Inhibitors of Cholesterol Biosynthesis. 6. *trans*-6-[2-(2-*N*-Heteroaryl-3,5-disubstituted-pyrazol-4-yl)ethyl/ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-ones[1]

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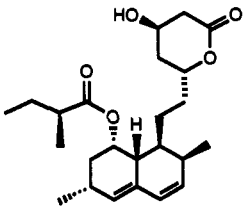
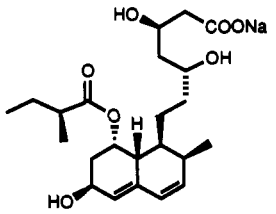
A series of *N*-heteroaryl-substituted mevalonolactones were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase both in vitro and in vivo, and to lower plasma cholesterol in a hypercholesterolemic dog model. The goal of the strategy employed was to design an inhibitor which possessed the pharmacological properties of lovastatin (1), and the physicochemical properties (increased hydrophilicity) of pravastatin (2). Two compounds **20a** and **20b**, were more potent than lovastatin at inhibiting cholesterol biosynthesis both in vitro and in vivo. In terms of plasma cholesterol lowering, **20a** was much more efficacious than lovastatin. In addition to possessing increased biological activity, these compounds are significantly less lipophilic than lovastatin, in fact, **20b** has a CLOGP value comparable to pravastatin.

Since the liver is the major site of cholesterol biosynthesis, it might be regarded as the primary target tissue for an HMG-CoA reductase (HMGR) inhibitor. Recently, there has been considerable controversy in the literature concerning both the nature and existence of tissue (liver) selectivity for various HMGR inhibitors, and whether confining their action to the liver would reduce the incidence of adverse reactions which have been noted with continued clinical use of lovastatin (Mevacor).[2]

Tsujita has reported that lovastatin (1) and pravastatin (2) were equipotent at inhibiting cholesterol biosynthesis in cultured rat hepatocytes, but pravastatin was much less potent at inhibiting biosynthesis in peripheral tissues such as human skin fibroblasts. In ex vivo rat studies these results were confirmed when it was demonstrated that pravastatin inhibited biosynthesis only in lipoprotein-producing organs (liver and intestine), whereas lovastatin inhibited biosynthesis significantly in all tissues examined (including such extrahepatic tissues as kidney, lung, spleen, testis, etc.).[3] We have confirmed these results in tissue cubes and demonstrated a linear relationship between lipophilicity and tissue selectivity irrespective of the inhibitor structure.[1]



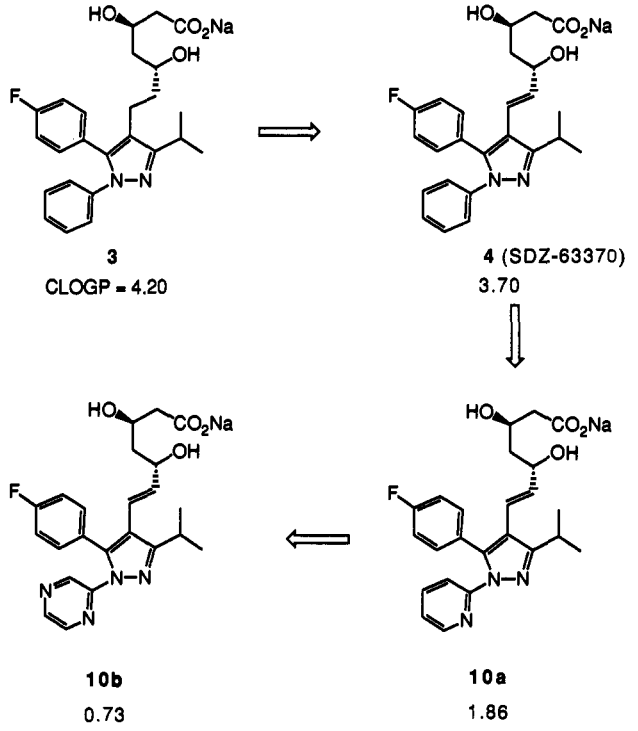
1, Lovastatin



2, Pravastatin

Pravastatin is structurally different from lovastatin. It contains the biologically essential moiety in the ring-opened dihydroxy acid form whereas lovastatin contains the closed ring lactone form, which ring opens in vivo. In addition, pravastatin also contains a hydroxyl group in the hexahydronaphthalene ring.[4] These structural differences make pravastatin much more hydrophilic than the other HMGR inhibitors.[5] It is this unique property which has been hypothesized to be responsible for the minimal penetration of pravastatin into the lipophilic membranes of peripheral cells.[1,5]

Scheme I. Effect on CLOGP of Introducing Polar Functionalities in Compound 3



We have previously described a series of 1,3,5-trisubstituted pyrazole mevalonolactones in which one member of this series, compound **3**, was shown to be a moderately

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(1) Part 5: Roth, B. D.; Bocan, T. M. A.; Blankley, C. J. et al. Relationship between Tissue Selectivity and Lipophilicity for Inhibitors of HMG-CoA Reductase. *J. Med. Chem.* **1991**, *34*, 463–466.
(2) Illingworth, D. R. Clinical implications of new drugs for lowering plasma cholesterol concentrations. *Drugs* **1991**, *41*, 151–160.
(3) Tsujita, Y.; Kuroda, M.; Shimada, Y. et al. CS-514, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase: tissue-selective inhibition of sterol synthesis and hypolipidemic effect on various animal species. *Biochim. Biophys. Acta* **1986**, *877*, 50–60.
(4) Haruyama, H.; Kuwano, H.; Kinoshita, A.; Terahara, T.; Nishigaki, T.; Tamura, C. Structure elucidation of the bioactive metabolites of ML-236B (mevastatin) isolated from dog urine. *Chem. Pharm. Bull.* **1986**, *34*, 1459–1467.
(5) Serajuddin, A. T. M.; Ranadive, S. A.; Mahoney, E. M. Relative Lipophilicities, Solubilities, and Structure-Pharmacological Considerations of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors Pravastatin, Lovastatin, Mevastatin, and Simvasatin. *J. Pharm. Sci.* **1991**, *80*, 830–834.

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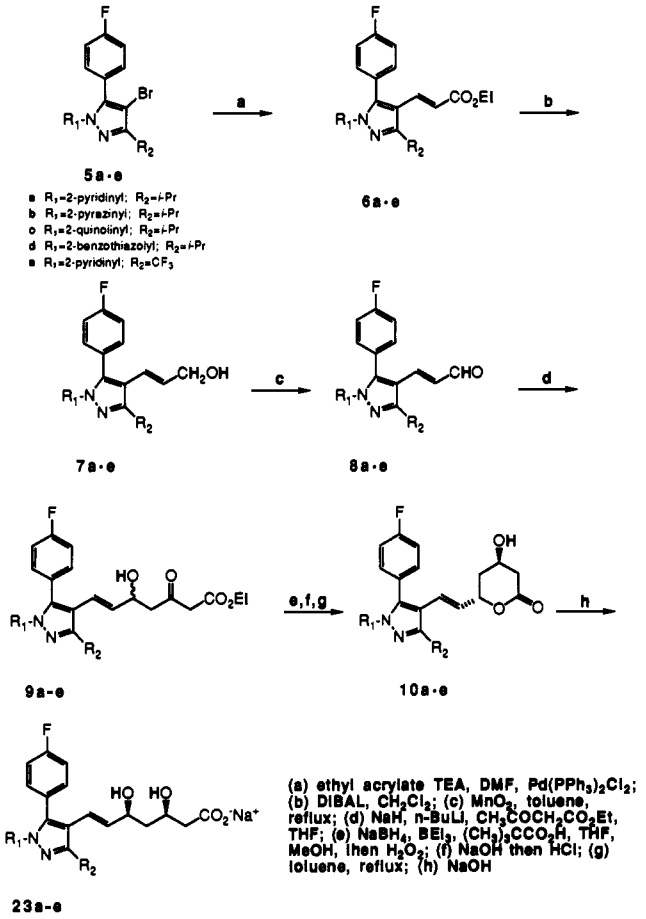
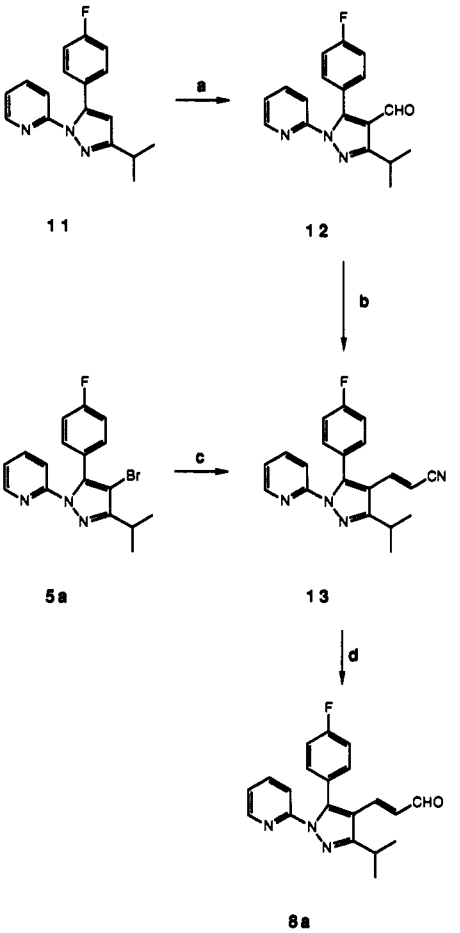
Scheme II



Scheme III



potent inhibitor of HMGR in vitro.[6] This report describes the synthesis and biological activity of a series of *N*-heteroaryl-substituted pyrazole mevalonolactones which were a direct consequence of our strategy in designing inhibitors of HMGR which possess the physicochemical properties of pravastatin (i.e. low lipophilicity) and the pharmacological properties of lovastatin. The substitution pattern at positions 3 and 5 of the pyrazole ring remained the same as in **3** (except in the case of **10e** where trifluoromethyl replaced isopropyl).

