H, CHH'). Anal. ($C_{10}H_{13}N_7O \cdot H_2O$) C, H, N.

(±)-*cis*-[3-(5,7-Diamino-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)cyclopentyl]carbinol (11b). Compound **9b** (268 mg, 1 mmol) was processed as described for **9a** to yield 220 mg of **11b** (88%), which was recrystallized from ethanol–water (1:2) to afford pink-white crystals: mp 223–225 °C; MS (30 eV, 250 °C) *m/e* 249 (M^+), 218 ($M^+ - 31$), 151 (B^+); IR (KBr) 3600–3100 (NH_2, OH), 1700, 1600 cm^{-1} (C=C, C=N); UV λ_{max} 253, 283 nm in 0.1 N HCl; NMR (dimethyl-d_6 sulfoxide) δ 7.85–7.25 (br, 2 H, NH_2, D_2O exchangeable), 6.50–6.30 (s, 2 H, NH_2, D_2O exchangeable), 4.95–4.85 (m, 1 H, H-1'), 4.65–4.60 (t, 1 H, CH_2OH, D_2O exchangeable), 3.50–3.40 (d, 2 H, CH_2OH), 2.35–1.60 (m, 7 H, H-4', CH_2CH_2, CHH'). Anal. ($C_{10}H_{15}N_7O$) C, H, N.

Acknowledgment. This work was supported by Public Health Service Grant CA23263 from the National Cancer Institute. We gratefully acknowledge the valuable assistance of Jay Brownell.

Registry No. **1a**, 61865-50-7; **1b**, 65898-98-8; **2a**, 122624-72-0; **2b**, 78795-20-7; **3a**, 122624-73-1; **3b**, 122624-74-2; **4a**, 122624-75-3; **4b**, 122624-76-4; **5a**, 122624-77-5; **5b**, 122624-78-6; **6a**, 118237-87-9; **6b**, 118237-86-8; **7a**, 118353-05-2; **7b**, 112915-00-1; **8a**, 118237-88-0; **8b**, 120330-36-1; **9a**, 122624-79-7; **9b**, 122624-80-0; **10a**, 122624-81-1; **10b**, 122624-82-2; **11a**, 122624-83-3; **11b**, 122624-71-9; 2-amino-4,6-dichloropyrimidine, 56-05-3; *p*-chloroaniline, 106-47-8.

Inhibitors of Cholesterol Biosynthesis. 1. *trans*-6-(2-Pyrrol-1-ylethyl)-4-hydroxypyran-2-ones, a Novel Series of HMG-CoA Reductase Inhibitors. 1. Effects of Structural Modifications at the 2- and 5-Positions of the Pyrrole Nucleus

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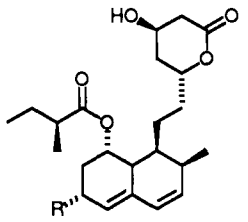
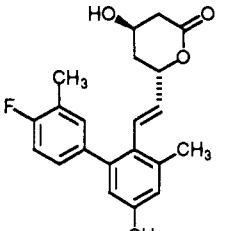
A novel series of *trans*-6-(2-pyrrol-1-ylethyl)-4-hydroxypyran-2-ones and their dihydroxy acid derivatives were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro. A systematic study of substitution at the 2- and 5-positions of the pyrrole ring revealed that optimum potency was realized with the 2-(4-fluorophenyl)-5-isopropyl derivative **8x** (Table III), which possessed 30% of the in vitro activity of the potent fungal metabolite compactin (I). A molecular modeling analysis led to the description of a pharmacophore model characterized by (A) length limits of 5.9 and 3.3 Å for the 2- and 5-substituents, respectively, as well as an overall width limit of 10.6 Å across the pyrrole ring from the 2- to the 5-substituent and (B) an orientation of the ethyl(ene) bridge to the 4-hydroxypyran-2-one ring nearly perpendicular to the planes of the parent pyrrole, hexahydronaphthalene, and phenyl rings of the structures examined (Figure 3, θ = 80–110°). Attempts to more closely mimic compactin's polar isobutyric ester side chain with the synthesis of 2-phenylpyrroles containing polar phenyl substituents resulted in analogues (Table III, **8m–p**) with equal or slightly reduced potencies when compared to the 2-[(unsubstituted or 4-fluoro)phenyl]pyrroles, supporting the hypothesis that inhibitory potency is relatively insensitive to side-chain polarity or charge distribution in this area.

The discovery that the fungal metabolites compactin (I)[1] and mevinolin (II)[2] are not only potent inhibitors of the enzyme HMG-CoA reductase (HMGR), the rate-limiting enzyme in cholesterol biosynthesis, but are also effective hypocholesterolemic agents in man[3] has led to a plethora of publications describing synthetic and biological studies of close structural analogues.[4]



I: R = H (compactin)
II: R = CH_3 (mevinolin)



III

The disclosure of a series of very potent 6-(*o*-biphenylyl)-substituted 4-hydroxypyran-2-ones (III) by Willard et al.[5] led us to hypothesize that the key structural

(1) (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, 1346–8. (b) Endo, A.; Kuroda, Y.; Tanzawa, K. *FEBS Lett.* **1976**, *72*(2), 323–6. (c) Brown, A. G.; Smale, T. C.; King, T. J.; Hassenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165–9.

(2) (a) Endo, A. *J. Antibiot.* **1979**, *32*, 852. (b) Alberts, A.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Pachett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*(7), 3957–61.

(3) (a) Therapeutic response to Lovastatin (Mevinolin) in Non-Familial Hypercholesterolemia. *J. Am. Med. Assoc.* **1986**, *256*, 2829. (b) Vega, L.; Grundy, S. *J. Am. Med. Assoc.* **1987**, *257*(1), 33–38 and references contained therein.

(4) For a review, see: Rosen, T.; Heathcock, C. *Tetrahedron* **1986**, *42* (18), 4909–51.

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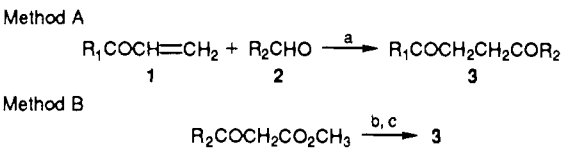
Scheme I[a]



[a] (a) 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, Et_3N, 70 °C. (b) NaH, R_1COCH_2Br. (c) NaOH, CH_3OH.

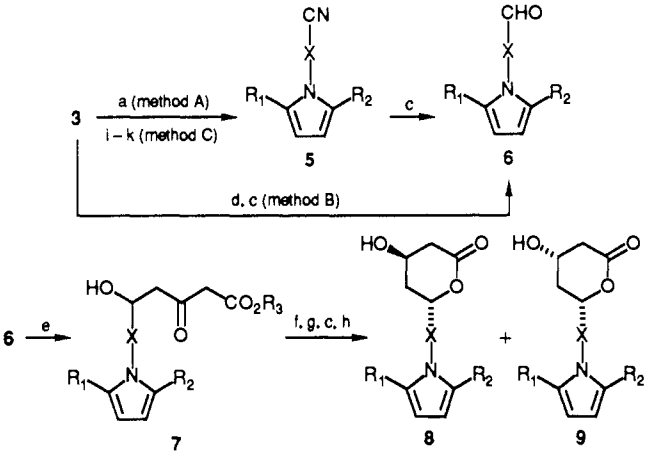
feature possessed by all of these agents was a large lipophilic group held in a particular spatial relationship with respect to the 4-hydroxypyran-2-one moiety. Indeed, examination of CPK models of these inhibitors suggested that the ortho phenyl ring might occupy the same space as the isobutyric ester moiety of compactin and mevinolin. This hypothesis is supported by the 100-fold loss in potency found on hydrolysis of the isobutyric ester group,[6] as well as the suggestion by Nakamura and Abeles that this portion of mevinolin fits into a lipophilic pocket in the active site of HMGR normally occupied by coenzyme A.[7] If this were true, then any connecting group that served to hold the lactone and the lipophilic moiety in the correct spatial relationship might be sufficient for potent inhibition. To investigate this, we selected the pyrrole ring as the anchor for various connecting groups, since there appeared to be sufficient synthetic methodology to allow for the simultaneous introduction of a variety of 2- and 5-substituents. By varying the steric and electronic properties of these substituents, modifying the connecting group, and employing a molecular modeling analysis, we hoped to discern, at least in part, the optimal spatial relationship between the lipophilic group and the 4-hydroxypyran-2-one moiety and use this information in the design of potent HMGR inhibitors.

We herein present our initial investigations into this series of inhibitors that define the structure–activity relationships at the 2- and 5-positions of the pyrrole nucleus and in the connecting group to the lactone ring. Also reported is the molecular modeling study and associated pharmacophore model, which describe conformational requirements of the side chain and steric requirements at the 2- and 5-positions of the pyrrole ring.

Chemistry

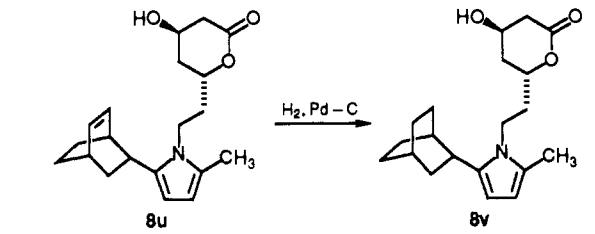
Our general synthetic strategy entailed the preparation of a suitable 1,4-diketone (**3**, Table I), either by the thiazolium salt chemistry developed by Stetter (Scheme I, method A)[8] or by alkylation of a β-keto ester with an α-halo ketone followed by hydrolysis and decarboxylation (method B). The Stetter reaction proved to be the more versatile and generally higher yielding of the two. Paal–Knorr cyclization with 3-aminopropionitrile or an ω-amino acetal provided the pyrroles in good yield (Scheme II). The one exception was 1-(4-fluorophenyl)-5,5-dimethyl-

Scheme II[a]

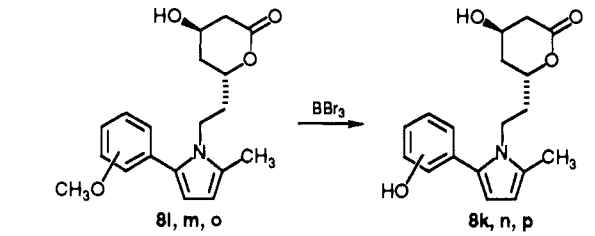


[a] (a) H_2N–X–CN, HOAc, reflux. (b) DIBAL-H, toluene, −78 °C. (c) aqueous HCl. (d) H_2N–X–$CH(OEt)_2$, toluene, cat. *p*-TSA, reflux. (e) $^-CH_2CO^-CHCH_3CH_3$, THF, −78 °C. (f) *n*-Bu_3B, $NaBH_4$, −78 °C. (g) H_2O_2, OH^-. (h) Toluene, reflux. (i) H_2N–X–OH, HOAc. (j) CH_3SO_2Cl, pyr. (k) KCN, DMF–H_2O, 100 °C.

