(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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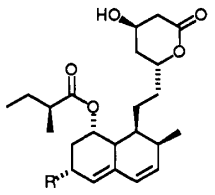
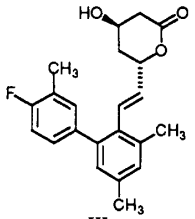
A novel series of *trans*-6-(2-pyrrol-1-ylethyl)-4-hydroxypyran-2-ones and their dihydroxy acid derivatives were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro. A systematic study of substitution at the 2- and 5-positions of the pyrrole ring revealed that optimum 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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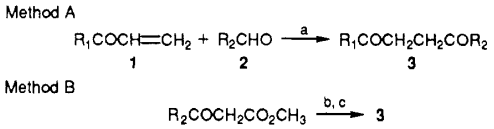
Scheme I[a]



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

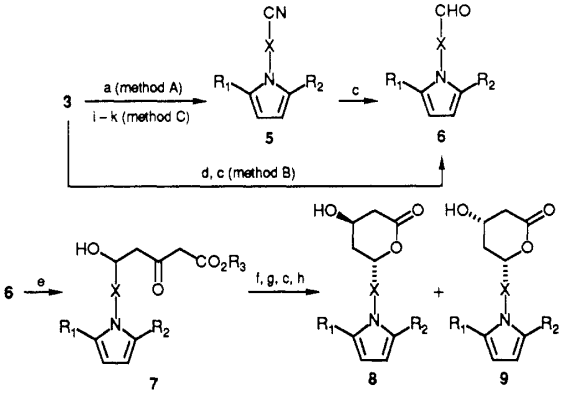
feature possessed by all of these agents was a large lipophilic group held in a particular spatial relationship with respect to the 4-hydroxypyran-2-one moiety. Indeed, examination of CPK models of these inhibitors suggested that the ortho phenyl ring might occupy the same space as the isobutyric ester 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

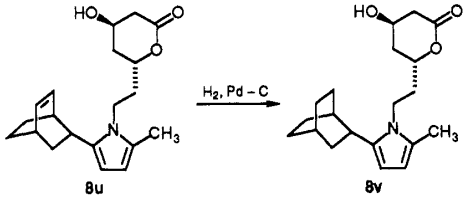
Our general synthetic strategy entailed the preparation of a suitable 1,4-diketone (**3**, Table I), either by the thiazolium salt chemistry developed by Stetter (Scheme I, method A)[8] or by alkylation of a β-keto ester with an α-halo ketone followed by hydrolysis and decarboxylation (method B). The 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]

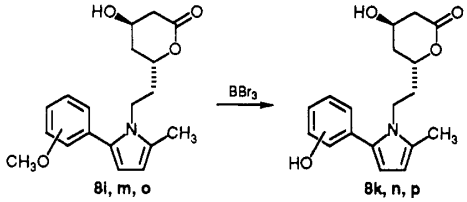


[a] (a) H_2N–X–CN, HOAc, reflux. (b) DIBAL-H, toluene, −78 °C. (c) aqueous HCl. (d) H_2N–X–$CH(OEt)_2$, toluene, cat. *p*-TSA, reflux. (e) $^-CH_2CO^-CHCH_3CH_3$, THF, −78 °C. (f) *n*-Bu_3B, $NaBH_4$, −78 °C. (g) H_2O_2, OH^-. (h) Toluene, reflux. (i) H_2N–X–OH, HOAc. (j) CH_3SO_2Cl, pyr. (k) KCN, DMF–H_2O,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

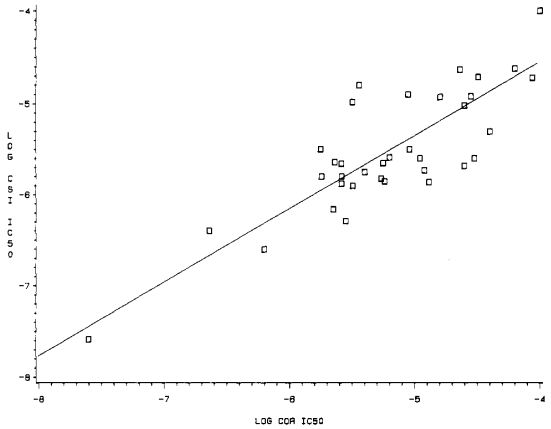


Figure 1. Correlation between CSI and COR IC_{50}'s.