Our primary strategy involved decreasing the log *P* of our known inhibitors by the introduction of polar moieties into the pyrazole nitrogen substituent. For example, introduction of a nitrogen atom into the 1-phenyl substituent of compound **3** lowers the CLOGP[7] by 1.84, introduction of a second nitrogen atom to yield a pyrazinyl substituent lowers the CLOGP by an additional 1.13 log units. A second minor modification involves replacement of the ethyl bridge, between the mevalonolactone moiety and the pyrazole, by an ethylene bridge; this has previously been shown to improve the in vitro potency against HMGR.[8] In addition to this, there is a minor lowering of CLOGP. The results of such modifications are exemplified in Scheme I. The CLOGP of compound **3** is 4.2. Introduction of a double bond (as in **4**) only lowers the CLOGP to a value of 3.7. The 2-pyridyl derivative **10a** has a CLOGP of 1.86, whereas the 2-pyrazinyl derivative **10b** has a CLOGP of 0.73. (For the purpose of comparison, the CLOGP of pravastatin (**2**) is 0.51.)

Chemistry

Compounds containing the ethenyl moiety between the heterocyclic nuclei and the lactone portion were synthesized by the general method shown in Scheme II.

The bromopyrazoles **5a–e** were prepared employing methods previously described by these laboratories.[6] Palladium-catalyzed vinylation of **5a–e** with ethyl acrylate gave the α,β-unsaturated esters **6a–e** (>95% *E* selectivity)[9] which were readily reduced, with DIBAL-H in dichloromethane, to the corresponding alcohols **7a–e**, and then reoxidized to the aldehydes **8a–e** using MnO_2 in refluxing toluene. Addition of the dianion of ethyl acetoacetate gave the racemic δ-hydroxy-β-keto esters **9a–e**.[10] Stereospecific reduction[11] ($NaBH_4$, BEt_3, pivalic acid, THF, MeOH) gave, after saponification, a mixture of *erythro* and *threo*-1,3-dihydroxy acids (>19:1) which were readily lactonized to the final products **10a–e**, as a mixture of diastereomers (>20:1 trans:cis by HPLC). The lactones **10a–e** could also

(6) Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. Inhibitors of Cholesterol Biosynthesis. 2. 1,3,5-Trisubstituted [2-(tetrahydro-4-Hydroxy-2-oxopyranyl-6-yl)ethyl]pyrazoles. *J. Med. Chem.* **1990**, *33*, 31–38.

(7) Pomona Medical Software, V.3.54. log *P* measurements were also made, but it was difficult to obtain consistent values. The correlation of measured with uncorrected calculated values was modest ($r = 0.74$).

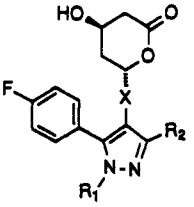
(8) Sliskovic, D. R.; Picard, J. A.; Roark, W. H.; et al. Inhibitors of Cholesterol Biosynthesis. 4. *trans*-6-[2-(Substituted-quinolinyl)ethenyl/ethyl]tetrahydro-2*H*-pyran-2-ones, a Novel Series of HMG-CoA Reductase Inhibitors. *J. Med. Chem.* **1991**, *34*, 367–373.

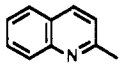
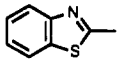
(9) Heck, R. F. Palladium Catalyzed Vinylation of Organic Halides. *Org. React.* **1982**, *27*, 345–390.

(10) Huckin, S. N.; Weiler, L. Alkylation of Dianions of β-Keto Esters. *J. Am. Chem. Soc.* **1981**, *96*, 1082–1087.

(11) Narasaka, K.; Pai, F-C. Stereoselective Reduction of β-Hydroxyketones to 1,3-Diols. *Tetrahedron* **1984**, *40*, 2233–2238.

Table I. Physical Properties and in Vitro and in Vivo HMG-CoA Reductase Inhibitory Activities of Heteroaryl-Substituted Pyrazole Mevalonolactones



no.	R_1	R_2	X	mp, °C	formula[a]	CLOGP[b]	COR[c,d] IC_{50}, μM	AlCS[e] (% inhibn) lactone form	AlCS[e] (% inhibn) ring opened form
1, lovastatin						3.11	0.020	64	ND
2, pravastatin						0.51	0.030	ND	48
3	Ph	$CH(CH_3)_2$	CH_2CH_2	165–167	$C_{25}H_{27}FN_2O_3$	3.39	0.040	54, 55 (1.5)	72 (1.5)
4	SDZ-63370					3.32	0.007	ND	94
10a		$CH(CH_3)_2$	CH=CH	131–133	$C_{24}H_{24}FN_3O_3$	1.86	0.024	83	85
10b		$CH(CH_3)_2$	CH=CH	145–148	$C_{23}H_{23}FN_4O_3$	0.73	0.066	80	75
10c		$CH(CH_3)_2$	CH=CH	179–181	$C_{28}H_{26}FN_3O_3$	3.25	0.062	75	69
10d		$CH(CH_3)_2$	CH=CH	168–170	$C_{26}H_{24}FN_3O_3S$	3.23	0.059	30	51
10e		CF_3	CH=CH	142–144	$C_{22}H_{17}F_4N_3O_3$	1.56	0.017	60	81
22		$CH(CH_3)_2$	CH_2CH_2	182–184	$C_{24}H_{26}FN_3O_3$	1.94	0.110	58 (1.5)	68 (1.5)
20a		$CH(CH_3)_2$	CH=CH	139–140	$C_{24}H_{24}FN_3O_3$	1.86	0.008	93	98
20b		$CH(CH_3)_2$	CH=CH	154–156	$C_{23}H_{23}FN_4O_6$	0.73	0.007	92	91

[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] Calculated as the active dihydroxy acid forms. [c] All compounds tested had a diastereomeric purity of >95% of the trans diastereomer as determined by HPLC and/or 200-MHz NMR. [d] HMG-CoA reductase inhibition (COR). Assays of each inhibitor concentration were performed in triplicate, and the precision for lovastatin was 37%. [e] All compounds were dosed in DMA/PEG solution at 1.0 mg/kg unless otherwise indicated in parentheses. ND = not determined.

be saponified to the corresponding, highly hygroscopic, 3,5-dihydroxy sodium carboxylates **23a–e**.

The key α,β-unsaturated aldehydes **8a–e** may also be synthesized as shown in Scheme III as exemplified for the 2-pyridyl compound **8a**. Vilsmeier–Haack formylation of pyrazole **11**, employing *N*-formylmorpholine[12] gave the aldehyde **12**; normal formylation conditions ($POCl_3$/DMF) gave only traces of **12**. This was then treated with diethyl cyanomethylphosphonate and NaH/THF in a Horner–Emmons coupling (method A) to yield the α,β-unsaturated nitrile **13** in high yield. Reduction to **8a** was achieved using Raney nickel in formic acid. Alternatively, Heck coupling of bromide **5a** with acrylonitrile also afforded **13**, but in poor yield (method B).

Interestingly, reduction of **6c** gave an inseparable mixture of the desired alcohol **7c** and the 3,4-dihydro quinoline derivative **14**. Reoxidation with MnO_2 gave the corresponding aldehydes, **8c** and **15**, which could easily be separated by column chromatography. Treatment of **15** with DDQ in THF gave **8c** (Scheme IV).