Scheme III



Scheme IV



hexane-1,4-dione (**3q**), which was extremely resistant to cyclization. After considerable experimentation, it was found that treatment with ethanolamine in acetic acid resulted in an exothermic reaction from which the pyrrole was isolated in 84% yield. Mesylation and displacement with potassium cyanide in DMF/H_2O afforded the requisite nitrile. Reduction of the nitriles **5** with DIBAL-H produced the desired aldehydes **6** in good yields (Table II). Condensation of **6** with the dianion of methyl or ethyl acetoacetate under the conditions of Weiler[9] afforded the corresponding alcohols **7**. Sih et al.[10] reported the reduction of a related δ-hydroxy-β-keto ester in their synthesis of compactin in which little stereoselectivity (2:1 erythro:threo) was found employing either sodium or zinc borohydride. We, and others,[5b] have found excellent selectivity (>10:1 erythro:threo) employing the procedure of Narasaka and Pai,[11] in which **7** was complexed with a trialkylborane prior to treatment with borohydride at low temperature. The resultant boronate was hydrolyzed with

(5) (a) Willard, A.; Novello, F.; Hoffman, W.; Cragoe, E. USP 4459422. (b) Stokker, G.; Hoffman, W.; Alberts, A.; Cragoe, E.; Deana, A.; Gilfillan, J.; Huff, J.; Novello, F.; Prugh, J.; Smith, R.; Willard, A. *J. Med. Chem.* **1985**, *28*, 347–358. (c) Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. J.; Hoffman, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170–181.

(6) Endo, A. *J. Med. Chem.* **1985**, *28*, 401–5.

(7) Nakamura, C.; Abeles, R. *Biochemistry* **1985**, *24*, 1364–76.

(8) (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639. (b) Stetter, H.; Kuhlmann, H. *Chem. Ber.* **1976**, *109*, 2890. (c) Stetter, H.; Schreckenberg, M. *Chem. Ber.* **1974**, *107*, 2453. (d) Stetter, H.; Kuhlmann, H. *Synthesis* **1975**, 379.

(9) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.

(10) Wang, N. Y.; Hsu, C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538–6539.

(11) (a) Narasaka, K.; Pai, H. C. *Chem. Lett.* **1980**, 1415–1418. (b) Ibid. *Tetrahedron* **1984**, *40*, 2233–2238.

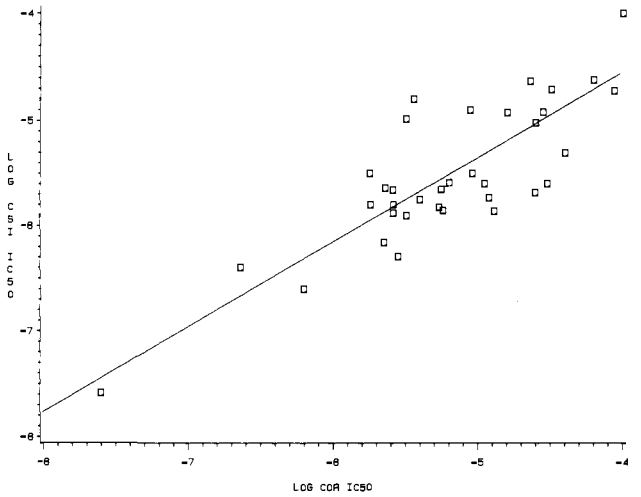


Figure 1. Correlation between CSI and COR IC_{50}'s.

Table I. Substituted 1,4-Diketones

$R_1COCH_2CH_2COR_2$

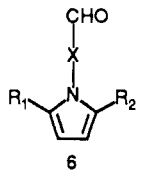
3

no.	R_1	R_2	bp (mmHg), °C	% yield[a] (procedure)
3a[8b]	Ph	CH_3	100 (0.1)	80 (A)
3b	4-*F*C_6H_4	CH_3	46–8	66 (A)
3c	4-PhC_6H_4	CH_3	109–112	73 (A)
3d[8c]	4-ClC_6H_4	CH_3	116–8 (1.0)	44 (A)
3e[8a]	4-$CH_3OC_6H_4$	CH_3	*b*	57 (A)
3f	3-$F_3CC_6H_4$	CH_3	*b*	38 (A)
3g	3-$CH_3OC_6H_4$	CH_3	143–5 (0.2)	80 (A)
3h	2-$CH_3OC_6H_4$	CH_3	133–5 (1.0)	51 (A)
3i	2-naphthyl	CH_3	87–8	55 (A)
3j	1-naphthyl	CH_3	105 (0.1)	83 (A)
3k		CH_3	114–6 (1.0)	76 (A)
3l		CH_3	*b*	98 (A)
3m[8d]	cyclohexyl	CH_3	110 (4)	88 (A)
3n	Ph_2CH	CH_3	*b*	61 (A)
3o	4-FC_6H_4	C_2H_5	*b*	89 (A)–55 (B)
3p	4-FC_6H_4	$CH(CH_3)_2$	133–5 (1.0)	58 (A)
3q	4-FC_6H_4	$C(CH_3)_3$	108–9 (0.2)	56 (A)
3r	4-FC_6H_4	$CH(C_2H_5)_2$	132–3 (0.2)	54 (A)
3s	4-FC_6H_4	cyclopropyl	*b*	75 (A)
3t	4-FC_6H_4	cyclobutyl	132–5 (1.0)	65 (A)
3u	4-FC_6H_4	cyclohexyl	150–5 (0.1)	51 (A)
3v	4-FC_6H_4	CF_3	*b*	25 (B)
3w	$CH(C_2H_5)_2$	$CH(C_2H_5)_2$	79–83 (0.2)	53 (A)
3x	3-FC_6H_4	$CH(CH_3)_2$	*b*	90 (B)
3y	2-FC_6H_4	$CH(CH_3)_2$	*b*	95 (A)
3z	2,4-$F_2C_6H_3$	$CH(CH_3)_2$	*b*	77 (A)
3aa	2-$CH_3OC_6H_4$	$CH(CH_3)_2$	138–141 (0.2)	71 (A)
3bb	2,6-$(CH_3O)_2C_6H_3$	$CH(CH_3)_2$	160–2 (2)	68 (B)

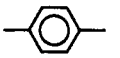
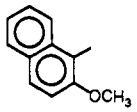
[a] All spectral data were consistent with assigned structures. [b] Purified by silica gel chromatography.

aqueous peroxide and base.[12] The dihydroxy acids were then lactonized by refluxing in toluene with azeotropic removal of water. Generally, the lactones were crystalline, such that the small amounts of the cis lactone stereoisomer **9** present were easily removed by recrystallization, providing >95% of the racemic trans stereoisomer (**8**). The conversion of **8u** to **8v** was accomplished by hydrogenation over Pd–C at 1 atm (Scheme III). Finally, the phenol analogues **8k**, **8h**, and **8p** were prepared from the corresponding methyl ethers **8i**, **8m**, and **8o** by BBr_3-mediated demethylation (Scheme IV).[13]

Table II. 2,5-Disubstituted Pyrrol-1-yl Carbox- or Benzaldehydes



6

no.	X	R_1	R_2	% yield[a,b] (method)
6a		4-FC_6H_4	CH_3	63 (A)
6b		4-FC_6H_4	CH_3	56 (A)
6c		4-FC_6H_4	CH_3	35 (A)
6d	$-CH_2CH_2CH_2-$	4-FC_6H_4	CH_3	65 (A)
6e	$-CH(CH_3)CH_2-$	4-FC_6H_4	$CH(CH_3)_2$	34 (C)
6f	$-CH_2CH_2-$	4-FC_6H_4	CH_3	45 (A)
6g	$-CH_2CH_2-$	Ph	CH_3	27 (A)
6h	$-CH_2CH_2-$	4-PhC_6H_4	CH_3	60 (A)
6i	$-CH_2CH_2-$	4-$CH_3OC_6H_4$	CH_3	32 (A)
6j	$-CH_2CH_2-$	4-ClC_6H_4	CH_3	56 (A)[c]
6k	$-CH_2CH_2-$	3-$F_3C_6H_4$	CH_3	37 (A)
6l	$-CH_2CH_2-$	3-$CH_3OC_6H_4$	CH_3	68 (A)
6m	$-CH_2CH_2-$	2-$CH_3OC_6H_4$	CH_3	58 (A)
6n	$-CH_2CH_2-$	2-naphthyl	CH_3	50 (A)
6o	$-CH_2CH_2-$	1-naphthyl	CH_3	23 (A)
6p	$-CH_2CH_2-$	cyclohexyl	CH_3	60 (A)
6q	$-CH_2CH_2-$		CH_3	63 (A)
6r	$-CH_2CH_2-$		CH_3	22 (A)
6s	$-CH_2CH_2-$	Ph_2CH	CH_3	32 (A)
6t	$-CH_2CH_2-$	4-FC_6H_4	$CH(CH_3)_2$	92 (A)
6u	$-CH_2CH_2-$	4-FC_6H_4	$C(CH_3)_3$	42 (C)
6v	$-CH_2CH_2-$	4-FC_6H_4	$CH(C_2H_5)_2$	46 (A)
6w	$-CH_2CH_2-$	4-FC_6H_4	cyclopropyl	25 (A)
6x	$-CH_2CH_2-$	4-FC_6H_4	cyclobutyl	34 (A)
6y	$-CH_2CH_2-$	4-FC_6H_4	cyclohexyl	22 (A)[d]
6z	$-CH_2CH_2-$	4-FC_6H_4	CF_3	55 (A)
6aa	$-CH_2CH_2-$	3-FC_6H_4	$CH(CH_3)_2$	29 (A)
6bb	$-CH_2CH_2-$	2-FC_6H_4	$CH(CH_3)_2$	17 (A)
6cc	$-CH_2CH_2-$	2,4-$F_2C_6H_3$	$CH(CH_3)_2$	20 (A)
6dd	$-CH_2CH_2-$	2-$CH_3OC_6H_4$	$CH(CH_3)_2$	42 (A)
6ee	$-CH_2CH_2-$	2,6-$(CH_3O)_2C_6H_3$	$CH(CH_3)_2$	36 (A)[e]
6ff	$-CH_2CH_2-$	2,5-$(CH_3)_2C_6H_3$	$CH(CH_3)_2$	43 (A)
6gg	$-CH_2CH_2-$	2-$[(CH_3)_2CHO]C_6H_4$	$CH(CH_3)_2$	79 (A)
6hh	$-CH_2CH_2-$	2-ClC_6H_4	$CH(CH_3)_2$	46 (A)
6ii	$-CH_2CH_2-$		$CH(CH_3)_2$	41 (C)
6jj	$-CH_2CH_2-$	$CH(C_2H_5)_2$	$CH(C_2H_5)_2$	60 (A)

[a] Isolated yields after chromatography on silica gel. [b] All compounds possessed ^1H NMR spectra in accord with assigned structure (aldehydic proton, singlet, δ 8.95–9.65). [c] Mp 70–3 °C. [d] Mp 104–6 °C. Anal. C, H, N. [e] Mp 105–7 °C. Anal. C, H, N.

Biological Results

The target lactones (**8**, Table III) were saponified and tested for their ability to inhibit HMGR employing two protocols. Method I[14] (cholesterol synthesis inhibition screen, or CSI) measured the rate of conversion of [^{14}C]-

(12) A detailed examination of this reaction has appeared: Kathawala, F.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M.; Stabler, R.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803–5.

(13) McOmie, J.; Watts, M.; West, D. *Tetrahedron* **1968**, *24*, 2289.

(14) Dugan, R.; Slakey, L.; Briedis, A.; Porter, J. *Arch. Biochim. Biophys.* **1972**, *152*, 21–7.