Table I. Substituted 1,4-Diketones

$$R_1COCH_2CH_2COR_2$$
3

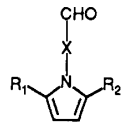
no.	R_1	R_2	bp (mmHg), °C	% yield[a] (procedure)
3a[8b]	Ph	CH_3	100 (0.1)	80 (A)
3b	4-*F*C_6H_4	CH_3	46–8	66 (A)
3c	4-PhC_6H_4	CH_3	109–112	73 (A)
3d[8c]	4-ClC_6H_4	CH_3	116–8 (1.0)	44 (A)
3e[8a]	4-$CH_3OC_6H_4$	CH_3	*b*	57 (A)
3f	3-$F_3CC_6H_4$	CH_3	*b*	38 (A)
3g	3-$CH_3OC_6H_4$	CH_3	143–5 (0.2)	80 (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.

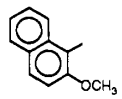
aqueous peroxide and base.[12] The dihydroxy acids were then lactonized by refluxing in toluene with azeotropic removal of water. Generally, the lactones were crystalline, such that the small amounts of the cis lactone stereoisomer **9** present were easily removed by recrystallization, providing >95% 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]

(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.

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)[a]
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]-

(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.

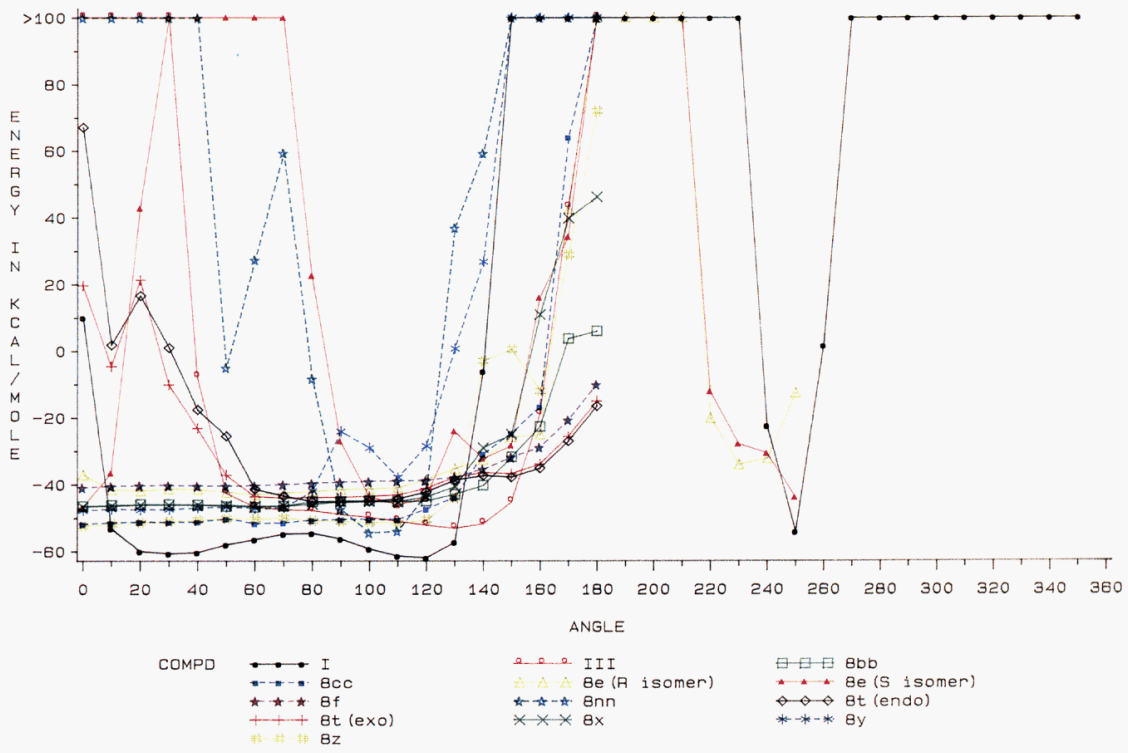


Figure 2. CAMSEQ-II energies calculated for comparable orientations of the lactone side chain. Dashed lines represent less potent analogues (**8j**, **8z**, **8bb**, **8cc**, and **8nn**; CSI $IC_{50} > 5$ μM).

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.

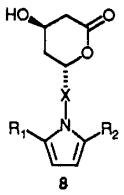
These results, combined with results from the molecular modeling study, confirmed our belief that **8x** possessed the optimum substitution pattern, since structural modifications at the 2- and 5-positions, as well as variation of the bridge to the lactone ring, led to decreased potency. A similar conclusion 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.

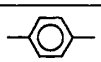
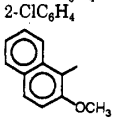
(16) Compounds **8c** and **8cc** were assigned IC_{50} values of 100 μM so they could be included in the correlation.

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

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



8

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	–	$C_{18}H_{21}NO_4$	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-i$PrOC_6H_4$	$CH(CH_3)_2$	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.

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