Selected examples of these racemic compounds (i.e. **10a,b**) were also synthesized in optically active form (**20a,b**) bearing the biologically active 4*R*,6*S* configuration (Scheme V). For example, treatment of aldehyde **8a** with the magnesium(II) enolate of (*S*)-phenyl 2-hydroxy-2,2-diphenylacetate (**16**) gave the chiral aldol product **17a** in good yield.[13] Treatment of **17a** with sodium methoxide gave the corresponding methyl ester **18a**. Reaction of **18a** with *tert*-butyl lithioacetate gave the (*S*)-hydroxy-β-keto ester **19a**, which was transformed to the trans lactone **20a** in a manner analogous to that employed in the synthesis of the racemic lactones. Chiral HPLC of **20a** indicated that this material was a 87:10:3 mixture which we tentatively assigned as the 4*R*,6*S*, 4*S*,6*R*, and 4*S*,6*S* isomers. This indicated an optical purity of 74% ee.

The synthesis of the 2-pyridyl analogue **22**, containing an ethyl bridge, was achieved by methods previously described, utilizing acetonide **21** in a Heck coupling with bromopyrazole **5a** (Scheme VI).[6]

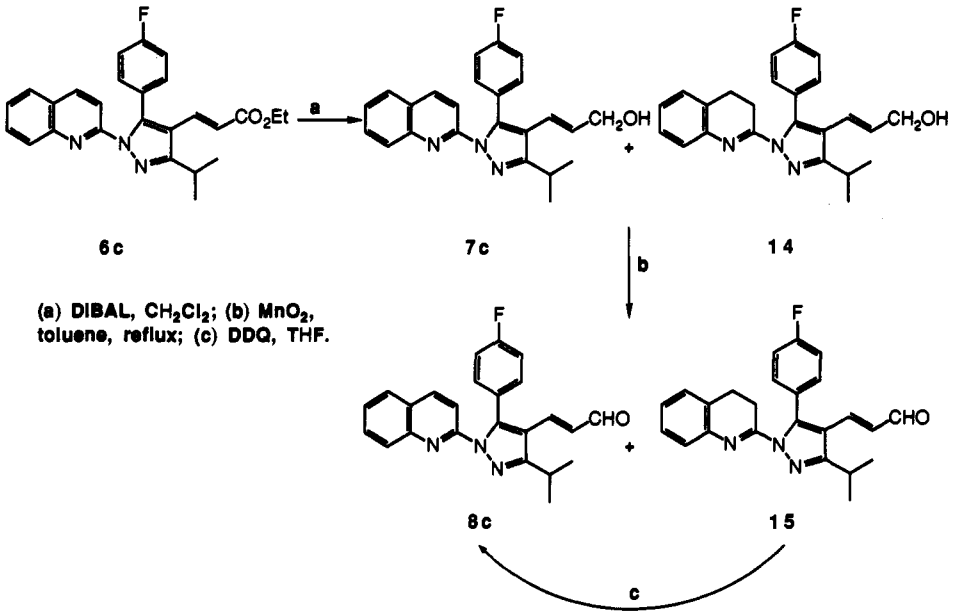
Biological Results and Discussion

Our testing strategy for these compounds evolved into a three-tier system. First, the lactones listed in Table I were saponified to the 3,5-dihydroxy acids and tested for their ability to inhibit cholesterol biosynthesis. The in vitro screen utilized a partially purified microsomal enzyme

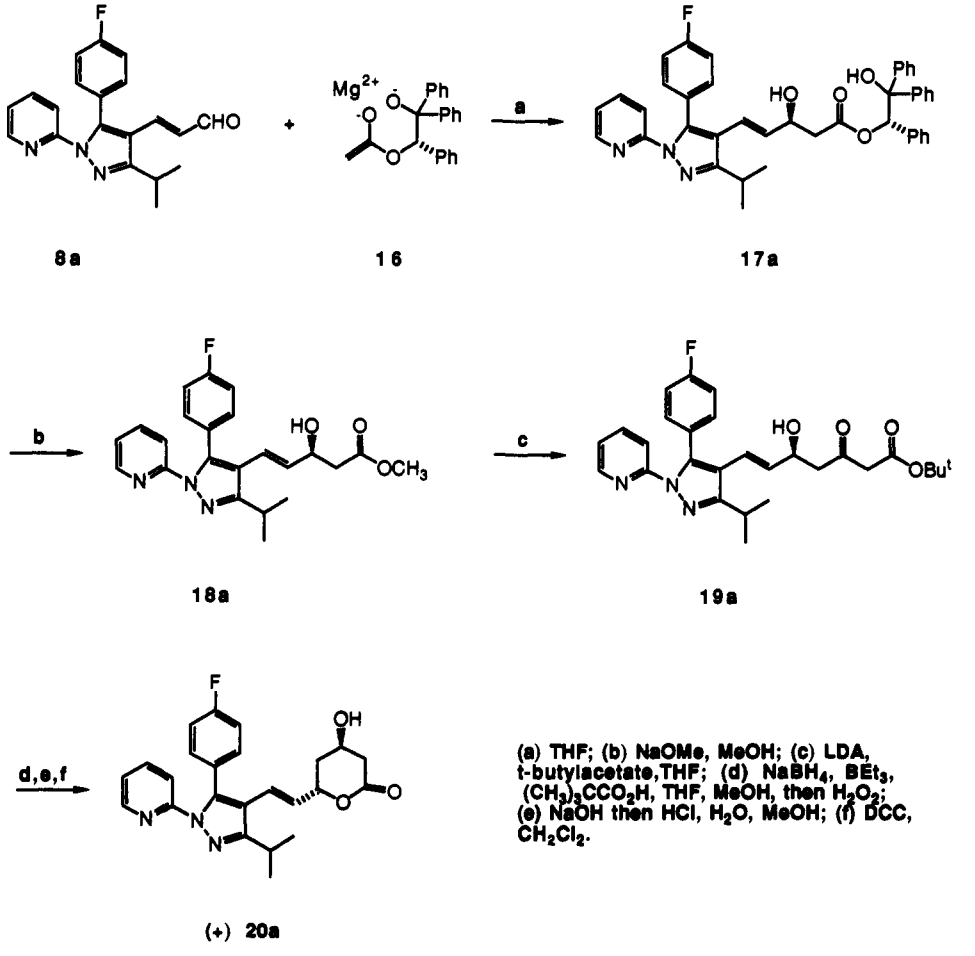
(12) Beccalli, E. M.; Marrchesini, A. The Vilsmeier-Haack Reaction of Isoxazolin-5-ones. Synthesis and Reactivity of 2-(dialkylamino)-1,3-oxazin-6-ones. *J. Org. Chem.* **1987**, *52*, 3426–3434.

(13) Braun, M.; Devant, R. (R)- and (S)-2-Acetoxy-1,1,2-triphenylethanol—effective synthetic equivalents of a chiral acetate enolate. *Tetrahedron Lett.* **1984**, *25*, 5031–5034.

Scheme IV



Scheme V

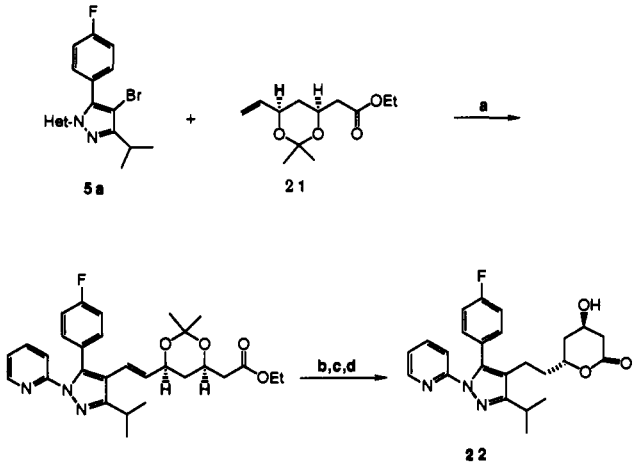


preparation to identify specific inhibitors of HMG-CoA reductase, and was termed COR[14] (Table I). The second tier of our strategy involved a measurement of cholesterol biosynthesis in vivo using rodents and thus small amounts of compound. Normal, chow-fed rats possess the ability to compensate for inhibition of cholesterol biosynthesis by synthesizing large amounts of enzyme, thereby preventing a fall in plasma cholesterol. Thus, HMG-CoA reductase inhibitors do not lower plasma cholesterol in normal rats.[15]

(14) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L. et al. 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. *J. Med. Chem.* **1990**, *33*, 21–31.

(15) Krause, B. R.; Newton, R. S. Animal models for the evaluation of inhibitors of HMG-CoA reductase. *Adv. Lipid Res.* **1991**, 57–72.

Scheme VI



(a) $(Ph_3P)_2PdCl_2$, Et_3N, DMF,70°C ; (b) H_2 Pd/C ; (c) HCl, NaOH ; (d) Toluene, reflux.