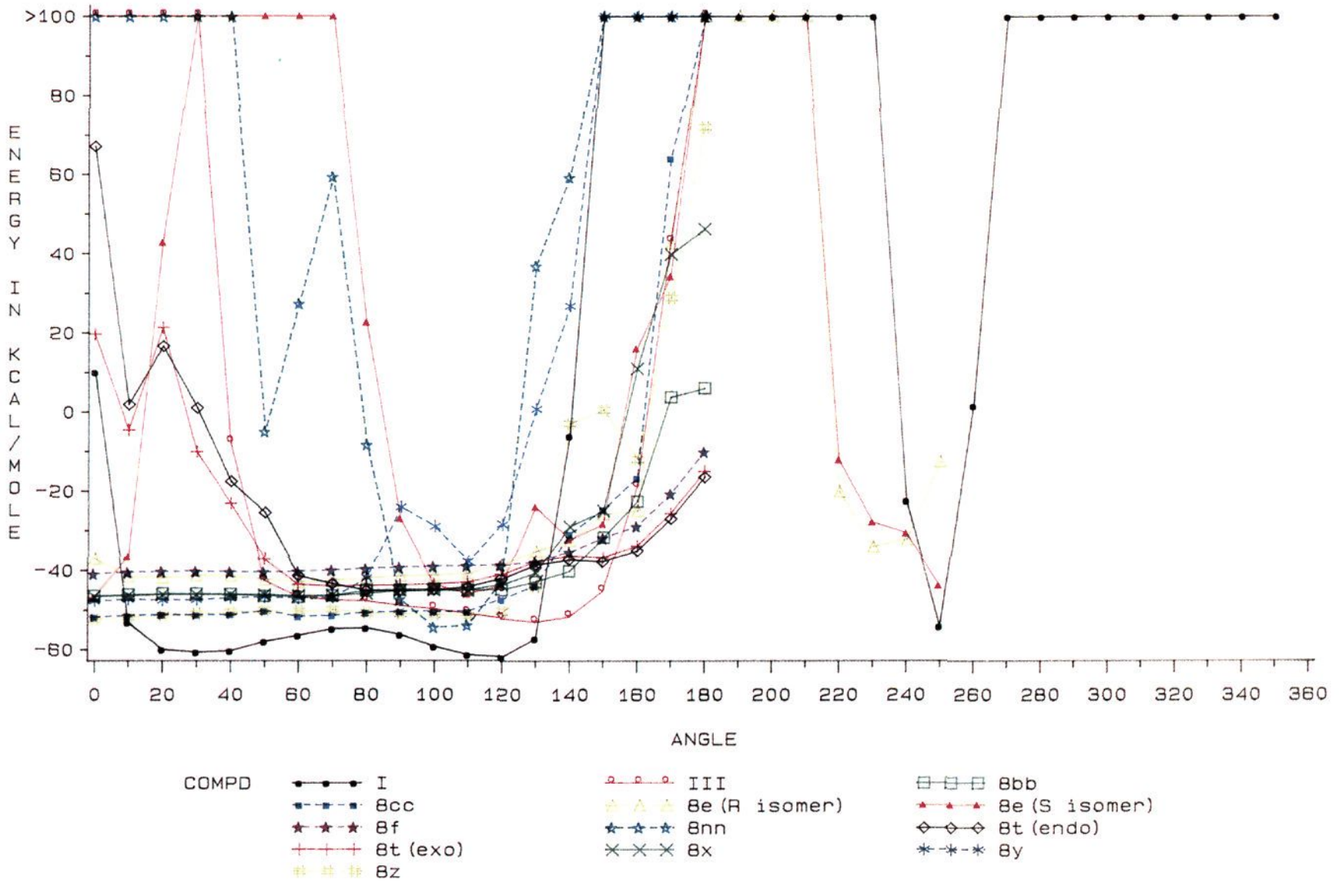


Figure 2. CAMSEQ-II energies calculated for comparable orientations of the lactone side chain. Dashed lines represent less potent analogues (**8j**, **8z**, **8bb**, **8cc**, and **8nn**; CSI $IC_{50} > 5$ μM).

acetate to cholesterol employing a crude liver homogenate derived from rats fed a chow diet containing 5% cholestyramine. Method II[15] (CoA reductase inhibition screen, or COR) was a more specific screen employing a partially purified microsomal enzyme preparation to measure the direct conversion of D,L-[^{14}C]HMG-CoA to mevalonic acid. The biological activities are reported as IC_{50} values and as a ratio to compactin, which was employed as the internal standard in each testing protocol. Compactin consistently displayed an IC_{50} between 0.02 and 0.03 μM. The IC_{50} values from the two assays were moderately correlated (eq 1,[16] Figure 1).

$$\log (IC_{50}, \text{COR}) = 0.81\ (\pm 0.09) \log (IC_{50}, \text{CSI}) - 1.32 \quad (1)$$

$$n = 36,\ r^2 = 0.70,\ F = 81,\ s = 0.39$$

Structure–Activity Relationships

As very little was known about heterocycle-containing inhibitors at the outset of this study, our strategy was to systematically examine each portion of the structure, keeping the 4-hydroxypyran-2-one ring intact. Initially, the optimum chain length between the lactone and the pyrrole ring was determined. A two-carbon bridge (**8f**) was superior to either a three-carbon (**8d**) or aryl spacer (**8a–c**) (Table III). This is consistent with the findings of Stokker et al.[5b]

Holding the bridge constant as ethyl, the structure–activity relationships of the 2 and 5 pyrrole substituents were explored. With 5-methyl substitution (**8f–w**), high potency was conferred by bulky cycloalkyl 2-substitutents (**8s–v**). Among 2-(substituted-phenyl)-5-methyl derivatives (**8f–r**), aside from a length limitation of the 2-substituent (see the molecular modeling section below), no obvious structure–activity relationships could be discerned. Optimum potency resided in the 4-fluorophenyl analogue, **8f**. With 2-substitution held constant as the optimal 4-fluorophenyl, potency increased with increasing length of the 5-substituent from methyl (**8f**) through cyclopentyl (**8aa**) to a maximum with isopropyl (**8x**) (length = 2.5 Å; see modeling section below). Potency decreased thereafter to a low of >100 μM with 5-cyclohexyl substitution (**8cc**).

With 5-substitution held constant as the optimal isopropyl, additional variation of the 2-phenyl substituents, now keeping within the length limit of 5.9 Å suggested by the modeling analysis (**8ee–mm**), failed to improve the potency over the 2-(4-fluorophenyl)-5-isopropyl derivative, **8x**. Indeed, an additional "front-to-back" width limitation (Figure 3) may be apparent with **8ii** and **8mm**, which project significantly greater bulk in these directions than the other analogs. Finally, of interest is the 2-(4-fluorophenyl)-5-trifluoromethyl analogue **8dd**, whose high potency may be due in part to stabilization of the pyrrole ring by the electron-withdrawing trifluoromethyl group, an aspect to be addressed in future communications.

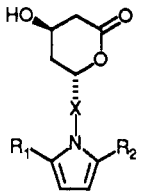
These results, combined with results from the molecular modeling study, confirmed our belief that **8x** possessed the optimum substitution pattern, since structural modifications at the 2- and 5-positions, as well as variation of the bridge to the lactone ring, led to decreased potency. A similar conclusion can be inferred from the examination of other 5-membered ring heterocycles reported in the patent literature.[17]

(15) Kita, T.; Brown, M.; Goldstein, J. *J. Clin. Invest.* **1980**, *66*, 1094–1100.

(16) Compounds **8c** and **8cc** were assigned IC_{50} values of 100 μM so they could be included in the correlation.

(17) Kathawala, F. G. WIPO Patent WO 84/02131, 1984.

Table III. *trans*-6-(2-Pyrrol-1-ylalkyl or -aryl)-4-hydroxypyran-2-ones



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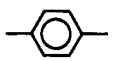
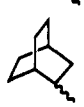
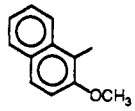
no.	X	R_1	R_2	mp, °C	% yield	formula[a]	IC_{50},[b,c] μM, CSI	log IC_{50}, CSI	relative potency,[d] CSI	IC_{50},[c,e] μM, COR	log IC_{50}, COR
8a		4-FC_6H_4	CH_3	155–7	32	$C_{22}H_{20}FNO_3$	20	−4.7	0.10	–	–
8b		4-FC_6H_4	CH_3	54–7	29	$C_{22}H_{20}FNO_3$	24	−4.6	0.01	63	−4.2
8c		4-FC_6H_4	CH_3	142–5	21	$C_{22}H_{20}FNO_3$	>100	−4.0	<0.01	>100	−4.0
8d	$-CH_2CH_2CH_2-$	4-FC_6H_4	CH_3	oil	41	$C_{19}H_{22}FNO_3$	53	−4.3	0.02	–	–
8e	$-CH(CH_3)CH_2-$	4-FC_6H_4	$CH(CH_3)_2$	167–9	30	$C_{21}H_{26}FNO_3$	5.0	−5.3	0.50	40	−4.4
8f	$-CH_2CH_2-$	4-FC_6H_4	CH_3	oil	32	$C_{18}H_{20}FNO_3$	0.51	−6.3	0.90	2.8	−5.6
8g	$-CH_2CH_2-$	Ph	CH_3	89–91	29	$C_{18}H_{21}NO_3$	1.4	−5.9	0.40	13	−4.9
8h	$-CH_2CH_2-$	4-PhC_6H_4	CH_3	104–7	35	$C_{24}H_{25}NO_3$	23	−4.6	0.10	23	−4.6
8i	$-CH_2CH_2-$	4-$MeOC_6H_4$	CH_3	95–96	50	$C_{19}H_{23}NO_4$	12	−4.9	0.10	28	−4.6
8j	$-CH_2CH_2-$	4-ClC_6H_4	CH_3	118–121	28	$C_{18}H_{20}ClNO_3$	10	−5.0	0.20	3.2	−5.5
8k	$-CH_2CH_2-$	4-HOC_6H_4	CH_3	161–2	–	$C_{18}H_{21}NO_4$	2.6	−5.6	1.0	6.3	−5.2
8l	$-CH_2CH_2-$	3-$F_3CC_6H_4$	CH_3	oil	65	$C_{19}H_{20}F_3NO_3$	1.5	−5.8	0.30	5.4	−5.3
8m	$-CH_2CH_2-$	3-$MeOC_6H_4$	CH_3	106–9	21	$C_{19}H_{23}NO_4$	2.5	−5.6	0.80	11	−5.0
8n	$-CH_2CH_2-$	3-HOC_6H_4	CH_3	144–5	–	$C_{18}H_{21}NO_4$	1.9	−5.7	1.40	12	−5.0
8o	$-CH_2CH_2-$	2-$MeOC_6H_4$	CH_3	112–3	38	$C_{19}H_{23}NO_4$	2.1	−5.7	0.90	25	−4.6
8p	$-CH_2CH_2-$	2-HOC_6H_4	CH_3	140–2	–	$C_{16}H_{21}NO_4$	2.5	−5.6	1.10	30	−4.5
8q	$-CH_2CH_2-$	2-naphthyl	CH_3	foam	30	$C_{22}H_{23}NO_3$[f]	16	−4.8	0.10	3.6	−5.4
8r	$-CH_2CH_2-$	1-naphthyl	CH_3	137–8	21	$C_{22}H_{23}NO_3$	1.8	−5.8	0.70	4.0	−5.4
8s	$-CH_2CH_2-$	cyclohexyl	CH_3	129–130	25	$C_{18}H_{27}NO_3$	0.69	−6.2	0.50	2.2	−5.6
8t	$-CH_2CH_2-$		CH_3	125–6	20	$C_{19}H_{25}NO_3$	1.4	−5.8	1.10	5.8	−5.2
8u	$-CH_2CH_2-$		CH_3	135–8	13	$C_{20}H_{27}NO_3$[g]	1.3	−5.9	1.60	3.2	−5.5
8v	$-CH_2CH_2-$		CH_3	135–9	68	$C_{20}H_{29}NO_3$	2.3	−5.6	1.10	2.3	−5.6
8w	$-CH_2CH_2-$	Ph_2CH	CH_3	129–132	33	$C_{25}H_{27}NO_3$	13	−4.9	0.10	8.9	−5.4
8x	$-CH_2CH_2-$	4-FC_6H_4	$CH(CH_3)_2$	105–6	34	$C_{20}H_{24}FNO_3$	0.40	−6.4	30.2	0.23	−6.6
8y	$-CH_2CH_2-$	4-FC_6H_4	$C(CH_3)_3$	117–8	24	$C_{21}H_{26}FNO_3$	1.6	−5.8	1.70	1.8	−5.7
8z	$-CH_2CH_2-$	4-FC_6H_4	$CH(C_2H_5)_2$	107–8	36	$C_{22}H_{28}FNO_3$	20	−4.7	0.10	32	−4.5
8aa	$-CH_2CH_2-$	4-FC_6H_4	cyclopropyl	foam	22	$C_{20}H_{22}FNO_3$	2.2	−5.7	1.30	2.6	−5.6
8bb	$-CH_2CH_2-$	4-FC_6H_4	cyclobutyl	88–9	5	$C_{21}H_{24}FNO_3$	17	−4.8	0.20	–	–
8cc	$-CH_2CH_2-$	4-FC_6H_4	cyclohexyl	64–6	30	$C_{23}H_{28}FNO_3$	>100	−4.0	<0.01	>100	−4.0
8dd	$-CH_2CH_2-$	4-FC_6H_4	CF_3	oil	58	$C_{18}H_{17}F_4NO_3$	0.25	−6.6	8.0	0.63	−6.2
8ee	$-CH_2CH_2-$	3-FC_6H_4	$CH(CH_3)_2$	87–9	40	$C_{20}H_{24}FNO_3$	1.3	−5.9	1.8	2.6	−5.6
8ff	$-CH_2CH_2-$	2-FC_6H_4	$CH(CH_3)_2$	oil	9	$C_{20}H_{24}FNO_3$[h]	3.2	−5.5	0.9	1.8	−5.8
8gg	$-CH_2CH_2-$	2,4-$F_2C_6H_3$	$CH(CH_3)_2$	75–7	8	$C_{20}H_{23}F_2NO_3$	1.6	−5.8	1.5	2.6	−5.2
8hh	$-CH_2CH_2-$	2-$MeOC_6H_4$	$CH(CH_3)_2$	oil	16	$C_{21}H_{27}NO_4$	2.2	−5.6	1.0	5.6	5.2
8ii	$-CH_2CH_2-$	2,6-$(MeO)_2C_6H_3$	$CH(CH_3)_2$	foam	36	$C_{22}H_{29}NO_5$	19	−4.7	0.2	87	−4.1
8jj	$-CH_2CH_2-$	2,5-$Me_2C_6H_3$	$CH(CH_3)_2$	oil	25	$C_{22}H_{29}NO_3$[i]	12	−4.9	0.2	16	−4.8
8kk	$-CH_2CH_2-$	2-$iPrOC_6H_4$	$CH(CH_3)_2$	oil	12	$C_{23}H_{31}NO_4$[j]	3.2	−5.5	0.9	–	–
8ll	$-CH_2CH_2-$	2-ClC_6H_4	$CH(CH_3)_2$	foam	25	$C_{20}H_{24}ClNO_3$	3.2	−5.5	0.5	9.1	−5.0
8mm	$-CH_2CH_2-$		$CH(CH_3)_2$	oil	34	$C_{25}H_{29}NO_4$[k]	9.6	−5.0	0.2	25	−4.6
8nn	$-CH_2CH_2-$	$CH(C_2H_5)_2$	$CH(C_2H_5)_2$	oil	20	$C_{21}H_{35}NO_3$	>100	−4.0	<0.01	–	–
I	compactin						0.026	−7.6	100	0.025	−7.6

[a] Analytical results are within ±0.4% of theoretical values unless otherwise noted. [b] Cholesterol synthesis inhibition screen; a measure of the rate of conversion of [^{14}C]acetate to cholesterol employing a crude liver homogenate. [c] IC_{50} values were determined with four dose levels of each inhibitor in the assay systems described in ref 14 (CSI) and 15 (COR). [d] Calculated as follows: (IC_{50} of test compound)/(IC_{50} of compactin determined simultaneously) × 100. [e] CoA reductase inhibition screen; a measure of the direct conversion of D,L-[^{14}C]HMG-CoA to mevalonic acid employing a partially purified microsomal enzyme preparation. [f] C: calcd, 75.62; found, 75.12. [g] C: calcd, 72.92; found, 72.50. [h] C: calcd, 69.54; found, 71.37; H: calcd, 7.01; found, 7.54. [i] C: calcd, 74.33; found, 74.78. [j] C: calcd, 71.66; found, 72.09. [k] C: calcd, 73.69; found, 72.09.

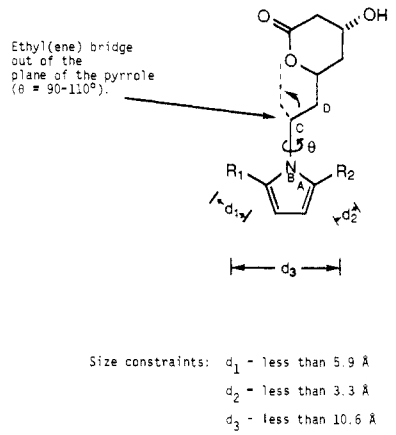


Figure 3. Summary of conclusions from the molecular modeling study.

Molecular Modeling

In order to identify the required spatial relationship between the lipophilic group (represented by the substituted pyrrole, phenyl, and hexahydronaphthalene ring systems) and the 4-hydroxypyran-2-one moiety, quantify steric tolerances across the pyrrole ring, and evaluate the relationship between potency and the polarity (charge distribution) of the side chains, selected analogues from Table III, compactin (I), and the potent biphenyl inhibitor III were modeled by using the CAMSEQ-II program package[18,19] (Table IV; see the Experimental Section). Conformational preferences of the ethyl (or ethylene) bridge to the lactone ring, size of the R_1 and R_2 substituents (Table IV), and charge distribution were compared to potency in the CSI screen (at the outset of this study, affinities in the COR screen were unavailable for the majority of the analogues studied) in order to develop a pharmacophore model for HMGR inhibition.

Lactone Side Chain Conformations. For reference purposes, calculated energies for the 0°, 90°, 180°, and lowest energy conformations of θ are summarized in Table IV. Figure 2 depicts the calculated energies for individual conformations. From Figure 2, all of the modeled compounds, including compactin (I), the biphenyl analogue III, and the less potent analogues **8z**, **8bb**, **8cc**, and **8nn**, can adopt an eneretically favorable conformation where the ethyl(ene) bridge is nearly perpendicular to the parent pyrrole, benzene, or hexahydronaphthalene ring systems. Indeed, for the potent derivatives 8t and III, the calculations show that the out of plane ($\theta \approx 80$–$110°$) orientation is the only one allowed. In addition, the reduced potency of the *tert*-butyl (**8y**) over the isopropyl (**8x**) analogue may be explained by the fact that the out of plane conformation ($\theta = 110°$) of **8y** is calculated to be energetically disfavored over the in-plane ($\theta = 0$–$70°$) orientations.

Thus, it is concluded that a conformation of the ethyl(ene) bridge to the 4-hydroxypyran-2-one ring out of the plane (90–120°) of the parent ring systems is consistent with increased potency as a HMGR inhibitor. Interestingly, this corresponds to the calculated minimum energy and not the X-ray conformation[1b] of compactin. The X-ray conformation represents a secondary minimum at θ = 24.6°, 1.2 kcal/mol higher in energy, probably due to packing interactions.

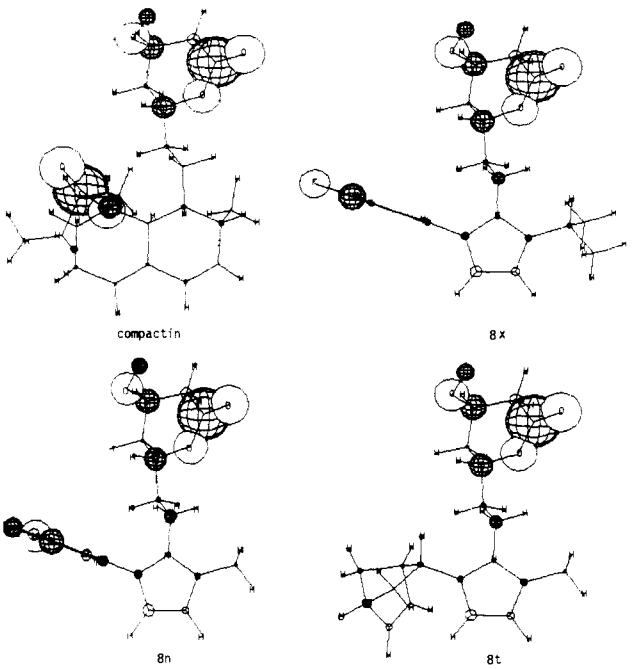


Figure 4. Charge distribution of compactin and selected analogues. Hatched and open spheres represent positive and negative charges, respectively. Sphere size is proportional to the magnitude of the atomic charge.

Steric Tolerances. In determining steric tolerances, the substituents were somewhat arbitrarily assigned. Larger substituents such as substituted phenyl, norbornenyl, and the isobutyric ester on compactin were placed at R_1 (Table IV); small alkyl groups were assigned to R_2. Changing the assignment would affect the conclusions regarding these tolerances. Low-energy, extended conformations of the substituents were used in the distance calculations; other orientations of flexible groups such as $CH(C_2H_5)_2$ could produce different distances.

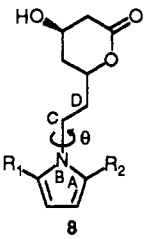
The maximum lengths of R_1 and R_2 and the overall width of the molecule across the parent ring system from R_1 to R_2 are given in Table IV. The calculations show a clear dependence of CSI potency on all three distances summarized in Figure 3. High potency ($IC_{50} < 1.6$ μM) is observed only for those analogues whose (a) maximum length of R_1 (Figure 3, d_1) is <5.9 Å (Table IV: compare 8f and **8j**), (b) maximum length of R_2 (Figure 3, d_2) is <3.3 Å (compare **8x** and **8z** or **8nn**), and (c) overall width (Figure 3, d_3) is <10.6 Å (compare **8y** and **8bb**). Other analogues not included in Table IV reinforce the length constraints at R_1: the 2-naphthyl analogue **8q** (d_1 = 6.40 Å) is less potent than the 1-naphthyl (d_1 = 4.20 Å), and the para-substituted derivatives **8h** and **8i** possess reduced potency.