Table II. Hypocholesterolemic Activity in Cholestyramine-Primed Beagle Dogs (n = 6, po)[a]

no.	dose (mg/kg)	2 weeks (% change)[b]	4 weeks (% change)[b]
controls	-	-10	+6
1	0.1	-7	-1
	0.3	-10	-2
	1.0	-25[c]	-17[c]
20a	0.1	-20[c]	-16[c]
	0.3	-31[c]	-32[c]
	1.0	-44[c]	-50[c]

[a] For experimental protocol see Experimental Section. [b] Values are the mean percent changes compared to pretreatment values within the same group. [c] Significantly different from untreated controls, $p < 0.05$.

However, efficacy can be demonstrated acutely using isotopic precursors such as [1-^{14}C]acetate. Using this model, designated AICS, cholesterol biosynthesis can be measured by determining the rate of incorporation of [1-^{14}C]acetate into plasma sterols (Table I).[8] The final step was evaluation in a true efficacy model. It has been shown that HMG-CoA reductase inhibitors can lower plasma cholesterol in normal, chow-fed dogs, however, the doses are often high and compound requirements are restrictive.[16] Workers at Merck have observed that pretreatment of dogs with a bile acid binding resin, such as cholestyramine, followed by resin plus a reductase inhibitor, results in a synergistic response. This increases the sensitivity of the model and thus allows lower doses to be used to demonstrate efficacy (Table II).[17]

We have previously demonstrated that **3** is a potent inhibitor of HMG-CoA reductase in vitro.[6] From Table I it can be seen that **3** inhibited cholesterol biosynthesis in vivo by 54% compared to 64% for **1** at a dose of 1 mg/kg po. The CLOGP of both of these compounds are comparable. Introduction of a double bond into **3** (i.e. **4**) had little effect on the CLOGP, but increased the potency 6-fold in the COR screen and also improved cholesterol

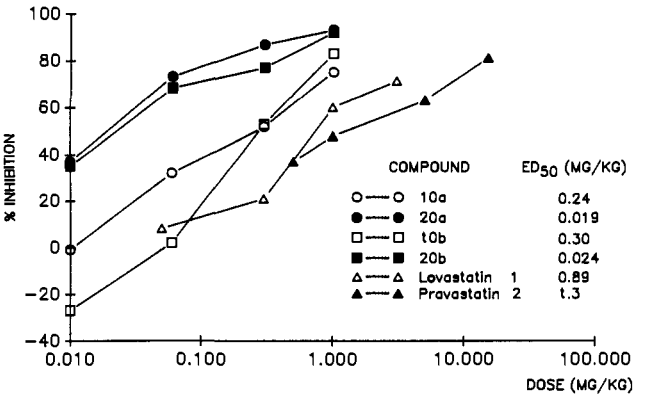


Figure 1. Acute inhibition of sterol synthesis in rats.

biosynthesis inhibition in vivo (94% as compared with 72% for the sodium salt of **3**). With this desired in vivo activity, we now began to look at the effects of lowering the CLOGP of these compounds. Replacement of the *N*-phenyl group in **3** by a 2-pyridyl group gave a compound (**22**) in which potency was retained in vivo, although it was less potent in vitro. This modification also decreased the CLOGP to 1.94. Double bond incorporation into this compound gave **10a**, which showed an additional small decrease in CLOGP (1.86) and greatly improved potency over **22**, both in vitro and in vivo. Replacement of the isopropyl group of **10a** with trifluoromethyl gave **10e**, which was equipotent in vitro but less active in vivo than **10a**. Introduction of a second nitrogen atom into the 2-pyridyl ring of **10a**, gave the 2-pyrazinyl derivative **10b**. This was 3-fold less potent in vitro than **10a**, but was equipotent in the in vivo screen. In addition, the CLOGP of this compound was now 0.73, which is of comparable magnitude to that obtained for pravastatin (0.51). For both **10a** and **10b** there was little difference in vivo between the lactone and ring opened forms, and both compounds were more potent than lovastatin (**1**) in vivo.

In our previous work,[6] replacement of the phenyl group in **1** with a naphthyl group resulted in a significant loss of potency in vitro. In contrast, in the heterocyclic series discussed here, replacement of the 2-pyridyl group in **10a** with a 2-quinolinyl group (**10c**) resulted in no loss of in vitro potency and only a slight decrease in in vivo activity. However, the 2-benzothiazolyl compound **10d** showed a large decrease in in vivo activity when compared to either **10a** or **10c**.

The optically active forms (**20a,b**) of compounds **10a,b** were much more potent in vitro than their racemic counterparts. Compound **20a** was 4 times more potent than **10a** in vitro; even greater differences were observed with **20b**. In vivo, both compounds **20a** and **20b** were considerably more effective than **10a** and **10b** in inhibiting cholesterol biosynthesis in vivo. A comparison of ED_{50} values (i.e. the effective dose at which there is a 50% inhibition of cholesterol biosynthesis) shows that both **20a** (ED_{50} = 0.019 mg/kg) and **20b** (ED_{50} = 0.024 mg/kg) are much more potent than both **1** (ED_{50} = 0.89 mg/kg) and **2** (ED_{50} = 1.3 mg/kg) (Figure 1). The reason for the remarkable improvements in in vitro and in vivo potencies on resolution of **10a** and **10b** is unclear. There was no difference in inhibition between the lactone and sodium salt forms. Compound **20a** was also found to be superior to **1** in cholestyramine-primed dogs at doses of 0.1, 0.3, 1.0 mg/kg. As can be seen from Table II, **20a** showed statistically significant changes at all dose levels after 2 and 4 weeks, achieving a maximal lowering of plasma cholesterol (50%) after 4 weeks of drug treatment at a dose of 1.0 mg/kg. Lovastatin (**1**) only showed a statistically

(16) Kovanen, P. T.; Bilheimer, D. W.; Goldstein, J. L.; Jaramillo, J.; Brown, M. S. Regulatory role for hepatic low density lipoprotein receptors in vivo in the dog. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 1194-1198.

(17) Duggan, M. E.; Alberts, A. W.; Bostedor, R. et al. 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 7. Modification of the Hexahydronaphthalene Moiety of Simvastatin: 5-Oxygenated and 5-Oxa Derivatives. *J. Med. Chem.* **1991**, *34*, 2489-2495.

significant (17% at 4 weeks) lowering at the high dose.

The in vitro tissue selectivity of **20a** and **20b** has recently been published and has been shown to be comparable to **2** and far superior to **1**.[1] In this study, as a measure of intrinsic potency, each compound was tested for its ability to inhibit microsomal HMGR in vitro, then, as a measure of hepatic vs peripheral effects, the effects of the compounds on the incorporation of [^{14}C]acetate into sterols was measured in tissue cubes derived from liver, spleen, and testis. When the tissue/liver ratios were plotted against CLOGP, linear relationships were observed. These relationships suggest that selectivity is directly dependent on lipophilicity. Thus, compounds with CLOGP < 2 (**2**, **20a**, and **20b**) all appear to possess a moderate degree of tissue selectivity as evidenced by tissue/liver ratios > 1. In general, compounds with CLOGP > 2 (**1** and **4**) are more potent in peripheral tissues than liver. Thus, we have identified, through our strategy of reducing the lipophilicity of our most potent HMGR inhibitors, two compounds **20a** and **20b**, which were as tissue selective or more tissue selective than pravastatin (**2**). The in vivo consequences of this in vitro tissue selectivity will be the subject of further communications from these laboratories.

In summary, we have identified two compounds, **10a** and **10b**, which were equipotent to **1** in vitro and superior in vivo. When evaluated in their optically active forms (**20a** and **20b**), both compounds were more potent than **1** both in vitro and in vivo. One of these compounds, **20a**, was also shown to be much more potent and efficacious than **1** in terms of cholesterol lowering in the cholestyramine-primed dog model. These compounds, in addition to possessing increased biological activity, are significantly less lipophilic than **1**, in fact, **20b** has a comparable CLOGP value of **2** (0.73 vs 0.51).

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. All organic extracts were dried over $MgSO_4$ except when otherwise noted. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on either a Varian EM-390 spectrometer, a Varian XL200, or a Bruker 250 MHz instrument. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Elemental analyses for carbon, hydrogen, and nitrogen were performed on a Perkin-Elmer 240C elemental analyzer and are within 0.4% of theory unless noted otherwise. Optical rotations were performed on a Perkin-Elmer 241 polarimeter. Routine HPLC analyses were performed on a Varian 5500 unit equipped with a Reodyne 7126 loop injector, a DuPont variable wavelength detector (wavelength was 254 nm) and an octadecylsilane column (Altex Ultrasphere C18, 5 μm; mobile phase was 50% 0.05 M citric acid pH = 4 with NH_4OH, 50% acetonitrile). Chiral HPLC analyses were performed on a Perkin-Elmer 410 system with a detection wavelength of 254 nm and a Chiralcel OF column (Diacel Chem. Ind. Ltd.) 5 μm, mobile phase of 85% hexane, 15% 2-propanol.

2-[4-Bromo-5-(4-fluorophenyl)-3-(1-methylethyl)-1*H*-pyrazol-1-yl]pyridine (5a). To a solution of 1-(4-fluorophenyl)-4-methyl-1,3-pentanedione[6] (10.0 g, 0.048 mol) in glacial acetic acid (100 mL) under a nitrogen atmosphere was added at room temperature 2-hydrazinopyridine (5.77 g, 0.053 mol). The resulting solution was then heated at 60 °C for 3 h, cooled to room temperature, and poured into water (100 mL). This was then extracted with diethyl ether, and the resultant organic solution was washed successively with saturated aqueous sodium bicarbonate solution, water, and brine, and dried. Concentration in vacuo yielded the crude product which was flash chromatographed on a silica gel column, eluting with 20% ethyl acetate in hexane to yield **11** (8.7 g, 64%), mp 80–81 °C; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, 1 H), 7.0–7.8 (m, 7 H), 6.35 (s, 1 H), 3.15 (hept, 1 H), and 1.3 (d, 6 H) ppm. Anal. ($C_{17}H_{16}FN_3$) C, H, N.

N-Bromosuccinimide (7.9 g, 0.028 mol) was added to a solution of this pyrazole (7.89 g, 0.028 mol) in 30 mL of dimethylformamide at 0 °C. The resulting solution was stirred at 0 °C for 4 h and then poured into water (100 mL). The white solid which precipitated was collected by filtration and dried to yield **5a** (9.0 g, 89%), mp 98–100 °C; ^{1}H NMR ($CDCl_3$) δ 8.3 (d, 1 H), 7.0–7.8 (m, 7 H), 3.15 (hept, 1 H), 1.4 (d, 6 H) ppm. Anal. ($C_{17}H_{15}BrFN_3$) C, H, N.

Ethyl (*E*)-3-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-2-propenoate (6a). Bis(triphenylphosphine)palladium(II) chloride (11.7 g, 0.0166 mol, 4 mol%) and ethyl acrylate (226 mL, 2.08 mol) were dissolved in dimethylformamide (600 mL) and triethylamine (660 mL) and heated to reflux under a nitrogen atmosphere until a homogeneous solution resulted. Bromopyrazole **5a** (150 g, 0.42 mol) was then added, and the resulting solution was heated to reflux overnight, after an additional 2 g of catalyst was added. The reaction was then cooled to room temperature and partitioned between diethyl ether and water. The organic layer was separated and washed with water and brine, dried, filtered, and concentrated in vacuo to give 191 g of a yellow solid which was recrystallized from 5:1 hexane/ethyl acetate to yield **6a** (105 g, 67%) as white crystals: mp 114–116 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, 1 H), 7.77 (m, 1 H), 7.56 (m, 2 H), 7.0–7.3 (m, 4 H), 6.0 (d, 1 H), 4.2 (q, 2 H), 3.34 (hept, 1 H), 1.62 (d, 6 H), 1.28 (t, 3 H) ppm. Anal. ($C_{22}H_{22}FN_3O_2$) C, H, N.

(*E*)-3-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-2-propen-1-ol (7a). To a solution of **6a** (50 g, 0.132 mol) in dichloromethane (350 mL) at −78 °C under an inert atmosphere was added DIBAL-H (290 mL, 1 M solution in dichloromethane) dropwise. After stirring for 1 h at −78 °C, the reaction was quenched by addition of saturated aqueous sodium sulfate (41 g) and allowed to warm to room temperature, after which it was filtered through Celite and sand. The filtrate was dried, filtered, and concentrated in vacuo to yield a white solid which was recrystallized from ethyl acetate/hexane (1:1) to give **7a** (34.1 g, 77%): mp 106–109 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, 1 H), 7.74 (m, 1 H), 7.0–7.3 (m, 6 H), 6.4 (d, 1 H), 5.9 (dt, 1 H), 4.2 (br d, 2 H), 3.2 (hept, 1 H), 1.4 (d, 6 H) ppm. Anal. ($C_{20}H_{20}FN_3O$) C, H, N.

(*E*)-3-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-2-propenal (8a). Manganese(IV) oxide (72.2 g, 0.83 mol) was suspended in toluene (2 L) and refluxed for 4 h with azeotropic removal of water. The unsaturated alcohol (**7a**, 28 g, 0.083 mol) was added, and heating was continued for 24 h. The suspension was then cooled to room temperature and filtered through a pad of silica. The filtrate was concentrated in vacuo to yield **8a** (27.0 g, 98%): mp 105–107 °C; ^{1}H NMR ($CDCl_3$) δ 9.45 (d, 1 H), 8.25 (d, 1 H), 7.75 (m, 1 H), 7.58 (d, 1 H), 7.0–7.3 (m, 6 H), 6.36 (dd, 1 H), 3.26 (hept, 1 H), 1.42 (d, 6 H) ppm. Anal. ($C_{20}H_{18}FN_3O$) C, H, N.

Ethyl (*E*)-7-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-5-hydroxy-3-oxo-6-heptenoate (9a). To a hexane-washed suspension of NaH (1.8 g, 60% oil dispersion, 0.045 mol) in tetrahydrofuran (THF) (50 mL) at 0 °C under a nitrogen atmosphere was added a solution of ethyl acetoacetate (5.23 mL, 0.041 mol) in THF (40 mL). The resulting solution was stirred at 0 °C for 20 min before *n*-BuLi (17.1 mL, 0.041 mol, 2.4 M solution in hexane) was added dropwise. The resulting orange solution was stirred at 0 °C for an additional 15 min before it was cooled to −78 °C and a solution of **8a** (12.5 g, 0.0373 mol) in THF (50 mL) was added dropwise over 20 min. The resulting solution was stirred at −78 °C for 1 h and then quenched by the addition of glacial acetic acid (20 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic extracts were washed with water, dried, filtered, and concentrated in vacuo to yield a product which was flash chromatographed on silica gel. Elution with 25% ethyl acetate/toluene gave **9a** (9.0 g, 52%) as a yellow oil and recovered aldehyde **8a** (5.1 g) which was resubmitted to the reaction conditions to yield an additional 5.2 g (30%) of **9a**: ^{1}H NMR ($CDCl_3$) δ 8.2 (d, 1 H), 6.8–7.5 (m, 7 H), 6.2 (d, 1 H), 5.5 (dd, 1 H), 4.4 (m, 1 H), 4.0 (q, 2 H), 3.3 (s, 2 H), 3.1 (hept, 1 H), 2.5 (d, 2 H), 1.3 (d, 6 H), 1.1 (t, 3 H) ppm. Anal. ($C_{26}H_{28}FN_3O_4$) C, H, N.

[4α,6β(*E*)]-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (10a). Triethylborane (33.8 mL, 1 M solution in THF, 0.0338 mol) was added via syringe to a solution of **9a** (14.3 g, 0.307 mol) and pivalic acid (0.31 g, 0.00307 mol) in THF (100 mL) under a dry air atmosphere. The resulting solution was stirred at room temperature for 5 min before cooling to −78 °C. Methanol (12 mL) was added, followed by sodium borohydride (1.28 g, 0.0338 mol). The resulting mixture was stirred at −78 °C for 6 h and then quenched by the slow addition of an ice-cold solution of 30% hydrogen peroxide (60 mL). This mixture was allowed to warm to room temperature overnight and then partitioned between chloroform and water. The organic extracts were washed extensively with water, dried, filtered and concentrated in vacuo to yield a yellow oil (16.8 g). This oil was dissolved in THF (150 mL) and methanol (100 mL), and 1 N aqueous sodium hydroxide (36 mL) was added. The resulting solution was stirred at room temperature for 1 **h** and then concentrated in vacuo. The residue was redissolved in water and washed with diethyl ether. The aqueous solution was then acidified with 1 N HCl and extracted with ethyl acetate. The organic extract was washed extensively with water, dried, filtered, and concentrated in vacuo to yield the corresponding 1,3-diols as a mixture of erythro and threo diastereomers which were used without any further purification. These were dissolved in toluene (200 mL) and heated to reflux with azeotropic removal of water for 3 **h**. The solution was cooled to room temperature and concentrated in vacuo. The residue was flash chromatographed on silica with 25% ethyl acetate/toluene to give **10a** (10.0 g, 77%). Recrystallization from toluene gave 6.33 g of **10a** as a white solid: mp 131–133 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, 1 H), 7.74 (m, 1 H), 7.4 (m, 1 H), 7.2–7.0 (m, 5 H), 6.4 (d, 1 H), 5.6 (dd, 1 H), 5.15 (m, 1 H), 4.3 (m, 1 H), 3.22 (hept, 1 H), 2.7 (m, 2 H), 2.0–1.7 (m, 3 H), 1.4 (d, 6 H) ppm. Anal. ($C_{24}H_{24}FN_3O_3$) C, H, N.