Charge Distribution. Initially, it was hypothesized that the spatial orientation of polar regions with relatively large partial charges within the molecule might be connected to CSI potency. Compactin contains two distinct regions of relatively large partial charges corresponding to the 4-hydroxypyran-2-one ring and the isobutyric ester side chain (Figure 4). The potent inhibitors 8f and **8x** also present relatively large partial charges, albeit weaker in strength, in roughly the same region as this side chain. However, attempts to increase potency by more closely mimicking the polar regions associated with the isobutyric ester of compactin with the more polar 2- and 3-(methoxy and hydroxy)phenyl analogues **8m–p** resulted in equipo-

(18) (a) Potenzone, R., Jr.; Cavicchi, E.; Weintraub, H. J. R.; Hopfinger, A. J. *Comput. Chem.* **1977**, *1*, 187. (b) Potenzone, R., Jr.; Hopfinger, A. J. *A Demonstration of the CAMSEQ-II Software System* In DHEW Publ. (FDA) (U.S.), Issue FDA 78-1046, Structural Correlations of Carcinogenesis and Mutagenesis, 1978, pp 102–103.

(19) In-house conversion of the program to run on an IBM 3033 under MVS/TSO (J. W. Vinson, unpublished work).

Table IV. Results of Modeling Studies on Compactin and Substituted Pyrroles



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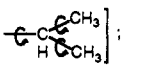
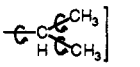
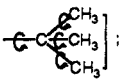
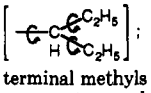
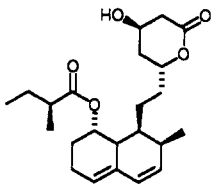
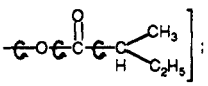
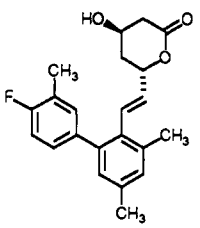
no.	R_1	R_2	IC_{50},[a] μM	lactone side chain rotations, CAMSEQ energies[b] 0°	90°	180°	min en conf	maximum overall width, Å (R_1 to R_2)	maximum lengths, Å R_1	R_2	other rotations[c]
8e	4-FC_6H_4 (α-Me)[d]	$CH(CH_3)_2$	5.0	−37.10[e]	−41.43[e]	100[e]	60°, −42.92[e]	10.12	5.58	2.48	 also bond from α-Me to lactone side chain from 0° to 60° by 20°
8e	4-FC_6H_4 (α-Me)[f]	$CH(CH_3)_2$	5.0	−46.93[e]	−27.09[e,g]	100[e]	0°, −46.93[j]	10.12	5.58	2.48	as above
8f	4-FC_6H_4	CH_3	0.51	−40.92	−39.27	−10.03	0°, −40.92	7.66	5.58	1.50	methyl group (R_2) from 0° to 60° by 10°
8j	4-ClC_6H_4	CH_3	10					9.33	5.89	1.50	as above
8t[h]		CH_3	1.4	67.11	−44.98	−16.40	90°, −44.98	7.22	3.64	1.50	bond from R_1 to pyrrole from 0° to 360° by 20°
8t[i]		CH_3	1.4	19.63	−43.65	−15.01	70°, −44.65	7.87	4.27	1.50	as above
8x	4-FC_6H_4	$CH(CH_3)_2$	0.40	−46.64	−45.06	46.29	0°, −46.64	10.12	5.58	2.48	
8y	4-FC_6H_4	$C(CH_3)_3$	1.6	−47.77	−24.10[j]	100	0°, −47.77	10.20	5.58	2.48	 all bonds from 0° to 60° by 20°
8z	4-FC_6H_4	$CH(C_2H_5)_2$	20	−52.35	−50.97	100	0°, −52.35	10.99	5.58	3.74	 terminal methyls set to a staggered conformation
8bb	4-FC_6H_4	cyclobutyl	17	−46.46	−44.82	6.01	60°, −46.64	10.62	5.58	3.35	bond from R_2 to pyrrole from 0° to 360° by 20°
8cc	4-FC_6H_4	cyclohexyl	100	−51.76	−50.31	100	0°, −51.76	11.92	5.58	4.33	bond from R_2 to pyrrole from 0° to 360° by 20°
8nn	$CH(C_2H_5)_2$	$CH(C_2H_5)_2$	100	100	−47.28	100	100°, −54.31	9.41	3.74	3.74	see compound **8z** above
I			0.026	10.17[l]	−56.04[l]	100[l]	120°, −61.74[l]	8.81	5.66	1.50	 terminal alkyl groups set to a staggered conformation
III			0.01	100	−48.89	100	130°, −52.92	8.74	5.52	1.50	bond from R_2 (Me) to phenyl from 0° to 60° by 20°; bond from R1 (4-F,3-MeC_6H_3) to phenyl from 0° (biphenyl coplanar) to 90° by 15°

[a] CSI screen (see Table III). [b] Counterclockwise rotation of θ from 0 to 180° by 10°, unless otherwise noted, starting from the in-plane conformation shown (atoms A, B, C, D in a cis orientation). Steric and electrostatic (using charges calculated via the CNDO/2 method) terms were used. Energies are in kilocalories/mole. [c] At each conformation of the lactone side chain, rotations were performed on the marked bonds from 0° to 180° by 20°, unless otherwise indicated. Substituted phenyl rings at R_1 were held perpendicular to the pyrrole. [d] *R* stereoisomer. [e] θ was scanned from 0° to 250° by 10°. [f] *S* stereoisomer. [g] θ = 110° conformer, −46.09 kcal/mol. [h] Endo isomer. [i] Exo isomer. [j] θ = 70° conformer, −46.93 kcal/mol. [k] Chair form; equatorial attachment to pyrrole. [l] θ was scanned from 0° to 350° by 10°.

tent, not more potent, analogues. In addition, compounds containing bicyclo moieties at R_1 (**8t–v**) demonstrated that a polar substituent in this area (or an aryl ring, for that matter) was not required for CSI potency at the 1 μM level. Thus, it is concluded that CSI potency is relatively insensitive to the polarity of the group at R_1.

Conclusions

A series of 6-(2-pyrrol-1-ylethyl)-4-hydroxypyran-2-ones (**8**) has been identified as inhibiting the enzyme HMG-CoA

reductase (HMGR). By measuring the inhibition of HMGR in vitro, the 2- and 5-substituents on the pyrrole ring have been optimized, thus obtaining a compound (**8x**) that possesses 30% of the in vitro potency of the potent fungal metabolite compactin.

From a molecular modeling study, it was determined that so long as the 2- and 5-substituents did not interfere with the ability of the ethyl bridge to the lactone ring to attain an out-of-plane conformation (θ = 90–110°), and the substituents were within the distance contraints given in Figure 3, one could expect to achieve potency at the 1 μm level in the CSI screen. Attempts to enhance potency by mimicking partial charges in the polar isobutyric ester side chain in compactin failed. It is concluded that there are no strong electronic requirements for binding in this area.

In addition, the reduced potency of **8w**, **8ii**, and **8mm** relative to other substituted phenyl derivatives suggests a steric intolerance off of one of the ortho phenyl positions of the R_1 substituent. One other noteworthy observation is that substitution of the 5-isopropyl with trifluoromethyl produced an analogue, **8dd**, of essentially equal potency, (Table III: compare **8dd** with **8f** and **8x**). This suggests the desirability of an electron-deficient pyrrole ring and a possible direction for future exploration. Efforts to further optimize the inhibitory potency of this series will be reported in subsequent publications from these laboratories.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium and benzophenone. All organic extracts were dried over $MgSO_4$ except where otherwise noted. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Nicolet MX-1 FT-IR spectrophotometer. NMR spectra were determined on either a Varian EM-390 spectrophotometer or a Varian XL-200 instrument. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Elemental analyses for carbon, hydrogen, and nitrogen were determined on a Perkin-Elmer Model 240C elemental analyzer and are within 0.4% of theory unless noted otherwise. HPLC analyses were performed with a Varian 5500 unit equipped with a Reodyne 7126 loop injector, a Dupont variable wavelength detector, and an octadecylsilane column (Alltech C18 600RP, CH_3CN–H_2O eluant, 60:40, v/v) interfaced to Varian 402 data system for computation of peak areas. All starting materials were commercially available unless indicated otherwise.

Preparation of 1-(4-Fluorophenyl)-5-methyl-1,4-hexanedione (3p). Method A. 1-(4-Fluorophenyl)-2-propen-1-one (43.0 g, 287 mmol) was mixed with 31.2 mL (344 mmol) of isobutyraldehyde, 28 mL (200 mmol) of triethylamine, and 14.5 g (58 mmol) of 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride. The mixture was stirred at 70 °C under nitrogen for 12 h, cooled to room temperature, and partitioned between ether (500 mL) and water (100 mL). The aqueous layer was further extracted with ether (300 mL). The combined ether extracts were washed successively with water (200 mL), 2 M HCl (2 × 100 mL), and brine (100 mL) and dried. Filtration and concentration to dryness in vacuo provided an oil which was distilled (bp 115–120 °C, 0.2 mmHg) to provide 36.7 g (58%) of the title compound which solidified on standing: 90-MHz NMR ($CDCl_3$) δ 1.15 (d, 6 H, J = 7 Hz), 2.7 (septet, 1 H, J = 7 Hz), 2.8 (m, 2 H), 3.05 (m, 2 H), 7.12 (t, 3 H), 7.95 (m, 2 H). An analytical sample could be obtained by recrystallization from hexane, mp 51–3 °C. Anal. ($C_{13}H_{15}FO_2$) C, H, N.

Alternate Synthesis of 3p. A mixture of 2-methyl-4-penten-4-one[8d] (2.0 g, 20 mmol), 4-fluorobenzaldehyde (2.4 g, 20 mmol), 2 mL (14 mmol) of triethylamine, and 1.0 g (4 mmol) of 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride was stirred under nitrogen for 5 h at 70 °C, cooled to room temperature, and partitioned between ether (200 mL) and water (50 mL). The water layer was extracted with ether (200 mL). The ether extracts were combined, washed successively with water (50 mL), 2 M HCl (50 mL), and brine (50 mL), and dried. After concentration to dryness in vacuo, the residue was flash chromatographed on silica gel with hexane–ethyl acetate (20:1 v/v) as eluant, affording 2.6 g of **3p**, mp 47–49 °C.

Method B. To a suspension of hexane-washed NaH (6.5 g, 270 mmol) in dry DMF (300 mL) at 0 °C under dry nitrogen was added a solution of methyl 4-methyl-3-oxopentanoate (37.5 g, 260 mmol) in 100 mL of dry DMF. When gas evolution had subsided, a solution of 2-bromo-4′-fluoroacetophenone (260 mmol) in dry DMF (100 mL) was added dropwise over 60 min. The mixture was allowed to warm to 25 °C overnight, poured into ice-cold 2 M HCl (300 mL), and extracted with ether (2 × 200 mL). The organic layer was washed with water (3 × 50 mL) and brine (50 mL) and concentrated to dryness in vacuo. The crude product was dissolved in 800 mL of 3:1 THF–water and treated with NaOH (24 g, 600 mmol), and the mixture was stirred overnight. The solution was made acidic with 6 N HCl and extracted with ether (2 × 300 mL). The ether extracts were washed with water (50 mL), bicarbonate (50 mL), and brine (50 mL) and dried. Distillation provided 40 g (69%) of **3p**.