Compounds **10b–e** were synthesized in an identical manner, and their physical properties are given below.

[4α,6β(*E*)]-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyrazinyl)-1*H*-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (10b): mp 145–148 °C; ^{1}H NMR ($CDCl_3$) δ 8.92 (d, 1 H), 8.37 (d, 1 H), 8.14 (dd, 1 H), 7.27–7.19 (m, 2 H), 7.12–7.05 (m, 2 H), 6.41 (d, 1 H), 5.70 (dd, 1 H), 5.18 (m, 1 H), 4.37 (m, 1 H), 3.23 (hept, 1 H), 2.76–2.46 (m, 3 H), 1.96–1.74 (m, 2 H), 1.41 (d, 6 H) ppm. Anal. ($C_{23}H_{23}FN_4O_3$) C, H; N: calcd, 13.26; found, 12.80.

[4α,6β(*E*)]-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-quinolinyl)-1*H*-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (10c): mp 179–181 °C; ^{1}H NMR (DMSO-d_6) δ 8.47 (d, 1 H), 7.96 (m, 2 H), 7.67 (t, 1 H), 7.54 (t, 1 H), 7.42–7.22 (m, 5 H), 6.41 (d, 1 H), 5.78 (dd, 1 H), 5.11 (m, 1 H), 4.12 (m, 1 H), 3.29 (hept, 1 H), 2.72–2.37 (m, 3 H), 1.81 (m, 2 H), 1.38 (d, 6 H) ppm. Anal. ($C_{28}H_{26}FN_3O_3$) C, H, N.

[4α,6β(*E*)]-6-[2-[1-(2-Benzothiazolyl)-5-(4-fluorophenyl)-3-(1-methylethyl)-1*H*-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (10d): mp 168–170 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 1 H), 7.59 (d, 1 H), 7.44–7.12 (m, 6 H), 6.38 (d, 1 H), 5.71 (dd, 1 H), 5.17 (m, 1 H), 4.37 (m, 1 H), 3.20 (hept, 1 H), 2.78–2.58 (m, 2 H), 2.00–1.72 (m, 3 H), 1.41 (d, 6 H) ppm. Anal. ($C_{26}H_{24}FN_3O_3S$) C, H, N.

[4α,6β(*E*)]-6-[2-[1-(2-Pyridinyl)-5-(4-fluorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (10e): mp 142–144 °C; ^{1}H NMR ($CDCl_3$) δ 8.3 (d, 1 H), 7.78 (m, 1 H), 7.5 (m, 1 H), 7.0–7.2 (m, 5 H), 6.48 (d, 1 H), 5.88 (dd, 1 H), 5.20 (m, 1 H), 4.38 (m, 1 H), 2.8 (m, 2 H), 2.05–1.70 (m, 3 H) ppm. Anal. ($C_{22}H_{17}F_4N_3O_3$) C, H, N.

2-Hydroxy-1,2,2-triphenylethyl [*S*-[*R,*R**-(*E*)]]-5-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-3-hydroxy-4-pentenoate (17a).** A solution of lithium diisopropylamide (LDA) was generated at room temperature by dropping *n*-butyl lithium (262 mL, 2.2 M in hexane) into a solution of diisopropylamine (82.0 mL, 0.585 mol) in 400 mL of THF. The LDA solution was cooled to 0 °C and added dropwise to a slurry of (*S*)-2-acetoxy-1,2,2-triphenylethanol[13] (**16**, 76.4 g, 0.23 mol) in 600 mL of THF at −78 °C under a dry nitrogen atmosphere. The resulting suspension was warmed to −20 °C to give an orange solution which was cannulated into a suspension of freshly prepared $MgBr_2$ [from 39 mL (0.45 mol) of 1,2-dibromoethane added dropwise to 16.7 g (0.69 mol) of magnesium] in 100 mL of THF at −78 °C. The resulting mixture was stirred for 20 min at −78 °C before a solution of **8a** (76.6 g, 0.228 mol) in 400 mL of THF was added dropwise. After 1.25 h, the reaction was quenched with saturated aqueous ammonium chloride solution and warmed to room temperature. The organic layer was separated, washed with brine, dried, and concentrated in vacuo. The residue was triturated with pentane to give **17a** (102 g, 67%) as an off-white solid: mp 195–198 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (m, 1 H), 7.70–6.95 (m, 22 H), 6.30 (d, 1 H), 5.58 (dd, 1 H), 4.37 (m, 1 H), 3.17 (hept, 1 H), 2.83 (s, 1 H), 2.48 (d, 2 H), 1.63 (bs, 2 H), 1.40 (d, 6 H) ppm. Anal. ($C_{42}H_{38}FN_3O_4$) C, H, N.

Methyl [*S*-(*E*)]-5-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-3-hydroxy-4-pentenoate (18a). Sodium methoxide (11.05 g, 0.205 mol) was added in portions over 5 min to a solution of **17a** (127.6 g, 0.191 mol) in methanol (1.8 L) at room temperature under an atmosphere of nitrogen. The resulting solution was stirred for 16 h, quenched with 15 mL of glacial acetic acid, and concentrated in vacuo. The residue was then partitioned between ethyl acetate and water, the organic layer was washed with water and brine, dried, and concentrated in vacuo. The crude product was flash chromatographed on silica gel, eluting with 40% ethyl acetate/hexanes to yield **18a** (63.66 g, 81%) as a yellow/orange oil: ^{1}H NMR ($CDCl_3$) δ 8.25 (m, 1 H), 7.68 (t, 1 H), 7.42 (d, 1 H), 7.27–6.99 (m, 5 H), 6.40 (d, 1 H), 5.70 (dd, 1 H), 4.55 (q, 1 H), 3.70 (s, 3 H), 3.23 (hept, 1 H), 3.04 (bs, 1 H), 2.54 (d, 2 H), 1.41 (d, 6 H) ppm; $[\alpha]_D$ = +8.9° (*c* = 0.56, MeOH); $[\alpha]_D$ = −1.7° (*c* = 0.53, $CHCl_3$). Anal. ($C_{23}H_{24}FN_3O_3 \cdot 0.33C_4H_8O_2$) C, H, N.

1,1-Dimethylethyl [*S*-(*E*)]-7-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-5-hydroxy-3-oxo-6-heptenoate (19a). A solution of LDA, generated at 0 °C by adding *n*-butyllithium (555 mL, 2.2 M in hexanes) to a solution of diisopropylamine (171 mL, 1.22 mol) in 500 mL of THF, was cooled to −45 °C and *tert*-butyl acetate (170 mL, 1.26 mol) was added dropwise. The resulting mixture was stirred for 1 h at −45 °C before a solution of **18a** (62.4 g, 0.152 mol) in THF (250 mL) was added. The reaction mixture was allowed to warm to −20 °C over 3.5 h and then cooled to −50 °C and quenched with 170 mL of glacial acetic acid. This was stirred for 16 h at −20 °C, diluted with ethyl acetate (1 L), and washed with water, saturated aqueous sodium bicarbonate solution, and brine. The organic extract was dried, filtered, and concentrated to give a yellow oil. Flash chromatography on silica gel, eluting with 40% ethyl acetate/hexanes gave **19a** (65.8 g, 87%) as a yellow foam. ^{1}H NMR ($CDCl_3$) δ 8.17 (d, 1 H), 7.60 (t, 1 H), 7.34 (d, 1 H), 7.15–6.92 (m, 5 H), 6.31 (d, 1 H), 5.61 (dd, 1 H), 4.53 (q, 1 H), 3.30 (s, 2 H), 3.15 (hept, 1 H), 2.65 (m, 3 H), 1.39 (s, 9 H), 1.32 (d, 6 H) ppm; $[\alpha]_D$ = +2.0° (*c* = 0.50, MeOH); $[\alpha]_D$ = −5.8° (*c* = 0.54, $CHCl_3$). Anal. ($C_{28}H_{32}FN_3O_4 \cdot 0.4C_4H_8O_2$) C, H, N.

[4*R*-[4α,6β(*E*)]]-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (+)-(20a). Triethylborane (36 mL, 1 M in THF) was added to a solution of pivalic acid (0.09 g, 0.0009 mol) and **19a** (15.24 g, 0.0309 mol) in 200 mL of THF at room temperature. The solution was stirred for 30 min and then cooled to −78 °C. Methanol (12 mL) was added, followed by sodium borohydride (1.33 g, 0.035 mol), and the resulting mixture was stirred at −78 °C for 6 h. The reaction was quenched by pouring into 30% aqueous H_2O_2 (100 mL) at 0 °C. This mixture was allowed to warm to room temperature, stirred for 72 h, diluted with chloroform, washed with water, aqueous sodium bisulphite, and brine, dried, filtered, and concentrated. The residue was chromatographed on silica gel, eluting with 50% ethyl acetate/hexanes to give 1,1-dimethylethyl [*R*-[*R**,*S**-(*E*)]]-7-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-3,5-dihydroxy-6-heptenoate (12.95 g, 85%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.24 (d, 1 H), 7.68 (t, 1 H), 7.42 (d, 1 H), 7.27–7.04 (m, 5 H), 6.38 (d, 1 H), 5.72 (dd, 1 H), 4.44–4.39 (m, 1 H), 4.24–4.16 (m, 1 H), 3.82–3.58 (bs, 1 H), 3.26 (hept, 1 H), 2.40 (d, 2 H), 1.79–1.62 (m, 3 H), 1.47 (s, 9 H), and 1.40 (d, 6 H) ppm. Anal. ($C_{28}H_{34}FN_3O_4 \cdot 0.1C_4H_8O_2$) C, H, N.

1 M Aqueous sodium hydroxide (15.5 mL) was added to a solution of this dihydroxyester (7.66 g, 0.0155 mol) in 200 mL of methanol. This was stirred for 1 h and then concentrated in vacuo.

The residue was partitioned between water and diethyl ether. The aqueous layer was acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, dried, filtered, and concentrated to give crude dihydroxy acid (6.35 g, 0.0144 mol).

The crude dihydroxy acid was redissolved in dichloromethane (800 mL), cooled to −45 °C, and treated dropwise with a solution of 1,3-dicyclohexylcarbodiimide (DCC) (2.76 g, 0.0134 mol) in 30 mL of dichloromethane. After complete addition, the reaction was warmed to room temperature over 5 h, concentrated, redissolved in ethyl acetate, filtered, and concentrated to give a yellow oil. Chromatography on silica gel, eluting with 50% ethyl acetate/hexanes, gave (+)-**20a** (5.92 g, 97%) as a white solid: mp 139–140 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (d, 1 H), 7.68 (t, 1 H), 7.43 (d, 1 H), 7.25–7.01 (m, 5 H), 6.42 (d, 1 H), 5.68 (dd, 1 H), 5.15 (m, 1 H), 4.37 (m, 1 H), 3.22 (hept, 1 H), 2.77–2.63 (m, 2 H), 1.99–1.81 (m, 2 H), 1.40 (d, 6 H) ppm; $[\alpha]_D$ = +16.0° (*c* = 0.50, MeOH); $[\alpha]_D$ = +15.7° (*c* = 0.49 $CHCl_3$). Anal. ($C_{24}H_{24}FN_3O_3$) C, H, N.

Compound (+)-**20b** was synthesized in a similar fashion, and its physical properties are listed below. **[4*R*-[4α,6β(*E*)]]-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyrazinyl)-1*H*-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one** (+)-(**20b**): mp 154–156 °C; ^{1}H NMR (DMSO-d_6) δ 8.96 (s, 1 H), 8.52 (d, 1 H), 8.26 (d, 1 H), 7.37–7.21 (m, 4 H), 6.39 (d, 1 H), 5.77 (dd, 1 H), 5.24 (d, 1 H), 5.16 (m, 1 H), 4.11 (m, 1 H), 3.26 (hept, 1 H), 2.66 (dd, 1 H), 2.38 (dd, 1 H), 1.80 (m, 2 H), 1.34 (d, 6 H) ppm; $[\alpha]_D$ = +14.40° (*c* = 0.50, MeOH); $[\alpha]_D$ = +21.85° (*c* = 0.54, $CHCl_3$). Anal. ($C_{23}H_{23}FN_4O_3$) C, H, N.

5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazole-4-carboxaldehyde (12). Phosphorus oxychloride (331.7 mL, 3.5 mol) was added dropwise with mechanical stirring to *N*-formylmorpholine (500 mL) at 10–20 °C under an atmosphere of nitrogen. A solution of pyrazole **11** (100 g, 0.35 mol) in *N*-formylmorpholine (200 mL) was then added dropwise, and the resulting brown suspension was heated to 70 °C for 48 h, cooled to room temperature, and carefully poured into saturated aqueous sodium carbonate (2 L). This mixture was extracted with ethyl acetate, after which the extracts were thoroughly washed with saturated aqueous sodium carbonate, water, and brine, dried, filtered, and concentrated to give crude **12**. Recrystallization from hexane/ethyl acetate (1:10) gave pure **12** (55.0 g, 50%): mp 105–108 °C; ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1 H), 8.30 (dd, 1 H), 7.78 (dt, 1 H), 7.57 (d, 1 H), 7.37–7.06 (m, 5 H), 3.61 (hept, 1 H), and 1.41 (d, 6 H) ppm. Anal. ($C_{18}H_{16}FN_3O$) C, H, N.

(*E*)-3-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]-2-propenenitrile (13). Method A: Horner–Emmons Reaction of Aldehyde 12. Diethyl (cyanomethyl)phosphonate (4.92 mL, 0.03 mol) was added dropwise to a slurry of sodium hydride (1.22 g, 60% dispersion, 0.03 mol) in THF at 0 °C. This was stirred at 0 °C for 10 min and then cooled to −78 °C. A solution of the aldehyde **12** (8.2 g, 0.026 mol) in THF was added dropwise, and the resulting mixture was warmed to room temperature over 1 h. The reaction mixture was quenched with water, stirred for 30 min and then extracted with ethyl acetate. The organic layer was washed extensively with water and brine, dried, filtered, and concentrated to give **13** (8.4 g, 93%): mp 121–123 °C; ^{1}H NMR ($CDCl_3$) δ 8.24 (dd, 1 H), 7.75 (dt, 1 H), 7.54 (d, 1 H), 7.28–7.11 (m, 6 H), 5.34 (d, 1 H), 3.18 (hept, 1 H), and 1.43 (d, 6 H) ppm. Anal. ($C_{20}H_{17}FN_4$) H, N; C: calcd, 72.27; found, 71.81.

Method B: Heck Arylation of Acrylonitrile with Bromide 5a. Acrylonitrile (4.6 mL, 0.069 mol), bis(triphenylphosphine)-palladium(II) chloride (0.39 g, 0.00055 mol), and triethylamine (20 mL) were mixed in 20 mL of DMF and warmed to reflux until a homogeneous yellow solution resulted. The bromopyrazole **5a** (5.0 g, 0.0138 mol) was added, and reflux was continued. Additional palladium catalyst (0.39 g, 0.00055 mol) was added after 16 h and again after 24 h. After 40 h of reflux, the reaction was cooled, diluted with diethyl ether, washed with water and brine, dried, filtered, and concentrated to give 7.0 g of crude product. Flash chromatography on silica gel, eluting with 10% ethyl acetate/toluene gave 4.0 g of **13** which was identical to the sample prepared above.

Raney Nickel/Formic Acid Reduction of 13 to 8a. The nitrile **13** (20.64 g, 0.061 mol) was dissolved in formic acid (400 mL) and heated to 60 °C with mechanical stirring. Raney nickel (10 g) was added in five separate portions over 3 h. The reaction mixture was then filtered through Celite and washed extensively with water and ethyl acetate. The filtrate was poured into water and extracted with ethyl acetate. The organic extract was washed with saturated aqueous sodium bicarbonate solution, water, and brine, dried, filtered, and concentrated in vacuo to give 17.1 g of crude **8a**. Flash chromatography on silica gel, eluting with 10% ethyl acetate/hexanes, gave **8a** (13.42 g, 66%), identical to a sample previously prepared.

(*E*)-3-[5-(4-Fluorophenyl)-1-(2-quinolinyl)-3-(1-methylethyl)-1*H*-pyrazol-4-yl]-2-propenal (8c) and (*E*)-3-[1-(3,4-Dihydro-2-quinolinyl)-5-(4-fluorophenyl)-3-(1-methylethyl)-1*H*-pyrazol-4-yl]-2-propenal (15). A solution of DIBAL-H (165.0 mL, 1.0 M in dichloromethane) was added dropwise to a solution of the ester **6c** (31.9 g, 0.43 mol) in 300 mL of dichloromethane at −78 °C under an atmosphere of nitrogen. After 1.5 h at −78 °C, TLC (silica gel, 30% ethyl acetate/hexanes) indicated incomplete reaction. An additional 40 mL of DIBAL-H solution (0.5 eq) was added dropwise, and the reaction mixture was stirred at −78 °C for an additional 1 h. The reaction was quenched by adding saturated aqueous sodium sulfate solution (125 mL), removing the cooling bath, and stirring overnight at room temperature. The reaction was filtered through Celite, dried, filtered, and concentrated to give a crude orange oil. Flash chromatography on silica gel, eluting with 10% ethyl acetate/hexanes, gave an inseparable mixture of the two alcohols (**7c** and **14**) as a yellow solid. The mixture of alcohols was added to a suspension of manganese(IV) oxide (26.88 g, 0.309 mol) in toluene (500 mL) that had been previously refluxed for 6 h with the azeotropic removal of water. After addition of the alcohols, reflux was continued for 40 h. TLC indicated incomplete reaction, and so an additional 26.88 g of manganese(IV) oxide was added. The suspension was then refluxed for an additional 8 h, cooled, and filtered through a pad of silica to give a crude brown oil.