Preparation of 2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-1-cyanoethane (5, R_1 = 4-FPh, R_2 = $CH(CH_3)_2$, X = $-CH_2CH_2-$). A mixture of **3p** (365 g, 1.65 mol), 3-aminopropionitrile $^1/_2$-fumarate (234 g, 1.83 mol), and 1 g of *p*-TSA in glacial acetic acid (1800 mL) was stirred and heated at reflux for 8 h. After cooling to room temperature, the solution was poured into ice water (3 L). The solid that formed was isolated by suction filtration and recrystallized from isopropyl ether and hexane (212 g, mp 75–78 °C). The filtrate was extracted with ether (2 × 1 L). The combined ether extracts were washed with water (1 L), saturated aqueous sodium bicarbonate (until gas evolution ceased), and brine (500 mL) and dried. Filtration and concentration to dryness in vacuo afforded a solid which was recrystallized from isopropyl ether to provide a further 98 g of the title compound (310 g total, 73%): IR (KBr) 2990, 2249, 1566, 1522, 1484, 1219, 1162, 847, 782 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.30 (d, 6 H, J = 7 Hz), 2.32 (t, 2 H, J = 7 Hz), 2.92 (septet, 1 H, J = 7 Hz), 4.22 (t, 2 H, J = 7 Hz), 6.00 (d, 1 H, J = 3.5 Hz), 6.10 (d, 1 H, J = 3.5 Hz), 7.0–7.4 (m, 4 H). Anal. ($C_{16}H_{17}FN_2$) C, H, N.

Preparation of 3-[2-(4-Fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]propanal (6t). A stirred solution of the above intermediate (200 g, 780 mmol) in 1500 mL of CH_2Cl_2 at ambient temperature under nitrogen was treated dropwise with 936 mL of a 1.0 M solution of diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 over 4 h. The resulting mixture was stirred overnight at room temperature, and then the excess hydride was destroyed by cautious addition of methanol. When gas evolution was complete, the solution was carefully poured into 1500 mL of vigorously stirred ice-cold 2 M HCl (exothermic). The emulsion that resulted was extracted with ether (2 × 1 L), and the combined ether extracts were washed successively with water (500 mL), saturated aqueous sodium bicarbonate (2 × 500 mL), and brine (500 mL) and dried. The solvents were removed in vacuo, and the residue was flash chromatographed over silica gel, eluting with hexane–ethyl acetate (10:1, v/v) to provide **6t** (187 g, 92%) as a colorless oil: IR (film) 2930, 1720, cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 1.25 (d, 6 H, J = 7 Hz), 2.50 (t, 2 H, J = 7 Hz), 2.85 (septet, 1 H, J = 7 Hz), 4.20 (t, 2 H, J = 7 Hz), 5.90 (d, 1 H, J = 2.5 Hz), 6.03 (d, 1 H, J = 2.5 Hz), 6.0–7.3 (m, 4 H), 9.45 (s, 1 H).

Preparation of Methyl 7-[2-(4-Fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxoheptanoate (7, R_1 4-FPh, R_2 = $CH(CH_3)_2$, X = $-CH_2CH_2-$). A stirred suspension of hexane-washed NaH (2.17 g, 91 mmol) in anhydrous THF (200 mL) at 0 °C under nitrogen was treated dropwise with a solution of methyl acetoacetate (8.9 mL, 82 mmol) in anhydrous THF (150 mL) over 30 min. When gas evolution was complete, *n*-butyllithium (39 mL of a 2.1 M solution in hexane) was added dropwise. The resulting solution was stirred for 30 min and then treated dropwise over 30 min with a solution of **6t** (19.4 g, 74.9 mmol) in anhydrous THF (150 mL). The solution was stirred for an additional 1 h and the reaction was quenched with saturated aqueous NH_4Cl (100 mL), followed by 2 M HCl (100 mL).

The resulting mixture was partitioned between ether (500 mL) and water (100 mL). The water layer was separated and extracted

with ether (300 mL). The ether extracts were combined, washed with brine (50 mL), and dried. The solvents were removed in vacuo, and the residue was flash chromatographed on silica gel, eluting with hexane–ethyl acetate (5:1, v/v) to yield 19.9 g (64%) of the title compound as a colorless oil: 200-MHz NMR ($CDCl_3$) δ 1.28 (d, 6 H, J = 7 Hz), 1.55 (m, 2 H), 2.45 (m, 2 H), 2.6 (br s, 1 H, J = 2.5 Hz), 7.0–7.4 (m, 4 H); IR (film) 3520, 2966, 2873, 1749, 1716, 1518, 1223, 1159, 845, 815, 767 cm^{-1}.

Preparation of *trans*-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (8x). Air (30 mL) was bubbled by syringe through a stirred solution of n-Bu_3B (58 mL of a 1 M THF solution) in dry THF (50 mL) containing 19.9 g (53 mmol) of the above intermediate at room temperature. The solution was stirred for 18 h at room temperature and cooled to −78 °C, and sodium borohydride (2.27 g, 60 mmol) was added in one portion. The mixture was stirred for 60 min at −78 °C and warmed to 0 °C for 90 min. A mixture of water (10 mL) and methanol (10 mL) was carefully added (gas evolution). NaOH (3 M, 60 mL) and 30% H_2O_2 (30 mL) were added simultaneously to the mixture from separate dropping funnels. The vigorously stirred mixture was held at 0 °C for 60 min and then at room temperature for 2 h.

The mixture was partitioned between water (300 mL) and ether (300 mL). The ether layer was extracted with 10% aqueous NaOH (50 mL). The aqueous layers were combined, acidified with concentrated HCl, and extracted with ethyl acetate (2 × 500 mL). The ethyl acetate extracts were combined, washed twice with brine (100 mL), and dried. Removal of the solvents in vacuo yielded 12.5 g of an oil which was dissolved in toluene (500 mL) and heated at reflux with azeotropic removal of water (Dean–Stark trap). The cooled solution was concentrated and the residue flash chromatographed on silica gel, eluting with hexane–ethyl acetate (5:1 v/v) to yield 11 g of a colorless solid. Recrystallization from isopropyl ether yielded 9.5 g (52%) of **8x**, mp 104–105 °C, which was a 97:3 mixture of diastereomers by HPLC: 200-MHz NMR ($CDCl_3$) δ 1.30 (d, 6 H, J = 7 Hz), 1.5–1.9 (m, 4 H), 2.60 (m, 2 H), 2.98 (septet, 1 H, J = 7 Hz), 4.0–4.3 (m, 3 H), 4.45 (m, 1 H), 5.98 (d, 1 H, J = 2.5 Hz), 6.08 (d, 1 H, J = 2.5 Hz), 7.10 (m, 2 H), 7.33 (m, 2 H); IR (KBr) 3440, 2966, 2870, 1690, 1518, 1268, 1223, 1075, 837, 773 cm^{-1}. Anal. ($C_{20}H_{24}FNO_3$) C, H, N.

Preparation of 2-[2-(4-Fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-1-cyanoethane (5, R_1 = 4-FPh, R_2 = $C(CH_3)_3$, X = $-CH_2CH_2-$). Glacial acetic acid (125 mL) was added in one portion to a stirred solution of **3q** (66 mmol) and ethanolamine (27 mL) at ambient temperature. A vigorous exothermic reaction ensued (the internal temperature rose to 95 °C). When the exotherm had subsided (TLC indicated reaction almost complete), the solution was stirred and heated at reflux for 30 min (TLC indicated all starting material was consumed, but a new high-R_f spot had appeared). The reaction mixture was cooled to room temperature and poured into ice water (200 mL). The aqueous mixture was extracted with ether (2 × 500 mL). The combined ether extracts were washed with water (2 × 200 mL), saturated aqueous bicarbonate (2 × 200 mL), and brine (100 mL), dried, and concentrated to dryness in vacuo. Flash chromatography of the residue on silica gel, eluting the ethyl acetate–hexane (10:1 v/v) provided 10.7 g of 2-[2-(4-fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-2-ethanol product (62%) and 5 g of a high-R_f material which appeared to be the corresponding *O*-acetate by NMR (3 H, s, δ 2.05). The high-R_f fraction was stirred with NaOH (2 g) in CH_3OH (50 mL) and water (10 mL) for 2 h. The solution was concentrated, diluted with water (20 mL), and extracted with ethyl acetate (2 × 200 mL). The ethyl acetate extracts were washed with brine (50 mL) and dried. Filtration and concentration to dryness in vacuo provided a further 3.7 g of the above alcohol (14.4 g total, 84%).

Mesyl chloride (1.93 mL, 25 mmol) was added dropwise to a stirred solution of the above alcohol (5 g, 19.1 mmol) in pyridine (15 mL) cooled in an ice bath. The mixture was stirred for 2.5 h at 0 °C, warmed to room temperature, poured into water (300 mL), and extracted with ether (2 × 300 mL). The combined ether extracts were washed with water (50 mL), 2 M HCl (50 mL), bicarbonate (2 × 50 mL), and brine (50 mL), dried, and concentrated to dryness in vacuo. The crude mesylate was used without further purification.

A solution of KCN (1.54 g, 23.6 mmol) and KI (1.16 g, 10 mmol) in water (12 mL) was added dropwise to a stirred, 70 °C solution of the mesylate (4.0 g, 18 mmol) in DMF (36 mL). The resulting solution was heated under reflux for 24 h, cooled, and poured into ice water. The mixture was extracted with ether (2 × 200 mL). The combined ether extracts were washed with water (50 mL), 2 M HCl (25 mL), bicarbonate (2 × 50 mL), and brine (25 mL), dried, and concentrated to dryness in vacuo. Flash chromatography of the residue on silica gel, eluting with hexane–ethyl acetate (20:1, v/v), provided 2.8 g (88%) of the title compound: 90-MHz NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.20 (t, 2 H), J = 2 Hz), 4.30 (t, 2 H, J = 7 Hz), 5.90 (d, 1 H, J = 4 Hz), 6.00 (d, 2 H, J = 4 Hz), 6.9–7.4 (m, 4 H).

Prepartion of 6-[2-(2-Bicyclo[2.2.2]oct-2-yl-5-methyl-1*H*-pyrrol-1-yl)ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (8v). To a solution of **8u** (0.3 g, 0.91 mmol) in ethyl acetate (10 mL) was added 0.03 g of 10% Pd–C. The mixture was evacuated, placed under a balloon of hydrogen (1 atm) at room temperature, and stirred overnight. The suspension was filtered through Celite and concentrated to dryness in vacuo, and the solid residue was recrystallized from isopropyl ether to afford 0.21 g of **8v** (68%), mp 135–139 °C. Anal. ($C_{20}H_{29}NO_3$) C, H, N.

General Demethylation Procedure (Preparation of 8n). BBr_3 (11 mmol) was dissolved in 8 mL of CH_2Cl_2 and added dropwise to a solution of **8m** (1.2 g, 3.64 mmol) in 100 mL of CH_2Cl_2 at −20 °C under dry nitrogen. The mixture was stirred for 2 h, and then a further 2 mmol of BBr_3 was added. The solution was allowed to warm slowly to 0 °C, poured into saturated aqueous bicarbonate (500 mL), and extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with 10% aqueous bisulfite (50 mL), saturated aqueous bicarbonate (30 mL), and brine (30 mL), dried, and concentrated to dryness in vacuo. Flash chromatography of the residue provided 450 mg of impure phenol. Two recrystallizations from isopropyl ether provided pure **8n**, mp 110–111.5 °C. Anal. ($C_{18}H_{21}NO_4$) C, H, N.

HMG-CoA Reductase Inhibition Assay 1: The Cholesterol Synthesis Inhibition Screen (CSI). The procedure is a modification of the protocol developed by Dugan et al.[14] Male rats (type CD from Charles River) weighing 300–400 g were kept in-house for at least 1 week before the day of the experiment. For 3 consecutive days before being used, they were fed a diet of 5% cholestyramine (by weight) in normal ground chow. On the day of the assay, the rats were anesthetized with ether and sacrificed. Their livers were removed, weighed, and placed on Saran Wrap on ice. The entire livers were minced and diluted with 2 volumes of ice-cold pH 7.4 homogenizing buffer (0.1 M KPO_4, 0.004 M $MgCl_2 \cdot 6H_2O$, 0.001 M EDTA, and 0.01 M 2-mercaptoethanol).

Liver homogenates were prepared by use of five to six passes of a Teflon pestle in a 50-mL glass homogenizer. The homogenates were pooled and centrifuged at 5000g for 10 min at 4 °C. Initial supernatants were pooled and centrifuged at 20000g for 15 min at 4 °C. Final supernatants were carefully drawn off, avoiding the loose pellet and lipid layer, pooled, and kept on ice. One-milliliter aliquots of this crude microsomal preparation were used for the assay.

Compounds were dissolved in 2 mL of toluene and sonicated if not fully soluble. The mixture was treated with 2 mL of 0.1 N NaOH and stirred constantly for 2 h in a water bath at 45–50 °C. Any remaining toluene was blown off under a stream of N_2. Approximately 6 mL of 0.1 N NaOH was added and the saponified drug placed on ice immediately. If the salt had crystallized, it was sonicated to achieve as uniform a suspension as possible. The pH was adjusted to 7.4 with HCl and the volume brought to 10 mL with H_2O. One-milliliter aliquots were frozen in dry ice–acetone and stored at −70 °C.

On the day of the screen, drugs were dissolved in 1 mL of 0.1 N KOH and diluted with 11 mL of homogenizing buffer to make a 2 mM stock solution. If necessary, sonication was used to achieve a solution, or in some cases, a suspension of drug. The 2 mM stock was diluted 1:1 with a mixture of 1 mL of 0.1 N KOH and 11 mL of homogenizing buffer. The resulting 1 mM solution was further diluted with homogenizing buffer alone to produce a series of 10 × stocks from 10^{-6} to 10^{-3} M. The sodium salt of compactin was used as a reference compound in every assay in a concentration range of 10^{-9} to 10^{-6} M.

Assay Conditions. The assay was carried out in duplicate in 16 × 125 mm screw-capped tubes. The reaction mixture contained the following, on ice (initial concentrations): 0.1 mL of 20 mM NAD, 0.1 mL of 20 mM NADP, 0.1 mL of 200 mM glucose 6-phosphate, 0.5 mL of 0.12 mM niacinamide, and 0.2 mL of the 10 × drug stocks. Controls were also run with 0.2 mL of a mixture of 1 mL of 0.1 N KOH, plus 11 mL of homogenizing buffer in place of drug. One milliliter of the crude microsomal preparation was added immediately after the drugs, to give a total volume of 2 mL. Final drug concentrations were 10^{-4} to 10^{-7} M, or in the case of compactin, 10^{-6} to 10^{-9} M. The samples were warmed at 37 °C for 5 min before adding the radioactive precursor. [1-^{14}C]Acetate was used in the amount of 2.88 μCi per sample, plus 98 μmol of sodium acetate as cold carrier. When [^{3}H]-mevalonate was used, the amount of 0.5 μCi per sample with cold carrier was added to make a total of 0.2 μmol per sample. Volume of radiolabel per sample was 100 μL. After receiving radiolabel, samples were incubated at 37 °C for 1 h and treated with 2.5 mL of 10% KOH in ethanol, and the saponification was carried out at 70 °C for 2 h in a water bath. After cooling to room temperature, the nonsaponifiable lipids (cholesterol accounts for approximately 80% of nonsaponifiable lipids; the remainder are methyl sterols) were extracted by shaking the samples with 4.2 mL of hexane for 10 min. After phase separation, 2 mL of the hexane layer was diluted with 8 mL of Handifluor and counted.

Percent inhibition was calculated as follows: 1.0 − (drug cpm/control cpm). Control refers to the samples that received buffer only. From a plot of percent inhibition versus the log of the drug concentration, the IC_{50} was determined. Every assay yielded an IC_{50} for the reference compound, compactin, thus providing a comparison for the other compounds as well as a standard to check for consistency between assays.

HMG CoA Reductase Inhibition Assay 2: Co-A Reductase Inhibition Screen (COR). This procedure is a modification of that reported by Kita et al.[15] Male Charles River (CD) rats weighing 200–300 g were fed a chow diet containing cholestyramine (5%) for 3 days in order to increase levels of liver microsomal HMG–CoA reductase. Between 9 a.m. and 10 a.m., fed animals were anesthetized with ether prior to a midline incision to open the abdomen. Traverse cuts were made to the left and right of abdominal cavity exposing the hepatic portal vein. A syringe with a 22-gauge needle containing 10 mL of exsanguinating buffer (40 mM Tris, 0.25 M sucrose, 0.3 mM EDTA, 5 mM dithiothreitol (DTT), pH 7.2) was injected into the portal vein after cutting the inferior vena cava. Prior to excision, the liver was cleared of blood by perfusion with exsanguinating buffer. Immediately after excision, the liver was added to ice-cold (4 °C) pH 7.4 buffer (0.3 M sucrose, 5 mM DTT, 50 mM leupeptin, 5 mM EGTA, 1 mM PMSF). Approximately 1 g samples were taken from the largest lobe and homogenized with 10 strokes of a tight-fitting Potter-Elvehjem homogenizer. Each homogenate was centrifuged for 15 min at 12000*g* in a Servall refrigerated-automatic centrifuge (SM-34 rotor). The supernatant was decanted and respun under the same conditions. The resulting supernatant was removed via pipet, with special care being taken not to remove any of the mitochondrial-rich pellet. The supernatants were then pooled and centrifuged with a 50 Ti or 60 Ti rotor in a Beckman L8-80 ultracentrifuge. After ultracentrifugation, the pellet was mixed with ice-cold KH_2PO_4 buffer (0.2 M, pH 7.4), homogenized, and stored in liquid nitrogen at 10 mg/mL microsomal protein. Microsomes maintained in liquid nitrogen retained HMG-CoA reductase activity for up to 1 year. Each pellet was resuspended in a solution of 0.3 M sucrose and 10 mM 2-mercaptoethanol and frozen immediately in liquid nitrogen. The aliquoted samples (500 μL) were then stored at −70 °C for no more than 1 month. For each microsomal isolation, an activity/microgram of microsomal protein curve was determined so that the amount of microsomal protein utilized in each assay was in the linear part of the activity curve.

Assay Conditions. Frozen microsomes (see above) were allowed to slowly thaw on ice. Assay solutions were prepared as follows:

A. Resuspension buffer: 0.2 M KH_2PO_4 buffer, pH 7.4.

B. Incubation buffer: 0.2 M KH_2PO_4 buffer (stock, 3 M $KH_2PO_4 \cdot 3H_2O$, 1 M KH_2PO_4, final 2 M); 0.01 M EDTA, 12 mM dithiothreitol; 40 mM glucose 6-phosphate; 4 mM NADPH; 0.45 μM DL-3-hydroxymethylglutaryl-coenzyme A (glutaryl-3-^{14}C) (stock, 7.4 μM unlabeled; HMG-CoA + 0.68 μM [^{14}C]HMG-CoA (4.5 μCi/μmol); final concentration 8.9 μM).

Resuspension buffer (70 μL) + microsomal solution (20 μL; 100 μg protein) + drug (10 μL) = 100 μL.

Incubation buffer (90 μL) + [^{14}C]HMG-CoA (10 μL) (final addition) = 100 μL.

Total volume of assay mix = 100 μL + 100 μL = 200 μL.

The assay solution was vortexed and incubated in a shaking water bath at 37 °C for 60 min. Termination of the reaction was accomplished with 30 μL of concentrated HCl. Conversion of the [^{14}C]mevalonic acid to the lactone form occurred in a water bath for 30 min at 37 °C. Conversion of [^{14}C]mevalonic acid to the lactone form occurred during refrigeration overnight. To each reaction tube was added DL-[2-^{3}H]mevalonic acid lactone (10000–15000 cpm + 200 μg of unlabeled mevalonolactone) as an internal standard to correct for incomplete recovery of [^{14}C]-mevalonate. After vortexing, an aliquot (50 μL) from the assay mix in each tube was put over a AG 1-X8 (200–400 mesh) formate form anion exchange resin column. The mevalonate was eluted with 3 × 750 μL of water into scintillation vials. Scintillation cocktail (Beckman Readi-Solv, 10 mL) was then added to each vial. The vials were vortexed and allowed to equilibrate for 1 h. Standards for the [^{14}C]HMG-CoA, [^{3}H]mevalonolactone, and acid-inactivated microsomes (blank) were also isolated by column separation in a Hewlett-Packard Model 3320 Tricarb scintillation spectrometer set for double label counting at maximum efficiency. Standards for [^{14}C]HMG-CoA, [^{3}H]mevalonolactone, and acid-inactivated microsomes (blank) were also isolated by TLC, scraped, and counted. Calculations were performed in the usual manner taking into consideration crossover of ^{3}H into the ^{14}C channel and visa versa, as well as dilution factors and specific activity of [^{14}C]HMG-CoA used. Reductase activity was expressed as picomole of [^{14}C]HMG-CoA converted to [^{14}C]mevalonic acid lactone/milligram of microsomal protein per minute. Compactin was used as a reference compound at concentrations of 10^{-9} and 10^{-7} M to determine the concentration at 50% inhibition from control value. Drugs were tested for their inhibitory characteristics at four concentrations run in triplicate. Statistical significance from control values was determined by using Dunnett's *t* test.

Molecular Modeling. Selected analogues were modeled by using an in-house modified version[17] of CAMSEQ-II[18] operating on an IBM 3083 machine. The structure of compactin was obtained from published[1b] X-ray data; the structure of pyrrole came from a compendium[20] of minimized structures. Coordinates for other groups were extracted from the library of fragments within CAMSEQ-II. Structures III and 8 were built to attaching the side chain containing the 4-hydroxypyran-2-one ring (coordinates for which were copied from the X-ray structure of compactin) to the benzene and pyrrole rings, respectively, and adding the other substituents. Side chains were rotated to remove steric contacts.