Flash chromatography on silica gel, eluting with 10% ethyl acetate/hexanes, gave **15** (9.0 g, 31%): mp 126–131 °C; ^{1}H NMR ($CDCl_3$) δ 9.42 (d, 1 H), 7.37–7.30 (m, 2 H), 7.25–7.07 (m, 6 H), 6.62–6.58 (m, 1 H), 6.32 (dd, 1 H), 3.25 (hept, 1 H), 3.18 (t, 2 H), 2.92 (t, 2 H), 1.41 (d, 6 H) ppm. Anal. ($C_{24}H_{22}FN_3O$) H, N; C: calcd, 74.40; found, 73.57.

Also isolated was **8c** (5.5 g, 19%): mp 145–148 °C; ^{1}H NMR ($CDCl_3$) δ 9.41 (d, 1 H), 8.12 (d, 1 H), 7.88 (d, 1 H), 7.76–6.95 (m, 9 H), 6.26 (dd, 1 H), 3.26 (hept, 1 H), 1.45 (d, 6 H) ppm. Anal. ($C_{24}H_{20}FN_3O$) H, N; C: calcd, 74.79; found, 74.30.

DDQ Oxidation of 15 to 8c. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.32 g, 0.0015 mol) was added in one portion to a solution of **15** (0.11 g, 0.0003 mol) in THF (10 mL). The resulting yellow solution was stirred for 3 h before quenching with 2 N sodium hydroxide (10 mL). The reaction was extracted with diethyl ether, and the organic extracts were dried, filtered, and concentrated to give **8c** (0.1 g, 100%) as a pale yellow solid, identical to the sample of **8c** obtained above.

[4α,6β]-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (22). A solution of **5a** (5.0 g, 0.0139 mol), **21** (5.54 g, 0.0243 mol), and bis(tri-*o*-tolylphosphine)palladium(II) chloride (0.21 g, 0.00028 mol) in 30 mL of a 50:50 mixture of triethylamine and dimethylformamide was stirred and heated to reflux overnight under a nitrogen atmosphere. The solution was cooled to room temperature, diluted with diethyl ether, washed with water, 2 M hydrochloric acid, water, saturated aqueous sodium bicarbonate, and brine, dried, filtered, and concentrated in vacuo to yield crude product. The residue was flash chromatographed on silica gel, eluting with 20% ethyl acetate in hexane, to give 1.44 g (20%) of coupled product, (*E*)-(±)-ethyl 6-[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1*H*-pyrazol-4-yl]ethenyl]-2,2-dimethyl-1,3-dioxane-4-acetate: ^{1}H NMR ($CDCl_3$) δ 8.2 (d, 1 H), 6.9–7.6 (m, 7 H), 6.25 (d, 1 H, *J* = 10 Hz), 5.65 (dd, 1 H, *J* = 10, 6 Hz), 4.3 (m, 2 H), 4.0 (q, 2 H), 3.2 (m, 1 H), 2.3–2.6 (m, 2 H), 1.0–1.6 (m, 14 H), 0.9 (t, 3 H) ppm.

This material was catalytically hydrogenated in absolute ethanol (100 mL), using 5% palladium on charcoal (0.5 g) at a pressure of 50 psi. The catalyst was removed by filtration through Celite, the filtrate was concentrated, and the resulting residue was dissolved in 4 mL of 50:50 THF/1 N hydrochloric acid. This was

stirred for 3 h at room temperature and then made basic by the addition of 25% aqueous sodium hydroxide solution. After stirring 30 min, the mixture was diluted with water and extracted with diethyl ether. The aqueous solution was then acidified with 2 M hydrochloric acid and extracted with ethyl acetate. The organic extracts were then washed with brine and dried. Filtration and concentration provided the crude dihydroxy acid, which was lactonized with azeotropic removal of water by refluxing in toluene (20 mL) for 1 h. This solution was cooled to room temperature and concentrated in vacuo. The residue was flash chromatographed, eluting with 75% ethyl acetate in hexane, to give pure **22** (0.05 g) as a white solid: mp 182–184 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, 1 H), 7.80 (m, 1 H), 7.64 (d, 1 H), 7.12–7.36 (m, 5 H), 5.16 (m, 1 H), 4.48 (m, 1 H), 4.10 (m, 1 H), 3.1 (hept, 1 H), 2.4–2.8 (m, 4 H), 1.6–1.9 (m, 4 H), 1.3 (m, 3 H) ppm. Anal. ($C_{24}H_{26}FN_3O_3$) C, H, N.

Biological Assays. The cholesterol biosynthesis inhibition assay (COR) was performed as previously described.[14] The acute inhibition of cholesterol synthesis (AICS) in rats was also performed as previously described (see Table I).[8]

Hypocholesterolemic Activity in Cholestyramine-Primed Dogs. Male and female dogs (7 to 12 kg) were randomly allocated to treatment groups based on their plasma cholesterol concentrations using the ALLOCATE program (Roy Hammond, Elsevier Science Publishers, Amsterdam). Single meals were provided from 6:30 a.m. to 10:30 a.m. The resin was mixed into the daily meal, and the test compound was given as a single dose (gelatin capsule) at 2:30 p.m. The dogs were treated with resin for a minimum of 4 weeks prior to each experiment. Lovastatin was purchased from local suppliers as Mevacor (Merck Sharpe and Dohme). Tablets (20 mg active drug) were pulverized by mechanical grinding and weighed into capsules.

Blood samples were taken weekly from the jugular vein of unanesthetized animals for total cholesterol determinations using the Abbot VP Analyzer. Statistical differences before and after treatment for each group were determined using paired, two-tailed *t*-tests. Comparisons among different doses of compounds at the same time point were determined using ANOVA followed by Fisher's least significant difference test (using individual percent changes for each group).

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Renin Inhibitors Containing C-Termini Derived from Mercaptoheterocycles

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A series of transition-state analogues having heterocyclylthio C-termini has been synthesized and evaluated for inhibition of human renin. Addition of mercaptoheterocycles to a chiral Boc-amino epoxide intermediate led, after several steps, to the target [(2*R*,3*S*)-3-(BocPheHis-amino)-4-cyclohexyl-2-hydroxy-1-butyl]thio derivatives. Oxidation of the thioether to sulfone was also investigated. Several of the compounds, especially those derived from N^1-substituted-5-mercaptotetrazoles or N^4-substituted-3-mercapto-5-(trifluoromethyl)-1,2,4-triazoles, were moderately potent inhibitors of human plasma renin, having IC_{50} values of 30–40 nM. When selected compounds were administered intravenously to sodium-deficient rhesus monkeys at 0.3–1.2 mg/kg, they reduced plasma renin activity by 75–98%. However, this inhibition and the accompanying drop in blood pressure were of short duration.

In recent years the renin–angiotensin system (RAS) has been a major focus for the therapy of cardiovascular disease. The RAS is a hormonal and enzymatic complex which can play a key role in the regulation of blood pressure and electrolyte/fluid balance.[1] In this cascade mechanism, the biologically inactive glycoprotein angiotensinogen, which circulates in the bloodstream, is cleaved by renin specifically at the Leu^{10}–Val^{11} linkage to give the decapeptide angiotensin I (AI). Further transformation of AI by angiotensin-converting enzyme (ACE) provides the active octapeptide, angiotensin II (AII), which is a potent vasoconstrictor and a major mediator of essential hypertension.[2-4]

ACE inhibitors are now widely used for the treatment of hypertension and congestive heart failure.[5] However, AI is not the only peptide substrate for ACE. Bradykinin is also degraded by this enzyme, and some side effects of ACE inhibitors have been attributed to the resulting elevated levels of bradykinin.[6] By virtue of its absolute specificity and its position as the rate-limiting enzyme in the synthesis of AII, renin is an attractive target for inhibition.[2,3] Reports of potent renin inhibitors have now appeared from several laboratories, and this class of compounds has been demonstrated to exert marked antihypertensive effects experimentally and clinically.[7] Unfortunately, renin inhibitors in general have suffered from poor oral bioavailability and a limited duration of action, the latter apparently resulting from rapid biliary excretion

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