After CNDO/2 was employed to generate atomic charges, counterclockwise rotations (unless otherwise noted, from 0° to 180° by 10°) were performed using the SCAN module about θ, starting from the in-plane conformation shown in the structure at the top of Table IV (atoms A–B–C–D coplanar). The conformation of the 4-hydroxypyran-2-one ring was held fixed throughout these calculations. Steric and electrostatic energy terms were used. At each conformation of θ, the conformational flexibility of the 2- and 5-substituents was investigated (Table IV; column headed by "other rotations"), including energy evaluation, to insure that a low-energy conformer of θ was selected. Both the endo and exo isomers of the norbornenyl analogue 8t as well as the *R* and *S* isomers of **8e** were modeled. The axial-attached isomer of **8cc** proved to be sterically hindered and was not included. Figures 1 and 2 were generated by using the SAS-GRAPH program package.[21] In eq 1, the number in parentheses is the standard error of the regression coefficient, *n* is the number of compounds, *r* is the correlation coefficient, *F* is a significance test, and *s* is the standard error.

(20) SYBYL Standard Fragment Library, generously supplied by Tripos Associates, St. Louis, MO.

(21) SAS Institute, Inc. SAS/GRAPH User's Guide, Version 5 Edition; SAS Institute, Inc., Cary, NC, 1985.

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Registry No. 1 (R_1 = Ph), 768-03-6; 1 (R_1 = 4-F-C_6H_4), 51594-59-3; 1 (R_1 = 4-Ph-C_6H_4), 42575-11-1; 1 (R_1 = 4-Cl-C_6H_4), 7448-87-5; 1 (R_1 = 4-CH_3O-C_6H_4), 7448-86-4; 1 (R_1 = 3-F_3C-C_6H_4), 123184-14-5; 1 (R_1 = 3-CH_3O-C_6H_4), 51594-60-6; 1 (R_1 = 2-CH_3O-C_6H_4), 77942-10-0; 1 (R_1 = 2-naphthyl), 4452-06-6; 1 (R_1 = 1-naphthyl), 22422-69-1; 1 (R_1 = bicyclo[2.2.1]-hept-5-en-2-yl), 100234-78-4; 1 (R_1 = bicyclo[2.2.2]-oct-5-en-2-yl), 123184-15-6; 1 (R_1 = cyclohexyl), 2177-34-6; 1 (R_1 = Ph_2CH), 93021-71-7; 1 (R_1 = $CH(C_2H_5)_2$), 123184-16-7; 1 (R_1 = 2-F-C_6H_4), 89638-21-1; 1 (R_1 = 2,4-F_2-C_6H_3), 123184-17-8; 1 (R_1 = $CH(CH_3)_2$), 1606-47-9; **2** (R_2 = CH_3), 75-07-0; **2** (R_2 = $CH(CH_3)_2$), 78-84-2; **2** (R_2 = $CH(C_2H_5)_2$), 97-96-1; **2** (R_2 = cyclopropyl), 1489-69-6; **2** (R_2 = cyclobutyl), 2987-17-9; **2** (R_2 = cyclohexyl), 2043-61-0; **2** (R_2 = $C(CH_3)_3$), 630-19-3; **2** (R_2 = 4-F-C_6H_4), 459-57-4; **2** (R_2 = C_2H_5), 123-38-6; **3a**, 583-05-1; **3b**, 123183-95-9; **3c**, 63472-37-7; **3d**, 53842-12-9; **3e**, 2108-54-5; **3f**, 123183-96-0; **3g**, 123183-97-1; **3h**, 104562-48-3; **3i**, 123183-98-2; **3j**, 123263-79-6; **3k**, 70353-45-6; **3l**, 123183-99-3; **3m**, 61771-79-7; **3n**, 123184-00-9; **3o**, 123184-01-0; **3p**, 104568-68-5; **3q**, 123184-02-1; **3r**, 123184-03-2; **3s**, 123184-04-3; **3t**, 123184-05-4; **3u**, 123184-06-5; **3v**, 123184-07-6; **3w**, 123184-08-7; **3x**, 123184-09-8; **3y**, 123184-10-1; **3z**, 123184-11-2; **3aa**, 123184-12-3; **3bb**, 123184-13-4; **5a**, 123184-20-3; **5b**, 123184-21-4; **5c**, 123184-22-5; **5d**, 123184-23-6; **5e**, 123184-89-4; **5f**, 123184-24-7; **5g**, 123184-25-8; **5h**, 123184-26-9; **5i**, 123184-27-0; **5j**, 123184-28-1; **5k**, 123184-29-2; **5l**, 123184-30-5; **5m**, 123184-31-6; **5n**, 123184-32-7; **5o**, 123184-33-8; **5p**, 123184-34-9; **5q**, 123184-35-0; **5r**, 123184-36-1; **5s**, 123184-37-2; **5t**, 104568-69-6; **5u**, 123184-88-3; **5v**, 123184-38-3; **5w**, 123184-39-4; **5x**, 123184-40-7; **5y**, 123184-41-8; **5z**, 104568-91-4; **5aa**, 104568-69-6; **5bb**, 123184-42-9; **5cc**, 123184-43-0; **5dd**, 123184-44-1; **5ee**, 123184-45-2; **5ff**, 123184-46-3; **5gg**, 123184-47-4; **5hh**, 123184-48-5; **5ii**, 123184-49-6; **5jj**, 123184-50-9; **6a**, 123184-51-0; **6b**, 123184-52-1; **6c**, 123184-53-2; **6d**, 123184-54-3; **6e**, 123184-55-4; **6f**, 123184-56-5; **6g**, 123184-57-6; **6h**, 123184-58-7; **6i**, 123184-59-8; **6j**, 123184-60-1; **6k**, 123184-61-2; **6l**, 123184-62-3; **6m**, 123184-63-4; **6n**, 123184-64-5; **6o**, 123184-65-6; **6p**, 123184-66-7; **6q**, 123184-67-8; **6r**, 123184-68-9; **6s**, 123184-69-0; **6t**, 104568-70-9; **6u**, 123184-70-3; **6v**, 123184-71-4; **6w**, 123184-72-5; **6x**, 123184-73-6; **6y**, 123184-74-7; **6z**, 123184-75-8; **6aa**, 123184-76-9; **6bb**, 123184-77-0; **6cc**, 123184-78-1; **6dd**, 123184-79-2; **6ee**, 123184-80-5; **6ff**, 123184-81-6; **6gg**, 123184-82-7; **6hh**, 123184-83-8; **6ii**, 123184-84-9; **6jj**, 123184-85-0; **7a**, 123184-90-7; **7b**, 123184-91-8; **7c**, 123184-92-9; **7d**, 123184-93-0; **7e**, 123184-94-1; **7f**, 123184-95-2; **7g**, 123184-96-3; **7h**, 123184-97-4; **7i**, 123184-98-5; **7j**, 123184-99-6; **7l**, 123185-00-2; **7m**, 123185-01-3; **7o**, 123185-02-4; **7q**, 123185-03-5; **7r**, 123185-04-6; **7s**, 123185-05-7; **7t**, 123185-06-8; **7u**, 123185-07-9; **7w**, 123185-08-0; **7x**, 104568-71-0; **7y**, 123185-09-1; **7z**, 123185-10-4; **7aa**, 123185-11-5; **7bb**, 123185-12-6; **7cc**, 123185-13-7; **7dd**, 123185-14-8; **7ee**, 123185-15-9; **7ff**, 123185-16-0; **7gg**, 123185-17-1; **7hh**, 123185-18-2; **7ii**, 123185-19-3; **7jj**, 123185-20-6; **7kk**, 123185-21-7; **7ll**, 123185-22-8; **7mm**, 123185-23-9; **7nn**, 123185-24-0; **8a**, 123185-25-1; **8b**, 123185-26-2; **8c**, 123185-27-3; **8d**, 123185-28-4; **8e** (stereoisomer 1), 123185-29-5; **8e** (stereoisomer 2), 123185-49-9; **8f**, 104568-74-3; **8g**, 105356-37-4; **8h**, 104568-81-2; **8i**, 104568-78-7; **8j**, 123185-30-8; **8k**, 123185-31-9; **8l**, 104568-80-1; **8m**, 123185-32-0; **8n**, 123185-33-1; **8o**, 104568-77-6; **8p**, 123185-34-2; **8q**, 104568-83-4; **8r**, 104568-82-3; **8s**, 104568-79-8; **8t** (stereoisomer 1), 123355-04-4; **8t** (stereoisomer 2), 123283-97-6; **8u**, 123185-35-3; **8v**, 123185-36-4; **8w**, 104568-85-6; **8x**, 104568-73-2; **8y**, 104568-76-5; **8z**, 123185-37-5; **8aa**, 104568-75-4; **8bb**, 123185-38-6; **8cc**, 123185-39-7; **8dd**, 104568-92-5; **8ee**, 123185-40-0; **8ff**, 123185-41-1; **8gg**, 123185-42-2; **8hh**, 105356-38-5; **8ii**, 123185-43-3; **8jj**, 123185-44-4; **8kk**, 123185-45-5; **8ll**, 123185-46-6; **8mm**, 123185-47-7; **8nn**, 123185-48-8; $EtCOCH_2CO_2Me$, 30414-53-0; $CF_3COCH_2CO_2Me$, 83643-84-9; *m*-$FC_6H_4COCH_2Br$, 53631-18-8; $(CH_3)_2CHCH_2CO_2Me$, 42558-54-3; *p*-$FC_6H_4COCH_2Br$, 403-29-2; 2,6-$(MeO)_2C_6H_3COCH_2Br$, 123184-19-0; 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, 4568-71-2; 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride, 123184-18-9; 3-aminopropionitrile $^1/_2$-fumarate, 2079-89-2; 2-[2-(4-fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-2-ethanol, 123184-86-1; 2-[2-(4-fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-2-ethyl methanesulfonate, 123184-87-2; methyl acetoacetate, 105-45-3; cholesterol, 57-88-5.

Supplementary Material Available: CAMSEQ-II energies calculated for individual conformations of θ for compounds appearing in Table IV. The data are plotted in Figure 2. Also, a description of the format of a CAMSEQ-II MOL file, followed by MOL files giving *x*, *y*, *z* coordinates for the conformations of compounds I, III, and **8x** used in the pharmacophore model (7 pages). Ordering information is given on any current masthead page.

Inhibitors of Cholesterol Biosynthesis. 2. 1,3,5-Trisubstituted [2-(Tetrahydro-4-hydroxy-2-oxopyran-6-yl)ethyl]pyrazoles

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A series of 1,3,5-trisubstituted pyrazole mevalonolactones were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro. Since previous studies suggested that the 5-(4-fluorophenyl) and 3-(1-methylethyl) substituents afforded optimum potency, attention was focused on variations in position 1 of the pyrazole ring. Biological evaluation of analogues bearing a variety of 1-substituents suggested that, although most substituents were tolerated, none afforded an advantage over phenyl, which exhibited potency comparable to that of compactin in vitro.

We previously described a series of 2,5-disubstituted pyrrole mevalonolactones whose 3,5-dihydroxyheptanoic acid derivatives were shown to possess varying degrees of intrinsic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity in vitro.[1] Structure–activity relationships (SAR) for this series of compounds were determined, and the preferred substituents in the 2- and 5-positions of the pyrrole nucleus were found to be 4-fluorophenyl and 1-methylethyl, respectively. This paper describes the synthesis and biological activity of a series of 1,3,5-trisubstituted pyrazole mevalonolactones[2] with

(1) Roth, B. D.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. Submitted to *J. Med. Chem.*

(2) During the course of this study, a series of trisubstituted pyrazole mevalonolactones were reported to inhibit HMG-CoA reductase by J. R. Wareing at Sandoz Pharmaceuticals Corp. U.S. Patent. 4613610.

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